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A chiral synthesis of the DEF-rings of nogalamycin

Yin, Htwe, Ph.D.

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U·M·I
300 N. Zeeb Rd.
Ann Arbor, MI 48106

A CHIRAL SYNTHESIS OF THE DEF-RINGS OF NOGALAMYCIN.

A

By

HTWE YIN

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy,

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8-20-90

Date

Richard W. Franck

Dr. Richard W. Franck

Chairman of Examining Committee

8/28/90

Date

Dr. Richard Pizer

Executive Officer

Robert Engel

Dr. Robert Engel

Klaus Grohmann

Dr. Klaus Grohmann

Supervisory Committee

The City University of New York

Abstract

A CHIRAL SYNTHESIS OF THE DEF-RINGS OF NOGALAMYCIN.

By

Htwe Yin

Advisor : Professor Richard W. Franck

Nogalamycin is a member of the anthracycline antibiotic family and is notable in possessing reduced cardiotoxicity compared to daunomycin and related compounds. The left hand portion of nogalamycin (DEF-rings) is different from the usual anthracyclines. An approach to the synthesis of DEF-rings of nogalamycin has been studied. The synthesis involves two key cycloadditions: (1) The regioselective cycloaddition of (2S)-2,3-O-cyclohexylidene-D-glyceronitrile oxide with furan to yield the furoisoxazolin **110**, and (2) the regio- and stereoselective Bradsher cycloaddition of furoisoxazoline with 2-(2,4-dinitrophenyl)isoquinolinium chloride, followed by acid hydrolysis and base aromatization to yield the naphthaldehyde **118**. A new method of Bradsher cycloaddition reaction, cycloaddition under pressure using soluble base has been discribed.

Naphthaldehyde **118** is oxidized to naphthol **121** before transforming the functional groups at the side chain. The LAH reduction of isoxazoline **123** to amino alcohol is face

selective. The F-ring is achieved by Swern oxidation of alcohol **188**. The naphthol **214** is oxidized to quinone **224**, but the final reduction of quinone **224** to hydroquinone followed by acid cyclization to construct E-ring was not successful.

Acknowledgements

I wish to express my deep gratitude to my research advisor, Professor Richard W. Franck, for his support, guidance, inspiration, patience and understanding. I will always remember and value the independence and freedom I was allowed in my research.

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Special thanks to the members of Professor Franck's group, both present and past, Drs. V. Bhat, R. B. Gupta, C. S. Subramanium, S. Ramesh and R. Tripathy and soon to be Drs. C. Soll, T. E. Nicolas, A. Choudhury, G. S. Grewal, N. Kaila, A. Geer and X. Ye for their friendship, understanding and assistance. I also thank my family for their moral support and encouragement during the course of this study.

This work is dedicated

to

my family

and

my teachers.

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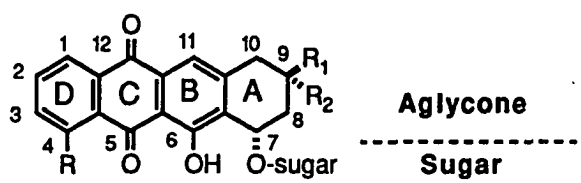
1. INTRODUCTION

Researchers have an intense interest in the chemistry and biological activities of anthracyclines,[1] since these are antibiotics, and are known to have antitumor properties.

An anthracycline is defined as an aglycone of four fused six-membered rings attached to at least one sugar moiety. The numbering pattern and letter designation of the rings in the aglycone are shown below:-[1]



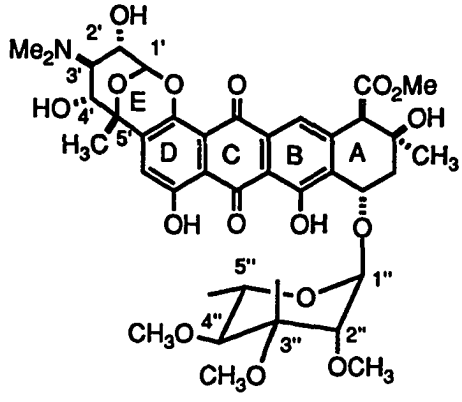
Anthracycline

Rings B and D are aromatic, ring C quinoid and ring A non-aromatic. Depending on the groups at C-4, C-7, C-9, C-10 and sugars, anthracyclines are different and have different anticancer activities.[1]

Nogalamycin **1** and its congeners are notable members of the anthracycline family.[2] Nogalamycin has a nogalose sugar attached to ring-A at C-7 and the amino sugar joined to the aromatic ring-D via a glycoside and C-C bond, forming a benzoxocin ring system.

The structure of nogalamycin, with the exception of the A-ring stereochemistry and configuration of the amino

glucose residue, was determined by P. F. Wiley et al.[3] The absolute stereochemistry of nogalamycin was established by S. K. Arora by X-ray crystallography in 1982.[4]



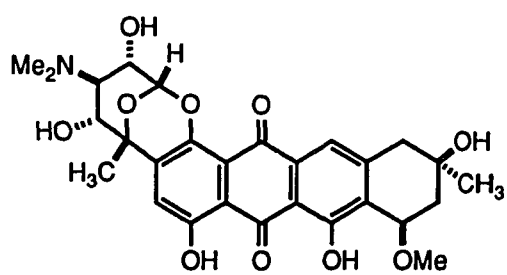
1 Nogalamycin

Nogalamycin was isolated from Streptomyces nogalater var, nogalater sp. n. by P. F. Wiley et al.[5] of the Unjohn Company in 1968. A fermentation broth was adjusted to pH 2 with concentrated hydrochloric acid and filtered using filter aid. The filtrate was extracted with n-butanol and was evaporated to dryness under reduced pressure. The residue was dissolved in water and the solution was neutralized with sodium hydroxide and extracted with dichloromethane. The organic layer was evaporated to dryness under reduced pressure. The residue was purified on silica gel using $CHCl_3$:CH_3OH:H_2O (78:20:2). 30-60mg of pure nogalamycin was isolated from 4-4.5 liters of fermentation broth.[5] About sixty analogs of nogalamycin have been prepared.[2]

According to Chemical Abstracts the nomenclature for nogalamycin is: 2,6-Epoxy-2H-naphthaceno {1,2-b} oxocin-14-

carboxylic acid, 11-{(6-deoxy-3-C-methyl-2,3,4-tri-O-methyl-a-L-mannopyranosyl)oxy}-4-(dimethylamino)-3,4,5,6,9,11,12,13,14,16-dioxomethyl ester,{2R-(2α,3β,4α,5β,6α,11β,13α,14α)}-.

Nogalamycin is highly active against Gram-positive micro organisms, L1210 leukemia and KB cell in vitro.[2, 5] It has broad spectrum activity and less cardiotoxicity compared to daunomycin, adriamycin and related compounds,[2, 4, 5] which are used in treatment. Although nogalamycin was found to exhibit antitumor activity against two types of solid tumors in vivo, its relatively poor activity and unacceptable toxicity in large animals caused cessation of testing.[2] The results of the biosynthesis and testing of numerous semi-synthetic derivatives of nogalamycin, showed that 7-Con-O-methyl nogarol **2** showed superior antitumor activity in comparison to its parent compound **1**.[2, 6]



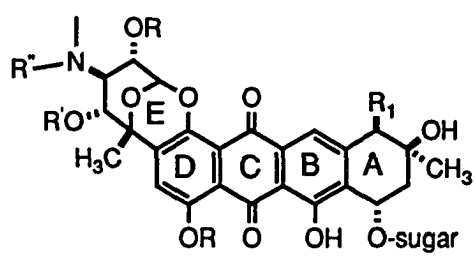
2 (+) 7-Con - O - methyl nogarol

From the crystallographic study of an anthracycline (daunomycin) and DNA hexamer {d(CGTACG)},[7] Arora[4] proposed that nogalamycin possibly intercalates into DNA with the amino sugar and nogalose interacting in major and minor grooves, respectively. The ^1H NMR spectroscopy of DNA

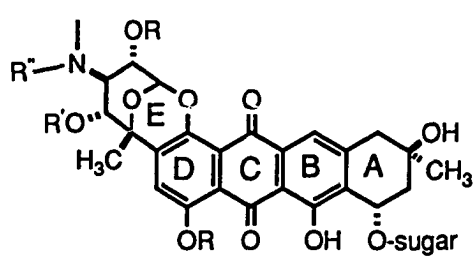
{d(GCATGC)}$_2$-nogalamycin complex studied by Wakelin and coworkers[8] confirmed Arora's proposal.

Recently, the crystal structure of nogalamycin bound to the DNA hexamer {d(^{m5}CGTsA^{m5}CG)} was reported by A. Rich et al.[9] He stated that the two nogalamycin molecules bind to the six-base pair fragment of double-helical DNA. The drug has threaded between the phosphodiester backbones with three aromatic rings intercalated within the DNA. In the major groove, the bicyclo amino sugar forms two direct hydrogen bonds to span a C-G base pair of the duplex via a water-mediated hydrogen bond. In the minor groove, a carbonyl oxygen of nogalamycin forms a hydrogen bond directly to N2 of a guanine.

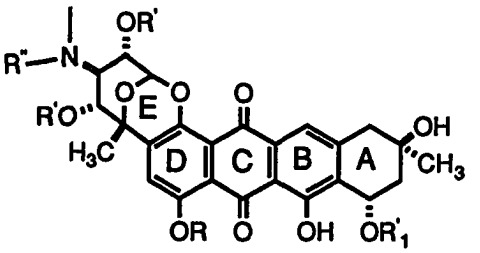
Nogalamycins screened by the National Cancer Institute are divided into three groups, based on the substituents at ring A.[1] There are nogalarols, nogamycins and nogarols.



3 Nogalarols



4 Nogamycins No substituent at C_{10}



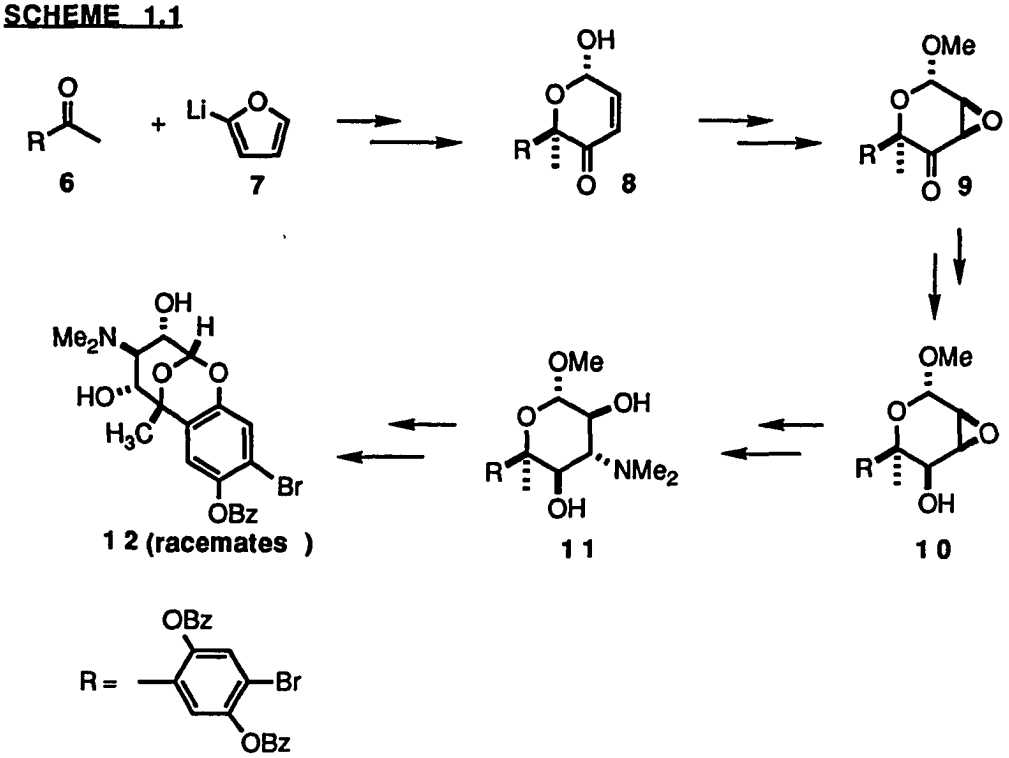
5 Nogarols No substituent at C_{10} and no sugar at C_7

Anthracyclines, containing the DEF-benzoxocin as nogalamycin, such as decilorubicin,[10] arugomycin[11, 12] and viriplanin,[13] have recently been reported.

The promising antitumor activity and unique structure of nogalamycin is challenging to organic chemists. A number of synthetic and biological studies have been reported.[14, 15, 16, 17, 18, 19, 20] However the total synthesis of nogalamycin has not yet been achieved. Recently the synthesis of (+)-7-Con-O-methyl nogarol **2** has been reported.[19, 20] The western portion of nogalamycin (DEF-ring) is different from classical anthracyclines by the amino sugar (F-ring) fused to the D-ring as a C-glycoside. This forms the E-ring as well. That is why all of the synthesis studies are focused on the DEF-ring portion.

P. G. Sammes[14] had reported a flexible method to construct the DEF-ring part of nogalamycin. **SCHEME 1.1.**

SCHEME 1.1

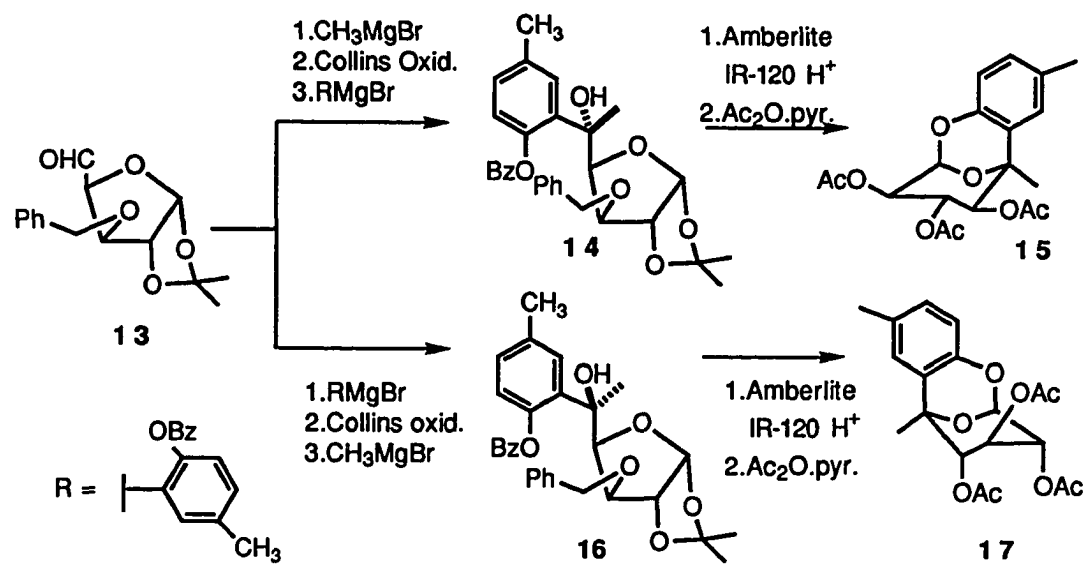


Reaction of 4-bromo-2,5-dibenzyloxy acetophenone **6** with 2-furyl lithium **7**, followed by m-chloroperbenzoic acid yield the diastereoisomeric pyranuloses **8**. Methylation of alcohol with methyl iodide - silver oxide, oxidation of the acetal (the isomer which had -OMe group trans to aromatic ring) with t-butyl hydroperoxide produced a single keto-epoxide **9**. Reduction of keto-epoxide with sodium borohydride gave the single alcohol **10**. Treatment of epoxy-alcohol with dimethylamine at 100°C for 15h gave the desired amine **11**. Treatment of methyl glycoside **11** with trimethylsilyl iodide (2equiv.) and trimethylsilyl chloride (2equiv.) in acetonitrile, cause selective debenzylation, demethylation and cyclization, to produce the required cyclic acetal **12**,

the C-glycoside DEF rings of nogalamycin.[14]

F. M. Hauser and T. C. Adams, Jr.,[15] had shown that optically active 2,6-epoxy-2H-1-benzoxocins **15** and **17** could be prepared from a single aldehydofuranose **13**. **SCHEME 1.2.**

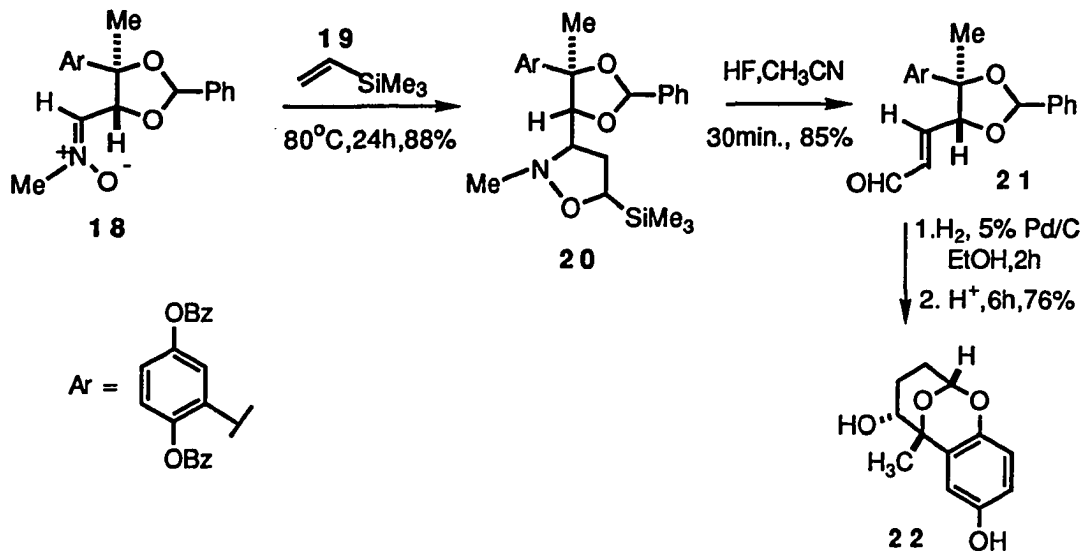
SCHEME 1.2



Depending on the sequence of Grignard addition to aldehydofuranose **13** followed by Collins oxidation and a second Grignard reaction, the product form was either t-carbinol **14** with D-gluco configuration or t-carbinol **16** with L-ido configuration. When t-carbinol (with D-gluco configuration) was treated with Amberlite IR-120 and acetylated, the product found was benzoxocin **15**. With L-ido configuration t-carbinol the product found was benzoxocin **17**. However this approach does not give the F-ring functionalities of nogalamycin. It was necessary to start with the appropriate amino sugar.

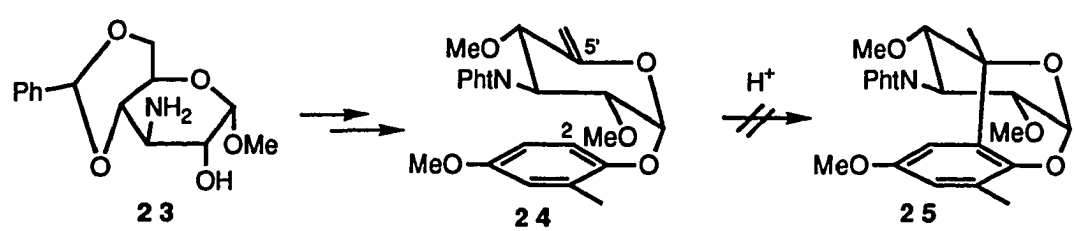
P. DeShong[16] is also engaged in the synthesis of sugars from non-carbohydrate precursors. With the precedent of nitrone dipolar cycloaddition to alkenes, he synthesized the tricyclic acetal **22**, in 52% yield. **SCHEME 1.3.**

SCHEME 1.3



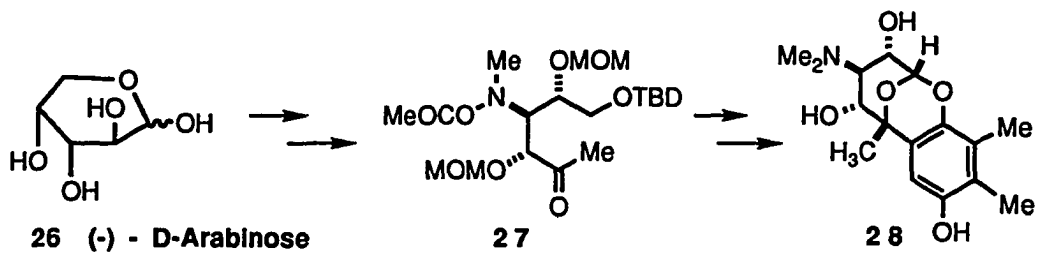
T. H. Smith and H. Y. Wu[18] did not get satisfactory results in preparing the western synthon of nogalamycin. They started from partially protected 3-aminoglycose derivative **23** and finally got the vinyl ether **24**. But the attempted cyclization of C-2 & C-5' failed.

SCHEME 1.4



The first total synthesis of optically pure bicyclic acetal **28** was published in 1985 by S. Terashima et al.[6] Acetal **28** was synthesized in 22 steps from D-arabinose. The key intermediate was the methyl ketone **27**. **SCHEME 1.5.**

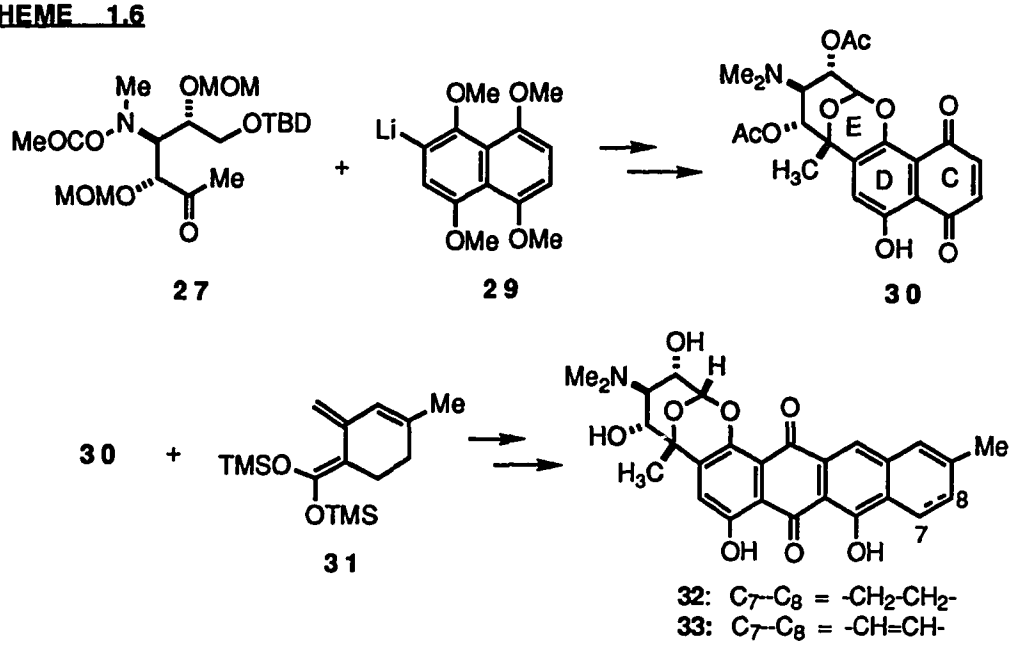
SCHEME 1.5



26 (-) - D-Arabinose **27** **28**

Furthermore, Terashima and coworkers achieved a preparation of (+)-7,8-dihydronogarene **33**.[21] This is the first total synthesis to construct the whole carbon framework of nogalamycin family. A protected 1,4,5,8-tetramethoxy naphthalene motiey was introduced into methyl ketone **27** and the CDEF-ring system **30** was constructed. The regioselective Diels Alder cycloaddition of **30** with bis-trimethylsilyl ketene acetal **31**, followed by spontaneous air oxidation of the addition product during mild acidic work-up gave (+)-7,8-dihydronogarene **32**. **SCHEME 1.6.** Dehydrogenation of compound **32** afforded nogarene **33**.

SCHEME 1.6

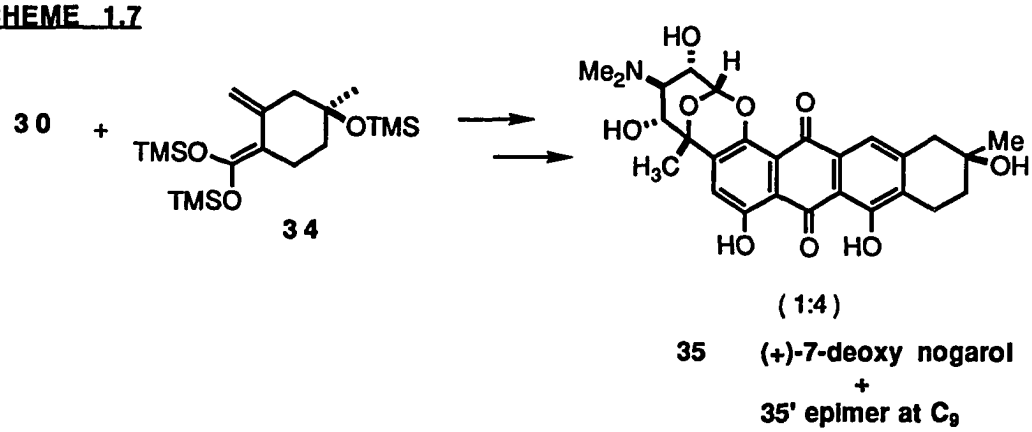


Recently, S. Terashima et al.[20] completed the total synthesis of (+)-7-deoxy nogarol **35** and (+)-7-Con-O-methyl nogarol **2**. Initially, they expected that the A-ring of **35** and **2** could be elaborated by functionalization of A ring of **32**. However they found out that the oxidation of C9-C10 double bond of **32** produced a complex mixture due to preferential oxidative removal of the C3'-dimethylamino group. This required them to synthesize the appropriate dienes for compound **35** and **2**.

Diels Alder cycloaddition of quinone **30** with racemic diene **34**, which had A-ring functionalities of (+)-7-deoxy nogarol **35**, followed by air oxidation of the addition product during mild acidic workup gave the mixture of (+)-2',4'-di-O-acetyl-7-deoxy nogarol and (+)-2',4'-di-O-acetyl-9-*epi*-7-deoxy nogarol in 1:4 ratio. Diacetylation of the products

gave (+)-7-deoxy nogarol **35** and its epimers **35'**. **SCHEME 1.7.**

SCHEME 1.7



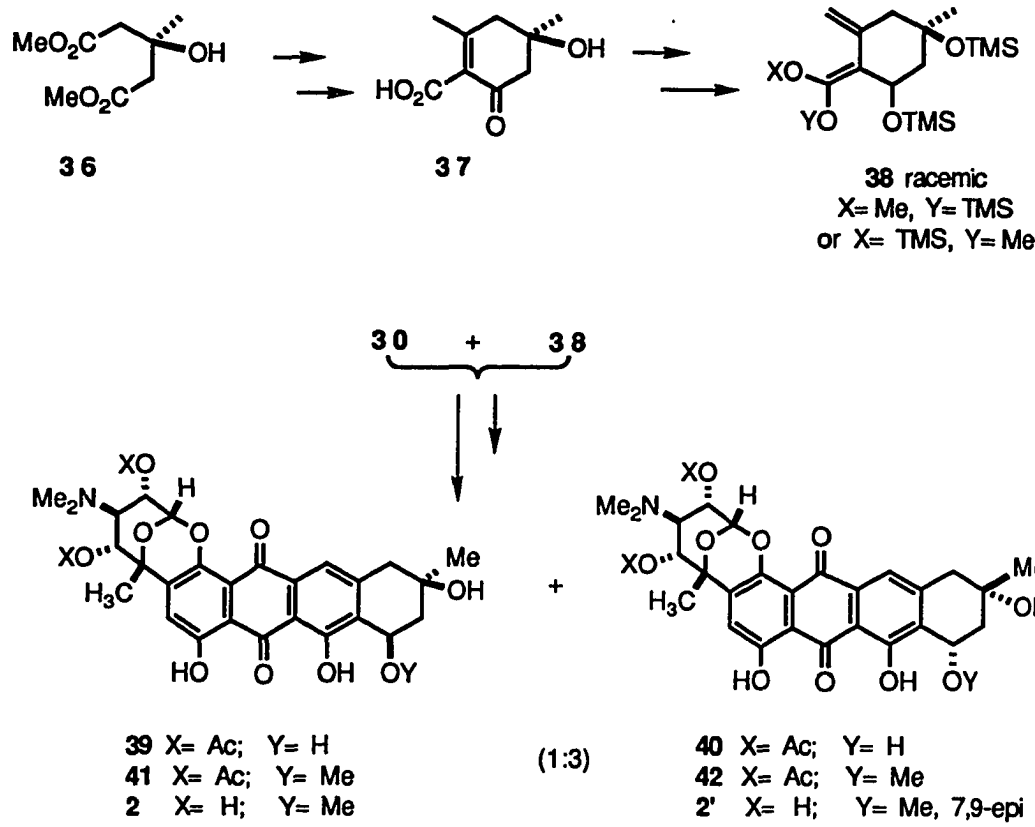
(1:4)

35 (+)-7-deoxy nogarol + 35' epimer at C_9

Similarly, Diels Alder cycloaddition of quinone **30** with racemic diene **38**, which had A-ring functionalities of (+)-7-Con-O-methyl nogarol **2**, followed by spontaneous air oxidation of the adduct during mild acidic workup gave the mixture of 2',4'-di-O-acetyl-Con-nogarol **39** and 2',4'-di-O-acetyl-7,9-di-epi-Con-nogarol **40** in 1:3 ratio. **SCHEME 1.8.**

Without separating the diastereomeric mixture of **39** and **40**, methoxy group was stereoselectively introduced at C7-OH using trifluoroacetic acid followed by sodium methoxide. They reported that they got the same ratio (1:3) of (+)-2',4'-di-O-acetyl-7-Con-O-methyl nogarol **41** and (+)-2',4'-di-O-acetyl-7,9-di-epi-7-Con-O-methyl nogarol **42**.

SCHEME 1.8



36 **37** **38** racemic X= Me, Y= TMS or X= TMS, Y= Me

39 X= Ac; Y= H
41 X= Ac; Y= Me
2 X= H; Y= Me

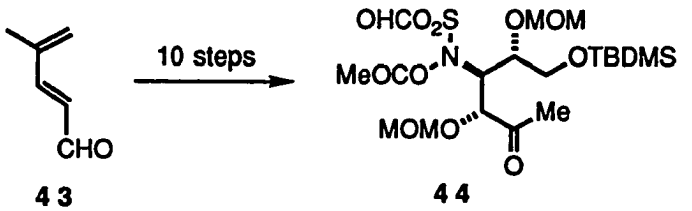
(1:3)

40 X= Ac; Y= H
42 X= Ac; Y= Me
2' X= H; Y= Me, 7,9-epi

Deacetylation of **41** and **42** gave (+)-7-Con-O-methyl nogarol **2** and its 7,9-epimer.

S. M. Weinreb[17] had also shown that methyl ketone **44**, similar to the key methyl ketone intermediate **27** from the Terashima synthesis, could be made in 10 steps from 4-methyl-2,4-pentadienal. **SCHEME 1.9**. This compound **44**, differs from the Terashima ketone **30** only in the presence of a formyl sulfonamide group rather than a N-methyl substituent. He stated that the synthesis of CDEF ring of nogalamycin could be carried out as Terashima's procedure from the ketone **44**.

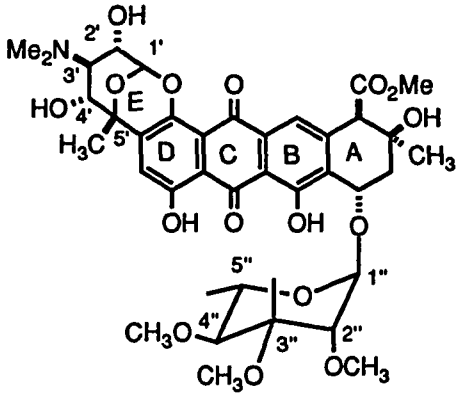
SCHEME 1.9



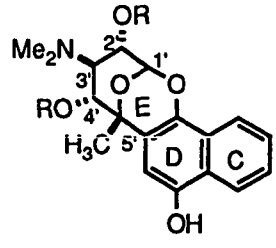
43 44

2. PROPOSED SYNTHETIC SCHEMES

As the western portion of nogalamycin (CDEF-ring) is the challenging part of the molecule, we decided to synthesize the western part, (model compound **45**) using the Bradsher cycloaddition of isoquinolinium salts as the method for combining the sugar and aromatic section.



1 Nogalamycin

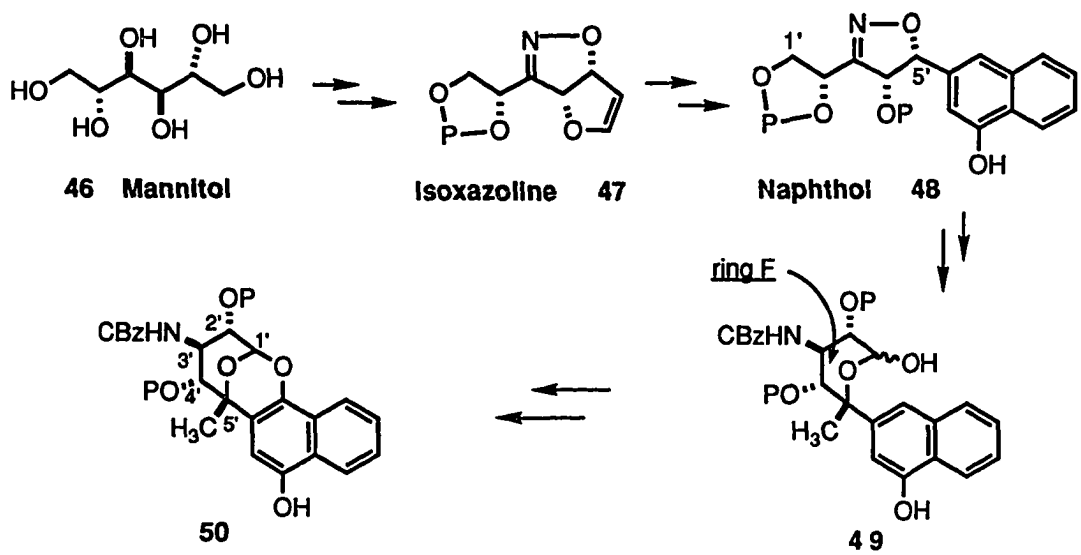


45 Model Compound

The synthesis was planned as follows. **SCHEME 2.1.** Initially we proposed a furoisoxazoline **47** with the appropriate functionalities and stereochemistry as the precursor for amino sugar F-ring. Furoisoxazoline **47** would then serve as the vinyl ether in the reaction sequence,i.e. Bradsher cycloaddition which would construct the aromatic CD-ring. After several intermediate steps this sequence would produce compound **48**. Reduction of furoisoxazoline **48**, C-methylation at C-5', followed by oxidation of the primary alcohol, then cyclization with C-5'-OH (according to

nogalamycin numbering system) would produce the amino sugar ring F, compound **49**. Finally, the oxidation of naphthol to naphthohydroquinone, through naphthoquinone, and acid catalyzed cyclization would produce the desired compound **50**.

SCHEME 2.1



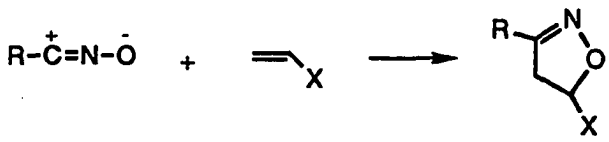
2.1. Preparation of Furoisoxazoline.

One of the key steps of our synthesis was to prepare furoisoxazoline **47**. This molecule had all the functional groups we needed for the EF-rings of nogalamycin. It had masked 1,3-amino alcohol group and aldehyde functionality. The dihydrofuran part of furoisoxazoline would serve as the vinyl ether in the second cycloaddition sequence, i.e., Bradsher cycloaddition.

One can prepare 2-isoxazolines in several ways.[22]

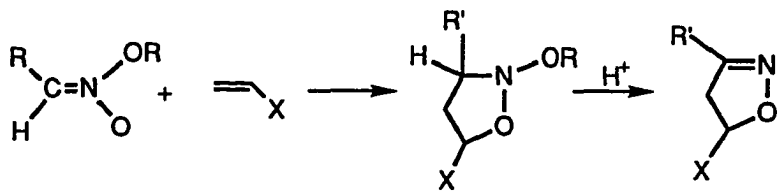
a) By the 1,3-dipolar cycloaddition of nitrile oxides to

olefins, **(eq.2.1)**.



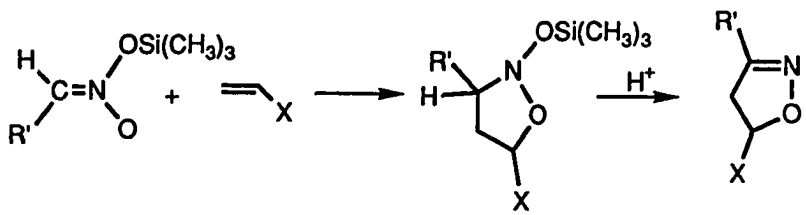
eq. 2.1

b) By the 1,3-dipolar cycloaddition of alkylnitronates to olefins followed by acid catalyzed elimination of alcohol. **(eq.2.2)**.



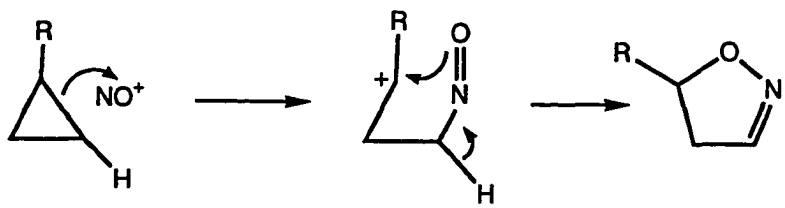
eq. 2.2

c) By 1,3-dipolar cycloaddition of silyl nitronates to olefins followed by acid catalyzed elimination of alcohol, **(eq.2.3)**, like case b.



eq. 2.3

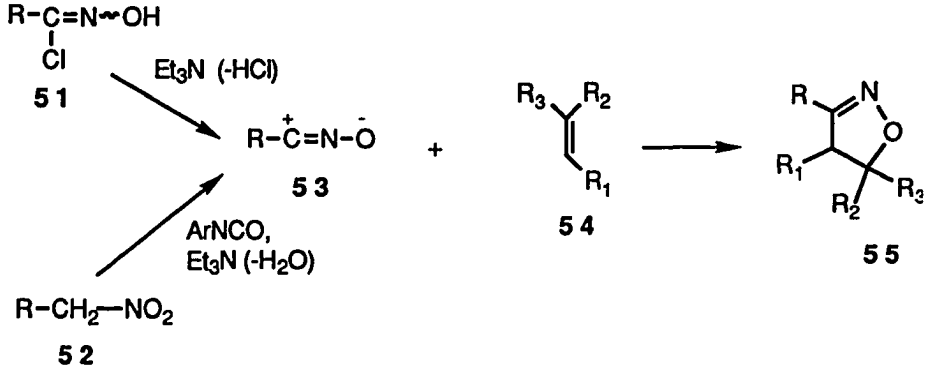
d) By nitrosation of cyclopropanes accompanied by ring cleavage and recyclization. **(eq.2.4)**.



eq. 2.4

Basically all the synthetic routes to 2-isoxazoline go through the 1,3-dipolar nitrile oxide intermediate except in the case d. The choice is determined by how easy the dipolar compound can be prepared. At present the most useful way of carrying out the 1,3-dipolar cycloaddition is the *in situ* generation of nitrile oxides **53** from either hydroxamic acid chloride **51** (Huisgen's method)[23, 24] or from nitroalkanes **52** (Mukaiyama's procedure),[25] in the presence of dipolarophiles **54** (alkenes)[26]. **SCHEME 2.2.**

SCHEME 2.2



The 1,3-dipolar nitrile oxide cycloaddition to olefins is a $4\pi+2\pi$ process.[27] The cycloaddition is stereospecific[28] and regioselective.[22] Parameterized MINDO calculations predict an asymmetrical or biradical intermediate.[22] An *ab initio* calculation and reaction mechanism studies show that the cycloaddition reaction is symmetric or concerted.[29, 30]

High regioselectivity is observed in the nitrile oxide cycloaddition to monosubstituted olefins. The substituent on the olefin can be either an electron withdrawing or electron

donating group and the product is a 5-substituted isoxazoline. Similarly, the dipolar cycloaddition reaction of mono-substituted acetylenes give 5-substituted isoxazoles.[22] 1,1-Disubstituted olefins show higher regioselectivity and give 5,5-disubstituted products. However very strong electron withdrawing group-substituted olefins give 4,4-disubstituted products.(e.g. $-SO_2R$, $-NO_2$). In the case of 1,2-disubstituted olefins and acetylenes, regioselectivity is poor.

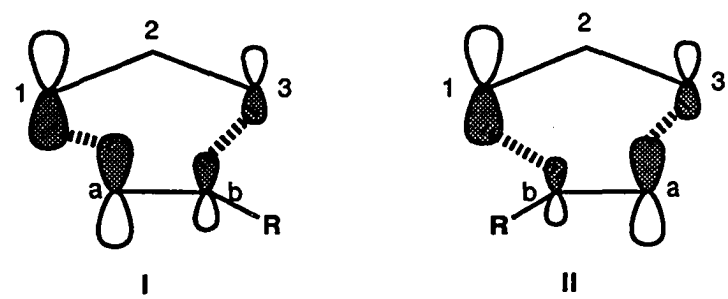


Figure 2.1 Schematic representation of the orbital interaction between the LUMO of a 1,3-dipole, 1-3 and the HOMO of dipolarophile, a-b. The orbital size represent the magnitude of the coefficients.

The regioselectivity of these reactions can not be explained by organic mechanisms, but can be explained by Fukui's frontier orbital concept.[31] He defined an energy expression for energy change in molecules which undergo cycloaddition reaction and generalized the statement that "the energy gain in bond formation is highest when those orbitals interact that are closest in energy and have best overlap". A schematic representation of orbital

stabilization in the transition state due to different coefficient magnitudes is shown in **Figure. 2.1.**[31]

The stabilization is more effective in **I** than in **II** because this alignment makes the summation of the product of coefficients ($\sum c_i c_i'$) larger, and this in turn increases the bond formation energy of Fukui's energy expression.

The size and energies of frontier orbitals of alkenes are affected by substituents in the following way.[22, 32]

1. Electron withdrawing groups lower the HOMO and LUMO energies. The effect is more on the LUMO. In both HOMO and LUMO, the unsubstituted end has the larger orbital coefficient.
2. Electron donating groups increase the HOMO and LUMO energies. The effect is more on HOMO. In HOMO, the unsubstituted end has larger orbital coefficient, whereas in LUMO, the unsubstituted end has smaller orbital coefficient.
3. Conjugation to alkenes increase the HOMO energy and decrease the LUMO energy. In both HOMO and LUMO, the unsubstituted end has the larger orbital coefficient.

Figure 2.2[22, 24, 33] is an example for the Fukui's frontial orbital concept on the regioselectivity of dipolar cycloaddition to mono-substituted alkenes, benzonitrile oxide cycloaddition to electron deficient methyl acrylate and to electron rich vinyl ethyl ether. Both reactions are LUMO controlled reaction and according to Fukui's frontial orbital concept, one can predict the regioselectivity of the

reaction.

3-Ethoxy-5-phenyl-2-isoxazoline is the only product obtained from vinyl ethyl ether[33] and 95:5 ratio of 3-methoxy carbonyl-5-phenyl-2-isoxazoline and 3-methoxy carbonyl-4-phenyl-2-isoxazoline are observed in methyl acrylate reaction.[23] The formation of a small amount of 4-substituted isoxazoline is from the less favorable HOMO controlled reaction.

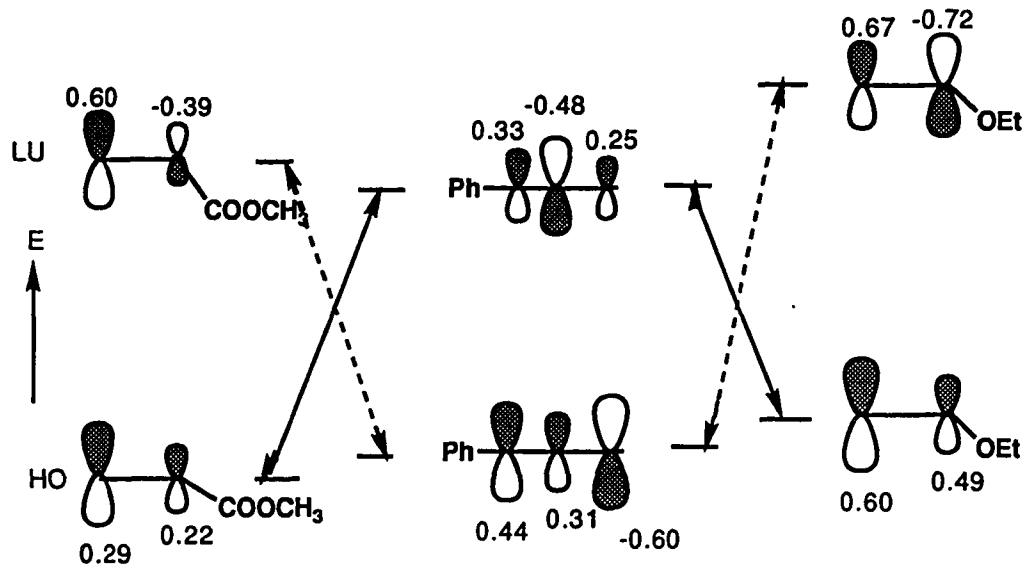
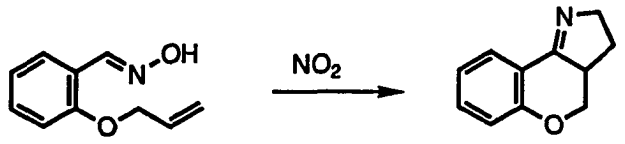
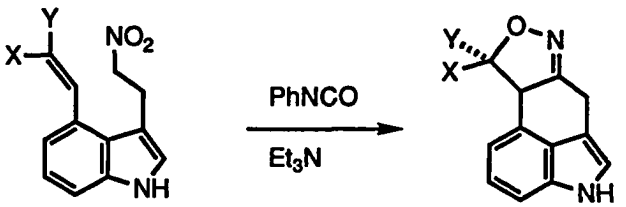


Figure 2.2. Regioselective LUMO alignment of methyl acrylate and vinyl ethyl ether to benzonitrile oxide.[22]

Though nitrile oxide cycloaddition is regioselective, it is possible to ignore the orbital control assumption when the steric requirements favor the formation of 4-substituted product. **(eq. 2.5,[34] 2.6[35])**.



eq. 2.5

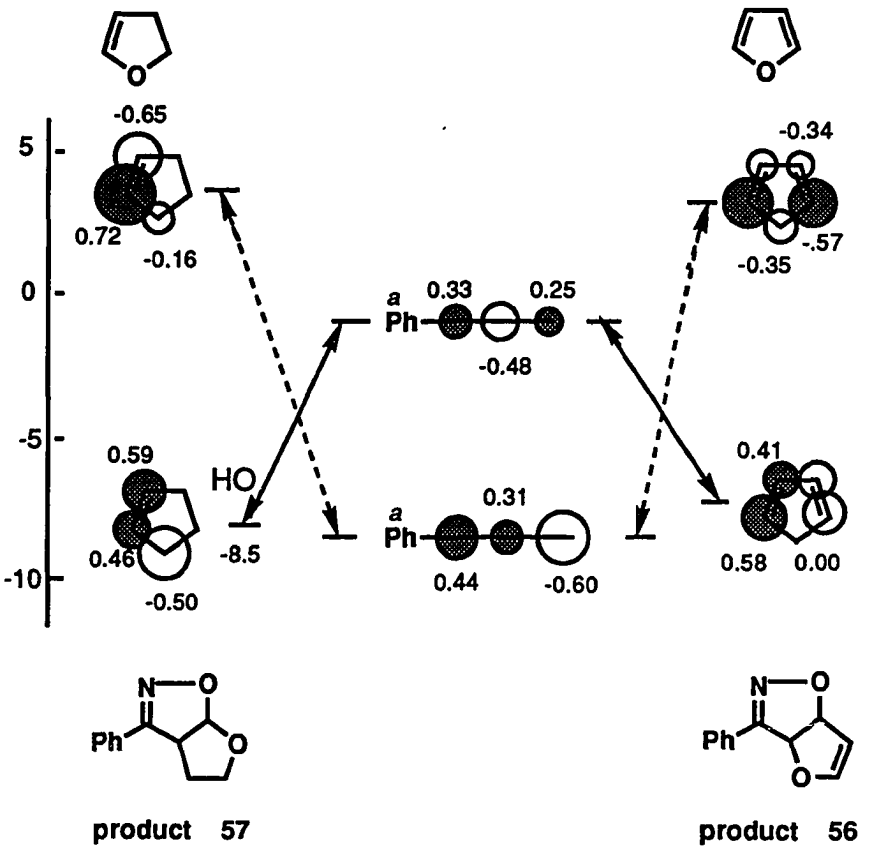


eq. 2.6

a: X, Y = H
b: X = OCH_3, Y = H

The regioselectivity of the nitrile oxide cycloaddition to furan is reversed from aliphatic olefins. The dipolar oxygen bonds to the 3-position of furan. This regioselectivity is explained by Caramella, Grunanger, Houk et al.[36] by frontier orbital theory and is supported by work of Jager and Schoke.[26]

The orbital interaction of the cycloaddition of benzonitrile oxide to dihydrofuran and to furan are shown in **Figure 2.3.** The orbital coefficients are calculated by K. N. Houk et al.[36] using CNDO/2. The radius of the circles represent the magnitudes of the atomic orbital coefficients. According to Fukui's frontier orbital concept, both cycloadditions are LUMO controlled and the cycloaddition with furan gives product **56** and the cycloaddition with dihydrofuran gives product **57.**



product 57 **product 56**

Figure 2.3. Regioselective LUMO alignment of dihydrofuran and furan to benzonitrile oxide. (The radius of the circles represent the magnitudes of the atomic orbital coefficients at each center, calculated by CNDO/2[36]; [a] from Torssell.[22]

Nitrile oxide cycloaddition reactions are stereospecific and regioselective. Is the reaction stereoselective ? The stereoselectivity of the reaction can be observed only with the dipolarophile having bulky chiral auxiliaries.[37] Little or no stereoselectivity is observed with the dipolarophile which has small or no chiral auxiliaries.

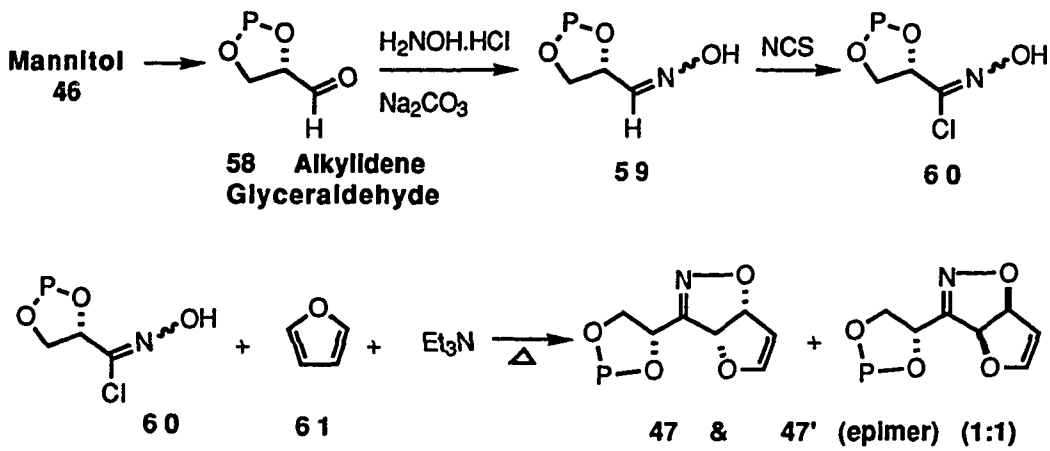
Asymmetric induction of chiral nitrile oxides with

achiral alkenes has been studied by A. P. Kozikowski et.al.[38] None or very little diastereoselection is found. They claim that it is a consequence of the developing asymmetric center being quite remote from the existing asymmetric center.

The cycloaddition reaction with furan would not show any stereoselectivity, because furan is a planar molecule. Therefore one would obtain two diastereomeric products with a chiral nitrile oxide.

We planned to apply the known furan-nitrile oxide cycloaddition methods[26, 36, 39, 40] to prepare our furoisoxazoline **47**, using alkylidene glyceraldehyde, as the nitrile oxide precursor. **SCHEME 2.3.**

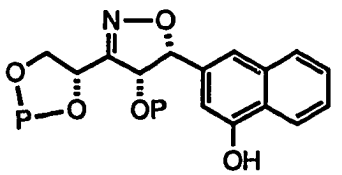
SCHEME 2.3



2.2. Preparation of Naphthol 48

The second step of our synthesis was to introduce aromatic aldehyde to furoisoxazoline **47** to obtain naphthol **48**. This could be achieved by Bradsher cycloaddition

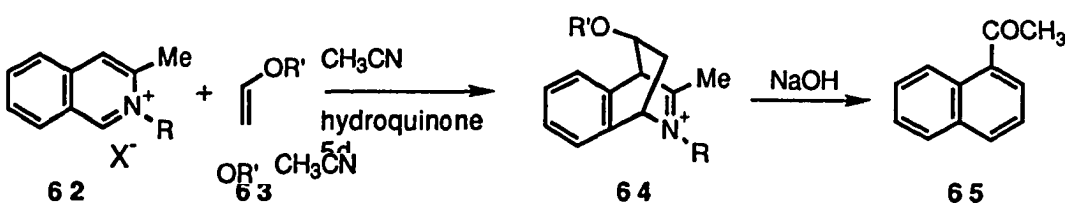
reaction.



48 Naphthol

In 1971, Bradsher and his co-workers[41, 42] studied the intermolecular cycloaddition reactions of 3-methyl isoquinolium salts **62** with vinyl ethers **63** and olefins,[43] in acetonitrile. **SCHEME 2.4.** They showed that the cycloaddition reaction is regio- and stereoselective.[44] When the cycloadduct **64** is treated with sodium hydroxide, the product isolated in high yield is methyl-1-naphthyl ketone **65**.[43]

SCHEME 2.4

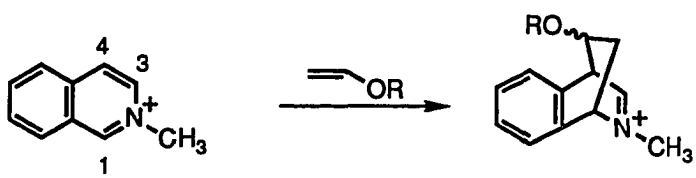


62 63 64 65

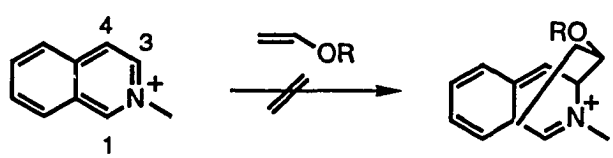
The Bradsher cycloaddition reaction is a $4\pi+2\pi$ cycloaddition, the electron-poor diene, isoquinolinium salt (IsoQ) adds to the electron-rich dieneophile, vinyl ether in $4\pi+2\pi$ fashion. This is a cationic polar cycloaddition or an inverse electron demand Diels-Alder cycloaddition.

The 1,4-cationic polar cycloaddition to vinyl ethers and unsymmetrical alkenes show a remarkable regioselectivity.[45] The β-carbon of alkene bonds to the most

electrophilic carbon center of the cationic polar compound. The C-1 and C-3 of IsoQ are the most electro-positive carbons in the molecule and C-4 and C-9 are the most electro-negative and have no positive charge in any of the resonance canonical forms. The 1,4-polar cycloaddition can form between C-1 & C-4 or C-3 & C-9 carbons of IsoQ. However, C-1 & C-4 addition **(eq. 2.7)** is more favorable than C-3 & C-9 addition **(eq. 2.8)** because the latter bond formation occurs at the C-9 tertiary carbon and this destroys the aromaticity of the B-ring.



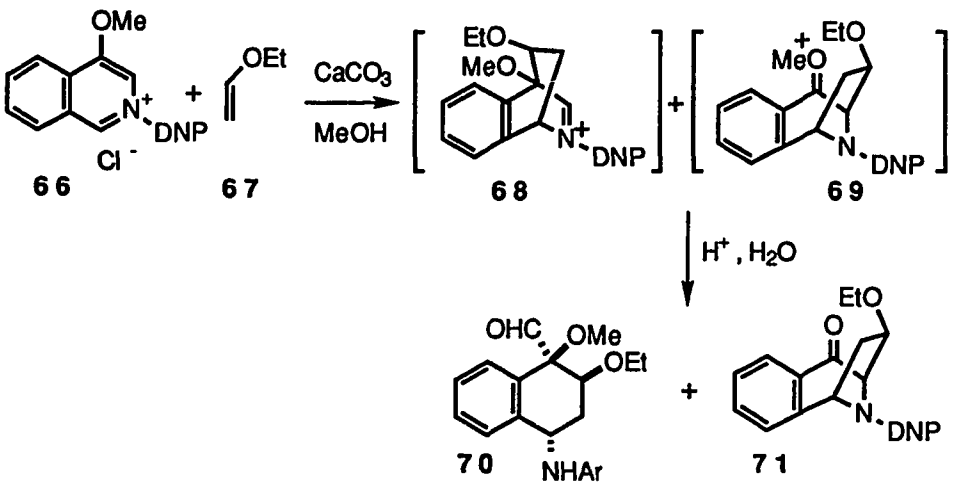
eq. 2.7



eq. 2.8

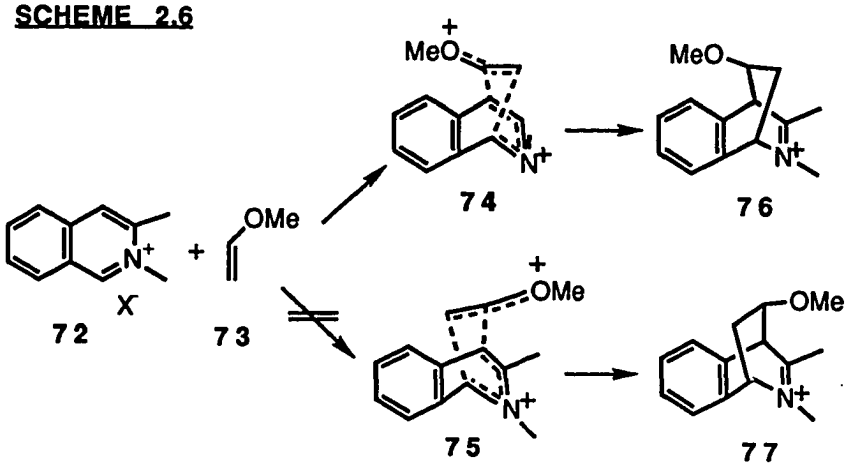
An interesting chemistry is observed from the cycloaddition of 4-methoxy isoquinoline **66** and ethyl vinyl ether **67**.[46] **SCHEME 2.5.** The tricyclic ketone **71** is observed with the expected aldehyde **70** after acid hydrolysis. Ketone **71** is obtained from the intermediate 1,3-cycloadduct **69**.

SCHEME 2.5



The Bradsher cycloaddition of isoquinolinium salt with vinyl ether is stereospecific. C. K. Bradsher et al.[41, 44] predicted that the preferred transition state of the adduct will be the one that gives the maximum separation of the like charge **74**, and yields adduct **76** rather than adduct **77** through **75**. They reported the single X-ray crystal analysis of the methyl vinyl ether adduct **76**,[42] which was the only stereoisomer obtained from the cycloaddition of methoxy vinyl ether **73** with N-2,3-dimethyl isoquinolinium salt **72**, (97% yield). **SCHEME 2.6.**

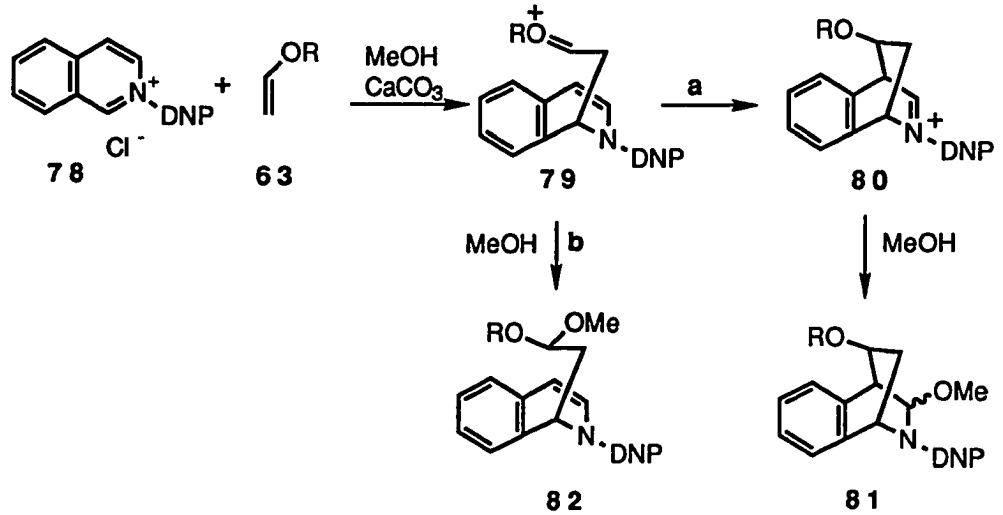
SCHEME 2.6



Bradsher stated that, the mechanism of 1,4-cationic polar cycloaddition is neither a carbonium ion intermediate nor a concerted cycloaddition.[44] It is the charge-transfer complexes which exist as intermediates or as stages along the reaction pathway. Mechanistic studies have been done in our laboratory[46] and it was concluded that cycloaddition of IsoQ to vinyl ethers is a two-step mechanism. The first step is C-C bond formation between C-1 of isoquinoline **78** and the β-C of vinyl ether **63** with formation of an oxocarbonium ion intermediate **79**. The second step is C-C bond formation of C-4 of IsoQ and the α-C of vinyl ether producing iminium ion **80**. The iminium ion is trapped by solvent and produces the cycloadduct **81**. **SCHEME 2.7**. The isolation and characterization of "one-bond product **82**", derived from the intermediate oxocarbonium ion **79** trapped by the solvent methanol is the evidence for a two-step mechanism. The stereospecificity is observed because the rotation of the σ bond of oxocarbonium ion intermediate **79** is slow compare to

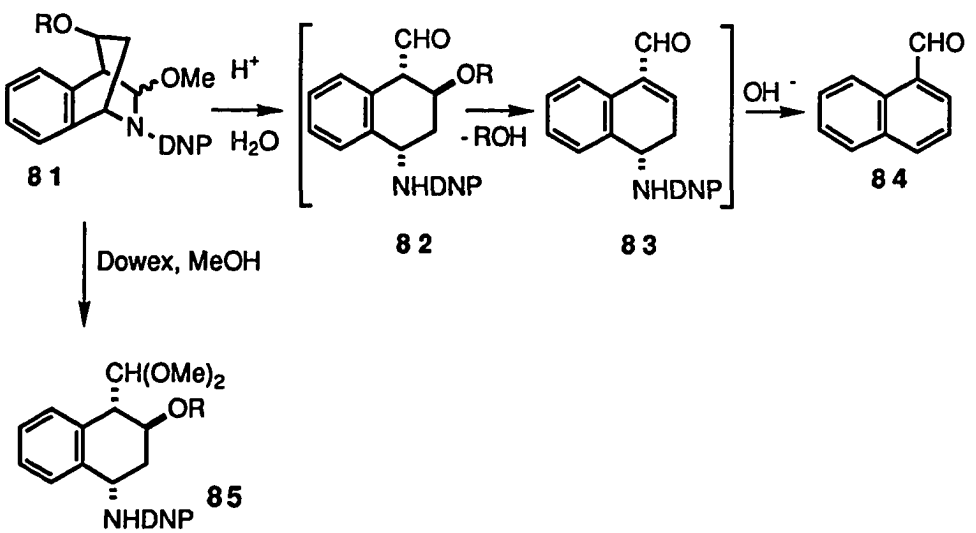
cyclization.

SCHEME 2.7



Falck et al.[47] showed that the tricyclic adduct **81** converts to naphthaldehyde **84** when hydrolyzed with acid and aromatized with base. **SCHEME 2.8.**

SCHEME 2.8



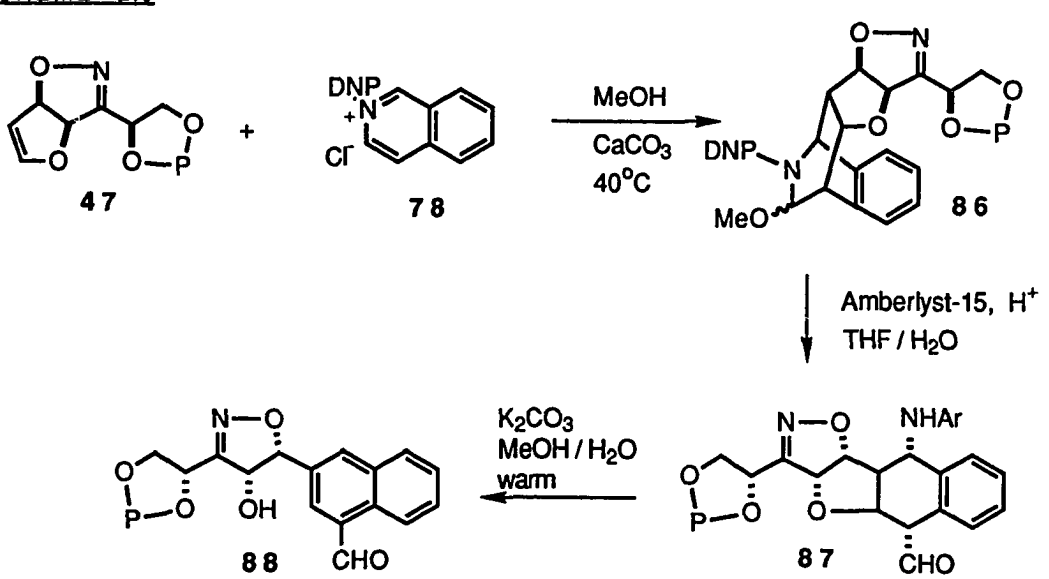
The β-substituted alkoxyl vinyl ethers produce 3-

substituted naphthaldehydes. A new application of the cycloadduct was achieved in our laboratory. Tetralin **85**, with up to four predictable chiral centers, is obtained when cycloadduct **81** is treated with Dowex and anhydrous methanol.[48]

This cycloaddition chemistry has been developed in our laboratory for several years. Some natural products have been synthesized in our lab using this chemistry as a key step.[49]

We intended to prepare our naphthaldehyde by applying the above method using N-2,4-dinitrophenyl isoquinolinium chloride salt **78** with our vinyl ether, furoisoxazoline **47**. **SCHEME 2.9.**

SCHEME 2.9



As the cycloaddition is regio- and stereoselective, we expected to get only cycloadduct **86**, i.e. the convex face of furan approach to isoquinolinium salt from the top (si face at C_1). After acid hydrolysis of cycloadduct to tetralin

and further aromatization with base, we would obtain naphthaldehyde **88**.

Oxidation of naphthaldehyde **88** to naphthol **48** could be achieved by transforming naphthaldehyde to formate using the Baeyer-Villiger reaction followed by hydrolysis with aqueous base and treatment of the formate with alumina, activity 1, in dichloromethane.[50]

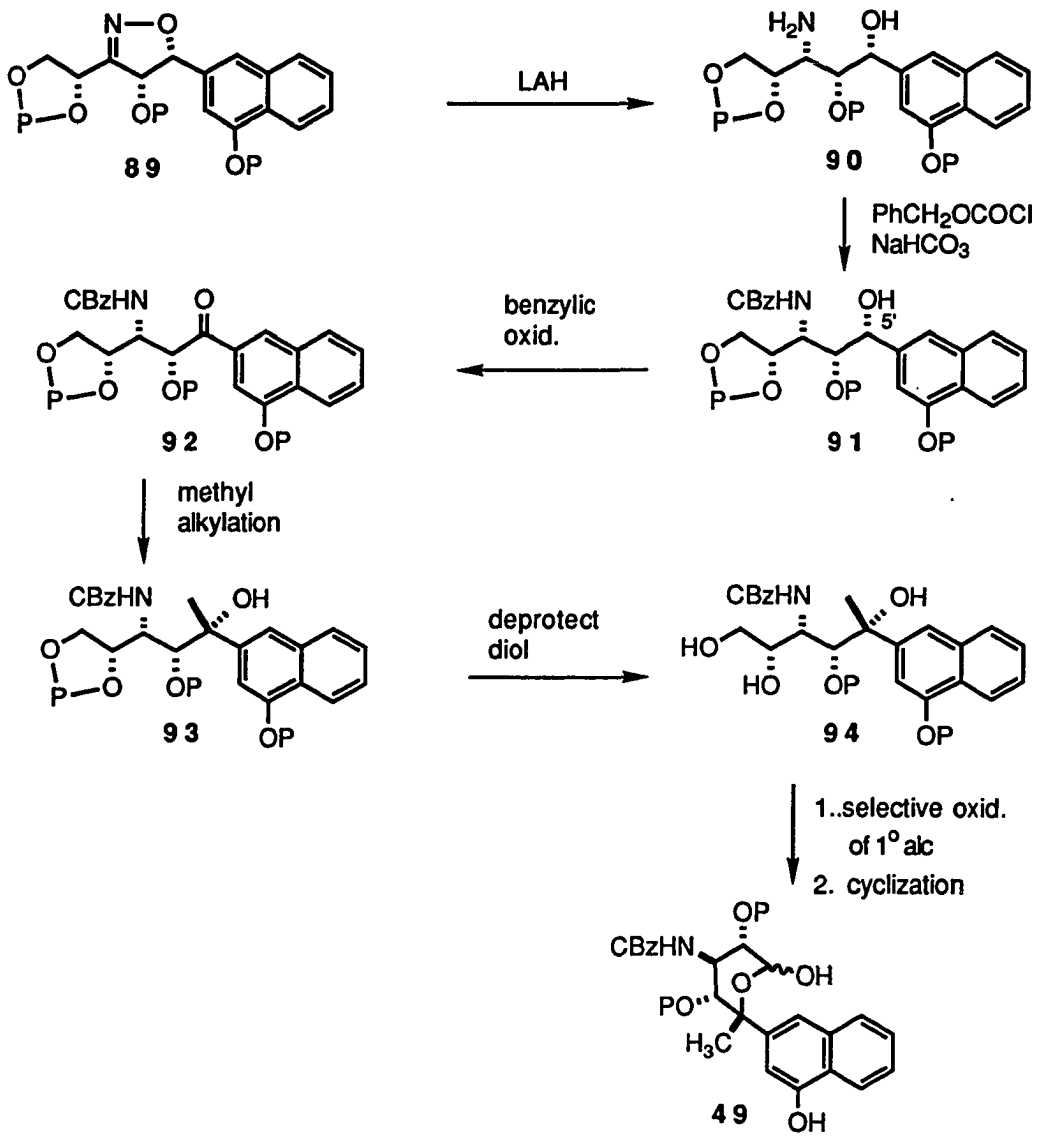
2.3. Construction of Amino Sugar Ring F

V.Jager and I. Muller showed that the reduction of isoxazolines with LAH give the syn γ-amino alcohol.[39] They also pointed out that in the case of furoisoxazolines the reduction gives the syn product. Therefore we expected to get the diastereoselective reduction of isoxazoline to amino alcohol **90** with the indicated stereochemistry. **SCHEME 2.10.** We could selectively protect the amino group as N-carbamate[51] **91** and eventually reduce the carbamate to N-methyl as required in nogalamycin.

At this point we would need to introduce the methyl group at C-5' in the right stereochemistry for nogalamycin. This can be achieved by oxidation of the benzylic alcohol to ketone **92**, followed by organometallic methylation. The benzylic alcohol **91** could be easily oxidized to ketone by using either MnO_2,[52] DDQ,[53] or K_2RuO_4.[54] Stereocontrolled methyl addition to ketone **92** by using either MeLi, MeMgBr[55] or $CH_3Li/TiCl_4$[56] would give the right methylated product **93**. We would have all the required functional groups with the

right stereochemistry for ring F of nogalamycin.

SCHEME 2.10



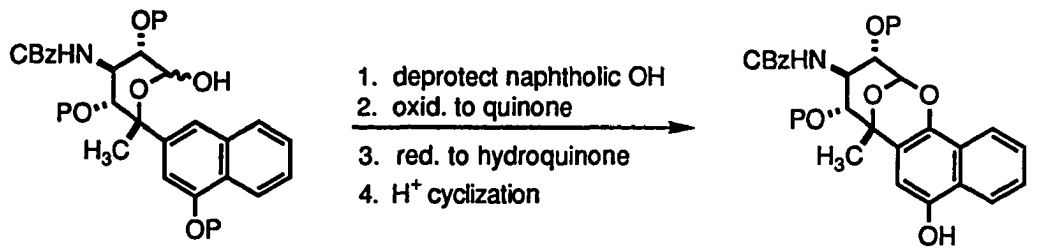
The desired amino sugar ring F could be obtained by deprotection of diol followed by selective oxidation of primary alcohol[55, 57, 58, 59] to aldehyde. Once the aldehyde was formed, the hydroxyl group from C-5' would attack the

aldehyde and would give the desired aryl-C-glycoside **49**.

2.4. Toward the Target Molecule

Once aryl-C-glycoside **49** were in hand, we would be close to the target molecule **50**. **SCHEME 2.11**.

SCHEME 2.11



49 **Target molecule 50**

The naphtholic-OH would be deprotected by a suitable method. There would be no harm if other hydroxyl groups were deprotected. Naphthol could be oxidized to naphthohydroquinone via naphthoquinone in several ways. The oxidizing agents, Fremy's salt or Salcomine[50] could be used to oxidize to quinone, which would then be converted to hydroquinone by treating it with $Na_2S_2O_3$.[21] Once the hydroquinone is formed, ring E could form by acid catalyzed cyclization and would give the desired target molecule **50**.

3. RESULTS AND DISCUSSION

3.1. Preparation of Furoisoxazoline.

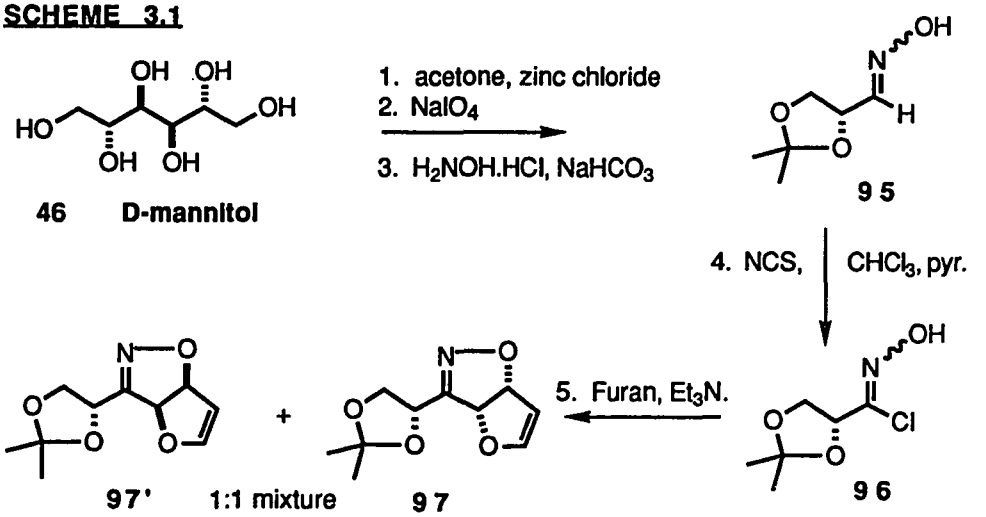
The first step of our synthesis was to prepare furoisoxazoline **47** by 1,3-dipolar nitrile oxide cycloaddition to furan. The desired optically active nitrile oxide was prepared *in situ* from the appropriate hydroximic acid chloride, which could again be easily prepared from an alkylidene glyceraldehyde.

Initially isopropylidene glyceraldehyde was chosen because this is the most common alkylidene glyceraldehyde used in organic synthesis.[60] The isopropylidene group could be easily put in by first derivatizing D-mannitol using acetone-zinc chloride[60] or 2-methoxy propene with *p*-toluene sulfonic acid[61], followed by periodate cleavage of the 1,2:5,6-O-diisopropylidene-D-mannitol.

To prepare furoisoxazoline, we modified the procedures developed by V.Jager and I.Muller.[39] They showed that the addition of phenyl isocyanate and nitroalkane through a dilution set-up into a refluxing solution of triethylamine (TEA) and furan within 100h gave the lowest yield of furoisoxazoline (7-25%). The addition of a hot solution of nitroalkane in furan (dilute solution) into a suspension of phenyl isocyanate, TEA and furan (approx. 0.4M solution) by means of a dilution set-up within 2d gave the highest product yield. (68-75%). *In situ* preparation of nitrile oxide by

adding hydroximic acid chloride (in furan) into a stirred solution of triethylamine and furan (0.25M) with a catalytic amount of $BF_3.Et_2O$ within 10d at room temperature gave a moderate yield of the product. (48%).

SCHEME 3.1

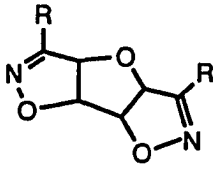


46 D-mannitol **95** **96** **97'** 1:1 mixture **97**

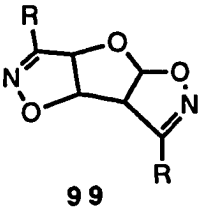
We prepared furoisoxazoline **97** by adding the solution of hydroximic acid chloride **96**, which was prepared by chlorination of aldoxime **95** with N-chlorosuccinimide in chloroform, into a refluxing solution of triethylamine in furan (0.1M) by means of syringe pump within 18h. **SCHEME 3.1**. The product was purified by column chromatography (Silica gel, 15% ethyl acetate / petroleum ether). (50-55% yield).

The nitrile oxide cycloaddition to reactive alkenes gives high yields of 2-isoxazolines (80-90%)[62] but the cycloadditions to furan affords lower yields of furoisoxazolines (7-75%).[39] The yield of the furoisoxazoline

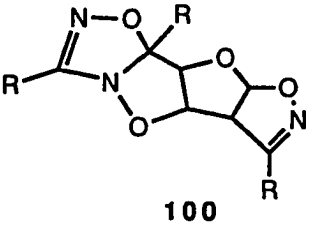
is low because furan is an aromatic compound and the double bond of furan is not as reactive as aliphatic alkenes. Only the *in situ* preparation of nitrile oxide in very large excess of furan (used as a solvent) produces furoisoxazoline. But once the monocycloadduct is formed, i.e. furoisoxazoline, the double bond of the furan residue becomes reactive as a vinyl ether. This gives further cycloaddition reaction.[36] Some of the possible polycycloadducts are shown below.



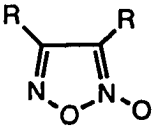
98



99

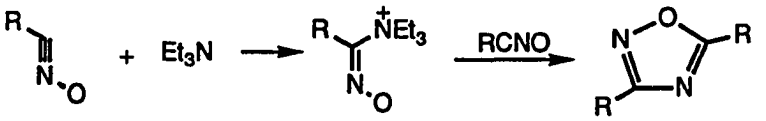


100



101

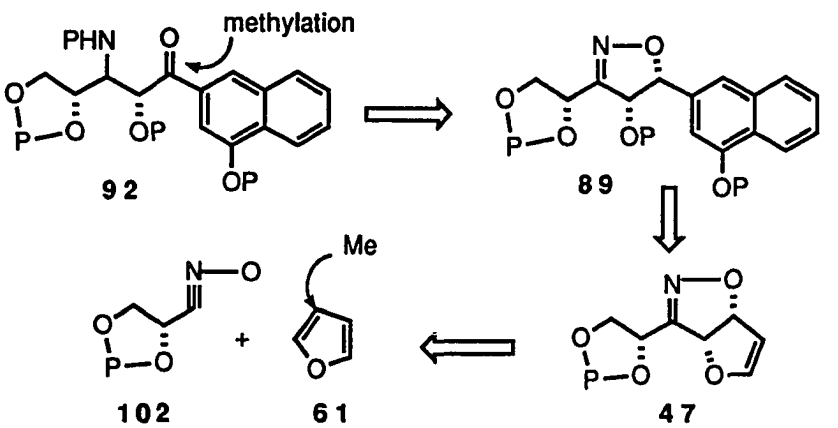
The major side reaction in the nitrile oxide-furan cycloaddition is the formation of furoxan **101** which is the dimer of nitrile oxide. Aliphatic nitrile oxides dimerize to furoxan more rapidly than aryl nitrile oxides.[36, 39] The polarity of furoxan is very close to furoisoxazoline and it hampers the isolation of pure furoisoxazoline. The dimer and polymers of nitrile oxide give nitrile oxide back on pyrolysis, ca. 550°C.[63, 64] The dissociation of furoxan into two molecules of nitrile oxide in refluxing xylene has been reported.[22] The dissociated nitrile oxide is trapped with olefin as isoxazoline. The other possible side reaction is the reaction between nitrile oxide and triethylamine.[22] (**eq. 3.1**).



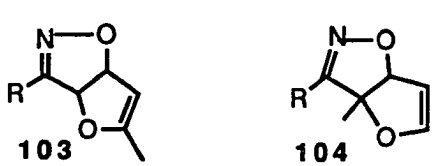
eq. 3.1

At one point of our synthesis, we faced difficulties in introducing the methyl group at C-1 of ketone **92**. In our scheme, this C-1 originates as C-3 of furan. **SCHEME 3.2.**

SCHEME 3.2



This late introduction of methyl might have been bypassed if we could have used 3-methyl furan instead of furan in the preparation of our required starting material. K. N. Houk et al.[36] and V. Jager et al.[39] showed that nitrile oxide cycloaddition to 2-methyl furan gives 5-methylfuroisoxazoline **103** rather than 3a-methyl furoisoxazoline **104**.



Jager explained the observation from the steric view

point, i.e. nitrile oxide cycloadds to the less hindered side of the double bond. K. N. Houk et al.[36] used the frontier molecular orbital view point to rationalize the result. They stated that in this cycloaddition, the LUMO of dipole interacts with the HOMO of dipolarophile furan. The energy coefficients of the HOMO of 2-methyl furan **105** and furan **61** are calculated by extended Huckel (EH) and the π-orbitals of **105** and **61** are shown below.

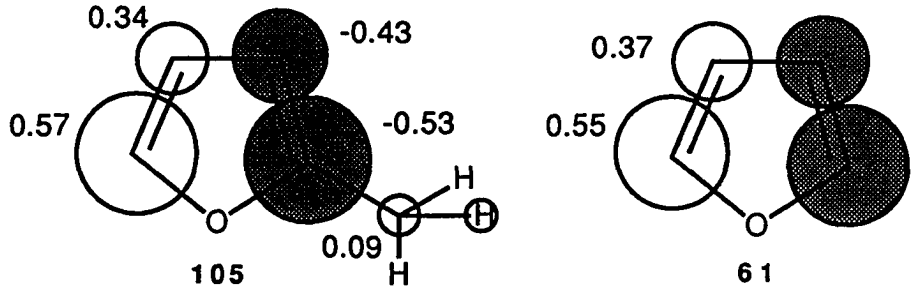
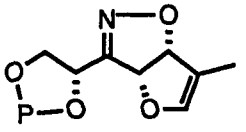


Figure 3.1. The orbital shape of the HOMO of 2-methyl furan **105** and furan **61** by EH calculation.

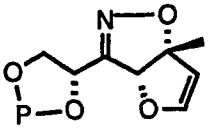
Due to the methyl perturbation, the HOMO of 2-methyl furan becomes asymmetric. The energy coefficients of the HOMO of 2-methyl furan shows that C-4 has the larger energy coefficient than that of C-1, and C-2 has the larger energy coefficient than that of C-3. Therefore the orbital interaction between the LUMO of nitrile oxide will be more favorable with C-4:C-3 pair than with the C-1:C-2 pair. The former interaction will give the better stabilization according to Fukui's energy equation.

This predicts that we would get furoisoxazoline **106**

rather than the furoisoxazoline **107**, in the nitrile oxide cycloaddition to 3-methyl furan.

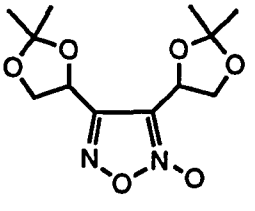


106



107

The nitrile oxide cycloaddition to optically active dipolarophiles shows stereoselectivity[37] but the cycloaddition reaction of chiral nitrile oxide to achiral alkene shows none or very little stereoselectivity.[38] We did not expect any diastereoselectivity in our cycloaddition reaction, because our dipolarophile is furan, which has no chirality. We got two isomers of the product, furoisoxazoline **97** and its epimer **97'** in approximately 1:1 ratio (from NMR) **SCHEME 3.1**. The two isomers were not separable. We carried them as a mixture of isomers for further reaction. Furoxan **108** was observed as the byproduct in about 15% yield. Other byproducts were also observed but they were not isolated and characterized.



108

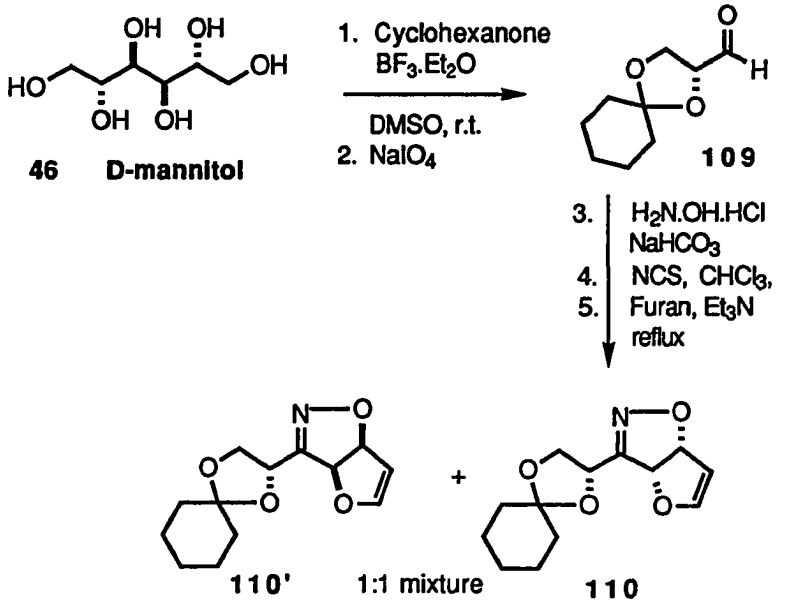
Though the O-isopropylidene group is considered to be a good protecting group for 1,2-diols in organic synthesis, we found it was unstable in our reaction sequence. The O-

isopropylidene group isomerized in the Bradsher cycloaddition reaction sequence and yielded unwanted product.

This forced us find a more robust protecting group than isopropylidene. We needed a protecting group that could not isomerize under Bradsher cycloaddition conditions. As an alternative, we chose cyclohexylidene, because this is more stable in most reaction conditions than isopropylidene.[65] Cyclohexylidene could not form vinyl ether like isopropylidene because of the ring strain.

Cyclohexylidene glyceraldehyde **109** was prepared in 60-66% yield as before by periodate cleavage of 1,2:5,6-di-O-cyclohexylidene-D-mannitol, which was prepared from D-mannitol by treating with cyclohexanone, triethyl orthoformate and boron trifluoride etherate in dry dimethyl sulfoxide.[65] Furoisoxazoline **110** and its epimer **110'** were prepared as before by the method of nitrile oxide cycloaddition. **SCHEME 3.3.**

SCHEME 3.3



The two furoisoxazoline epimers **110 & 110'** were not separable. So we carried the mixture of epimers in the Bradsher cycloaddition reaction sequence.

3.2. Preparation of Naphthol.

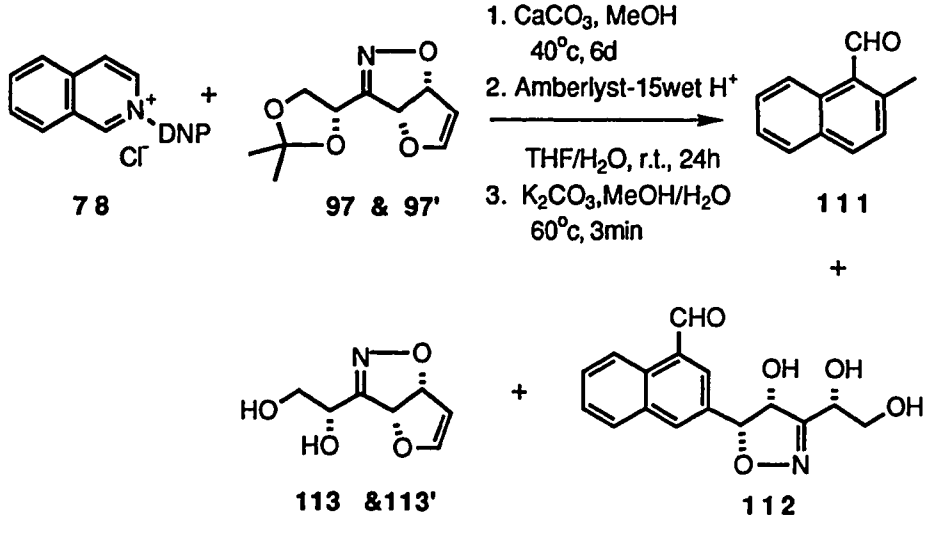
3.2.1. Bradsher Cycloaddition Reaction.

The second step of our plan was to prepare naphthaldehyde by Bradsher cycloaddition reaction, applying the procedure developed in our lab[48] by using N-2,4-dinitrophenyl isoquinolinium chloride salt (IsoQ) with furoisoxazoline **97 & 97'**.

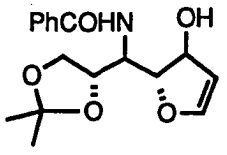
There was no reaction when 1 equivalent of furoisoxazoline was treated with 1.2 equivalent of IsoQ and 8 equivalent of calcium carbonate in methyl alcohol at 35°C for 1d. A slight disappearance of furoisoxazoline was observed

but no cycloadduct was detected on TLC. Half equivalent of furoisoxazoline was added every day and the temperature was raised to 40°C and the reaction mixture was stirred for 6d. Then the reaction was processed by acid hydrolysis and base aromatization using a procedure developed in our lab.[48] This reaction gave many products. However, most of the products were not characterizable. About 20% of the product was 2-methyl naphthaldehyde **111** and less than 5% of the product was the desired naphthaldehyde **112**. Furoisoxazoline **113 & 113'**, which had deprotected 1,2-dihydroxyethyl at 3-position, was also observed. **SCHEME 3.4**. We assumed that the cis fused five membered rings of furoisoxazoline **97 & 97'** were somehow hindered and the cycloaddition was slow. Therefore a prolonged heating of furoisoxazoline led to the variety of products. The labile isopropylidene group[65] also came off at the acid hydrolysis stage.

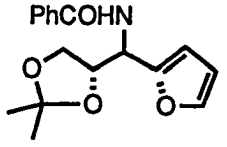
SCHEME 3.4



Bradsher cycloaddition of IsoQ with dihydrofuran has been reported.[48] Therefore we assumed that the cycloaddition would be accelerated when we reduced furoisoxazoline **97 & 97'** to amino alcohol and used N-benzamide **114** as our vinyl ether.



114



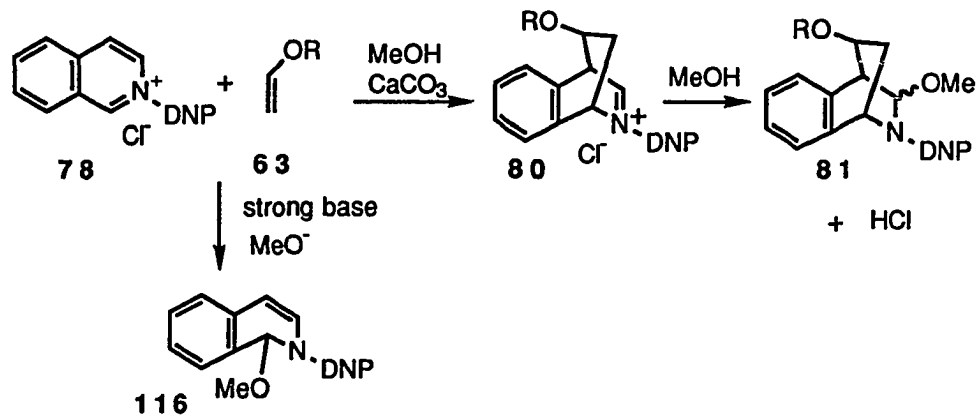
115

This cycloaddition reaction did not give the desired naphthaldehyde. The products were not characterizable. No cycloaddition reaction was detected. 3-Hydroxy-2-dihydrofruan **114** was very acid sensitive and could easily be dehydrated to furan **115**.[66]

Bradsher cycloaddition of IsoQ with furan **61** was tried but there was no reaction. A + B --> C type of reactions are favorable under pressure and this is also true for Diels Alder reactions, especially with hindered compounds. We wanted to try our Bradsher cycloaddition under pressure. The problem of performing the reaction under pressure was to find a suitable soluble acid scavenger in place of the anhydrous calcium carbonate. An acid scavenger is necessary in the cycloaddition reaction because the cycloaddition reaction produces one equivalent of acid.[67] **SCHEME 3.5.** If the acid evolved is not trapped by base, this acid would protonate the double bond of vinyl ether **63**

and suppress the cycloaddition reaction. A suitable base had to be soluble in the solvent we used for cycloaddition, ie. methyl alcohol, as we were unable to stir the reaction mixture in the high pressure apparatus.

SCHEME 3.5



Another problem was the basicity of base. A very strong base could remove the proton from methyl alcohol and generate methoxide ion which could compete with vinyl ether by attacking the electrophilic C-1 of IsoQ salt and forming compound **116**. On the other hand, a weak base would not be strong enough to trap the hydrogen chloride, once it evolved. Falck et al.,[67] reported that calcium carbonate is the best acid scavenger for Bradsher cycloaddition reactions. Other commonly used acid scavengers, inter alia, tertiary amines, alumina glycidol, sodium bicarbonate and sodium acetate are either ineffective in preventing polymerization of the dienophile or are too basic.

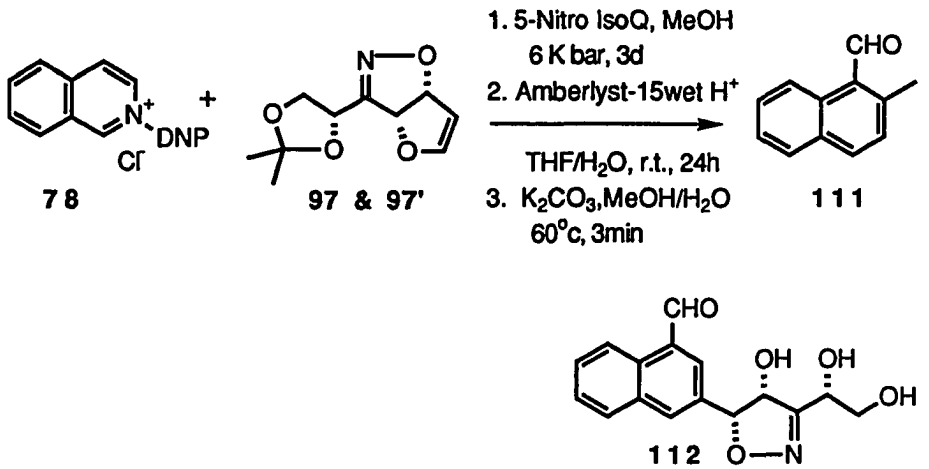
When we studied the pKa's of bases, we found that pyridinium series (pKa 5 - 1) and quinoline series (pKa 6 -

2)[68] would be possible bases for our purpose. After screening bases for the unwanted methanol addition process, we finally discovered 5-nitroisoquinoline as the suitable base.

One equivalent of furoisoxazoline **97 & 97'**, 1.1 equivalent of IsoQ salt and 1.3 equivalent of 5-nitro isoquinoline were dissolved in the minimum amount of dry methyl alcohol. The mixture was transferred into a 10ml plastic syringe and the syringe was sealed with a teflon screw cap stopper. Then the syringe was placed inside the pressure apparatus, which has a steel chamber filled with castor oil. A pressure of 6Kbar was applied from outside to the oil. The disappearance of furoisoxazoline and the appearance of 5-nitroisoqunolinium salt were observed in 3d. The precipitate was filtered and washed with dichloromethane. The filtrate was concentrated, hydrolyzed with Amberlyst-15-wet H^+ and aromatized with potassium carbonate as before.[48, 67]

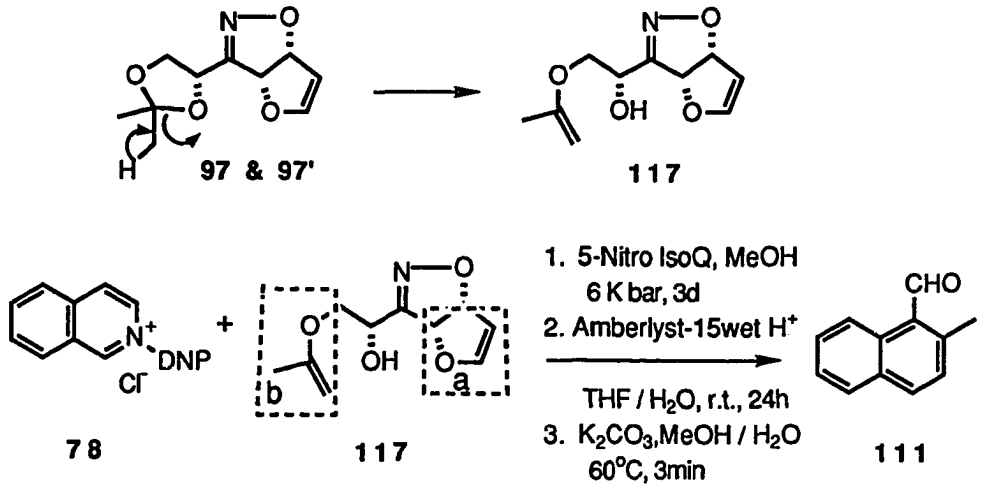
SCHEME 3.6.

SCHEME 3.6



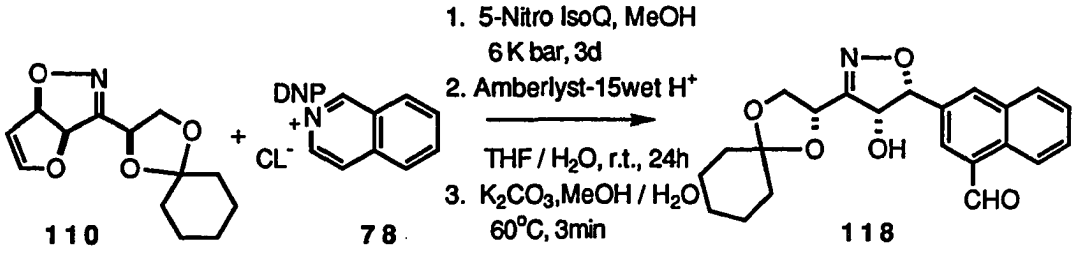
We observed 2-methyl naphthaldehyde as the major product. The cycloaddition reaction was cleaner than before. We assumed that the product, 2-methyl naphthaldehyde was obtained from the addition between IsoQ salt and vinyl ether which was generated from the isopropylidene of furoisoxazoline **117**. **SCHEME 3.7.** The ^{1}H NMR analysis of the compound **111** did not show any aliphatic proton except one methyl signal at δ 2.86. There were six aromatic signals and one aldehyde signal.

SCHEME 3.7



We could not easily rationalize how the isopropylidene could isomerize into the isopropenyl ether (**97** ---> **117**). The cycloaddition reaction took place with the isopropenyl ether (box b) rather than the furoisoxazoline double bond (box a). This isomerization could be avoided if we used cyclohexylidene glyceraldehyde[65] to prepare furoisoxazoline **110 & 110'**. **SCHEME 3.3.** Bradsher cycloaddition was carried out using IsoQ and furoisoxazoline **110 & 110'** with 5-nitroisoquinoline under pressure (6Kbar) as before. After acid hydrolysis and base aromatization we obtained the desired naphthaldehyde **118** in 50-55% yield. **SCHEME 3.8.**

SCHEME 3.8



110 **78** **118**

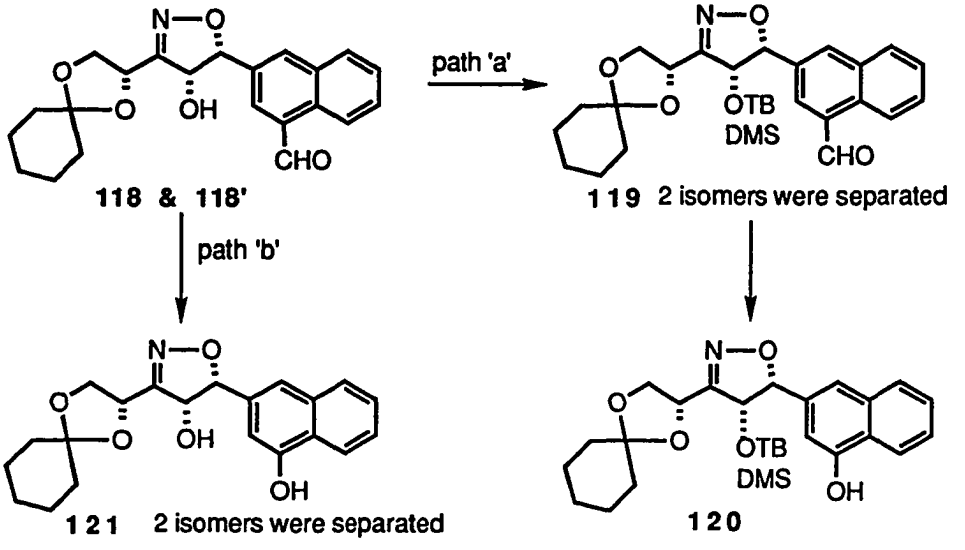
We expected to get only one regioisomer of product from the cycloaddition as the cycloaddition is regioselective.[44, 45] As the mixture of furoisoxazoline **110 & 110'** was used, we obtained a mixture of two naphthaldehydes **118** and **118'**. The two diastereoisomers were not separable. The ^{1}H NMR showed a broad aldehyde peak at δ 10.39, ^{13}C NMR showed two carbonyl peaks at δ 193.56 and 193.37 and the IR spectrum exhibited a strong carbonyl stretching vibration at 1690 cm^{-1}. The two isomers of naphthaldehyde **118 & 118'** were separated by the partial separation of the mixture. The ^{1}H NMR spectra of the two isomers were almost the same except for the two methylene protons of 1,3-dioxolane group. In one isomer the methylene protons appeared as a doublet (at δ4.32) and in the other isomer it appeared as two sets of doublets (at δ 4.34 and 4.20). Naphthaldehyde **112**, which had the diol deprotected, was obtained in less than 5% yield.

3.2.2. Oxidation of Naphthaldehyde to Naphthol.

After we had the naphthaldehyde mixture **118 & 118'** in hand, we could oxidize it to naphthol using two possible pathways. **SCHEME 3.9.** In **path a**, the 4-hydroxyl group of

isoxazoline was protected as silyl ether **119** and was oxidized to naphthol **120**.[50] In **path b**, naphthaldehydes **118 & 118'** were directly oxidized to naphthols **121 & 121'**.

SCHEME 3.9



We first started our synthesis through **path a** in order to use different protecting groups for the aliphatic and phenolic OH's. The 4-hydroxyisoxazolyl group of naphthaldehyde **118 & 118'** was protected as its *tert*-butyldimethylsilyl ether.[51] Fortunately we could separate the two isomers of compound **119 & 119'**, though we did not know the absolute stereochemistry. One isomer moved faster on TLC than the other. The two isomers were separated and carried separately in the reaction sequence.

The oxidation of naphthaldehyde to naphthol could be achieved by the method developed in our lab,[50] using Baeyer-Villiger oxidation followed by alumina treatment.

Naphthaldehyde **119** was treated with m-chloroperbenzoic acid in anhydrous dichloromethane at room temperature for 1d to obtain naphthylformate. The reaction could be neutralized by aqueous sodium sulfite[69] or anhydrous potassium fluoride.[50] Since a fluoride sensitive *tert*-butyldimethylsilyl ether was present in our system, we used the aqueous sodium sulfite method. Naphthylformate so obtained was not purified and was treated with alumina, activity 1, in anhydrous dichloromethane to afford naphthol **120**. The disappearance of the aldehyde peak in ^{1}H NMR, the carbonyl peak in ^{13}C NMR and the carbonyl stretching vibration at 1690 cm^{-1} in IR and the appearance of a broad OH stretching signal at 3550 cm^{-1} showed the formation of 1-naphthol. The chemical shift of the protons in ^{1}H NMR showed that the ortho-, para- and peri-protons of the naphthol shifted from low field to higher field (about 1ppm) each. No significant chemical shift difference for isoxazolyl protons was observed. This showed that there was no change in the neighborhood of those protons, because isoxazolines are stable towards peracids.[70, 71]

Eventually we found that the *tert*-butyldimethylsilyl was not a stable protecting group for our system. The silyl ether was converted to hydroxy in the lithium aluminum hydride (LAH) reduction of the isoxazolyl group and that created problems in the benzylic alcohol oxidation step. (See reduction of isoxazoline, p.60, and benzylic alcohol

oxidation, p.66).

Therefore we altered our synthetic route to **path b (SCHEME 3.9)**. Naphthaldehydes **118 & 118'** were oxidized to naphthols **121** by Baeyer-Villiger oxidation using m-chloroperbenzoic acid followed by treatment with alumina, activity 1 as before. The two isomers of naphthol were easily separated at this step because one isomer dissolved in dichloromethane and the other isomer only dissolved slightly. A crystal structure[72] of the insoluble isomer showed that it had 4R,5R-isoxazolyl and 5S-dioxolyl stereocenters. **Fig. 3.2.** It is the right isomer for nogalamycin. All the functional groups on the carbon chain were syn to each other. Only the right isomer was carried through the entire synthetic sequence. The wrong isomer was used in some model reactions.

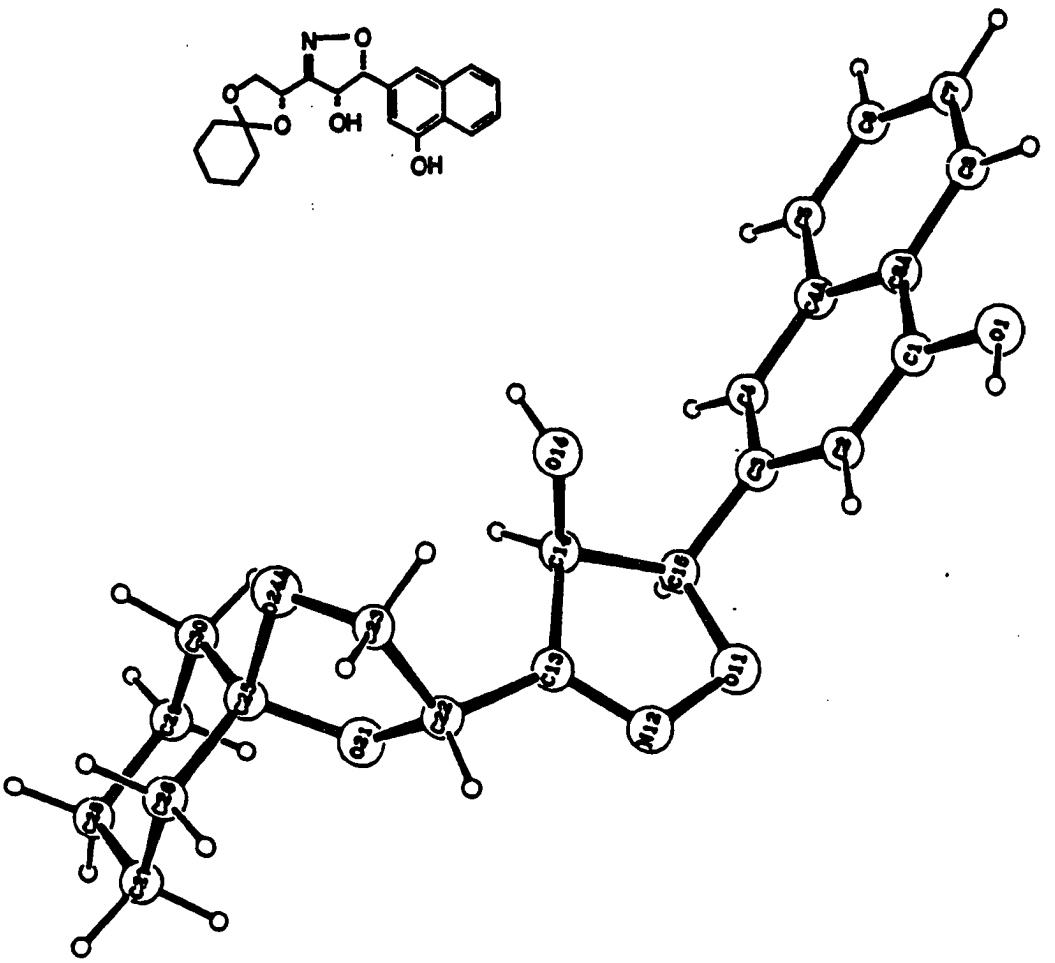
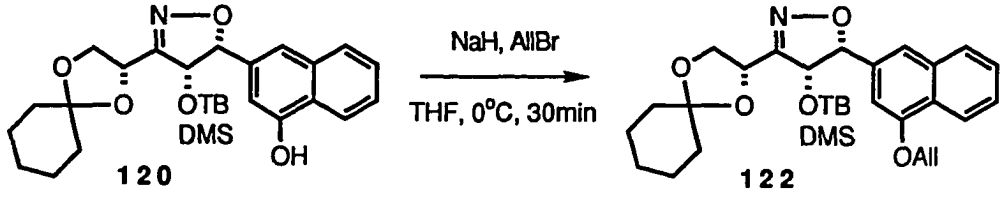


FIGURE 3.2. The crystal structure of 3-{(4R,5R)-[3-(5S)-2,2-cyclohexylidene-1,3-dioxolan-5-yl]-[4-hydroxyl]-4,5-dihydroisoxazolin-5-yl-}-1-naphthol **121**.

To continue the synthesis, the naphtholic-OH needed to be protected. Generally, hydroxyl groups are protected either as ethers or esters.[51] Esters were not suitable in our case because the next step of the synthesis was to be the reduction of isoxazoline with lithium aluminum hydride, which could reduce ester back to alcohol. Various kinds of ethers could be used but the allyl ether seemed to be a good protecting group, because ethers need acidic conditions to cleave back to alcohols. Preparation and deprotection of allyl ethers is simple.[51] The alcohol is treated with allyl bromide in the presence of any base to obtain allyl ether, and cleavage back to alcohol occurs upon treatment with organometallic catalysts.

A solution of naphthol **120** was added to a suspension of potassium hydride in tetrahydrofuran at 0°C. After stirring for 5 min, allyl bromide was added dropwise and the reaction mixture was stirred for 30min. Allyloxy naphthol **122** was obtained in 82% yield after aqueous workup. **SCHEME 3.10.**

SCHEME 3.10



The formation of allyl ether was observed by ^1H NMR

analysis. The significant peaks for allyl ether were seen at δ 6.21 (m, 1H, $OCH_2\underline{CH}=CH_2$), 5.55 (dd, J=1.9, 17.3Hz, 1H, $OCH_2CH=\underline{CH_2}$, trans), 5.35 (dd, J=1.3, 12.1Hz, 1H, $OCH_2CH=\underline{CH_2}$, cis) and 4.73 (d, J=5.2Hz, 2H, $O\underline{CH_2}CH=CH_2$).

The allylation of naphthol **121** (**path b** of **SCHEME 3.9**) was not as easy as naphthol **120**. The formation of alkoxy anion was observed by the disappearance of potassium hydride but there was no characterizable product after addition of allyl bromide. We expected a faster moving product on TLC as we saw in naphthol **122**, but no product with higher R_f than that of starting naphthol **120** was observed. The product formed was not characterizable. Other bases such as sodium hydride or triethylamine were used, but we did not obtain material of assignable structure.

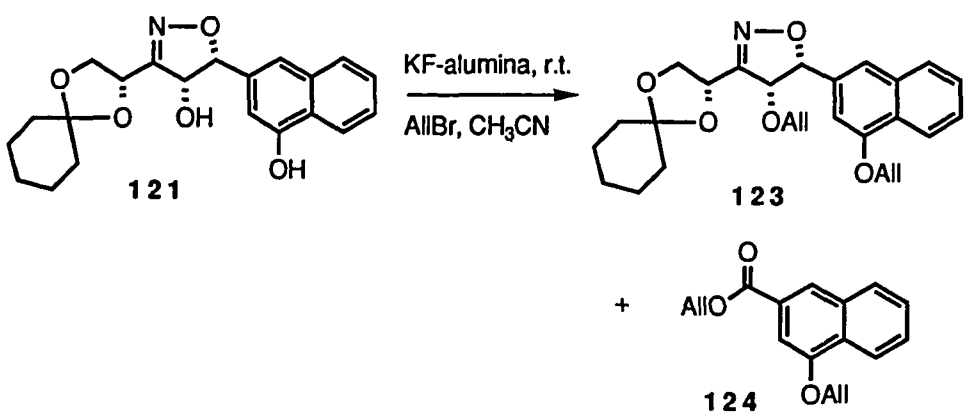
The labile protons in the isoxazoline portion could be deprotonated with strong base and that could lead to polar products. The use of alkali metal fluoride impregnated in alumina as a reagent for alkylation of phenols and alcohols, modified by T. Ando et al.,[73] was found to be the suitable base in our synthesis.

Potassium fluoride impregnated alumina was prepared by mixing potassium fluoride with alumina, activity 1, at the weight ratio of 2:3, which corresponded to 1.15mol of potassium fluoride on 100g of alumina, in water. The water was removed at 50-60°C in a rotary evaporator and the impregnated alumina was further dried under vacuum (0.02mm

Hg) at 50°C for several hours.

The alkylation procedure was simple and mild. Allyl bromide (10 equiv.) was added dropwise to the suspension of naphthol **121** and potassium fluoride impregnated alumina (10 equiv. by potassium fluoride) in dry acetonitrile and the suspension was stirred at room temperature. When the complete disappearance of naphthol **121** was seen on TLC, the suspension was filtered and the alumina was washed with dichloromethane several times. The crude bis-allylated naphthol **123** was obtained after concentrating the filtrate, which was then purified by radial chromatography. (80% yield). **SCHEME 3.11.**

SCHEME 3.11



The formation of bis-allyl naphthol **123** was confirmed by ^1H NMR, IR and MS spectroscopy. In the ^1H NMR spectrum, in addition to a set of allyl naphthyl ether peaks similar to allyl naphthyl ether **122**, another set of allyl signals was observed. The proton signals at δ 5.46-5.36 (m. 1H.

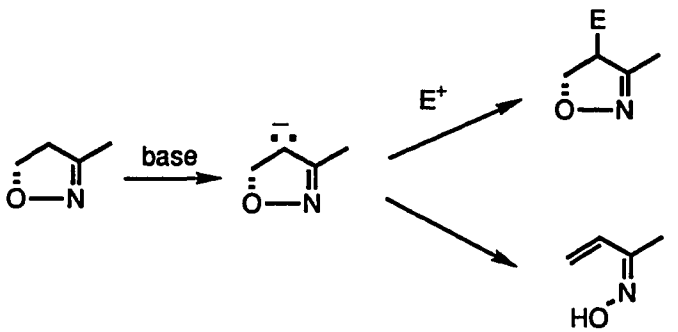
$OCH_2\underline{CH}=CH_2$), 4.97-4.85 (m, 3H, $OCH_2CH=\underline{CH_2}$, H-4 isoxo) 3.55 (dd, J=6.0, 11.8Hz, 1H, $O\underline{CH_2}CH=CH_2$) and 3.35 (dd, J=6.0, 11.8Hz, 1H, $O\underline{CH_2}CH=CH_2$) showed the presence of a secondary allyl ether. The chemical shifts were upfield compared to the allyl ether of naphthol because this allyl group might be somehow located in the shielding region of isoxazoline due to the congestion.

The disappearance of the OH stretching vibration at 3340 cm^{-1} in IR spectrum and the molecular ion peak in MS confirmed the formation of bis-allyl naphthol ether **123**.

As pointed out before, protons on the isoxazoline are labile[71] and can lead to fragmentation products. About 10% of bis-naphthol ether **124** was observed in the reaction. A five-fold excess of fluoride and allyl bromide were used to suppress the fragmentation.

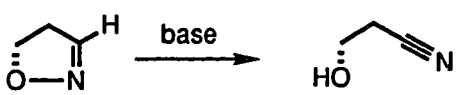
In his review, Jager reported that the deprotonation of C-3, C-4, C-5, C-3' or C-5' in isoxazolines is possible with very strong bases (e.g. LDA). The product depends on the nature of the isoxazoline with respect to the substituents and substitution pattern.

A stable carbanion can be generated with the 3-position blocked (alkyl or aryl group). Electrophilic substitution occurs in the presence of electrophile and ring opening occurs when electrophile is absent. **eq. 3.2.**



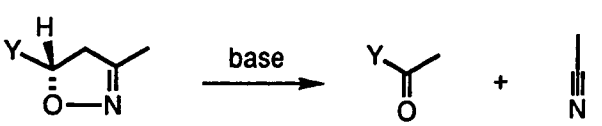
eq. 3.2

The 4-endo deprotonation is preferred when secondary C-H bonds are to be broken. The ring opening to β-hydroxy nitrile occurs when the 3-position of isoxazoline is unsubstituted. **eq. 3.3.**



eq. 3.3

Further, activating group Y at position 5 or 5' of isoxazoline results the fragmentation or ring opening. **eq. 3.4.** and **eq. 3.5.**



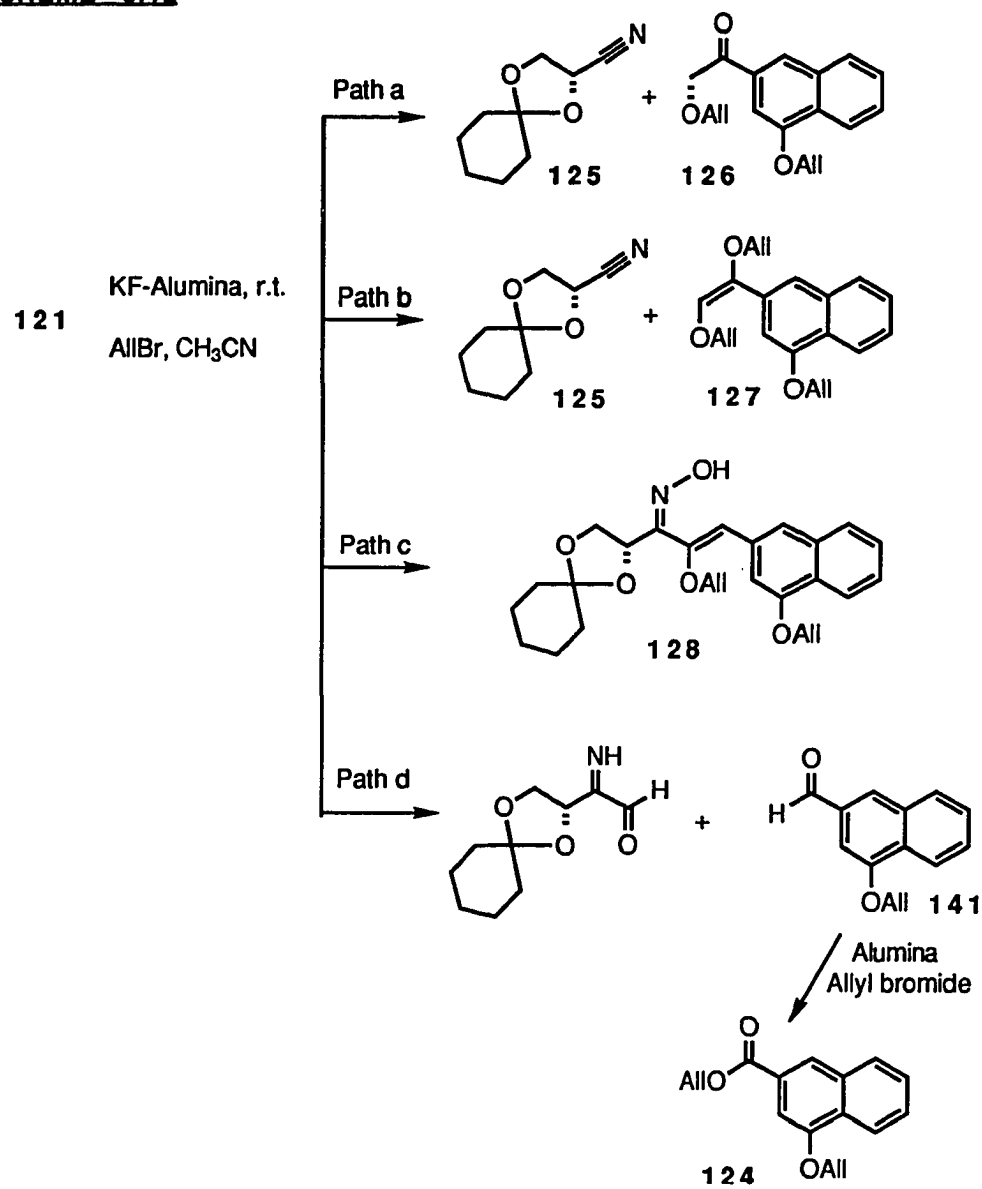
eq. 3. 4

eq. 3.5

Our isoxazoline was 3, 4, and 5-substituted and the group on C-4 and C-5 are the hydroxy and naphthalene respectively. The possible fragmentation paths are shown in **SCHEME 3.12,** and we assumed that path d was the most

possible fragmentation path.

SCHEME 3.12

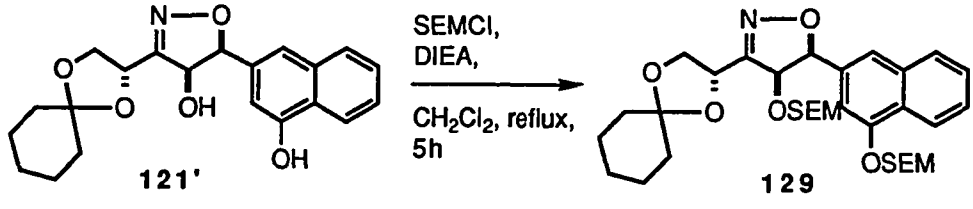


The 4-hydroxy group was deprotected and gave a fragmentation product naphthaldehyde, and in the presence of aluminium oxide, it yielded the ester **124** by the Cannizzaro or Tishchenko type reaction.[74] The ^1H NMR spectroscopy of the

side product showed six aromatic signals and two sets of allyl signals with no signals for methylene and cyclohexylidene. The IR and MS analysis confirmation the formation of ester.

Many researchers have used allyl ether as a protecting group in their synthesis but unfortunately we faced some difficulties in removing the allyl group in our system. (See deallylation of naphthol, p.96). Therefore we chose to study other protecting groups. Preparation of bis-methoxyethoxymethyl ether (MEM ether)[75] failed. The bis-trimethylsilylethoxymethyl ether (SEM ether)[76] **129** was obtained from 4S,5S-naphthol isomer **121'** (the wrong diastereoisomer of nogalamycin), **SCHEME 3.13**, but failed with the 4R,5R-isomer **121**.

SCHEME 3.13



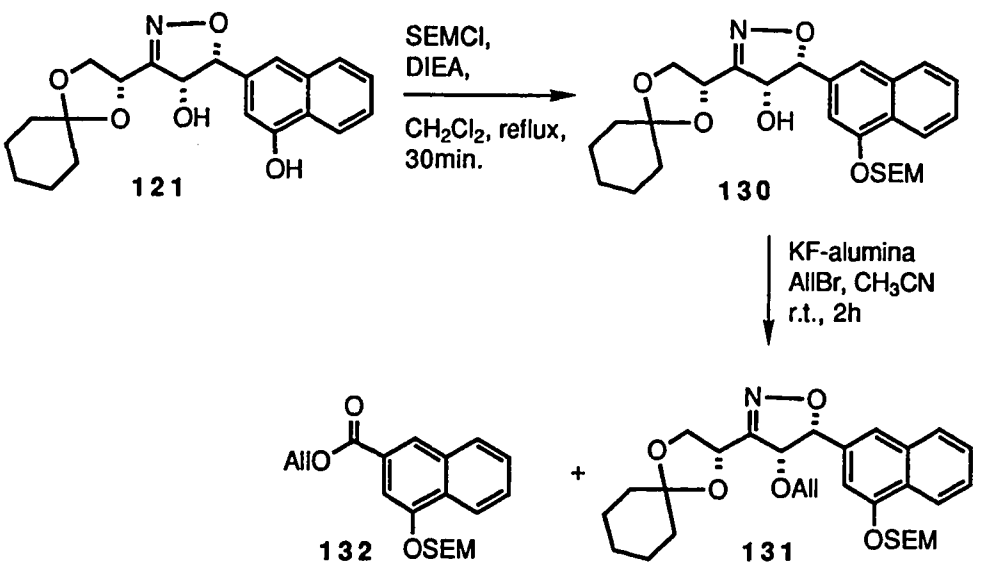
In the ^1H NMR spectrum of compound **129**, a set of proton signals from the secondary SEM ether appeared at higher field than that of the naphthyl SEM ether as we observed in the bis-allyl naphthyl ether **123**. The proton signals appeared at δ 5.44 (dd, J-6.6, 11.2Hz, 2H, NpO$\underline{CH_2}$OCH$_2$CH$_2$TMS), 3.84 (t, J=8.2, 2H, NpOCH$_2$O$\underline{CH_2}$CH$_2$TMS), 1.10

(t, J=8.3Hz, 2H, $NpOCH_2OCH_2\underline{CH_2}TMS$) and 0.01 (s, 9H, TMS) for naphthyl allyl ether and 4.40-4.15 (ABq, J=7.1Hz, 2H, $O\underline{CH_2}OCH_2CH_2TMS$), 3.34-3.25 (m, 1H, $OCH_2O\underline{CH_2}CH_2TMS$), 3.05-3.00 (m, 1H, $OCH_2O\underline{CH_2}CH_2TMS$), 0.76-0.62 (m, 2H, $OCH_2OCH_2\underline{CH_2}TMS$) and -0.10 (s, 9H, TMS) for secondary allyl ether.

A difference of reactivity in the formation of ether was observed between naphtholic-OH and secondary-OH. The naphtholic-OH formed the SEM ether within 10min but the formation of secondary SEM ether took 5h at reflux for naphthol **121'**. Naphthol **121** gave very low yields of bis-SEM ether. It changed into uncharacterizable polar materials while refluxing.

The formation of the mono SEM ether from naphthol **121** was quantitative. Then the product was allylated using KF-alumina/ allyl bromide as before.[73] **SCHEME 3.14.**

SCHEME 3.14

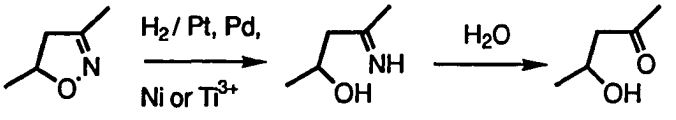


The ^1H NMR analysis confirmed the formation of compound **131**. The fragmentation product **132** formed in less than 5% yield.

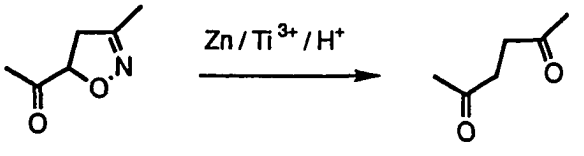
3.3 Reduction of Isoxazoline.

Isoxazolines can be viewed as masked γ-hydroxy amines, β-hydroxy ketones (aldol) or β-hydroxy acids, depending on the type of reducing agents used to unravel the ring.

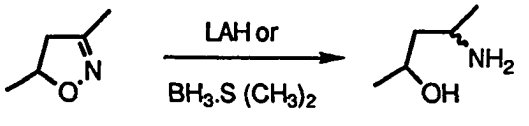
Catalytic hydrogenation cleaves the N-O bond first without reducing the imino function.[22, 39] **eq. 3.6.** Zinc powder and acid not only cleave the N-O bond, but also cleave the C-O bond. **eq. 3.7.** With lithium aluminum hydride, borane complexes, sodium amalgam or sodium in ethanol, isoxazolines are reduced to amino alcohols. **eq.3.8.**



eq. 3.6



eq. 3.7

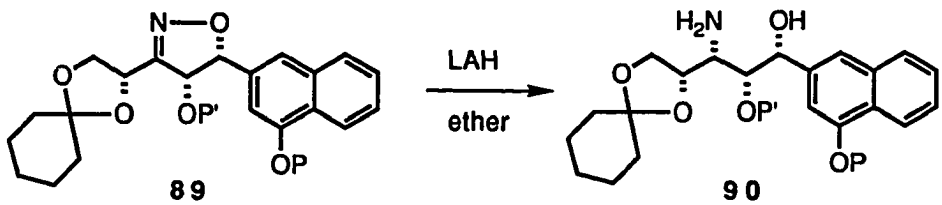


eq. 3.8

In the course of our work, the desired reduction product from isoxazoline was the amino alcohol where all the functional groups were syn to each other, **SCHEME 3.15.**,

i.e., where hydride or hydrogen is delivered from the anti face of the 4-substituent of the isoxazoline.

SCHEME 3.15

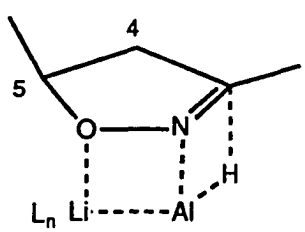


89 90

122 : P = Allyl, P' = TBDMS
123 : P = P' = Allyl
129 : P = P' = SEM
131 : P = SEM, P' = Allyl

133 : P = Allyl, P' = H
134 : P = P' = Allyl
135 : P = P' = SEM
136 : P = SEM, P' = Allyl

The stereoselectivity of the lithium aluminum hydride (LAH) / ether system has been studied by V. Jager et al.[71], K. B. G. Torssell et al.[22] and others. They showed that LAH reduces the C=N bond of the isoxazoline first and the N-O bond of the resulting isoxazolidine cleaves later, structure **137**. The corresponding isoxazolidine is isolated when sodium cyanoborohydride in concentrated hydrochloric acid is used.[77]



137

The stereochemistry outcome of the γ-amino alcohol, depends on the size and nature of substituents at C-4 and C-5 of the isoxazoline. Lithium aluminum hydride approaches from

the less hindered face of isoxazoline when the substituents at C-4 and C-5 are alkyl or aryl. **(i to viii), Fig. 3.3.** Therefore the larger selectivity is observed in bicyclic isoxazoline. **(vi to viii), Fig. 3.3.**

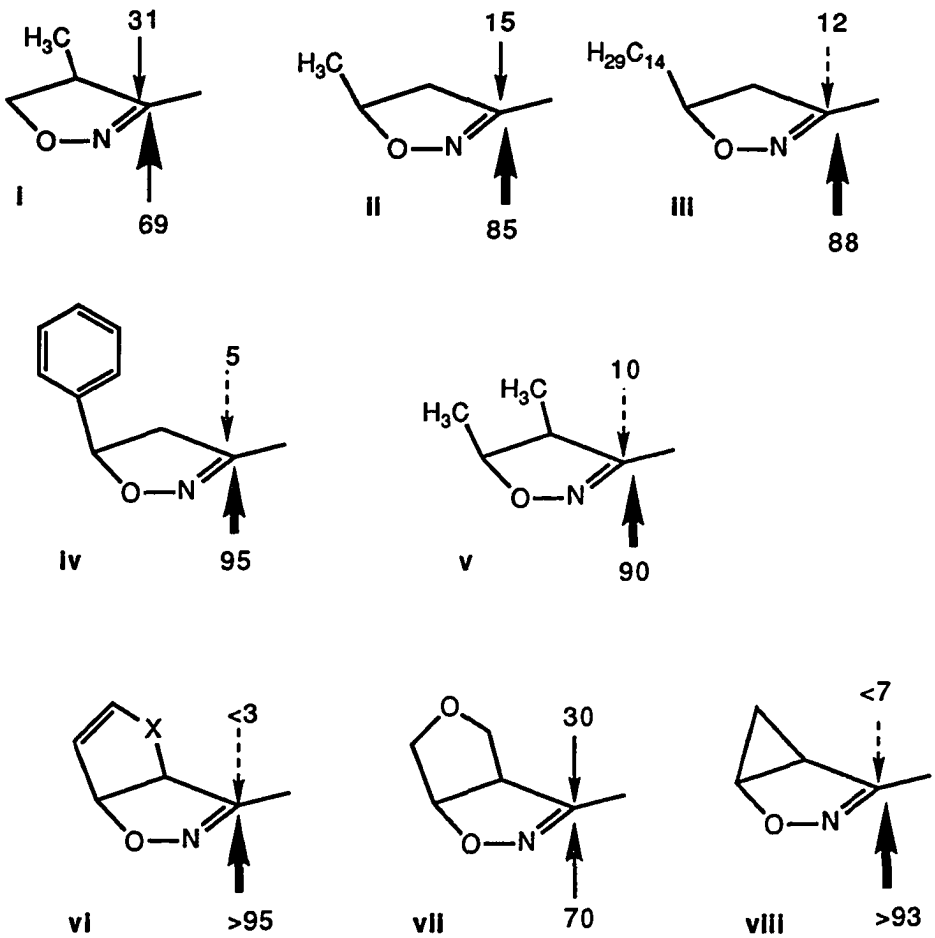


Figure 3.3. LAH reduction of alkyl substituted isoxazolines.[71]

The selectivity is reversed when hydroxyl groups are at C-4 or C-5 of the isoxazoline. The hydride comes from the same face as the hydroxy substituent. **(ix to xiii) Fig.**

3.4. V. Jager et al.[71] compared the stereoselective reduction of 4-α-hydroxy isopropyl-3-methyl isoxazoline by LAH and by catalytic hydrogenation. **(xii & xiii) Fig. 3.4.** They reported that hydride is delivered from the syn-face of 4-hydroxyisopropyl in LAH reduction and hydrogen comes from the anti-face in catalytic hydrogenation.

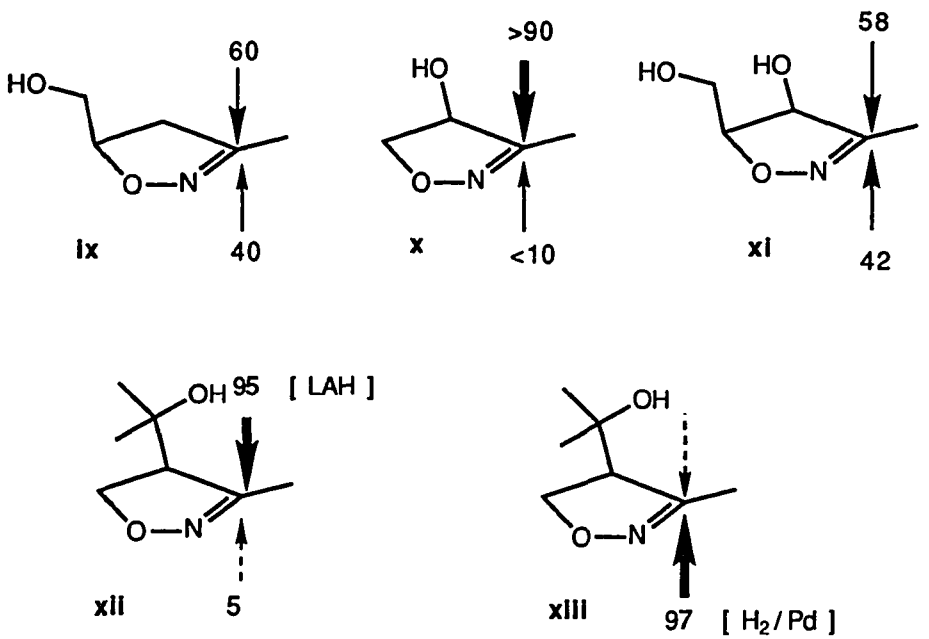


Figure 3.4. LAH reduction of hydroxy substituted isoxazolines.[71]

The stereochemistry of LAH with alkyl ether substituted isoxazolines was also studied by V. Jager et al. The stereochemistry outcome is similar to the alkyl substituent case. **(xii to xv), Fig. 3.5.**

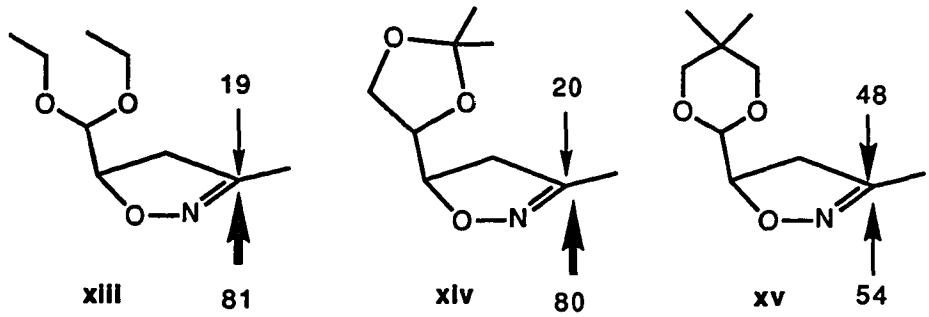
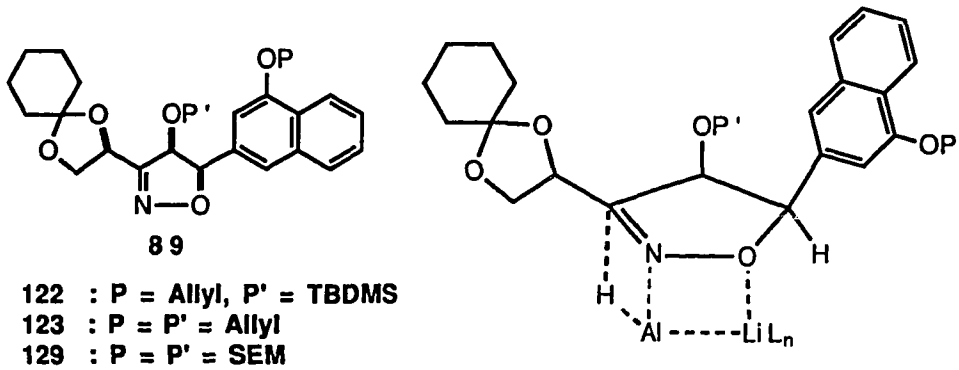


Figure 3.5. LAH reduction of alkyloxy substituted isoxazolines.[71]

Overall the stereoselectivity of the reduction of substituted isoxazolines with LAH depends on how much the steric hindrance discriminates between two faces and how well the oxygen on the respective side chain are suited to allow the O-Li chelation for hydride delivery from the syn- face.



122 : P = Allyl, P' = TBDMS
123 : P = P' = Allyl
129 : P = P' = SEM
131 : P = SEM, P' = Allyl

Our isoxazoline **89** had substituents on all carbons; 1,3-dioxolyl at C-3, ether at C-4 (TBDMS or allyl or SEM ether) and naphthalene at C-5. We predicted that hydride would be delivered from the bottom face (anti-face of the substituents) as the top face was hindered with naphthalene group, *tert*-butyldimethylsilyl ether **122** or allyl ether **123**

& 129' or trimethylsilylethoxy methyl ether **131**. The expected face selectivity would give the syn amino alcohol with respect to C-4 ether.

The reduction of isoxazoline **123** was performed with LAH solution (1.3M in ether) in ether. We obtained one major stereoisomer in quantitative yield. The stereochemistry of the product could not be assigned at this stage but later we found that it had the stereocenters as we had predicted. (X-ray crystal structure of compound **176**, p.80, **Fig. 3.8**).

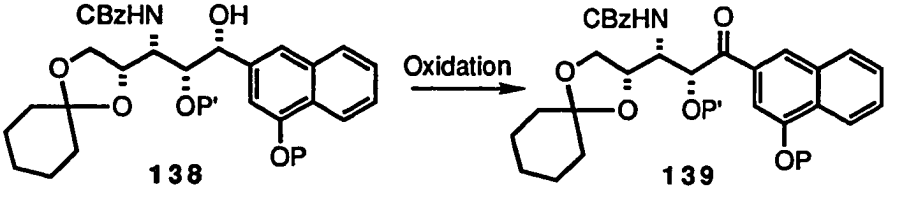
The product amino alcohol **90** was purified in some cases and not in others. The amino group was protected as its N-benzyloxy carbamate, using benzyl chloroformate and sodium bicarbonate in ether / water.[66] We chose N-benzyloxy carbamate as the N-protecting group because it is known to give N-methyl when reduced with LAH.

In the reduction of compound **122**, the protecting group *tert*-butyldimethylsilyl group was cleaved by LAH. **SCHEME 3.15**. This was an unusual reaction and could not be easily explained. Though the *tert*-butyldimethylsilyl ether did not survive under the LAH reduction reaction conditions, we found that the allyl ether and SEM ether remained unchanged.

In conclusion, LAH reduction of our isoxazoline was face selective and afforded amino alcohol *syn* to alkyl ether at C-4.

3.4 Oxidation of Benzylic Alcohol.

Once the isoxazoline had been reduced to amino alcohol, the generated benzylic alcohol needed to be oxidized to ketone **139. eq.3.9.**

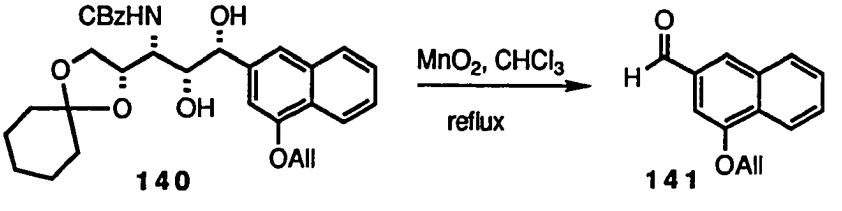


eq. 3.9

Oxidizing agents such as MnO_2[52], $BaMnO_4$[78], dimethyl amino pyridinium chlorochromate[79], DDQ[53, 80], K_2RuO_4[54], $(Bu_3Sn)_2O$-Br_2[81] are known as selective oxidation agents for allylic and benzylic alcohols. The higher selectivities are observed with allylic or benzylic alcohols compared to primary alcohols and reasonable selectivity is observed with secondary alcohols.

Initially we tried the oxidation of compound **140** with MnO_2, by refluxing in chloroform.[52]

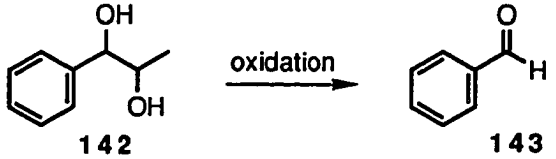
SCHEME 3.16



We observed only 4-allyloxy-2-naphthaldehyde **141**, not even a trace of expected ketone. **SCHEME 3.16.** The oxidation of diol **140** with barium manganate also yielded

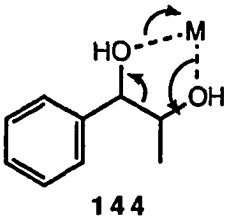
naphthaldehyde **141**.

In order to find the proper oxidation agent we prepared a model diol **142** which had a benzylic alcohol with a secondary alcohol functional group next to it, by oxidizing methylstyrene with osmium tetraoxide and N-methylmorpholine.[82] The model compound **142** was oxidized with MnO_2, $BaMnO_4$, DDQ, and DMAP-$HCrO_3Cl$ and all of them afforded benzaldehyde **143**. **eq. 3.10**.



142 **143** **eq. 3.10**

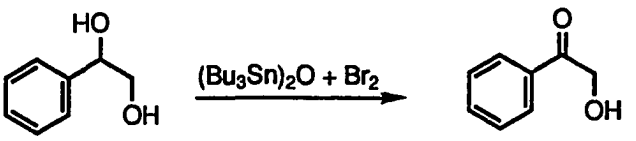
All of the above oxidation agents are reported to afford selective oxidation of benzylic alcohols in the presence of secondary alcohol, when the two hydroxy groups are not vicinal. We assumed that the metal of the oxidation agents complexed with both OH's and caused the C-C bond cleavage by oxidation in our case. **144**.



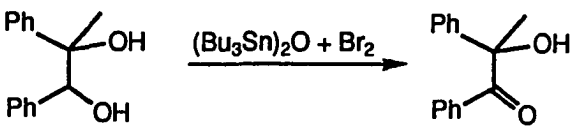
144

S. David and S. Hanessian[83] reported in a review that benzylic alcohols could be selectively oxidized to ketones in 1,2-diols of benzylic alcohol and primary[81, 84] or tertiary alcohol[85] by hexabutyl distannoxane-bromine. **eq.3.11** and

3.12.



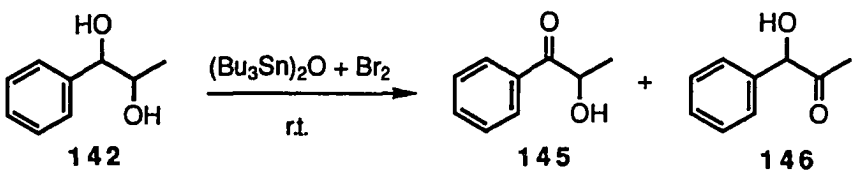
eq. 3.11



eq. 3.12

When we tried this procedure with our model compound diol **142**, we observed two oxidized products in approximately 1:1 ratio. **SCHEME 3.17.**

SCHEME 3.17

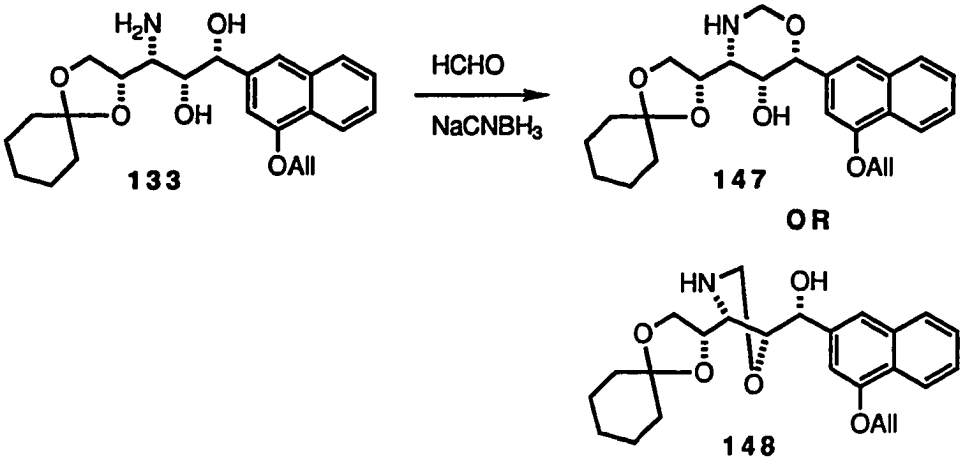


142 **145** **146**

No selectivity between benzylic and secondary alcohol was observed even at very low temperature (-78°C). When this method was applied to our system **140**, only 4-allyloxy-2-naphthaldehyde **141** was observed.

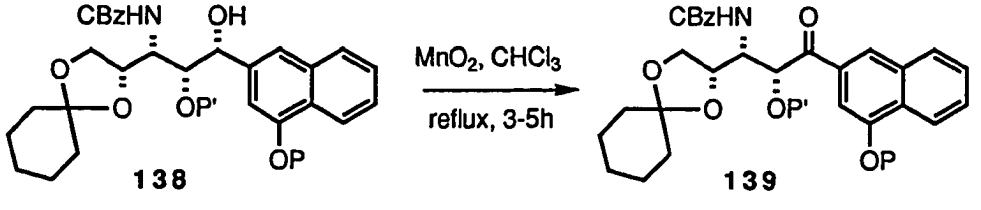
We considered protecting the amino group and secondary alcohol as a cyclic hemiaza-acetal by using formaldehyde. **SCHEME 3.18.** We could not predict, whether we would get five-membered or six-membered acetal. However the reaction failed.

SCHEME 3.18



We assumed that the fragmentation was observed due to the presence of the free secondary OH, compound **140**. We found that the oxidation of benzylic-OH of naphthyl ethers, where the secondary alcohol is protected **(150, 151, 152)**, went smoothly with MnO_2 (activated) in dry chloroform at reflux within 3-5h. **SCHEME 3.19**. Less than 5% of fragmentation aldehyde was detected.

SCHEME 3.19



150 : P = P' = Allyl
151 : P = P' = SEM
152 : P = SEM, P' = Allyl

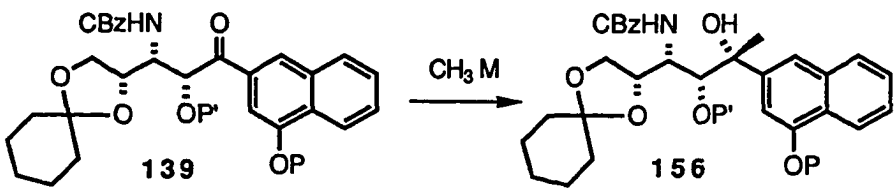
153 : P = P' = Allyl
154 : P = P' = SEM
155 : P = SEM, P' = Allyl

The formation of ketones were confirmed by ^1H NMR, ^{13}C NMR, IR and MS analysis. In their ^1H NMR, the protons on C-2

and C-4 of naphthyl shifted down field about 0.8ppm due to the deshielding effect of carbonyl. The carbonyl stretching frequency was observed at about 1690 cm^{-1} in IR spectrum. A ^{13}C NMR showed a carbonyl carbon peak at about δ 197.

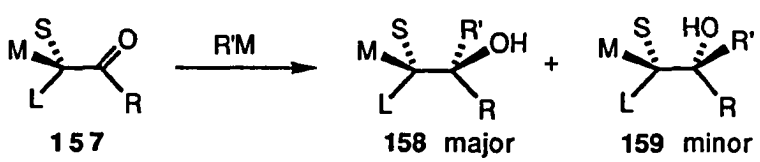
3.5. Methylation of Ketone

The next stage of the synthesis was to introduce the methyl group from the si-face of ketone **139**. **(eq. 3.13)**



eq. 3.13

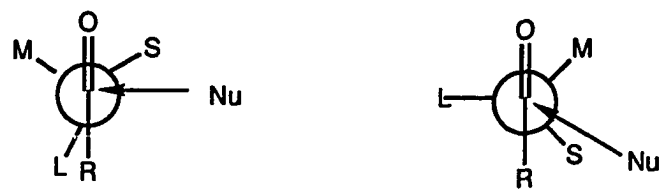
The nucleophilic addition of organometallic reagent, metal hydride or Grignard with simple open chain aldehyde and ketone **157** (L,M,S and R being groups containing carbon and hydrogen only) gives predominantly product **158**, which is known as Cram's product and is explained by Cram[86, 87, 88], Felkin[88] and others[89, 90]. **(eq. 3.14)**



eq. 3.14

According to Cram, the favorable conformation is the one where the largest group (L) is anti-periplanar to the carbonyl function and the nucleophile comes perpendicular to carbonyl π orbital from the less hindered side (S group) of the molecule, **model 160, Fig. 3.6.** However, Cram's model

cannot explain why in some cases, the product ratio varies when the R group becomes bulky.



160
Cram's model

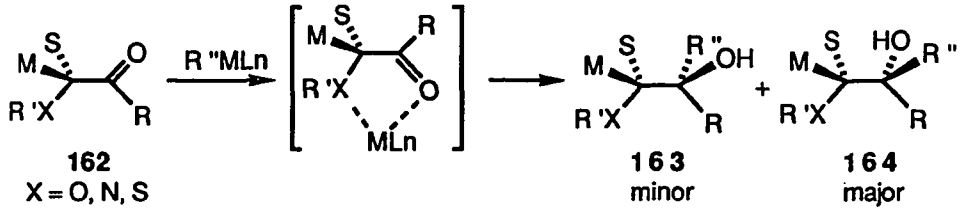
161
Felkin & Anh's model

Figure 3.6. Favorable conformations of carbonyl compound for the nucleophilic addition to carbonyl.

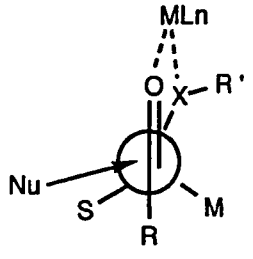
Felkin proposed an assumption that as the R group becomes bulkier, the steric interaction between L and R becomes larger. Therefore the most possible reaction conformation is the one where the L group is perpendicular to carbonyl group; the M group lies towards O of carbonyl; the S group towards R. (**Model 161**). The nucleophile then approaches the carbonyl from the face that is sterically less hindered, the face blocked by the S group. Anh refined the Felkin's model by postulating the non-perpendicular attack of nucleophile, as shown in **161**, on the basis of molecular orbital considerations.[56]

These models are true when L, M, S groups contain only carbon and hydrogen. The product ratio is reversed when oxygen, nitrogen or sulfur are contained in L, M, and S groups. The favorable conformation is controlled by the

chelation between the metal of organometallic reagent, oxygen of carbonyl and oxygen, nitrogen or sulfur form the α-carbon.[55, 88, 91] **eq. 3.15** and **Figure 3.7.** The nucleophile comes from si-face rather than from the re-face and the product is called anti-Cram's product.



162 X = O, N, S **163** minor **164** major **eq. 3.15**

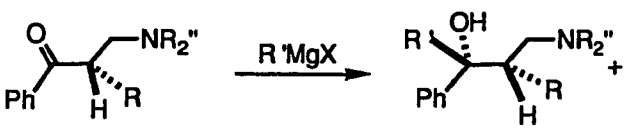


Metal chelated Anti-Cram's Model

Figure 3.7. Metal chelated anti-Cram's Model of the nucleophilic addition to carbonyl compound.

Work done by R. Andrisano et al.[92] was interesting and relevant to our problem. The reaction between Grignard reagents and α-asymmetric β-amino ketones were examined (**eq. 3.12**). They showed that the reactions are highly stereospecific and the stereochemistry outcome is predicted by the hypothesis of a cyclic model where the magnesium atom of Grignard coordinates both the carbonyl oxygen and the amine nitrogen from the β-carbon, model **168**. The nucleophile

methyl adds from the re-face of carbonyl when α center is S **(model 168 & 166).**

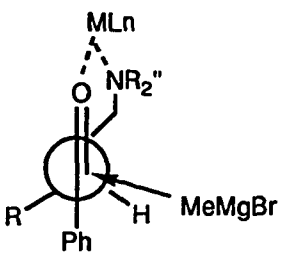


eq. 3.16

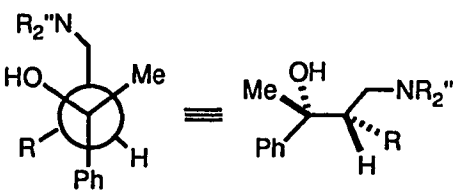
165
R = C and H only
R'MgX = CH_3MgI ; PhMgI

166
major

167
minor



168

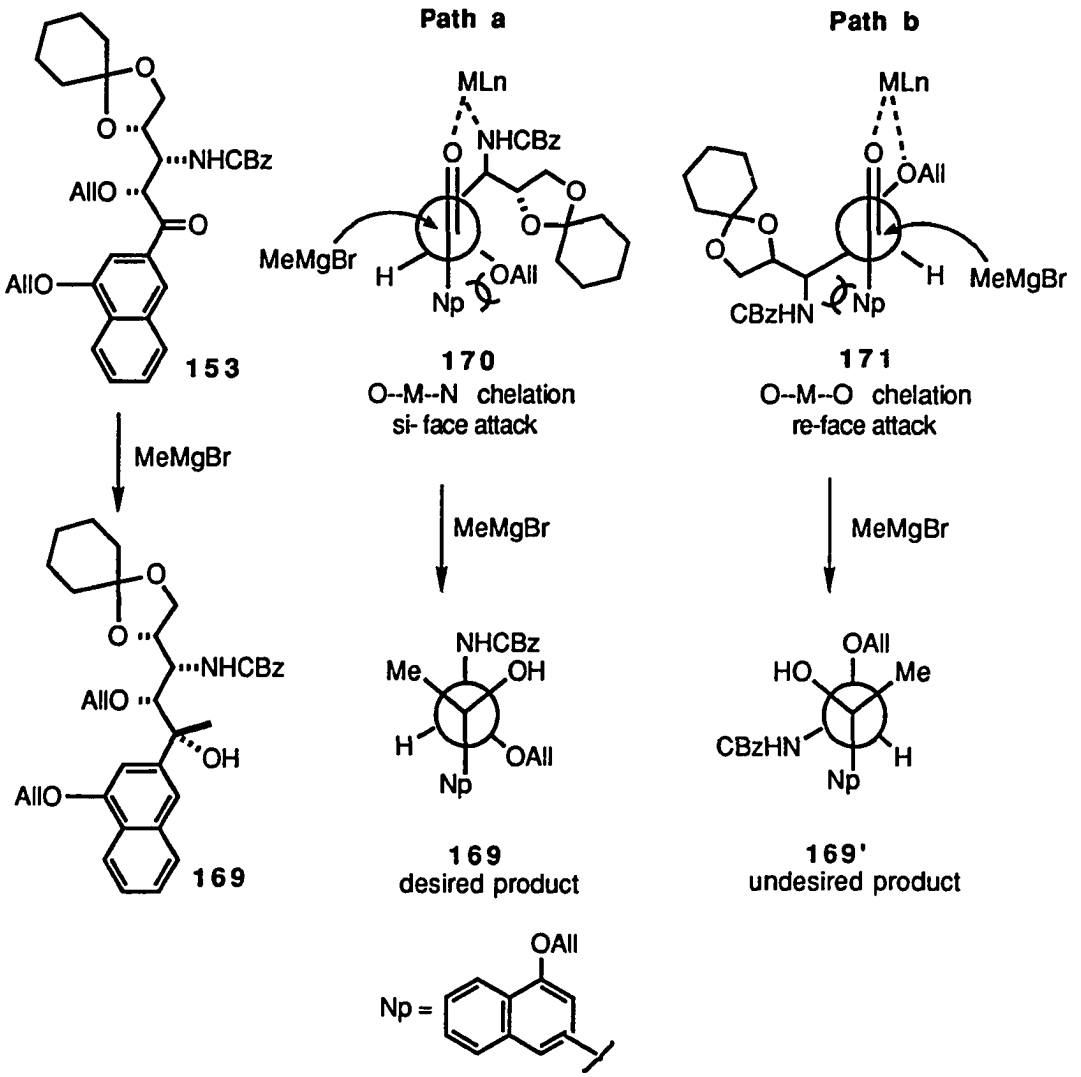


166 major

In our synthesis, the desired methyl addition to the ketone **153,** was from the si-face of carbonyl group. Ketone **153** had O-alkoxy and N-benzyloxy carbonyl functional groups at the α and β carbon as R and S centers respectively. If the chelation between carbonyl-metal-nitrogen of β-carbamate is favorable, the reaction would go through **Path a** (**SCHEME 3.20**) and yield the desired methylated product **169.** If the chelation between carbonyl-metal-oxygen of α-alkoxy is favorable, the major product would be **169'.** (**Path b**). We hoped that carbonyl-metal-N chelation would be more favorable than carbonyl-metal-O chelation and the reaction would go through **Path a** and yield the desired methylated product **169.** The steric interaction between naphthalene and alkoxy in **170**

would be less than that of naphthalene and NHCBz group on methine **171**. On the other hand, five member ring formation is kinetically more favorable than six member ring. This would favor the reaction **Path b** and yield product **169'**, the anti Cram's product.

SCHEME 3.20



In order to get the O-Met-N chelation (as **170**), we

added isopropyl magnesium bromide (0.5 equiv.) to the solution of ketone **153** at -40°C and stirred for 10 min. Then methyl lithium was added as a source of methyl anion. The reaction did not go to completion for 5h, although the reaction mixture was warmed to 0°C. This reaction yielded both isomers, **169** and its epimer **169'**. This showed that methyl attacked from both faces of carbonyl. Beside the epimeric mixture, the third product, the addition of isopropyl Grignard to ketone, was also observed. The ^{1}H NMR showed only one isomer of isopropyl adduct. We assumed that isopropyl Grignard gave better chelation between O-Mg-N and that yielded the major product through **Path a**.

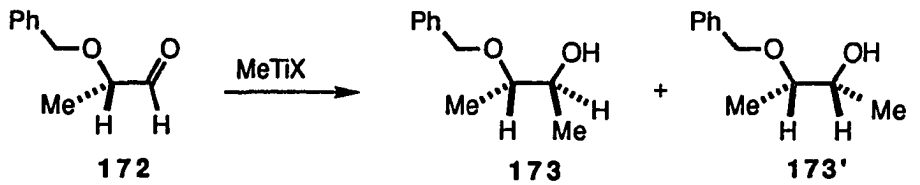
Therefore, the methylating agent was switched to methyl Grignard and the reaction was performed in reverse order. A solution of ketone **153** was added into a solution of methyl Grignard (10 equiv.) in ether at -30°C and the reaction mixture was stirred for 30min. Then the mixture was warmed to 0°C, and stirring was continued for an additional hour. Finally the reaction was quenched with 10% ammonium chloride solution and the product was extracted with ether / water. About 85-88% yield of major isomer and less than 5% of minor isomer were observed.

The absolute stereochemistry of the two isomers were not known at this stage. After we deprotected the diol, we were able to obtain the X-ray crystal structure of the major isomer and found that the major product was the undesired product. (X-ray crystal structure of compound **176**, p.80,

Fig 3.8) The methyl group attacked from the re-face of the carbonyl through the O-Mg-O chelation, **Path b**, the anti-Cram's product. The methyl addition reaction to ketone **153**, using only methyl lithium was tried but the reaction was not complete and the stereoselectivity was not great. The formation of Li-enolate and O-Li-O chelation were responsible for the observations.

M. T. Reetz[56] explained that chelation or non-chelation control is possible in a predictable way by using different methyl titanium complexes. For example, by changing the reagent from $MeTiCl_3$ to $MeTi(OCHMe_2)_3$, the diastereomeric excess is reversed in the case of α-benzyloxy propanal **172**. **SCHEME 3.21**. Since the acidity of methyltitanium reagents decrease drastically in going from $MeTiCl_3$ to $MeTi(OCHMe_2)_3$, the latter becomes incapable of chelation. The reaction of aldehyde **172** with the complex $MeTiCl_3$ affords preferentially the anti-Cram's product **173** and the reaction with the complex $MeTi(OCHMe_2)_3$ yields predominantly the Cram's product or non-chelating product **173'**.

SCHEME 3.21

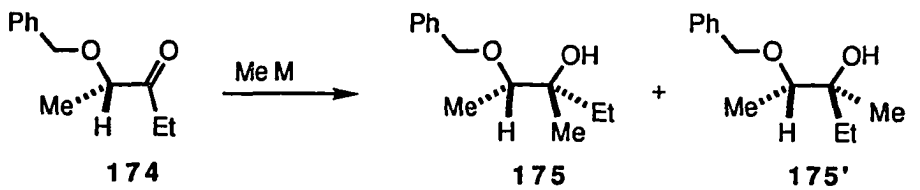


172 173 173'

MeTiX = $MeTiCl_3$	92	8
MeTiX = $MeTi(OCHMe_2)_3$	8	92

However, this is not the case with ketones. The ratios of products are same in all the cases, either with $MeTiCl_3$, $MeTi(OCHMe_2)_3$ or MeMgBr, when adds to 2-benzyloxy-3-carbonyl pentane **174**.[56] **SCHEME 3.22.**

SCHEME 3.22



174 175 175'

MeM = $MeTiCl_3$, $MeTi(OCHMe_2)_3$, MeMgBr	>98	<2

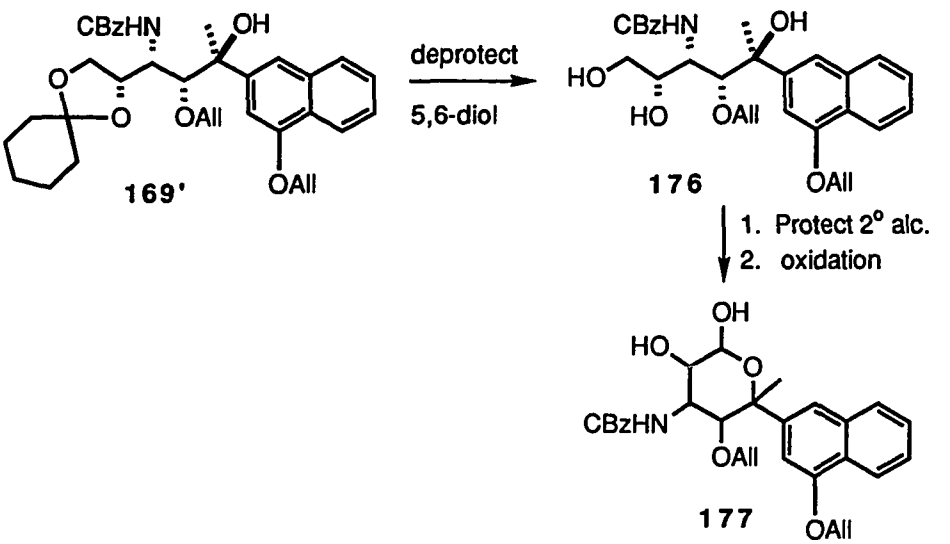
The exploration for a suitable organometallic methylating agent for ketone **153**, to afford the non-chelation control product **169**, is still unsolved. At this stage, we decided to carry **169'** through to an 5'-epi-nogalamycin model.

3.6 Oxidation of Primary Alcohol

Compound **169'** had all the functional groups for CDEF

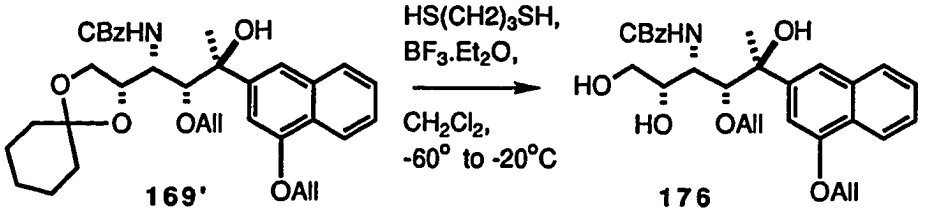
ring of nogalamycin. In order to construct the F-ring, 5,6-O-cyclohexylidene was to be converted to 5,6-diol and then the primary alcohol (C-6 OH) was to be oxidized to aldehyde. The hydroxy group at C-2 would participate in the formation of F-ring. **SCHEME 3.23.**

SCHEME 3.23



The deprotection of cyclohexylidene with various acid hydrolysis methods failed. Finally, the cyclohexylidene was cleaved with propane-1,3-dithiol-BF_3.Et_2O in dichloromethane. **SCHEME 3.24.** The X-ray crystal structure of compound **176** is shown in **Figure 3.8.**[93]

SCHEME 3.24



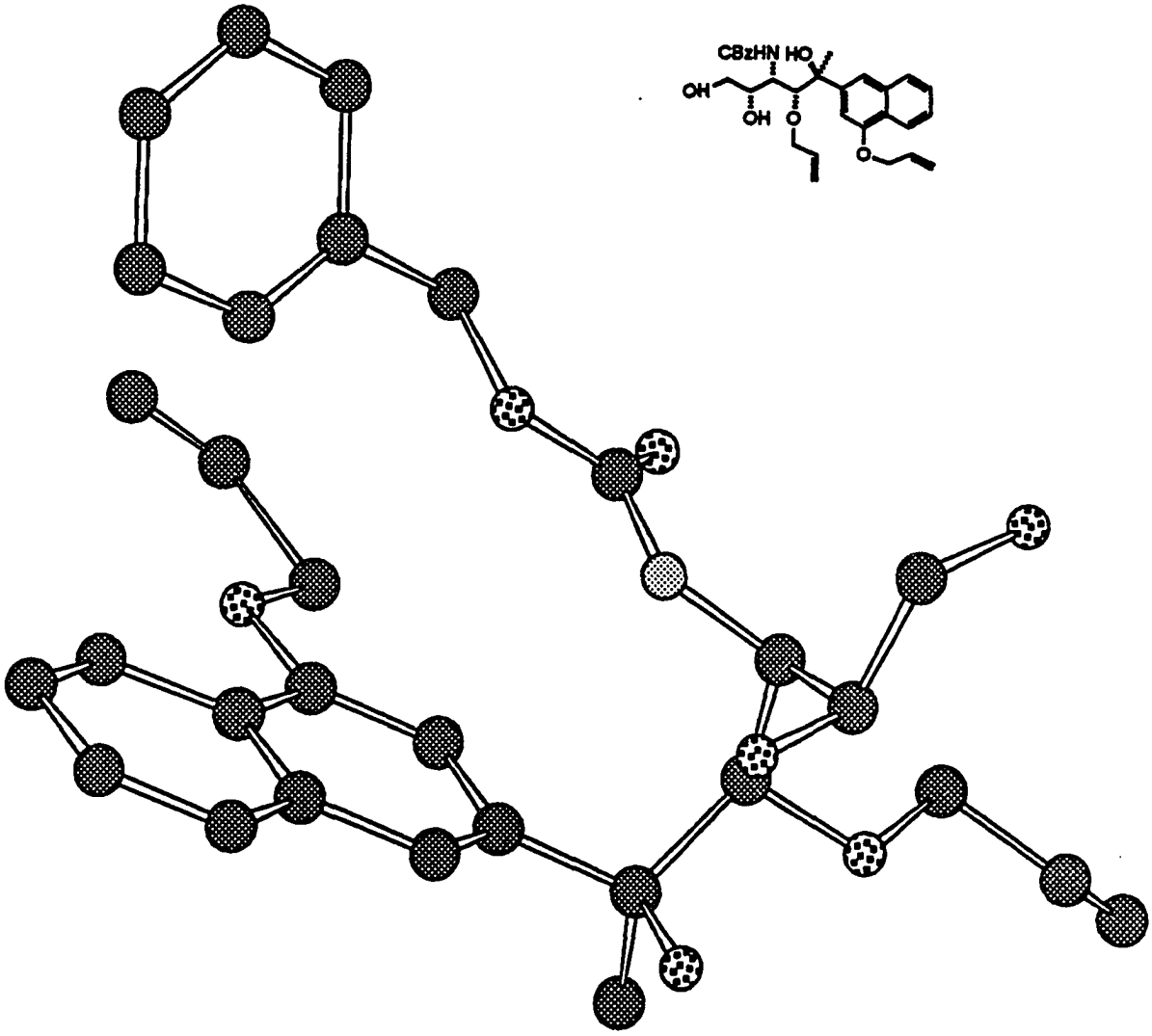
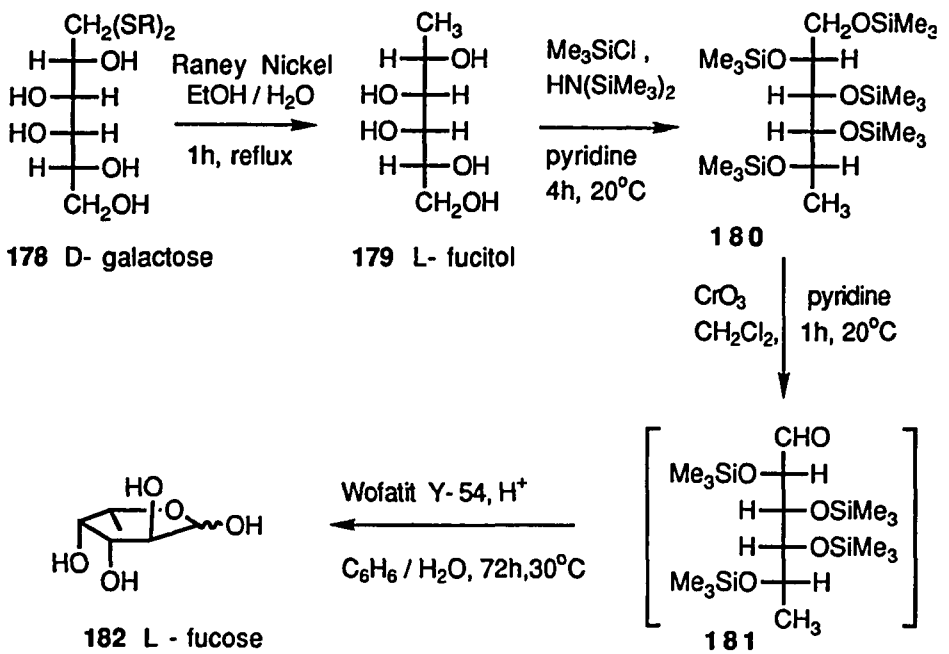


FIGURE 3.8. The crystal structure of (2S,3R,4S,5S)-3-(allyloxy)-4-(N-benzyloxycarbonyl)-5,6-(dihydroxy)-2-[1-(allyloxy)-naphth-3-yl]-2-hexanol **(176)**.

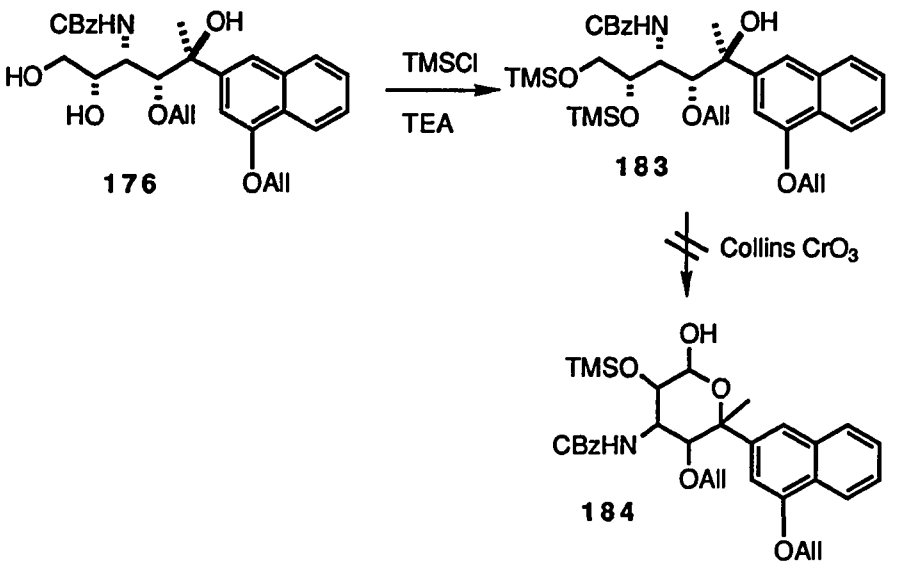
The oxidation of primary alcohols in the presence of secondary alcohols through trimethylsilyl ether intermediates was reported by R. Mahrwald et al.[58] in the synthesis of prostaglandin intermediates. This selective oxidation procedure, the combination of silylating the hydroxyls and oxidizing with Collins reagent, was applied in the conversion of D-galactose into L-fucose by H. Kristen, R. Mahrwald and co-workers.[59] **SCHEME 3.25.**

SCHEME 3.25



We assumed that we could apply this method in the oxidation of our diol **176**. **SCHEME 3.26.** The diol **176** was silylated, using trimethylsilyl chloride and triethylamine, and the crude bis-silylether **183** was used in Collin's oxidation without further purification.

SCHEME 3.26



Collin's oxidizing agent (1.2 equiv.) was prepared from chromium(VI)oxide (dried under high vacuum for 30min) and pyridine (1:2 ratio) in dry dichloromethane. The complex was cooled to 0°C and a solution of bis-silylether **183** was added. The reaction mixture was stirred at 0°C for 3h. The TLC of the reaction showed many products. However, we could not detect any characterizable product after the chromium oxidant was removed from the mixture.

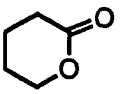
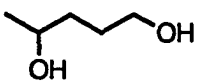
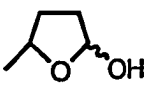
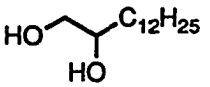
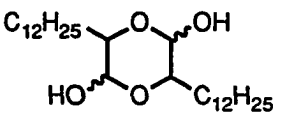
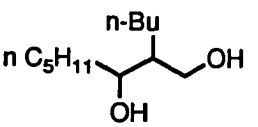
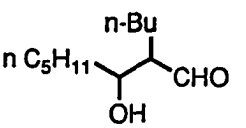
Another selective oxidation method was demonstrated by Y. Ishii et al.[94] Diols (1,2- or α,ω-) are oxidized to aldehyde by bis-(cyclopentadienyl) zirconium dihydride, Cp_2ZrH_2, in the presence of an appropriate hydrogen acceptor such as cyclohexanone or benzaldehyde. Diol (1 equiv.), hydrogen acceptor (2 equiv.) and Cp_2ZrH_2 (0.2 equiv.) is placed in a glass sealed tube and then the mixture is

mechanically agitated at 150°C to 170°C for 8 to 10h. The reported yields vary from 39 to 98%, depending upon the diol. We did not try this procedure because our diol might not be stable at such high temperatures for a prolonged period of time.

Another rare oxidizing agent for primary over secondary alcohol is tris(triphenylphosphine)ruthenium chloride, $Ru(PPh_3)_3Cl$. It was reported by K. Oshima et al.[95]. The chemoselectivity for the oxidation of primary over secondary alcohols are 83/6 to 95/3 depending on the type of alcohols. The oxidation of α,ω-diol had been studied (89% yield) but not the oxidation of 1,2-diol.

Chemically mediated electrooxidation and non-electrooxidation of alcohols, using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), were investigated by M. F. Semmelhack et al.[96, 97] The optimum conditions for non-electrooxidation involve mixing the alcohol (50mmol), with TEMPO (10mmol), $CuCl_2$ (110mmol), and CaH_2 (150mmol) in acetonitrile at 25°C with overhead stirring.

The oxidation of alcohol with TEMPO or 4-MeO-TEMPO, sodium hypochlorite (NaOCl) and KBr in two-phase reaction condition was reported by P. L. Anelli et al.[98] They observed the overoxidation of primary alcohol to acid in some cases and the oxidation of α,ω-diol to keto-aldehyde and to lactone in some cases. **Table 3.1**, entry **1-3**.

	Starting diol	Product	Yield GC (Isolated)
1	$CH_3CH(OH)(CH_2)_8CH_2OH$	$CH_3CH(OH)(CH_2)_8CHO$	68 [a]
2	$CH_3CH(OH)(CH_2)_8CH_2OH$	$CH_3CO(CH_2)_8CHO$	69 [b]
3			58 [b]
4			43 (40)
5			(71)
6			76 (70)

a. 1.1 equiv.of NaOCl

b. 2.2 equiv. of NaOCl

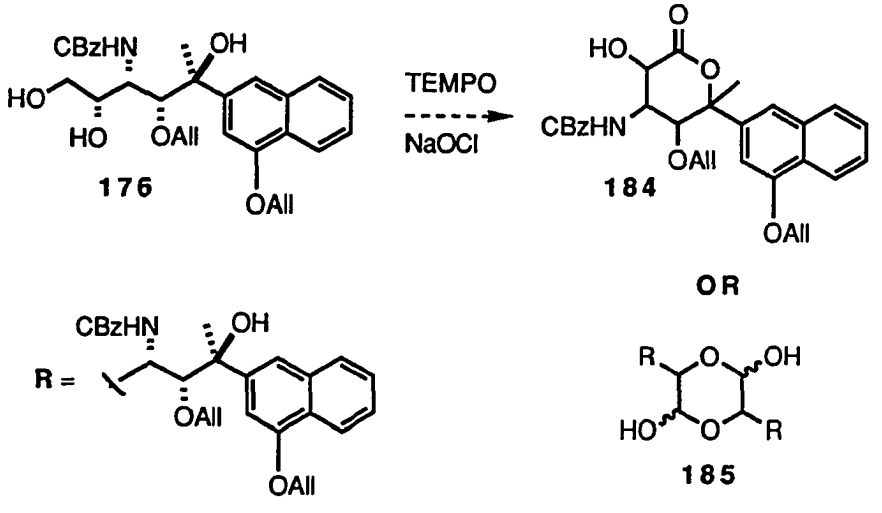
Table 3.1. Oxidation of various alcohol with sodium hypochlorite in the presence of TEMPO.[98, 99]

Recently, J. Skarzewski et al.[99] has modified the application of TEMPO for the selective oxidation of primary alcohols. The procedure is not straightforward. A solution of alcohol (3mmol) in dichloromethane (8ml), TEMPO (1mol%) and a saturated aqueous solution of sodium bicarbonate (5ml) containing potassium bromide (10mol%) and tetrabutylammonium chloride (5mol%) are cooled to 0°C and stirred vigorously. A solution of sodium hypochlorite (3.9mmol, 30% excess) in 2ml

of water, 3ml of saturated sodium bicarbonate solution and 6ml of brine are added into the above solution dropwise during 45min. The mixture is stirred for 1h at 0°C, and for 20min at 20°C and then the phases are separated. After the usual workup this affords 43 to 98% yield of aldehyde depending on the starting alcohol. Some examples are shown in **Table 3.1**, entry **4 & 5**.

From those experiments we assumed that the oxidation of our 1,2-diol **178**, using TEMPO and sodium hypochlorite, was not a good procedure. Our alcohol might get over oxidized to lactone **184** or might produce dioxane **185**. **SCHEME 3.27**.

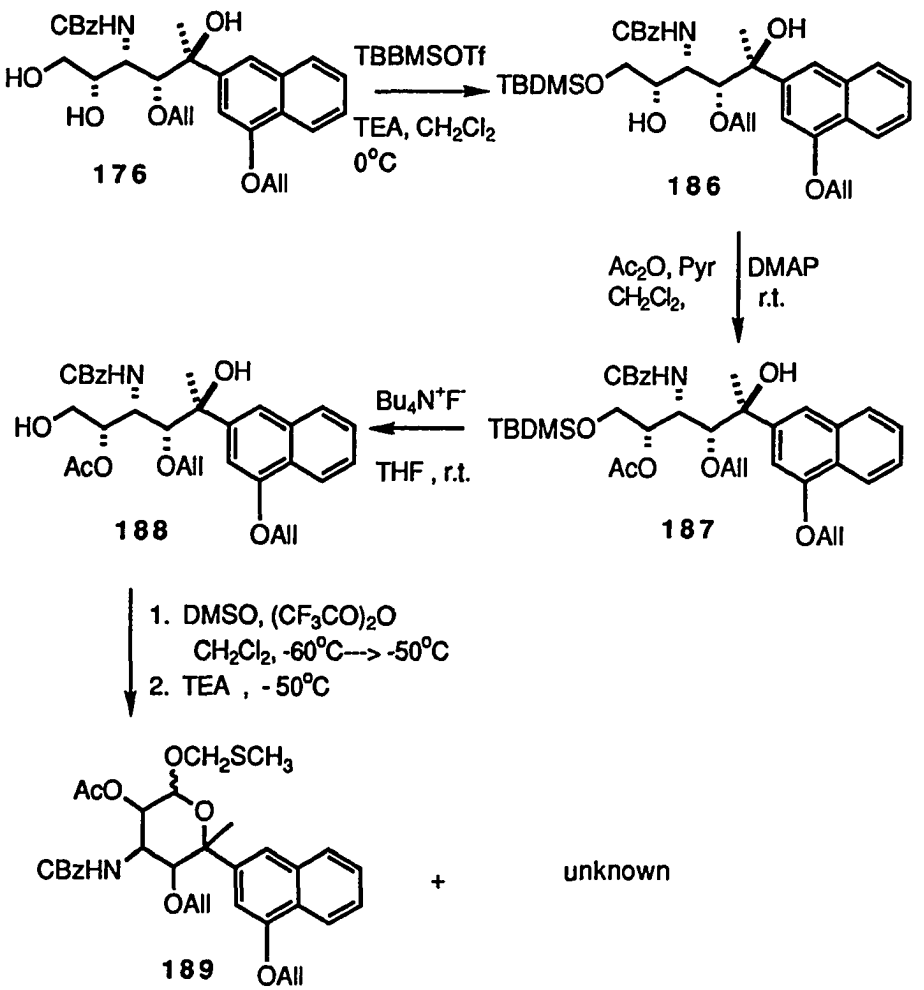
SCHEME 3.27



In order to simplify our synthesis the oxidation was carried out in a stepwise manner. The primary alcohol was selectively protected as TBDMS ether **186**, using *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane

at 0°C, and the secondary alcohol was protected as acetate **187**, using acetic anhydride, pyridine, dimethylaminopyridine in dichloromethane at room temperature. Then the silyl ether was deblocked to alcohol **188** with tetrabutylammonium fluoride in THF. The primary alcohol was oxidized to aldehyde under the mild conditions of Swern oxidation.[100] **SCHEME 3.28.**

SCHEME 3.28



The Swern oxidizing agent, trifluoroacetoxydimethyl-

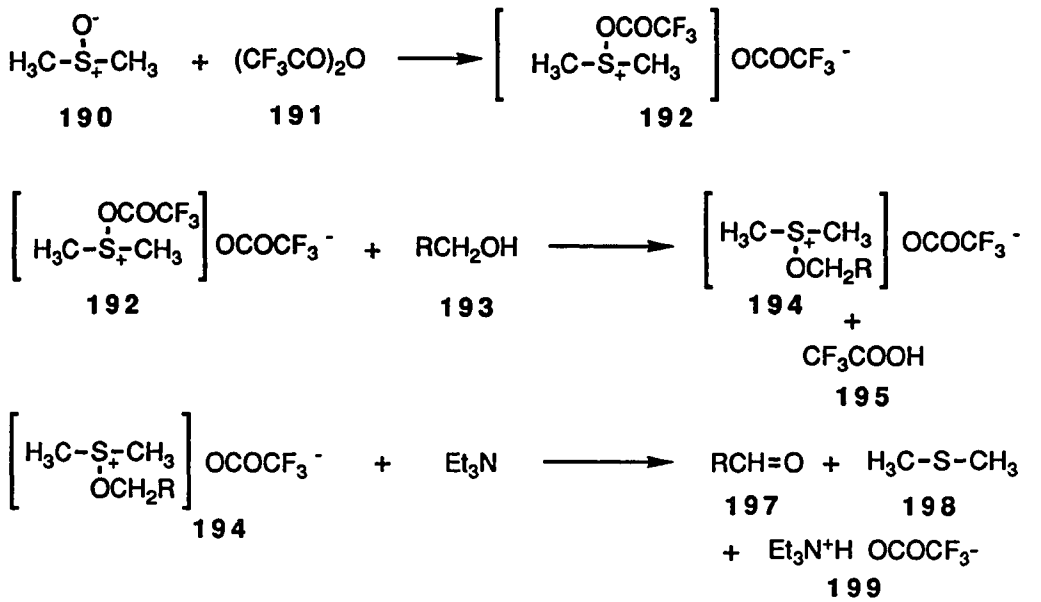
sulfonium trifluoroacetate **192**, was prepared *in situ* from dimethyl sulfoxide(DMSO) **190** and trifluoroacetic anhydride (TFAA) **191** at -60°C in dichloromethane. A solution of alcohol **188** was added dropwise into Swern reagent. A ten to fifteen fold excess of Swern reagent was used because three to four equivalents of Swern reagent did not give complete reaction. The mixture was continuously stirred between -60°C to -50°C for 3h, then 20 equivalent of triethylamine (TEA) was added. We expected that once the aldehyde was formed, the hydroxy at C-2 would attack the carbonyl and would produce the desired lactol and some lactone if over oxidation occurred. The TLC of the reaction showed the formation of two products, both had higher R_f than the starting alcohol. To our surprise, we found that the faster moving product was the methylthiomethyl glycoside **189**, rather than expected lactol or lactone.

The ^1H NMR of the product showed one new singlet at δ 2.25 for $-OCH_2S\underline{CH}_3$, and one new ABq at δ 4.41 and 4.38 for $-O\underline{CH}_2SCH_3$ besides all the original signals. The multiplet of C-6 protons (methylene protons) at δ 3.95 shifted down field. The proton signal from the secondary allyloxy group which showed two sets of dd at δ 4.32 & 4.12 were now shifted to high field as two sets of dd at δ 3.65 & 3.39. There were two sets of dd at δ 3.81 & 2.93. This was evidence for the formation of two pyranoside sugar isomers, the α-glycoside and β-glycoside.

Similarly the proton signal of the CH from the secondary allyloxy group which showed a multiplet at δ 6.05-5.93 was now shifted upfield (approx. d 5.48) and was overlapped with other proton signals. We assumed that these protons were somehow lying in a shielded region due to the formation of the six-member sugar ring. The formation of the methylthiomethyl glycoside **189** was confirmed by MS analysis. The mass calculated for $(C_{34}H_{39}NO_8S - H)^-$ ion was 620.2318 and the value observed was 620.2318.

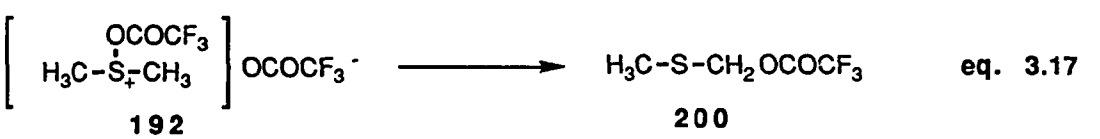
The general mechanism for Swern oxidation is shown in **SCHEME 3.29**. *In situ* formation of trifluoroacetoxydimethyl-sulfonium trifluoroacetate **192** takes place in first step. This salt is converted to alkoxydimethylsulfonium trifluoroacetate **194** when alcohol RCH_2OH is added. Alkoxysulfonium salt **194** yields a carbonyl compound **197** when treated with base, TEA.

SCHEME 3.29



Swern stated that beside the carbonyl compound, other side products are also possible depending on the structure of alcohol and the reaction conditions, such as reaction temperature, concentration of the solution and the temperature when TEA added.

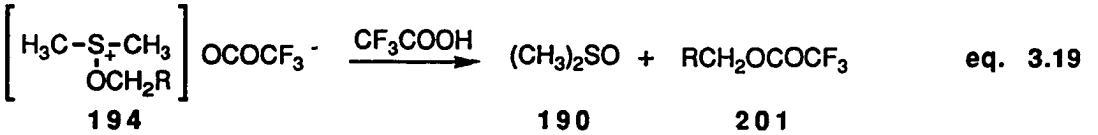
The intermediate salt **192** undergoes Pummerer rearrangement at room temperature to trifluoroacetoxymethyl methyl sulfide **200**. **(eq. 3.17)**. The Pummerer rearranged product gives trifluoroacetate ester when reacted with alcohol. **(eq. 3.18)**.



eq. 3.17

eq. 3.18

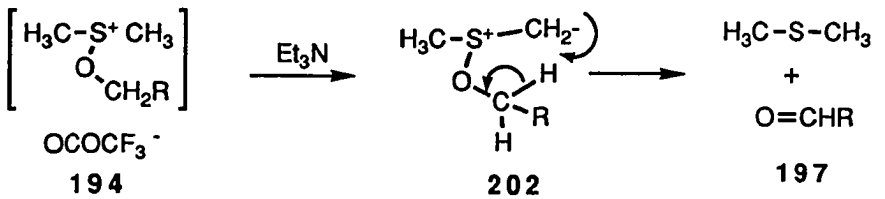
The formation of trifluoroacetate is also possible from the intermediate salts **194**, due to the presence of trifluoroacetic acid (TFA) in TFAA. **(eq. 3.15)**. The formation of trifluoroacetate is greater when an alcohol is allylic or benzylic.



194 **190** **201** **eq. 3.19**

Swern proposed the mechanism for the formation of carbonyl compound by TEA as shown in **SCHEME 3.30.**

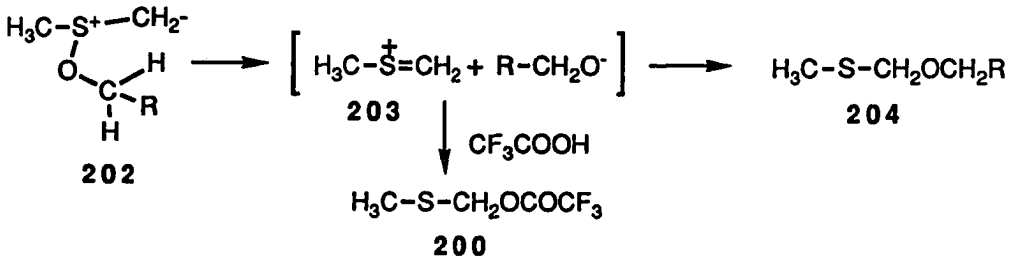
SCHEME 3.30



194 **202** **197**

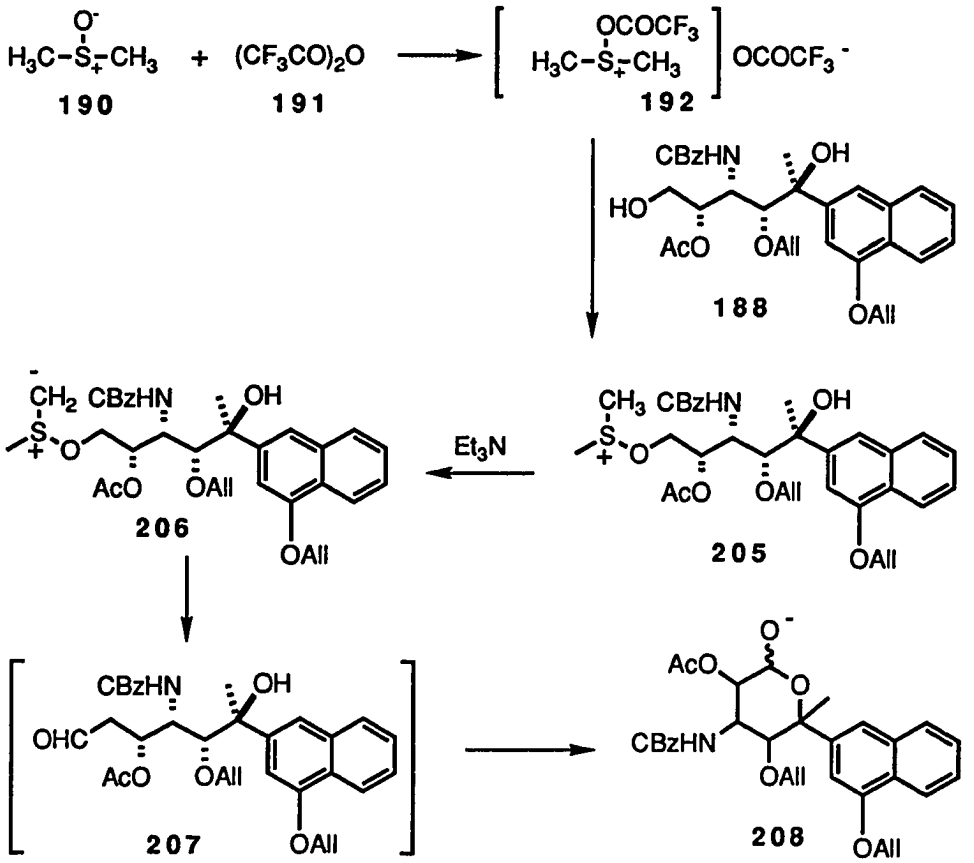
Pummerer-type rearrangement also occurs at this step and produces the reactive cationic intermediate $CH_3S^+=CH_2$ **203**, which is trapped partly by alcohol and partly by TFA. This explains the formation of trifluoroacetoxymethyl methyl sulfide **204** and ester **200**. **SCHEME 3.31.**

SCHEME 3.31



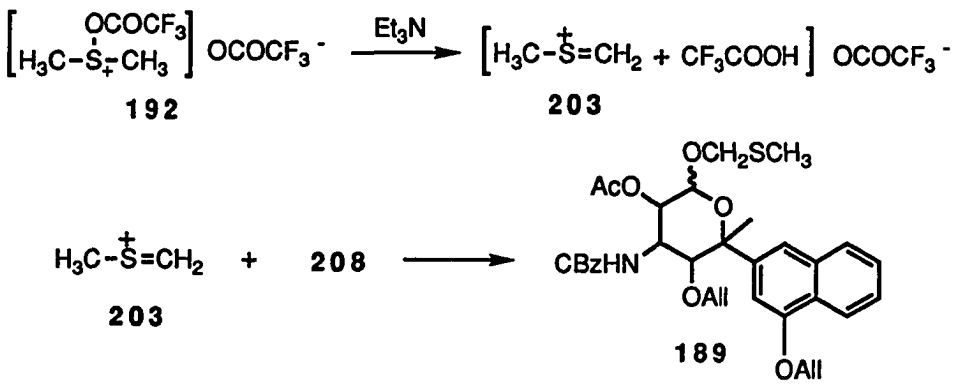
We proposed the mechanism for the formation of methylthiomethyl glycoside **189** as follows. **SCHEME 3.32.** When alcohol **188** was added to the Swern oxidizing agent **192** at -60°C, it formed a complex **205.** The aldehyde **207** was obtained when TEA was added to the mixture at that temperature, and this produced compound **208** with the formation of pyranose F-ring of nogalamycin.

SCHEME 3.32



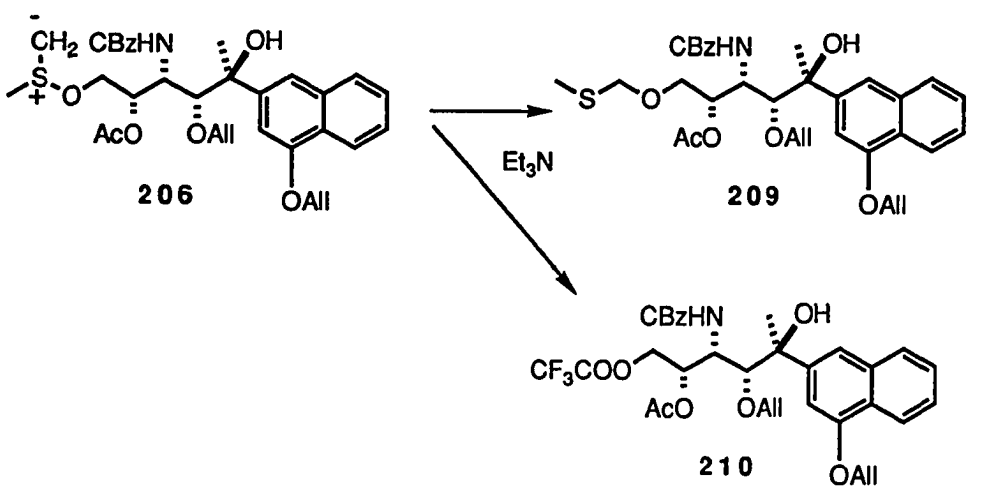
---> structure contd:

As an excess of Swern reagent was used, the reactive cationic intermediate $CH_3S^+=CH_2$ **203** would be generated by addition of TEA. This would trap the compound **208**, and prevent further oxidation, and yield the observed product **189**.



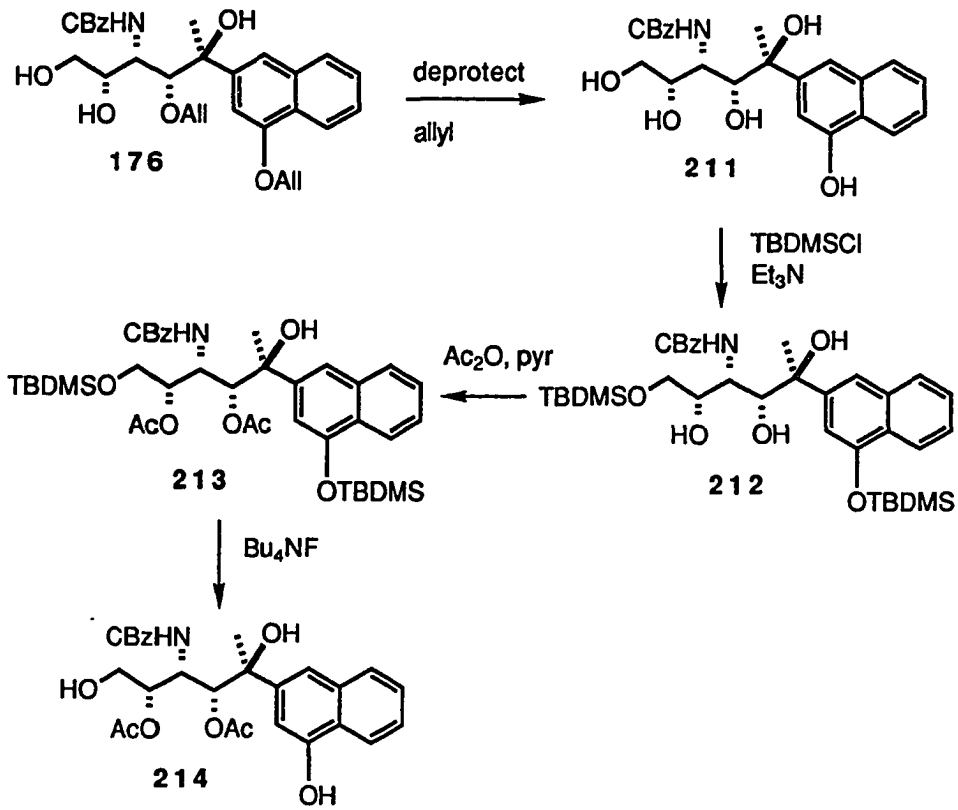
We could not characterize the second product, which had lower R_f than **189**. We assumed it to be either ester **210** or Pummerer rearranged product **209**. **SCHEME 3.33.**

SCHEME 3.33



Later we faced difficulties in removing allyl groups from compound **189**. The methylthiomethyl group might be a poison for the catalyst $[(PPh_3)_3RhCl]$ that was used in allyl cleavage. Therefore we altered our synthetic route by deprotecting the allyl group before oxidation. **SCHEME 3.34.**

SCHEME 3.34

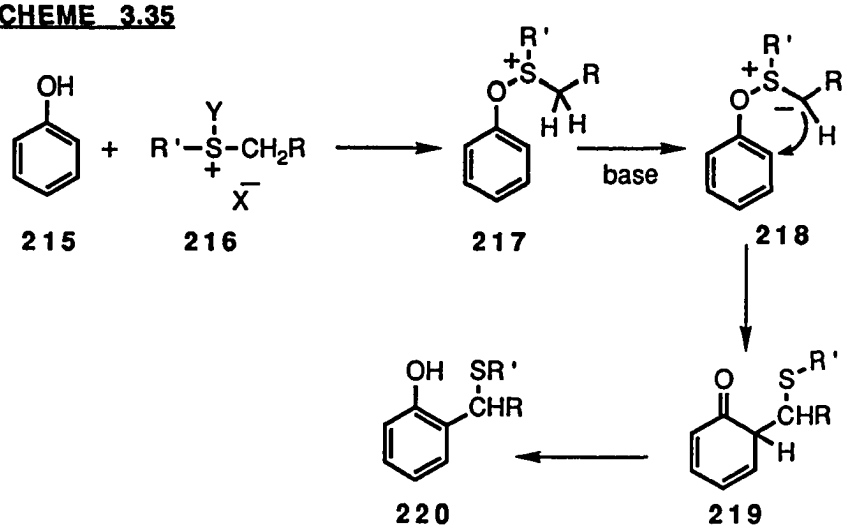


We planned the oxidation of compound **211** in a stepwise manner as before. The primary alcohol was protected as TBDMS ether **212**. Unfortunately, the naphtholic-OH was also protected as TBDMS ether because it is more acidic and more reactive. The secondary hydroxy groups were acetylated with acetic anhydride / pyridine. (compound **213**). Bis-silyl ether was converted to naphthol **214** with $Bu_4N^+F^-$ / THF. In this desilylation reaction we also observed the migration of acyl group from C-5 acetoxy to C-6 hydroxy.

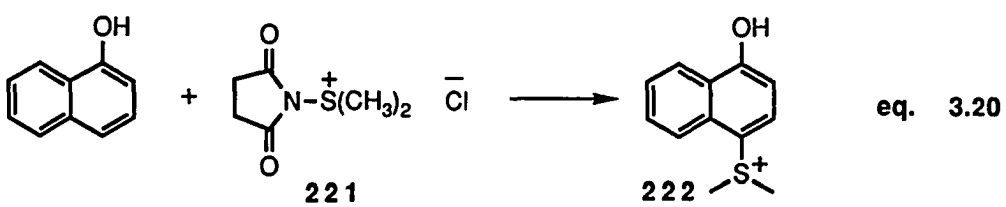
P. G. Gassman et al.[101] pointed out that dialkylsulfonium salts **216**, which have α-H's, add to phenol

and form oxasulfonium salts. These salts generate ylides when treated with base and rearrange to ortho alkylated phenol **220**. **SCHEME 3.35.**

SCHEME 3.35



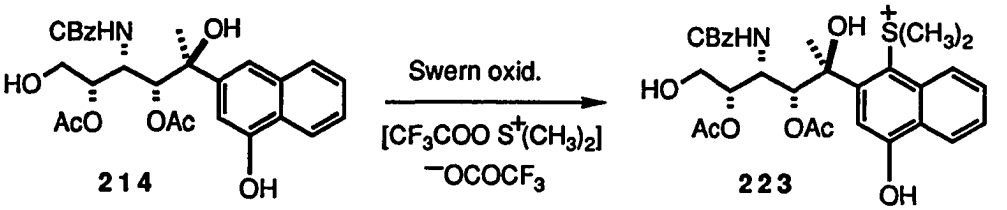
The para sulfonium salt formation was reported by Claus and Rieder in the reaction of phenol and dimethylchlorosulfonium chloride.[102] Similarly, Vilsmaier and Sprugel[103] showed that α-naphthol gives para-sulfonium salt **222** rather than oxasulfonium salt when treated with azasulfonium salt **221**. **eq. 3.20.**



eq. 3.20

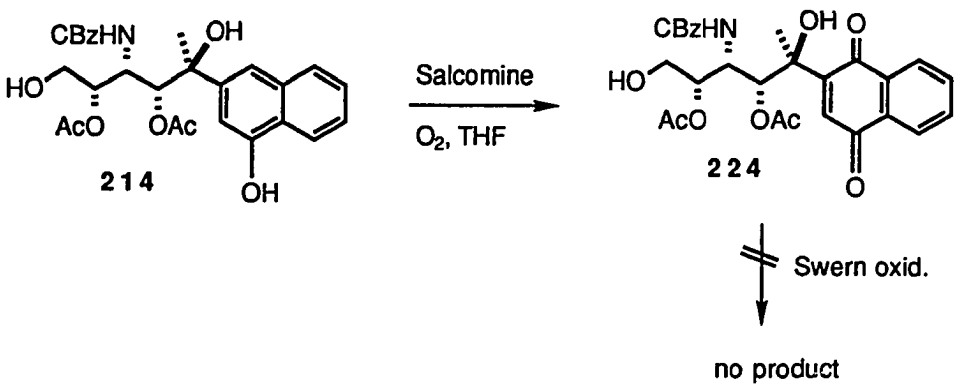
This showed that we would get sulfonium salt **223** upon Swern oxidation of alcohol **214**. **SCHEME 3.36.**

SCHEME 3.36



The other alternative was to oxidize naphthol **214** to naphthoquinone **224** followed by the Swern oxidation. **SCHEME 3.37.** Naphthoquinone **224** had been prepared[50] but the Swern oxidation failed.

SCHEME 3.37

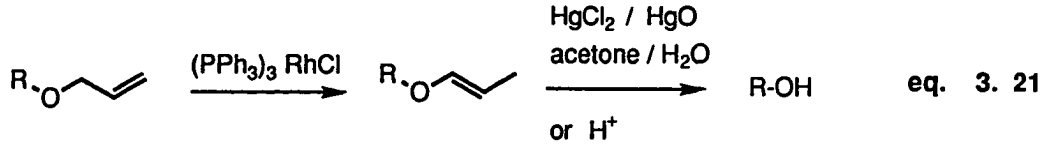


Other oxidation methods, such as Dess-Martin oxidation[104], pyridinium dichlorochromate (PDC) were tried but the reaction failed. We found that Swern oxidation was the best method for our system.

3.7. Deprotection of Allyl Group.

The most common way of selective cleavage of allyl ether to alcohol under mild conditions is the method using tris(triphenylphosphine)rhodium(I) chloride catalyst,

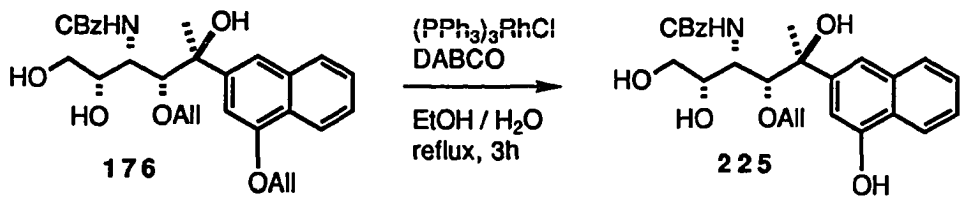
$(PPh_3)_3RhCl$.[105] Rhodium complex catalyzes the isomerization of allyl ether to 1-propenyl ether and the resulting 1-propenyl ether is hydrolyzed with mercuric chloride ($HgCl_2$) and mercuric oxide (HgO) in aqueous acetone to obtain an alcohol.[106] An acid hydrolysis of 1-propenyl ether also produces a free alcohol, as vinyl ethers are very sensitive to acid.[107] **eq. 3.21.**



However the deallylation of methylthiomethyl glycoside **189** with $(PPh_3)_3RhCl$ did not take place. We assumed that the thio-group in glycoside **189** poisoned the catalyst and the reaction did not occur. We tried the deallylation of analogous naphthyl allyl ethers. We noticed that naphthyl allyl ether gave naphthol directly before treating with $HgCl_2$/ HgO or acid. A catalytic amount (0.2 equiv.) of $(PPh_3)_3RhCl$ gave incomplete deallylation. Therefore, approximately half an equivalent of catalyst was used. A solution of bis-allyl ether **176** and 1,4-diazabicyclo[2.2.2]octane (Dabco, 0.5 equiv.) in ethanol (5% water) was refluxed for 10min before $(PPh_3)_3RhCl$ (1 equiv.) was added. Then the reaction mixture was refluxed for 3h. The mixture was cooled to room temperature, filtered to remove catalyst, diluted with toluene and evaporated *in vacuo* to dryness. The products were purified by PLC (5% MeOH/ CH_2Cl_2). About 50% of naphthol

225, and 25% of unknown product were observed. **SCHEME 3.38**.

SCHEME 3.38



+ unknown **226**

From the ^{1}H NMR of naphthol **225**, we found that only allyl ether of naphthalene was cleaved and allyl ether of C-3 remained. The signal at δ 5.81-5.13 (m, 1H, $OCH_2\underline{CH}=CH_2$) and 5.19-5.08 (m, 2H, $OCH_2CH=\underline{CH_2}$) were indicative of the secondary allyloxy at C-3. There was no signal for the allyl ether of naphthalene. On the other hand, we assumed that the minor product was 1-propenyl ether. But this product did not yield any naphthol **211** after treating with $HgCl_2/HgO$. However, the cleavage of allyl ether with rhodium catalyst was not reproducible.

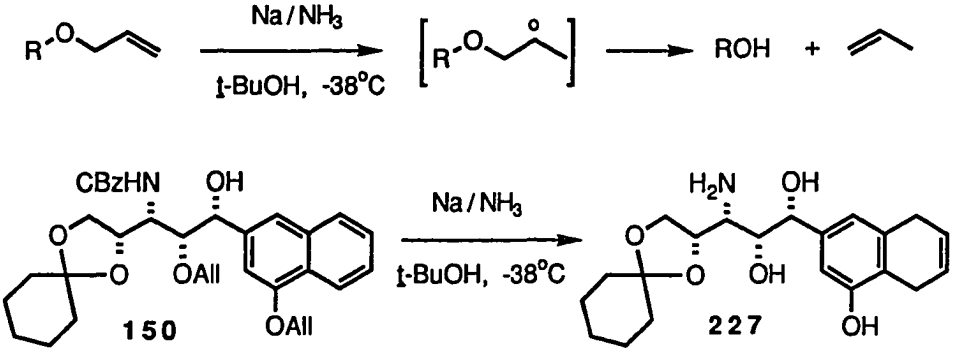
The deprotection of allyl ether, containing an acid labile group, could be done with potassium *t*-butoxide with DMSO at 100°C to isomerize the double bond of allyl to 1-propenyl ether.[108] This method is used especially in carbohydrate chemistry.[109] The reaction condition seemed to be very drastic for our bis-allyl ether **176**, no product could be detected at the end of reflux period.

The combination of palladium-carbon with *p*-toluenesulfonic acid in aqueous ethanol to cleavage bis-allyl ether **176** did not give a satisfactory result.[110]

Deallylation was tried with iridium complex, 1,5-cyclooctadiene-bis[methyldiphenylphosphine]-iridium hexafluorophosphate, $\{Ir(COD)[PCH_3(C_6H_5)_2]_2\}PF_6$, in THF under hydrogen atmosphere.[111] Only the starting material was observed at the end of the reaction.

Reductive cleavage of allyl ether to alcohol by using Na/NH_3 (Birch's reduction) was tried with bis-allyl ether **150**. **SCHEME 3.39.**

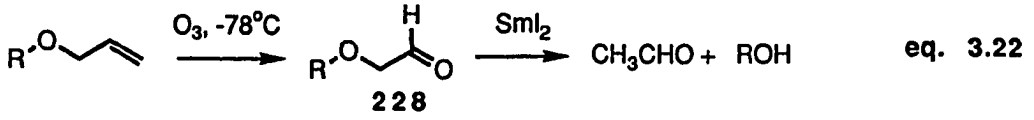
SCHEME 3.39



The reduction of naphthalene was observed in this reaction. The allyl groups were deprotected in the reaction condition to naphthol and it was further reduced by Na/NH_3 to 5,6,7,8-tetrahydro-1-naphthol **227**.

The other method we planned for deallylation was by ozonolysis, and then followed by samarium diiodide reduction.[112] The double bond of allyl would oxidize to

aldehyde by ozonolysis and the product α-alkoxy aldehyde **228** would cleave to alcohol when treated with SmI_2. **eq. 3.22.**

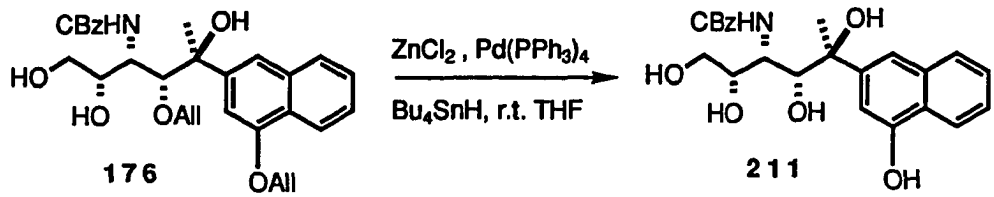


228 **eq. 3.22**

The model compound, 2-allyloxy naphthalene was prepared and ozonolysis was done at -78°C in dichloromethane. The only characterisible product observed at the end of the reaction was phthalaldehyde. The reaction was hard to control and over oxidation yielded the observed product.

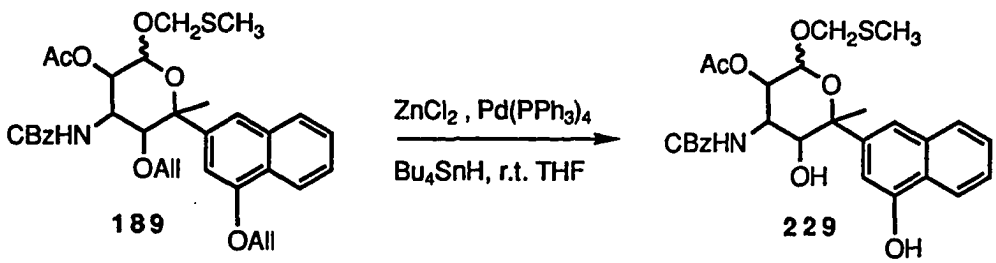
Finally, the bis-allyl ether **176** was cleaved to alcohol **211** by palladium-catalyzed tributyltin hydride reduction.[113, 114]. Tetrakis(triphenylphosphine)palladium[0], [$(PPh_3)_4Pd$, 0.02 equiv.] was added into the oxygen free THF solution of bis-allyl ether **176** and dry zinc chloride (2.5 equiv.) and stirred at room temperature for 5min under nitrogen atmosphere. Tributyltin hydride (4 equiv.) was added dropwise to the above solution and the solution was continuously stirred for 15 min. The reaction was quenched with 5% HCl solution and after usual workup and purification, it yielded 90% of naphthol **211**. **SCHEME 3.40.**

SCHEME 3.40



Allyl ether groups in methylthiomethyl glycoside **189** were deblocked by applying this Pd[0]-Bu_3SnH method. It produced naphthol **229** in 78% yield. **SCHEME 3.41.**

SCHEME 3.41



The ^1H NMR of compound **229** became cleaner in the aliphatic region and the aromatic proton pattern did not change much. There were no allyl protons signal. The naphtholic OH showed as a singlet at δ 9.9 and secondary OH showed as doublet at δ 2.74. The doublet of methine proton of secondary allyoxy (H-3) shifted from δ 5.61 to δ 4.00 as secondary alcohol methine triplet.

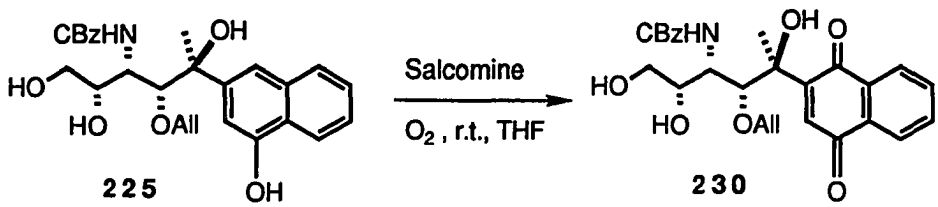
3.8. Construction of E-ring.(Toward Target Molecule).

3.8.1. Oxidation of Naphthol to Naphthoquinone.

Naphthoquinones are prepared from naphthol by Fremy's

salt or by Salcomine-O_2 oxidation.[50] Naphthol **225** was dissolved in dry THF with Salcomine (0.5 equiv.) and oxygen gas was bubbled to the solution for 90min. Then the solution was passed through a short column of Florisil in order to remove Salcomine and the eluent was concentrated to yield naphthoquinone **230**. **SCHEME 3.42.**

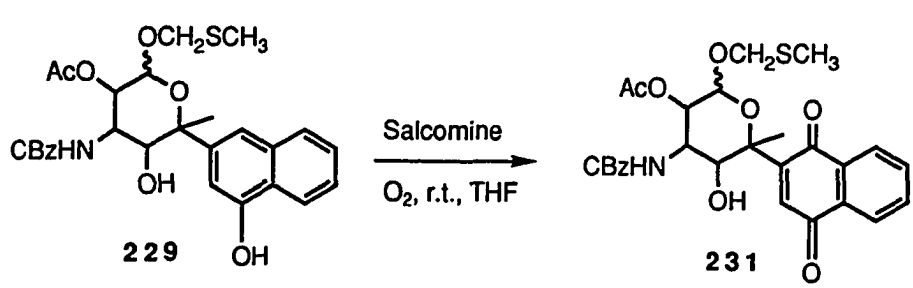
SCHEME 3.42



The starting naphthol **225** could not purified. It was difficult to remove all the rhodium complex catalyst. Therefore the ^1H NMR of the products were broad and we could not find the exact δ values and coupling constant J values for naphthol **225** and naphthoquinone **230**.

Naphthol **229** was easily oxidized to naphthoquinone **231** by the same procedure. **SCHEME 3.43.**

SCHEME 3.43



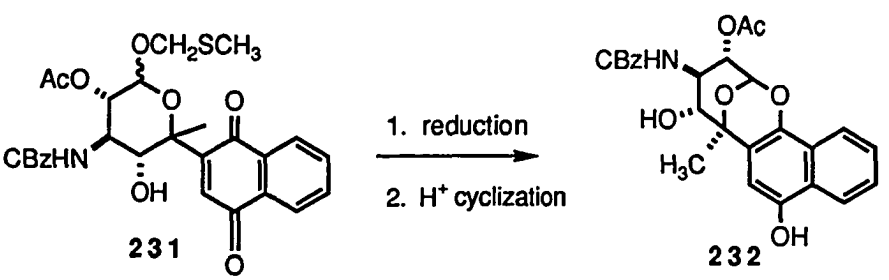
The proton signals in the aromatic region were

significant for the formation of naphthoquinone. There were only ten proton signals in aromatic region. The naphtholic OH and H-4 signal disappeared and naphthalene protons H-5 and H-8 appeared as multiplet at δ 8.13-8.08, H-6 and H-7 appeared as multiplet at 7.81-7.76 and H-3 as singlet at 7.24. The strong carbonyl stretching frequency was observed at 1675 cm^{-1} in IR spectrum. The ^{13}C NMR showed a carbonyl peak at δ 183.93.

3.8.2. Reduction of naphthoquinone and acid cyclization to ring E.

The final step of our synthesis was to reduce the naphthoquinone **231** to naphthohydroquinone **232** and construct the E-ring by acid catalyzed cyclization.

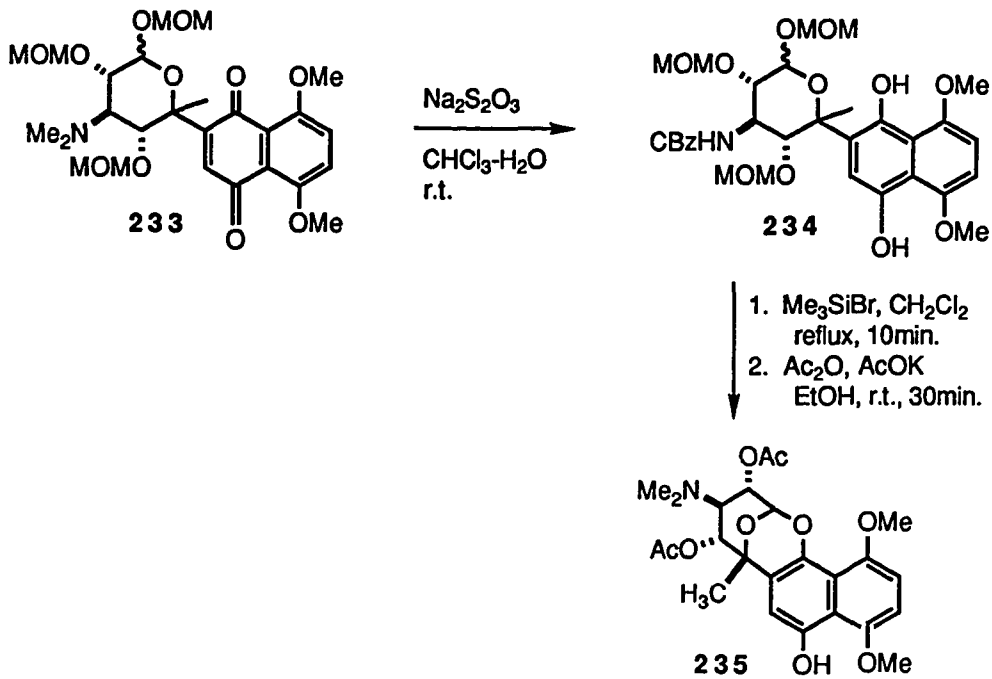
SCHEME 3.44



In the synthesis of CDEF-rings of nogalamycin by Terashima et al.[21], the naphthoquinone **233**, which is similar to our quinone **231**, was reduced to naphthohydroquinone by treating with $Na_2S_2O_3$ in $CHCl_3$-H_2O. The naphthohydroquinone so obtained was refluxed with trimethylsilyl bromide in dichloromethane and the resulting bicyclic acetal was

acetylated. **SCHEME 3.45.**

SCHEME 3.45



We treated our naphthoquinone **231** with $Na_2S_2O_3$ in $CHCl_3$-H_2O for 90 min and the chloroform layer was washed with water (under nitrogen atmosphere) and concentrated. The concentrate was dissolved in dichloromethane with a catalytic amount of p-toluenesulfonic acid and stirred at room temperature for 2h. The product isolated was not the bicyclic acetyl as expected. The ^1H NMR analysis showed that the proton chemical shifts were different from reference data. The homonueclear COSY NMR analysis showed that there were four sets of proton coupled to each other. The ^1H at δ 5.00 & 4.46, 4.70 & 4.58, 3.92 & 3.80 and 3.28 & 2.89 were

coupled to each other. We could not characterize the product.

Methyl alcohol was used in the acid catalyzed cyclization reaction. But no characterizable product was detected.

3.9. Conclusion.

In conclusion, our studies showed that the main frame with certain appropriate key features of the DEF-rings of nogalamycin can be prepared by using the two cycloaddition reactions, i.e. nitrile oxide dipolar cycloaddition and Bradsher cycloaddition reactions. The desired nitrile oxide is easily prepared in three steps from commercially available D-mannitol. The pressure assisted Bradsher cycloaddition reaction, using 5-nitroisoquinoline as soluble base, is the new achievement in the field of Bradsher cycloaddition studies.

As for the stereochemical strategies:- (1) the reduction of isoxazoline with LAH yields the syn γ-amino alcohol with the stereochemistry as we predicted, (2) the non-face selective chiral nitrile oxide dipolar cycloaddition to furan yields two diastereoisomers of furoisoxazoline in 1:1 ratio. The difficulty in the separation of the diastereoisomers led us to carry the mixture of diastereoisomers in Bradsher cycloaddition reaction which was separated only after a naphthol **123** is formed. The naphthol

123' which has (4R)-4-hydroxy isoxazole is easily converted to (4S)-4-hydroxy isoxazole (the desired stereochemistry) by Mitsunobu reaction. However, the LAH reaction of this isoxazoline was not as stereoselective as before.

The methyl Grignard addition to α-alkyloxy ketone **153** affords the chelation controls product **169'**. We should investigate more extensively the non-chelation controlled organometallic methyl alkylating agents to obtain the desired stereoisomer **169**. Or alternately, we must find an organometallic reagent that favor N-Metal-O chelation over O-Metal-O bonding.

The final step, the reduction of naphthoquinone **233** to naphthohydroquinone followed by acid cyclization to construct E-ring failed. We believe that the problem could be solved if we had sufficient material to try the reaction with different reaction conditions, such as solvent, acid catalyst and reaction temperature. Overall the synthesis is successful because the key steps proved effective and we can formulate plans to overcome the steps that have given us problems.

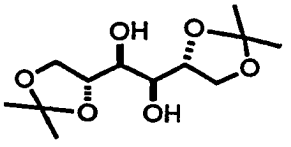
4. EXPERIMENTAL

Nuclear magnetic resonance spectra were obtained on GE QE-300 MHz instrument. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. The high-resolution mass spectra were obtained by the Mass Spectrometric Biotechnology Resource, Rockefeller University, New York. High pressure experiments were performed with a LECO TEM-Press pressure Generator (Model PG-100 HPC). Melting points were determined on a Fisher-John melting point apparatus and were uncorrected.

Thin-layer chromatograms were done on precoated TLC sheets of silica gel 60 F_{254} (E. Merck) with use of (2,4-dinitrophenylhydrazine spray, potassium permanganate spray, ninhydrin spray, phosphomolybdic acid and / or short-and longwave ultraviolet light to visualize the spots. PLC plates were prepared by using Kieselgel 60 PF_{254} (E. Merck). Chromatotron (radial chromatography) plates were prepared by using Kieselgel 60 PF_{254} gipshaltig (E. Merck) and all separations using the chromatotron were done under nitrogen atmosphere.

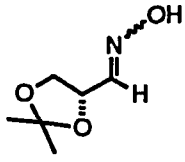
Chemicals used were purchased from Aldrich Chemical Co. All solvents used were purified and dried by using standard procedures.

4.1. Preparation of 1,2:5,6-di-O-isopropylidene-D-mannitol.



Anhydrous zinc chloride (30g, 220mmol) was dissolved in 150ml of dry acetone and freed of insoluble zinc salt by decantation. Powdered D-mannitol (20g, 110mmol) was added into the zinc salt solution and the mixture was vigorously stirred for 4h. The filtrate was poured into a solution of potassium carbonate (40g, 290mmol) in 40ml of water covered by 100ml of ether. A white precipitate (zinc carbonate) came out. The mixture was vigorously stirred for 30min and was filtered. The solid, zinc carbonate pellets were washed with 1:1 acetone-ether mixture (50ml x 3times). All the filtrates were combined and concentrated under reduced pressure. The resulting aqueous solution was cooled to 0°C, upon which 1,2:5,6-di-O-isopropylidene-D-mannitol crystallized out. The crystals were filtered and recrystallized from chloroform/hexane. (12.76g, 45% yield). m.p. 119 - 120°C. Lit. m.p. 119°C.(65). ^{1}H NMR, 300MHz, ($CDCl_3$): δ 4.17-4.10 (m, 2H, $C\underline{H}_2$, $C\underline{H}CH_2$), 4.07-3.95 (m, 1H, CH_2), 3.72 (t, J=6.6Hz, 1H, $C\underline{H}CHCH_2$), 2.98 (d, 1H, OH), 1.42 (s, 3H, CH_3), 1.34 (s, 3H, CH_3). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 109.36, 75.97, 71.01, 66.75, 26.75, 25.22.

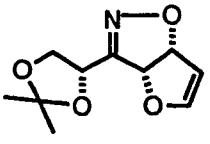
4.2. Preparation of (2R)-2,3-O-isopropylidene-D-glyceraldoxime (95).

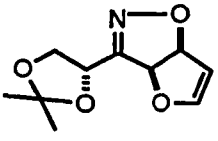


1,2:5,6-di-O-isopropylidene-D-mannitol (5g, 19mmol) was added to a cooled solution of sodium periodate (6.4g, 30mmol) in 75ml water and was stirred at room temperature for 45min. Ethyl alcohol (150ml) was poured into the above solution. This resulted in the precipitation of white sodium iodate. The mixture was stirred for 15min and filtered. (The product, D-glyceraldehyde acetonide was not isolated at this stage.) The filtrate was added slowly into 50ml of a cooled solution of hydroxylamine hydrochloride (3.4g, 48mmol) and sodium hydrogen carbonate (5.2g, 62mmol). Ethyl alcohol was evaporated under reduced pressure and the aqueous solution was extracted with dichloromethane (25ml x 3 times). All the organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The product, (2R)-2,3-O-isopropylidene-D-glyceraldoxime was used without any further purification. (3.59g, 65% yield). b.p.: 60°C / 0.1mm. Lit. b.p.: 80°C / 0.5mm. ^{1}H NMR, 300MHz, ($CDCl_3$): Mixture of cis and trans isomers, δ 9.20 (s, 1H, OH), 8.88 (s, 1H, OH), 7.45 (d, J=4.1Hz, 1H, C<u>H</u>=NOH), 6.95 (d, J=4.3Hz, 1H, C<u>H</u>=NOH), 5.12 (m,

1H, CH_2CHCH), 4.70-4.62 (q, J=6.5Hz, 1H, CH_2CHCH), 4.40-4.34 (dd, J=7.1, 8.5Hz, 1H, CH_2CH), 4.21-4.15 (dd, J=6.5, 8.6Hz, 1H, CH_2CH), 3.90-3.85 (dd, J=6.3, 8.6Hz, 1H, CH_2CH), 3.84-3.78 (dd, J=6.7, 8.5Hz, 1H, CH_2CH), 1.43 (s, 6H, $2CH_3$), 1.41 (s, 6H, $2CH_3$); ^{13}C NMR, 75Mz, ($CDCl_3$): δ 154.52, 150.09, 73.31, 71.02, 67.98, 68.01, 37.43, 37.11, 36.36, 36.19, 24.85, 23.34.

4.3. Preparation of (3aR,6aR)-3-[(5S)-2,2-dimethyl-1,3-dioxolan-5-yl]-3a,6a-dihydro-furo(2,3-d) isoxazole (97) and (3aS,6aS)-3-[(5S)-2,2-dimethyl-1,3-dioxolan-5-yl]-3a,6a-dihydro-furo(2,3-d) isoxazole (97').



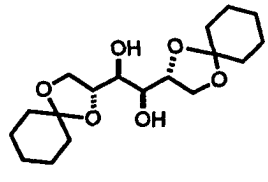


(2R)-2,3-O-isopropylidene-D-glyceraldoxime **95** (2.44g, 16.82mmol) was added into a suspension of N-chlorosuccinimide (2.4g, 17.6mmol) in chloroform (10ml) and a catalytic amount of pyridine (0.05ml). The mixture was stirred for 15min. The completion of chlorination was observed by the disappearance of the suspended N-chlorosuccinimide. The solution turned bright blue.

The above solution was added into a refluxing solution of triethylamine (1.75g, 17.3mmol) in 350ml of furan within 18h by using a syringe pump. The solution was refluxed for an additional 5h. Then most of the furan was removed by

distillation and the remainder was concentrated under reduced pressure. The concentrate was diluted with ethyl acetate (25ml) and washed with water. The aqueous layer was extracted with ethyl acetate (25ml x 3 times). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The product was purified by column chromatography. (Silica gel, 2-10% ethyl acetate/ petroleum ether, 2.4g, 66% yield). The two isomers were not separable. ^{1}H NMR, 300MHz, ($CDCl_3$): Mixture of two diastereoisomers, δ 6.62 (m, 2H, H-5, H-5'), 5.99-5.84 (m, 4H, H-3a, H-3a', H-6a, H-6a'), 5.34-5.31 (m, 2H, H-6, H-6'), 5.10 (t, J=6.9Hz, 1H, H-5 dioxo), 4.92 (t, J=6.2Hz, 1H, H-5' dioxo), 4.30-4.27 (d, J=6.2Hz, 2H, H-4' dioxo), 4.25-4.13 (m, 2H, H-4 dioxo), 1.52 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.44 (s, 6H, $2CH_3$). **Note**: Furoxan 108 was isolated in about 15% yield. ^{1}H NMR, 300MHz, ($CDCl_3$): δ 5.33-5.22 (m, 1H, H-3), 4.44-4.24 (m, 2H, H-1, H-2), 1.6-1.42 (m, 6H, $2CH_3$).

4.4. Preparation of 1,2:5,6-di-O-cyclohexylidene-D-mannitol.

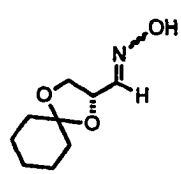


A mixture of D-mannitol (9g, 49.45mmol), cyclohexanone (15ml, 157.5mmol), triethyl orthoformate (5.4ml 50mmol),

boron trifloride etherate (0.5ml, 4mmol) and dry dimethyl sulfoxide (20ml) was stirred for 10h at room temperature. The mixture was then poured into 50ml of 10% ice cooled sodium hydrogen carbonate solution and was extracted with ether (25ml x 3 times). All the organic layers were combined, washed with brine, dried with anhydrous sodium hydrogen sulfate and concentrated on a rotary evaporator. Most of the excess cyclohexanone was removed *in vacuo*. After addition of hexane to the concentrate, a nice white solid, which was 1,2:5,6-di-O-cyclohexylidene-D-mannitol, crystallized out.

The crystals were filtered, washed with hexane and dried *in vacuo*. The product was used for further reaction without any purification. (5g, 56% yield). mp. 104-105°C, Lit. mp. 105-106°C. IR ($CHCl_3$): 3500, 2940, 2860, 1450, 1370, 1090, 920 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 4.18 (dd, J=6.1, 12.0Hz, 2H, H-1a), 4.11 (t, J=6.1, 8.3Hz, 2H, H-2), 4.00 (dd, J=5.1, 8.2Hz, 2H, H-1b), 3.75 (t, J=6.7Hz, 2H, H-3), 2.98 (d, J=6.7Hz, 2H, OH), 1.41-1.61 (br m, 20H, cyhx).

4.5. Preparation of (2R)-2,3-O-cyclohexylidene-D-glyceraldoxime (109).

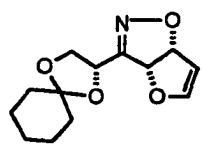


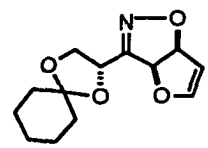
To a solution of 1,2:5,6-di-O-cyclohexylidene-D-mannitol (5.04g, 14mmol) in 50ml of ether was added a solution of sodium metaperiodate (3.64g, 17mmol) and tetrabutyl ammonium iodide (0.1g, 0.27mmol) in 30ml of water and the mixture was stirred for 4h at room temperature. The product, cyclohexylidene glyceraldehyde was obtained at this stage but was not isolated or purified at this stage. The reaction mixture was poured into an aqueous solution of hydroxylamine hydrochloride (2.35g, 41.8mmol in 50ml water) and sodium bicarbonate (3.52g, 41.8mmol) and was stirred for 4h. Glyceraldoxime was extracted with dichloromethane (50ml x 3times). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*.

The oily crude (2R)-2,3-O-cyclohexylidene-D-glyceraldoxime was sufficiently pure for further reactions. (4.6g, 89% yield). A mixture of cis and trans isomers: IR ($CHCl_3$): 3580, 3320, 2920, 2870, 1450, 1350, 1120, 930 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 9.19 (s, 1H, OH), 8.9 (s, 1H, OH), 7.44 (d, J=6.9Hz, 1H, NCH), 6.99 (d, J=4.2, 1H, NCH), 5.18-5.12 (dq, J=4.2, 6.8Hz, 1H, H-2), 4.72-4.65 (q, J=6.5Hz, 1H, H-2'), 4.42-4.37 (dd, J=7.1, 8.4Hz, 1H, H-3'), 4.23-4.18 (dd, J=6.4, 8.6Hz, 1H, H-3'), 3.94-3.90 (dd, J=6.2, 8.5Hz, 1H, H-4), 3.86-3.81 (dd, J=6.8, 8.5Hz, 1H, H-4'), 1.77-1.45 (br m, 20H, cyhx, cyhx'). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 153.02, 149.89, 110.93, 110.40, 72.84, 70.26, 67.49, 67.00, 36.15, 35.66, 34.97, 34.77, 25.02, 23.87, 23.80. MS m/e (rel%): 186.1

(12), 185.1 (36), 156.1 (18), 142.0(100), 124.00(8), 99 (15), 97 (8), 88 (10), 81 (12), 73 (15), 70 (32). Calcd. for $C_9H_{15}NO_3^{+\cdot}$: 185.1052, Found: 185.1036 (-8.5ppm).

4.6. Preparation of (3aR,6aR)-3-[(5S)-2,2-cyclohexylidene-1,3-dioxolan-5-yl]-3a,6a-dihydrofuro-(2,3-d) isoxazole (110) and its (3aS,6aS)-epimer (110').





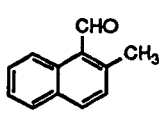
A solution of (2R)-2,3-O-cyclohexylidene-D-glyceraldoxime (3.89g, 20mmol in 10ml of chloroform) was added to a suspension of N-chlorosuccinimide (2.8g, 20.9mmol) in 10ml of dry chloroform and pyridine (0.1ml, catalytic amount) at room temperature. The completion of chlorination was observed by the disappearance of suspended N-chlorosuccinimide (about 30min). This reaction mixture was added to a refluxing solution of triethylamine (3.06ml, 22mmol) in 350ml of furan within 18h by using a syringe pump. At the end of the addition, the mixture was refluxed for another 10h. Most of the furan was removed by distillation. The remainder was poured into water (50ml) and extracted with ethyl acetate (50ml x 3 times). All the organic layers were combined, washed with brine, dried over anhydrous sodium

sulfate and concentrated *in vacuo*.

The concentrate was purified by column chromatography (1cm dia. column, 12cm silica gel, 10% ethyl acetate/ petroleum ether) to provide 3.06g of the diastereomeric mixture of product. (61% yield) b.p.: 120-122°C / 0.4mm. IR ($CHCl_3$): 2920, 2835, 1610, 1100, 900 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$) δ 6.64-6.62 (m, 2H, H-5, H-5'), 6.02-5.99 (d, J=8.8Hz, 1H, H-3a), 5.97-5.96 (d, J=8.8Hz, 1H, H-3a'), 5.92-5.88 (m, 2H, H-6a, H-6a'), 5.39-5.35 (m, 2H, H-6, H-6'), 5.16-5.11 (t, J=7.0Hz, 1H, H-5 dioxo), 4.98-4.94 (t, J=6.4Hz, 1H, H-5 dioxo'), 4.33-4.30 (m, 2H, H-4 dioxo), 4.22-4.12 (m, 2H, H-4 dioxo'), 1.81-1.46 (br m, 20H, cyhx, cyhx'). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 154.81, 149.86, 111.07, 110.87, 101.10, 88.99, 88.66, 88.11, 87.84, 87.33, 70.45, 69.93, 66.69, 66.55, 35.59, 34.78, 24.97, 23.83. MS m/e (rel%): 251.11(73), 234(8), 222(13), 208(100), 154(45), 153(86), 141(22), 137(27), 136(54), 125(9), 124(17), 123(28), 109(15), 108(73), 107(22), 100(10), 93(11), 83(12), 81(40), 78(16), 76(24), 68(81). Calcd. for $C_{13}H_{17}NO_4^{+\cdot}$: 251.1158, Found: 251.1100 (-23.1ppm).

Note: Approximately 15 % of furoxan was isolated.

4.7. Bradsher Cycloaddition of IsoQ and 3a,6a-dihydro-furo(2,3-d) isoxazole 97 & 97'.



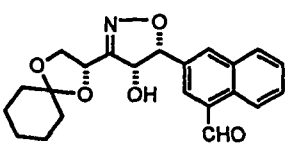
A solution of furoisoxazoline **97** & **97'** (1.08g, 5.15mmol). IsoQ salt **78** (1.7g, 5.15mmol) and anhydrous calcium carbonate (3.09g, 30.9mmol) in dry methyl alcohol (5ml) was stirred at 40°C for 6d. Then the mixture was filtered through celite and the celite was washed with dichloromethane / methyl alcohol (1:1). The filtrate was concentrated and dried *in vacuo*. Then the concentrate was dissolved in 55ml of THF / 5ml of water and was stirred at room temperature with Amberlyst-H^+-15 wet (1.7g) for 3d. The mixture was filtered, Amberlyst was washed with ethyl acetate and the filtrate was concentrated under reduced pressure. The concentrate was then extracted with ethyl acetate / water (50ml x 3 times). The organic layers were combined, washed with brine, dried with anhydrous sodium sulfate and concentrated.

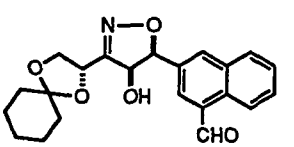
One half of the residue (1.5g) was dissolved in 3ml of THF and added to the solution of 15ml of 5% potassium carbonate in 80% aqueous methyl alcohol. The reaction mixture was warmed to 45°C in a hot water bath for 2min. Then it was poured into 15ml of ice cooled water and was extracted with ethyl acetate (50ml). The aqueous layer was saturated with sodium chloride and extracted with ethyl acetate (50ml x 2 times). All the organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, concentrated and dried *in vacuo*.

The products were purified by column chromatography.

(Silica gel, 0-5% methyl alcohol/ dichloromethane.) The products, which were isolated, are 2-methyl naphthaldehyde **111** and 2,4-dinitroaniline. (The yields were not calculated.) ^1H NMR, 300MHz, ($CDCl_3$): (**2-methyl naphthaldehyde**) δ 11.01 (s, 1H, CHO), 9.02 (d, 1H, H-8), 7.95 (d, 1H, H-4), 7.88 (d, 1H, H-5), 7.68 (t, 1H, H-7), 7.55 (t, 1H, H-6), 7.40 (d, 1H, H-3), 2.86 (s, 3H, CH_3).

4.8. Preparation of 3-{(4R,5R)-[3-(5S)-2,2-cyclohexylidene-1,3-dioxolan-5-yl]-[4-hydroxy]-4,5-dihydroisoxazolin-5-yl}-1-naphthaldehyde (118) and its (4S,5S)-epimer (118').





N-2,4-dinitrophenyl isoquinolinium chloride salt **78** (1.74g, 5.23mmol), 5-nitroisoquinoline (1.35g, 7.7mmol) and furoisoxazoline **110 & 110'** (1.3g, 5.18mmol) were dissolved in 5ml of dry methyl alcohol. The solution was transferred into a 10ml plastic syringe and placed in the high pressure apparatus to subject it to 6KBar pressure for 3d. The precipitate, 5-nitroisoquinolium chloride salt, was filtered and washed with dichloromethane. The filtrate, which contained cycloadduct, was concentrated and dried *in vacuo*.

Then the concentrate was dissolved in 50ml of tetrahydrofuran / 3ml of water and magnetically stirred with

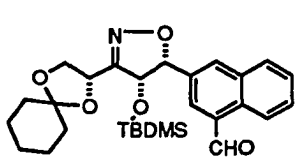
Amberlyst-H^+-15 wet (2.1g) for 10h. The mixture was filtered and most of the tetrahydrofuran was removed on the rotary evaporator. The concentrate was then dissolved in water (50ml) and extracted with ethyl acetate (30ml x 3 times). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*.

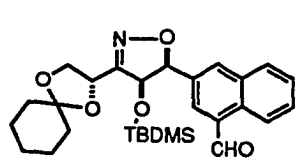
The residue was dissolved in a small amount of tetrahydrofuran (4ml) and was added to the solution of 50ml of 5% potassium carbonate in 80% aqueous methyl alcohol. The reaction mixture was warmed to 45°C in a hot water bath for 2min. Then it was poured into 25ml of ice cooled water and was extracted with ethyl acetate (50ml). The aqueous layer was saturated with sodium chloride and extracted with ethyl acetate (50ml x 2 times). All the organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, concentrated and dried *in vacuo*.

The product naphthaldehyde was purified by radial chromatography. (Silica gel, 0.3% methyl alcohol/ dichloromethane, 1.18g, 60% yield). Two diastereoisomers were not separable. Pure isomers were separated by partial separation for analysis. IR ($CHCl_3$): 3430, 2910, 2830, 1690, 1110, 890 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): **Isomer A;** δ 10.41 (s, 1H, CHO), 9.22 (d, J=8.6Hz, 1H, H-8 Np), 8.14 (s, 1H, H-4 Np), 8.01 (d, J=1.7Hz, 1H, H-2 Np), 7.98 (d, J=8.5Hz, 1H, H-5 Np), 7.71 (dt, J=1.3, 7.0Hz, 1H, H-6 Np), 7.61 (dt, J=1.1, 7.0Hz, 1H, H-7 Np), 5.61 (d, J=7.4Hz, 1H, H-5 isoxo),

5.34 (dd, J=4.0, 7.4Hz, 1H, H-4 isoxo), 5.15 (t, J=6.0Hz, 1H, H-5 dioxo), 4.32 (d, J=6.0Hz, 2H, H-4 dioxo), 2.52 (d, J=4.0Hz, 1H, OH), 1.74-1.41 (br m, 10H, cyhx). ^{1}H NMR, 300MHz, ($CDCl_3$): **Isomer B;** δ 10.35 (s, 1H, CHO), 9.17 (d, J=8.5Hz, 1H, H-8 Np), 8.12 (s, 1H, H-4, Np), 8.01 (d, J=1.7Hz, 1H, H-2 Np), 7.90 (d, J=8.1Hz, 1H, H-5 Np), 7.68 (dt, J=1.4, 7.0, 8.5Hz, 1H, H-6 Np), 7.58 (dt, J=1.1, 7.0, 8.0Hz, 1H, H-7 Np), 5.54 (d, J=7.2Hz, 1H, H-5 isoxo), 5.28 (d, J=7.2Hz, 1H, H-4 isoxo), 5.17 (t, J=6.3Hz, 1H, H-5 dioxo), 4.34 (dd, J=6.7, 8.7Hz, 1H, H-4 dioxo), 4.20 (dd, J=6.1, 8.7Hz, 1H, H-4 dioxo), 3.02 (br s, 1H, OH), 1.75-1.39 (br m, 10H, cyhx). ^{13}C NMR, 75Mz, ($CDCl_3$): **mixture of two isomers;** δ 193.56, 193.37, 159.27, 159.08, 152.83, 146.30, 136.50, 136.29, 134.46, 133.46, 131.18, 130.30, 129.45, 128.65, 127.38, 124.78, 124.69, 111.47, 111.26, 86.11, 85.92, 71.04, 70.40, 67.16, 67.03, 35.95, 35.85, 34.55, 25.00, 24.03, 23.78. MS : Calcd. for $C_{22}H_{23}NO_5$: 381.1576, Found: 381.1814.

4.9. Preparation of 3-{(4R,5R)-[4-*tert*butyldimethylsilyloxy]-[3-(5S)-2,2-cyclohexylidene-1,3-dioxolan-5-yl]-4,5-dihydro-isoxazolin-5-yl}-1-naphthaldehyde (119) and its (4S,5S)-epimer (119').





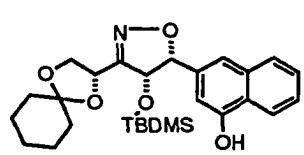
The mixture of 1-naphthaldehyde **118 & 118'** (1.00g, 2.61mmol) in 1ml of dichloromethane was added dropwise to a solution of *tert*-butyldimethylsilyl chloride (0.69g, 4.57mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.1ml, 7.3mmol) in 25ml of dry dichloromethane and the mixture was stirred at room temperature for 5h. The reaction was quenched with water and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*.

The two diastereoisomers of silyl ethers were purified and separated by radial chromatography. (Silica gel, 10% ethyl acetate/ petroleum ether). (Isomer A 0.59g, isomer B 0.58g, 91% total yield). **Isomer A** mp. 187-188°C. IR ($CHCl_3$): 2900, 2825, 1680, 1250, 1100, 890, 830, 690 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 10.37 (s, 1H, CHO), 9.27 (d, J=8.5Hz, 1H, H-8 Np), 8.06 (s, 1H, H-4 Np), 8.00 (s, 1H, H-2 Np), 7.92 (d, J=8.2Hz, 1H, H-1, H-5 Np), 7.72 (dd, J=7.0, 8.4Hz, 1H, H-7 Np), 7.60 (dd , J=7.0, 8.1Hz, 1H, H-6 Np), 5.43 (d, J=7.1Hz, 1H, H-5 isoxo), 5.26 (d, J=7.1Hz, 1H, H-4 isoxo), 4.92 (t, J=6.0, 6.1Hz, 1H, H-5 dioxo), 4.50 (dd, J=6.4, 8.4Hz, 1H, H-4 dioxo), 4.36 (dd, J=6.2, 8.4Hz, 1H, H-4 dioxo), 1.73-1.42 (br m, 10H, cyhx), 0.56 (s, 9H, *t*BuSi), 0.00 (s, 3H, $SiCH_3$), -0.57 (s, 3H, $SiCH_3$). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 193.40, 159.32, 137.71, 135.30, 133.41, 129.48, 128.48, 127.34, 124.97, 124.90, 110.67, 86.19, 77.05, 69.45,

66.28, 36.22, 35.20, 25.39, 25.27, 25.15, 24.09, 23.89,-5.15, -5.18.

^{1}H NMR, 300MHz, ($CDCl_3$): **Isomer B**, δ 10.38 (s, 1H, CHO), 9.24 (d, J=8.5Hz, 1H, H-8 Np), 8.07 (s, 1H, H-4 Np), 8.02 (d, J=1.5Hz, 1H, H-2 Np), 7.90 (d, J=8.2Hz, 1H, H-1,H-5 Np), 7.72 (ddd, J=1.2, 7.0, 8.4Hz, 1H, H-7 Np), 7.62 (ddd, J=0.8, 7.0, 8.0Hz, 1H, H-6 Np), 5.44 (d, J=7.0Hz, 1H, H-5 isoxo), 5.15 (d, J=7.0Hz, 1H, H-4 isoxo), 5.09 (t, J=7.0Hz, 1H, H-5 dioxo), 4.29-4.18 (m, 2H, 2H-4 dioxo), 1.84-1.45 (br m, 10H, cyhx), 0.63 (s, 9H, tBuSi), 0.03 (s, 3H, $SiCH_3$), -0.85 (s, 3H, $SiCH_3$). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 193.30, 158.49, 137.91, 135.82, 133.34, 131.08, 130.38, 129.94, 129.53, 128.53, 127.33, 124.92, 111.19, 86.96, 77.14, 70.85, 66.64, 35.84, 34.63, 25.54, 25.14, 23.99, 23.80, 17.69,-4.79, -5.04.

4.10. Preparation of 3-{[4-tertbutyldimethyl-silyloxy]-[3-(5S)-2,2-cyclohexylidene-1,3-dioxolan-5-yl]-4,5-dihydro- isoxazolin-5-yl}-1-naphthol (120).



To a solution of 1-naphthaldehyde **119** (isomer A) (0.52g, 1.05mmol) in 25ml of anhydrous dichloromethane, was added a solid m-chloroperbenzoic acid (0.55g, 3.15mmol) and the solution was stirred at room temperature under a nitrogen

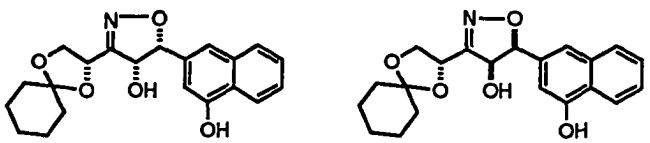
atmosphere for 24h. After addition of 10% aqueous sodium sulfite solution, the water layer was extracted with dichloromethane. All the organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo.

The formate so obtained was dissolved in anhydrous dichloromethane (25ml). Neutral alumina (2.5g, activity 1) was added to the solution and the suspension was stirred for 24h at room temperature. The mixture was filtered. Alumina was washed thoroughly with dichloromethane-methyl alcohol (1:1) (25ml x 3 times) and the combined filtrate was concentrated under reduced pressure.

The purification of the concentrate by radial chromatography yielded the desired naphthol. (0.40g, 80% yield). **Isomer A:** IR ($CHCl_3$): 3550, 2910, 2830, 1600, 1585, 1400, 1260, 1230, 1110, 840, 690 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.25 (m, 1H, H-8 Np), 7.78 (m, 1H, H-5 Np), 7.50 (m, 2H, H-6, H-7 Np), 7.38 (s, 1H, H-4 Np), 6.99 (s, 1H, H-2 Np), 5.32 (d, J=6.8Hz, 1H, H-5 isoxo), 5.20 (d, J=6.8Hz, 1H, H-4 isoxo), 4.97 (t, J=6.1Hz, 1H, H-5 dioxo), 4.51 (dd, J=6.1, 8.4Hz, 1H, H-4 dioxo), 4.38 (dd, J=6.2, 8.4Hz, 1H, H-4 dioxo), 3.5 (s, 1H, OH), 1.71-1.48 (m, 10H, cyhx), 0.68 (s, 9H, *t*BuSi), 0.00 (s, 3H, $SiCH_3$), -0.56 (s, 3H, $SiCH_3$). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 159.82, 152.12, 134.11, 130.61, 127.45, 126.51, 125.30, 122.08, 120.21, 110.70, 109.24, 87.28, 78.20, 69.57, 66.31, 36.16, 35.18, 25.39, 25.10,

24.03, 23.85, -5.39, -5.48. **Note**: Assuming **isomer A** had the assigned 4R,5R- stereochemistry.

4.11. Preparation of 3-{(4R,5R)-[3-(5S)-2,2-cyclohexylidene -1,3-dioxolan-5-yl]-[4-hydroxy]-4,5-dihydroisoxazolin -5-yl}-naphthol (121) and its (4S,5S)-epimer (121').

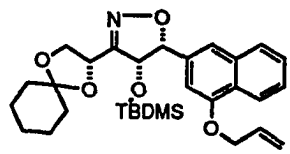


To a solution of naphthaldehyde **118 & 118'** (2.8g, 5.66mmol) in anhydrous dichloromethane (60ml) was added m-chloroperbenzoic acid (1.95g, 11.31mmol). The solution was stirred at room temperature under nitrogen for 24h. Then 10% aqueous sodium sulfite solution (25ml) was added to destroy the excess m-chloroperbenzoic acid. The aqueous layer was extracted with dichloromethane (25ml x 3 times). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The formate so obtained was dissolved in anhydrous dichloromethane (60ml) with 10g of neutral alumina (activity 1) and was stirred for 24h. Then the mixture was filtered. The alumina was stirred with dichloromethane-methyl alcohol (1:1) (30ml x 3 times, 15min each) and filtered. The filtrates were combined and concentrated under reduced pressure. One isomer of naphthol was separated by

crystallization from the above concentrate with dichloromethane. The soluble isomer was purified by radial chromatography (Silica gel, 0 - 10% methyl alcohol/ dichloromethane. (1.78g, 85% total yield). **(4R,5R)-isomer (121):** mp.: 220°C. IR ($CHCl_3$): 3340, 2960, 2890, 1690, 1600, 1590, 1410, 1140, 920 cm^{-1}. ^1H NMR, 300MHz, (CD_3COCD_3): δ 8.22 (m, 1H, H-8 Np), 7.81 (m, 1H, H-5 Np), 7.51-7.43 (m, 3H, H-4, H-6, H-7 Np), 6.99 (d, J=1.2Hz, 1H, H-2 Np), 5.35 (d, J=7.0Hz, 1H, H-5 isoxo), 5.24 (d, J=7.0Hz, 1H, H-4 isoxo), 5.05 (t, J=7.0Hz, 1H, H-5 dioxo), 4.32-4.19 (m, 2H, 2H-4 dioxo), 3.01 (br s, 2H, 2-OH), 1.75-1.39 (m, 10H, cyhx). ^{13}C NMR, 75Mz, (CD_3COCD_3): δ 127.44, 126.18, 124.64, 121.92, 118.43, 108.25, 87.11, 75.58, 71.26, 66.54, 35.48, 34.95, 24.87, 23.72, 23.64. MS m/e (rel%) 369.1500(36), 286(6), 202(21), 171(100), 143(46), 124(77), 115(32), 89(23). Calcd. for $C_{21}H_{23}NO_5^{+\cdot}$: 369.1576, Found: 369.1500 (-20.6ppm).

(4S,5S)-isomer (121'): mp. 146-147°C. ^1H NMR, 300MHz, (CD_3COCD_3): δ 8.21 (m, 1H, H-8 Np), 7.81 (m, 1H, H-5 Np), 7.49-7.43 (m, 3H, H-4, H-6, H-7 Np), 6.98 (d, J=1.2Hz, 1H, H-2 Np), 5.36 (d, J=7.2Hz, 1H, H-5 isoxo), 5.25 (d, J=7.3Hz, 1H, H-4 isoxo), 5.03 (t, J=6.0Hz, 1H, H-5 dioxo), 4.35 (dd, J=5.6, 8.2Hz, 1H, H-4 dioxo), 4.25 (dd, J=6.5, 8.2Hz, 1H, H-4 dioxo), 3.01 (br s, 1H, OH), 1.64-1.40 (m, 10H, cyhx). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 127.44, 126.17, 124.64, 121.93, 118.43, 108.31, 86.59, 76.69, 69.98, 66.08, 35.85, 34.90, 24.85, 23.71, 23.62.

4.12. Preparation of 1-(allyloxy)-3-{(4R,5R)-[4-*tert*butyldimethylsilyloxy]-[3-(5S)-2,2-cyclohexylidene-1,3-dioxolan-5-yl]-4,5-dihydro-isoxazolin-5-yl}-naphthalene (122).

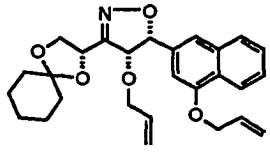


To a suspension of potassium hydride (0.13g, 1.2mmol) in tetrahydrofuran (2ml) was added a solution of naphthol **120 (isomer A)** (0.45g, 0.94mmol in tetrahydrofuran) at 0°C. The reaction mixture was stirred for 5min and allyl bromide (0.1ml, 1.2mmol) was added dropwise. The mixture was stirred for an additional 30min. After hydrolysis of the mixture at 0°C, the aqueous layer was extracted with ethyl acetate (25ml x 3 times). Ethyl acetate layers were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*.

The product allyloxy naphthol **122** was purified by radial chromatography. (Silica gel, 0 -2 % methyl alcohol/ dichloromethane, 0.40g, 82% yield). **Isomer A**, ^{1}H NMR, 300MHz, ($CDCl_3$): δ 8.31 (m, 1H, H-8 Np), 7.80 (m, 1H, H-5 Np), 7.52 (m, 2H, H-6, H-7 Np), 7.40 (s, 1H, H-4 Np), 6.82 (s, 1H, H-2 Np), 6.21 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.55 (dd, J=1.9, 17.3Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.35 (dd, J=1.3, 12.1Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.32 (d, J=7.2Hz, 1H, H-4 isoxo), 5.21 (d, J=7.1Hz, 1H, H-5 isoxo), 4.95 (m, 1H, H-5 dioxo), 4.73 (d, J=5.2Hz, 2H,

$OCH_2CH=CH_2$), 4.50 (dd, J=6.2, 8.3Hz, 1H, H-4 dioxo), 4.36 (dd, J=6.2, 8.3Hz, 1H, H-4 dioxo), 1.73-1.44 (br m, 10H, cyhx), 0.61 (s, 9H, *t*BuSi), -0.01 (s, 3H, $SiCH_3$), -0.50 (s, 3H, $SiCH_3$). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 159.35, 154.11, 136.94, 133.88, 133.22, 133.76, 128.38, 127.41, 126.64, 125.50, 122.12, 120.83, 117.46, 110.53, 105.85, 87.38, 78.21, 69.56, 69.03, 66.16, 36.18, 35.23, 25.36, 25.26, 25.14, 24.04, 23.86, -5.25, -5.45.

4.13. Preparation of 1-(allyloxy)-3-{(4R,5R)-[4-allyloxy]-[3-(5S)-2,2-cyclohexylidene-1,3-dioxolan-5-yl]-4,5-dihydroisoxazolin-5-yl}-naphthalene (123).

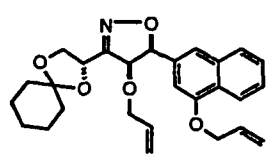


A mixture of naphthol **121** (1.78g, 4.84mmol), allyl bromide (4.2g, 48.3mmol) and 40% potassium fluoride-alumina (7.01g, ca. 48mmol KF) in 25ml of acetonitrile was magnetically stirred at room temperature for 24h. The solid material was filtered and washed with dichloromethane and the filtrate was concentrated.

Purification by radial chromatography yielded 1.73g of the desired product. (Silica gel, 0 - 4% methyl alcohol/ dichloromethane, 80% yield). IR ($CHCl_3$): 2980, 2870, 1610, 1590, 1410, 1280, 1115, 915 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.32 (m, 1H, H-8 Np), 7.82 (m, 1H, H-5 Np), 7.54-7.48 (m, 3H,

H-4, H-6, H-7 Np), 6.93 (s, 1H, H-2 Np), 6.23-6.13 (m, 1H, $NpOCH_2C\underline{H}=CH_2$), 5.52 (dd, J=1.0, 17.3Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.46-5.36 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.34 (dd, J=0.6, 10.7Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.31 (d, J=6.7Hz, 1H, H-5 isoxo), 5.13 (t, J=6.8Hz, 1H, H-5 dioxo), 4.97-4.85 (m, 3H, $OCH_2CH=C\underline{H}_2$, H-4 isoxo), 4.75 (d, J=5.1Hz, 2H, $NpOC\underline{H}_2CH=CH_2$), 4.27 (d, J=7.0Hz, 2H, 2H-4 dioxo), 3.55 (dd, J=6.0, 11.8Hz, 1H, $OC\underline{H}_2CH=CH_2$), 3.35 (dd, J=6.0, 11.8Hz, 1H, $OC\underline{H}_2CH=CH_2$), 1.80-1.43 (m, 10H, cyhx). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 157.97, 154.26, 133.88, 133.53, 133.17, 130.41, 127.58, 126.79, 125.99, 125.75, 122.23, 120.65, 117.75, 117.45, 110.80, 105.41, 86.72, 82.61, 72.25, 71.19, 69.04, 67.09, 38.06, 34.77, 25.15, 24.03, 23.84. MS: Calcd. for $(C_{27}H_{31}NO_5 - H)^-$: 448.2124, Found: 448.2060 (-14.3ppm).

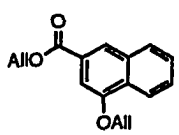
4.14. Preparation of 1-(allyloxy)-3-{(4S,5S)-[4-allyloxy]-[3-(5S)-2,2-cyclohexylidene-1,3-dioxolan-5-yl]-4,5-dihydroisoxazolin-5-yl}-naphthalene (123').



The procedure was same as above. (86% yield). ^1H NMR, 300MHz, ($CDCl_3$): δ 8.31 (m, 1H, H-8 Np), 7.82 (m, 1H, H-5 Np), 7.52-7.48 (m, 3H, H-4, H-6, H-7 Np), 6.91 (d, J=6.0Hz, 1H, H-2 Np), 6.22-6.13 (m, 1H, $NpOCH_2C\underline{H}=CH_2$), 5.56 (dd, J=1.7,

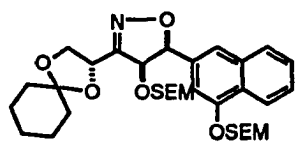
17.1Hz, 1H, NpOCH$_2$CH=C$\underline{H}_2$), 5.55-5.46 (m, 1H, OCH$_2$C$\underline{H}$=CH$_2$), 5.44-5.28 (m, 2H, NpOCH$_2$CH=C$\underline{H}_2$, H-5 isoxo), 5.04-4.87 (m, 3H, OCH$_2$CH=C$\underline{H}_2$, H-4 isoxo), 4.72 (dd, J=1.3, 5.1Hz, 2H, NpOC$\underline{H}_2$CH=CH$_2$), 4.44-4.39 (m, 1H, H-4 dioxo), 4.32-4.30 (m, 1H, H-4 dioxo), 4.25 (t, J=6.9Hz, 1H, H-5 dioxo), 3.68-3.61 (m, 1H, OC$\underline{H}_2$CH=CH$_2$), 3.55-3.49 (m, 1H, OC$\underline{H}_2$CH=CH$_2$), 1.78-1.26 (m, 10H, cyhx).

The fragmentation product, **1-(Allyloxy)-3-[(2-allyloxy-1-oxo)-eth-1-yl]-naphthalene (124)**, was obtained form the above allylation reaction.



^{1}H NMR, 300MHz, ($CDCl_3$): δ 8.33 (dd, J=1.2, 7.4Hz, 1H, H-8 Np), 8.25 (s, H, H-4), 7.90 (d, J=2.7, 7.3Hz, 1H, H-5 Np), 7.62-7.55 (m, 2H, H-6, H-7 Np), 6.21-6.05 (m, 2H, NpOCH$_2$C$\underline{H}$=CH$_2$, OCH$_2$C$\underline{H}$=CH$_2$), 5.55 (dd, J=1.3, 17.3Hz, 1H, NpOCH$_2$CH=C$\underline{H}_2$), 5.45 (dd, J=1.3, 17.3Hz, 1H, OCH$_2$CH=C$\underline{H}_2$), 5.35 (d, J=11.1Hz, 1H, NpOCH$_2$CH=C$\underline{H}_2$), 5.32 (d, J=11.6Hz, 1H, OCH$_2$CH=C$\underline{H}_2$), 4.88 (dd, J=1.1, 5.64Hz, 2H, NpOC$\underline{H}_2$CH=CH$_2$), 4.78 (dd, J=1.0, 5.2Hz, 2H, OC$\underline{H}_2$CH=CH$_2$). MS: (Low resolution) Calcd. for ($C_{17}H_{16}O_3$ + H)$^+$: 269, Found: 269.

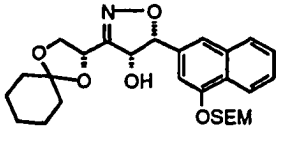
4.15. Preparation of 3-{(4S,5S)-3-[(5S)-2,2-cyclohexylidene-1,3-dioxolan-5-yl]-4-[trimethylsilyl-ethoxymethoxy]-4,5-dihydroisoxazolin-5-yl}-1-(trimethylsilylethoxymethoxy)-naphthalene (129').



Naphthol **121'** (0.11g, 0.30mmol) was dissolved in 5ml of dichloromethane. 2-(Trimethylsilyl)ethoxymethyl chloride (0.25g, 1.5mmol) and N,N-diisopropylethylamine (0.37g, 2.87mmol) were added to the above solution and the mixture was refluxed for 5h. The reaction mixture was cooled to room temperature, poured into 10ml of 5% sodium hydrogen carbonate solution and extracted with dichloromethane (10 x 3 times). All the organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The product was purified by radial chromatography. (Silica gel, 5 - 10 % ethyl acetate / petroleum ether, 0.12g, 63% yield). IR ($CHCl_3$): 2960, 2910, 2895, 1610, 1570, 1380, 1115, 1065, 910, 860, 840 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.26 (m, 1H, H-8 Np), 7.80 (m, 1H, H-5 Np), 7.54 (s, 1H, H-4 Np), 7.52-7.48 (m, 2H, H-6, H-7 Np), 7.11 (s, 1H, H-2 Np), 5.44 (dd, J=6.6, 11.2Hz, 2H, $NpOCH_2OCH_2CH_2TMS$), 5.39 (d, J=7.3Hz, 1H, H-5 isoxo), 5.28 (d, J=7.3Hz, 1H, H-4 isoxo), 5.02 (t, J=6.0Hz, 1H, H-5 dioxo), 4.50 (dd, J=5.6, 8.4Hz, 1H, H-4 dioxo), 4.40-4.15 (ABq,

J=7.1Hz, 2H, $OC\underline{H}_2OCH_2CH_2TMS$), 4.31 (dd, J=6.5, 8.3Hz, 1H, H-4 dioxo), 3.84 (t, J=8.2Hz, 2H, $NpOCH_2OC\underline{H}_2CH_2TMS$), 3.34-3.25 (m, 1H, $OCH_2OC\underline{H}_2CH_2TMS$), 3.05-3.00 (m, 1H, $OCH_2OC\underline{H}_2CH_2TMS$), 1.73-1.46 (br m, 10H, cyhx), 1.01 (t, J=8.3Hz, 2H, $NpOCH_2OCH_2C\underline{H}_2TMS$), 0.76-0.62 (m, 2H, $OCH_2OCH_2C\underline{H}_2TMS$), 0.01 (s, 9H, TMS), -0.10 (s, 9H, TMS). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 158.81, 153.92, 133.93, 130.56, 127.77, 126.73, 125.98, 125.80, 122.12, 122.05, 121.19, 121.13, 110.76, 107.93, 94.07, 93.38, 86.28, 80.42, 69.94, 66.63, 66.59, 65.54, 36.12, 35.27, 25.10, 24.01, 23.93, 18.13, 17.67, -1.36, -1.69

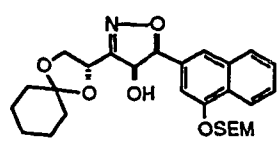
4.16. Preparation of 3-{(4R,5R)-3-[(5S)-2,2-cyclohexylidene-1,3-dioxolan-5-yl]-4-[hydroxy]-4,5-dihydroisoxazolin-5-yl}-1-(trimethylsilylethoxy-methoxy)-naphthalene (130).



2-(Trimethylsilyl)ethoxymethyl chloride (0.64ml, 3.6mmol) was added to a solution of naphthol **121** (0.54g, 1.46mmol) and diisopropylethylamine (0.75ml, 4.3mmol) in 25ml of acetonitrile at room temperature. After stirring for 30min, the reaction was quenched with 10ml of 0.5% sodium hydrogen carbonate solution. The solution was extracted with dichloromethane (20ml x 3 times). The organic layers were combined, washed with brine, dried over anhydrous sodium

sulfate and concentrated under reduced pressure. The product was purified by radial chromatography. (Silica gel, 25% ethyl acetate / petroleum ether, 0.68g, 94% yield). ^{1}H NMR, 300MHz, ($CDCl_3$): δ 8.24 (m, 1H, H-8 Np), 7.80 (m, 1H, H-5 Np), 7.56 (s, 1H, H-4 Np), 7.52-7.50 (m, 2H, H-6, H-7 Np), 7.05 (s, 1H, H-2 Np), 5.50-5.41 (m, 3H, $NpOCH_2OCH_2CH_2TMS$, H-5 isoxo), 5.24-5.18 (dd, J=5.2, 7.0Hz, 1H, H-4 isoxo), 5.10 (t, J=6.6Hz, 1H, H-5 dioxo), 4.29-4.25 (m, 2H, H-4 dioxo), 3.84 (t, J=8.0Hz, 2H, $NpOCH_2OCH_2CH_2TMS$), 2.26 (d, J=5.0Hz, 1H, OH), 1.75-1.40 (m, 10H, cyhx), 1.00 (t, J=8.2Hz, 2H, $NpOCH_2OCH_2CH_2TMS$), 0.00 (s, 9H, TMS). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 159.22, 153.44, 134.12, 129.71, 127.79, 126.95, 125.91, 122.06, 120.14, 111.11, 106.86, 93.30, 86.91, 76.08, 71.12, 67.05, 66.76, 35.77, 34.82, 25.04, 24.01, 23.82, 18.07, -1.37

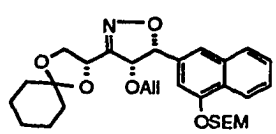
4.17. Preparation of 3-{(4S,5S)-3-[(5S)-2,2-cyclohexylidene-1,3-dioxolan-5-yl]-4-[hydroxy]-4,5-dihydroisoxazolin-5-yl}-1-(trimethylsilylethoxy-methoxy)-naphthalene (130').



The procedure was same as above. (85 % yield). IR ($CHCl_3$): 3560, 2960, 2905, 2880, 1610, 1580, 1385, 1120, 1075, 980, 920, 865, 840 cm^{-1}. ^{1}H NMR, 300MHz, ($CDCl_3$): δ 8.24 (m, 1H, H-8 Np), 7.80 (m, 1H, H-5 Np), 7.55 (s, 1H, H-4

Np), 7.51-7.48 (m, 2H, H-6, H-7 Np), 7.07 (s, 1H, H-2 Np), 5.45-5.40 (m, 3H, $NpOC\underline{H}_2OCH_2CH_2TMS$, H-5 isoxo), 5.19 (d, J=7.2Hz, 1H, H-4 isoxo), 5.08 (t, J=6.3Hz, 1H, H-5 dioxo), 4.30 (m, 2H, H-4 dioxo), 3.83 (t, J=8.3Hz, 2H, $NpOCH_2OC\underline{H}_2CH_2TMS$), 2.61 (br s, 1H, OH), 1.70-1.40 (m, 10H, cyhx), 1.00 (t, J=8.3Hz, 2H, $NpOCH_2OCH_2C\underline{H}_2TMS$), 0.00 (s, 9H, TMS). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 159.21, 153.23, 134.09, 129.90, 127.78, 126.87, 125.98, 125.85, 122.05, 120.32, 120.27, 111.22, 107.13, 107.07, 93.25, 86.94, 76.59, 70.34, 66.86, 66.75, 35.94, 34.75, 25.01, 24.01, 23.81, 18.06, -1.37

4.18. Preparation of 3-{(4R,5R)-4-[allyloxy]-3-[(5S)-2,2-cyclohexylidene-1,3-dioxolan-5-yl]-4,5-dihydroisoxazolin-5-yl}-1-(trimethylsilylethoxy-methoxy)-naphthalene (131).

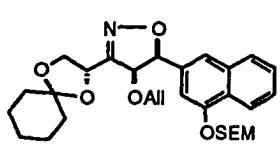


Allyl bromide (0.93ml, 7.9mmol) was added to a suspension of 4-[hydroxy]-4,5-dihydroisoxazolin-5-yl}-1-(trimethylsilyl ethoxymethoxy)-1-naphthalene **130** (0.65g, 1.3mmol) and 40% potassium fluoride-alumina (0.9g, 6.2mmol KF) in 10ml of acetonitrile at room temperature and the mixture was stirred for 2h. Then the mixture was filtered and alumina was washed with dichloromethane (20ml x 3 times). The oily crude product was obtained by concentrating the

filtrate.

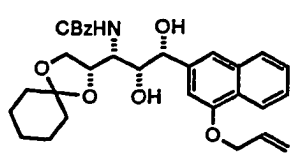
The product was purified by radial chromatography. (Silica gel, 1 - 10 % ethyl acetate / petroleum ether, 0.66g, 93% yield). IR ($CHCl_3$): 2940, 2900, 2880, 1595, 1585, 1450, 1400, 1380, 1260, 1130, 1085, 970, 910, 840 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.29 (m, 1H, H-8 Np), 7.80 (m, 1H, H-5 Np), 7.56 (s, 1H, H-4 Np), 7.54-7.47 (m, 2H, H-6, H-7 Np), 7.17 (s, 1H, H-2 Np), 5.50-5.38 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.44 (d, J=2.8Hz, 2H, $NpOC\underline{H}_2OCH_2CH_2TMS$), 5.29(d, J=6.7Hz, 1H, H-5 isoxo), 5.13 (t, J=6.9Hz, 1H, H-5 dioxo), 4.94-4.88 (m, 3H, H-4 dioxo, $OCH_2CH=C\underline{H}_2$), 4.25 (d, J=7.0Hz, 2H, H-4 dioxo), 3.84 (t, J=8.3Hz, 2H, $NpOCH_2OC\underline{H}_2CH_2TMS$), 3.60-3.35 (dd, J=5.6, 11.8,Hz, 2H, $O\underline{CH}_2CH=CH_2$), 1.71-1.44 (m, 10H, cyhx), 1.00 (t, J=8.4Hz, 2H, $NpOCH_2OCH_2C\underline{H}_2TMS$), 0.00 (s, 9H, TMS). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 157.81, 153.03, 133.95, 133.55, 130.41, 127.75, 126.69, 126.09, 125.79, 122.08, 121.30, 117.74, 110.73, 108.00, 93.44, 86.61, 82.43, 72.28, 71.18, 67.05, 66.60, 36.05, 34.74, 25.15, 24.02, 23.83, 18.11, -1.32.

4.19. Preparation of 3-{(4S,5S)-4-[allyloxy]-3-[(5S)-2,2-cyclohexylidene-1,3-dioxolan-5-yl]-4,5-dihydroisoxazolin-5-yl}-1-(trimethylsilylethoxy-methoxy)-naphthalene (131').



The procedure was same as above. (90% yield). IR ($CHCl_3$): 2940, 2900, 2860, 1610, 1585, 1385, 1100, 1070, 915, 860 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.26 (m, 1H, H-8 Np), 7.80 (m, 1H, H-5 Np), 7.56 (s, 1H, H-4 Np), 7.53-7.49 (m, 2H, H-6, H-7 Np), 7.13 (s, 1H, H-2 Np), 5.50-5.44 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.44 (d, J=0.5Hz, 2H, $NpOC\underline{H}_2OCH_2CH_2TMS$), 5.36 (d, J=7.1Hz, 1H, H-5 isoxo), 5.03-4.91 (m, 3H, H-4 isoxo, $OCH_2CH=C\underline{H}_2$), 4.45, 4.27 (dd, J=6.0, 8.4Hz, 2H, H-4 dioxo), 4.25 (t, J=6.8Hz, 1H, H-5 dioxo), 3.84 (t, J=8.4Hz, 2H, $NpOCH_2OC\underline{H}_2CH_2TMS$), 3.66-3.57 (ABdd, J=1.0, 5.8Hz, 2H, $OC\underline{H}_2CH=CH_2$), 1.67-1.43 (m, 10H, cyhx), 1.00 (t, J=8.3Hz, 2H, $NpOCH_2OCH_2C\underline{H}_2TMS$), 0.00 (s, 9H, TMS). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 158.48, 152.97, 133.96, 133.61, 130.54, 127.77, 126.68, 125.99, 125.76, 122.03, 121.03, 117.88, 117.81, 110.75, 107.84, 93.40, 86.13, 83.27, 72.30, 72.26, 69.99, 66.65, 36.13, 35.16, 25.12, 24.04, 23.94, 18.13, -1.36.

4.20. Reduction of 1-(allyloxy)-3-{(4R,5R)-[4-*tert*butyldimethylsilyloxy]-[3-(5S)-2,2-cyclohexylidene-1,3-dioxolan-5-yl]-4,5-dihydro-isoxazolin-5-yl}-naphthalene (122).

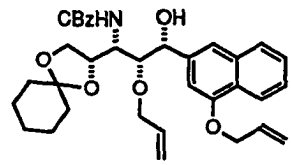


To a solution of lithium aluminium hydride (2ml of 1M solution, 2mmol) in ether at 0°C was added a solution of

122 (0.4g, 0.76mmol, in 0.5ml of dry ether). The mixture was stirred at 0°C for 1h. After hydrolysis of the mixture with alkaline water (2 equiv. of water as 20% sodium hydroxide solution), dichloromethane was added, stirred for 2h at room temperature. The precipitate was filtered and washed thoroughly with dichloromethane. The filtrate was concentrated and dried *in vacuo*.

The concentrate was dissolved in ether (5ml) and poured into sodium carbonate solution (0.21g, 2mmol, 6ml) and then the mixture was cooled to 5°C and benzyl chloroformate (0.12ml, 0.84mmol) was added slowly. The mixture was stirred for 3h. Then the aqueous layer was extracted with ethyl acetate (10ml x 3 times). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The product, **1-(allyloxy)-3-{(1R,2R,3S,5S)-3-[N-benzyloxycarbonyl]-4,5-[O-cyclohexylidene]-1,2-[dihydroxy]-pent-1-yl}-naphthalene 141**, was purified by radial chromatography. (Silica gel, 0 - 5% ethyl acetate / dichloromethane, 0.28g, 68% yield). The product was : ^{1}H NMR, 300MHz, ($CDCl_3$): δ 8.29 (m, 1H, H-8 Np), 7.76 (m, 1H, H-5 Np), 7.53-7.29 (m, 8H, H-4, H-6, H-7 Np, 5H Ph), 6.80 (s, 1H, H-2 Np), 6.16 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.55-5.48 (m, 2H, $OCH_2CH=C\underline{H}_2$, H-1), 5.35 (dd, J=1.3, 10.5Hz, 1H, $OCH_2CH=C\underline{H}_2$),5.20 (m, 2H, CH_2Ph), 4.78-4.62 (m, 2H), 4.16 (m, 2H), 3.90 (m, 1H), 3.66 (m, 1H), 3.55 (m, 1H), 3.29 (br s, 1H, OH), 1.54-1.26 (br m, 10H, cyhx).

4.21. Preparation of 1-(allyloxy)-3-{(1R,2R,3S,4S)-2-[allyloxy]-3-[N-benzyloxycarbonyl]-4,5-[O-cyclohexylidene]-1-[hydroxy]-pent-1-yl}-naphthalene (150).



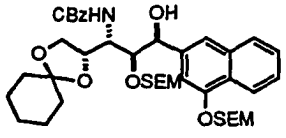
The procedure was same as Expt. 4.20. The product was purified by radial chromatography. (Silica gel, 0 - 5% ethyl acetate/ dichloromethane, 81% yield). IR ($CHCl_3$): 3430, 2940, 2890, 1705, 1590, 1105 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.32 (m, 1H, H-8 Np), 7.82 (m, 1H, H-5, Np), 7.53-7.46 (m, 3H, H-4, H-6, H-7 Np), 7.38-7.27 (m, 5H, Ph), 6.92 (s, 1H, H-2 Np), 6.24-6.15 (m, 1H, $NpOCH_2C\underline{H}=CH_2$), 5.91-5.84 (m, 1H, $OCH_2\underline{CH}=CH_2$), 5.58 (d, J=17.3Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.38 (d, J=10.6Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.28 (d, J=17.2Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.24 (d, J=12.6Hz, 1H, H-1), 5.20 (d,J=11.0Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.05 (ABq, J=10.0Hz, 2H, $PhCH_2$), 4.87 (d, J=4.8Hz, 1H), 4.71 (br s, 2H, $NpOC\underline{H}_2CH=CH_2$), 4.34 (t, J=6.3Hz, 1H), 4.20-3.96 (m, 4H), 3.76-3.73 (m, 1H), 3.68 (m, 2H), 1.65-1.44 (m, 10H, cyhx). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 156.39, 154.45, 138.68, 136.49, 134.54, 134.28, 133.44, 128.53, 128.11, 127.93, 127.73, 126.69, 125.55, 125.26, 122.14, 118.58, 117.61, 117.34, 110.22, 104.16, 83.58, 75.01, 73.69, 73.46, 68.95, 66.87, 66.24, 50.95, 35.94, 34.73, 25.17,

24.03, 23.92.

4.22. Preparation of 1-(allyloxy)-3-{-2-[allyloxy]-3-[N-benzyloxycarbonyl]-4,5-[O-cyclohexylidene]-1-[hydroxy]-pent-1-yl}-naphthalene (150').

The procedure was same as Expt. 4.20. ^{1}H NMR, 300MHz, ($CDCl_3$): δ 8.28 (m, 1H, H-8 Np), 7.80 (m, 1H, H-5, Np), 7.50-7.26 (m, 8H, H-4, H-6, H-7 Np, Ph), 6.83 (s, 1H, H-2 Np), 6.23-6.14 (m, 1H, $NpOCH_2C\underline{H}=CH_2$), 6.06-5.97 (m, 1H, $OCH_2CH=CH_2$), 5.56 (d, J=17.3Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.36 (2d, J=12.5, 15.2Hz, 2H, $NpOCH_2CH=C\underline{H}_2$, $OCH_2CH=C\underline{H}_2$), 5.25 (d, J=10.5Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.17-5.03 (m, 2H,), 4.80-4.65 (m, 3H), 4.42-4.28 (m, 2H), 3.95 (d, J=8.4Hz, 1H), 3.90 (m, 1H), 3.80 (m, 1H), 3.65 (t, J=9.0Hz, 1H), 2.85 (d, J=1.8Hz, 1H), 1.74-1.39 (m, 10H, cyhx). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 154.74, 138.57, 134.29, 133.23, 127.59, 126.76, 125.54, 125.29, 122.08, 117.94, 117.44, 109.39, 103.51, 76.95, 73.00, 69.01, 65.39, 55.02, 36.37, 34.77, 25.10, 23.96, 23.73.

4.23. Preparation of 3-{(1S,2S,3S,5S)-3-[N-benzyloxycarbonyl]-4,5-[O-cyclohexylidene]-1-[hydroxy]-2-[trimethylsilylethoxymethoxy]-pent-1-yl}-1-(trimethylsilylethoxymethoxy)-naphthalene (151').

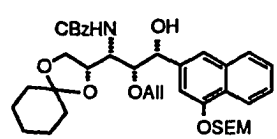


The procedure was same as Expt. 4.20. The product was purified by PLC. (Silica gel, 25% ethyl acetate / petroleum ether, 92% yield). IR ($CHCl_3$) : 3605, 3415, 2945, 2915, 2900, 1723, 1605, 1585, 1380, 1055, 910, 863, 840 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.24 (m, 1H, H-8 Np), 7.75 (m, 1H, H-5 Np), 7.45-7.26 (m, 8H, H-4 Np, H-6, H-7 Np, Ph), 7.05 (s, 1H, H-2 Np), 5.54-5.40 (ABq, J=6.4Hz, 2H, $NpOCH_2OCH_2CH_2TMS$), 5.30 (d, J=9.7Hz, 1H, H-5 isoxo), 5.12 (m, 2H), 4.98-4.90 (dd, J=6.7, 11.5Hz, 5H), 4.73 (m, 4H), 4.12 (d, J=8.8Hz, 1H), 3.91-3.70 (m, 4H), 3.50 (t, 1H), 1.96 (br s, 1H, OH), 1.45-1.27 (br m, 10H, cyhx), 1.10-1.00 (m, 4H, $NpOCH_2OCH_2CH_2TMS$, $OCH_2OCH_2CH_2TMS$), 0.06 (s, 9H, TMS), 0.04 (s, 9H, TMS). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 155.79, 153.32, 137.40, 134.33, 128.63, 128.56, 128.29, 128.24, 127.85, 127.63, 127.00, 126.57, 126.53, 126.44, 125.61, 125.29, 122.03, 121.92, 120.01, 119.95, 109.96, 106.94, 97.46, 93.45, 85.16, 75.21, 74.66, 67.03, 66.67, 66.59, 65.32, 53.28, 36.18, 35.18, 25.02, 23.82, 23.76, 18.25, 18.13, -1.36, -1.38.

Note: In this reaction we were able to take the ^1H NMR and ^{13}C NMR analysis of **3-{(1S,2S,3S,5S)-3-[amino]-4,5-[O-cyclohexylidene]-1-[hydroxy]-2-[trimethylsilylethoxy-methoxy]-pent-1-yl}-1-(trimethylsilylethoxymethoxy)-naphthalene.** ^1H NMR, 300MHz, ($CDCl_3$): δ 8.24 (m, 1H, H-8 Np), 7.81 (m, 1H, H-5 Np), 7.54 (s, 1H, H-4 Np), 7.50-7.44 (m, 2H, H-6, H-7 Np), 7.12 (s, 1H, H-2 Np), 5.44 (s, 2H, $NpOCH_2OCH_2CH_2TMS$), 4.99 (d, J=6.5Hz, 1H, H-5 isoxo), 4.75-4.64 (ABq, J=6.6Hz, 2H, $OCH_2OCH_2CH_2TMS$), 4.02 (m, 2H), 3.91-3.78

(m, 4H), 3.74-3.60 (m, 4H), 2.55 (d, J=8.3Hz, 1H), 1.47-1.29 (br m, 10H, cyhx), 1.03-0.90 (m, 4H, $NpOCH_2OCH_2CH_2TMS$, $OCH_2OCH_2CH_2TMS$), 0.01 (s, 9H, TMS), 0.00 (s, 9H, TMS). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 153.32, 138.65, 134.37, 127.72, 126.51, 125.71, 125.26, 121.95, 119.30, 109.66, 106.55, 97.07, 93.31, 84.84, 76.61, 76.05, 66.84, 66.63, 66.51, 55.69, 36.59, 34.99, 25.12, 24.02, 23.84, 18.19, -1.34, -1.40.

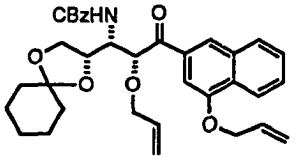
4.24. Preparation of 3-{(1R,2R,3S,4S)-2-[allyloxy]-3-[N-benzyloxycarbonyl]-4,5-[O-cyclohexylidene]-1-[hydroxy]-pent-1-yl}-1-(trimethylsilylethoxymethoxy)-naphthalene (152).



The procedure was same as Expt. 4.20. The product was purified by radial chromatography. (Silica gel, 5 - 10% ethyl acetate / petroleum, 93% yield). IR ($CHCL_3$): 3520, 3440, 2945, 2900, 2865, 1720, 1610, 1590, 1500, 1385, 1285, 1070, 920, 865 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.27 (m, 1H, H-8 Np), 7.82 (m, 1H, H-5 Np), 7.56 (s, 1H, H-4 Np), 7.51-7.48 (m, 2H, H-6, H-7 Np), 7.40-7.30 (m, 5H, Ph), 7.16 (s, 1H, H-2 Np), 5.87-5.81 (m, 1H, $OCH_2CH=CH_2$), 5.52-5.43 (ABq, J=6.5Hz, 2H, $NpOCH_2OCH_2CH_2TMS$), 5.25-5.00 (m, 6H, H-4, H-5 isoxo, $OCH_2CH=CH_2$, $PhCH_2$), 4.90 (d, J=5.1Hz, 1H, NH), 4.35 (t, J=6.8Hz, 1H), 4.18-4.03 (ddd, J=5.7, 11.9, 13.7Hz, 2H,

$OCH_2CH=CH_2$), 4.02-3.83 (m, 3H), 3.75 (t, J=3.5Hz, 1H), 3.64 (t, J=7.9Hz, 1H), 3.56 (br s, 1H, OH), 1.64-1.43 (m, 10H, cyhx), 1.02 (t, J=8.3Hz, 2H, $NpOCH_2OCH_2CH_2TMS$), 0.04 (s, 9H, TMS). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 156.41, 153.24, 138.66, 136.40, 134.46, 134.27, 128.55, 128.48, 128.36, 128.16, 128.05, 127.88, 127.46, 126.93, 126.62, 125.70, 125.38, 122.00, 119.48, 117.71, 110.25, 106.50, 93.35, 83.55, 74.95, 73.80, 73.41, 67.97, 66.65, 66.23, 50.95, 35.91, 34.68, 25.15, 24.03, 23.91, 18.14, -1.29.

4.25. Preparation of 1-(allyloxy)-3-{(2R,3S,4S)-2-[allyloxy]-3-[N-benzyloxycarbonyl]-4,5-[O-cyclohexylidene]-1-[oxo]-pent-1-yl}-naphthalene (153).

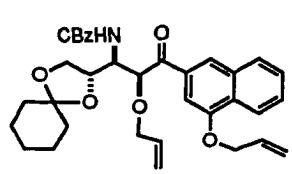


Activated manganese (IV) oxide (1.33g, 15.33mmol), was added to a solution of alcohol **150** ((0.8g. 1.36mmol) in 10ml of dry chloroform and was stirred at reflux for 5h. The mixture was cooled to room temperature and was filtered through celite. The celite was washed with chloroform. The filtrate was evaporated to dryness under reduced pressure.

The desired ketone, was purified by radial chromatography. (Silica gel, 0 - 2% methyl alcohol/ dichloromethane, 0.74g, 90% yield). IR ($CHCl_3$ with little

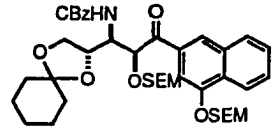
$CDCl_3$): 3440, 2940, 2895, 2265, 1715, 1690, 1585, 1290, 1110, 905 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.34 (d, J=8.0Hz, 1H H-8 Np), 8,24 (s, 1H, H-4 Np), 7.88 (d, J=8.0Hz, 1H, H-5 Np), 7.64-7.53 (m, 2H, H-6, H-7 Np), 7.41 (s, 1H, H-2 Np), 7.33-7.31 (m, 5H, Ph), 6.28-6.15 (m, 1H, $NpOCH_2C\underline{H}=CH_2$), 6.02-5.90 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.58 (d, J=17.3Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.38-5.18 (m, 4H, $NpOCH_2CH=C\underline{H}_2$, $OCH_2CH=C\underline{H}_2$, H-e), 5.05 (s, 2H, $PhCH_2$), 4.80 (d, 2H, $NpOC\underline{H}_2CH=CH_2$), 4.45-4.38 (m, 2H), 4.25-4.19 (m, 1H, $OC\underline{H}_2CH=CH_2$), 4.06-3.94 (m, 3H, H-a, H-b, $OC\underline{H}_2CH=CH_2$), 1.68-1.41 (m, 10H, cyhx). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 197.63, 156.24, 154.80, 136.28, 134.00, 133.48, 133.21, 132.92, 129.43, 128.69, 128.49, 128.25, 128.11, 128.09, 127.35, 123.94, 122.36, 118.27, 117.80, 110.17, 102.53, 78.91, 73.96, 71.39, 69.09, 67.00, 65.53, 53.35, 36.10, 34.20, 25.19, 24.10, 23.67. MS m/e (rel%) 584.2478(100), 560(11), 544(74), 527(88), 486(57), 478(37), 436(52), 419(24). Calcd. for $(M-H)^-$ $(C_{35}H_{39}NO_7-H)^-$: 584.2648, Found: 584.2478 (-29.2ppm).

4.26. Preparation of 1-(allyloxy)-3-{(2S,3R,4S)-2-[allyloxy]-3-[N-benzyloxycarbonyl]-4,5-[O-cyclohexylidene]-1-[oxo]-pent-1-yl}-naphthalene (153').



Ketone **153'** was prepared as Expt. 4.25. (80% yield). ^{1}H NMR, 300MHz, ($CDCl_3$): δ 8.37 (m, 1H H-8 Np), 8,09 (s, 1H, H-4 Np), 7.82 (m, 1H, H-5 Np), 7.63-7.56 (m, 2H, H-6, H-7 Np), 7.37-7.27 (m, 6H, H-2, Ph), 6.25-6.11 (m, 1H, $NpOCH_2C\underline{H}=CH_2$), 6.06-5.91 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.57 (d, J=17.3Hz, 2H, $NpOCH_2CH=C\underline{H}_2$, NH), 5.37-5.21 (m, 4H, $NpOCH_2CH=C\underline{H}_2$, $OCH_2CH=C\underline{H}_2$, H-e), 5.04-5.93 (ABq, J=12.5Hz, 2H, $PhCH_2$), 4.72 (d, 2H, $NpOC\underline{H}_2CH=CH_2$), 4.32-3.89 (m, 6H), 1.82-1.49 (m, 10H, cyhx).

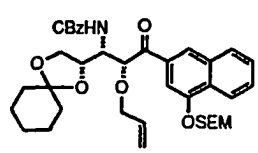
4.27. Preparation of 3-{(1S,2S,3S,5S)-3-[N-benzyloxycarbonyl]-4,5-[O-cyclohexylidene]-1-[oxo]-2-[trimethylsilylethoxymethoxy]-pent-1-yl}-1-(trimethylsilylethoxymethoxy)-naphthalene (154').



Ketone **154'** was prepared as Expt. 4.25. (80% yield). IR ($CHCl_3$): 2995, 2950, 2900, 1720, 1690, 1400, 1265, 1120, 915, 865 cm^{-1}. ^{1}H NMR, 300MHz, ($CDCl_3$): δ 8.32 (m, 1H, H-8 Np), 8.15 (s, 1H, H-4 Np), 7.87 (m, 1H, H-5 Np), 7.63-7.52 (m, 3H, H-2, H-6, H-7 Np), 7.40-7.30 (m, 5H, Ph), 5.90 (s, 1H, OH), 5.50-5.43 (dd, J=6.3, 13.7Hz, 2H, $NpOC\underline{H}_2OCH_2CH_2TMS$), 5.35 (m, 1H), 5.08-4.95 (ABq, J=12.4Hz, 2H, $PhCH_2$), 4.90 (d, J=7.1Hz, 1H), 4.76 (d, J=7.1Hz, 1H), 4.23-3.64 (m, 7H), 1.79-

1.45 (br m, 10H, cyhx), 1.04-0.89 (m, 4H, $NpOCH_2OCH_2CH_2TMS$, $OCH_2OCH_2CH_2TMS$), 0.01 (s, 9H, TMS), 0.00 (s, 9H, TMS). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 196.44, 156.03, 153.69, 136.38, 133.48, 132.76, 130.90, 129.04, 128.91, 128.75, 128.45, 128.18, 128.01, 127.85, 127.28, 123.68, 122.34, 110.44, 104.76, 94.01, 93.94, 93.35, 74.92, 74.44, 67.17, 66.89, 66.02, 56.13, 38.74, 36.87, 35.14, 25.22, 24.33, 23.94, 23.77, 18.02, -1.38.

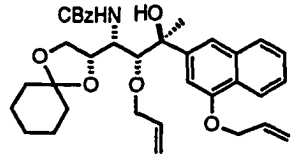
4.28. Preparation of 3-{(1R,2R,3S,4S)-2-[allyloxy]-3-[N-benzyloxycarbonyl]-4,5-[O-cyclohexylidene]-1-[oxo]-pent-1-yl}-1-(trimethylsilylethoxymethoxy)-naphthalene (155).



Ketone **154'** was prepared as Expt. 4.25. (88% yield. IR ($CHCL_3$): 3440, 2960, 2905, 2880, 1725, 1715, 1605, 1500, 1380, 1295, 1080, 920, 870 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.30 (m, 2H, H-4, H-8 Np), 7.87 (m, 1H, H-5 Np), 7.66 (s, 1H, H-2 Np), 7.64-7.55 (m, 2H, H-6, H-7 Np), 7.32 (br m, 5H, Ph), 5.94-5.86 (m, 1H, $OCH_2CH=CH_2$), 5.49 (s, 2H, $NpOCH_2OCH_2CH_2TMS$), 5.40 (d, J=8.8Hz, 1H, $OCH_2CH=CH_2$), 5.28 (d, J=17.2Hz, 1H, $OCH_2CH=CH_2$), 5.18 (m, 2H, NH, H-2), 5.06 (s, 2H, $PhCH_2$), 4.41 (m, 2H), 4.25-4.19 (dd, J=5.3, 12.4Hz, 1H, $OCH_2CH=CH_2$), 4.06-3.96 (m, 3H, H-5, $OCH_2CH=CH_2$), 3.87 (dd, J=8.0, 8.4Hz, 2H,

$NpOCH_2OCH_2CH_2TMS$), 1.69-1.40 (m, 10H, cyhx), 1.02 (dd, J=8.0, 8.4Hz, 2H, $NpOCH_2OCH_2CH_2TMS$), 0.01 (s, 9H, TMS). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 197.36, 156.24, 153.51, 136.31, 134.03, 133.53, 133.23, 129.54, 128.64, 128.49, 128.30, 128.09, 127.27, 124.49, 122.45, 118.23, 110.15, 105.19, 93.32, 78.90, 74.05, 71.33, 66.98, 66.86, 65.54, 53.37, 36.09, 34.23, 25.20, 24.12, 23.68, 18.06, -1.32.

4.29. Preparation of (2S,3R,4S,5S)-3-(allyloxy)-4-(N-benzyloxycarbonyl)-5,6-(O-cyclohexylidene)-2-[1-(allyloxy)-naphth-3-yl]-2-hexanol (169').

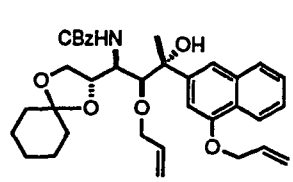


A solution of ketone **153** (0.7g, 1.19mmol in 5ml anhydrous ether) was slowly added to methyl magnesium bromide (4ml, 3M solution in ether) in 4ml of ether at -30°C. Stirring was continued for 30min at -30°C, 30min at 0°C and 1h at room temperature. After addition of 5ml of 25% ammonium chloride, the aqueous layer was extracted with ether (20ml x 3 times). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure.

The concentrate so obtained was purified by radial chromatography. (Silica gel, 0 - 2 % methyl alcohol/ dichloromethane, 0.63g, 88% yield). IR ($CHCl_3$): 3440, 2960,

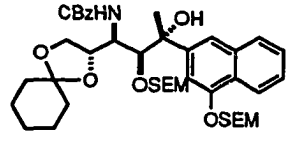
2880, 1712, 1600, 1585, 1500, 1285, 1100, 93cm^{-1}. ^{1}H NMR, 300MHz, ($CDCl_3$): δ 8.29 (m, 1H, H-8 Np), 7.81 (m, 1H, H-5 Np), 7.56 (s, 1H, H-4 Np), 7.52-7.40 (m, 2H, H-6, H-7 Np), 7.39-7.25 (m, 5H, Ph), 7.03 (s, 1H, H-2 Np), 6.24-6.15 (m, 1H, $NpOCH_2C\underline{H}=CH_2$), 5.91-5.81 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.58 (dd, J=1.2, 17.3Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.39 (d, J=10.6Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.27 (d, J=17.2Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.20 (d, J=10.4Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.12 (d, J=9.4Hz, 1H, H-3), 5.07, 4.90 (ABq, J=12.3Hz, 2H, $PhCH_2$), 4.76 (d, J=5.0Hz, 2H, $NpOC\underline{H}_2CH=CH_2$), 4.27-4.04 (m, 3H, $OC\underline{H}_2CH=CH_2$), 3.92-3.84 (m, 2H), 3.76 (s, 2H), 3.64 (t, J=7.9Hz, 1H), 1.71 (s, 3H, CH_3), 1.68-1.34 (m, 10H, cyhx). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 156.62, 154.24, 143.59, 136.36, 134.60, 134.14, 133.39, 128.48, 128.02, 127.83, 126.71, 125.21, 124.84, 122.02, 121.96, 117.41, 117.35, 116.63, 116.58, 110.58, 110.07, 103.49, 84.64, 76.47, 73.84, 68.98, 66.90, 65.98, 50.24, 35.89, 34.64, 26.24, 25.13, 23.96, 23.91. MS : Calcd. for $(M-H)^-$ $(C_{36}H_{43}NO_7-H)^-$: 600.2961, Found: 600.2963 (+0.3ppm).

4.30. Preparation of (2S,3S,4S,5S)-3-(allyloxy)-4-(N-benzyloxycarbonyl)-5,6-(O-cyclohexylidene)-2-[1-(allyloxy)-naphth-3-yl]-2-hexanol.



The procedure was same as above. (88 % yield). ^1H NMR, 300MHz, ($CDCl_3$): δ 8.25 (m, 1H, H-8 Np), 7.76 (m, 1H, H-5 Np), 7.51-7.24 (m, 8H, H-4, H-6, H-7 Np, Ph), 7.06 (s, 1H, H-2 Np), 6.21-6.14 (m, 1H, $NpOCH_2C\underline{H}=CH_2$), 6.00-5.88 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.55 (d, J=17.3Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.35 (d, J=10.5Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.28 (d, J=17.1Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.18 (d, J=10.3Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.10 (d, J=8.7Hz, 1H, H-3), 4.99 (ABq, J=12.2Hz, 1H, $PhCH_2$), 4.74 (s, 2H, $NpOC\underline{H}_2CH=CH_2$), 4.72 (ABq, J=12.2Hz, 1H, $PhCH_2$) 4.24-4.14 (m, 2H), 4.01 (s, 1H, NH), 3.93-3.76 (m, 4H), 2.54 (br s, 1H, OH), 1.73 (s, 3H, CH_3), 1.52-1.26 (br m, 10H, cyhx).

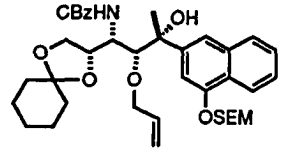
4.31. Preparation of (2S,3S,4S,5S)-4-(N-benzyloxycarbonyl)-5,6-(O-cyclohexylidene)-3-(trimethylsilylethoxymethoxy)-2-[1-(trimethylsilyl-ethoxymethoxy)-naphth-3-yl]-2-hexanol.



Ketone **154'**(0.03g, 0.04mmol) was dissolved in 2ml of ether and cooled to 0°C. Methyllithium (0.3ml, 0.4mmol, 1.3M in ether) was added slowly and the solution was warmed to room temperature within 1h. The solution was hydrolyzed with water and was extracted with dichloromethane (10ml x 3 times). All the organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated

in vacuo. The product was purified by PLC. (Silica gel, 2% methyl alcohol / dichloromethane, 0.02g, 75% yield, 7% starting material was recovered). IR ($CHCl_3$) : 3520, 2950, 2900, 2870, 1720, 1500, 1380, 1110, 865, 843 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.20 (m, 1H, H-8 Np), 7.83 (m, 1H, H-5 Np), 7.50 (s, 1H, H-4 Np), 7.46-7.38 (m, 2H, H-6, H-7 Np), 7.34-7.27 (br s, 4H, Ph), 7.08 (m, 2H, H-2 Np, Ph), 5.49-5.45 (dd, J=6.2, 12.3Hz, 2H, $NpOC\underline{H}_2OCH_2CH_2TMS$), 4.89-4.83 (m, 4H, $OC\underline{H}_2OCH_2CH_2TMS$, H-3, $PhCH_2$), 4.35 (d, J=10.9Hz, 1H, $PhCH_2$), 4.18 (s, 1H, NH), 3.91-3.58 (m, 9H), 1.75 (s, 3H, CH_3), 1.67-1.30 (br m, 10H, cyhx), 1.06-0.98 (m, 4H, $NpOCH_2OCH_2C\underline{H}_2TMS$, $OCH_2OCH_2C\underline{H}_2TMS$), 0.06 (s, 9H, TMS), 0.00 (s, 9H, TMS).

4.32. Preparation of (2R,3R,4S,5S)-3-(allyloxy)-4-(N-benzyloxycarbonyl)-5,6-(O-cyclohexylidene)-2-[1-(trimethylsilyl-ethoxymethoxy)-naphth-3-yl]-2-hexanol.



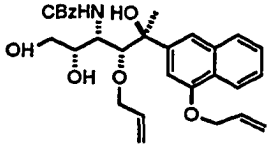
Ketone **155** (0.08g, 0.12mmol) was dissolved in 2ml of ether and cooled to 0°C. Methyllithium (0.14ml, 0.18mmol, 1.3M in ether) was added. The solution was warmed to room temperature within 30 min. TLC analysis indicated an incomplete reaction. Therefore more methyllithium (0.28ml, 0.24mmol) was added. Stirring was continued for another 1h, but the reaction was not completed. The solution was

hydrolyzed with water. The mixture was extracted with dichloromethane (10ml x 3 times). All the organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated under reduce pressure.

Two methylated products were observed. The products were separated by PLC. (Silica gel, 20% ethyl acetate / petroleum ether, 23% overall yield). **Isomer I:** IR ($CHCL_3$): 3440, 2940, 2900, 2870, 1710, 1600, 1582, 1500, 1370, 1060, 980, 865, 840 cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.22 (m, 1H, H-8 Np), 7.80 (m, 1H, H-5 Np), 7.64 (s, 1H, H-4 Np), 7.50 (m, 2H, H-6, H-7 Np), 7.32 (m, 5H, Ph), 7.18 (s, 1H, H-2 Np), 5.91-5.85 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.42 (s, 2H, $NpO\underline{CH_2}OCH_2CH_2TMS$), 5.25 (d, J=17.2Hz, 1H, $OCH_2CH=C\underline{H_2}$), 5.17 (d, J=10.4Hz, 1H, $OCH_2CH=C\underline{H_2}$), 5.08 (d, J=9.6Hz, 1H, H-3), 5.05-4.90 (ABq, J=12.2Hz, 2H, $PhCH_2$), 4.27-4.21 (dd, J=5.1, 11.8Hz, 1H, $OC\underline{H_2}CH=CH_2$), 4.10 (t, J=7.1Hz, 1H), 4.00-3.82 (m, 5H), 3.75 (d, J=2.1Hz, 1H, NH), 3.54 (dd, J=7.3, 8.2Hz, 2H, $NpOCH_2OC\underline{H_2}CH_2TMS$), 1.68 (s, 3H, CH_3), 1.60-1.40 (m, 10H, cyhx), 1.00 (dd, J=7.8, 8.6Hz, 2H, $NpOCH_2OCH_2C\underline{H_2}TMS$), 0.01 (s, 9H, TMS). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 156.63, 153.11, 143.56, 136.34, 134.54, 134.15, 128.56, 128.47, 128.04,, 127.98, 126.62, 125.32, 125.04, 121.84, 117.45, 117.36, 110.03, 106.01, 104.93, 93.49, 84.57, 76.56, 76.50, 73.85, 66.90, 66.62, 65.98, 50.14, 35.84, 34.65, 26.32, 25.09, 23.91, 23.89, 18.10, -1.34. **Isomer II:** ^1H NMR, 300MHz, ($CDCl_3$): δ 8.14 (m, 1H, H-8 Np), 7.80 (m, 1H, H-5 Np), 7.56 (s, 1H, H-4

Np), 7.43 (m, 2H, H-6, H-7 Np), 7.30-7.13 (m, 6H, H-2 Np, Ph), 5.80-5.73 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.42-5.35 (m, 2H, $NpOC\underline{H}_2OCH_2CH_2TMS$), 5.15-5.03 (m, 3H, H-3, $OCH_2CH=C\underline{H}_2$), 4.90-4.55 (ABq, J=12.1Hz, 2H, $PhCH_2$), 4.26 (m, 1H, $OC\underline{H}_2CH=CH_2$), 4.00-3.75 (m, 5H), 3.62 (s, 1H, NH), 3.50 (t, J=7.7Hz, 2H, $NpOCH_2OC\underline{H}_2CH_2TMS$), 2.74 (s, 1H, OH), 1.60 (s, 3H, CH_3), 1.58-1.48 (m, 10H, cyhx), 0.94 (t, J=8.1Hz, 2H, $NpOCH_2OCH_2C\underline{H}_2TMS$), -0.04 (s, 9H, TMS).

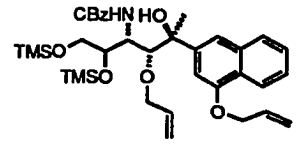
4.33. Preparation of (2S,3R,4S,5S)-3-(allyloxy)-4-(N-benzyloxycarbonyl)-5,6-(dihydroxy)-2-[1-(allyloxy)-naphth-3-yl]-2-hexanol (176).



To a solution of 2-hexanol **169** (0.83g, 1.38mmol) and propane-1,3-dithiol (0.17ml, 1.61mmol) in dichloromethane (2ml) at -78°C was added boron trifluoride etherate (0.20ml, 1.65mmol) dropwise and the mixture was magnetically stirred for 2h. Stirring was continued for an additional 2h at -40°C and 1h at 0°C. Then the reaction was diluted with dichloromethane (5ml) and quenched with water (2ml) and sodium bicarbonate solution (5 %, 2ml). The solution was then extracted with dichloromethane (10ml x 3 times). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The

product was purified by radial chromatography. (Silica gel, 0 - 10 % methyl alcohol / dichloromethane, 0.65g, 90% yield). IR ($CHCl_3$): 3680, 3430, 2980, 2890, 1710, 1600, 1585, 1505, 1100, 910cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.29 (m, 1H, H-8 Np), 7.80 (m, 1H, H-5 Np), 7.48-7.41 (m, 3H, H-4, H-6, H-7 Np), 7.33-7.12 (m, 5H, Ph), 6.92 (s, 1H, H-2 Np), 6.24-6.09 (m, 1H, $NpOCH_2C\underline{H}=CH_2$), 5.92-5.83 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.50 (dd, J=1.4, 17.3Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.31 (dd, J=1.3, 10.5Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.22 (dd, J=1.0, 17.2Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.21 (d, J=10.3Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.00 (d, 1H, H-3), 4.94, 4.66 (ABq, J=12.2Hz, 2H, $PhCH_2$), 4.73 (d, J=5.0Hz, 2H, $NpOC\underline{H}_2CH=CH_2$), 4.20 (dd, J=5.6, 12.1Hz, 1H, $OC\underline{H}_2CH=CH_2$), 4.01-3.88 (m, 4H, $OC\underline{H}_2CH=CH_2$, H-3, H-4, NH), 3.54-3.37 (m, 5H, H-6, 3-OH), 1.70 (s, 3H, CH_3). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 156.87, 154.27, 142.36, 135.98, 134.25, 134.11, 133.26, 128.40, 128.18, 128.03, 127.90, 127.85, 126.78, 125.29, 124.85, 121.96, 117.74, 117.43, 116.34, 116.28, 103.15, 103.08, 83.87, 76.72, 73.72, 71.27, 68.97, 66.88, 63.70, 51.44, 27.34. MS : Calcd. for $(M-H)^-$ $(C_{30}H_{35}NO_7-H)^-$: 520.2335, Found: 520.2305 (-5.9ppm).

4.34. Preparation of (2S,3R,4S,5S)-3-(allyloxy)-4-(N-benzyloxycarbonyl)-5,6-(bis-trimethylsilyloxy)-2-[1-(allyloxy)-naphth-3-yl]-2-hexanol (183).

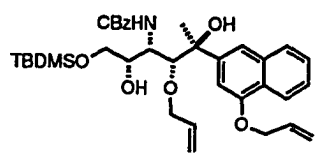


Trimethylsilyl chloride (0.01ml, 0.07mmol) was added to a solution of 5,6-dihydroxyl-2-hexanol **176** (0.01g, 0.019mmol) and triethylamine (0.014ml, 0.1mmol) in 0.5ml of dichloromethane at 0°C. The reaction was first stirred at 0°C for 15min, then at room temperature for 30min and finally quenched with water. The mixture was extracted with dichloromethane (5ml x 3 times). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*.

The product was not purified and was used for further reaction. (0.01g, 79% yield). ^{1}H NMR, 300MHz, ($CDCl_3$): δ 8.27 (m, 1H, H-8 Np), 7.80 (m, 1H, H-5 Np), 7.54 (s, 1H, H-4 Np), 7.50-7.31 (m, 7H, H-6, H-7 Np, Ph), 7.07 (s, 1H, H-2 Np), 6.31-6.15 (m, 1H, $NpOCH_2C\underline{H}=CH_2$), 5.90-5.74 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.58 (dd, J=1.3, 17.2Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.37 (dd, J=1.1, 10.5Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.27 (dd, J=1.4, 17.3Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.19 (d, J=10.3Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.13 (d, J=10.5Hz, 1H, H-3), 5.12 (d, J=12.1Hz, 1H, $Ph\underline{C}H_2$), 4.78 (d, J=12.0Hz, 1H, $Ph\underline{C}H_2$), 4.77 (d, J=5.2Hz, 2H, $NpOC\underline{H}_2CH=CH_2$), 4.17 (s, 1H, OH), 4.14-4.02 (ddd, J=5.5, 12.3,

18.4Hz, 2H, $OCH_2CH=CH_2$), 3.88-3.84 (m, 1H, H-4), 3.64 (d, J=4.5Hz, 1H, NH), 3.21-3.10 (m, 3H, H-5, 2H-6), 1.73 (s, 3H, CH_3), 0.06 (s, 9H, TMS), -0.12 (s, 9H, TMS). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 157.33, 154.36, 143.30, 134.53, 134.15, 133.35, 128.54, 128.39, 128.21, 127.97, 127.77, 126.61, 125.05, 124.82, 122.00, 117.45, 117.25, 116.75, 116.64, 103.57, 84.30, 74.83, 73.70, 68.97, 67.07, 63.94, 52.34, 27.15, 0.60, -1.07.

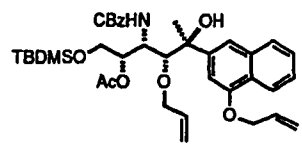
4.35. Preparation of (2S,3R,4S,5S)-3-(allyloxy)-4-(N-benzyloxycarbonyl)-6-(*tert*butyldimethylsilyloxy)-5-(hydroxy)-2-[1-(allyloxy)-naphth-3-yl]-2-hexanol (186)



A solution of tert-butyldimethylsilyl trifluoromethanesulfonate (0.02ml, 0.17mmol) was added dropwise to a solution of alcohol **176** (0.08g, 0.15mmol) and DBU (0.03ml, 0.20mmol) in 3ml of dichloromethane at 0°C. The reaction mixture was stirred at 0°C for 40min and then diluted with 5ml of dichloromethane and washed with water (5ml x 3 times). The organic layers was washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The product was purified by PLC (silica gel, 4% methyl alcohol / dichloromethane, 0.07g, 75% yield). IR ($CHCl_3$): 3560, 3420,

2950, 2910, 2860, 1705, 1600, 1580, 1495, 1400, 1245, 1100, 830cm^{-1}. ^{1}H NMR, 300MHz, ($CDCl_3$): δ 8.29 (m, 1H, H-8 Np), 7.82 (m, 1H, H-5 Np), 7.56 (s, 1H, H-4 Np), 7.50-7.44 (m, 2H, H-6, H-7 Np), 7.43-7.28 (m, 3H, Ph), 7.14-7.13 (m, 2H, Ph), 6.94 (s, 1H, H-2 Np), 6.28-6.15 (m, 1H, $NpOCH_2C\underline{H}=CH_2$), 6.08-5.94 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.55 (dd, J=1.2, 17.3Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.38 (dd, J=1.0, 10.5Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.35 (dd, J=1.3, 17.2Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.24 (d, J=10.3Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.01 (d, J=12.1Hz, 1H, $Ph\underline{CH}_2$), 4.84 (d, J=8.86Hz, 1H, H-3), 4.77 (d, J=5.0Hz, 2H, $NpOC\underline{H}_2CH=CH_2$), 4.68 (d, J=12.1Hz, 1H, $Ph\underline{CH}_2$), 4.35-4.29 (dd, J=5.5, 12.3, 1H, $OC\underline{H}_2CH=CH_2$), 4.15-4.08 (dd, J=6.8, 12.0, 1H, $OC\underline{H}_2CH=CH_2$), 4.04-3.96(m, 3H, H-5, OH), 3.78 (m, 1H, H-4), 3.61 (br s, 1H, NH), 3.48-3.42 (m, 1H, H-6), 3.34-3.30 (dd, J=5.9, 9.9Hz, 1H, H-6), 1.74 (s, 3H, CH_3), 0.84 (s, 9H, t-Bu), -0.00 (s, 3H, $SiCH_3$), -0.01 (s, 3H, $SiCH_3$). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 156.38, 154.11, 142.72, 134.38, 134.11, 133.19, 128.52, 128.29, 128.23, 128.10, 127.88, 127.75, 126.65, 125.05, 124.65, 121.91, 117.55, 117.35, 115.93, 102.84, 83.28, 76.56, 73.21, 70.14, 68.80, 66.58, 63.70, 50.59, 28.18, 25.72, 18.06, -5.64, -5.72.

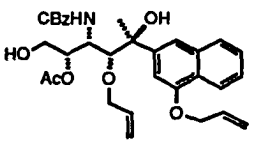
4.36. Preparation of (2S,3R,4S,5S)-5-(O-acetyl)-3-(allyloxy)-4-(N-benzyloxycarbonyl)-6-(*tert*butyl-dimethylsilyloxy)-2-[1-(allyloxy)-naphth-3-yl]-2-hexanol (187).



Acetic anhydride (0.04ml, 0.38mmol) was added to a solution of alcohol **186** (0.08g, 0.16mmol), pyridine (0..07ml, 0.82mmol) and dimethylamino pyridine (0.002ml) in 2ml of dichloromethane. After stirring 2h at room temperature, the reaction was diluted with 2ml of dichloromethane and was washed with water (3ml x 2 times). The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The product was purified by PLC. (Silica gel, 3% methyl alcohol / dichloromethane, 0.07g, 85% yield). IR ($CHCl_3$): 3580, 3440, 2980, 2940, 2860, 1740, 1720, 1600, 1580, 1500, 1460, 1410, 1380, 1250, 1110, 935, 840cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.29-8.26 (m, 1H, H-8 Np), 7.82-7.79 (m, 1H, H-5 Np), 7.56 (s, 1H, H-4 Np), 7.50-7.45 (m, 2H, H-6, H-7 Np), 7.43-7.25 (m, 5H, Ph), 7.01 (s, 1H, H-2 Np), 6.27-6.23 (m, 1H, $NpOCH_2C\underline{H}=CH_2$), 5.90-5.82 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.54 (d, J=17.3Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.34 (d, J=10.5Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.26 (dd, J=1.2, 17.9Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.19 (dd, J=1.2, 10.5Hz, 1H, $OCH_2CH=C\underline{H}_2$), 5.12

(d, J=8.1Hz, 1H, H-3)5.10 (d, J=12.2Hz, 1H, $PhC\underline{H}_2$), 4.90 (d, J=12.1Hz, 1H, $PhC\underline{H}_2$), 4.84-4.70 (m, 3H, H-5, $NpOC\underline{H}_2CH{=}CH_2$), 4.17-4.12 (m, 1H, H-4), 4.03-43.94 (m, 2H, $OC\underline{H}_2CH{=}CH_2$), 3.70 (d, 1H, NH), 3.50-3.38 (m, 2H, H-6), 3.23 (s, 1H, OH), 2.00 (s, 3H, OAc), 1.69 (s, 3H, CH_3), 0.75 (s, 9H, t-Bu), -0.09 (s, 6H, $SiCH_3$). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 170.33, 156.57, 154.29, 142.68, 134.27, 134.12, 133.98, 133.48, 128.51, 128.29, 128.19, 127.94, 126.64, 125.22, 124.93, 121.98, 117.57, 117.33, 117.25, 117.09, 117.03, 103.50, 84.11, 76.78, 75.53, 74.33, 74.17, 70.14, 68.90, 68.96, 62.19, 50.48, 26.36, 25.74, 25.64, 21.02, 20.93,-5.69, -5.75 MS : Calcd. for $(M-H)^-$ ($C_{38}H_{51}NO_8Si$ - H)$^-$ ion: 676.3306, Found: 676.3284 (-3.2ppm).

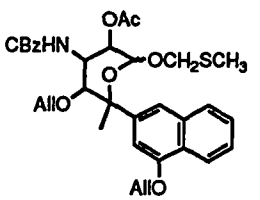
4.37. Preparation of (2S,3R,4S,5S)-5-(O-acetyl)-3-(allyloxy) -4-(N-benzyloxycarbonyl)-6-(hydroxy)-2-[1-(allyloxy)-naphth-3-yl]-2-hexanol (188).



Silyl ether **187** (0.04g, 0.06mmol) was dissolved in 1ml of tetrahydrofuran and tetrabutylammonium fluoride (0.2ml, 0.2mmol in 1M THF) was added. The mixture was stirred for 1h at room temperature and was concentrated under reduced pressure. The concentrate was purified by PLC to obtain the desired product. (Silica gel, 50% ethyl acetate /

petroleum ether, 0.03g, 84% yield). IR ($CHCl_3$): 3585, 3420, 2980, 2940, 1730, 1710, 1635, 1605, 1585, 1495, 1450, 1410, 1375, 1245, 1070, 995, 910cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.30-8.25 (m, 1H, H-8 Np), 7.82-7.77 (m, 1H, H-5 Np), 7.52-7.46 (m, 3H, H-4, H-6, H-7 Np), 7.34-7.28 (m, 4H, Ph), 7.09 (m, 1H, Ph), 6.88 (s, 1H, H-2 Np), 6.24-6.10 (m, 1H, $NpOCH_2C\underline{H}=CH_2$), 6.01-5.92 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.58-5.51 (dd, J=1.4, 17.3Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.36-5.32 (dd, J=1.2, 10.5Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.36-5.30 (m, 2H, $OCH_2CH=C\underline{H}_2$, H-3), 5.25 (d, J=10.5Hz, 1H, $OCH_2CH=C\underline{H}_2$), 4.96 (d, J=12.1Hz, 1H, $Ph\underline{CH}_2$), 4.79-4.74 (m, 3H, H-4, $NpOC\underline{H}_2CH=CH_2$), 4.64 (d, J=12.1Hz, 1H, $Ph\underline{CH}_2$), 4.28-3.82 (m, 8H, $OC\underline{H}_2CH=CH_2$, H-5, H-6, NH, OH), 1.96 (s, 3H, OAc), 1.72 (s, 3H, CH_3). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 171.00, 156.30, 154.33, 141.86, 134.13, 133.18, 128.56, 128.39, 128.30, 128.25, 128.01, 127.93, 127.83, 126.86, 125.30, 124.77, 121.98, 117.92, 117.49, 117.43, 115.83, 102.59, 82.95, 76.93, 73.60, 68.92, 67.76, 66.76, 65.75, 52.06, 28.64, 20.72. MS : Calcd. for $(M+H)^+$ ($C_{32}H_{37}NO_8$ + H)$^+$ ion: 564.2597, Found: 564.2535 (-11.1ppm).

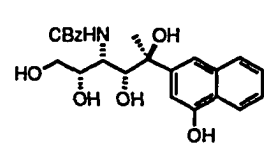
4.38. Preparation of (2S,3R,4S,5S,6R)-5-(acetoxy)-3-(allyloxy)-4-(N-benzyloxycarbonyl)-2-(methyl)-6-(methylthiomethoxy)-2-[1-(allyloxy)-naphth-3-yl] tetrahydropyran (189) and its (2S,3R,4S,5S,6S) epimer.



Dimethylsulfoxide (0.126ml, 1.78mmol) was dissolved in dichloromethane and the solution was cooled to -70°C. Trifluoroacetic acid (0.25ml, 1.78mmol) was added into the above solution dropwise. A white precipitate of trifluoroacetate salt was formed after 10min. A solution of alcohol **188** (0.05g, 0.089mmol) in 1ml of dichloromethane was added dropwise and the solution was stirred at -70 to -60°C for 180min. Then the reaction was quenched with triethylamine (0.3ml) at -60°C and the reaction mixture was allowed to warm up to 0°C (ca. 1h). Dimethylsulfoxide and triethylamine were removed under reduced pressure and the concentrate was dissolved in dichloromethane and washed with water. After usual workup, the product was purified by PLC (silica gel, 35% ethyl acetate / petroleum ether, 0.03g, 55% yield). IR ($CHCl_3$): 3420, 2920, 2860, 1735, 1715, 1605, 1585, 1490, 1410, 1380, 1280, 1200, 1100, 1025, 930, 785, 700cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.31 (m, 1H, H-8 Np),

7.80 (m, 1H, H-5 Np), 7.52-7.48 (m, 2H, H-6, H-7 Np), 7.39-7.30 (m, 6H, H-4, Ph), 7.01 (s, 1H, H-2 Np), 6.26-6.14 (m, 1H, $NpOCH_2C\underline{H}=CH_2$), 5.61 (d, J=8.6Hz, 1H, H-3), 5.59-5.52 (dd, J=1.5, 17.3Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.51-5.39 (m, 1H, $OCH_2C\underline{H}=CH_2$), 5.39-5.34 (dd, J=1.4, 10.5Hz, 1H, $NpOCH_2CH=C\underline{H}_2$), 5.06 (d, J=12.1Hz, 1H, $PhC\underline{H}_2$), 4.97-4.88 (m, 6H, H-4, H-5, H-6, $PhC\underline{H}_2$, $OCH_2CH=C\underline{H}_2$), 4.87-4.75 (m, 2H, $NpOC\underline{H}_2CH=CH_2$), 4.42 (d, J=10.4Hz, 1H, $OC\underline{H}_2S$), 4.30 (d, J=10.4Hz, 1H, $OC\underline{H}_2S$), 4.16 (d, J=1Hz, 1H, NH), 3.70-3.64 (dd, J=5.8, 12.1Hz, 1H, $OC\underline{H}_2CH=CH_2$), 3.44-3.38 (dd, J=5.9, 11.9Hz, 1H, $OC\underline{H}_2CH=CH_2$), 2.26 (s, 3H, $SC\underline{H}_3$), 2.19 (s, 3H, OAc), 1.74 (s, 3H, CH_3). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 183.36, 156.06, 139.48, 133.97, 133.77, 133.25, 128.54, 128.46, 128.25, 128.12, 127.84, 126.84, 125.72, 125.34, 121.98, 119.68, 117.75, 117.54, 103.97, 82.06, 74.13, 68.97, 67.77, 67.20, 67.08, 57.32, 20.52, 18.11, 14.95. MS : Calcd. for $(M-H)^-$ ($C_{34}H_{39}NO_8S$ - H)$^-$ ion: 620.2318, Found: 620.2317 (-0.3ppm).

4.39. Preparation of (2S,3R,4S,5S)-4-(N-benzyloxy-carbonyl)-3,5,6-(trihydroxy)-2-[1-(hydroxy)-naphth-3-yl]-2-hexanol (211).

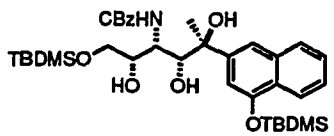


Anhydrous zinc chloride (0.02g, 0.15mmol, dried at 110°C / 0.5mm for 5h) was added to the solution of allyl

ether **176** (0.03g, 0.05mmol) in dry tetrahydrofuran (1ml) and the suspension was stirred at room temperature for 15min. Then tetrakis(triphenylphosphine)palladium (0.01g, 0.01mmol) was added and stirring was continued for 5min. Tributyltin hydride (0.05g, 0.17mmol) was added into the above suspension slowly. After stirring for 30min, the reaction mixture was diluted with 5ml of ethyl acetate and 1ml of water. The mixture was acidified with 5% hydrochloric acid solution and the product was extracted with ethyl acetate (10ml x 3 times). All the ethyl acetate layers were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The concentrate was dissolved in acetonitrile-hexane (5ml-10ml) and the solution was stirred for 15min. Acetonitrile layer, which contained the product, was collected and concentrated under reduced pressure. The hexane layer, which contained tributyltin compound, was discarded.

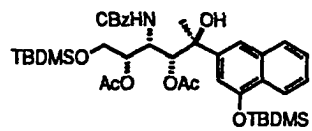
The product was purified by PLC. (Silica gel, 5% methyl alcohol / dichloromethane, 0.02g, 90% yield). ^{1}H NMR, 300MHz, (CD_3OD): δ 8.13 (d, J=8.1Hz, 1H, H-8 Np), 7.80-7.74 (m, 2H, H-4, H-5, Np), 7.73-7.23 (m, 7H, H-6, H-7 Ph), 7.02 (d, J=1.3Hz, 1H, H-2 Np), 5.02 (d, J=6.6Hz, 1H, H-3), 4.95-4.91 (m, 6H, Ph$\underline{C}H_2$, 5 OH, CD_3OD), 4.74 (d, J=12.3Hz, 1H, Ph$\underline{C}H_2$), 4.12 (d, J=1.7Hz, 1H, NH), 3.84-3.82 (m, 1H, H-4), 3.70-3.82 (m, 1H, H-5), 3.50-3.42 (m, 2H, H-6), 1.66 (s, 3H, CH_3).

4.40. Preparation of (2S,3R,4S,5S)-4-(N-benzyloxycarbonyl)-6-(*tert*butyldimethylsilyloxy)-3,5-(dihydroxy)-2-[1-(*tert*butyldimethylsilyloxy)-naphth-3-yl]-2-hexanol (212).



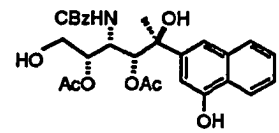
A solution of *tert*-butyldimethylsilyl chloride (0.02g, 0.15mmol in 0.3ml dichloromethane) and a solution of triethylamine (0.02ml, 0.17mmol in 0.3ml dichloromethane) were added to a solution of alcohol **211** (0.02g, 0.04mmol in 0.5ml dichloromethane) with dimethylaminopyridine (0.001g). After stirring 1h at room temperature, the reaction was diluted with 2ml of dichloromethane and washed with water (3ml x 2 times). The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The product was purified by PLC (silica gel, 8% methyl alcohol / dichloromethane, 0.02g, 75% yield). ^{1}H NMR, 300MHz, ($CDCl_3$): δ 8.12 (d, J=9.0Hz, H-8 Np), 7.80 (m, 1H, H-5 Np), 7.55 (s, 1H, H-4 Np), 7.46-7.42 (m, 2H, H-6, H-7 Np), 7.33-7.23 (m, 5H, Ph), 6.95 (s, 1H, H-2 Np), 5.40 (d, J=8.2Hz, 1H, H-3), 5.03 (d, J=12.0Hz, 1H, Ph$\underline{CH_2}$), 4.81 (d, J=12.0Hz, 1H, Ph$\underline{CH_2}$), 4.15 (s, 1H, NH), 3.74-3.70 (m, 2H, H-4, H-5), 3.43-3.40 (m, 2H, H-6), 1.66 (s, 3H, CH_3), 1.10 (s, 9H, *t*Bu), 0.77 (s, 9H, *t*Bu), 0.30 (s, 3H, CH_3), 0.29 (s, 3H, CH_3), -0.05 (s, 3H, CH_3), -0.06 (s, 3H, CH_3).

4.41. Preparation of (2S,3R,4S,5S)-3,5-(di-O-acetyl)-4-(N-benzyloxycarbonyl)-6-(*tert*butyldimethylsilyloxy)-2-[1-(*tert*butyldimethylsilyloxy)-naphth-3-yl]-2-hexanol (213)



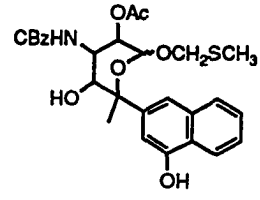
Acetic anhydride (0.01g, 0.1mmol) was added to a solution of alcohol **212** (0.02g, 0.03mmol), lutidine (0.02g, 0.18mmol) and dimethylamino pyridine (0.001ml) in 1ml of dichloromethane. After stirring 2h at room temperature, the reaction was diluted with 2ml of dichloromethane and was washed with water (3ml x 2 times). The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The product was purified by PLC. (Silica gel, 4% methyl alcohol / dichloromethane, 0.02g, 67% yield). ^{1}H NMR, 300MHz, ($CDCl_3$): δ 8.14 (m, 1H, H-8 Np), 7.86 (m, 1H, H-5 Np), 7.64 (s, 1H, H-4 Np), 7.46-7.42 (m, 2H, H-6, H-7 Np), 7.42-7.32 (br s, 5H, Ph), 7.00 (s, 1H, H-2 Np), 5.40 (d, J=2.4Hz, 1H, NH), 5.26 (d, J=9.7Hz, 1H, H-3), 5.20 (d, J=11.9Hz, 1H, Ph$\underline{CH_2}$), 5.08 (d, J=11.9Hz, 1H, Ph$\underline{CH_2}$), 4.70-4.66 (m, 1H, H-5), 4.22 (d, J=9.7Hz, 1H, H-4), 4.10 (s, 1H, OH), 3.42-3.32 (m, 2H, H-6), 2.12 (s, 3H, OAc), 1.90 (s, 3H, OAc), 1.55 (s, 3H, CH_3), 1.12 (s, 9H, *t*Bu), 0.62 (s, 9H, *t*Bu), 0.35 (s, 3H, CH_3), 0.33 (s, 3H, CH_3), -0.16 (s, 3H, CH_3), -0.17 (s, 3H, CH_3).

4.42. Preparation of (2S,3R,4S,5S)-3,5-(di-O-acetyl)-4-(N-benzyloxycarbonyl)-6-(hydroxy)-2-[1-(hydroxy)-naphth-3-yl]-2-hexanol (214).



Bis-silyl bis-acetate **213** (0.01g, 0.013mmol) was dissolved in 1ml of tetrahydrofuran and tetrabutylammonium fluoride (0.3ml, 0.03mmol in 0.1M THF) was added. The mixture was stirred for 1h at room temperature and was diluted with 2ml of ethyl acetate. The solution was washed with water (3ml x 2 times). The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The concentrate was purified by PLC to obtain the desired product. (Silica gel, 5% methyl alcohol / dichloromethane, 0.005g, 70% yield). ^{1}H NMR, 300MHz, ($CDCl_3$): δ 8.20 (d, J=7.0Hz, 1H, H-8 Np), 7.84 (d, J=7.3Hz, 1H, H-5 Np), 7.50-7.44 (m, 3H, H-4, H-6, H-7 Np), 7.32-7.24 (m, 5H, Ph), 7.00 (s, 1H, H-2 Np), 5.33 (d, J=8.9Hz, 1H, H-3), 5.12-5.06 (m, 2H, H-5, NH), 5.04 (d, J=11.9Hz, 1H, Ph$\underline{CH_2}$), 4.86 (d, J=11.9Hz, 1H, Ph$\underline{CH_2}$), 4.13-4.00 (m, 6H, H-4, H-6, OH), 1.96 (s, 3H, OAc), 1.74 (s, 3H, OAc), 1.65 (s, 3H, CH_3).

4.43. Preparation of (2S,3R,4S,5S,6R)-5-(acetoxy)-4-(N-benzyloxycarbonyl)-3-(hydroxy)-2-(methyl)-6-(methylthiomethoxy)-2-[1-(hydroxy)-naphth-3-yl] tetrahydropyran (229). and its (2S,3R,4S,5S,6S) epimer.

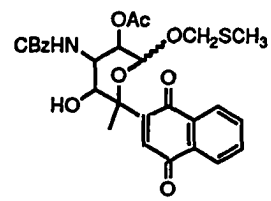


Anhydrous zinc chloride (0.032g, 0.236mmol, dried at 110°C / 0.5mm for 5h) was added to the solution of allyl ether **189** (0.04g, 0.09mmol) in dry tetrahydrofuran (2ml) and the suspension was stirred at room temperature for 15min. Then tetrakis(triphenylphosphine)palladium (0.02g, 0.02mmol) was added and stirring was continued for 10min. Tributyltin hydride (0.104g, 0.36mmol) was added into the above suspension slowly. After stirring for 30min, the reaction mixture was diluted with 5ml of ethyl acetate and 1ml of water. The mixture was acidified with 5% hydrochloric acid solution and the product was extracted with ethyl acetate (10ml x 3 times). All the ethyl acetate layers were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The concentrate was dissolved in acetonitrile-hexane (5ml-10ml) and the solution was stirred for 15min. Acetonitrile layer,

which contained the product, was collected and concentrated under reduced pressure. The hexane layer, which contained tributyltin compound, was discarded.

The product was purified by PLC. (Silica gel, 45% ethyl acetate / petroleum ether, 0.036g, 78% yield). **Note:** Could not removed tributyltin hydroxide completely. IR ($CHCl_3$): 3520, 3405, 3250, 2960, 2930, 2885, 1745, 1695, 1610, 1505, 1460, 1385, 1290, 1080, 1045cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 9.90 (s, 1H, OH-Np), 8.35 (m, 1H, H-8 Np), 7.79 (m, 2H, H-4, H-5 Np), 7.55-7.52 (m, 2H, H-6, H-7 Np), 7.44-7.38 (m, 5H, Ph), 7.29 (s, 1H, H-2 Np), 5.82 (br s, 1H, NH), 5.22 (s, 2H, OCH_2S), 4.55 (d, J=11.4Hz, 1H, $PhCH_2$), 4.55-4.50 (m, 1H, H-4), 4.44-4.36 (m, 2H, H-5, $PhCH_2$), 4.20-4.16 (d, J=10.6Hz, 1H, H-6), 4.03-3.95 (t, J=11.5, 11.8Hz, 1H, H-3), 2.74 (d, J=12.0Hz, 1H, OH), 1.91 (s, 3H, SCH_3), 1.89 (s, 3H, OAc), 1.78 (s, 3H, CH_3). ^{13}C NMR, 75Mz, ($CDCl_3$): δ 169.73, 160.47, 154.42, 135.38, 133.04, 133.21, 128.74, 128.66, 128.43, 127.44, 127.41, 126.10, 122.74, 118.28, 114.33, 77.23, 72.96, 68.29, 67.50, 64.96, 59.33, 29.70, 27.86, 20.59, 14.50.

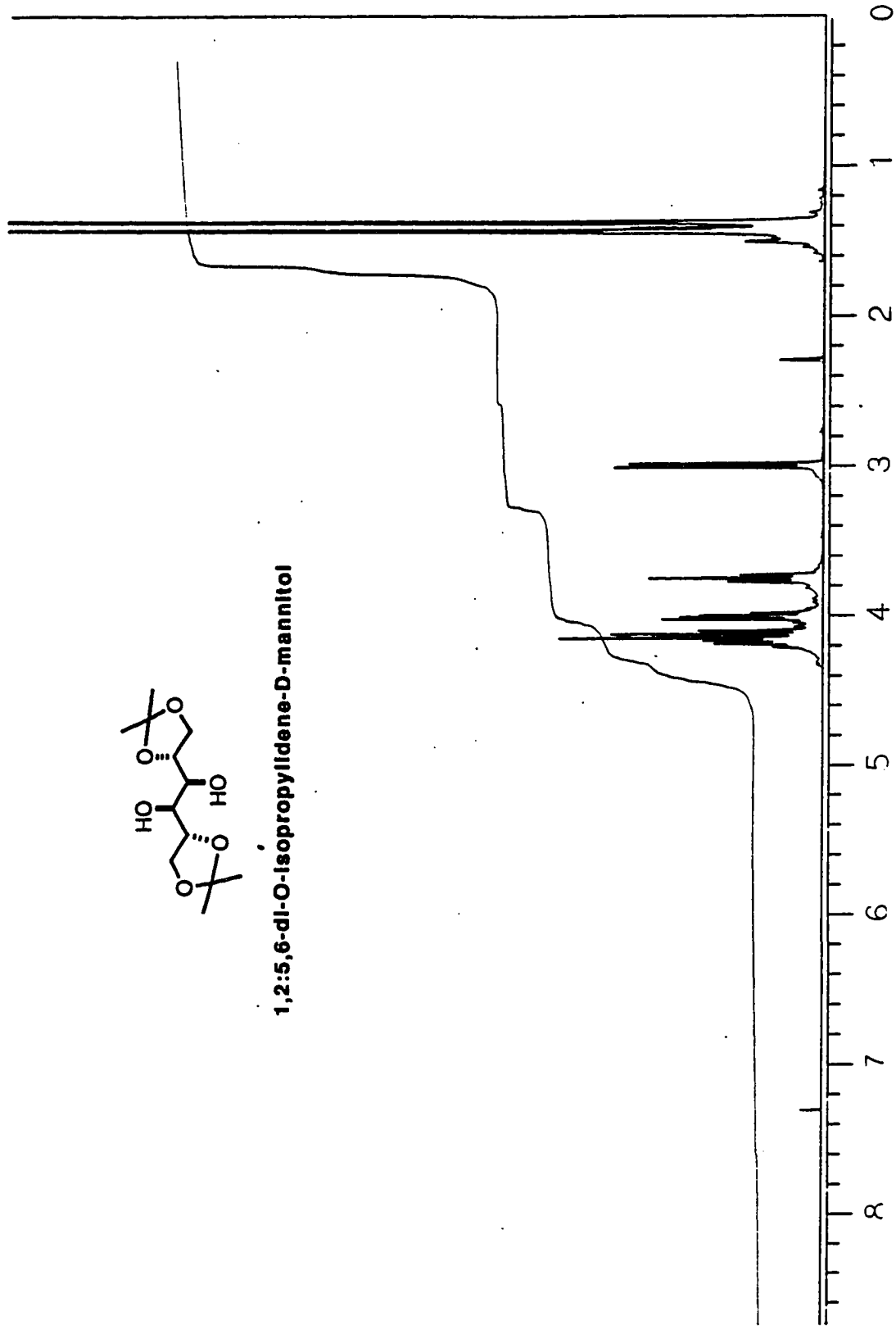
4.44. Preparation of (2S,3R,4S,5S,6R)-5-(acetoxy)-4-(N-benzyloxycarbonyl)-3-(hydroxy)-2-(methyl)-6-(methylthiomethoxy)-2-[1,4-(dioxo)-naphth-3-yl] tetrahydropyran (231).

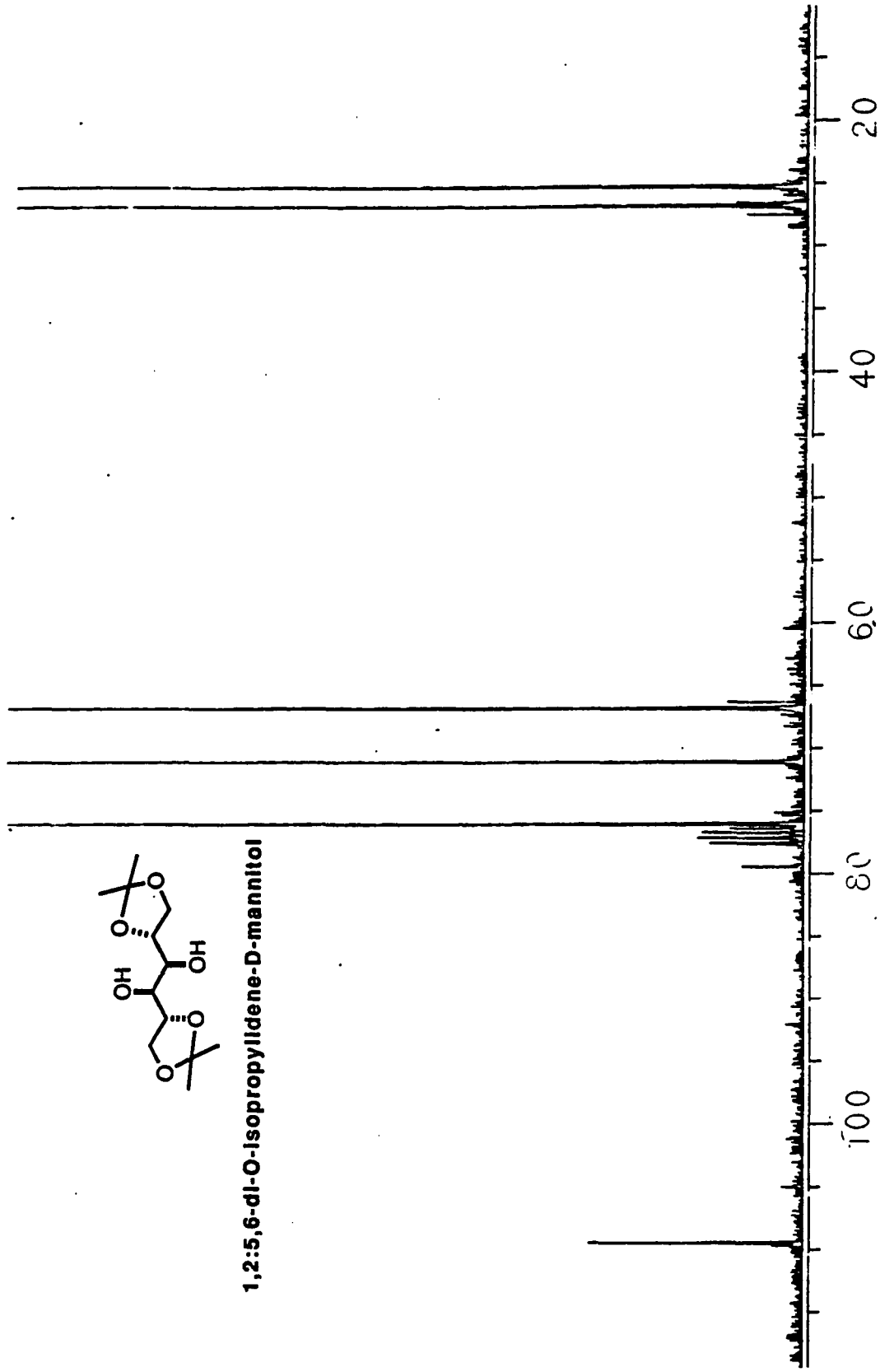


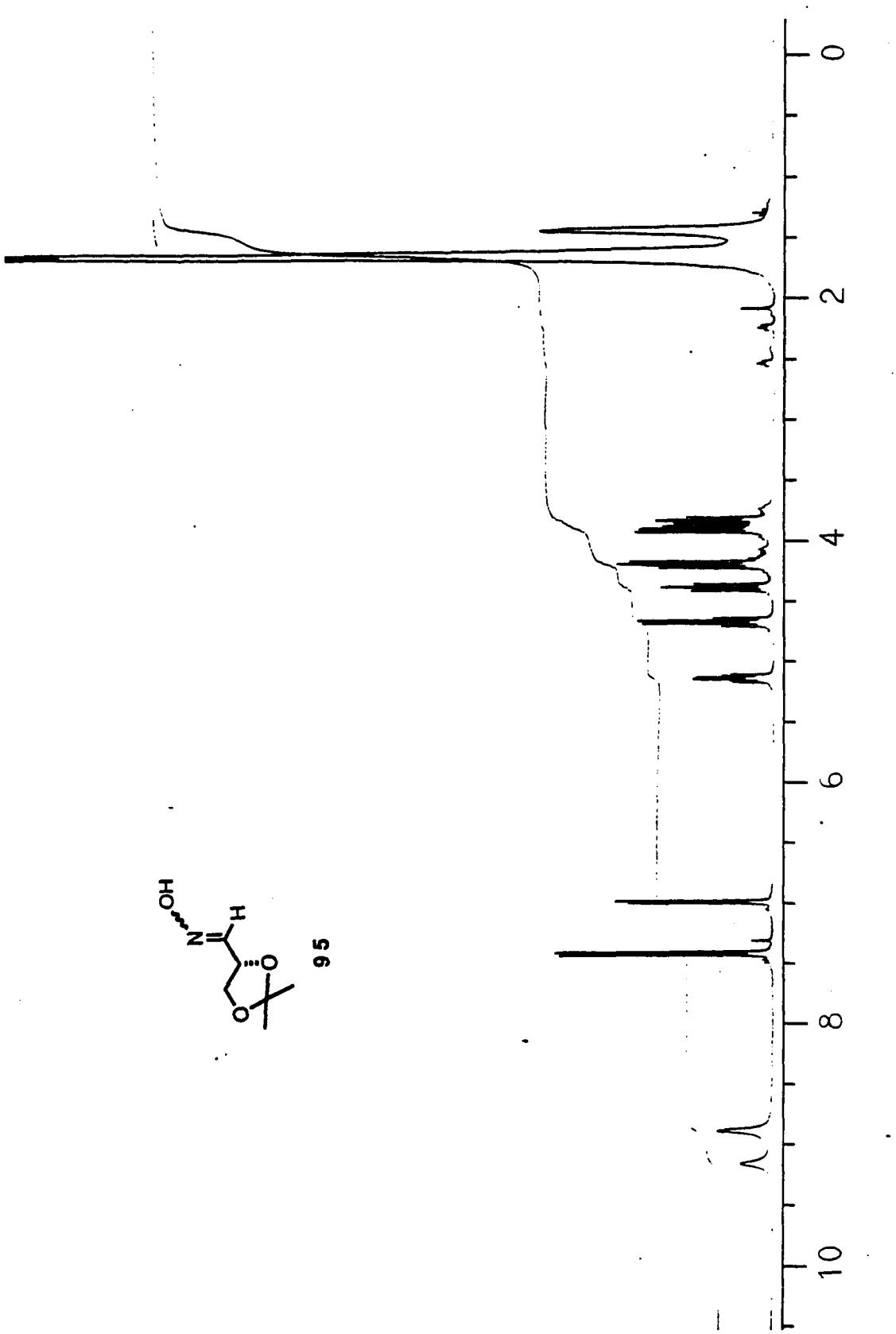
Naphthol **229** (0.019g, 0.037mmol) was dissolved in dry THF (3ml) with Salcomine (0.006g, 0.018mmol) and oxygen gas was bubbled into the solution for 1h at room temperature. Then the reaction was diluted with ethyl acetate (0.5ml) and Salcomine was filtered by passing through a short column of florisil and throughly washed with ethyl acetate. The filtrate was concentrate and the product was purified by PLC. (Silica gel, 45% ethyl acetate / petroleum ether, 0.015g, 73% yield). IR ($CHCl_3$): 3440, 2930, 1735, 1720, 1670, 1600, 1505, 1380, 1290, 1090, 1045, 915cm^{-1}. ^1H NMR, 300MHz, ($CDCl_3$): δ 8.13-8.08 (m, 2H, H-5, H-8 Np), 7.81-7.76 (m, 2H, H-6, H-7 Np), 7.41-7.33 (m, 5H, Ph), 7.26 (s, 1H, H-3 Np), 5.36-5.31 (br s, 1H, NH), 5.20 (s, 2H, $OC\underline{H}_2S$), 5.08 (d, J=11.6Hz, 1H, $PhC\underline{H}_2$), 4.98 (d, J=11.6Hz, 1H, $PhC\underline{H}_2$), 4.74 (d, J=12.0Hz, 1H, H-5), 4.54 (d, J=11.7Hz, 1H, H-6), 4.41-4.34 (dd, J=7.6, 11.8Hz, 1H, H-4), 3.70 (t, J=11.8, 11.9Hz, 1H, H-3), 3.04 (d, J=11.4Hz, 1H, OH), 2.22 (s, 3H, $SC\underline{H}_3$), 1.97 (s, 3H, OAc), 1.88 (s, 3H, CH_3). ^{13}C NMR, 75Mz,

($CDCl_3$): δ 183.93, 169.66, 144.22, 141.67, 136.09, 134.52, 134.11, 132.32, 131.89, 128.57, 128.24, 128.16, 126.95, 126.57, 74.80, 72.35, 70.93, 67.48, 65.33, 57.19, 20.83, 20.21, 14.85.

5. APPENDIX







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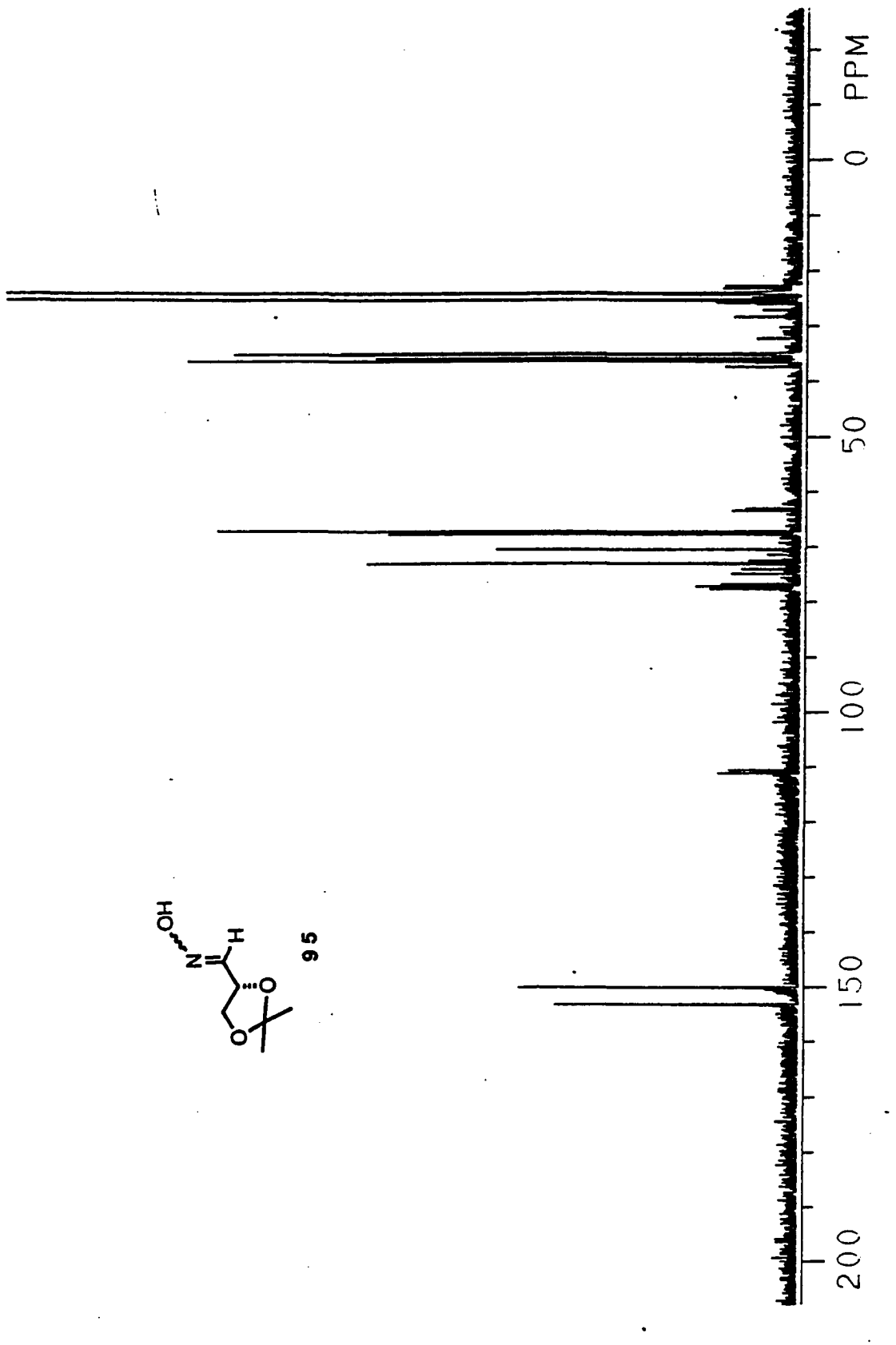

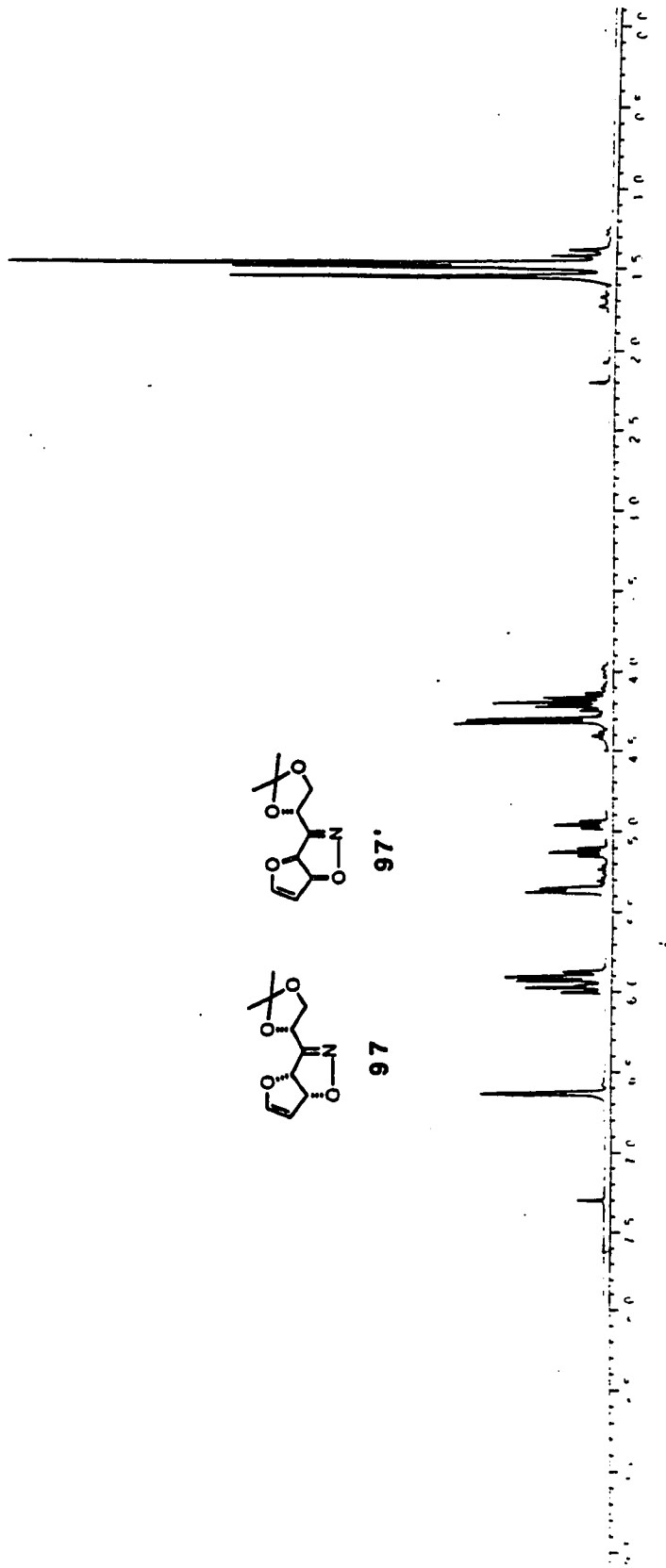

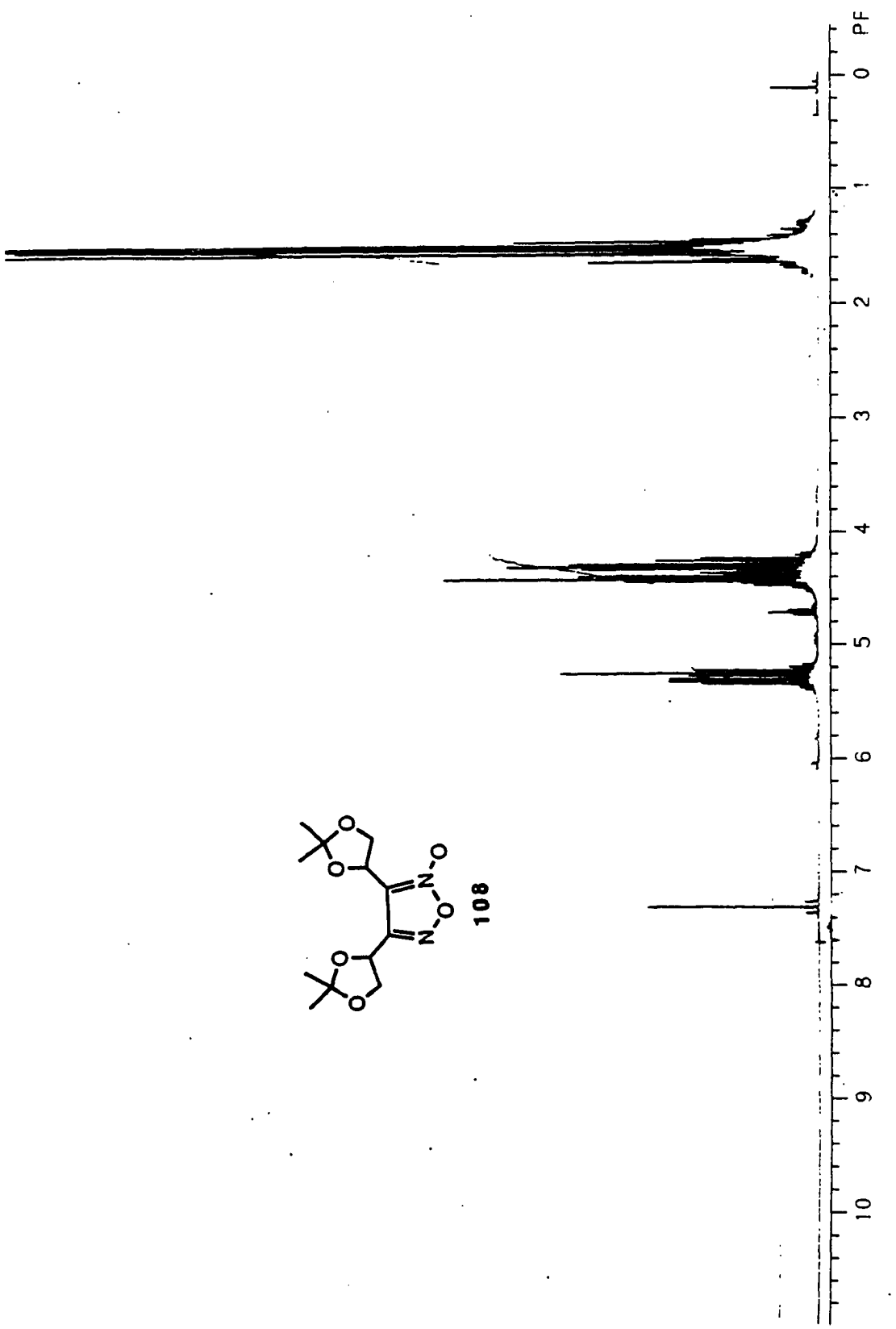

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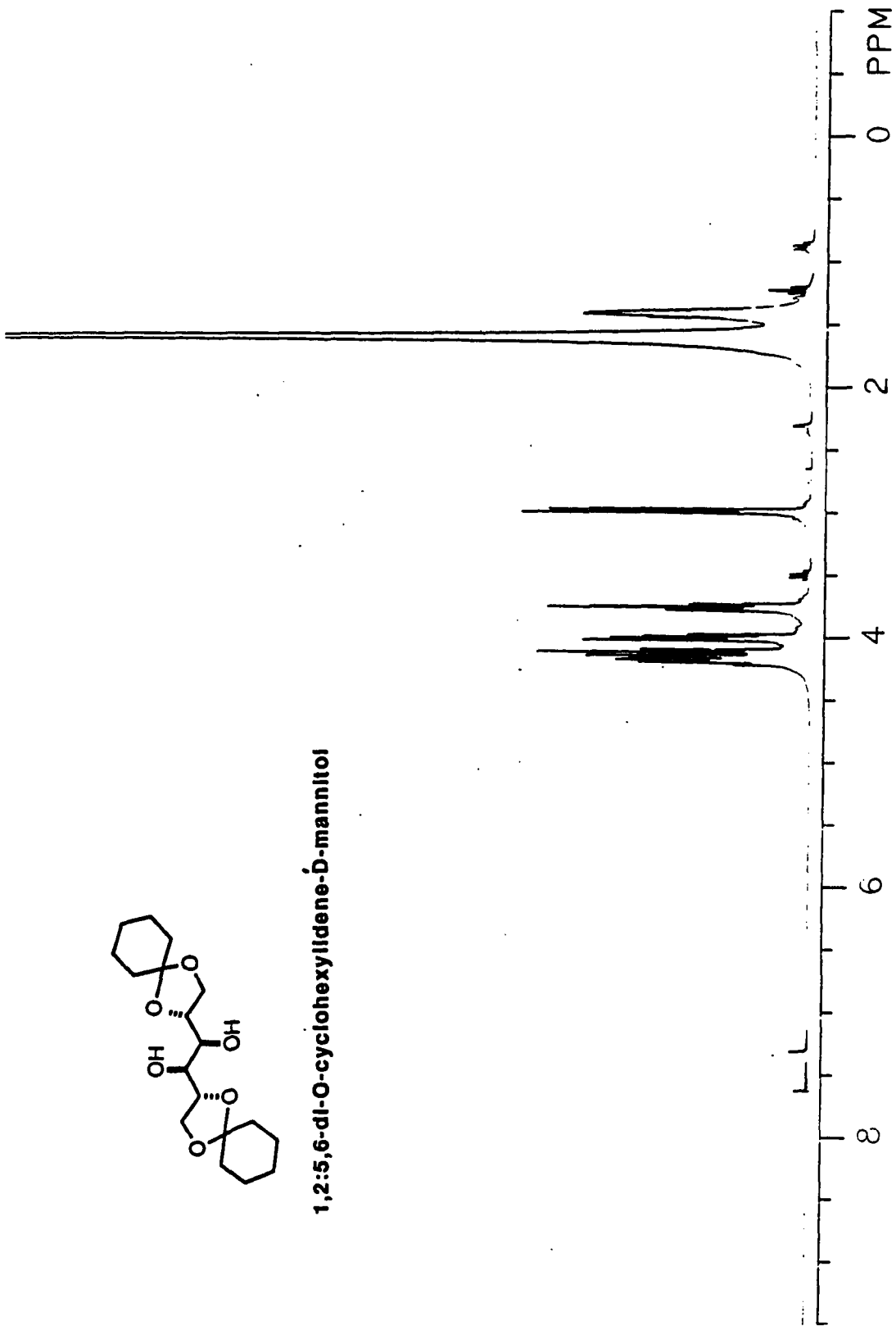

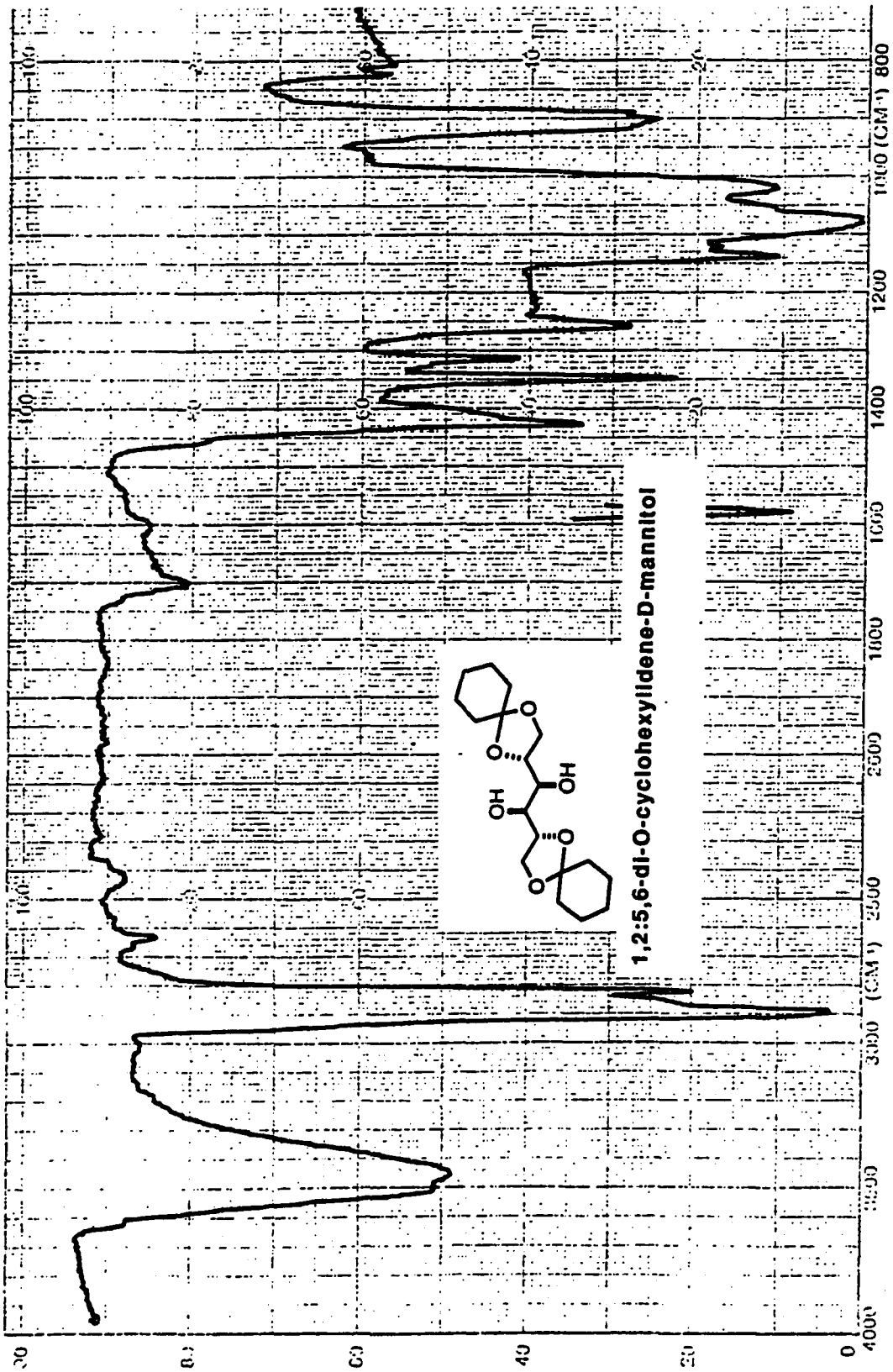

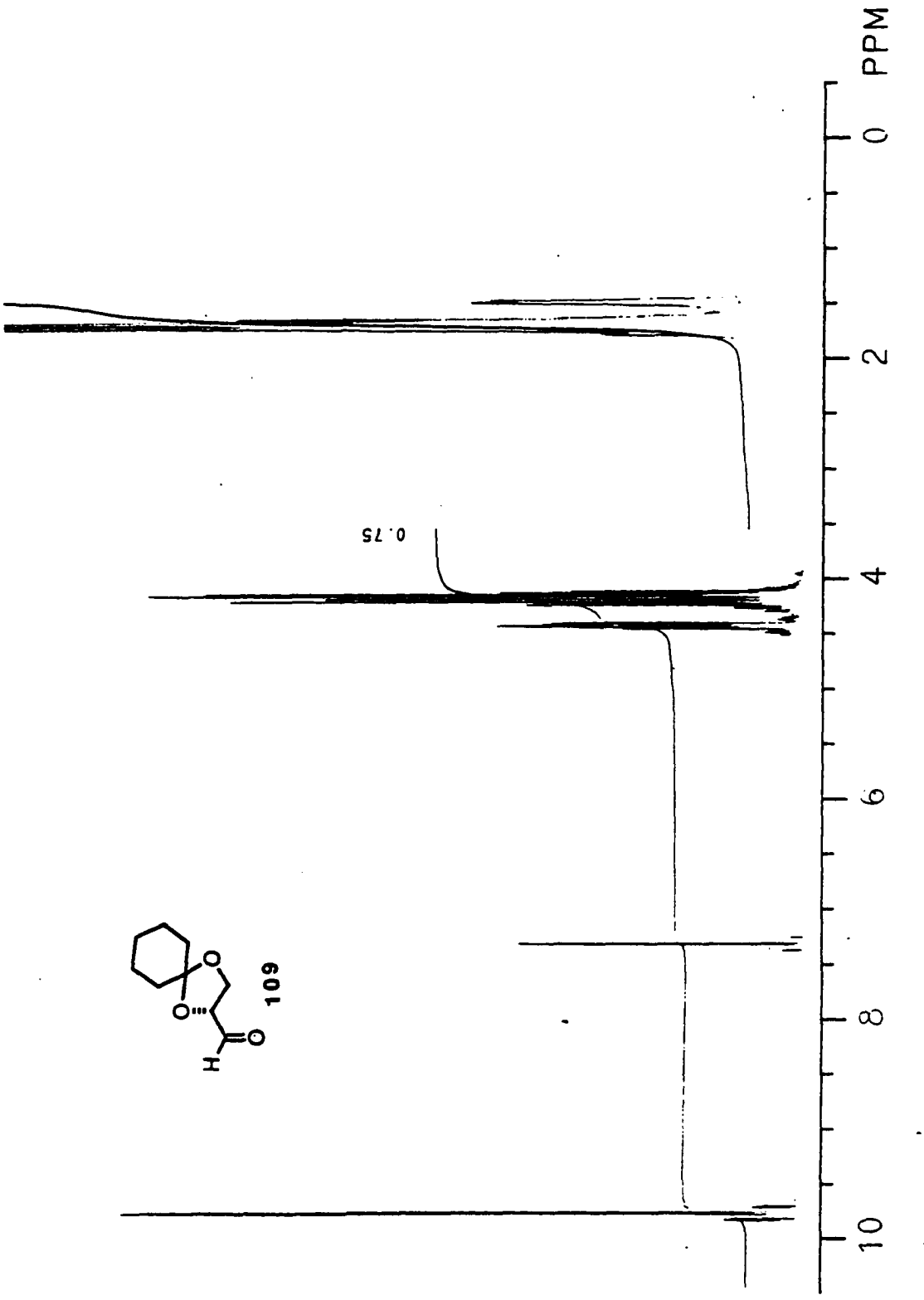

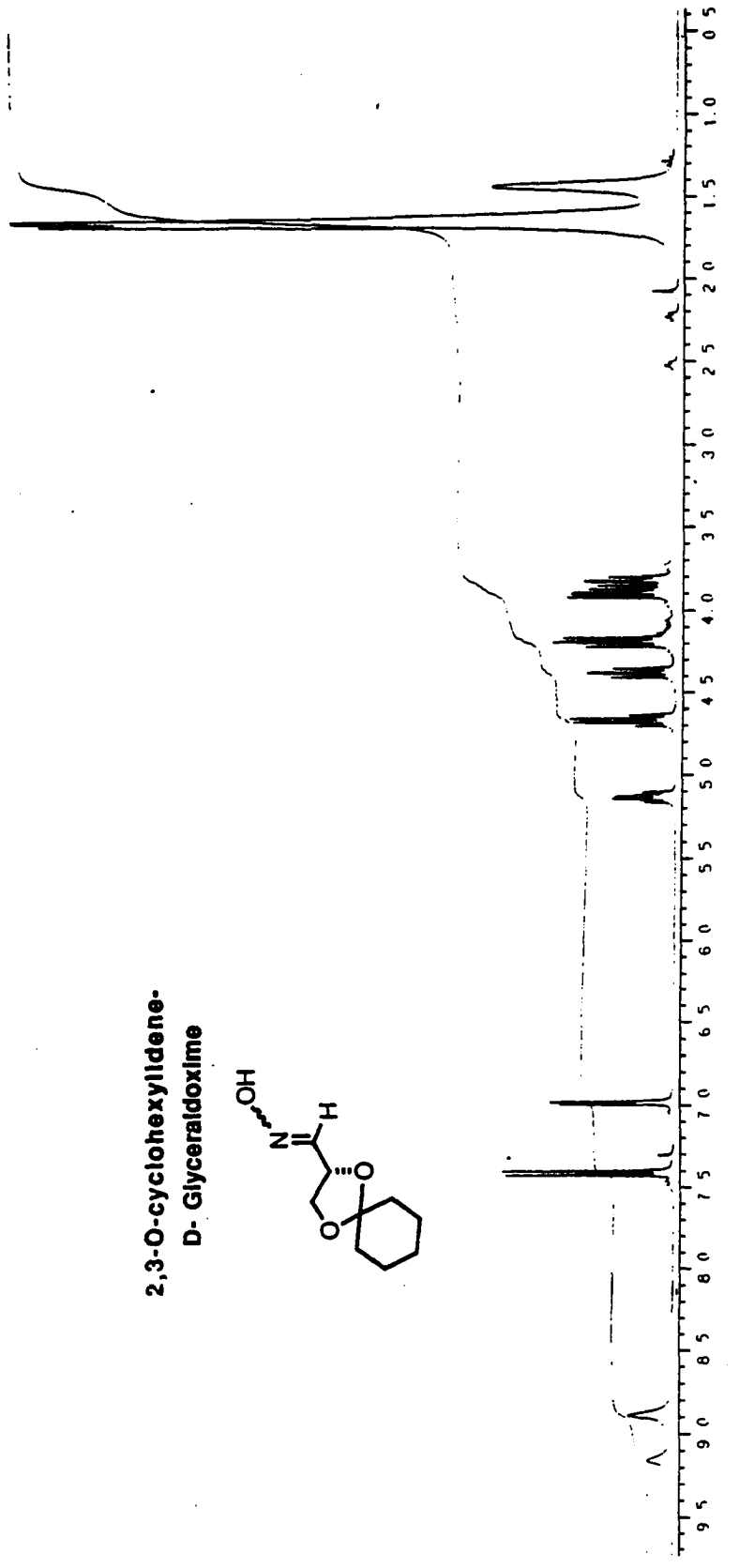

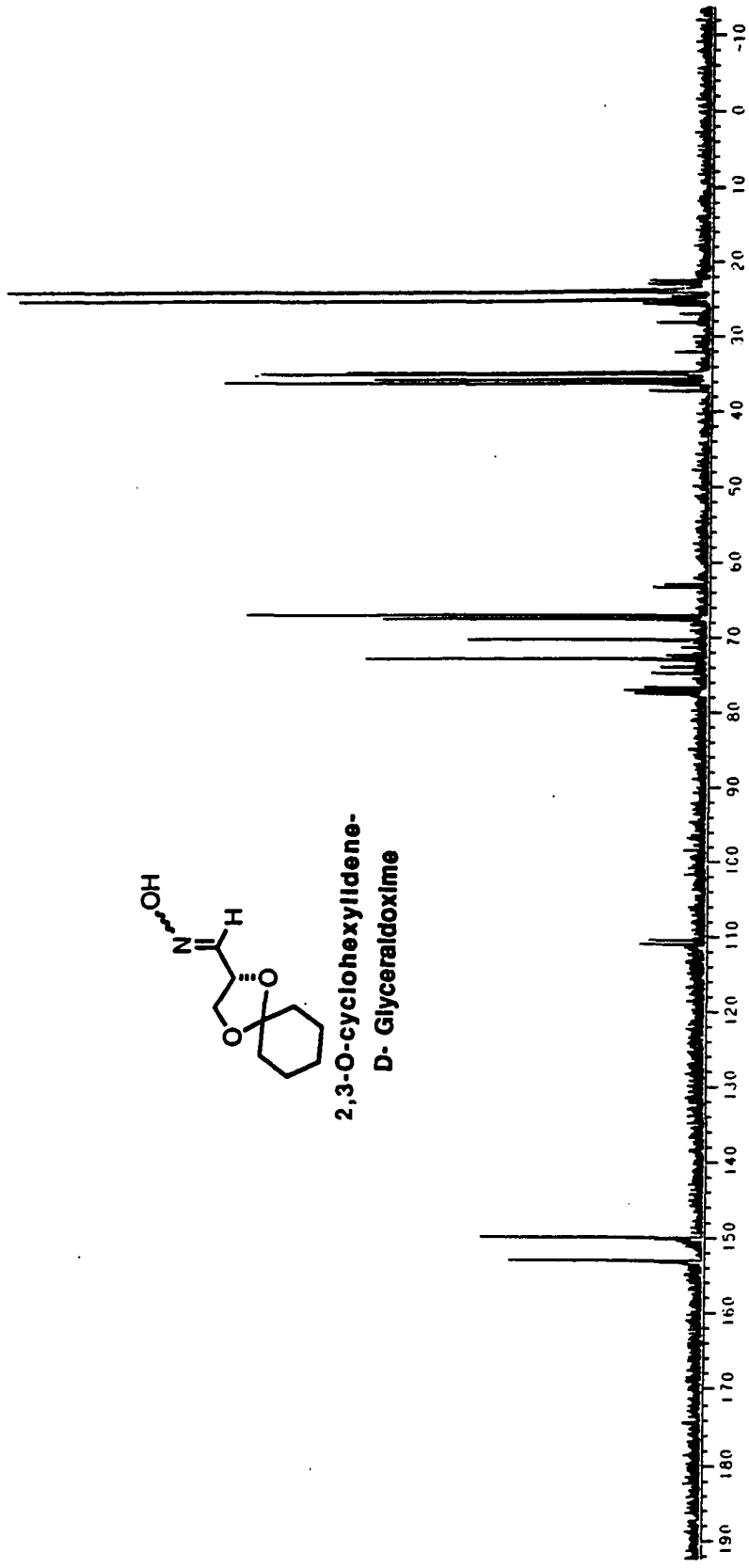

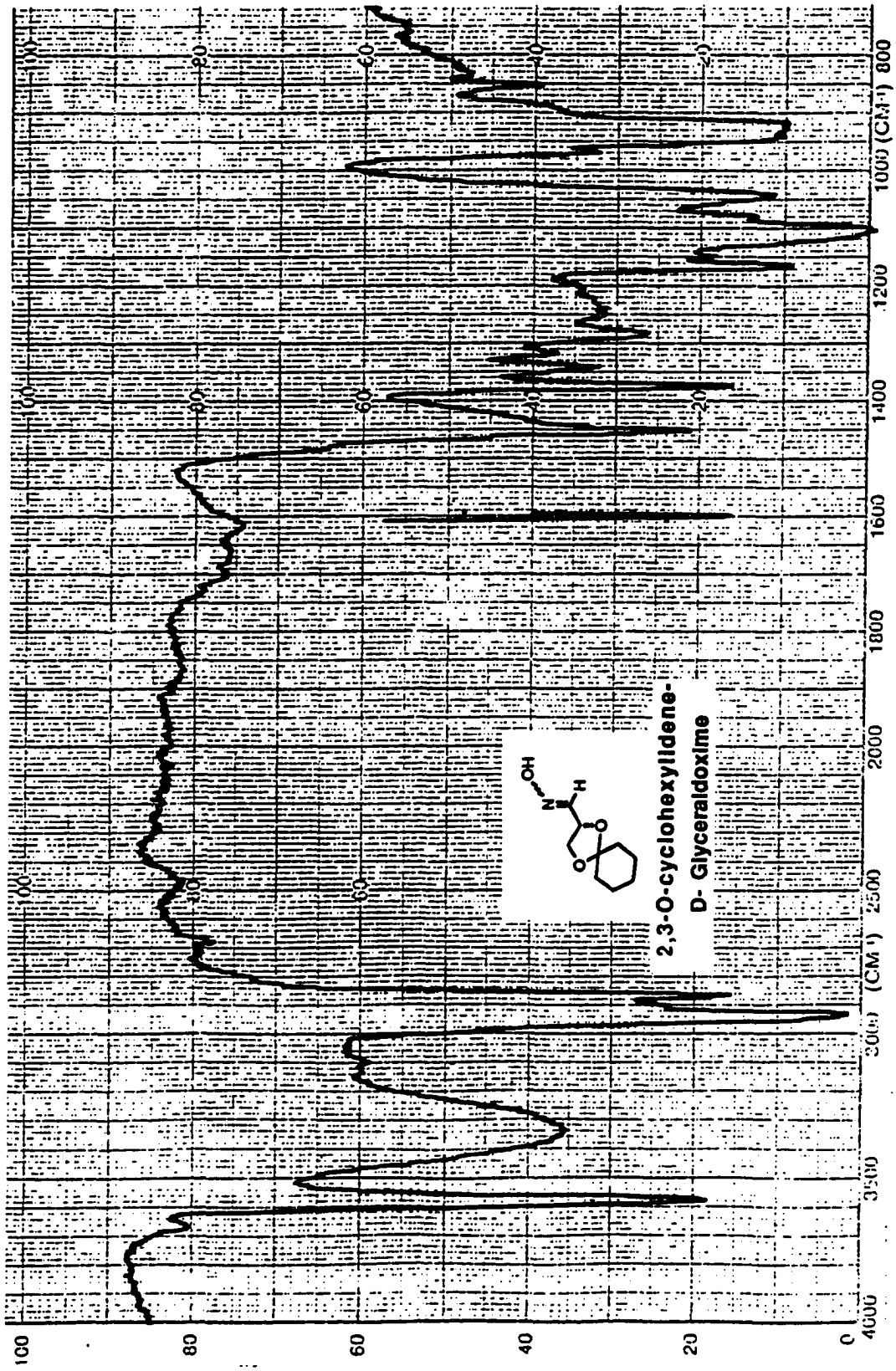

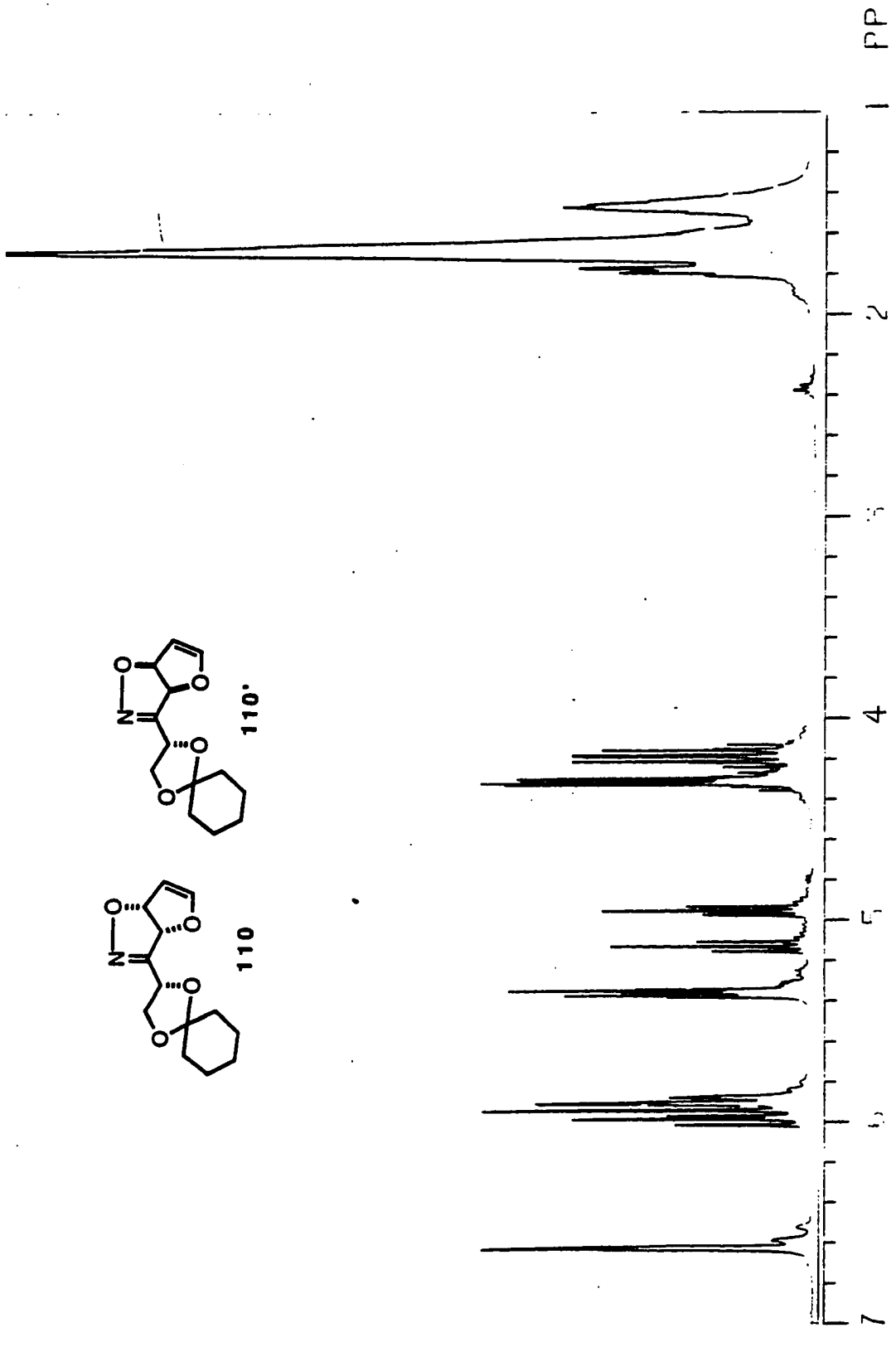

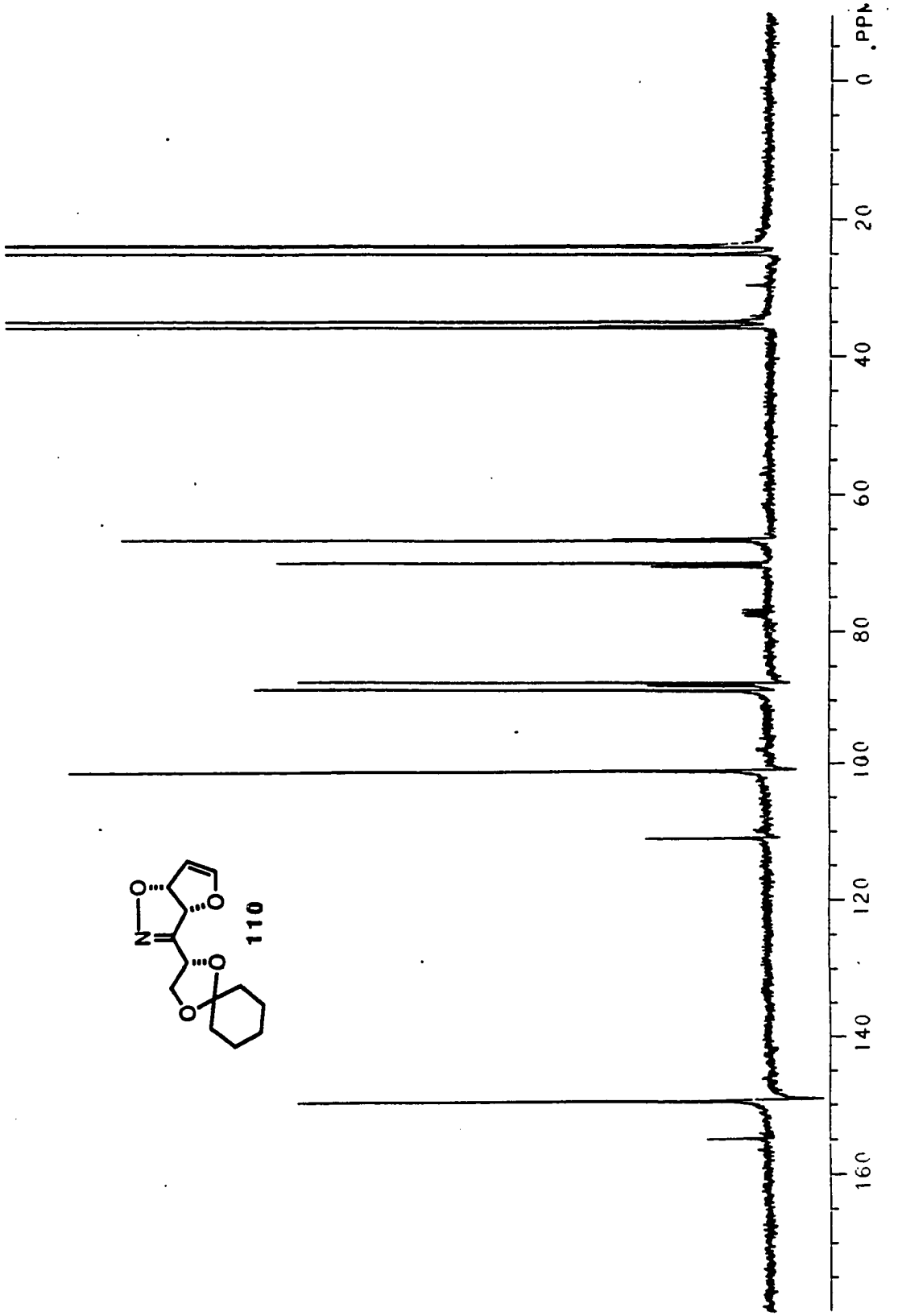

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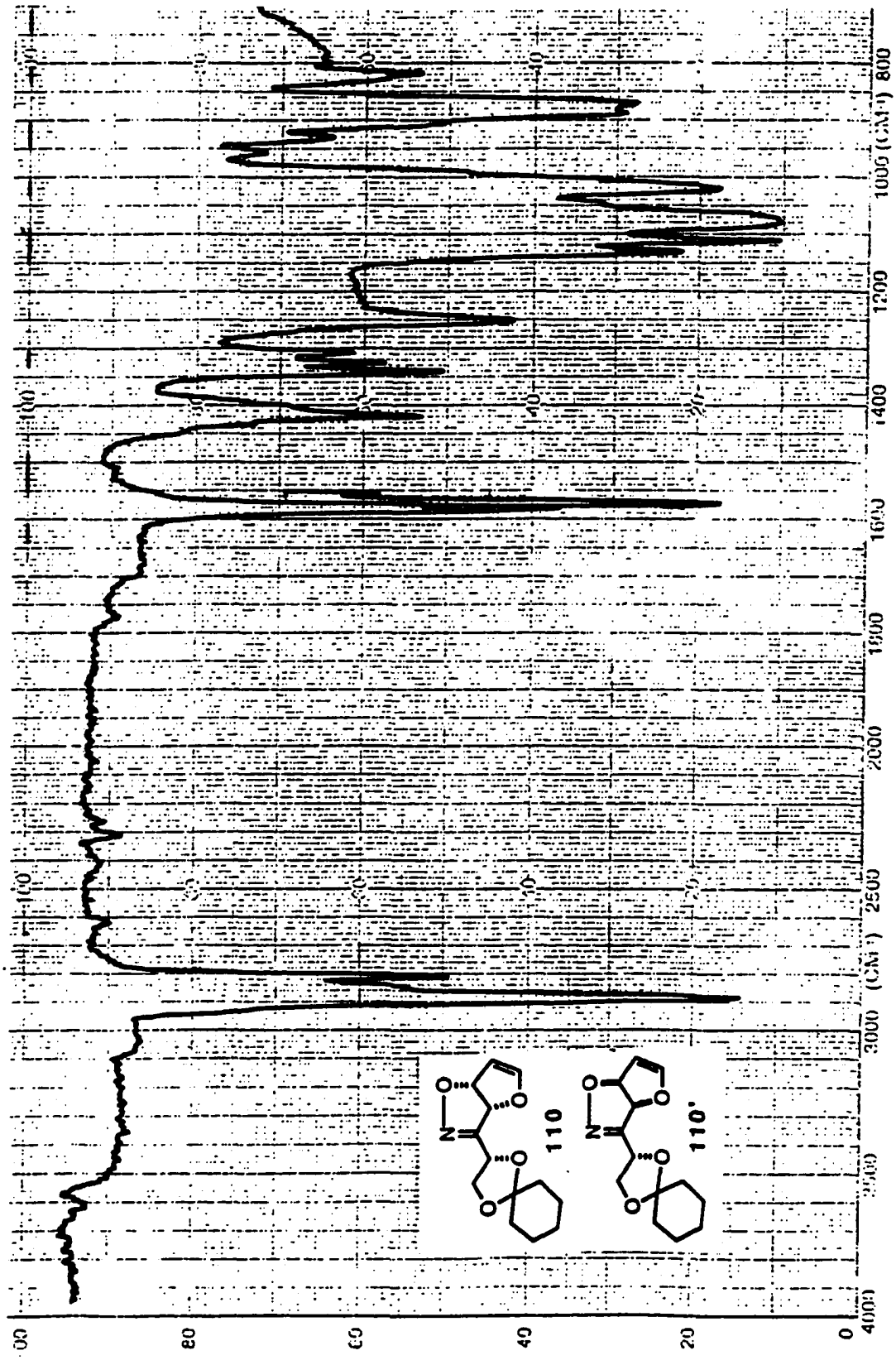

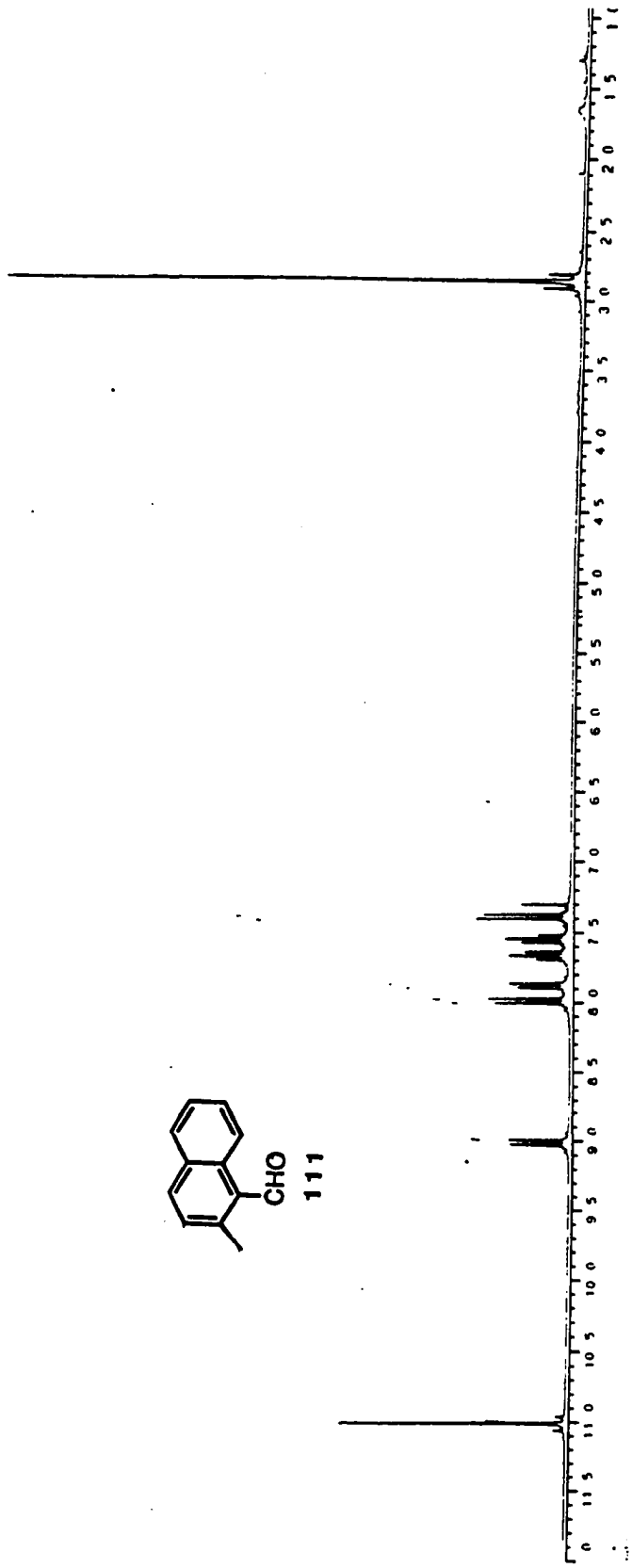

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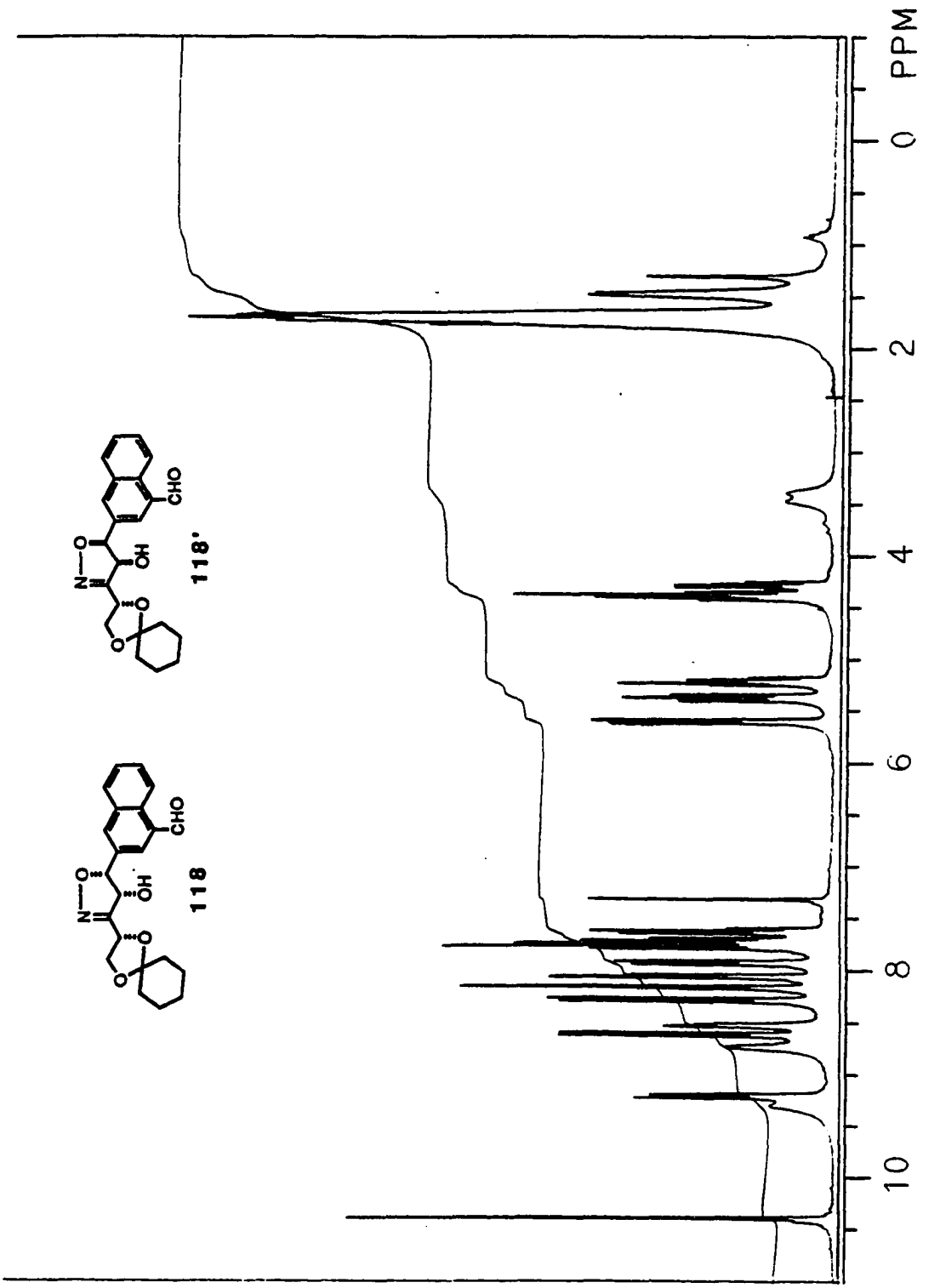

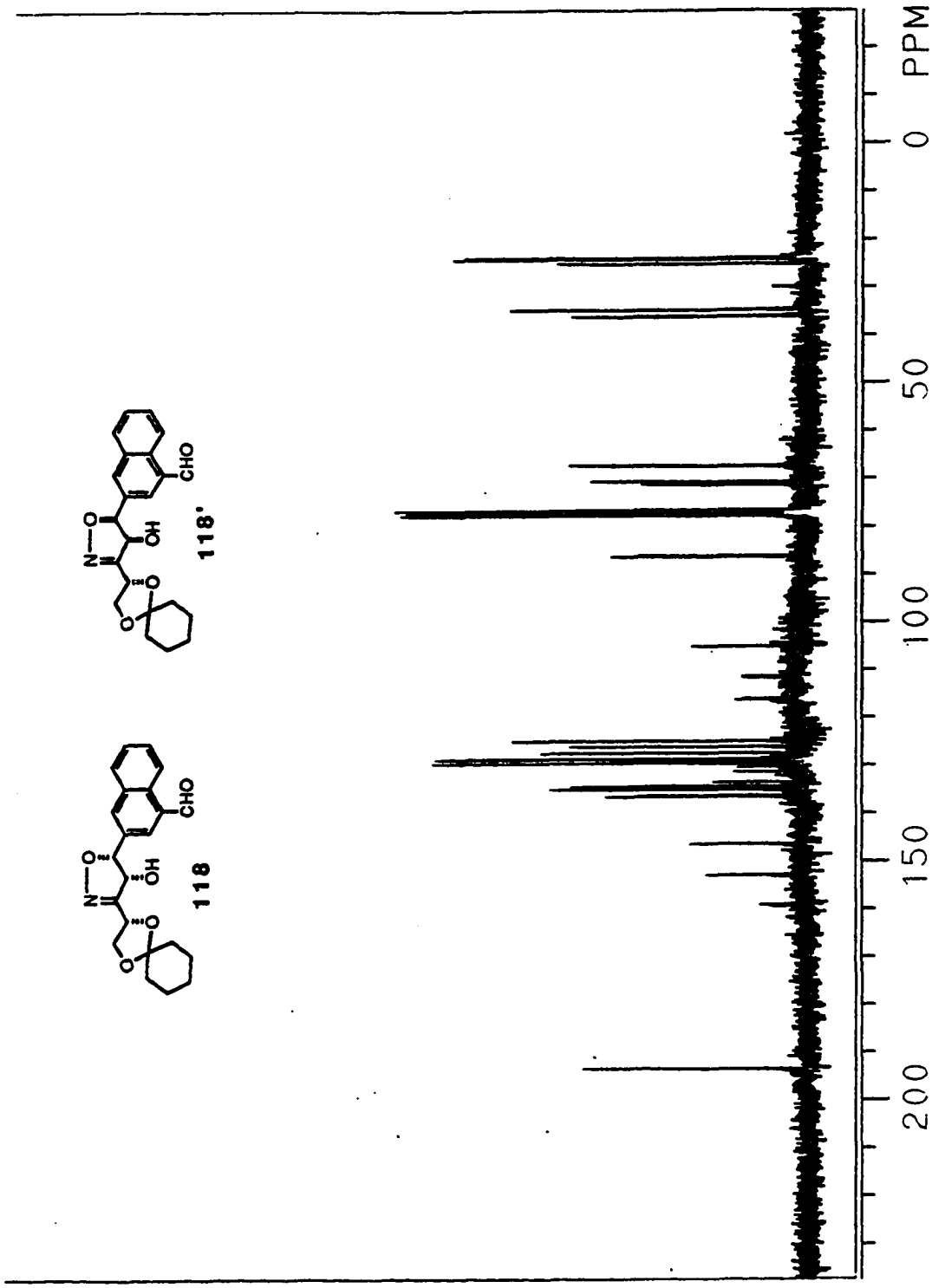

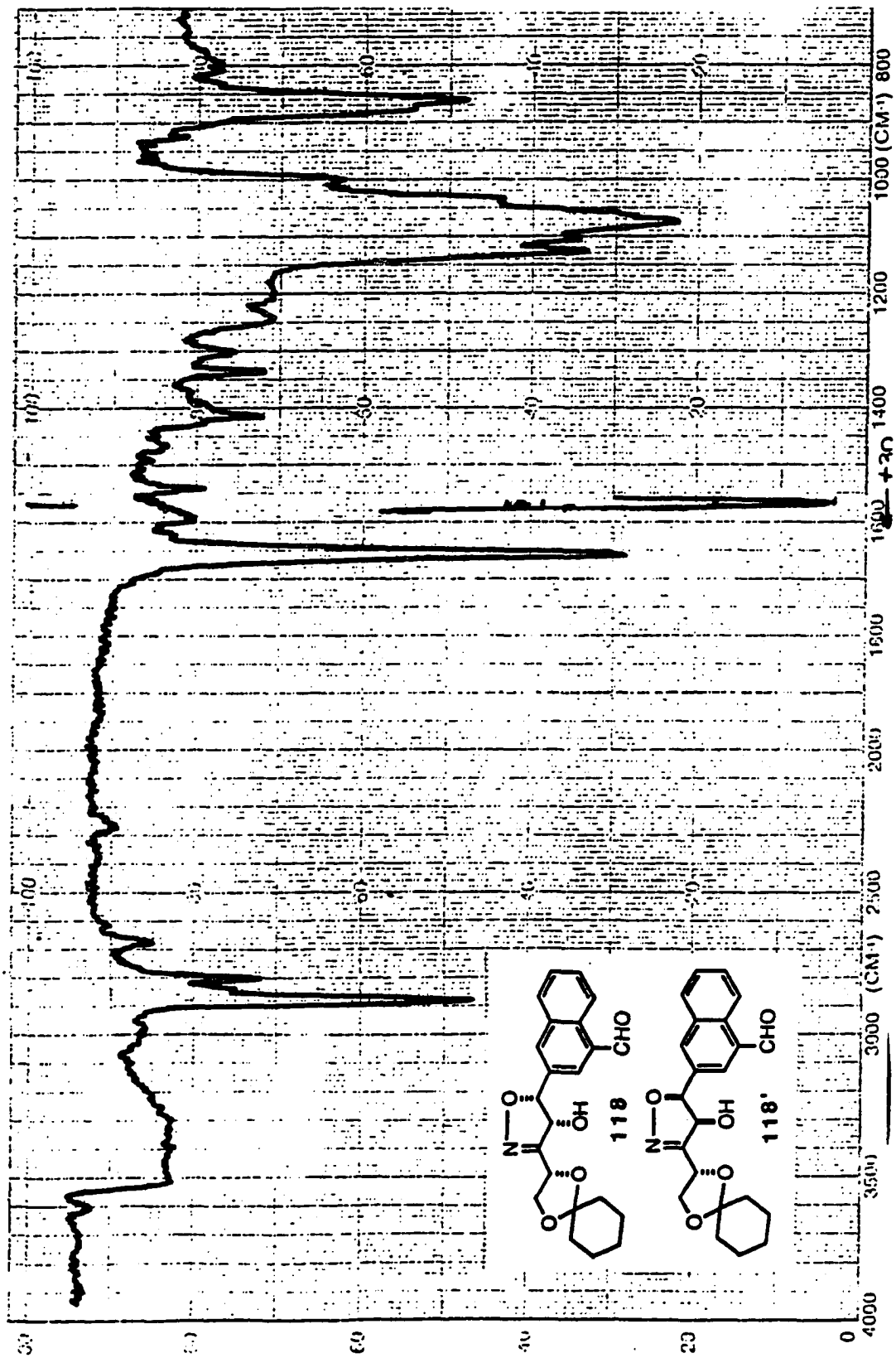

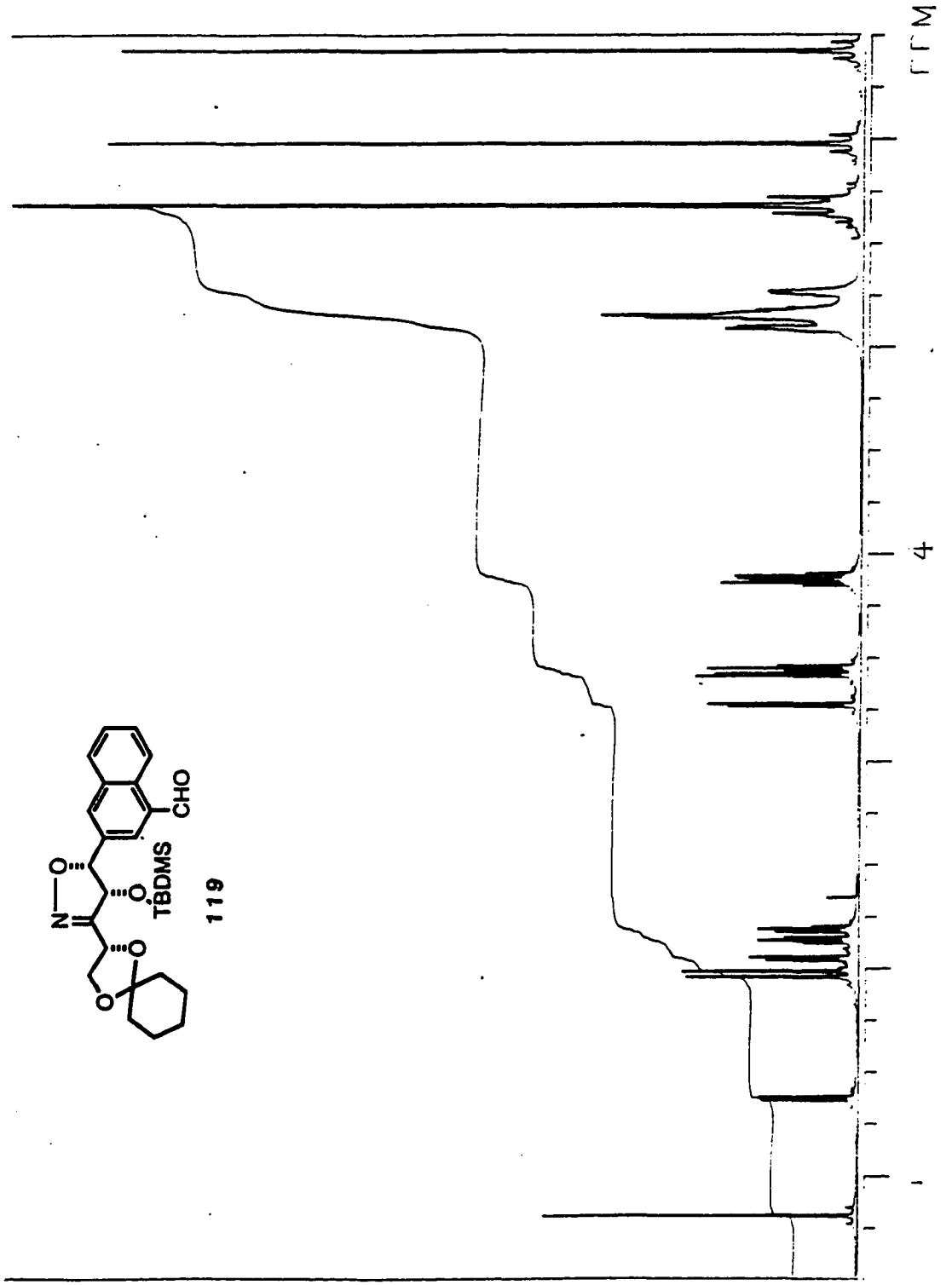

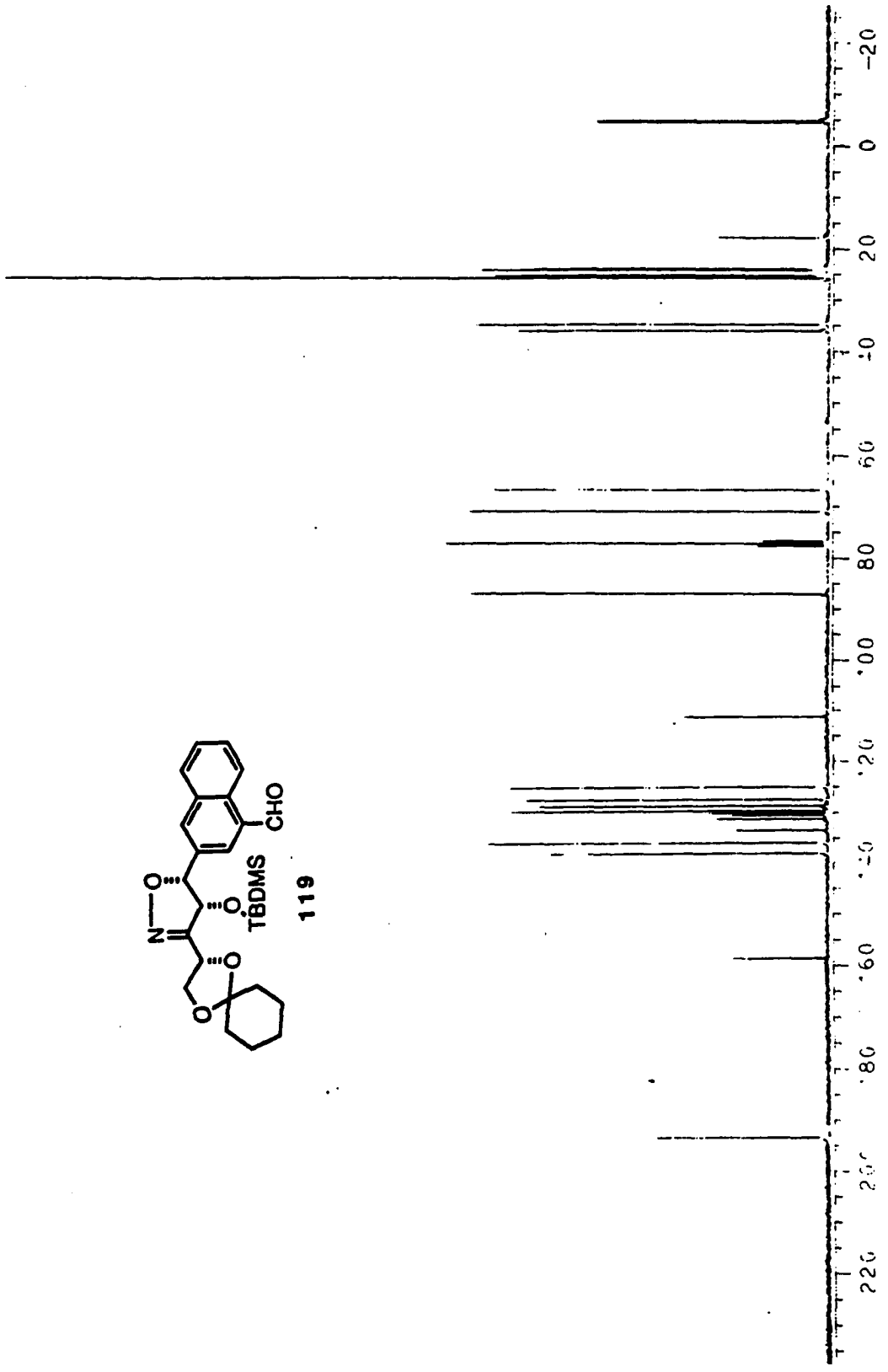

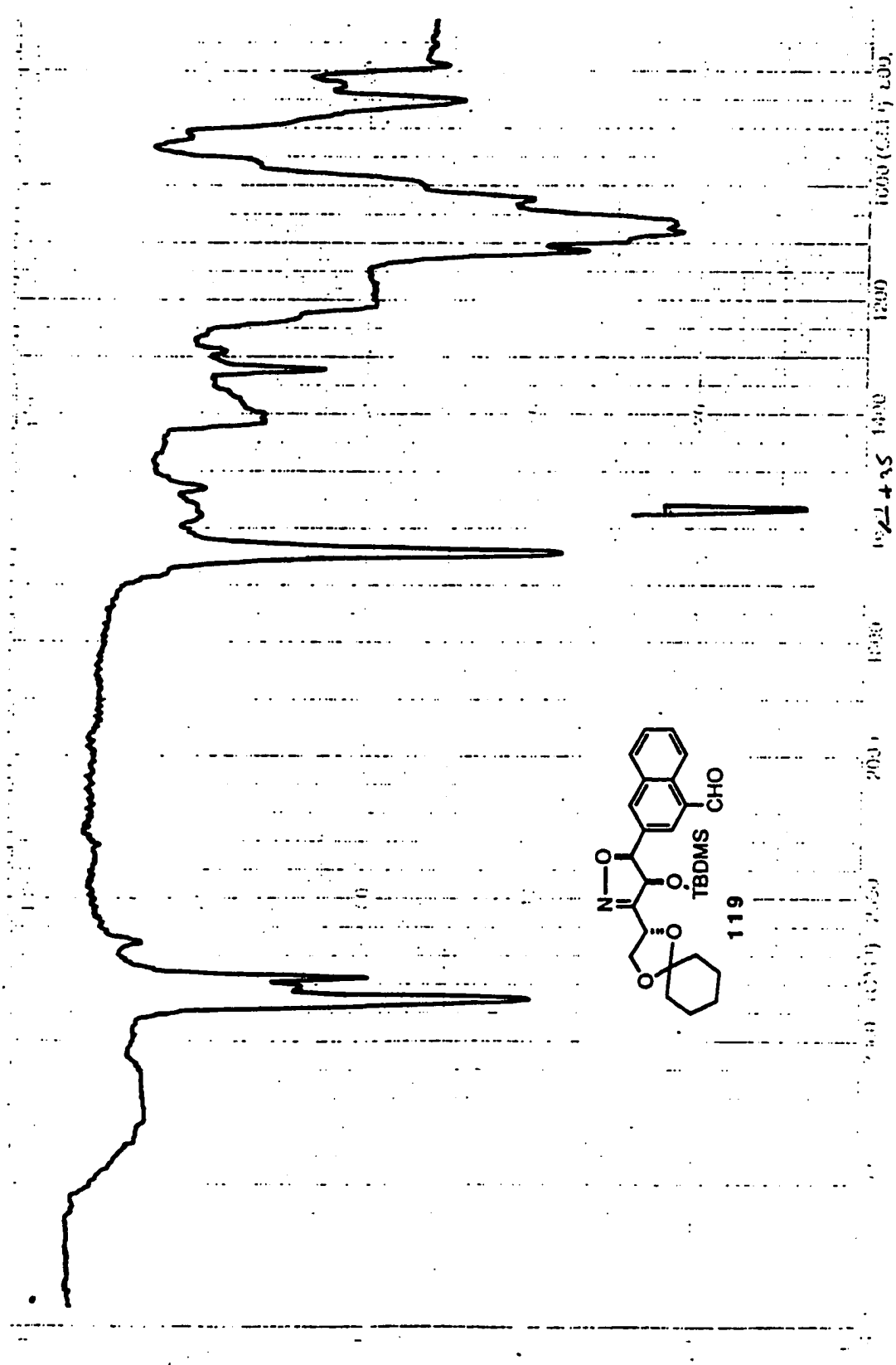

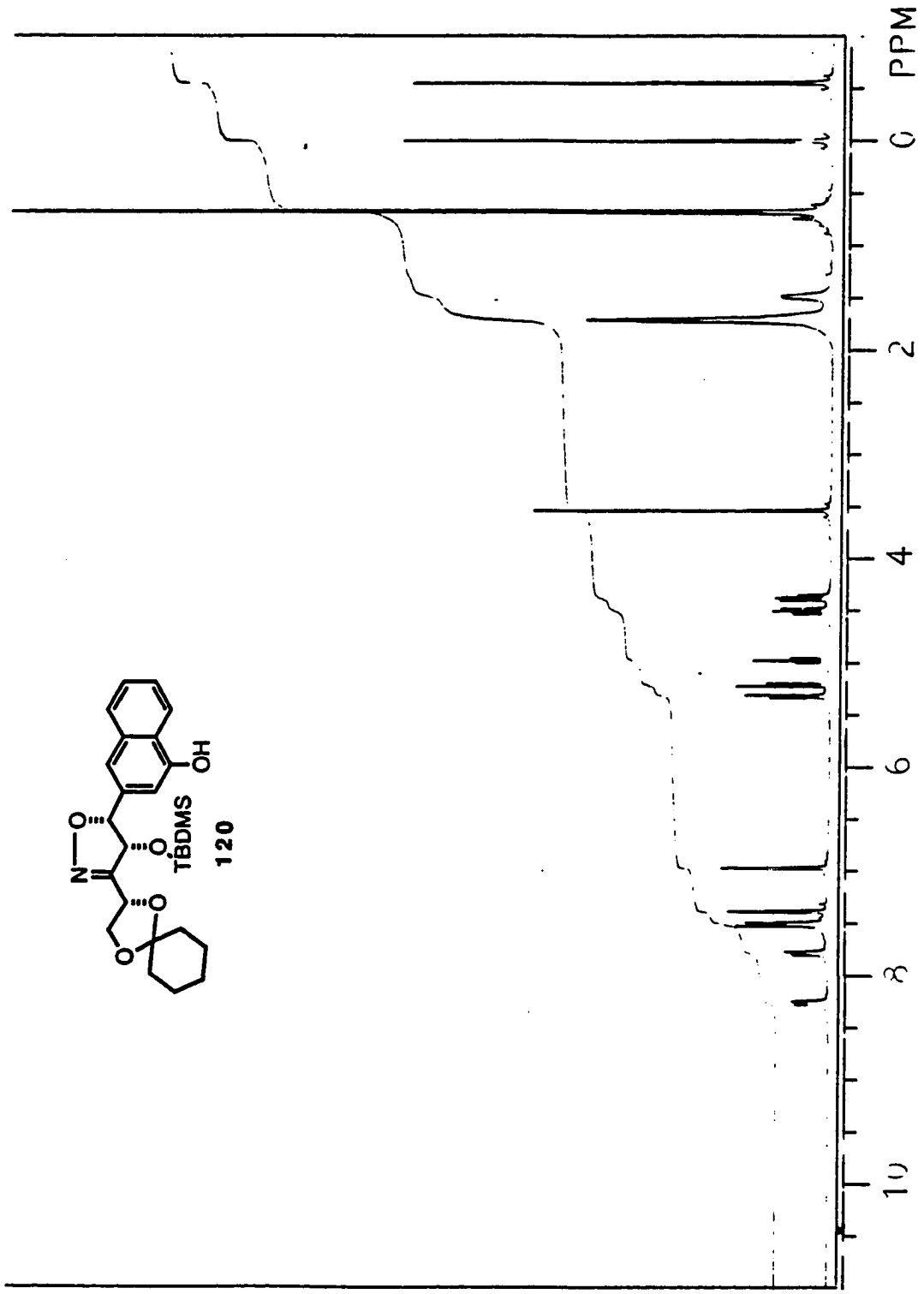

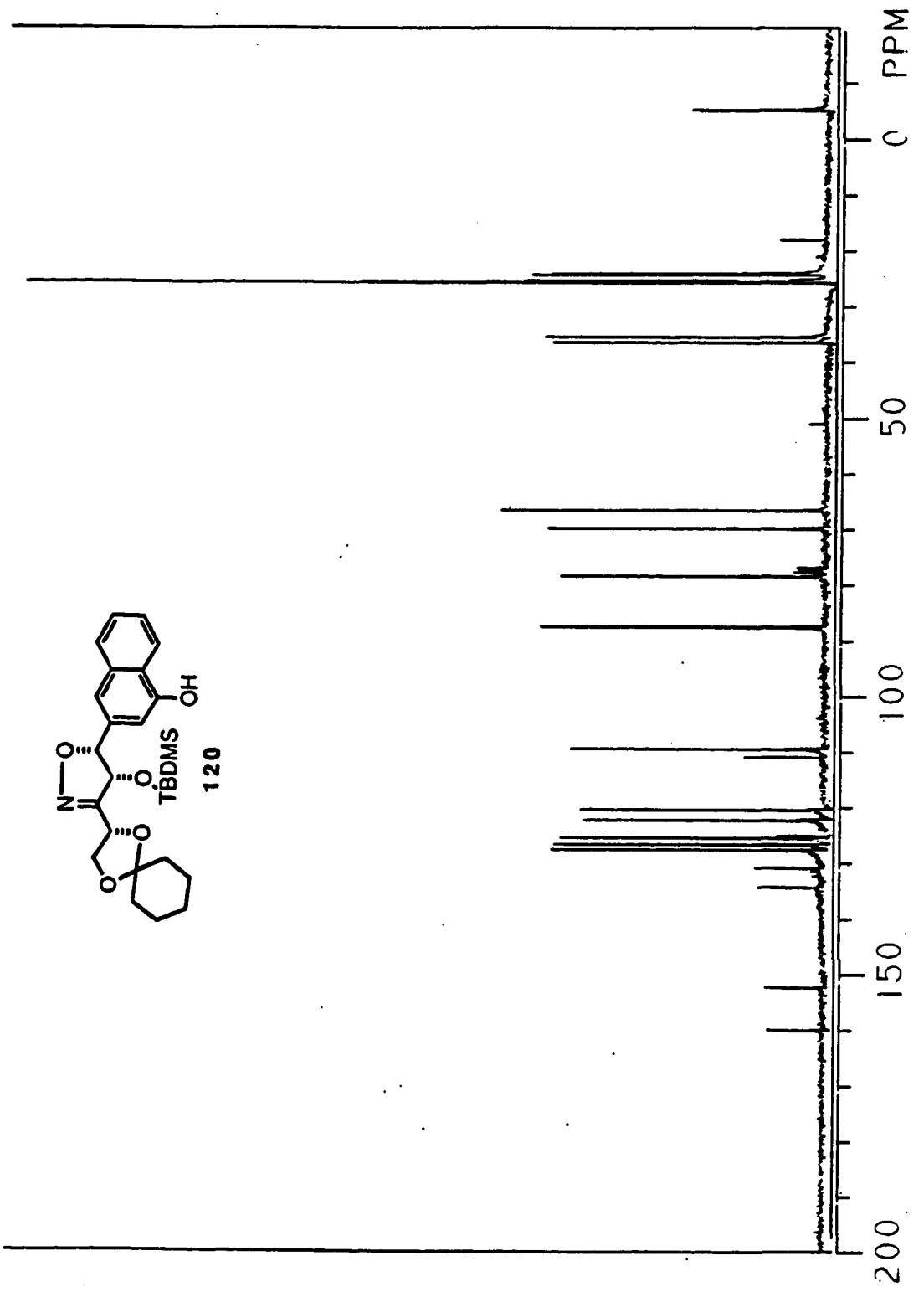

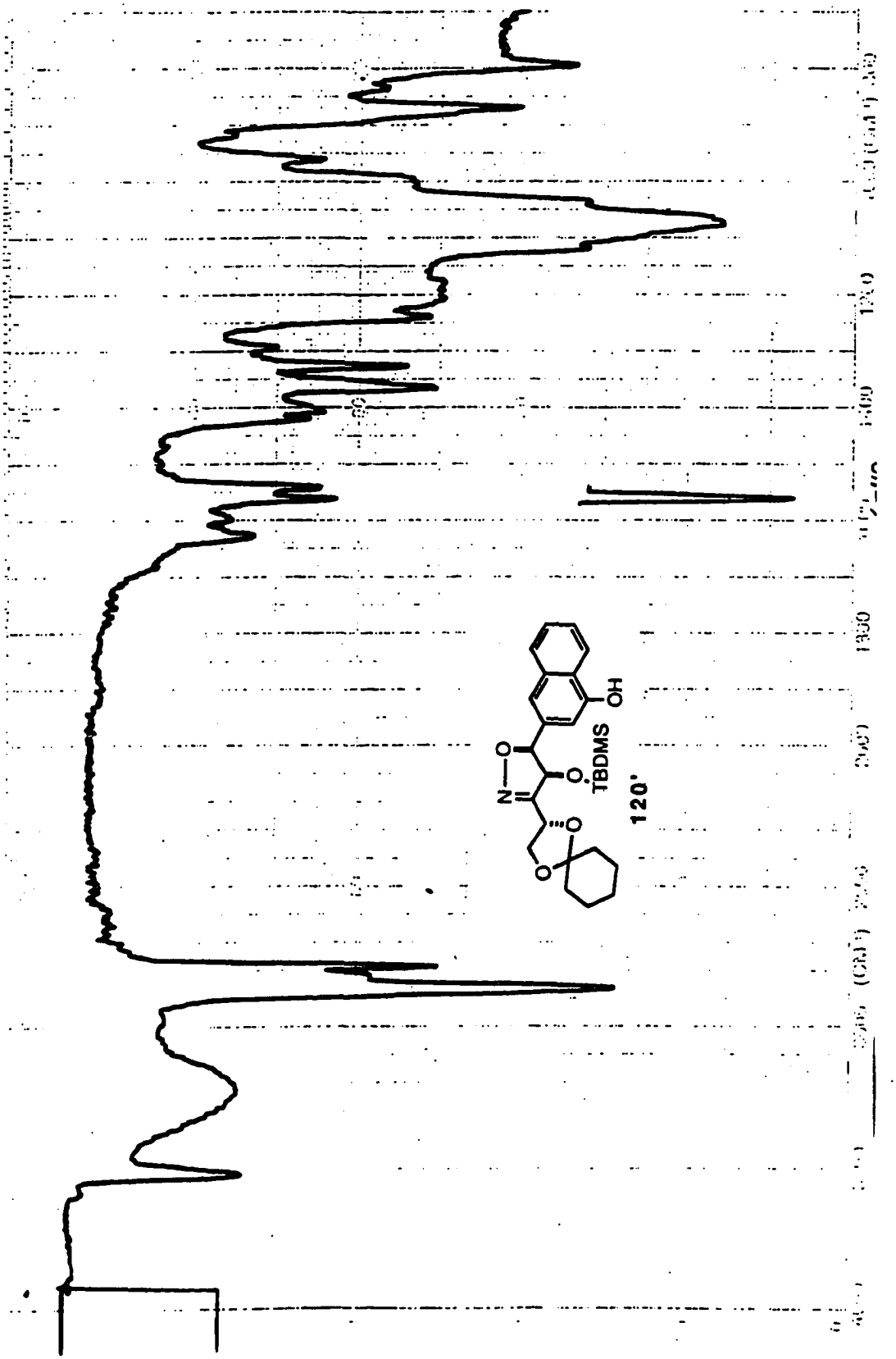

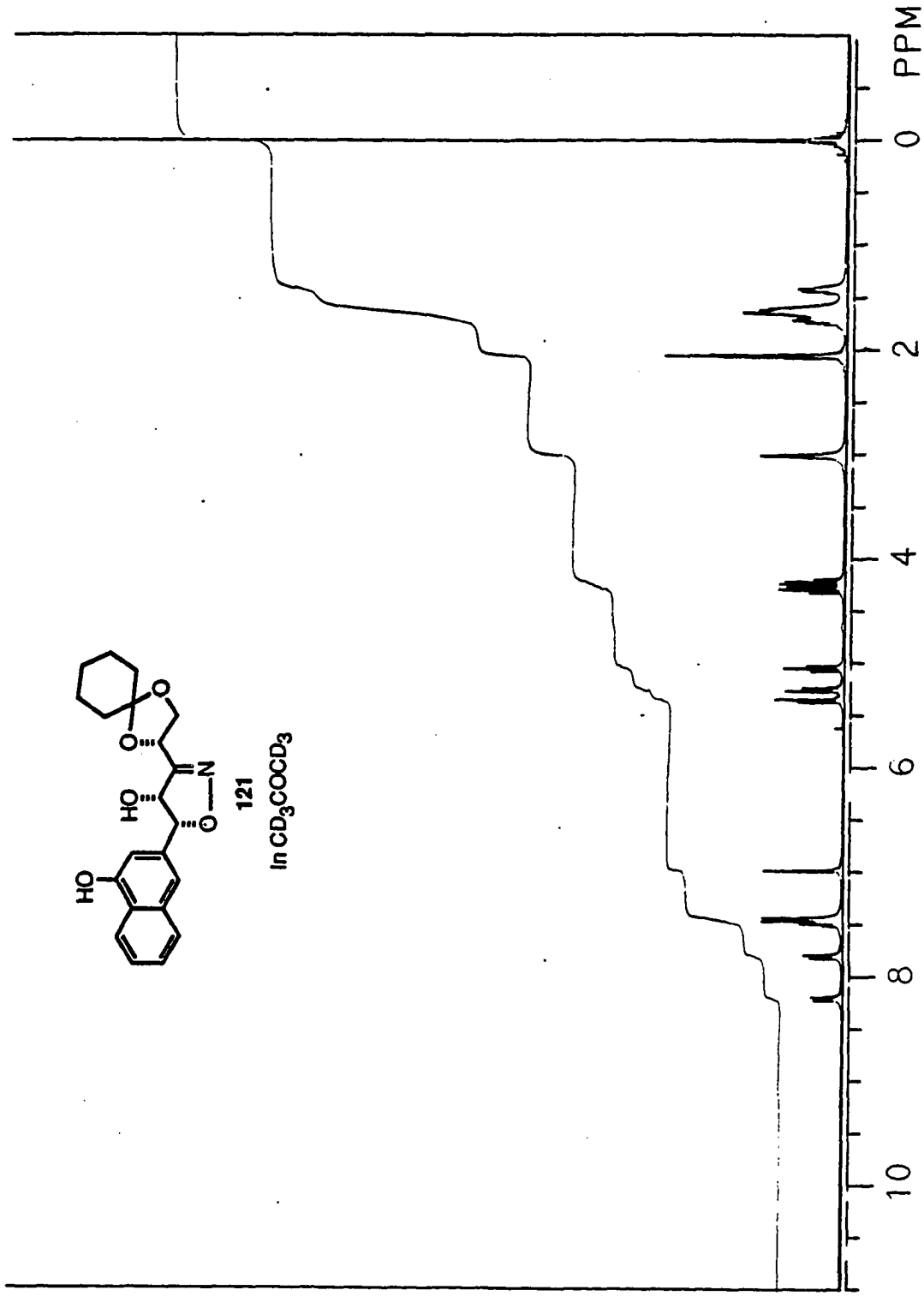

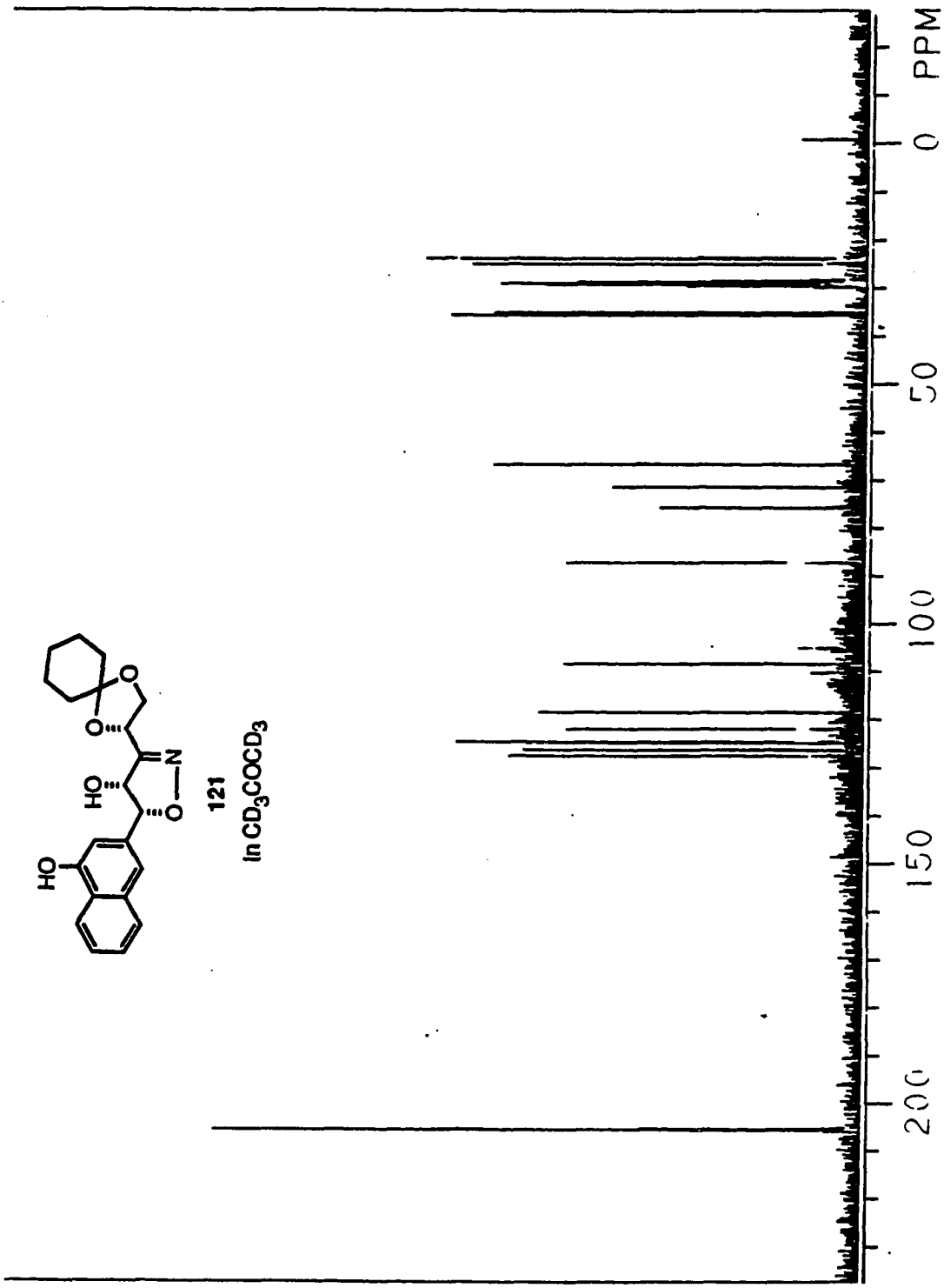

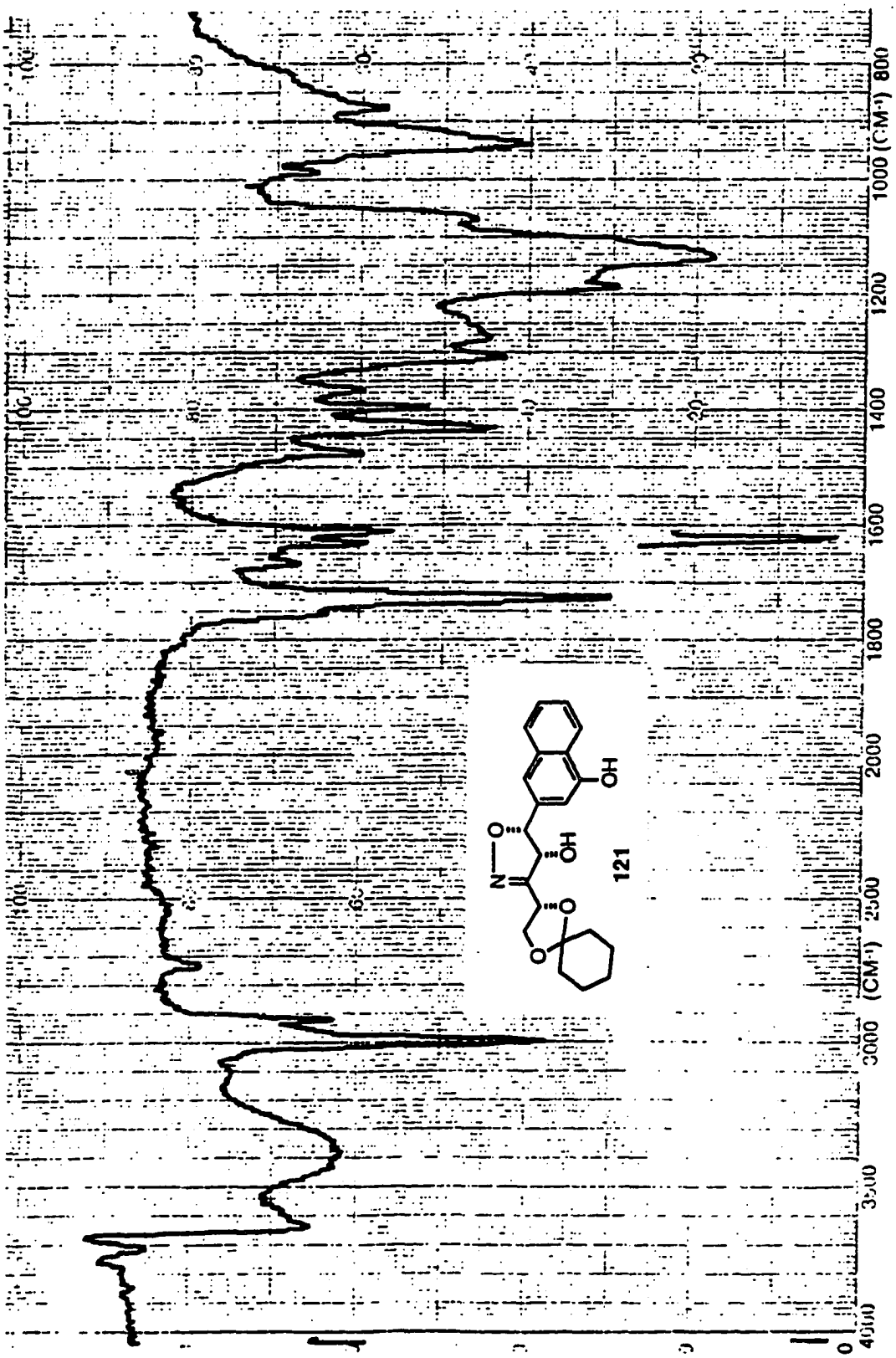

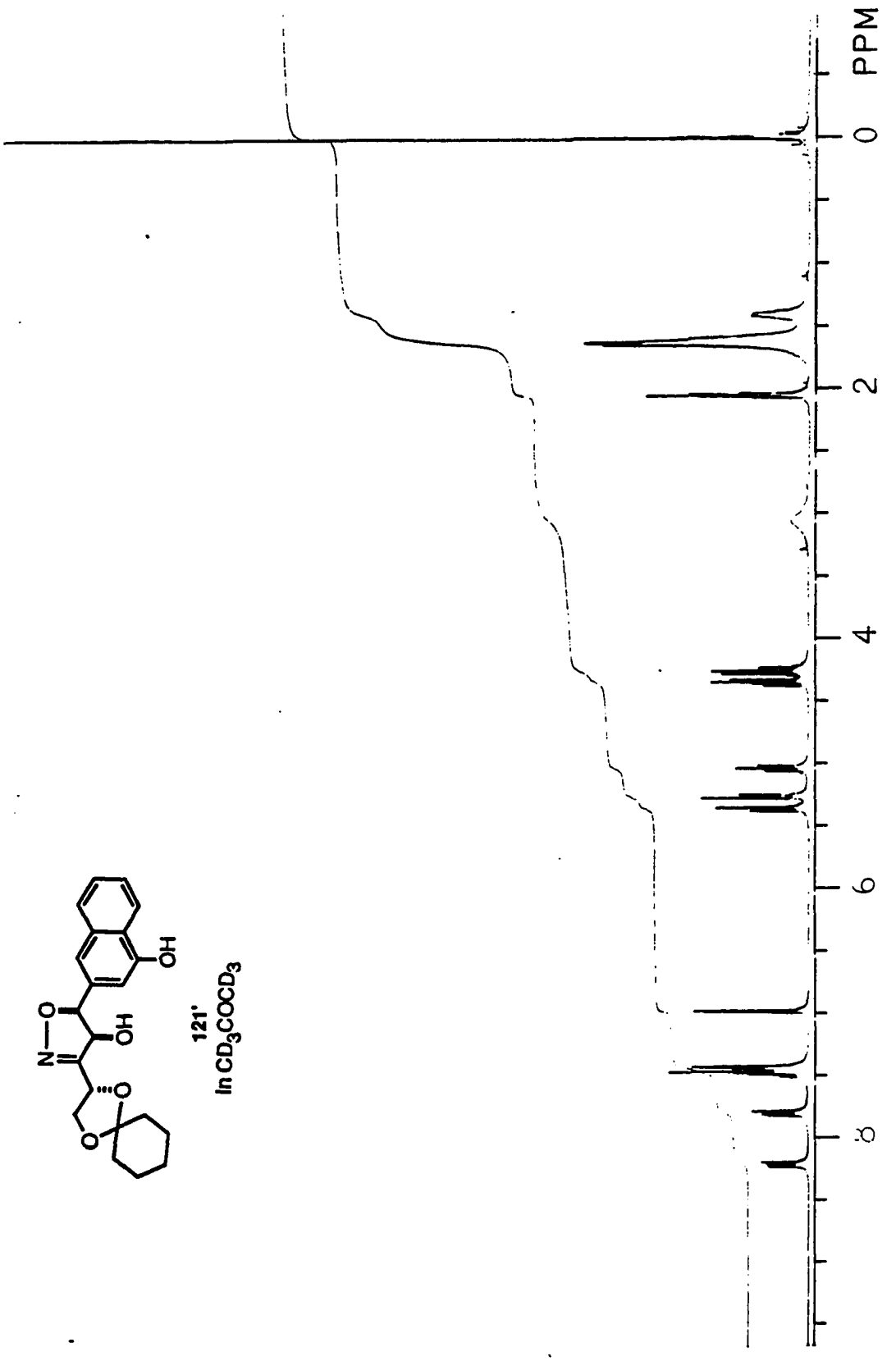

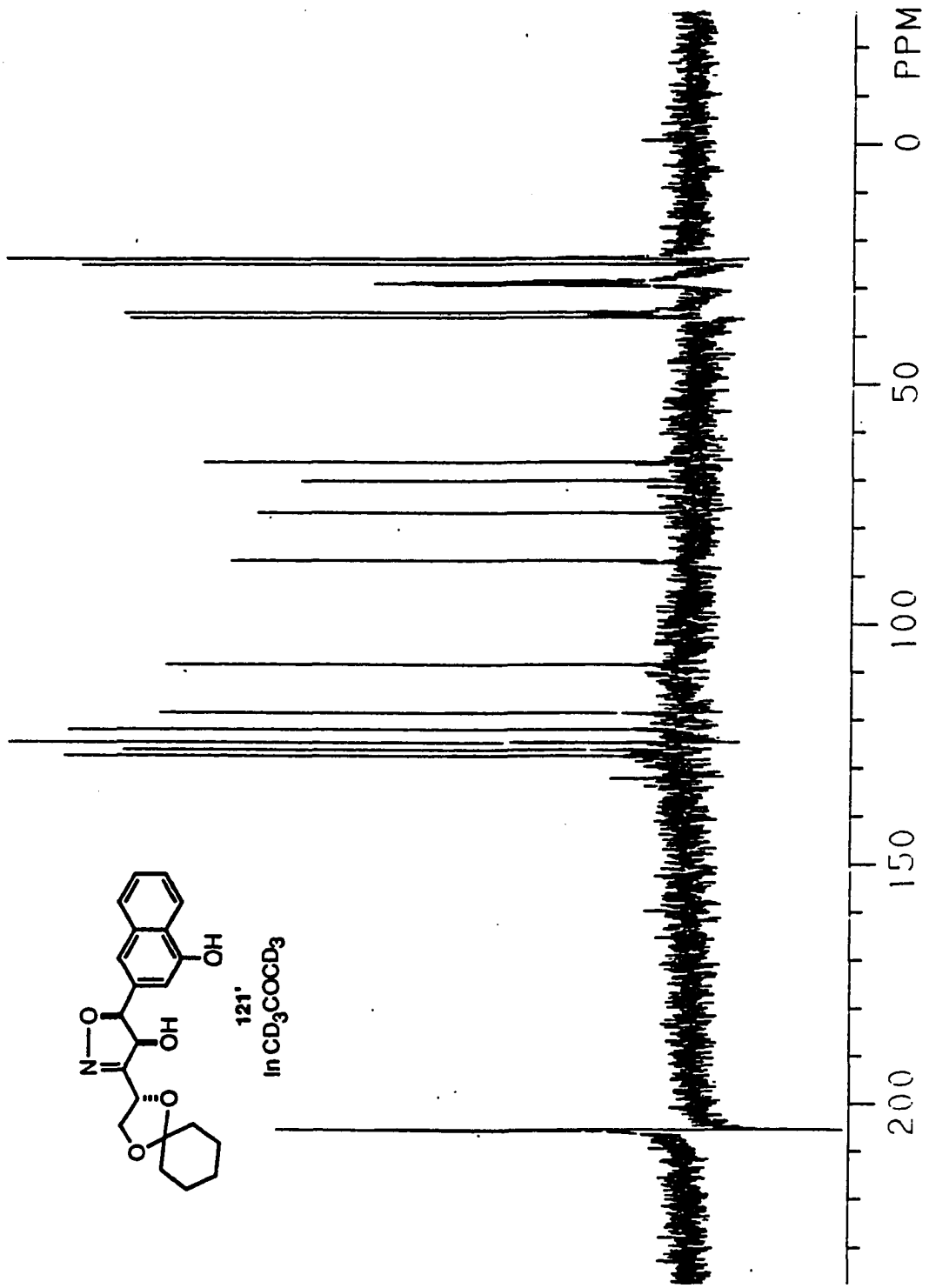

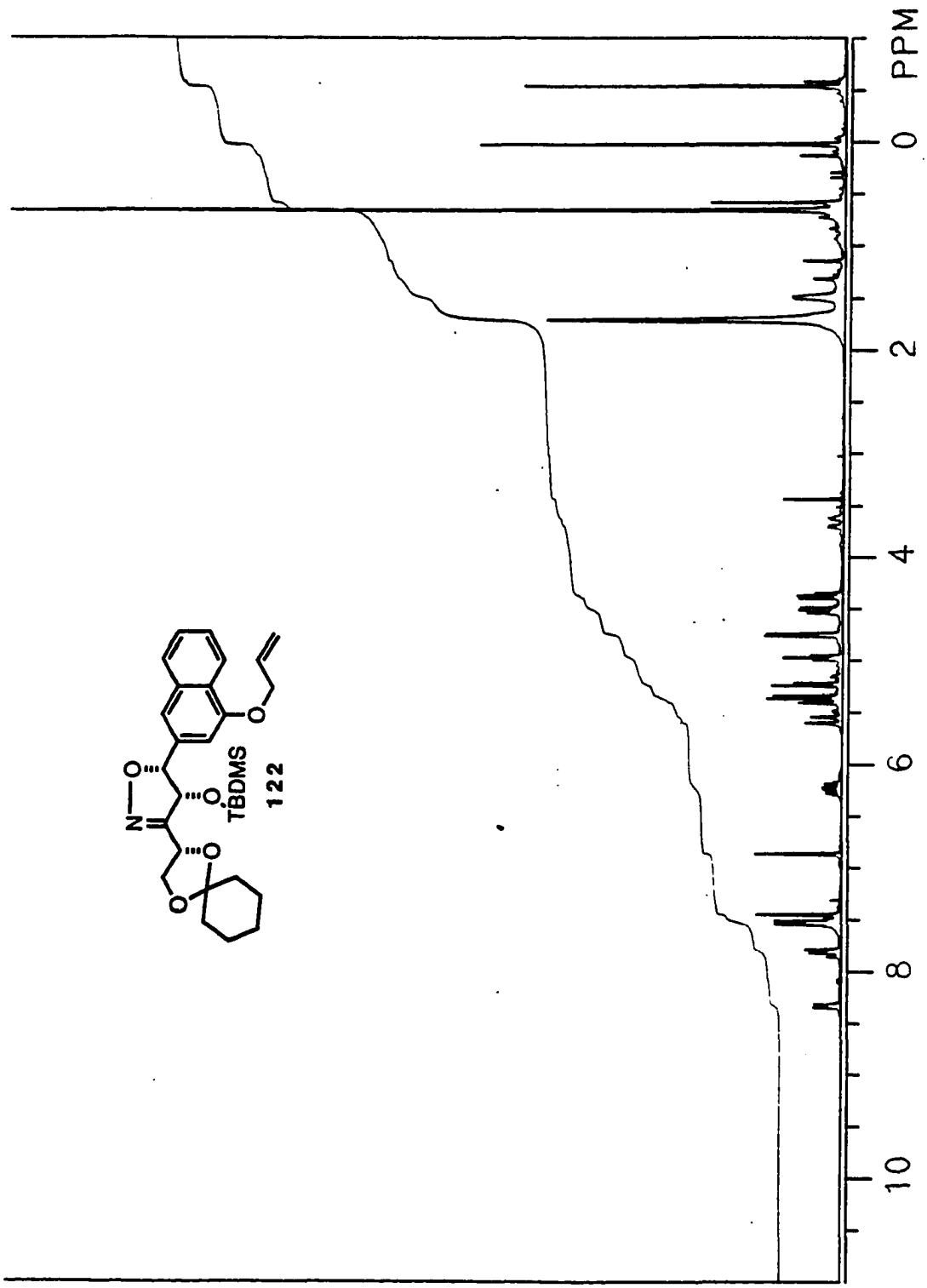

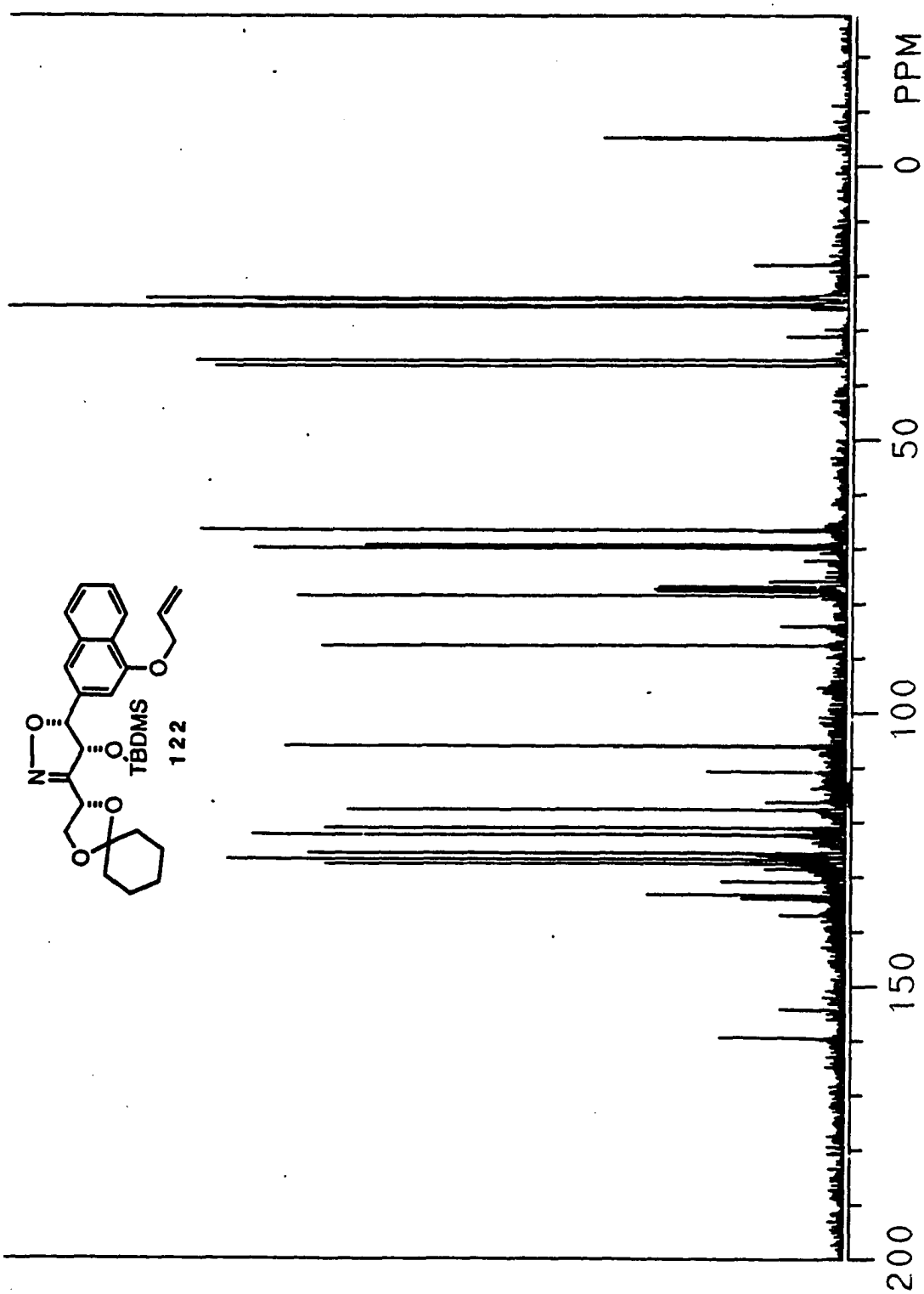

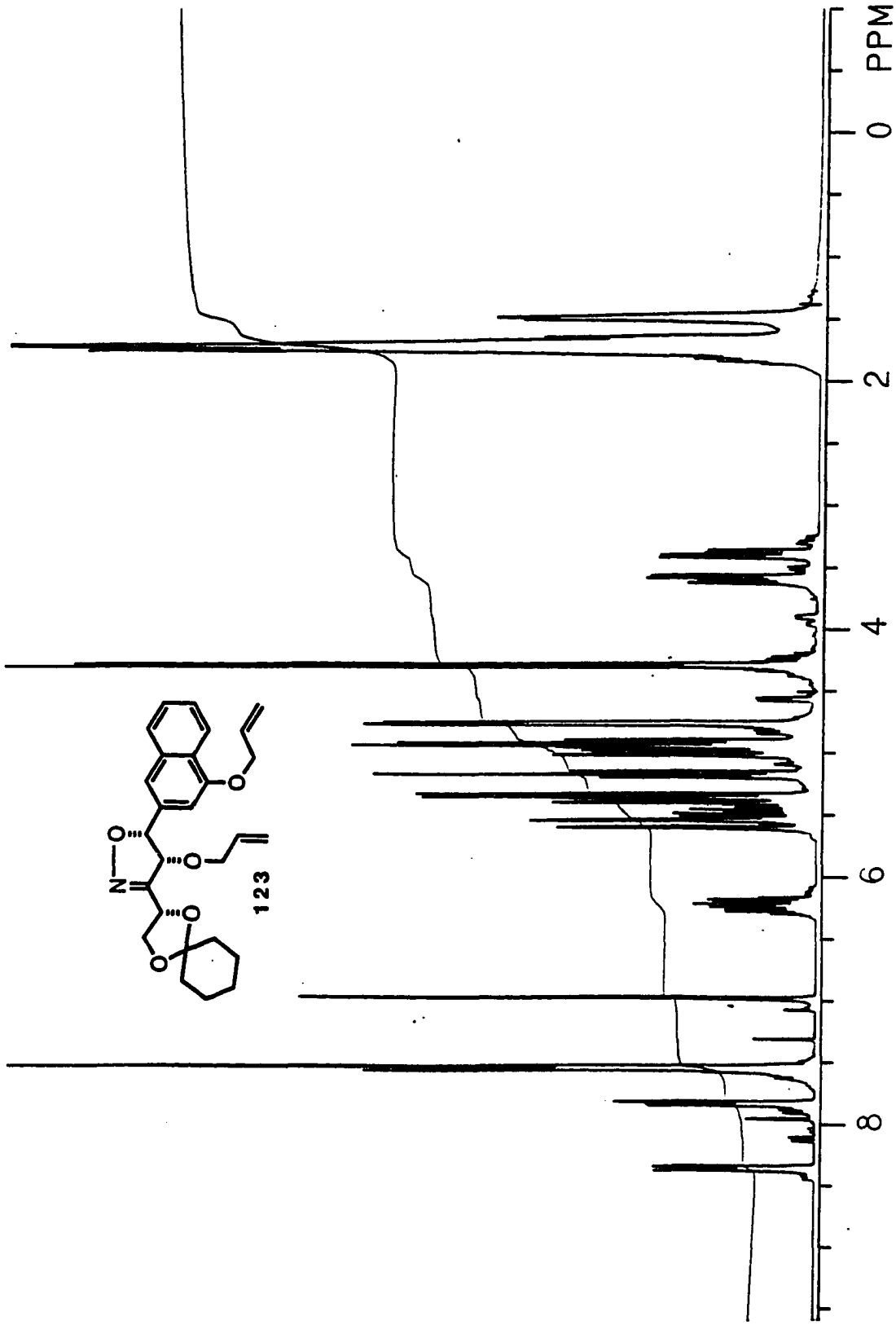

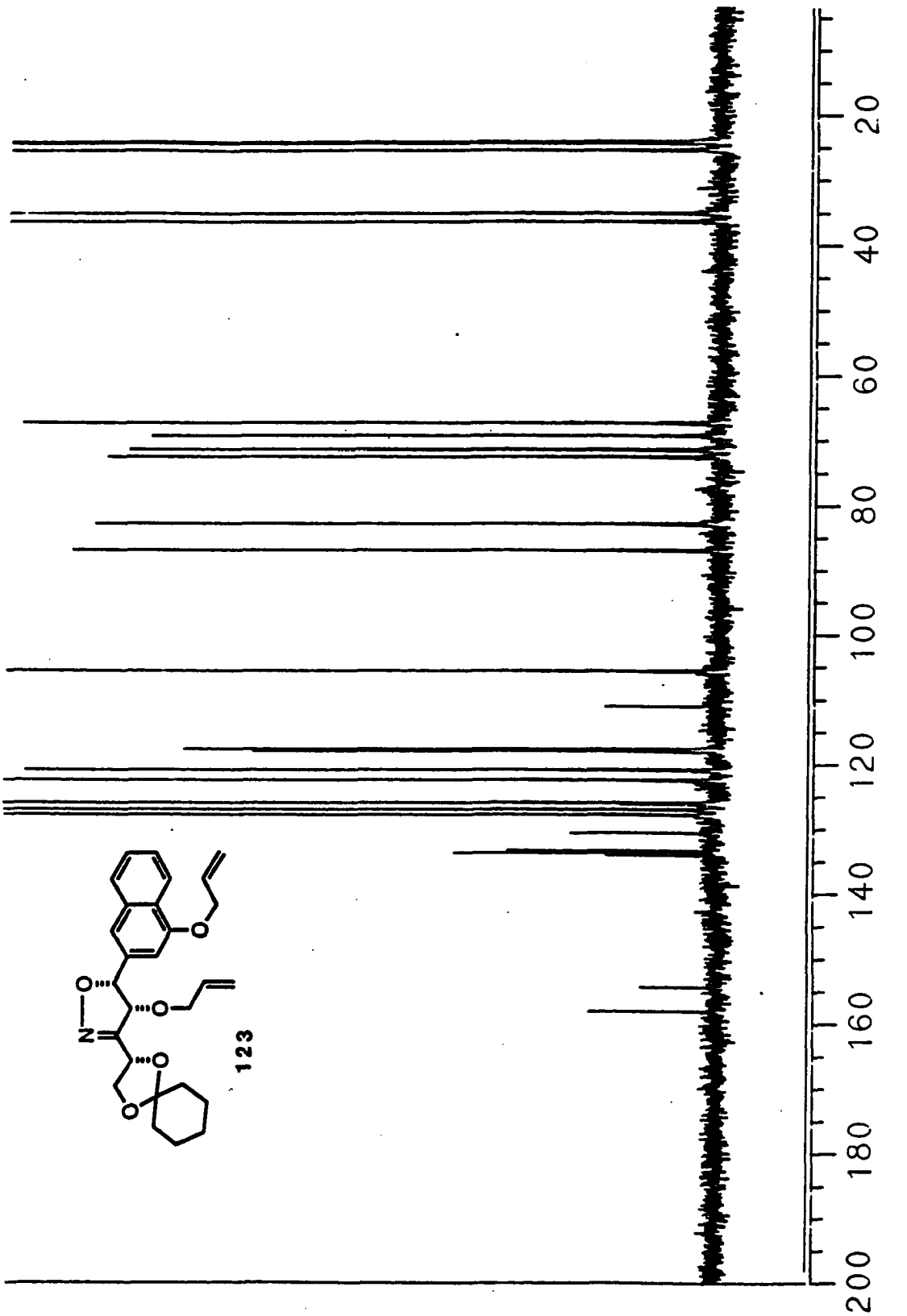

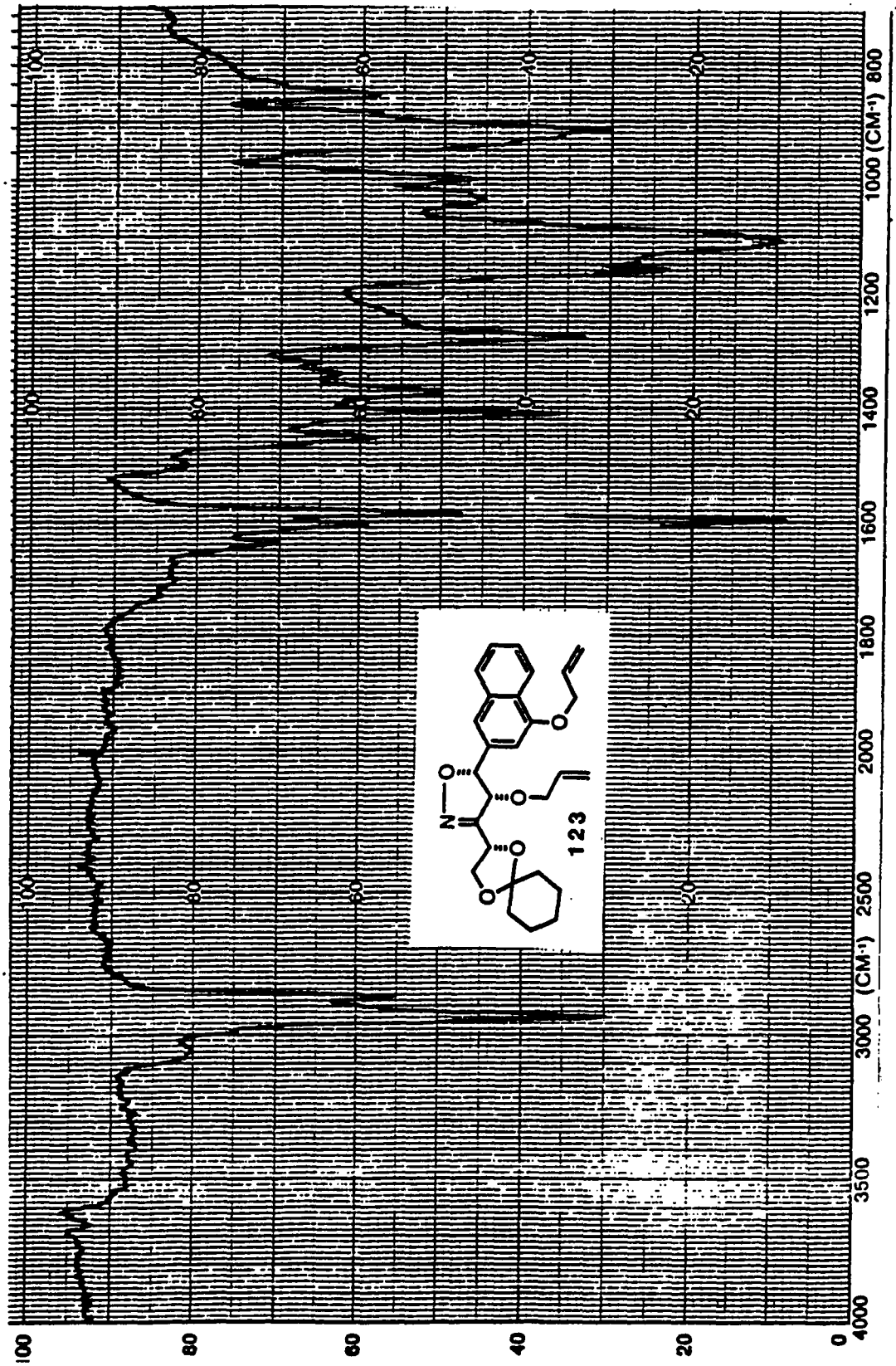

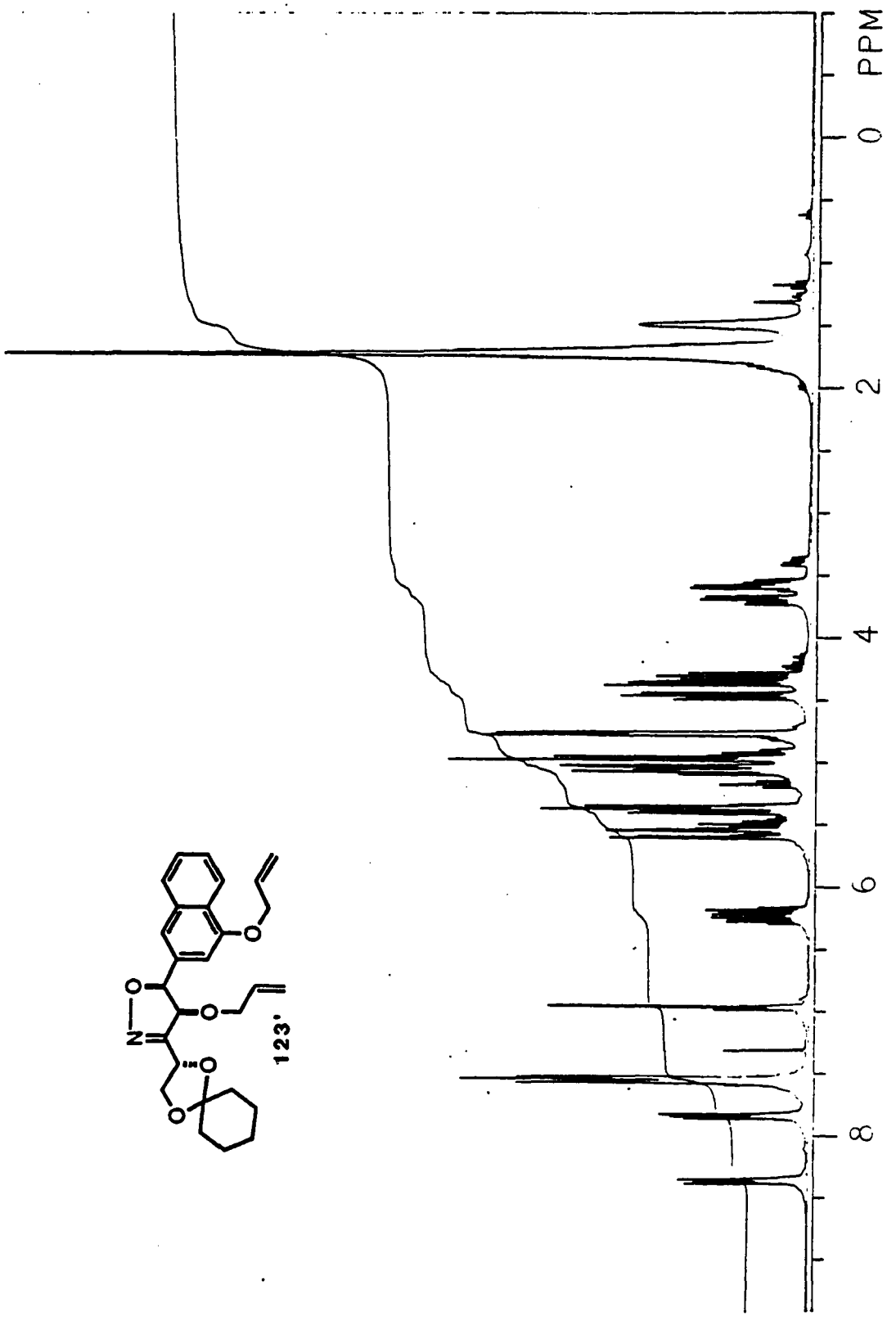

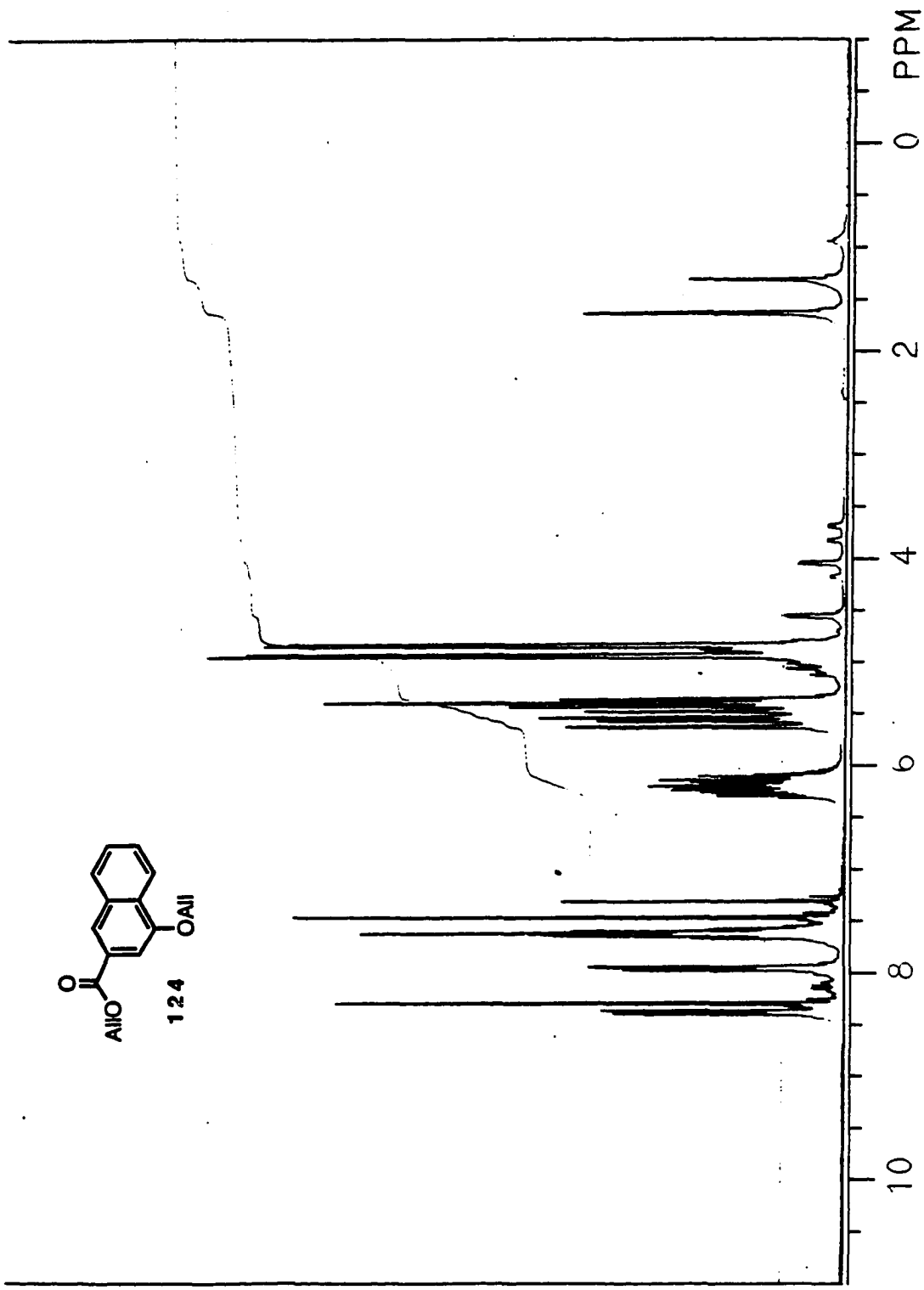

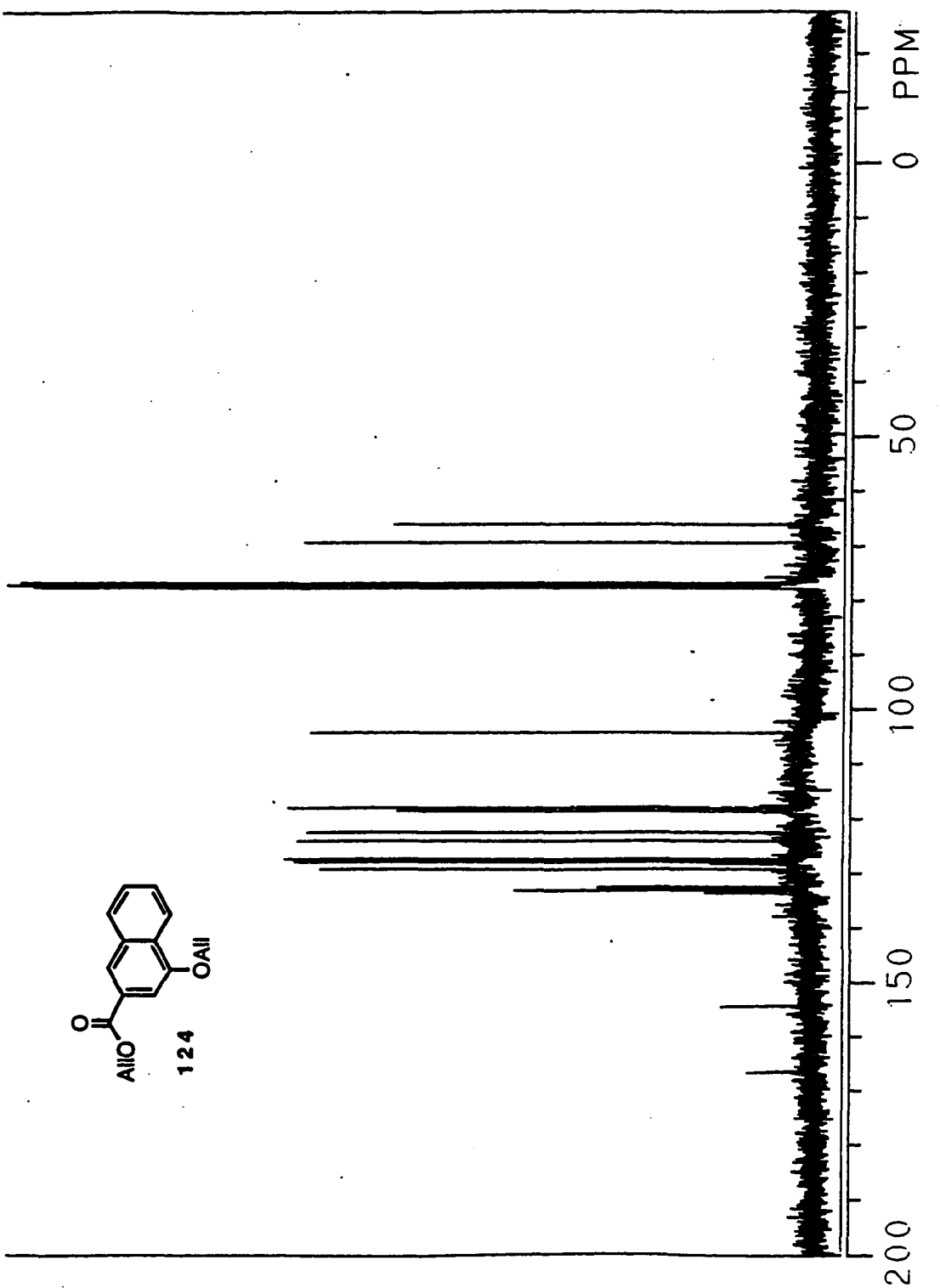

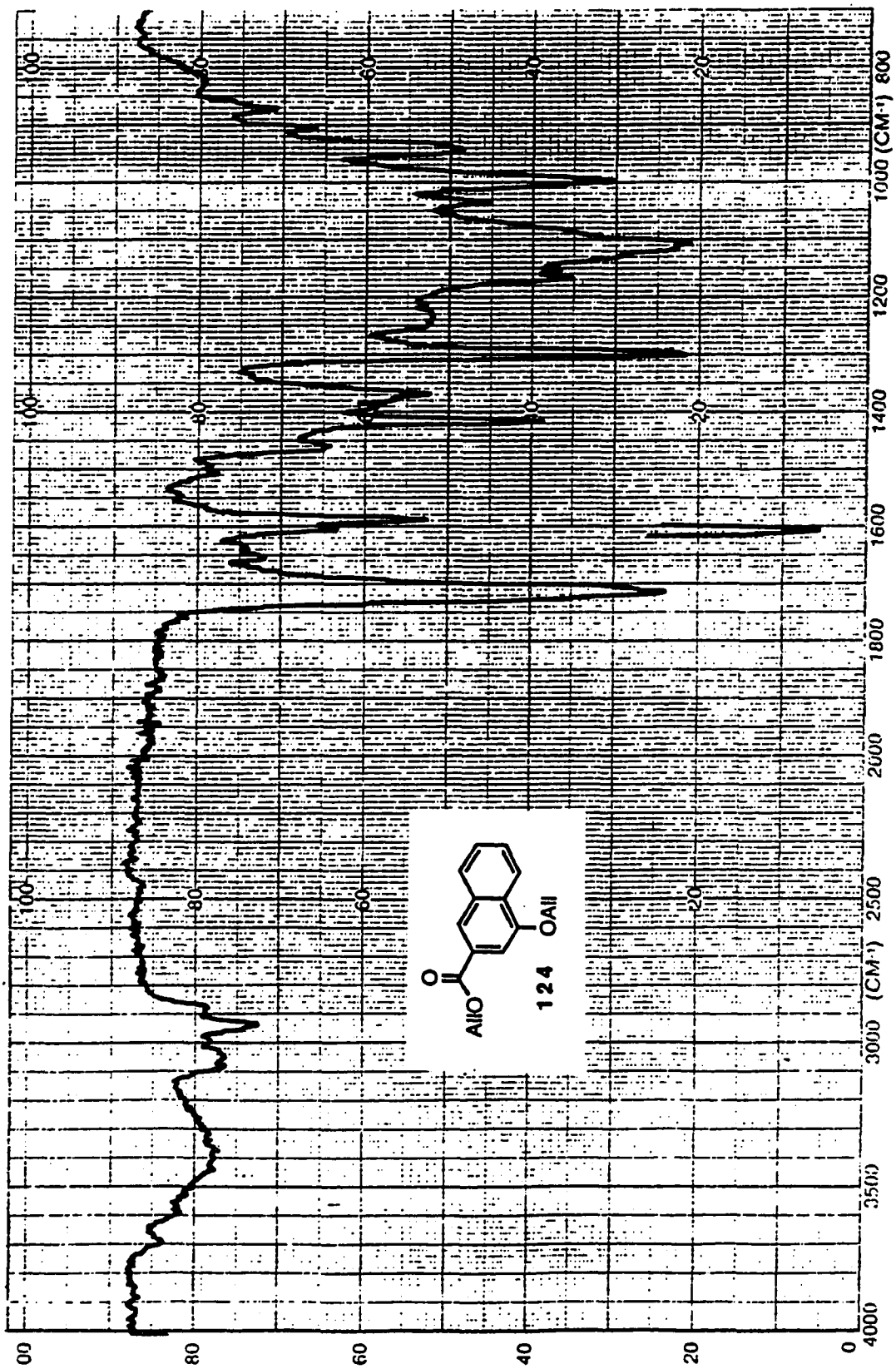

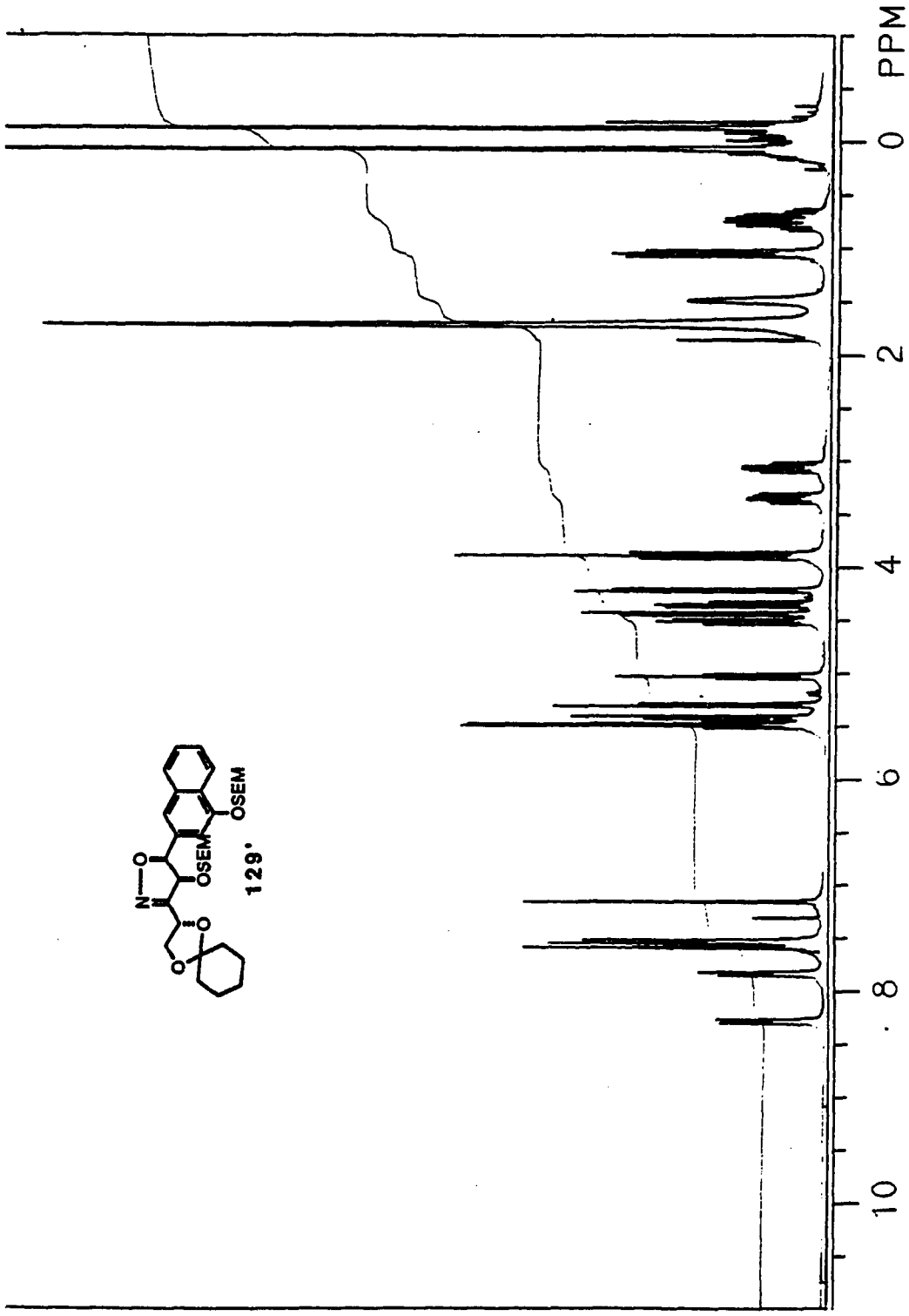

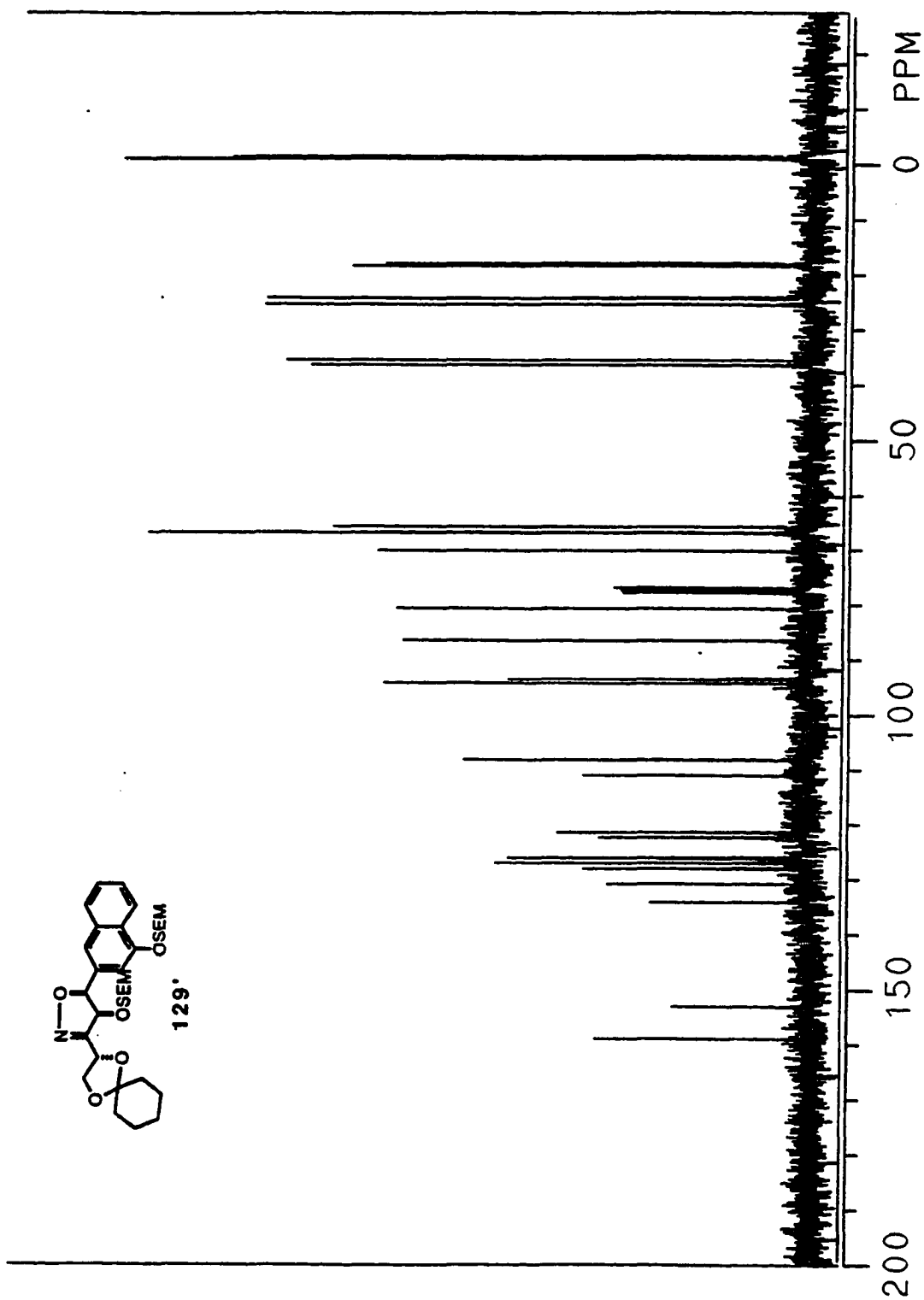

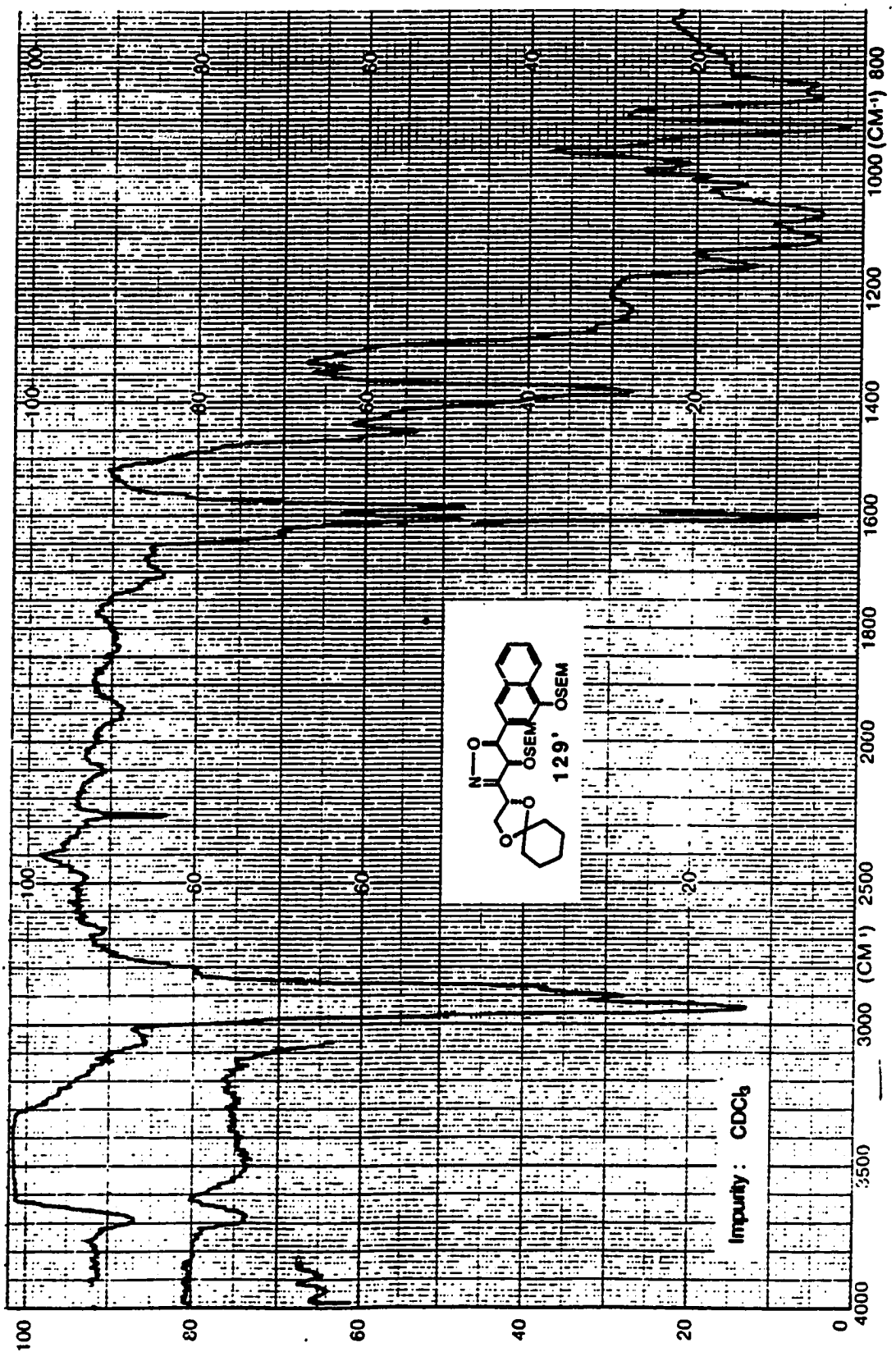

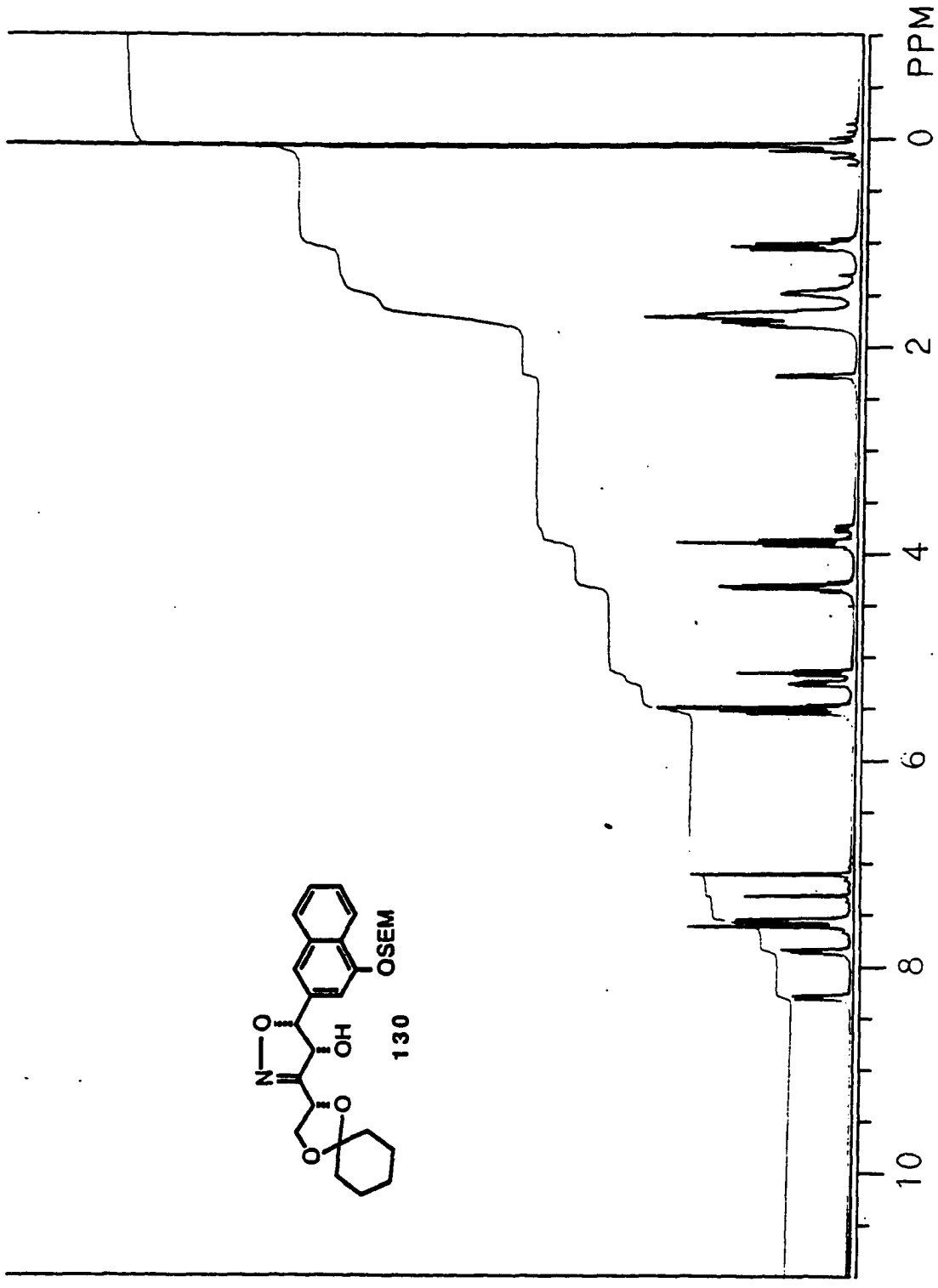

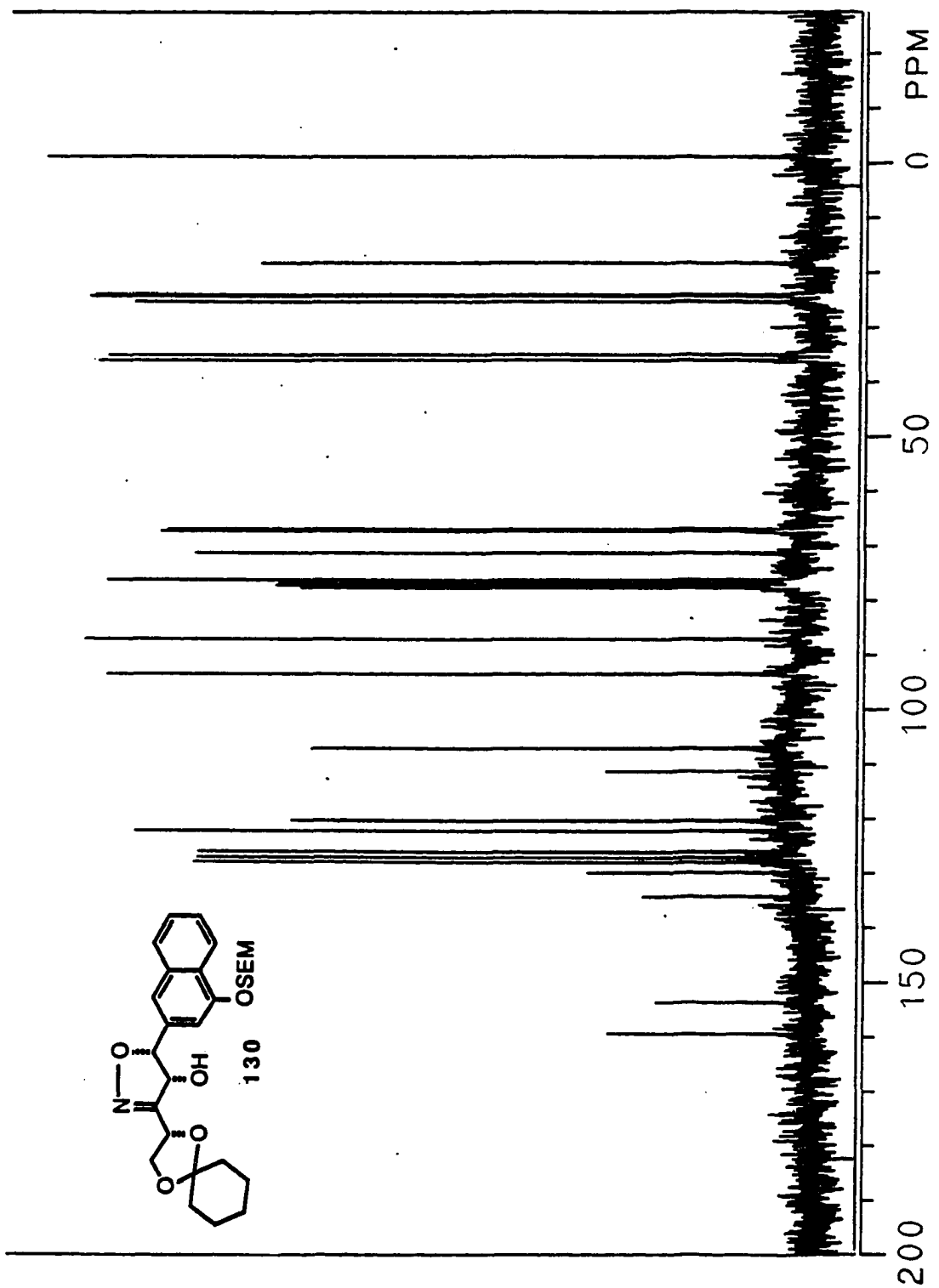

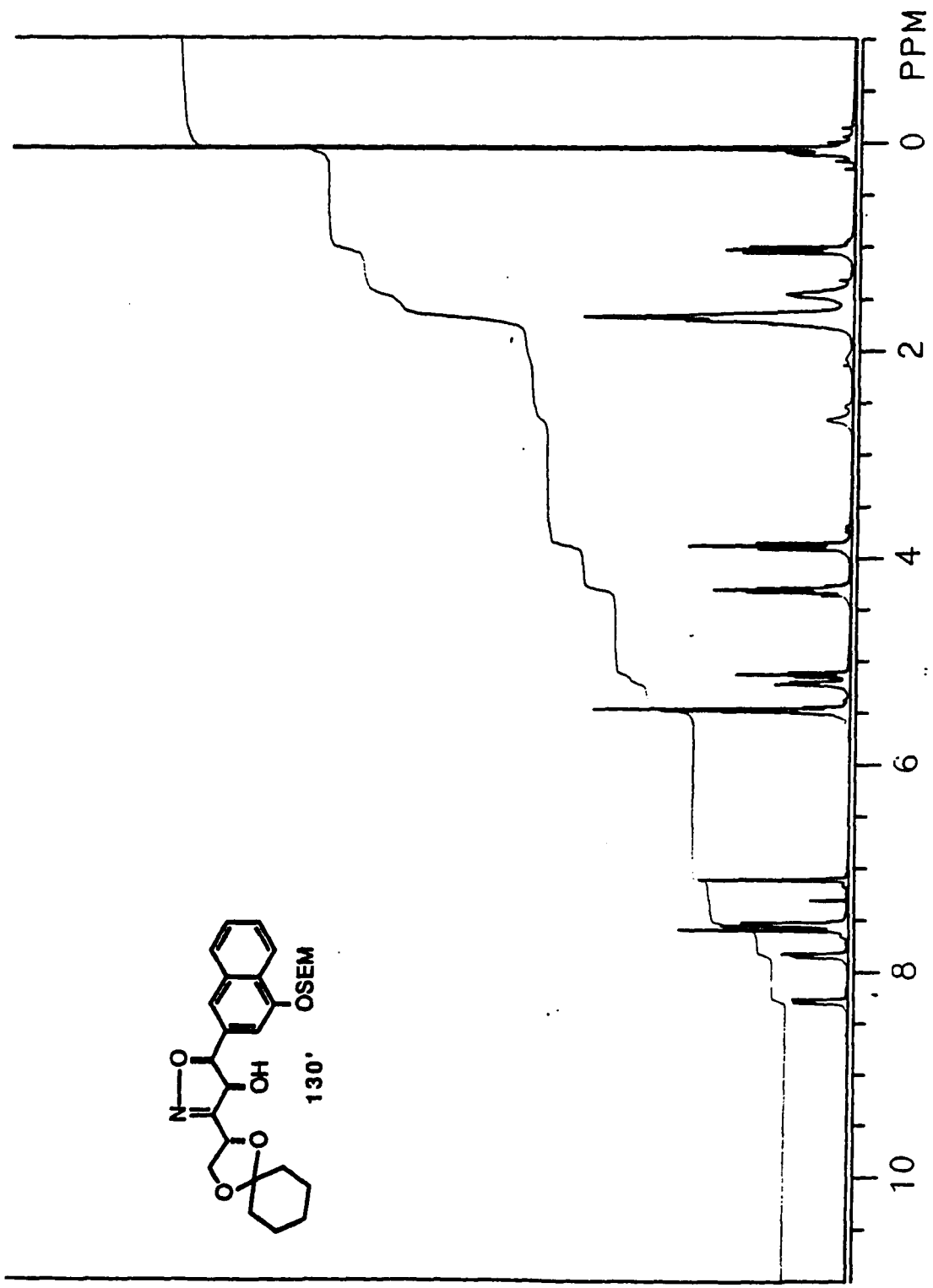

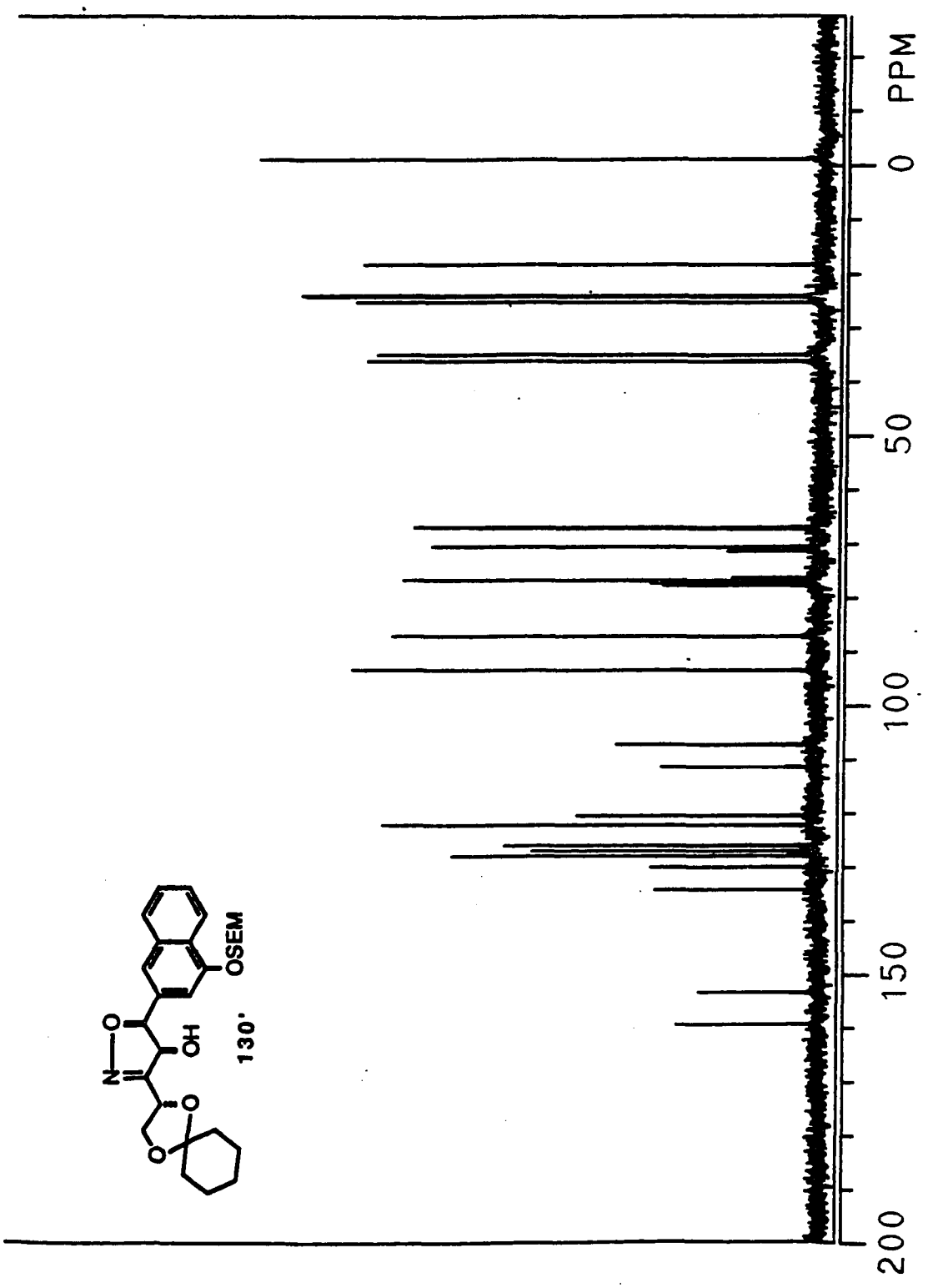

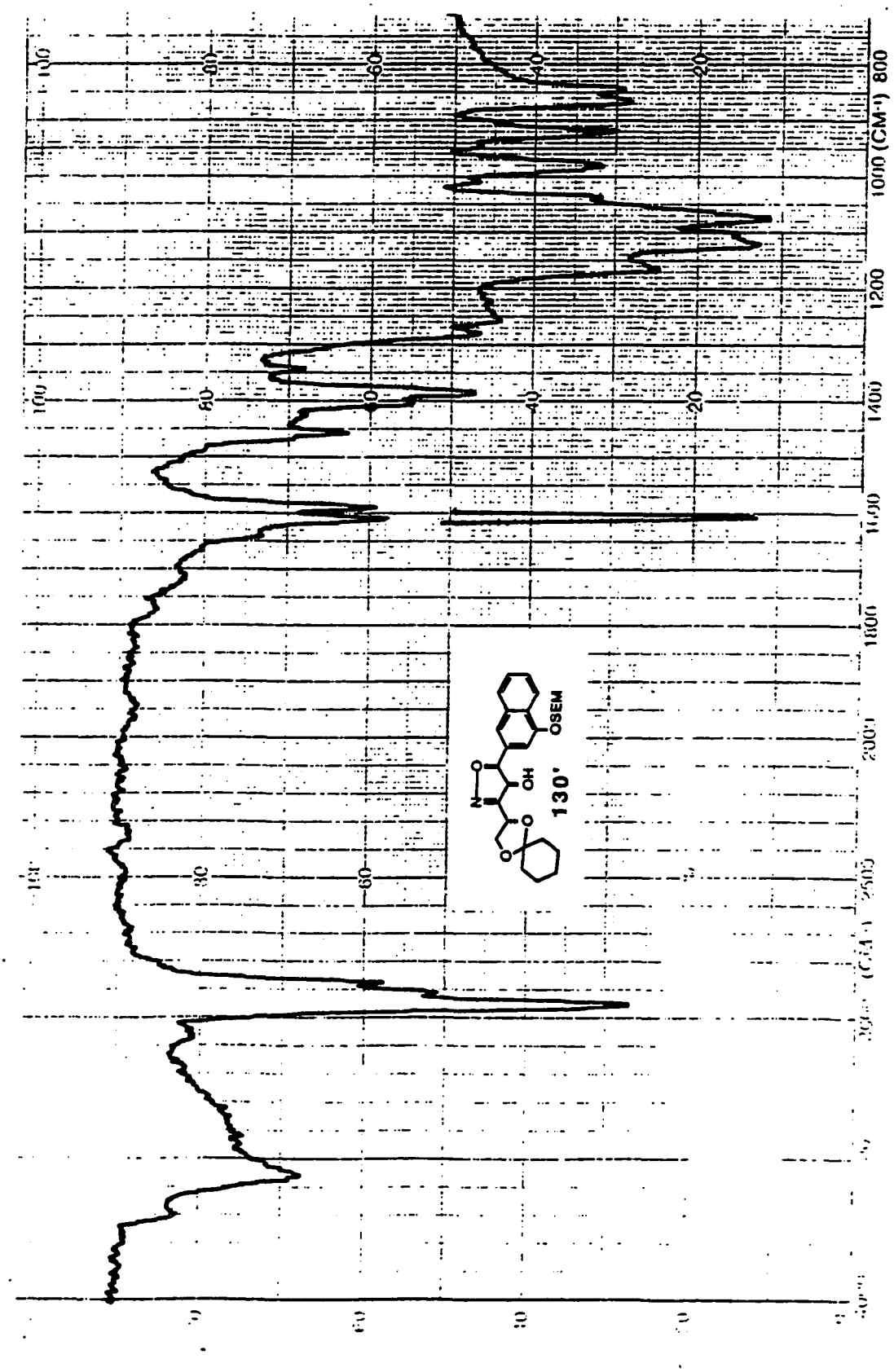

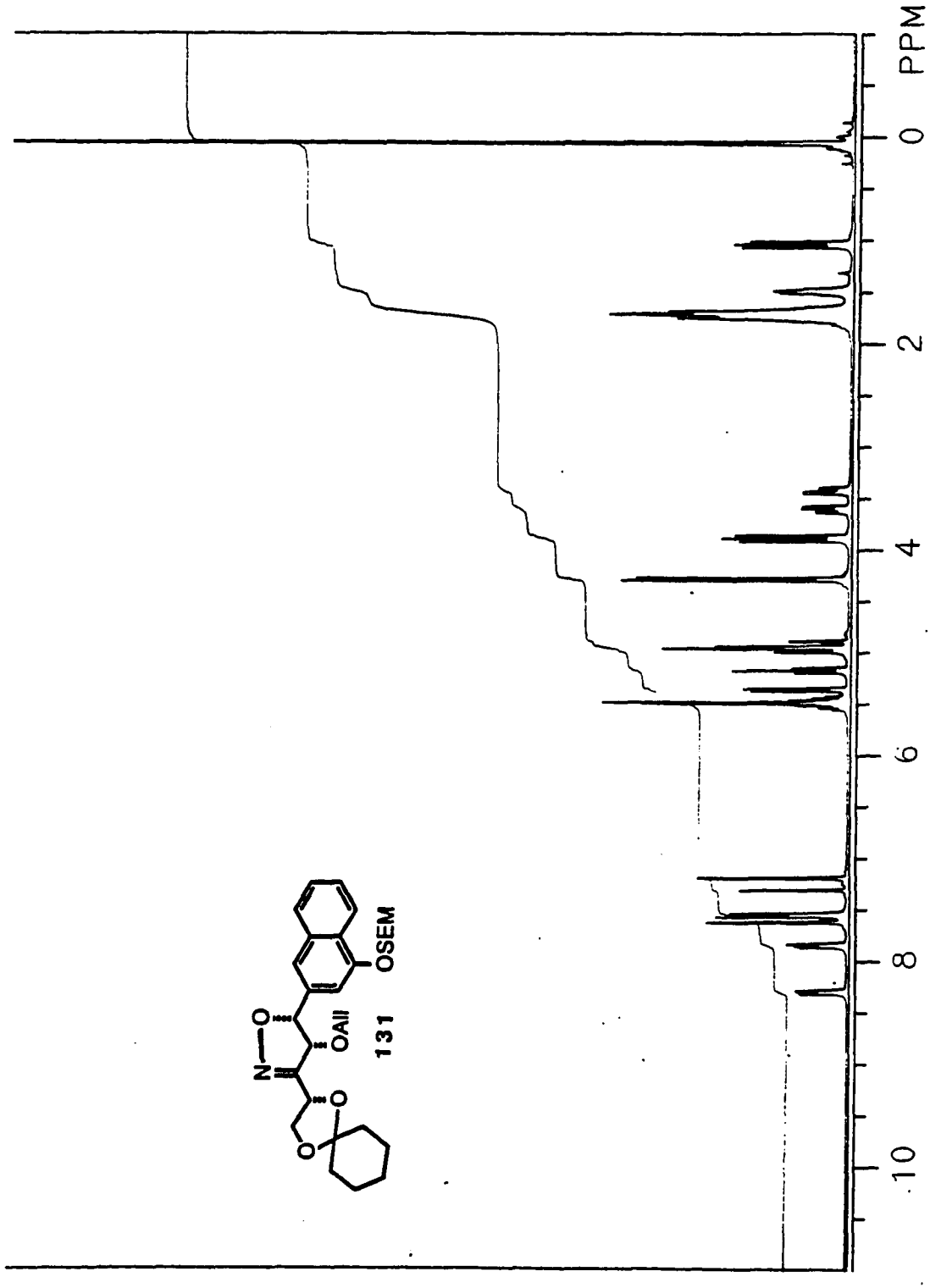

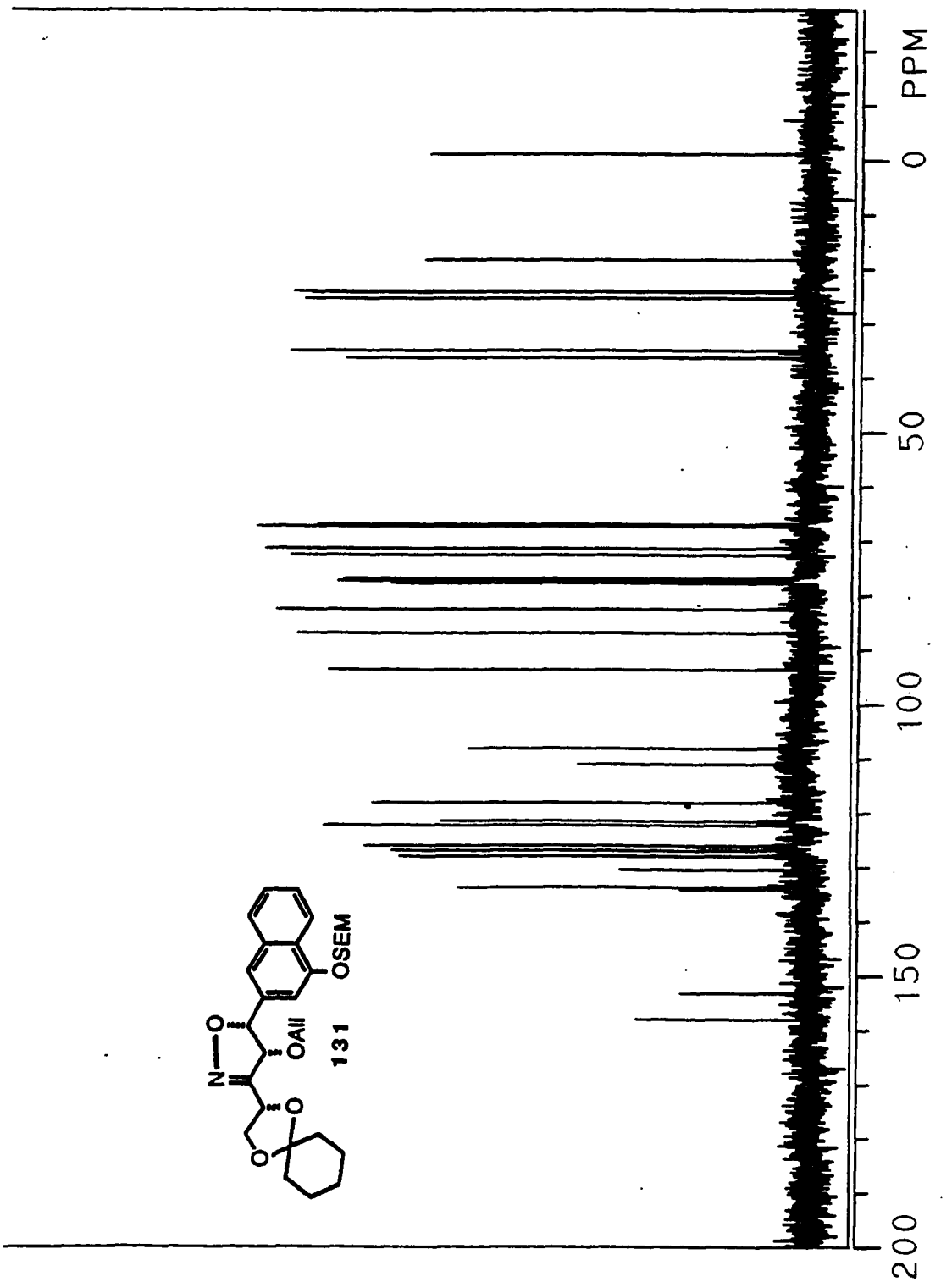

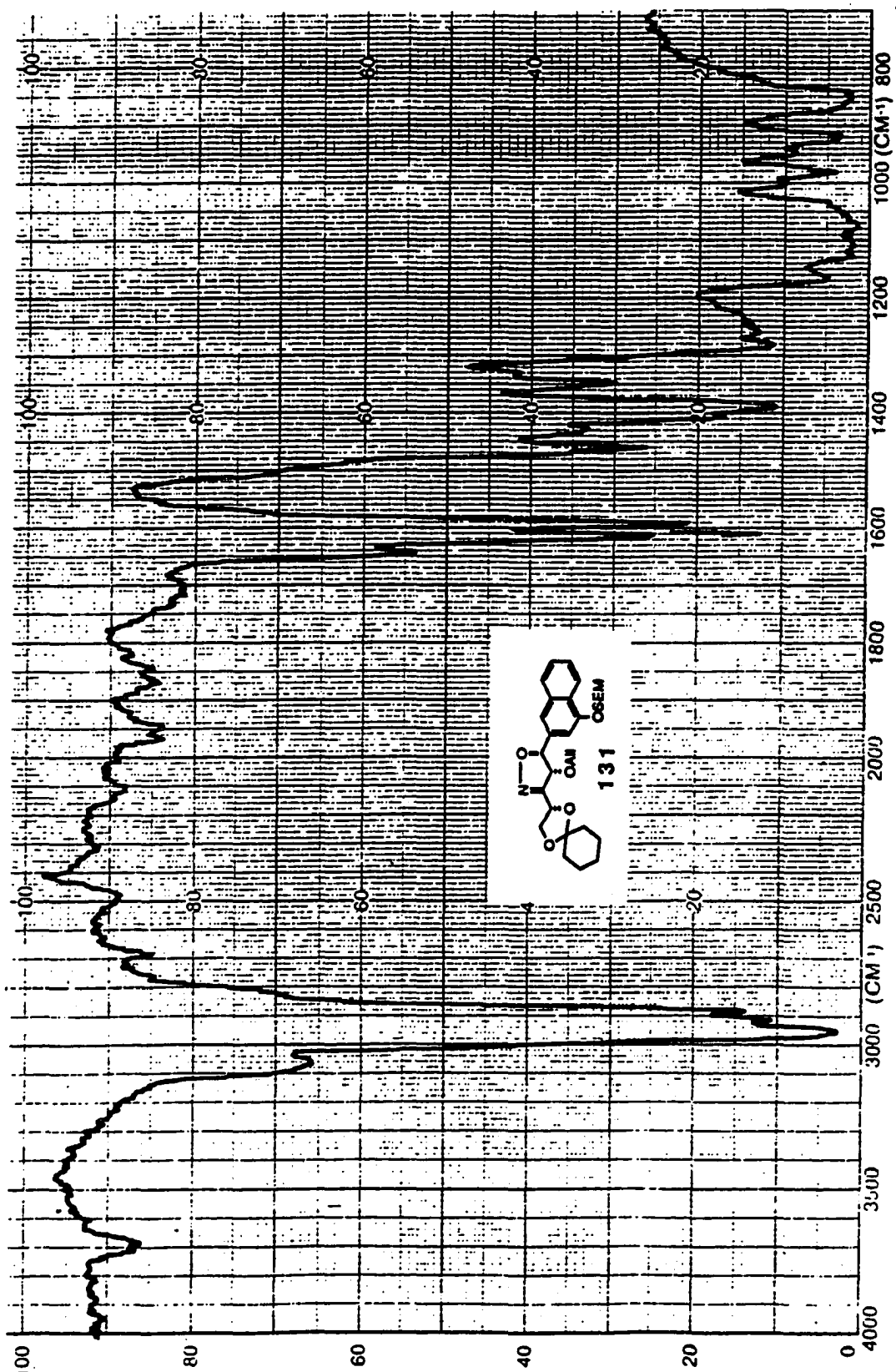

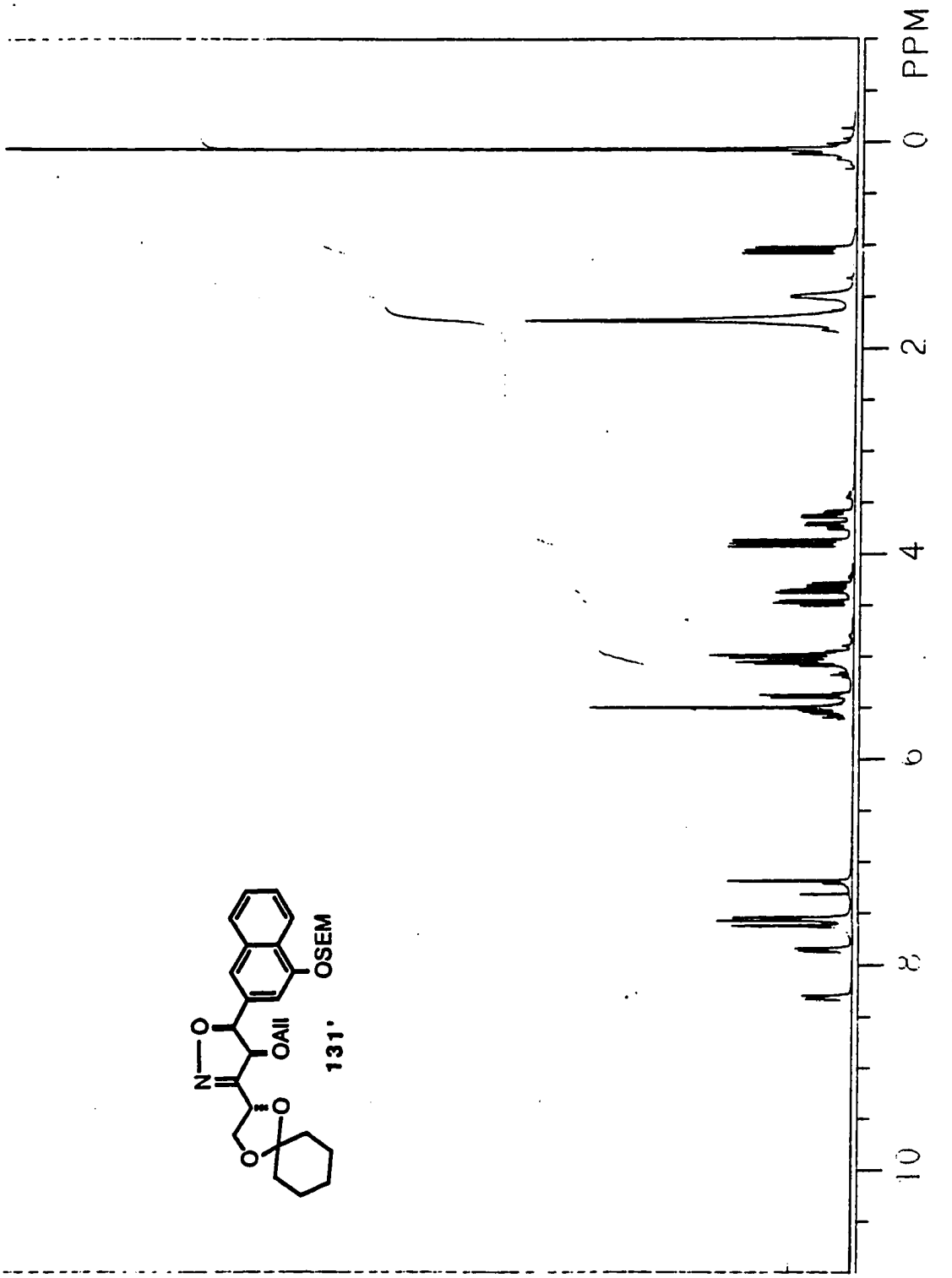

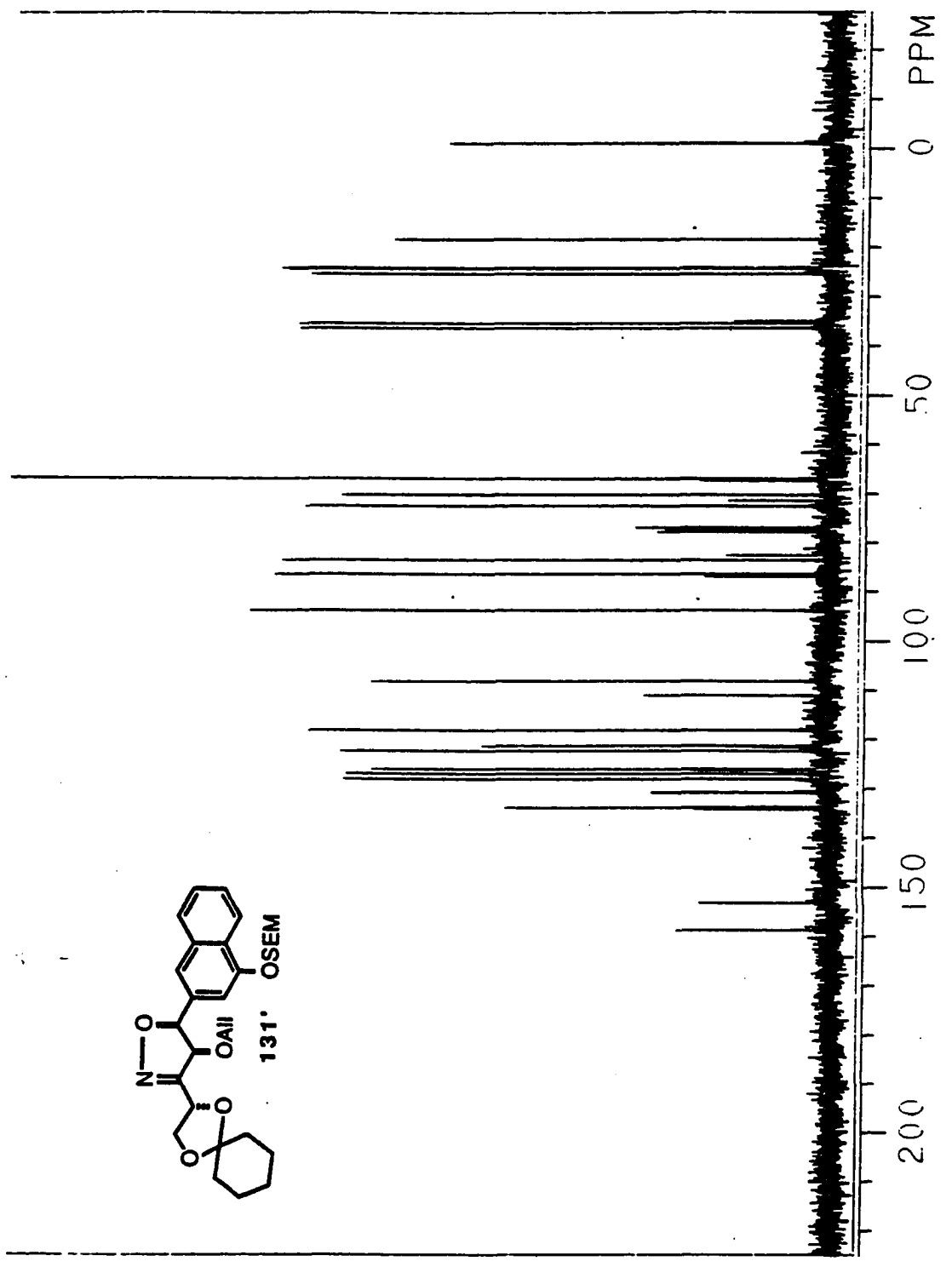

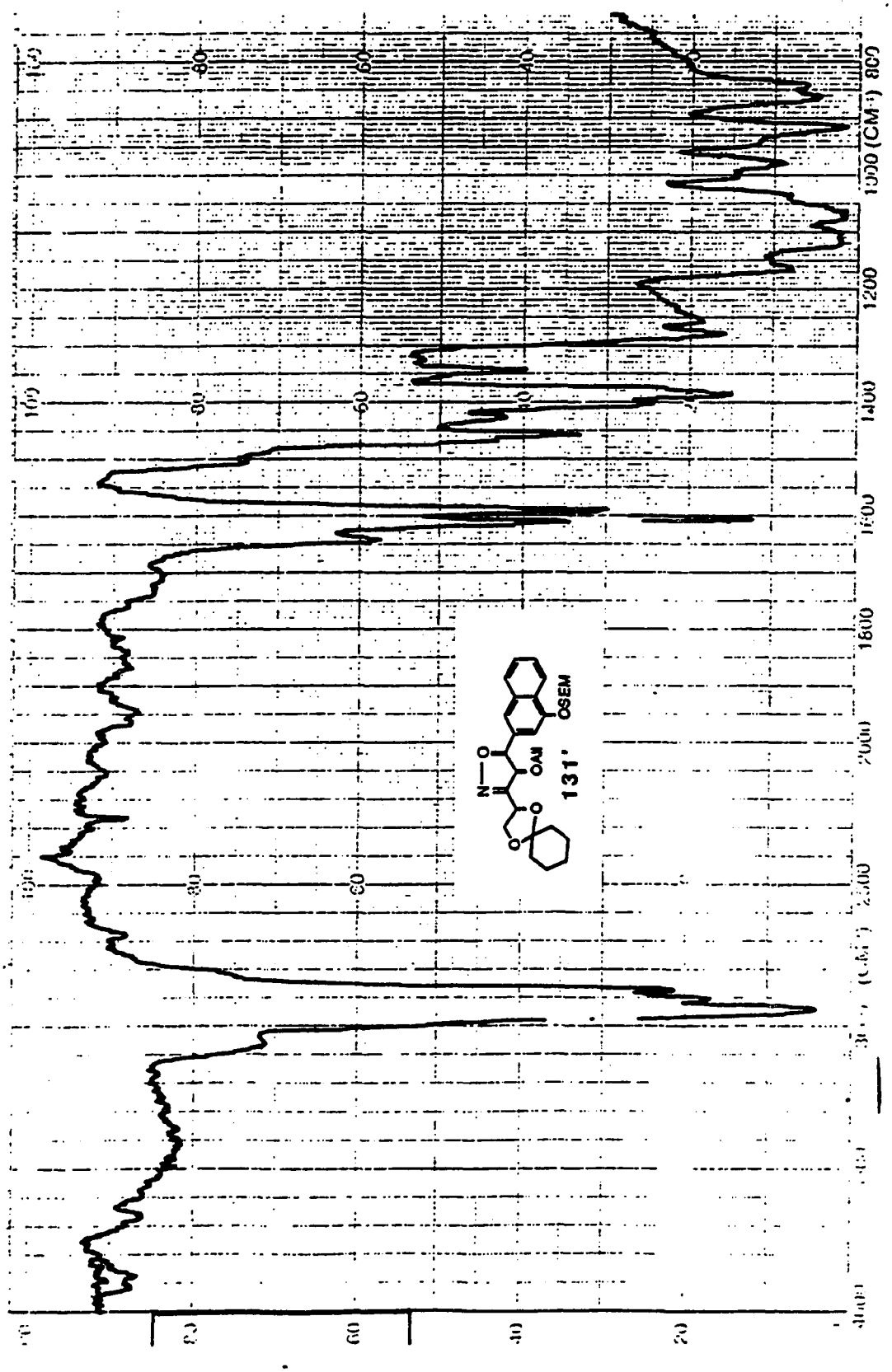

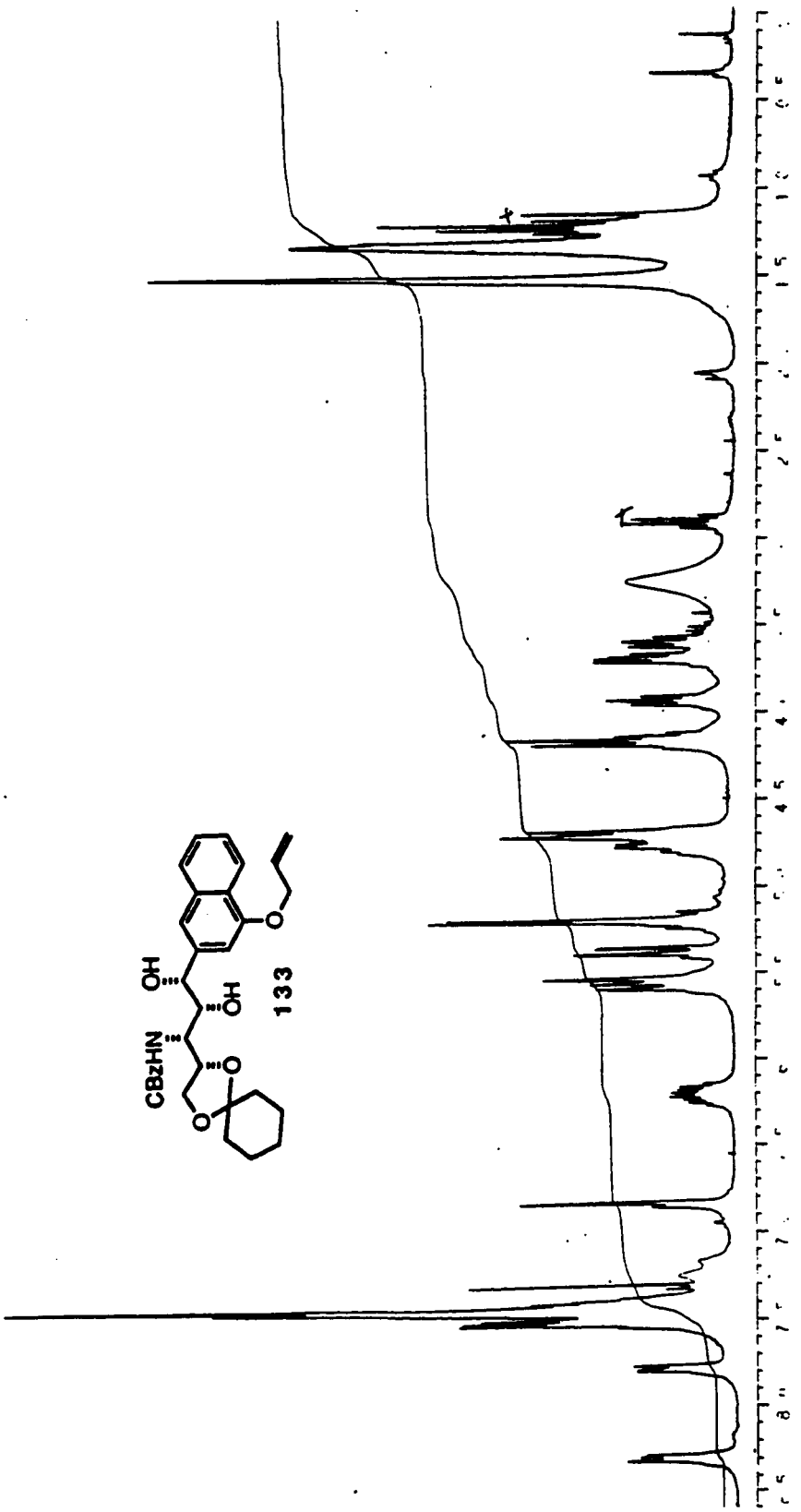

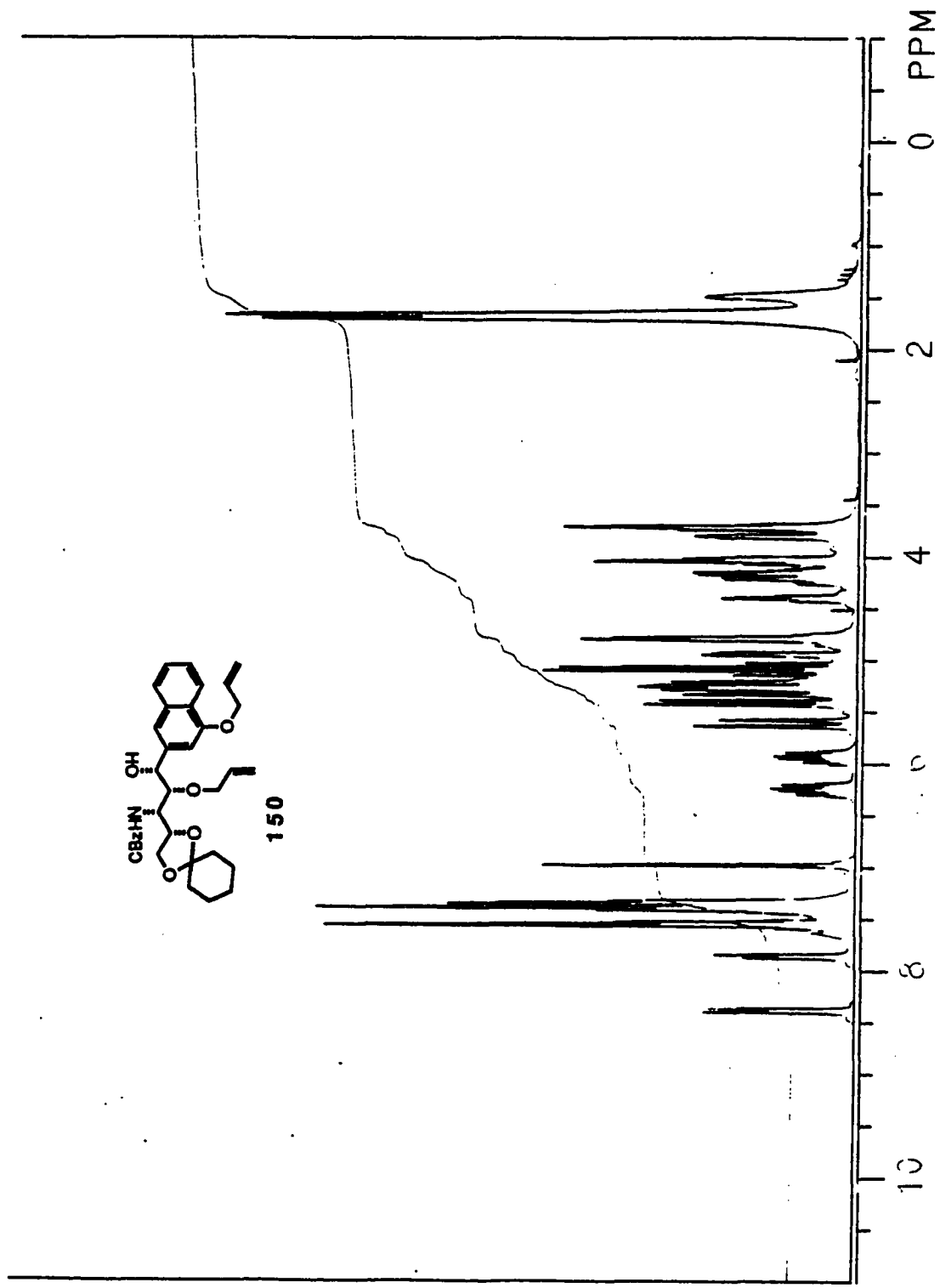

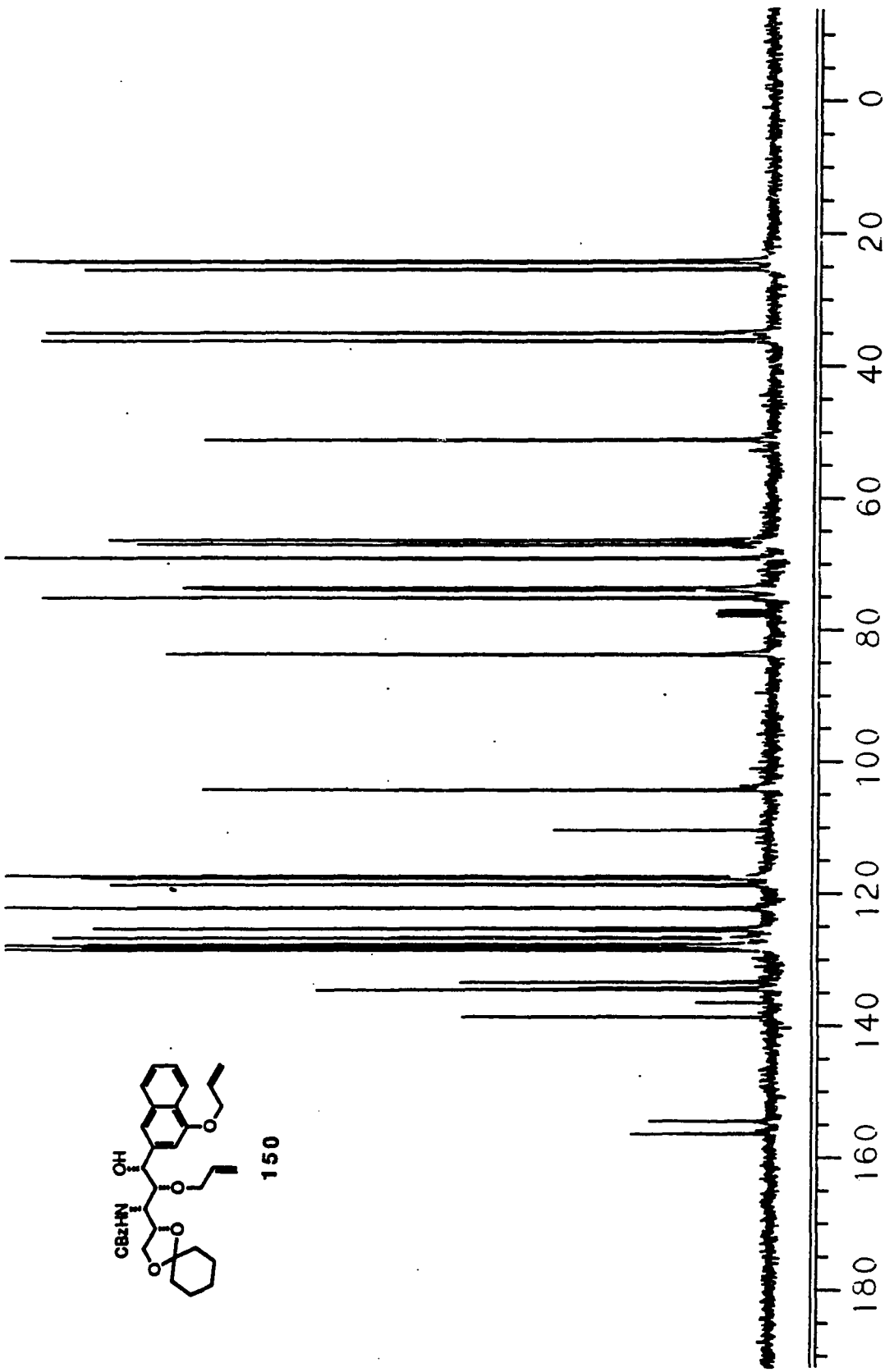

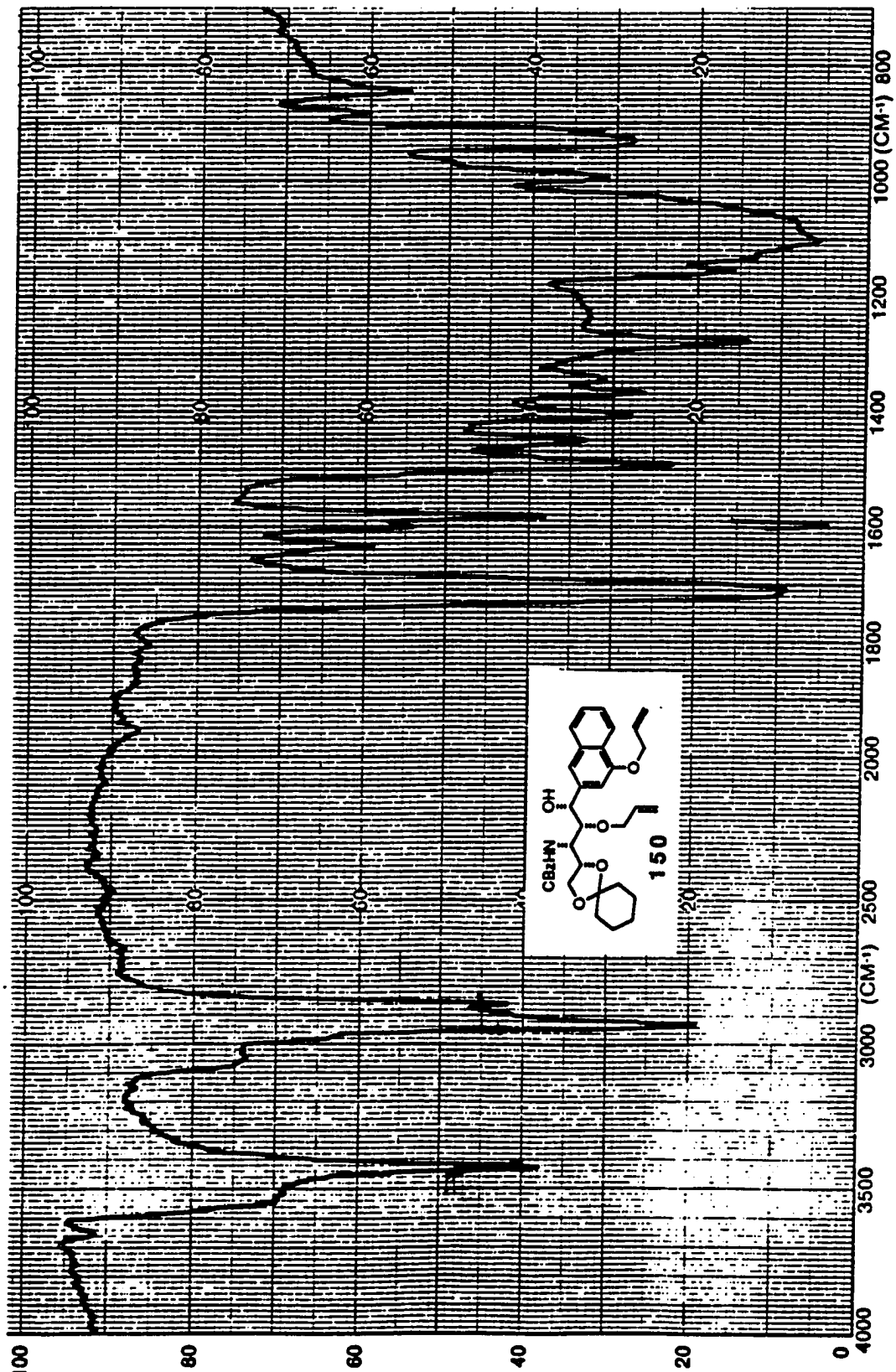

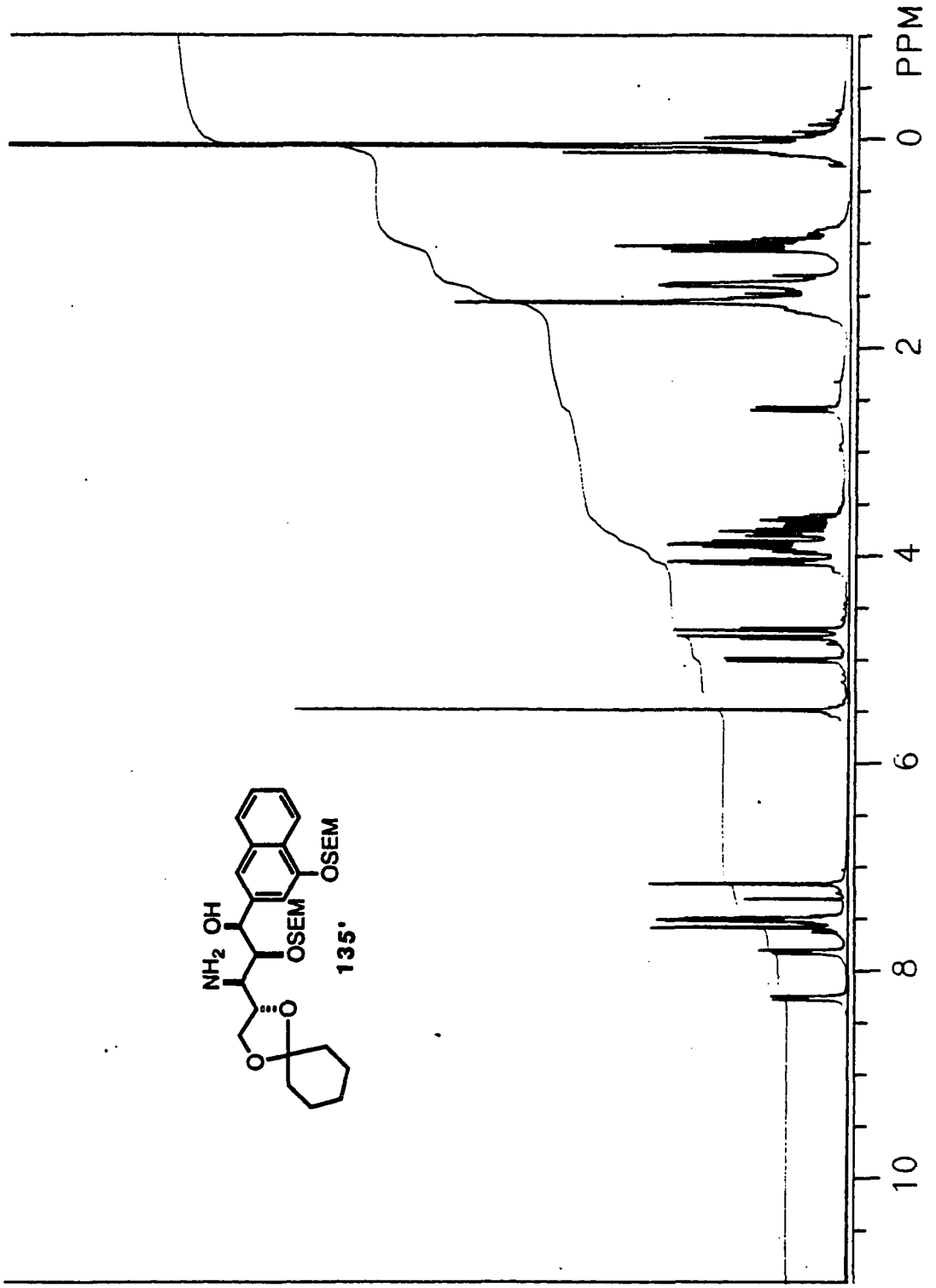

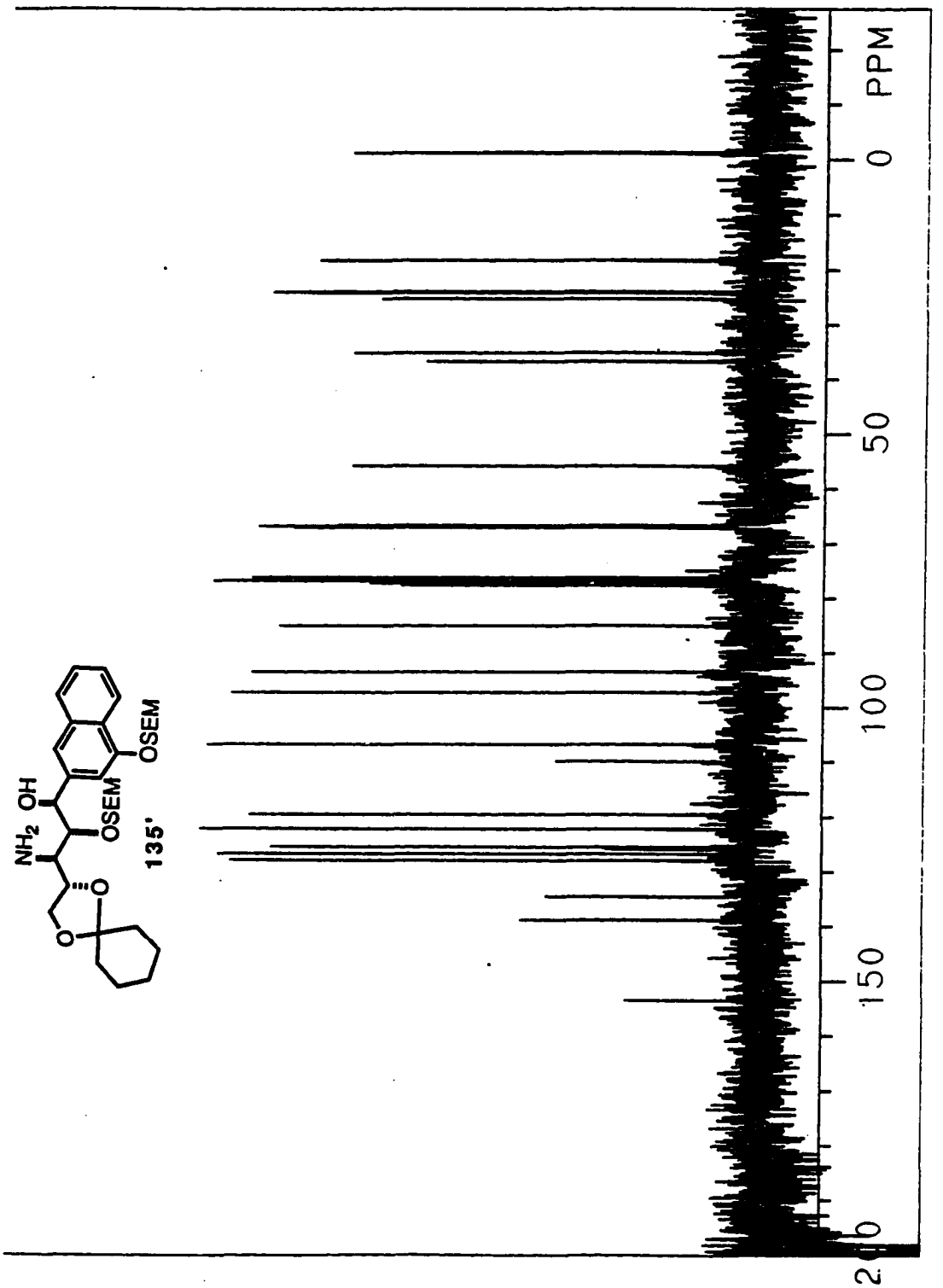

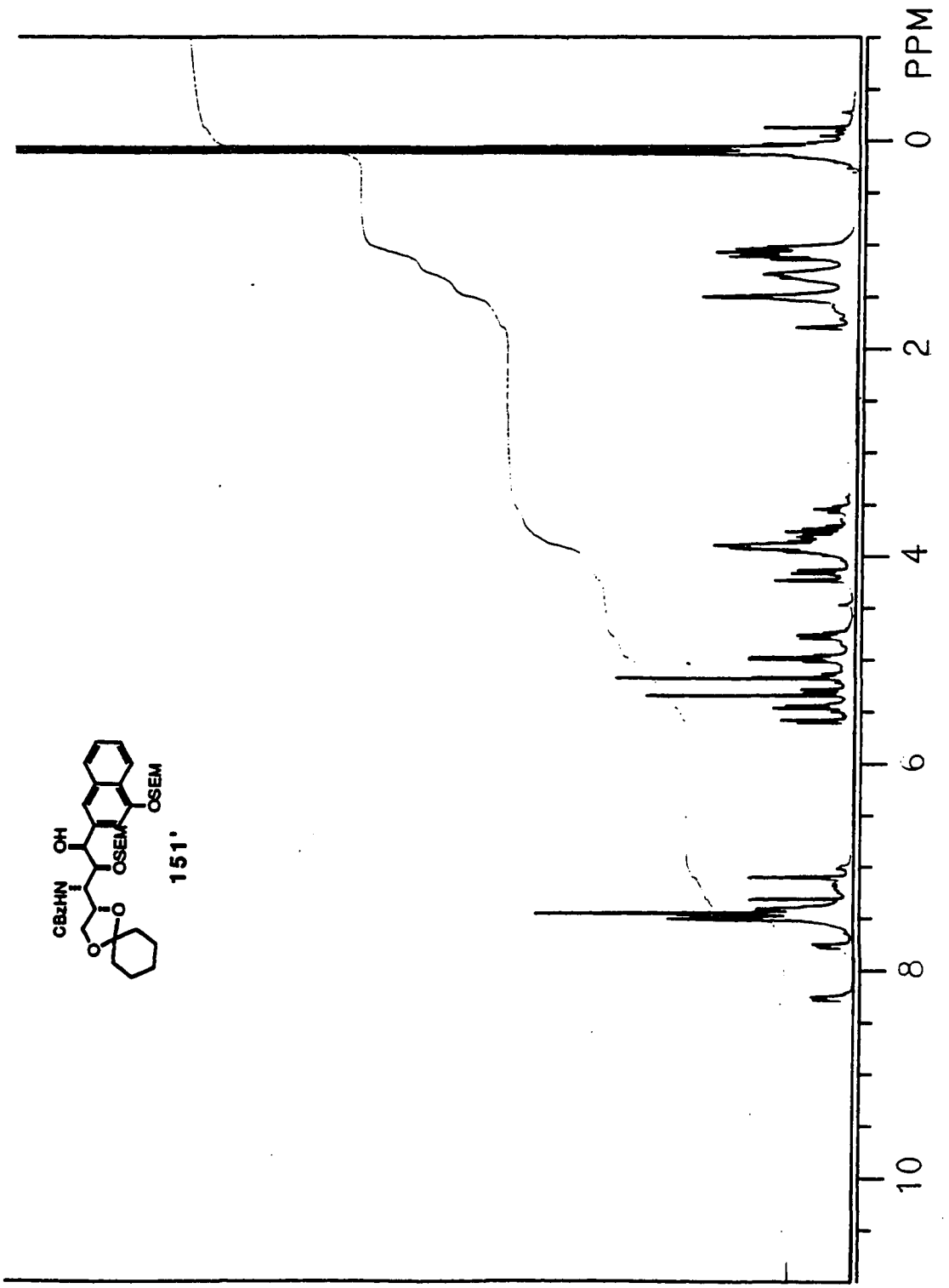

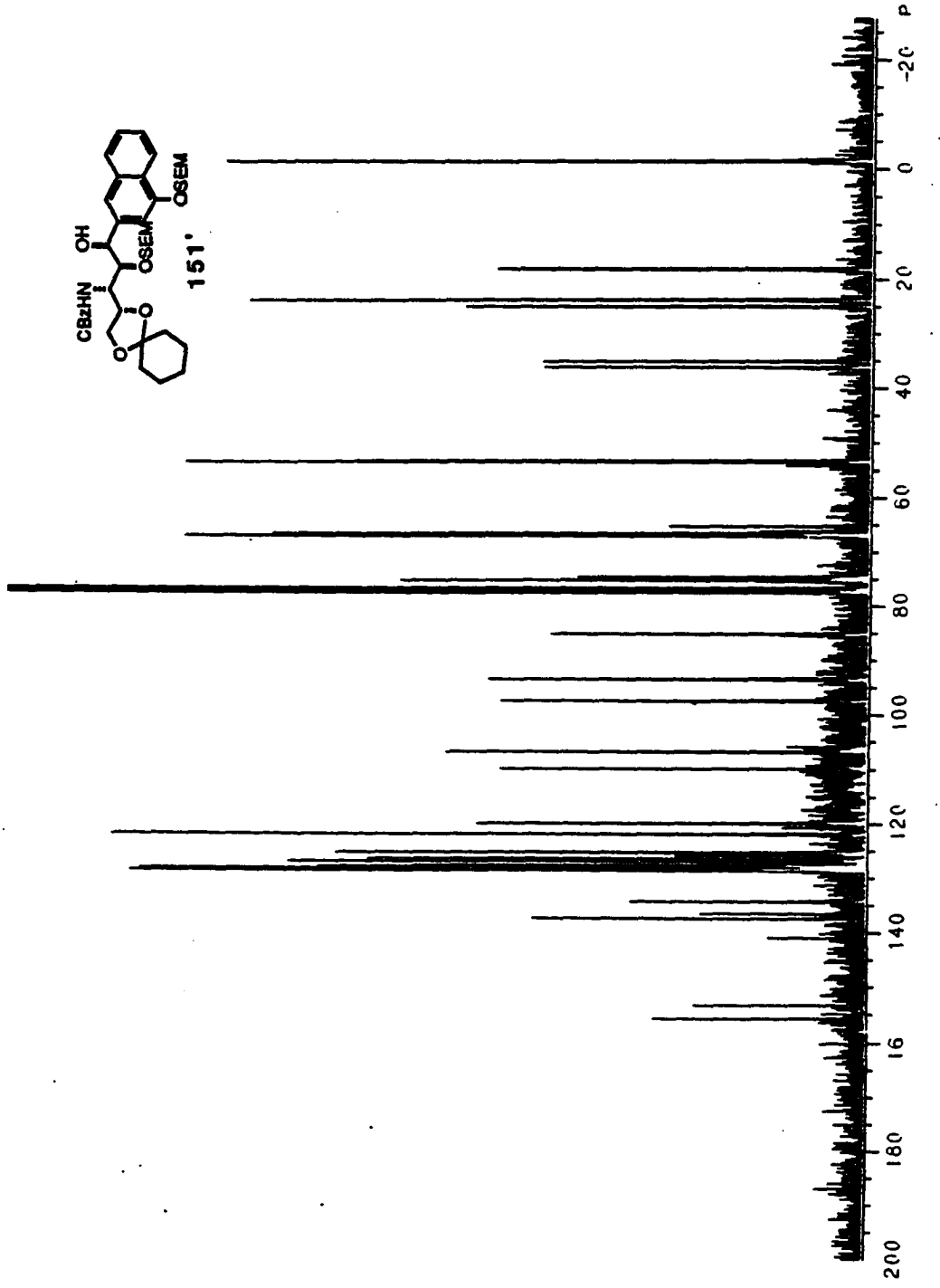

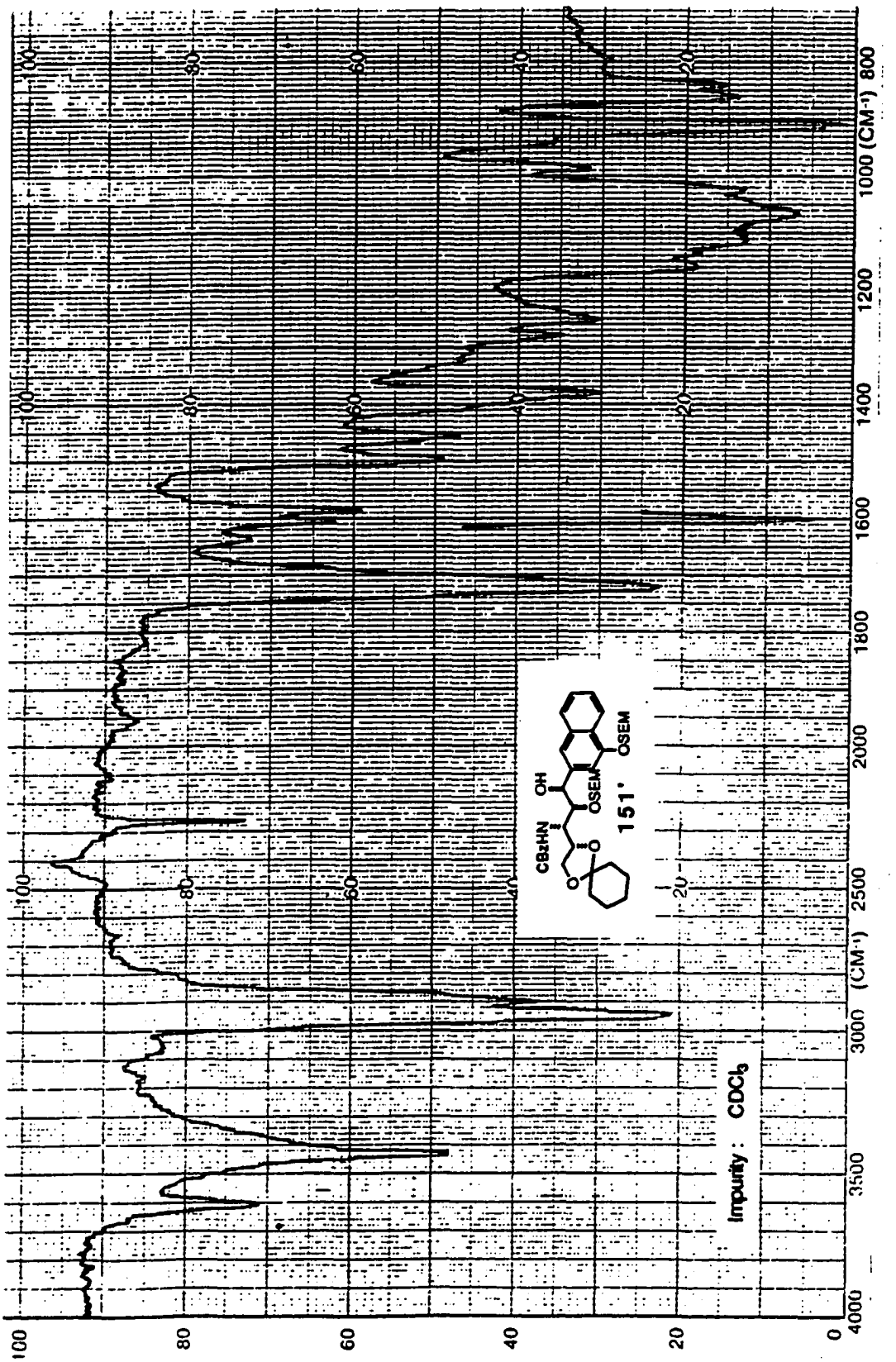

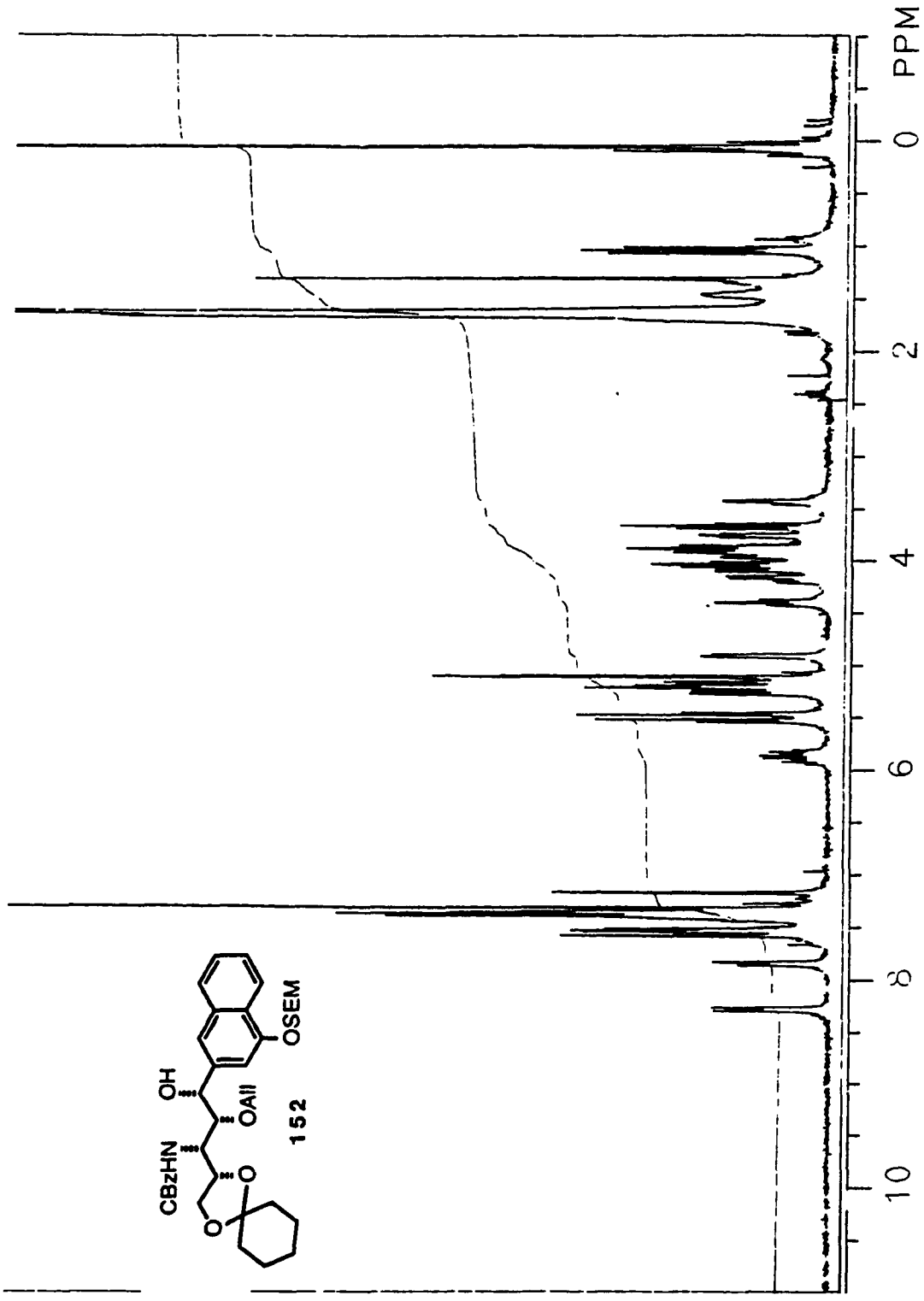

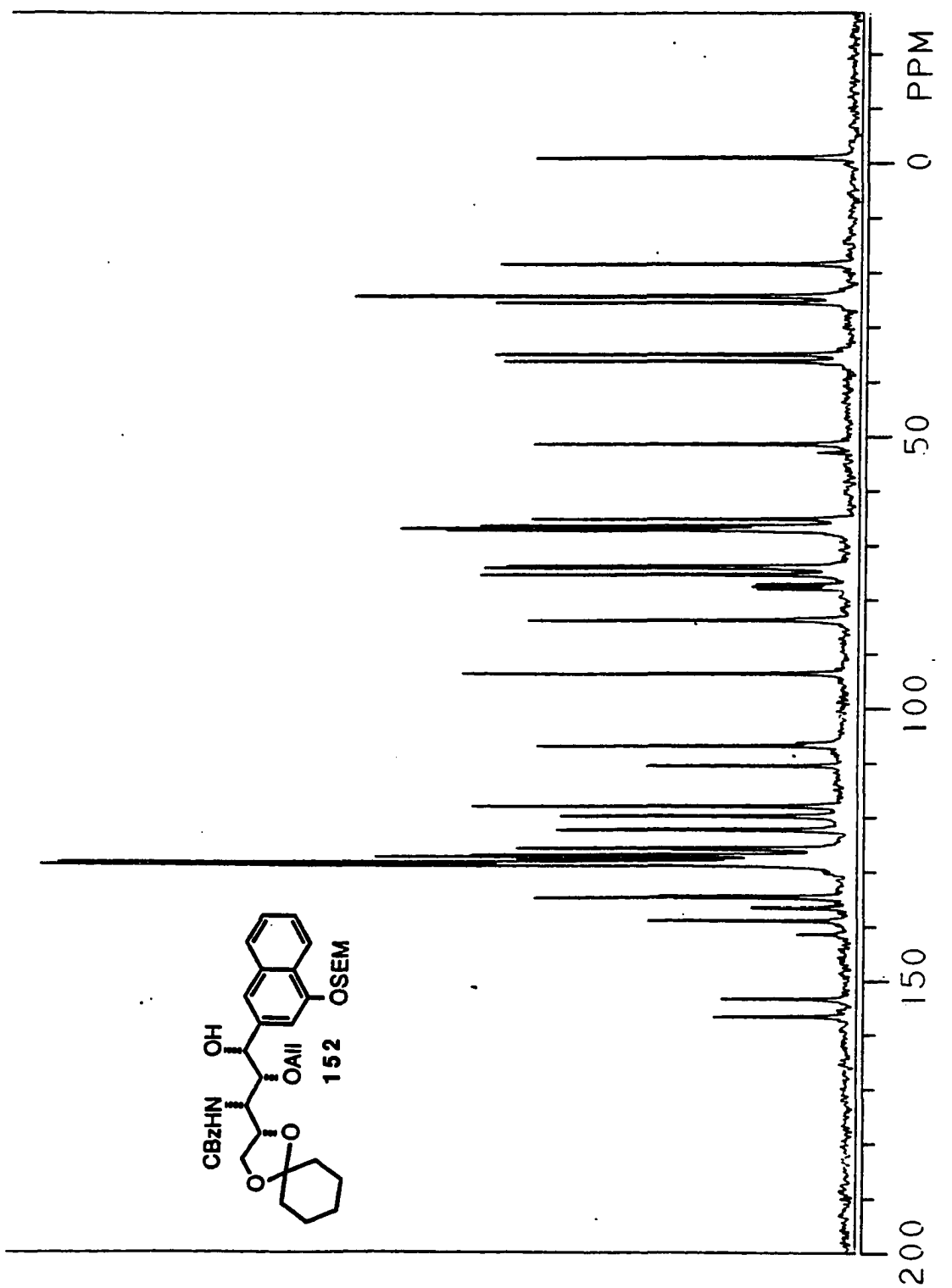

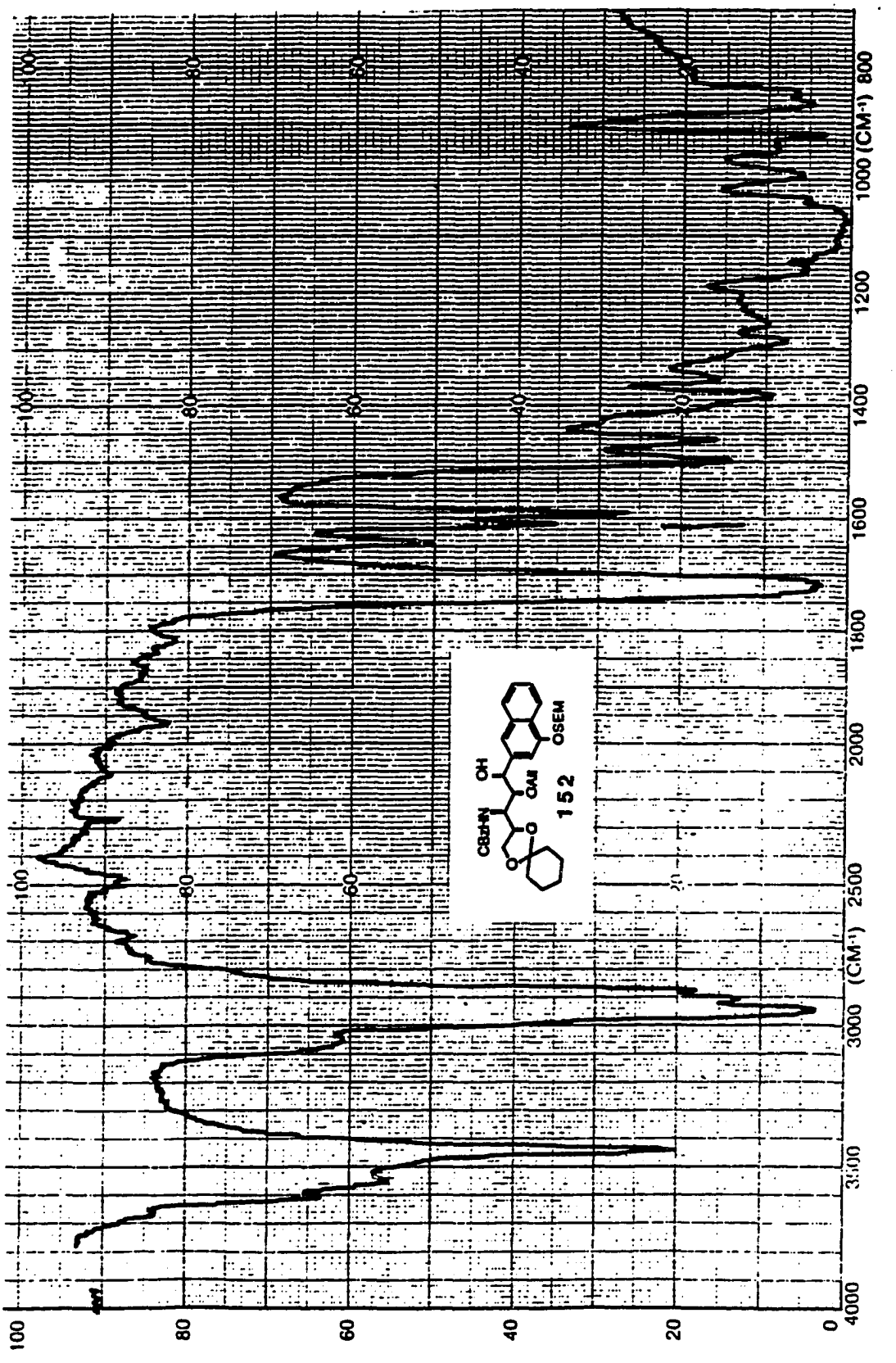

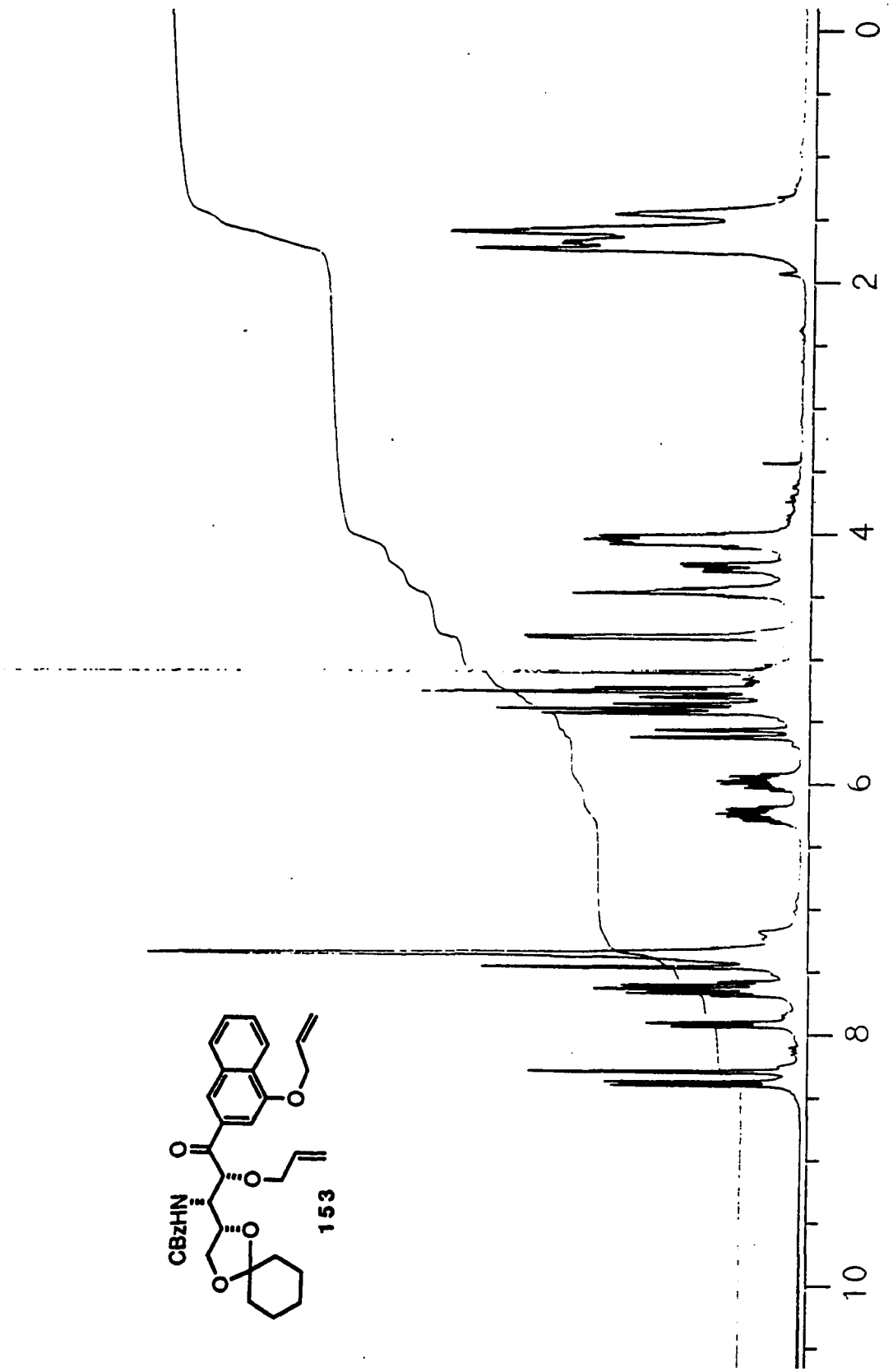

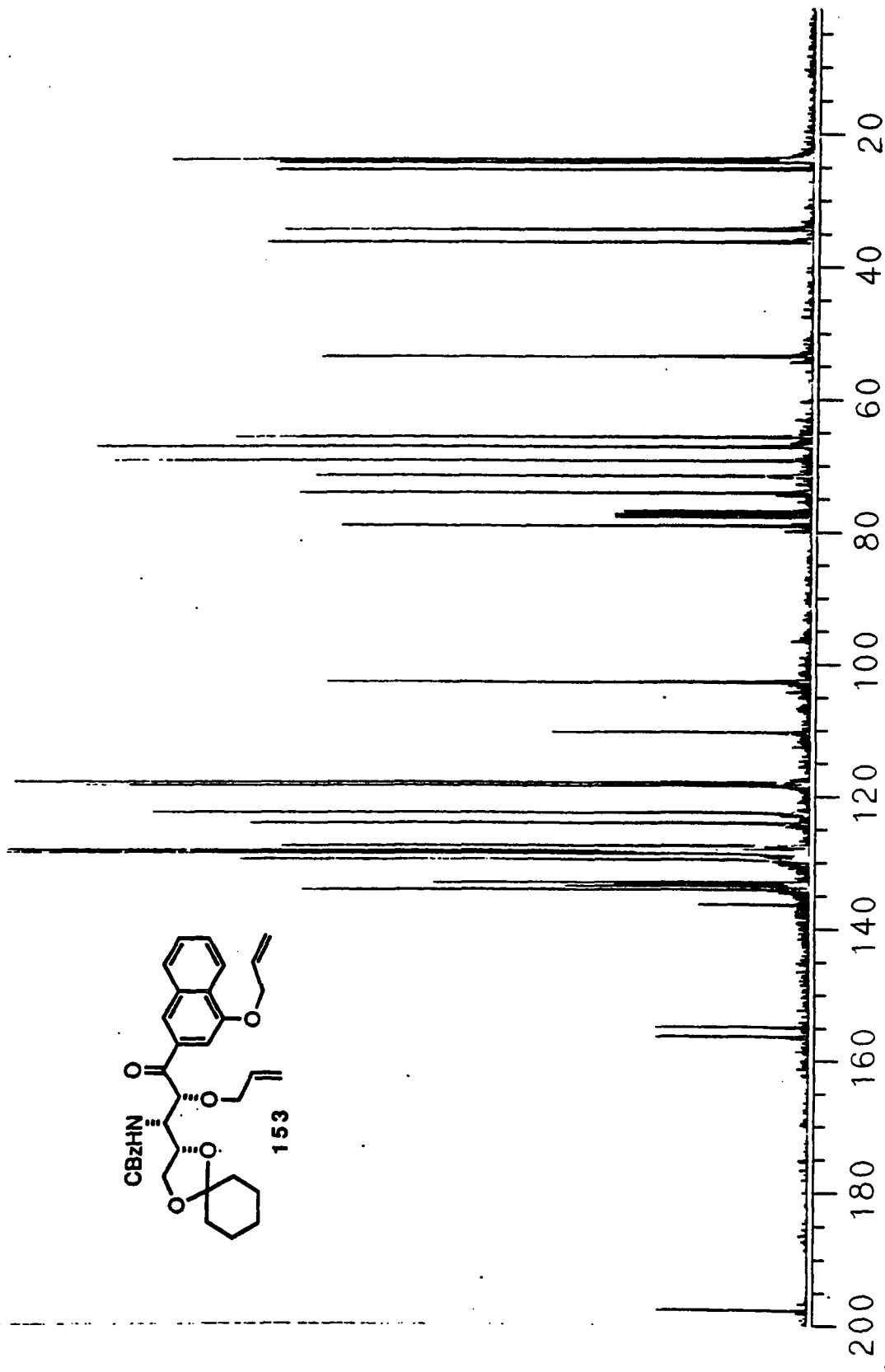

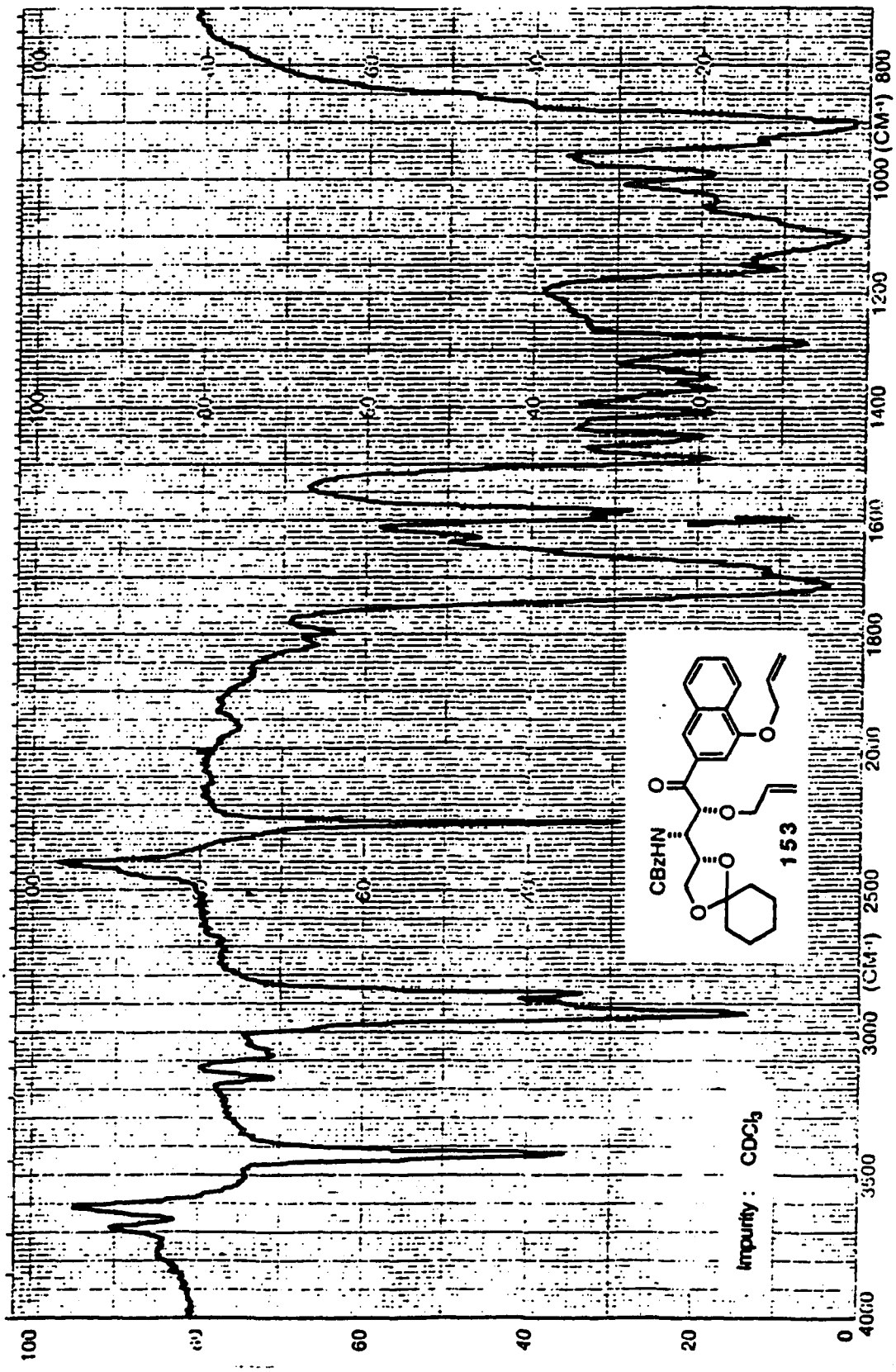

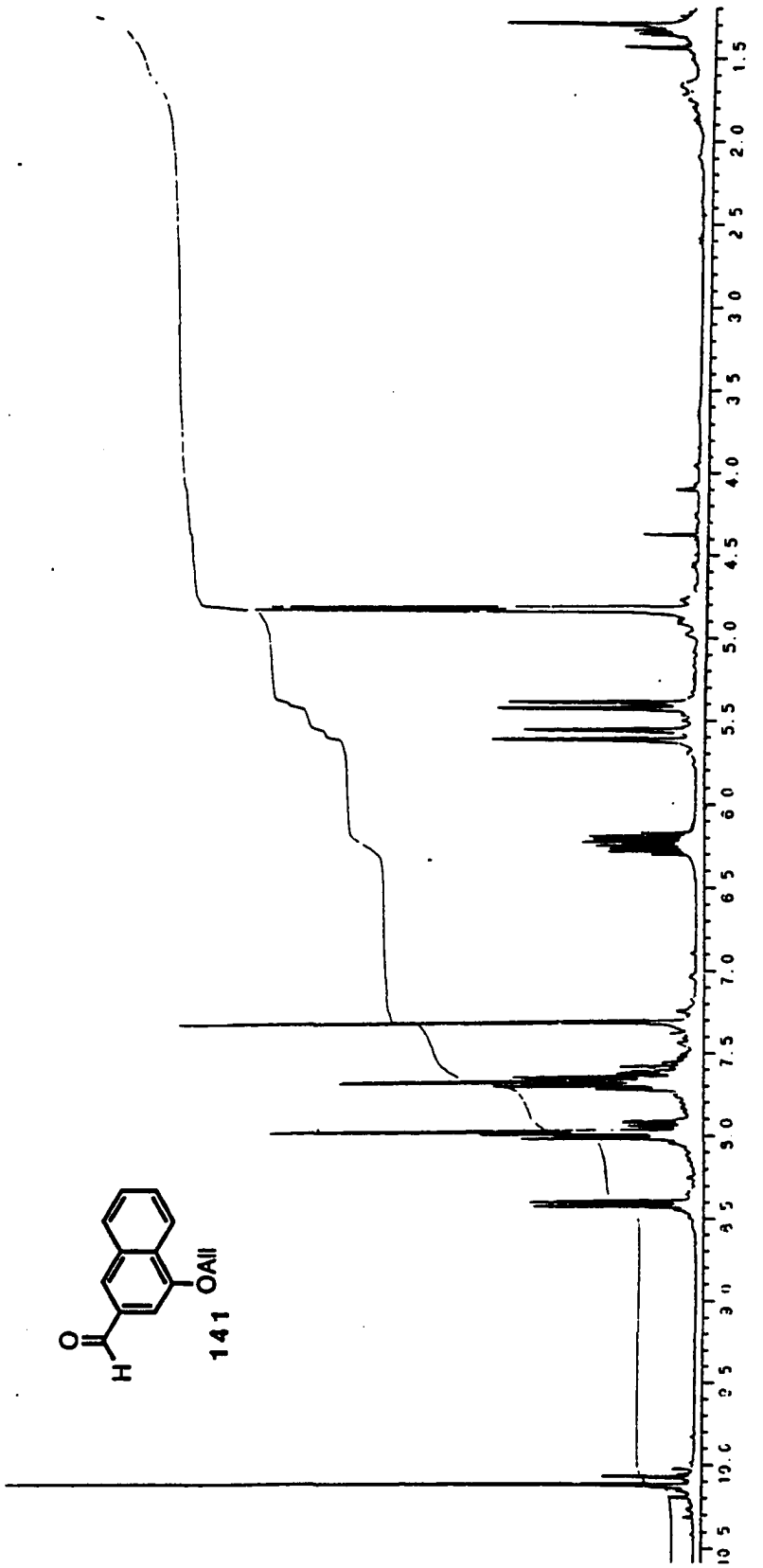

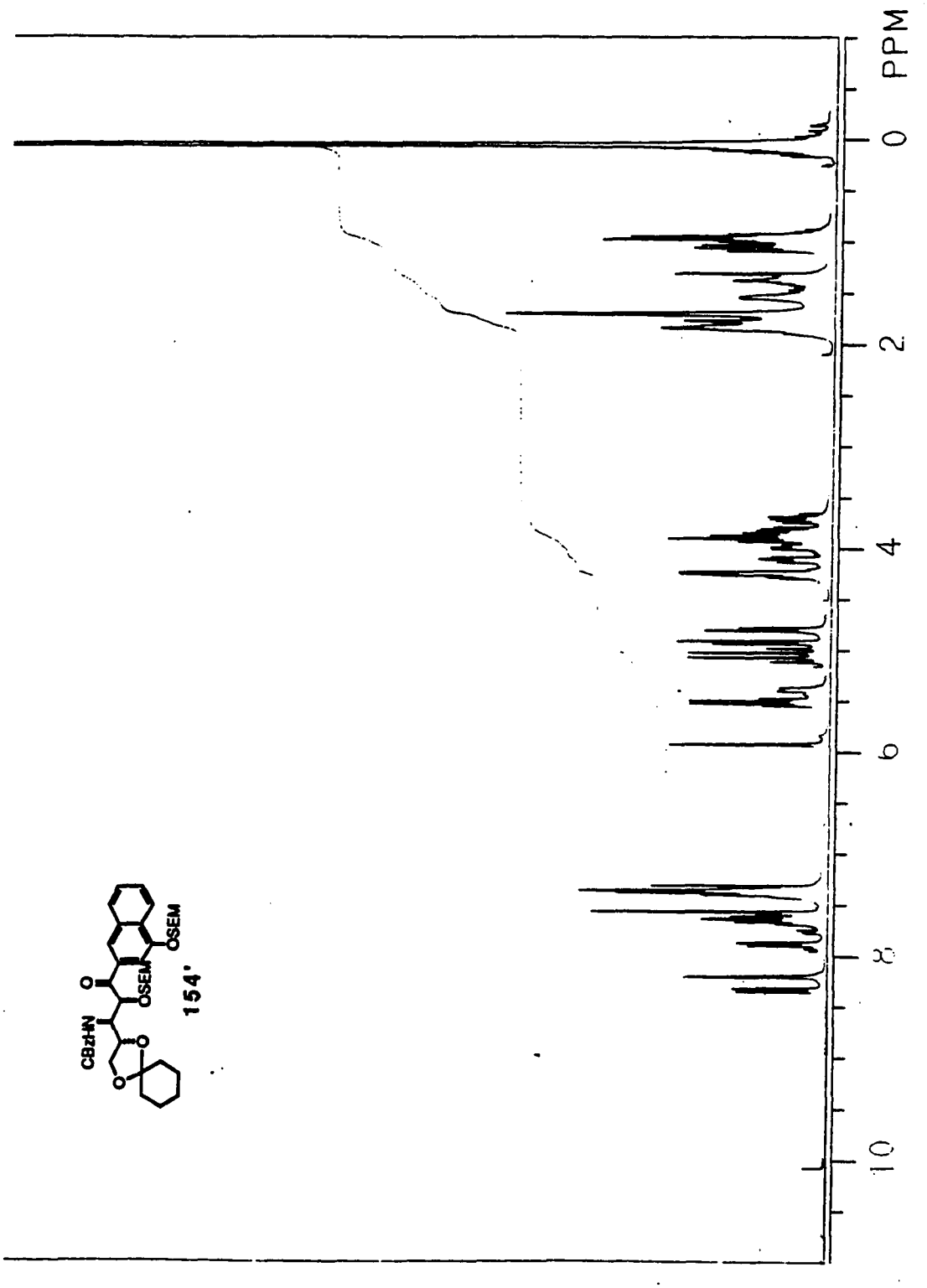

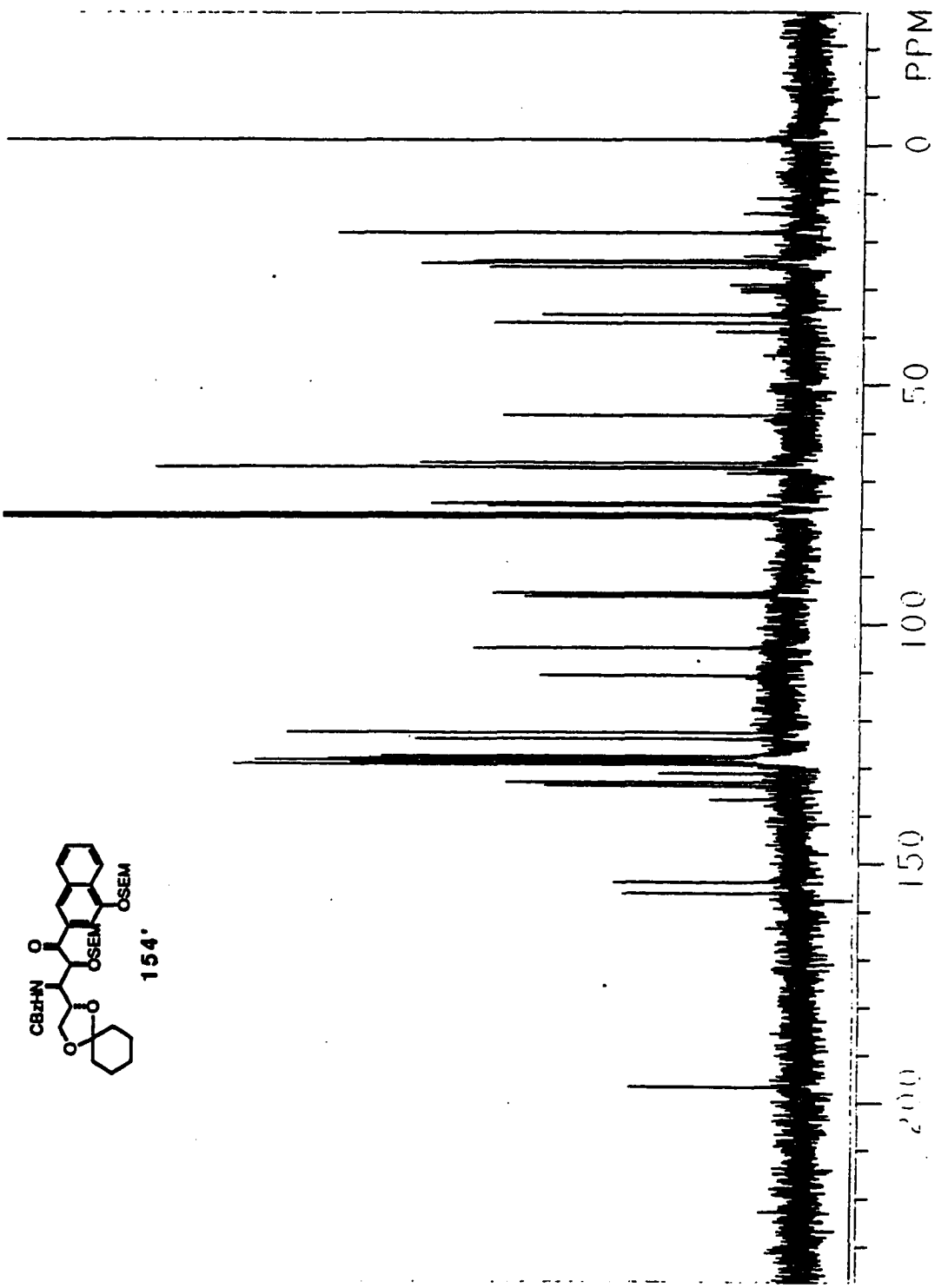

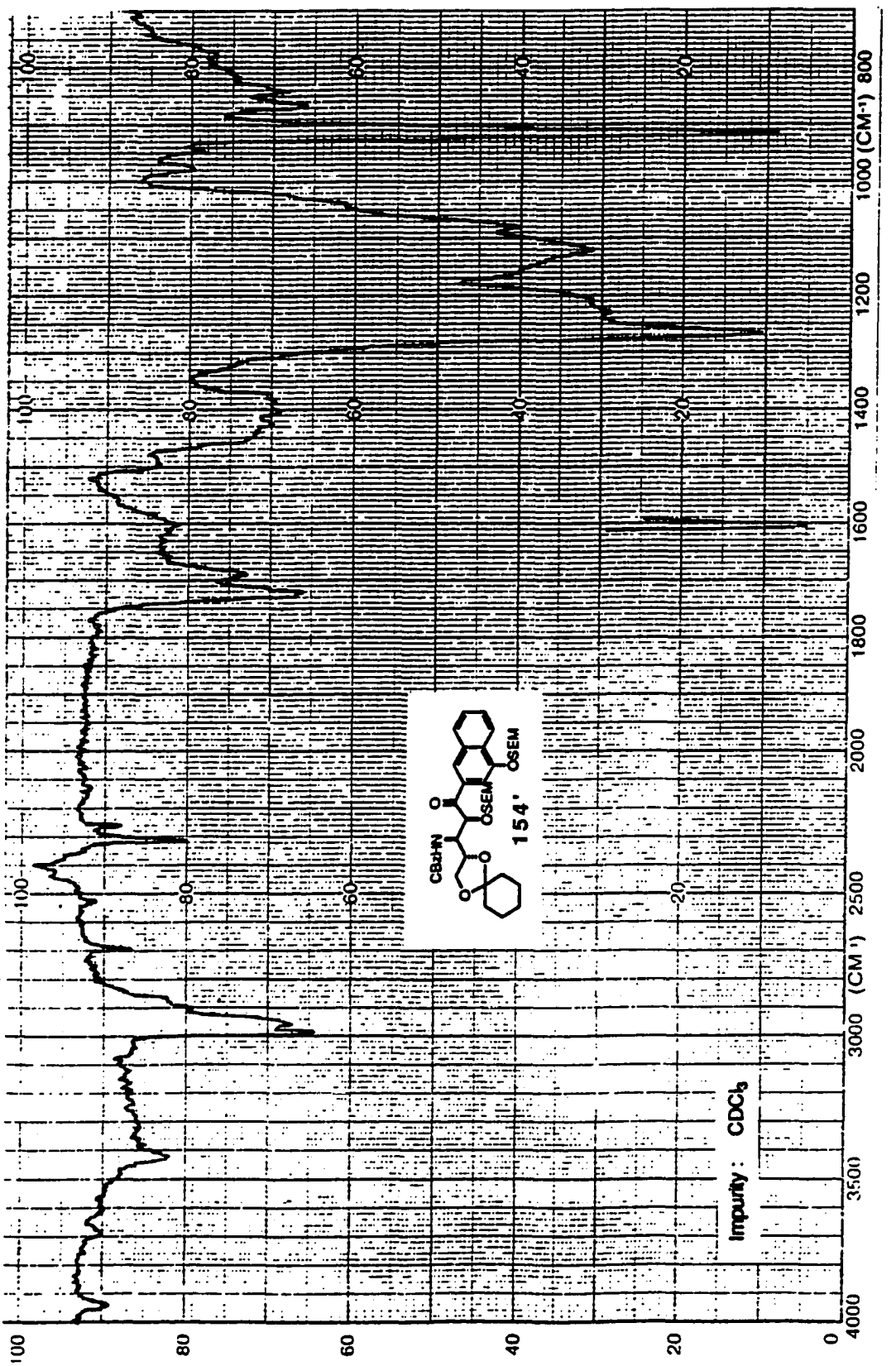

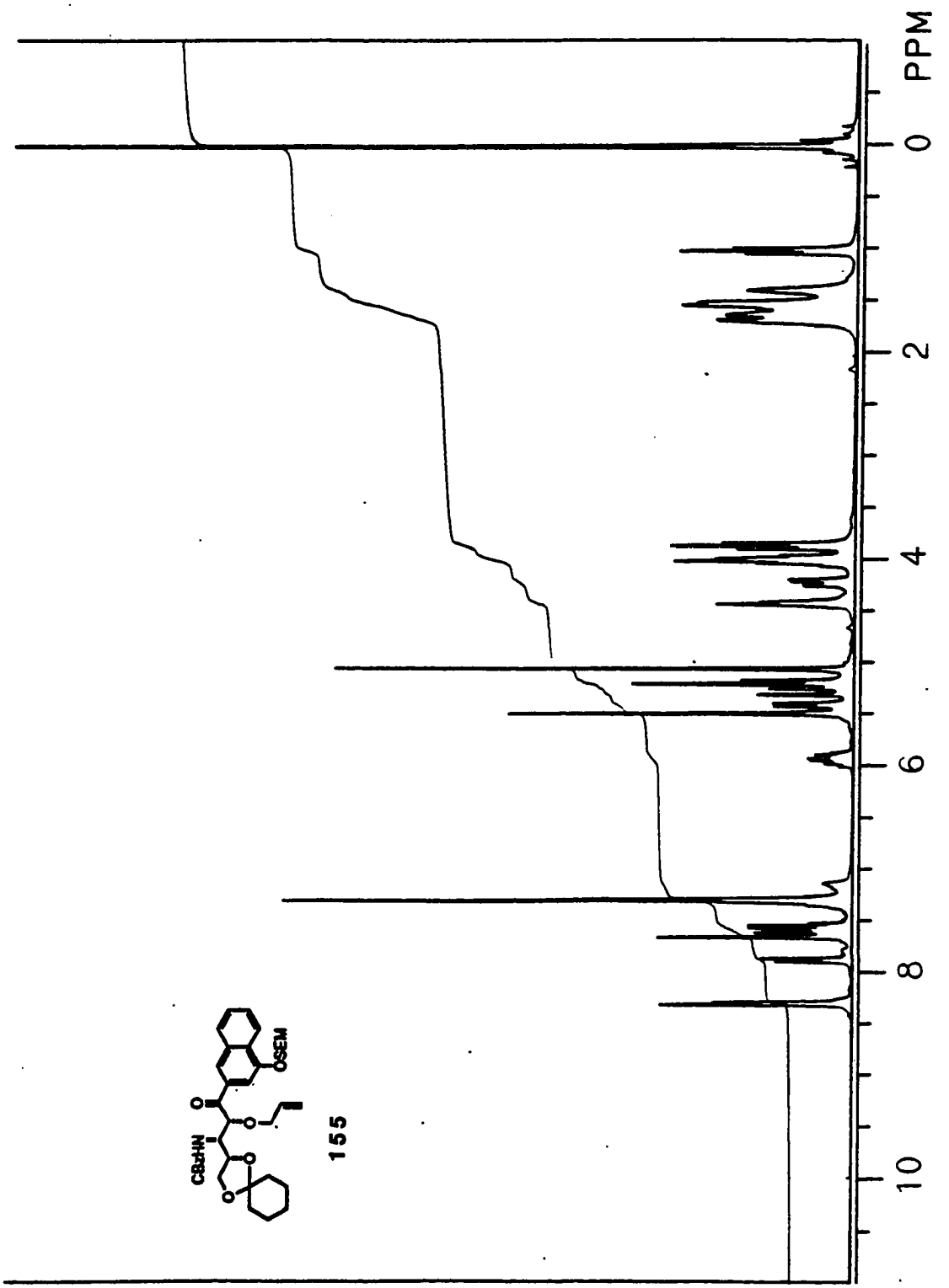

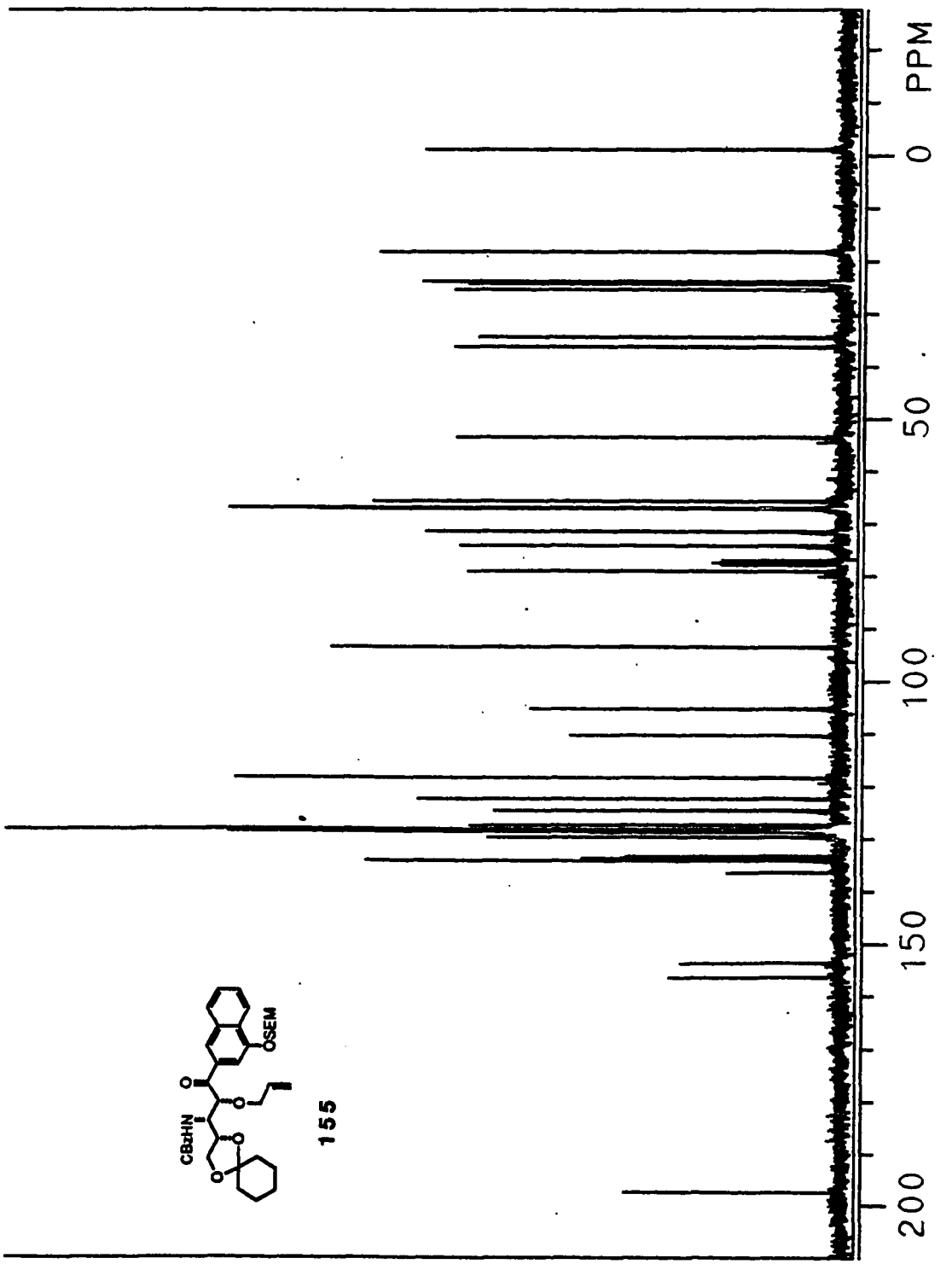

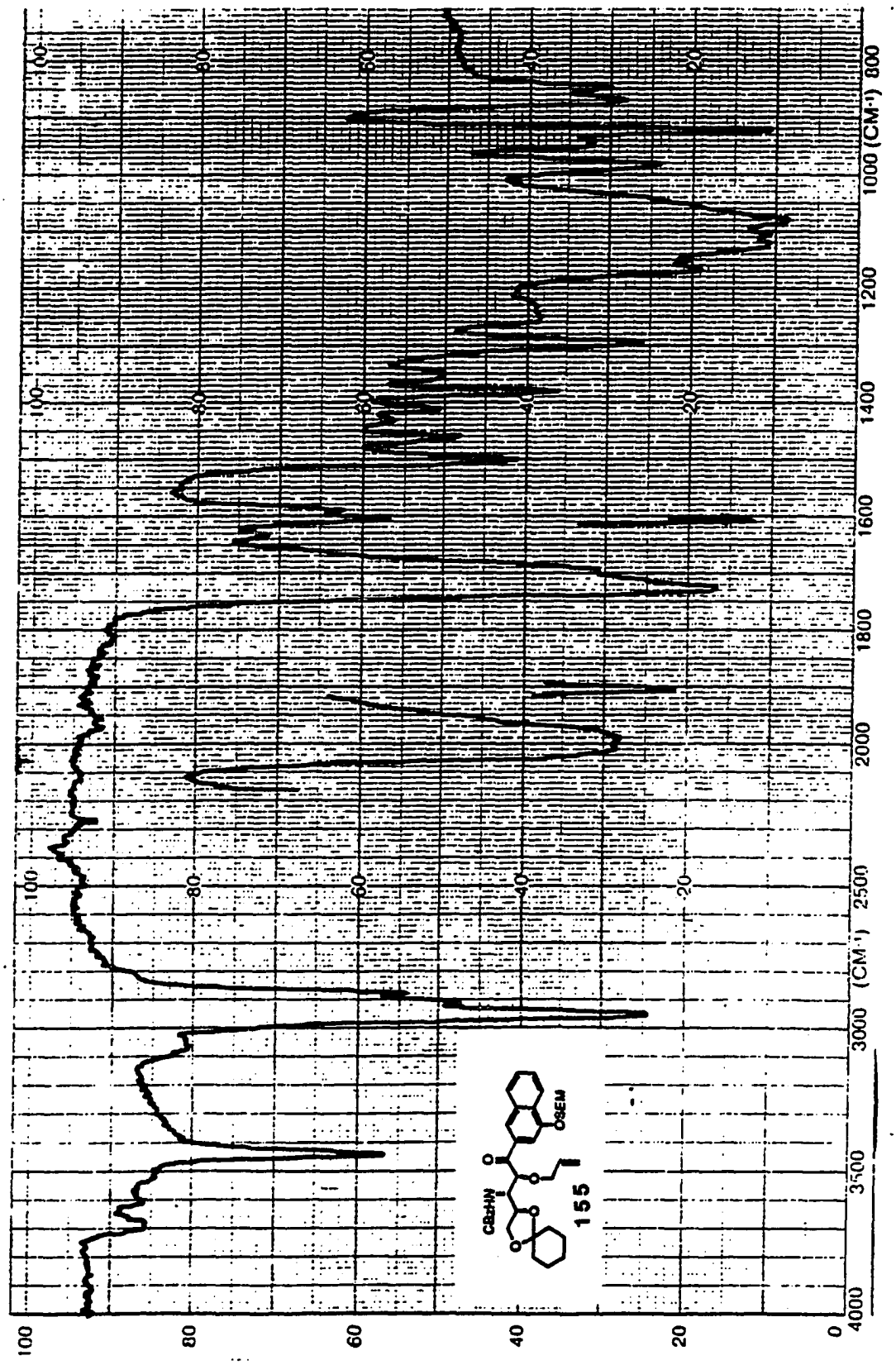

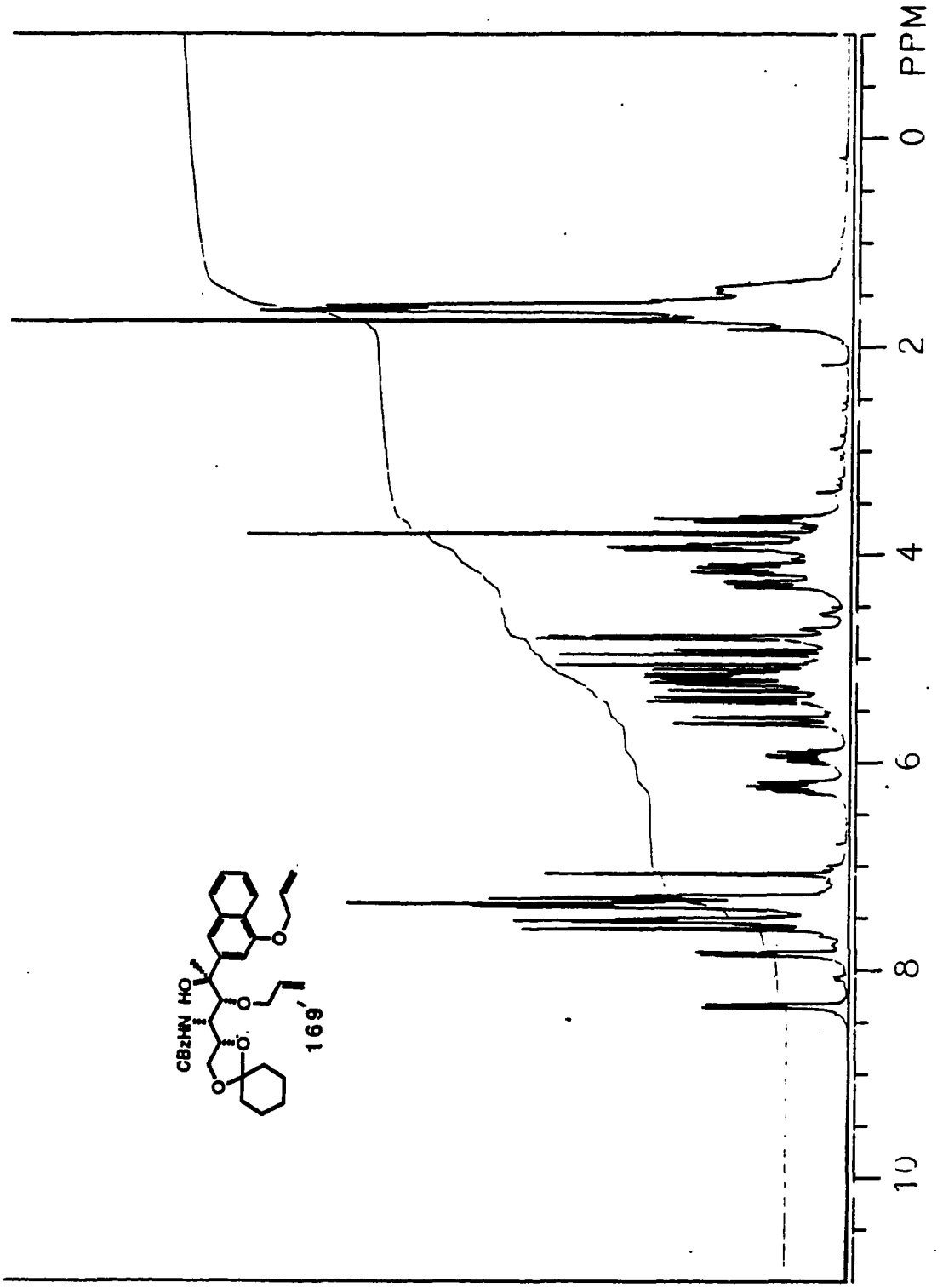

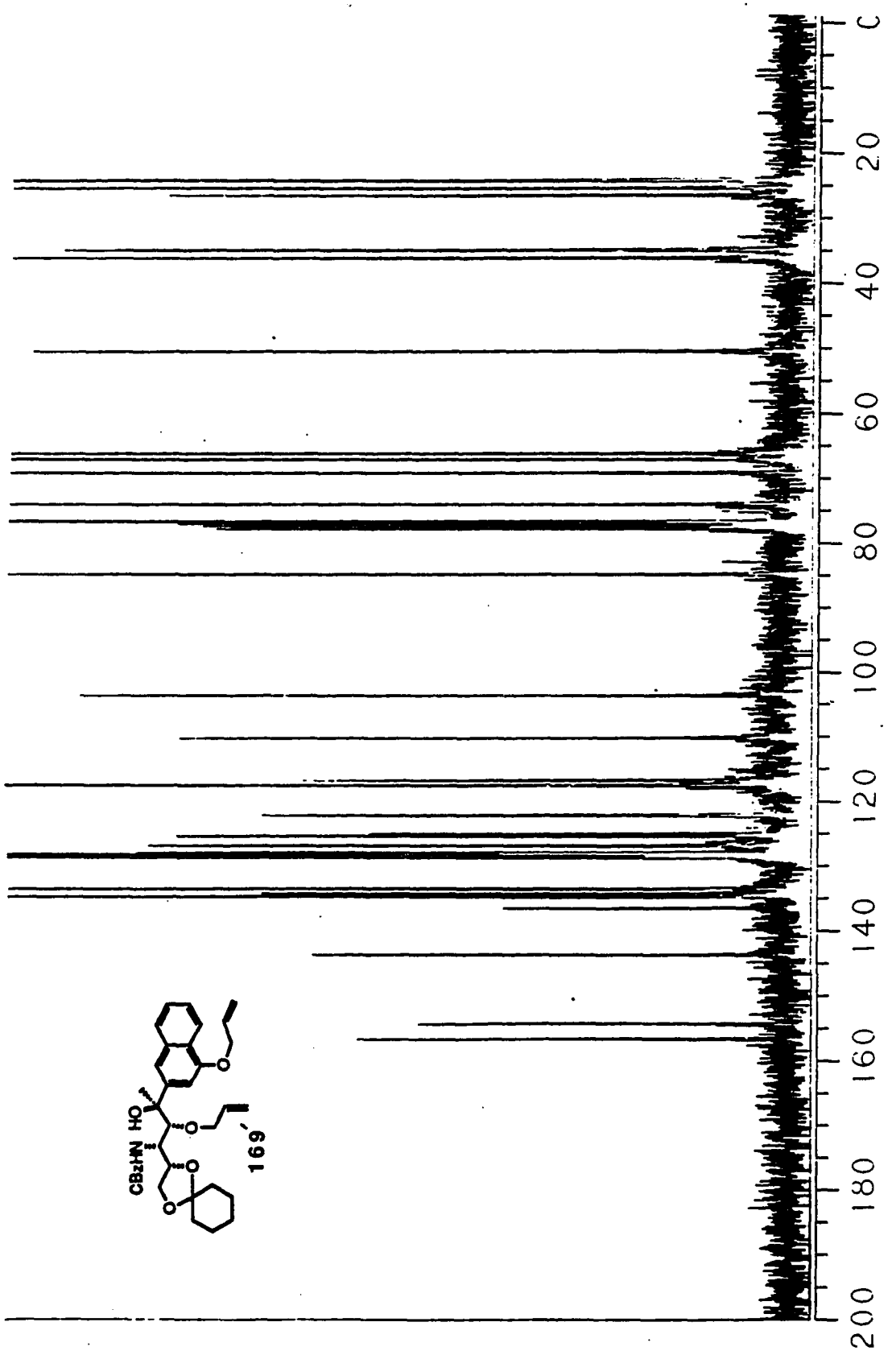

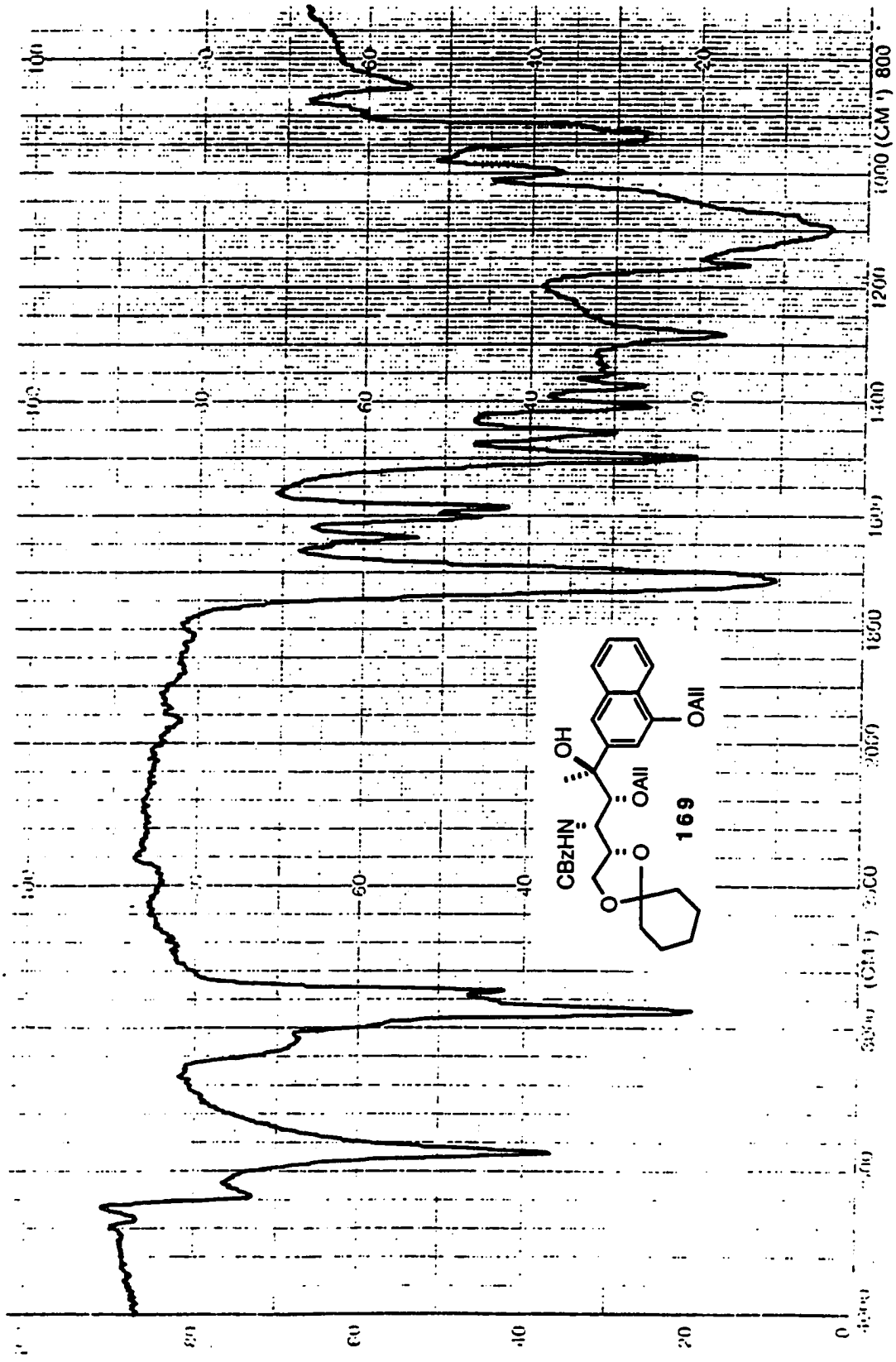

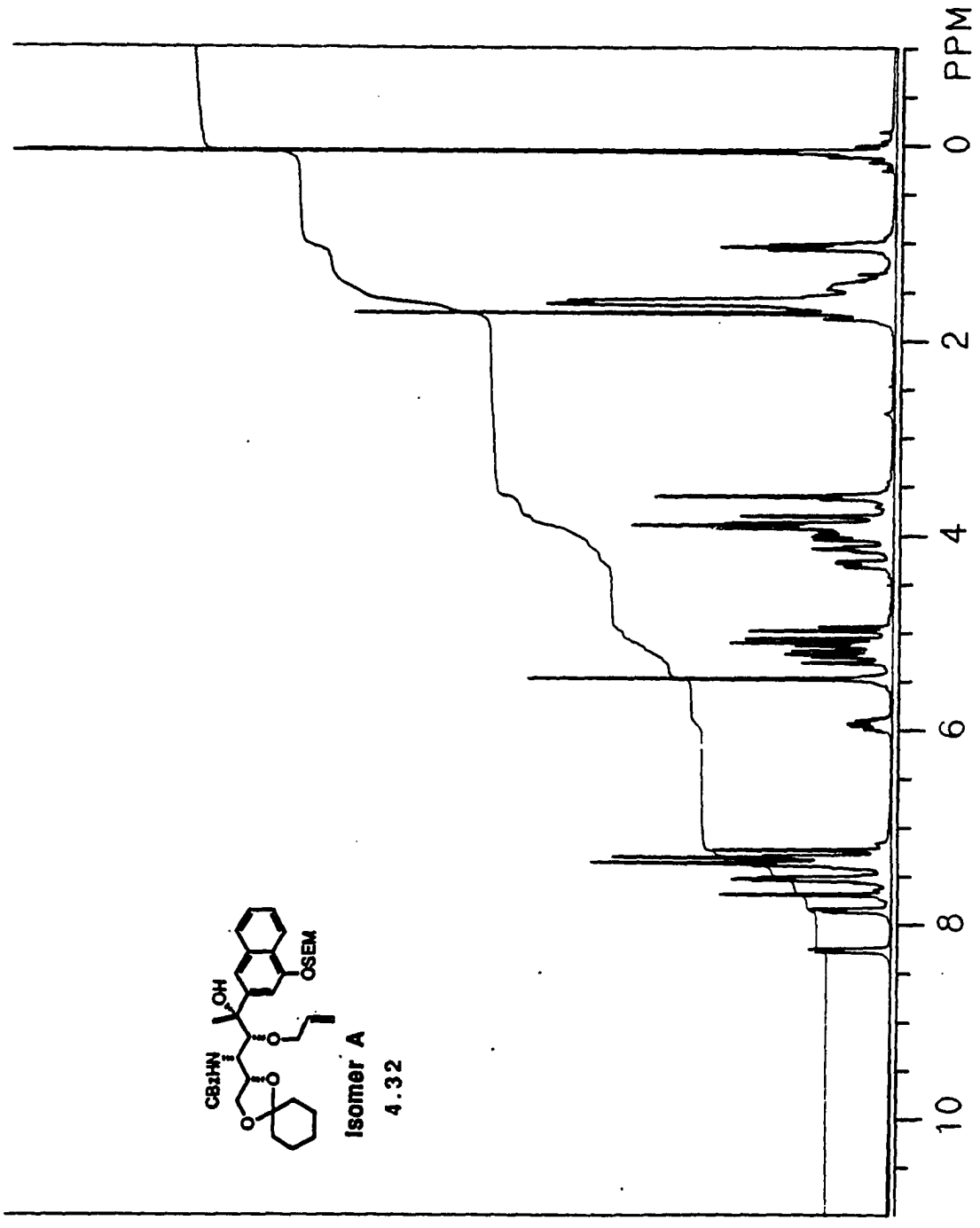

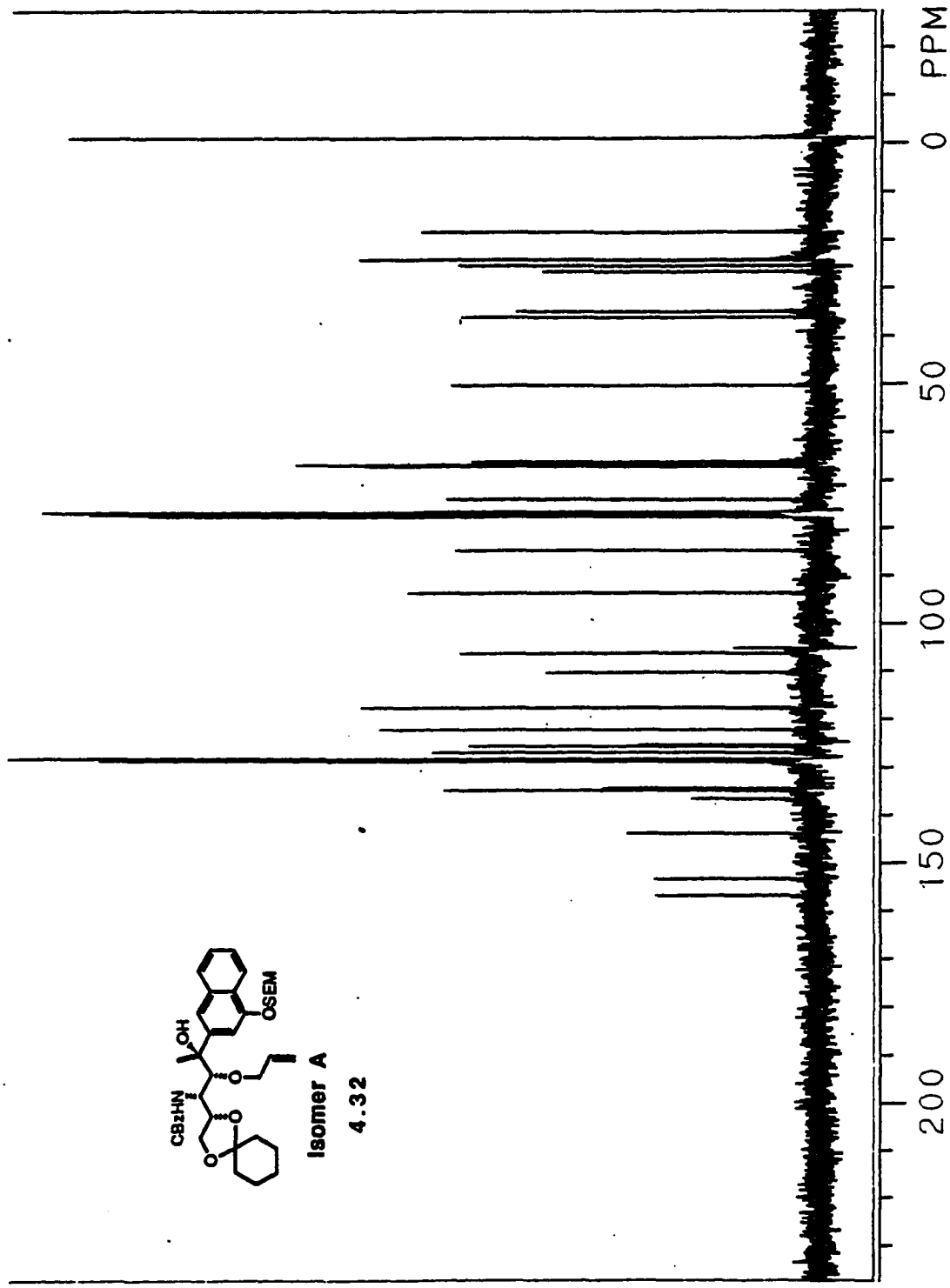

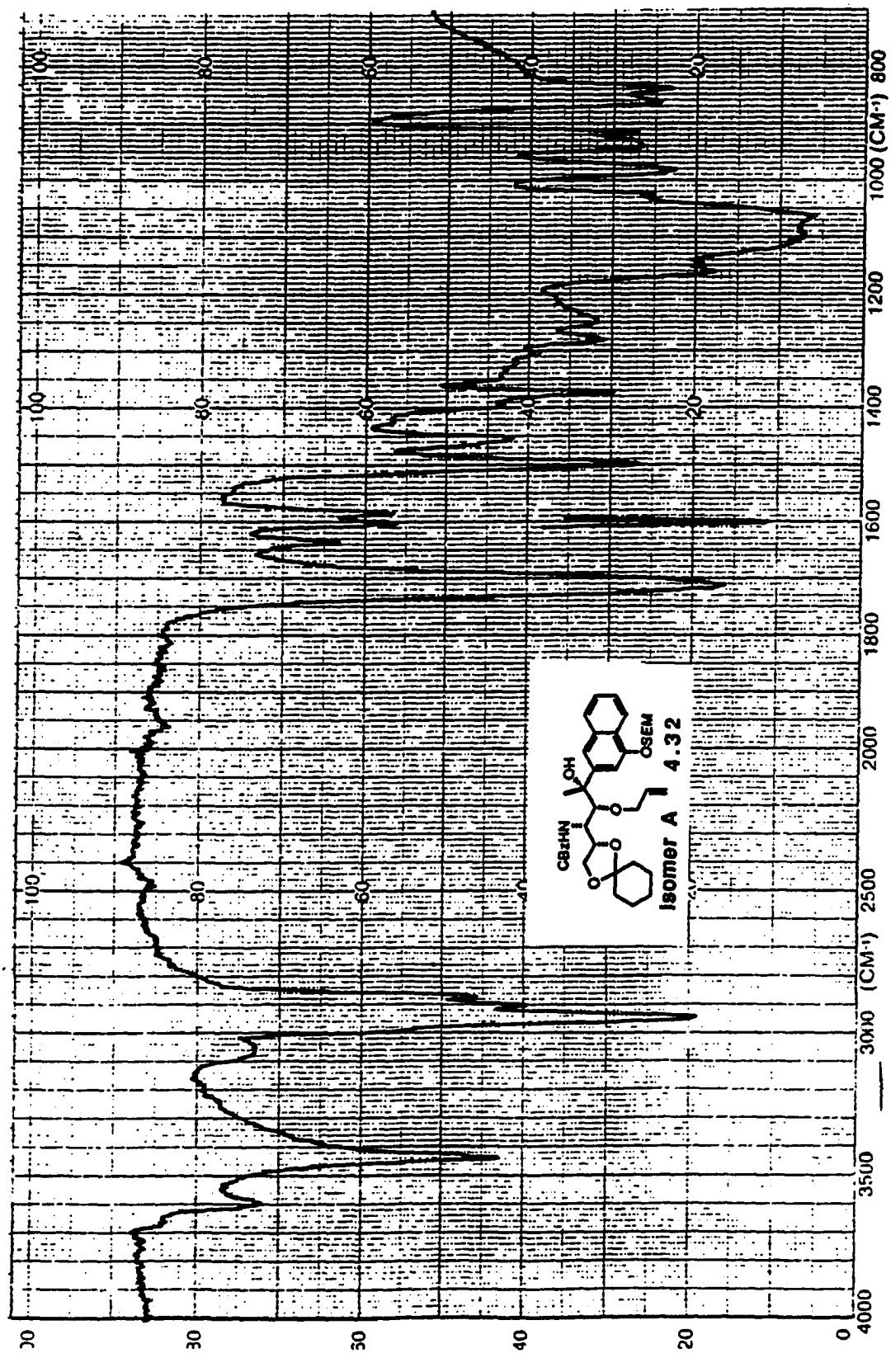

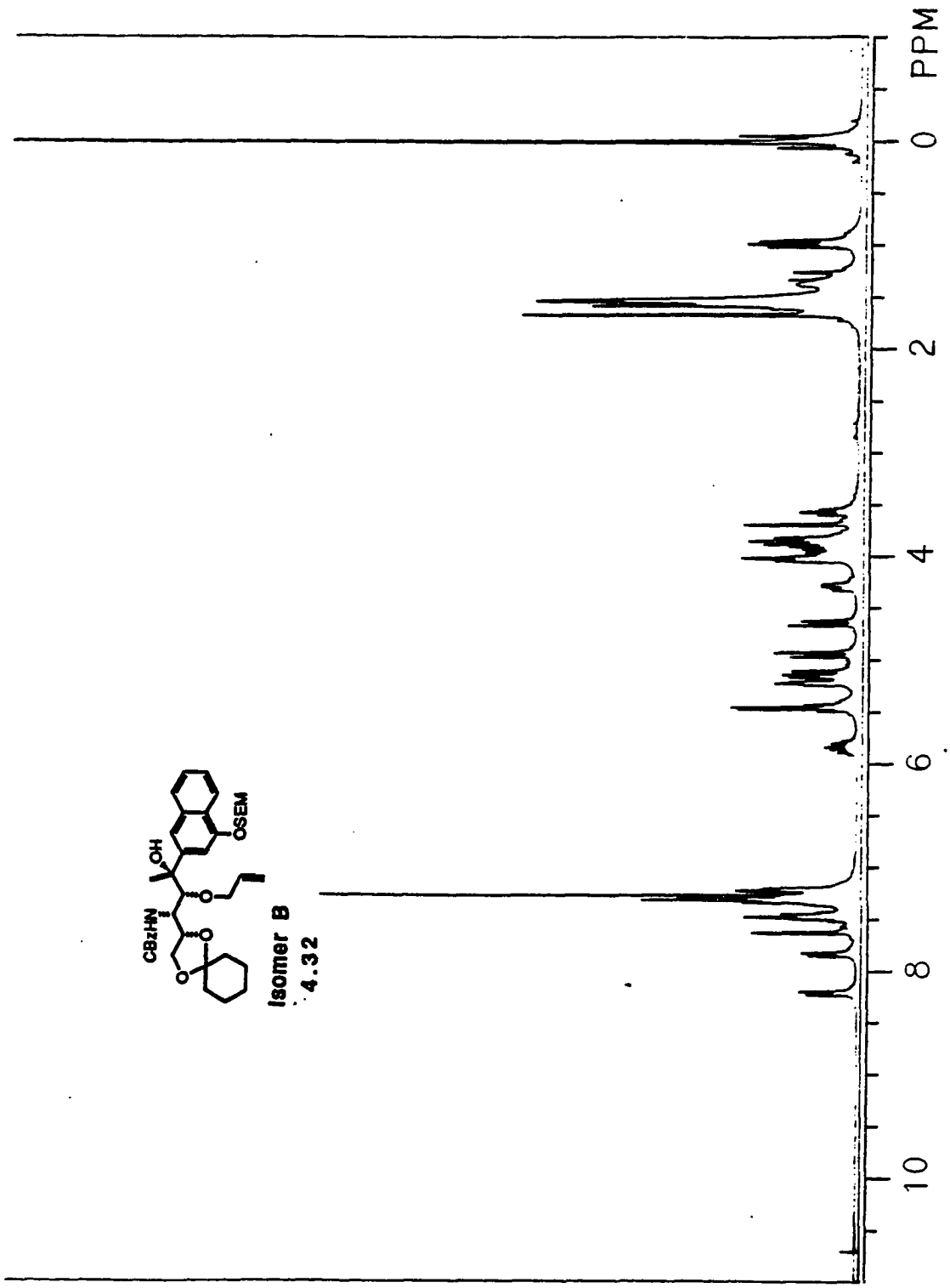

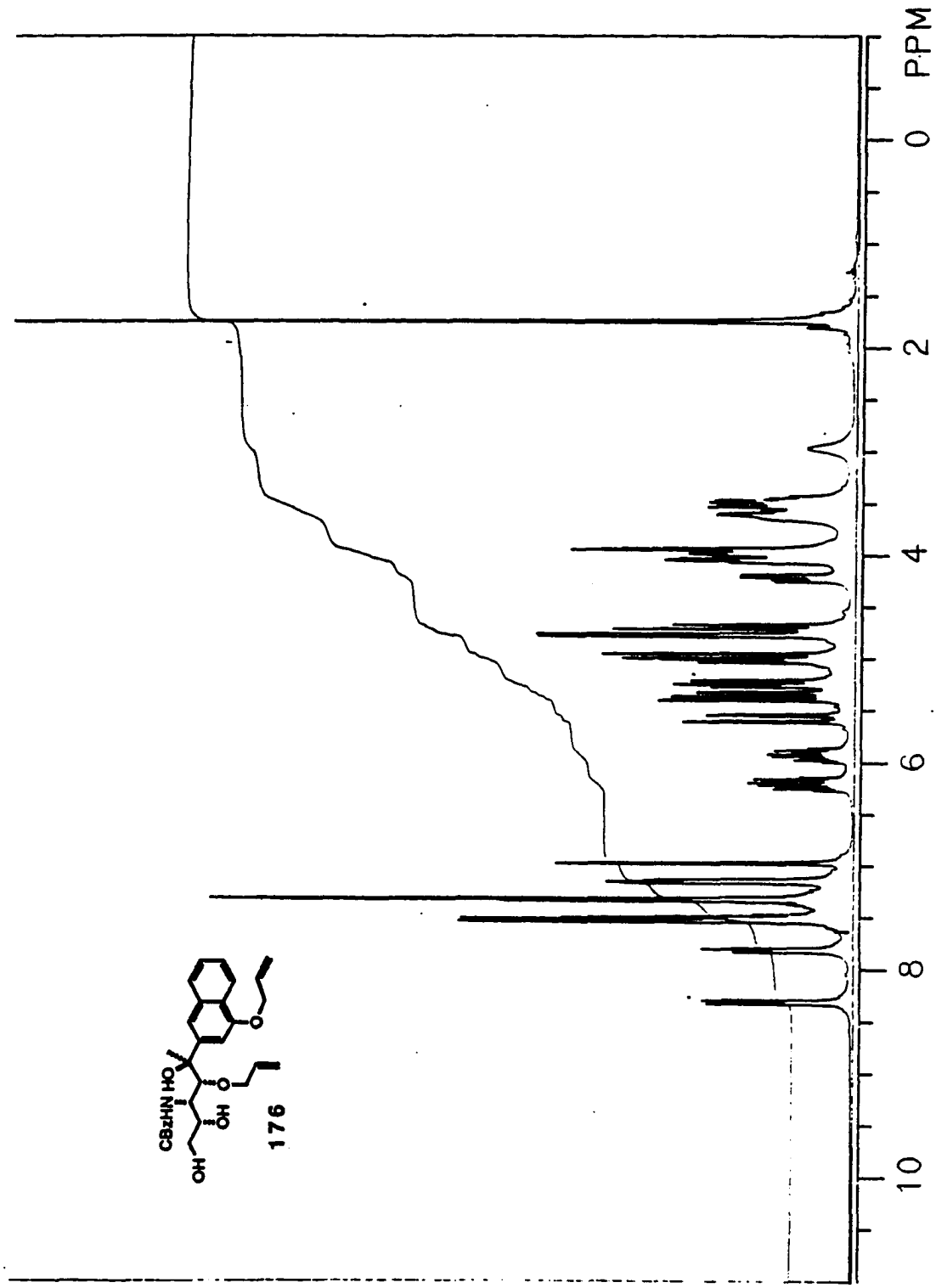

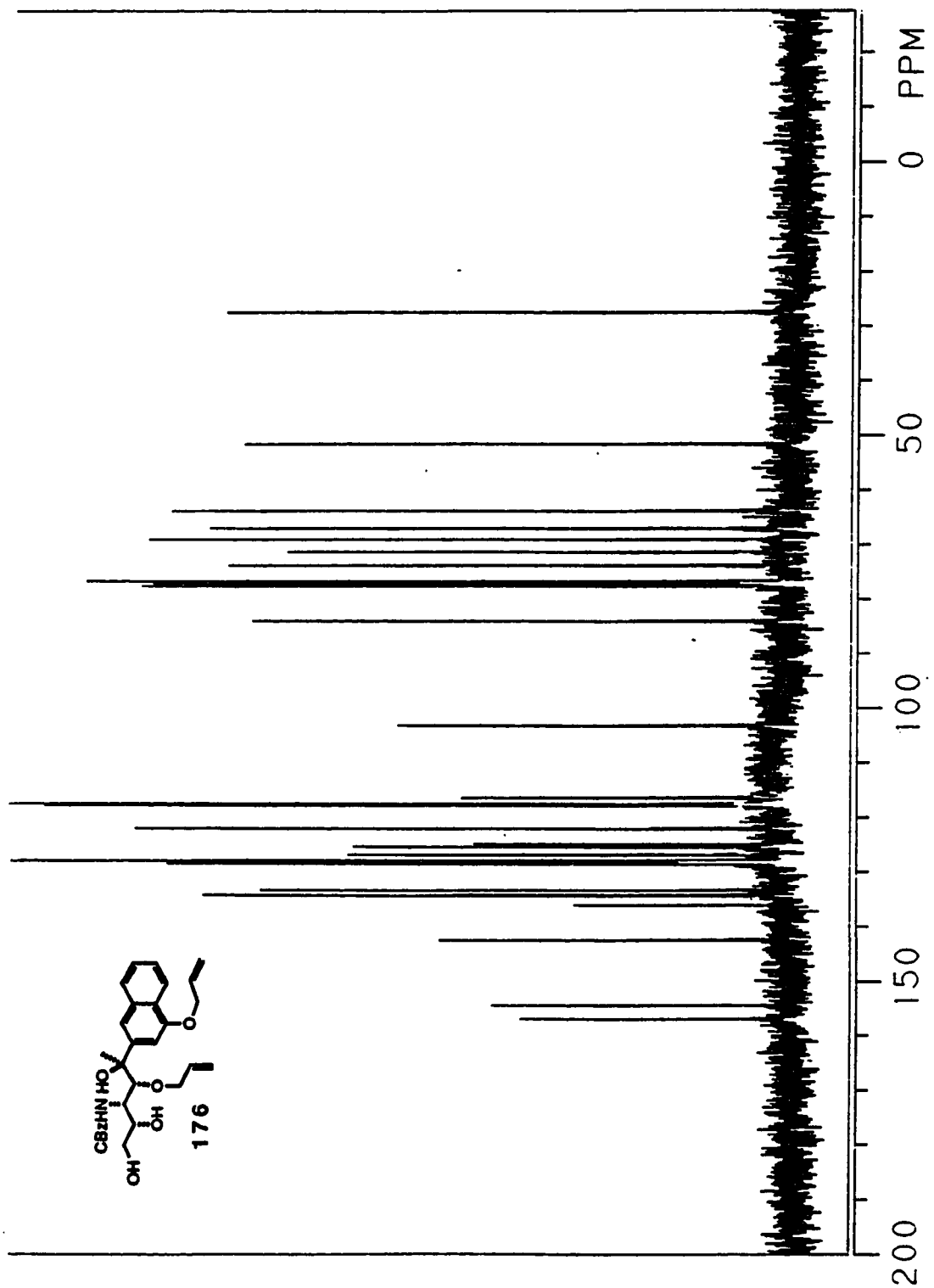

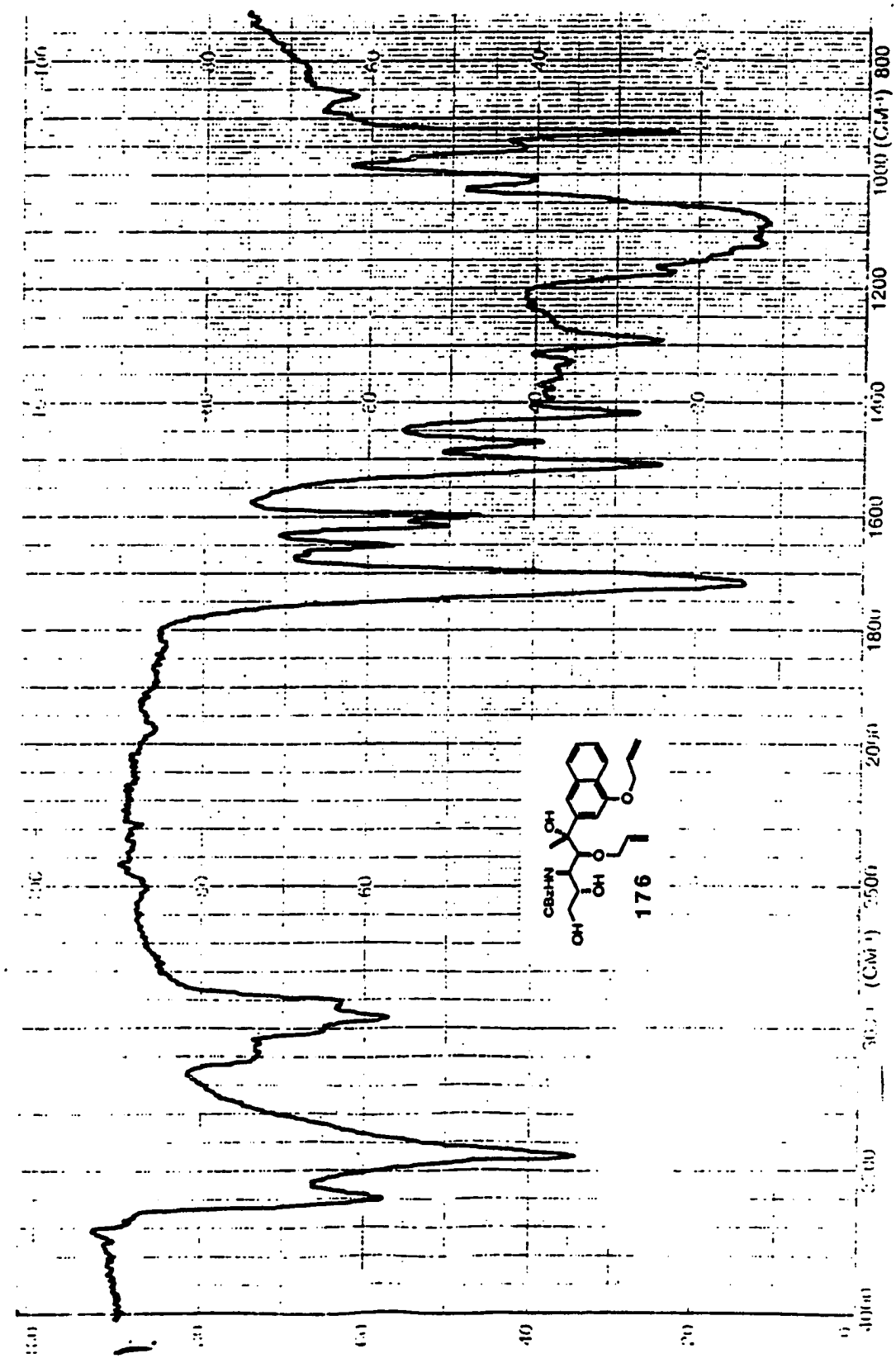

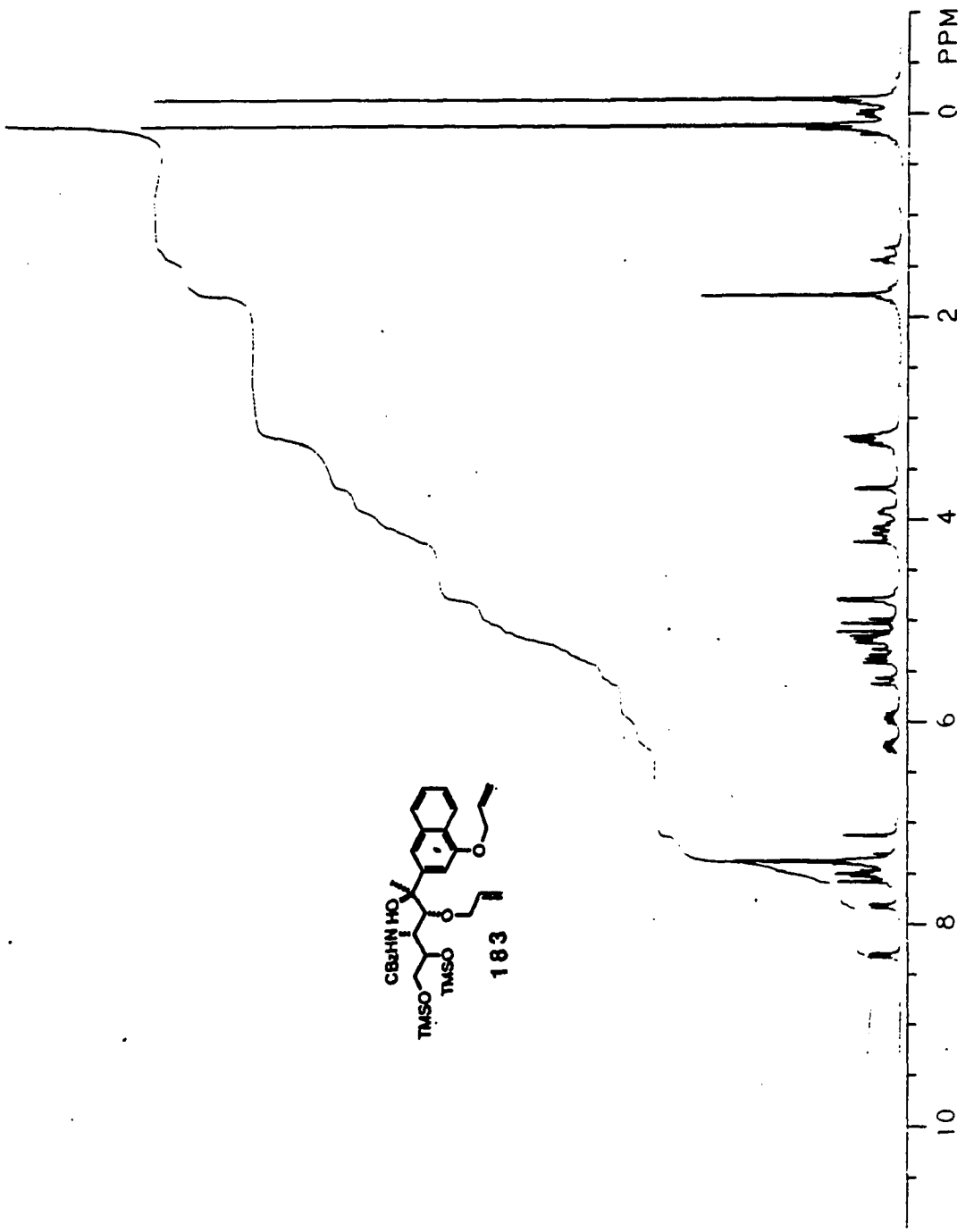

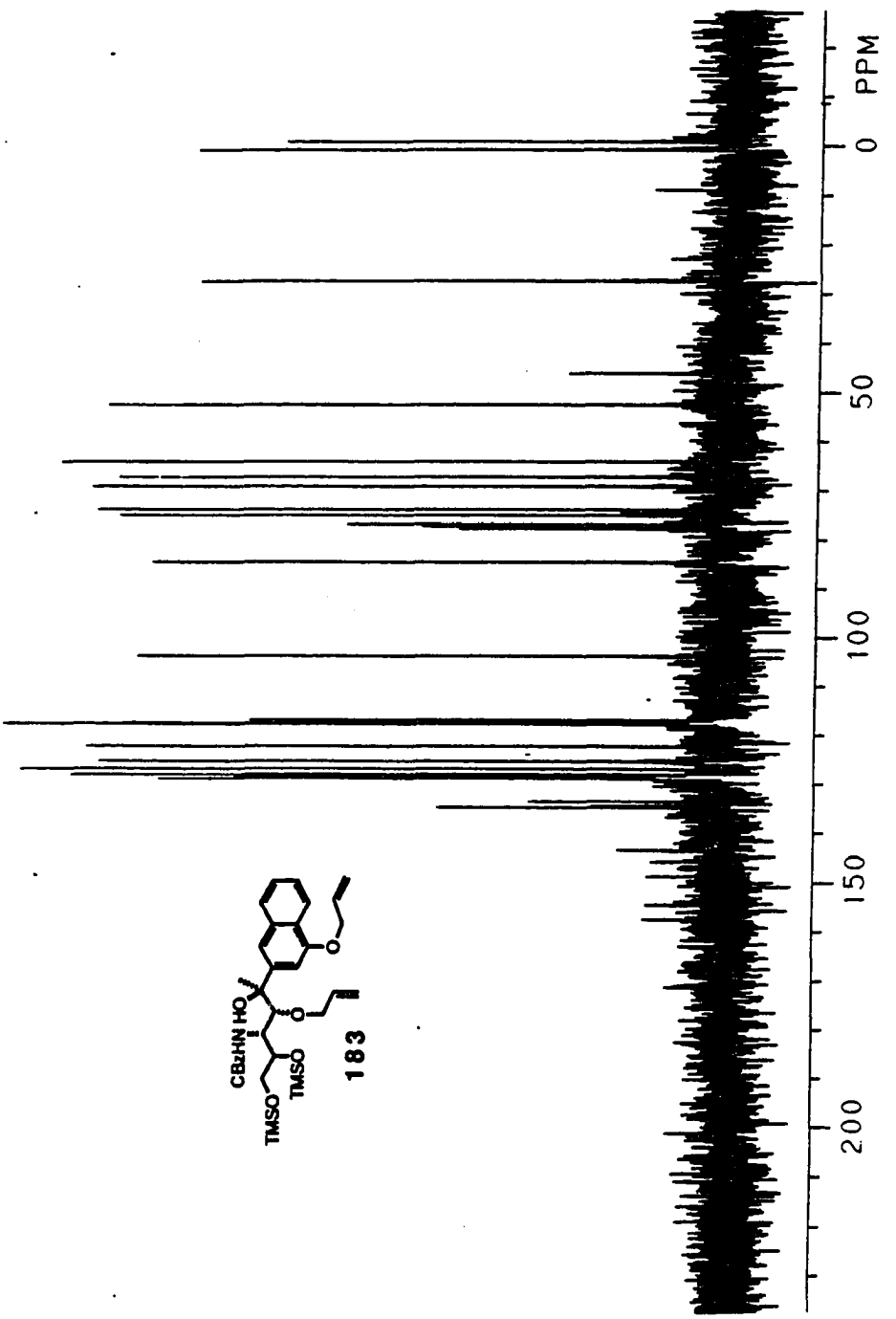

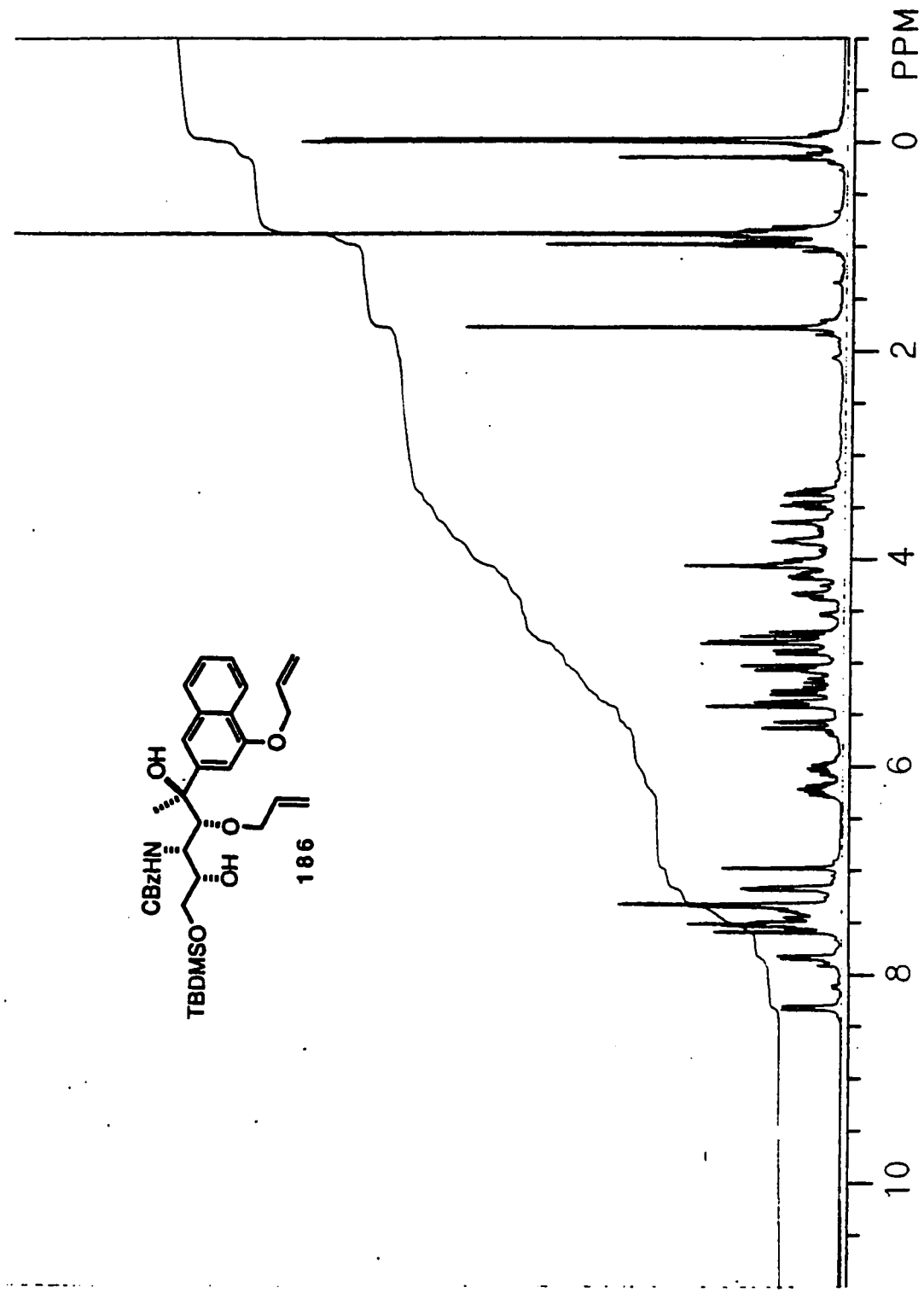

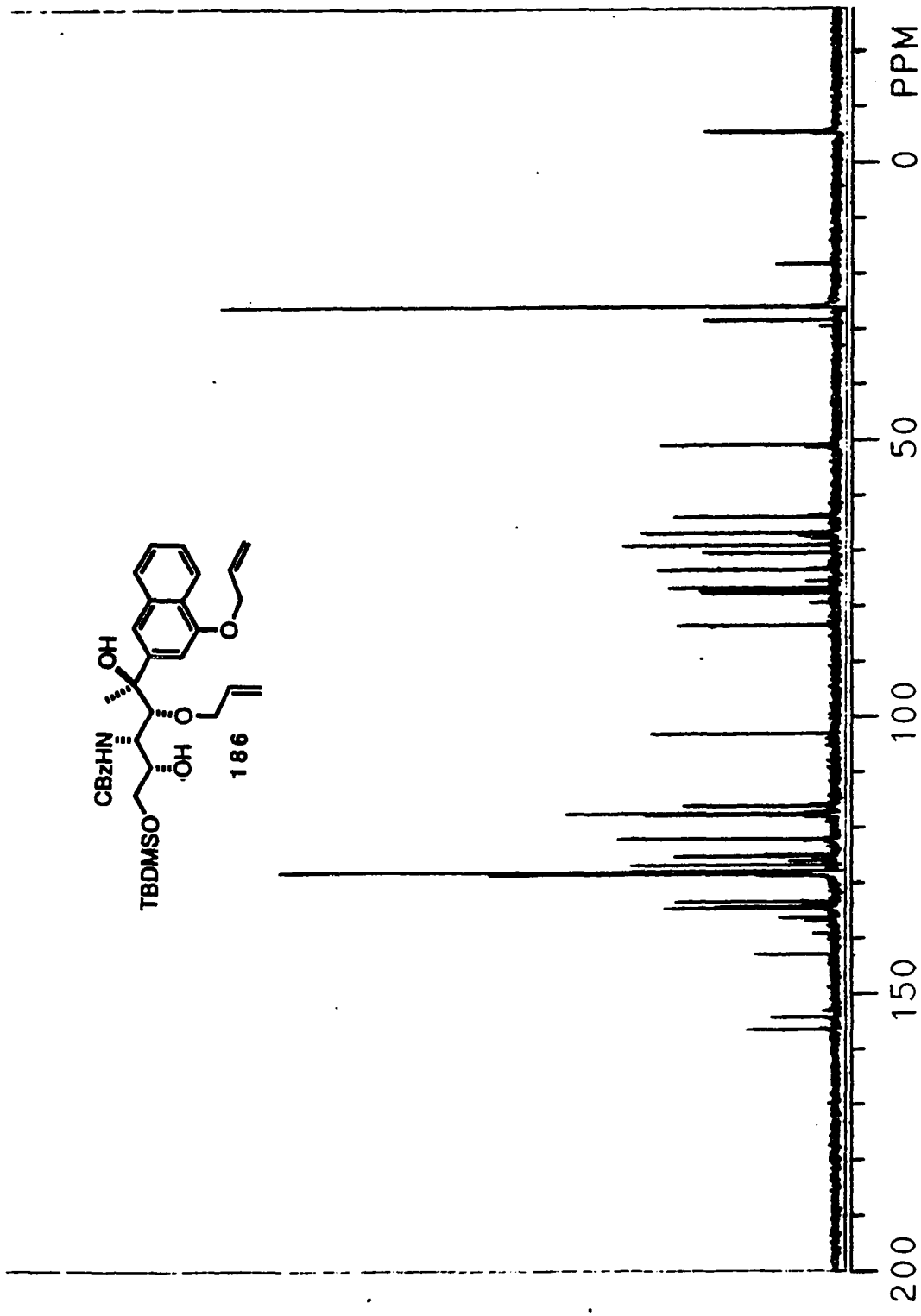

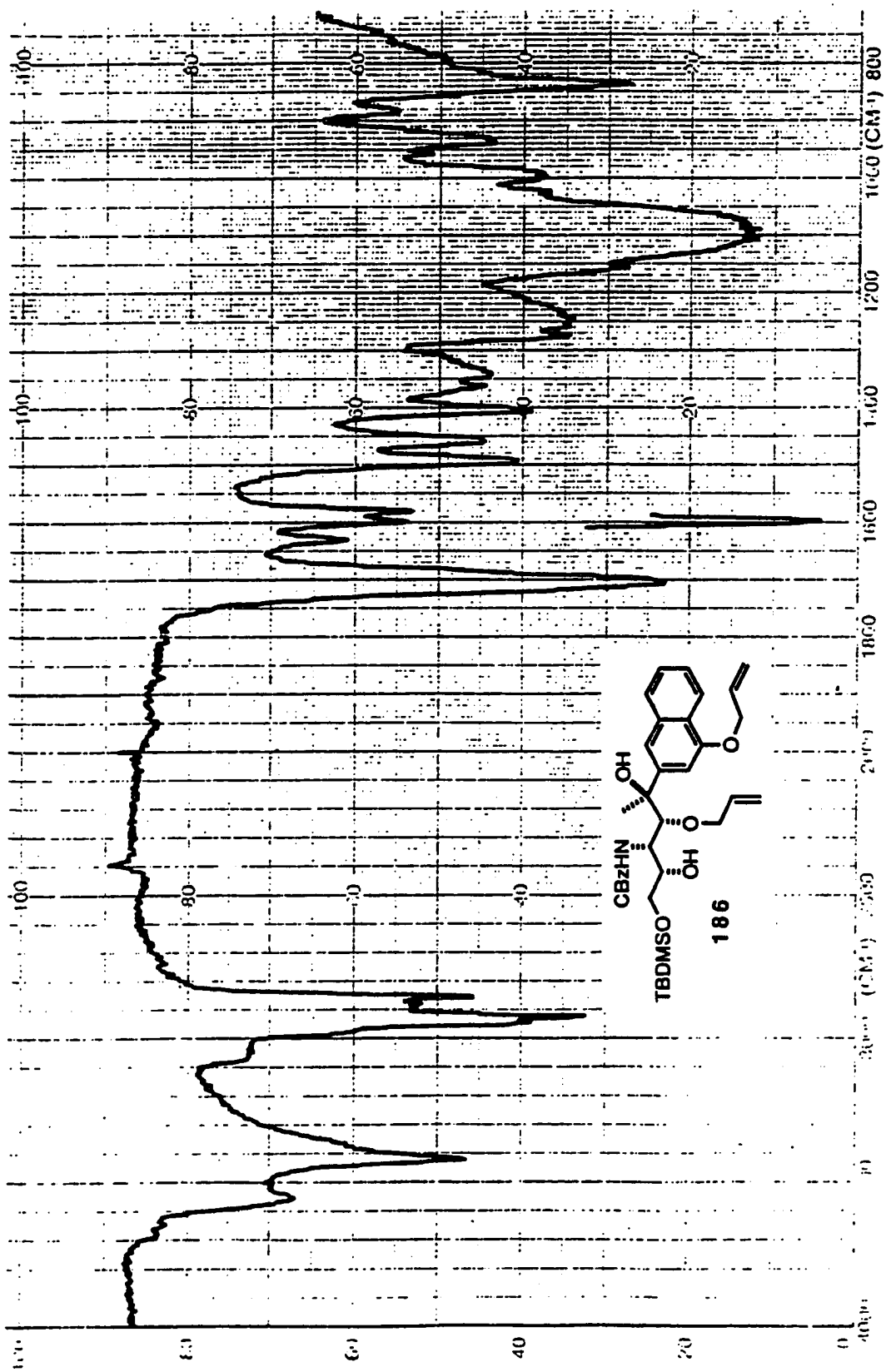

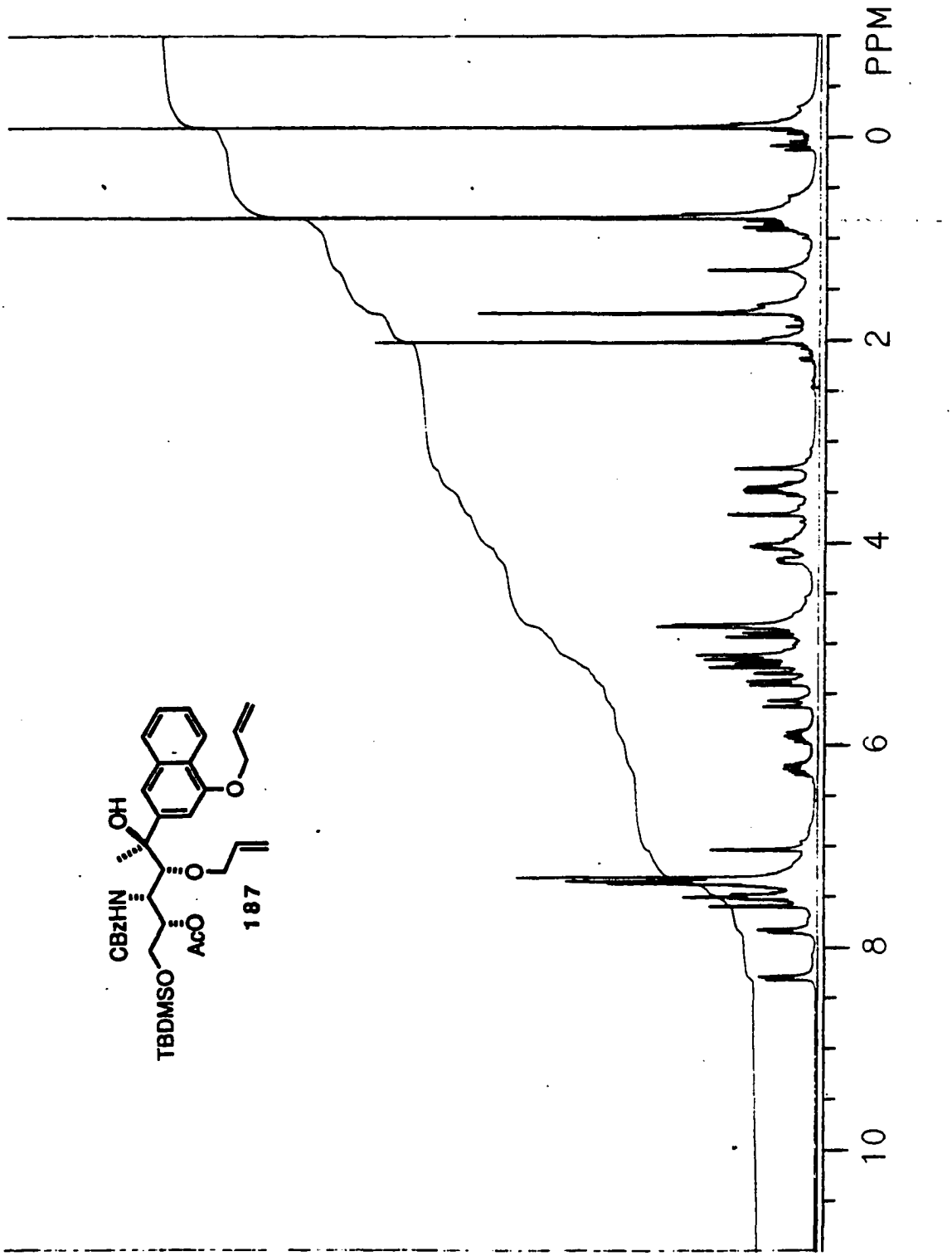

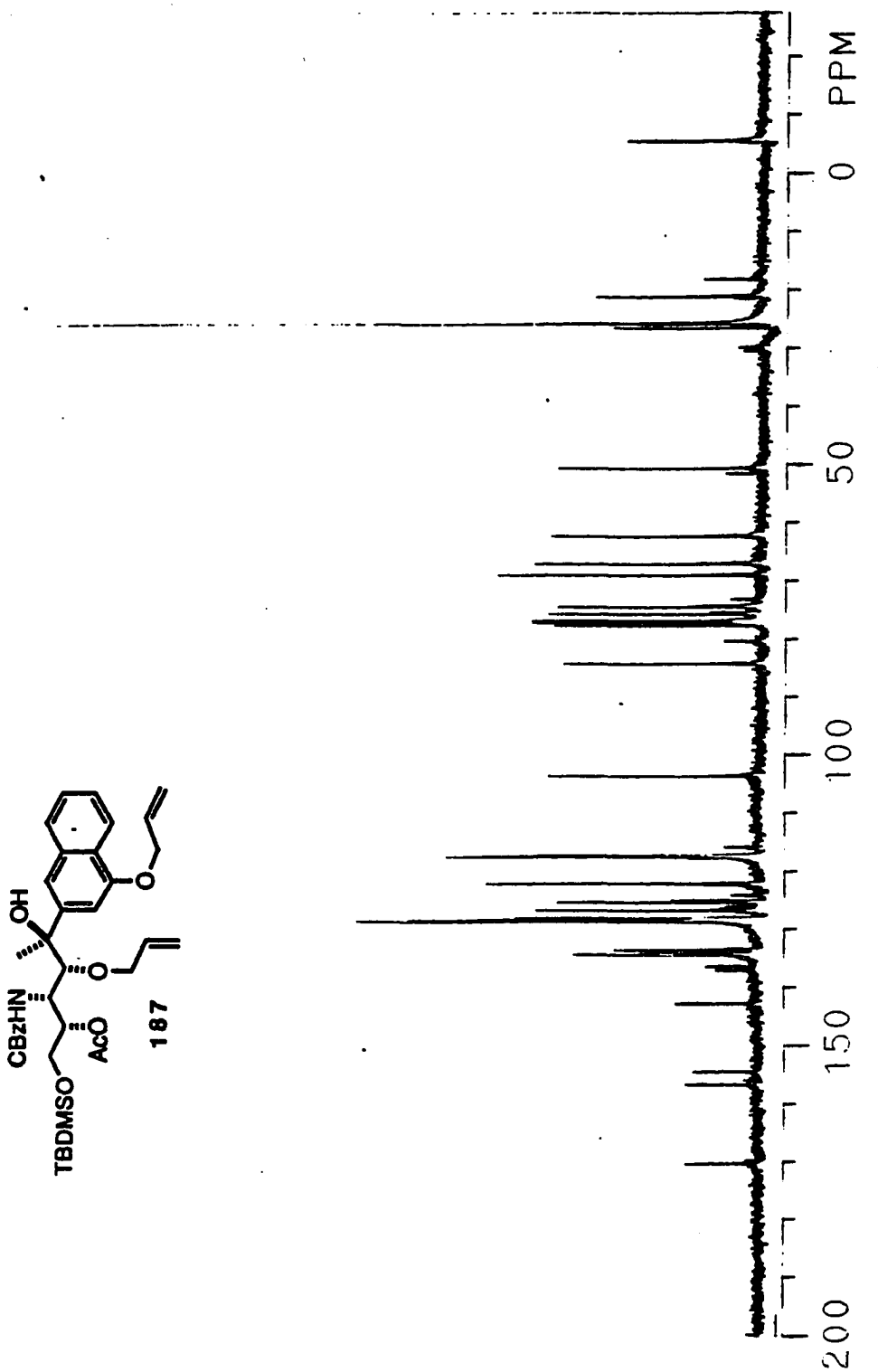

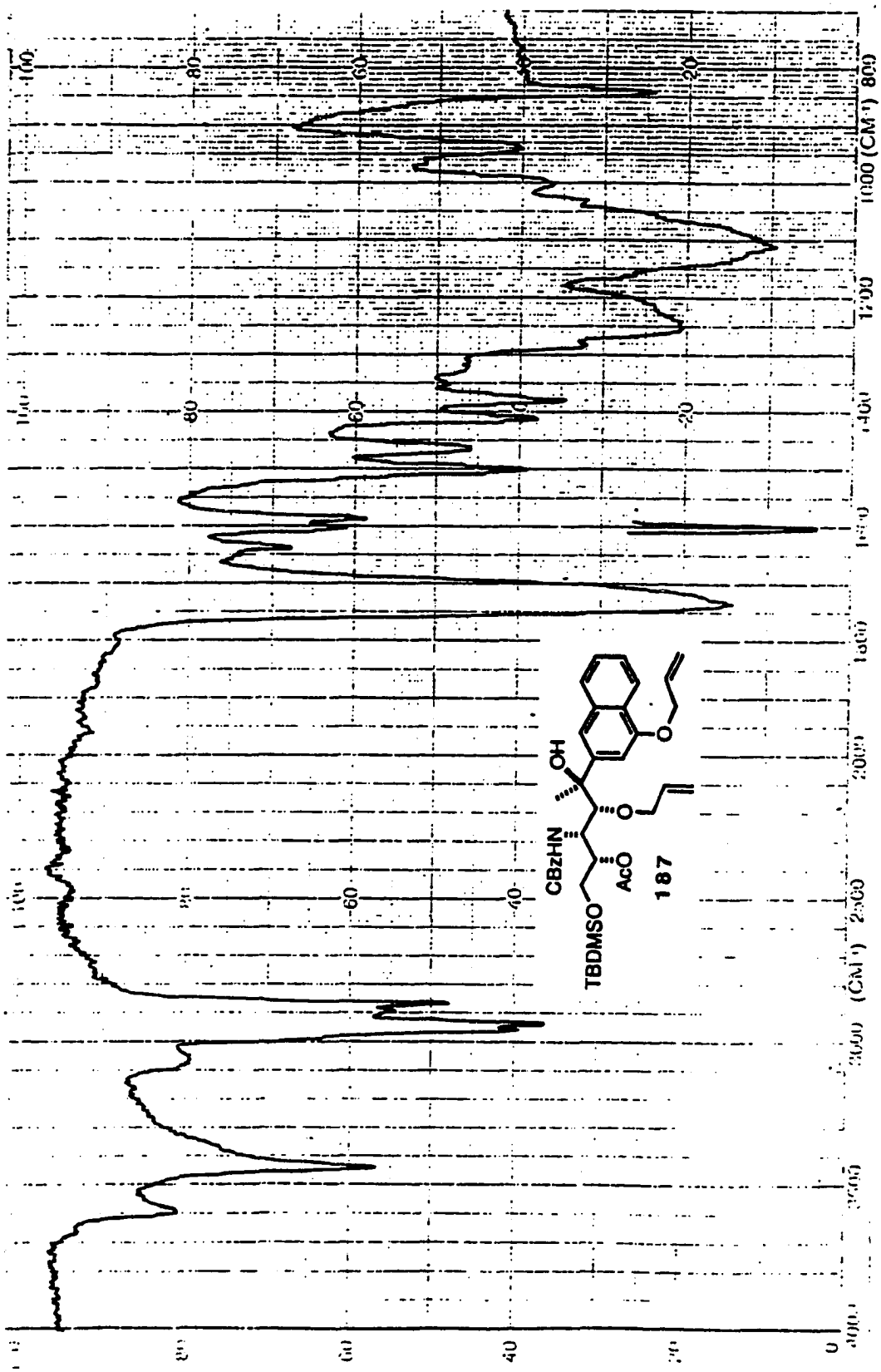

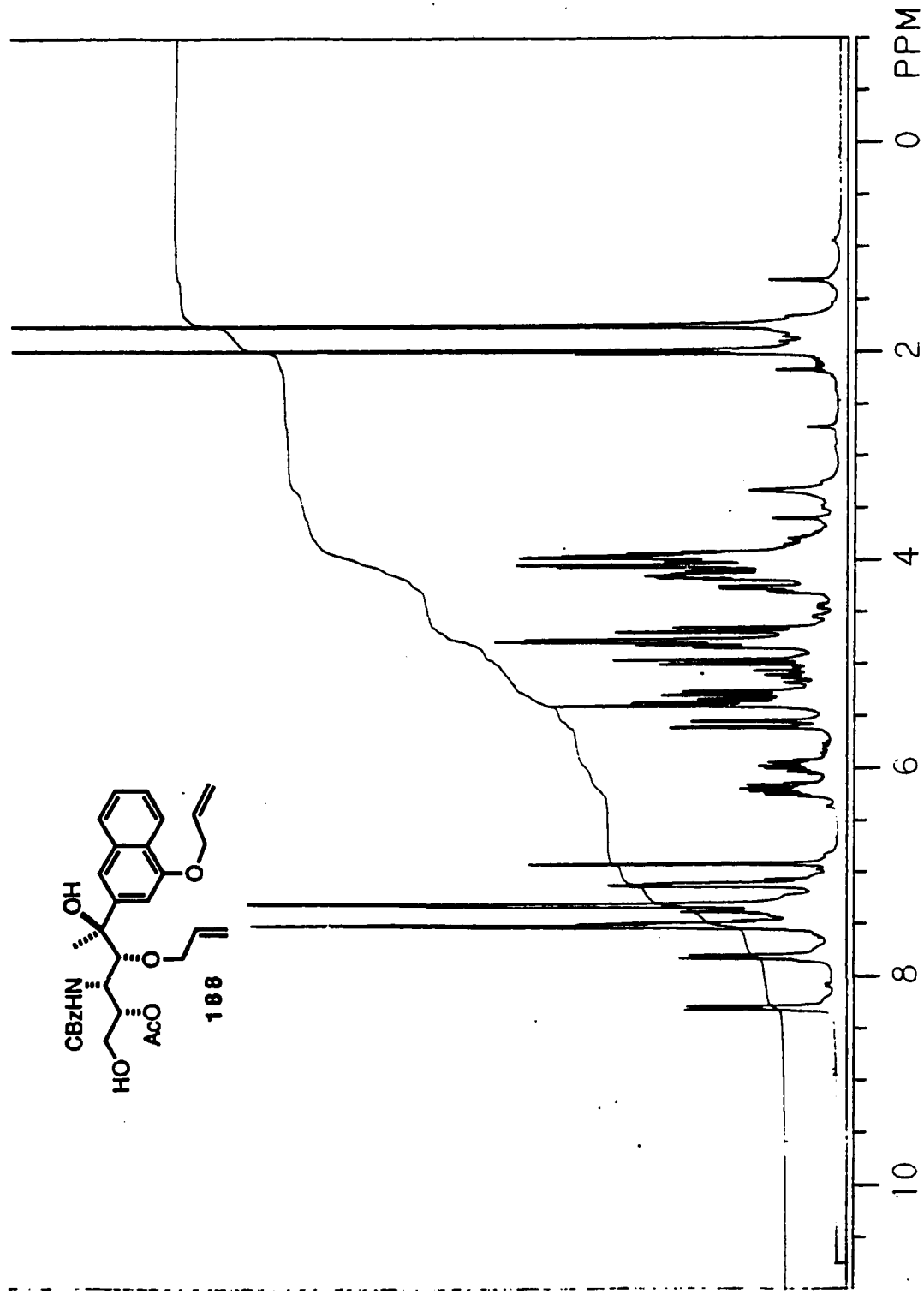

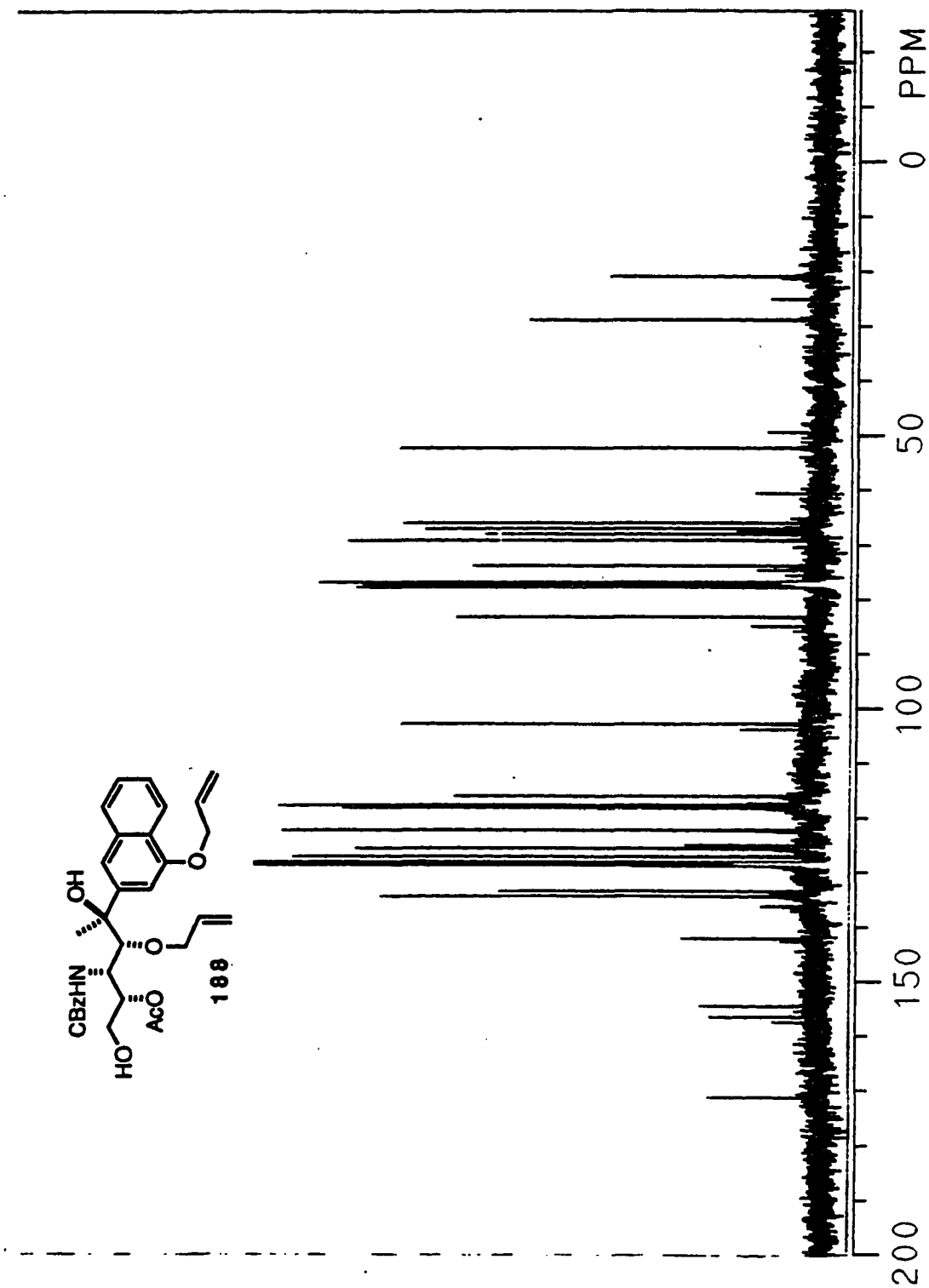

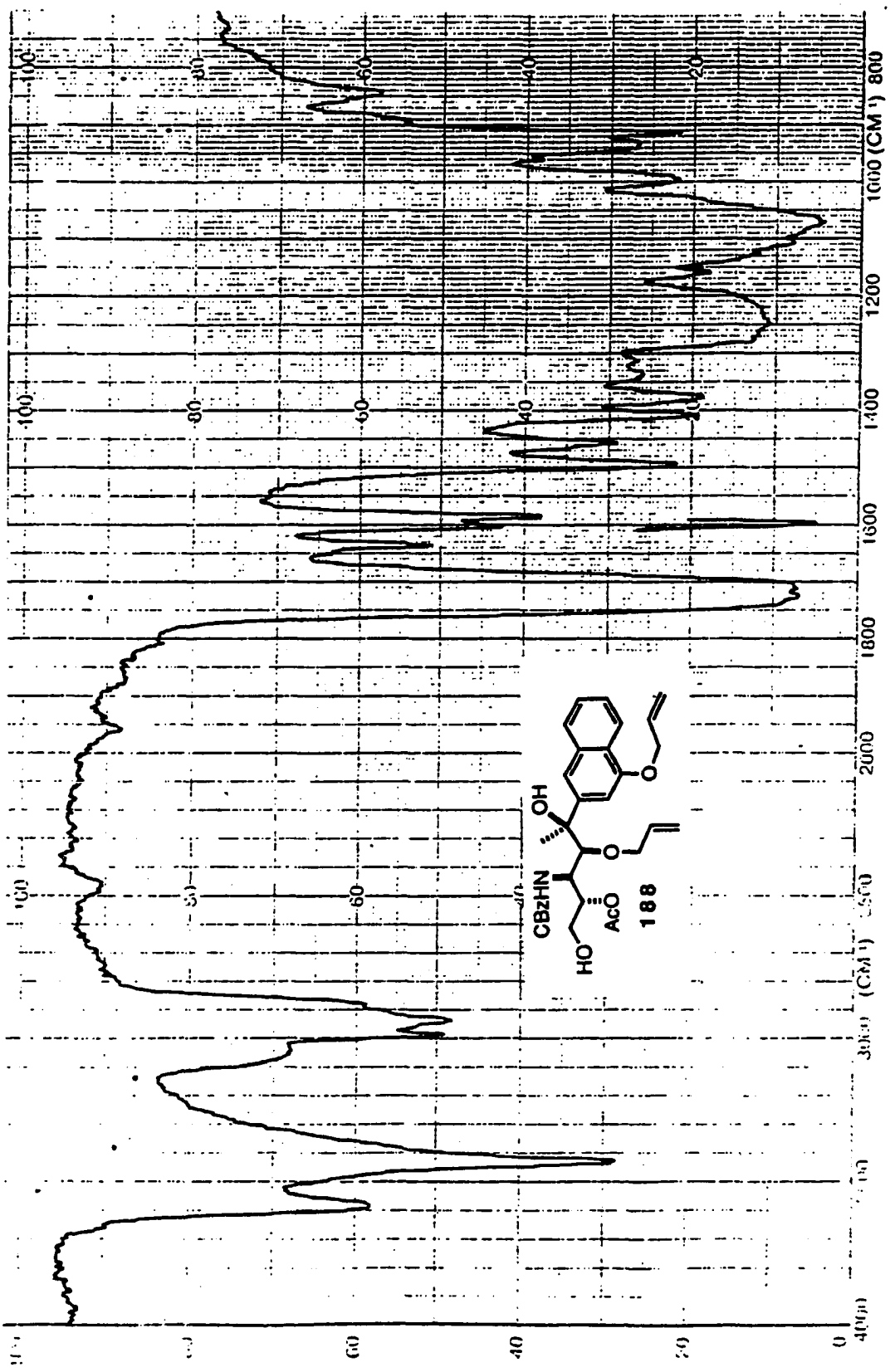

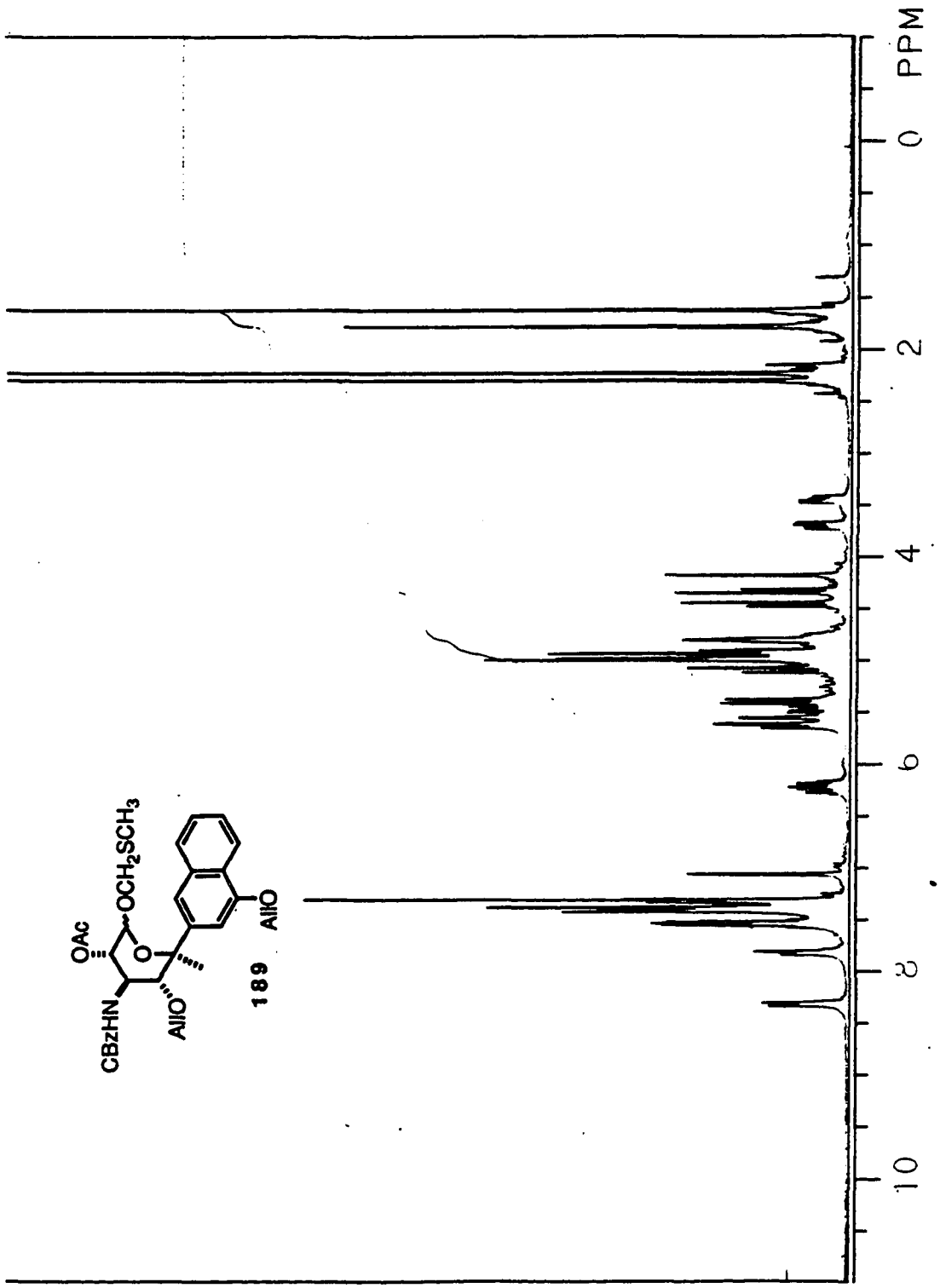

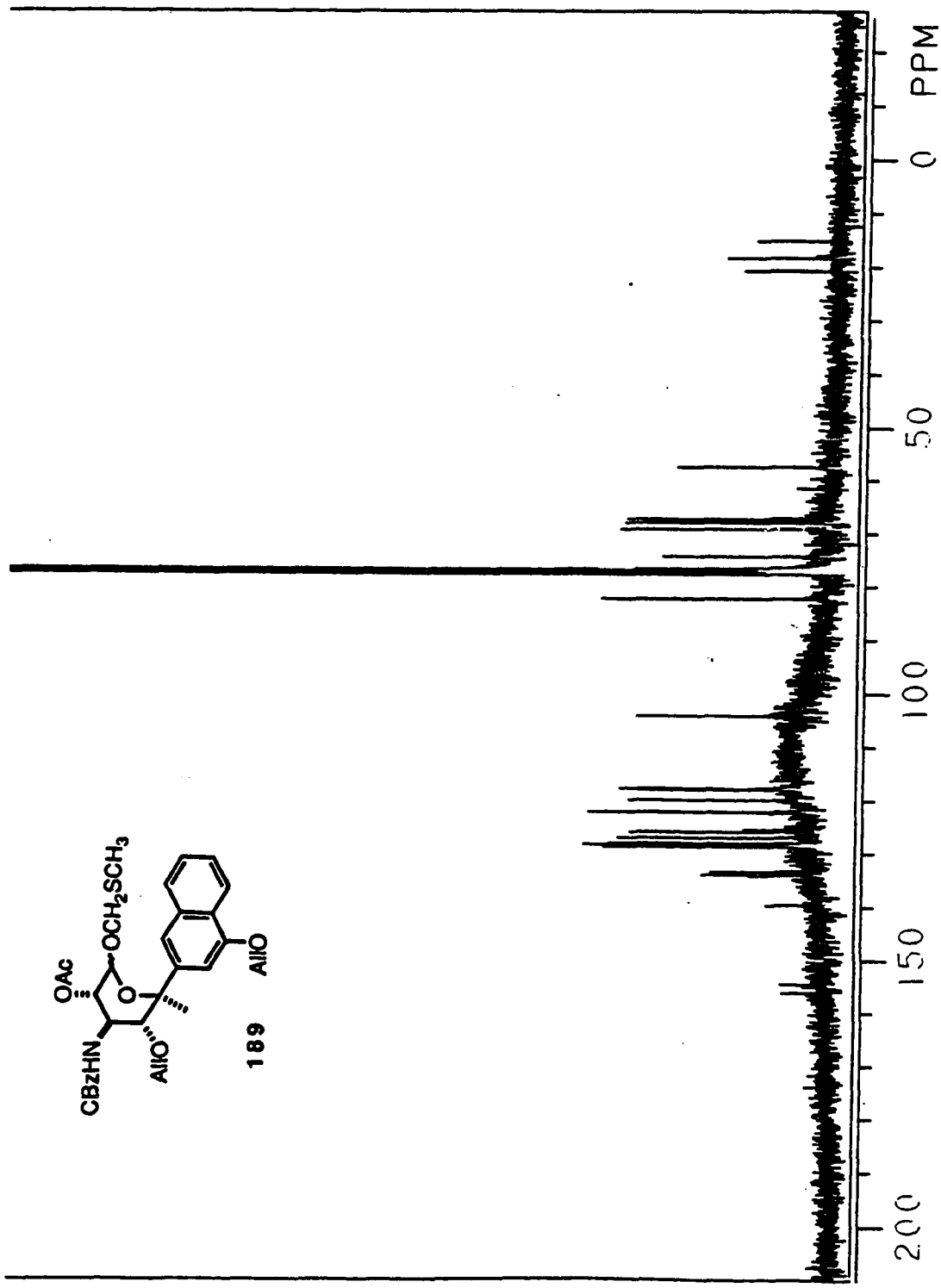

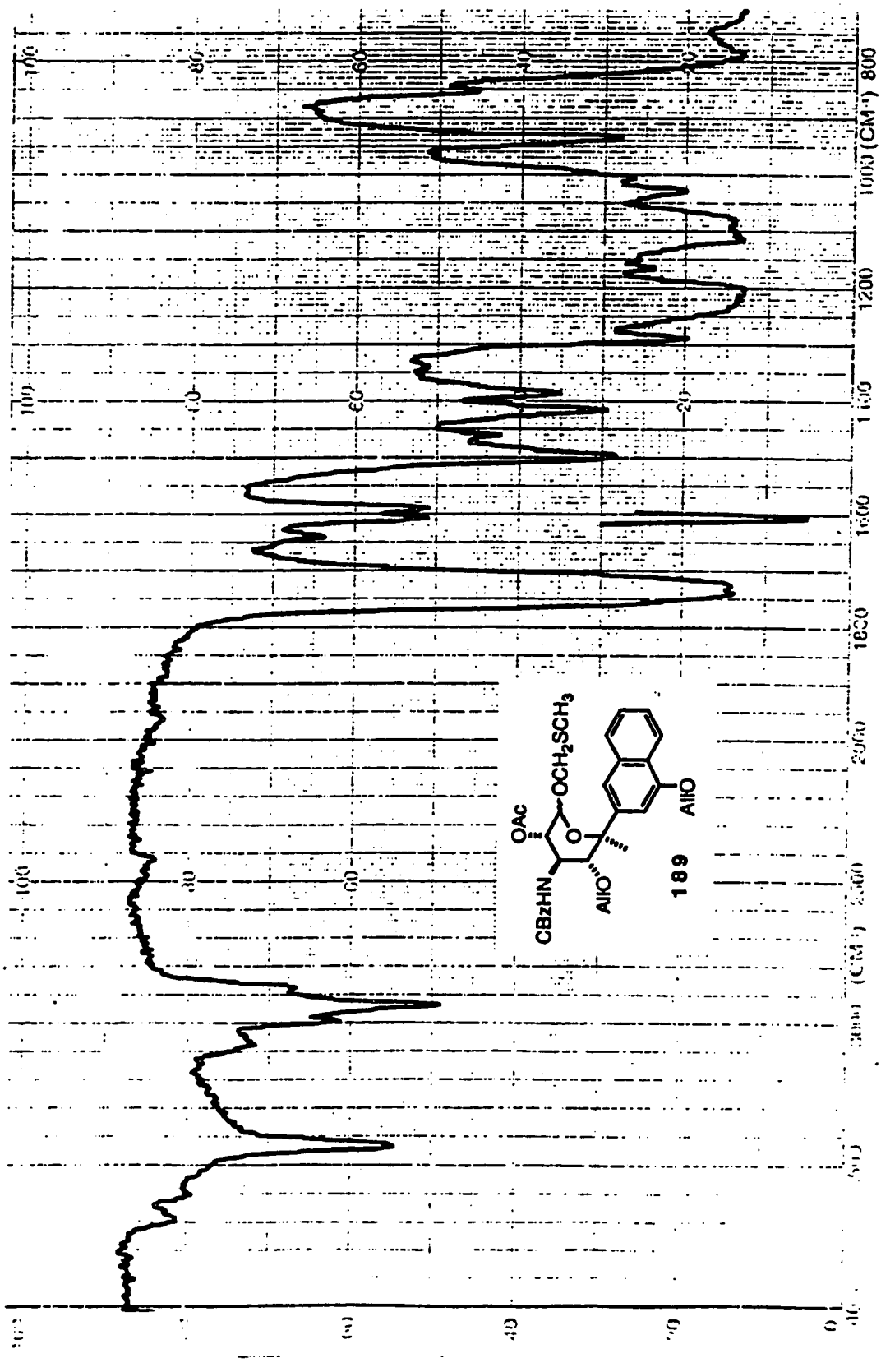

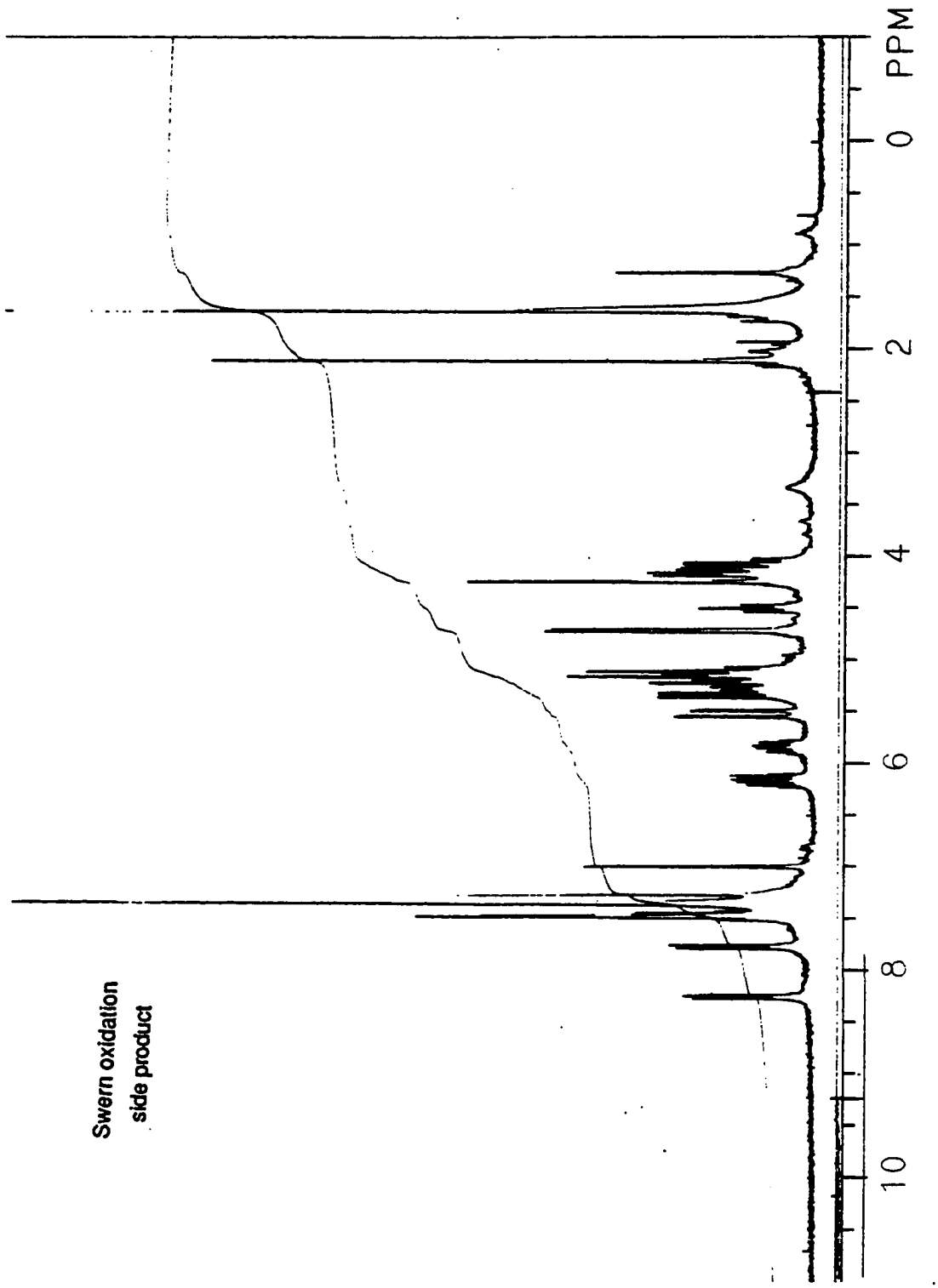

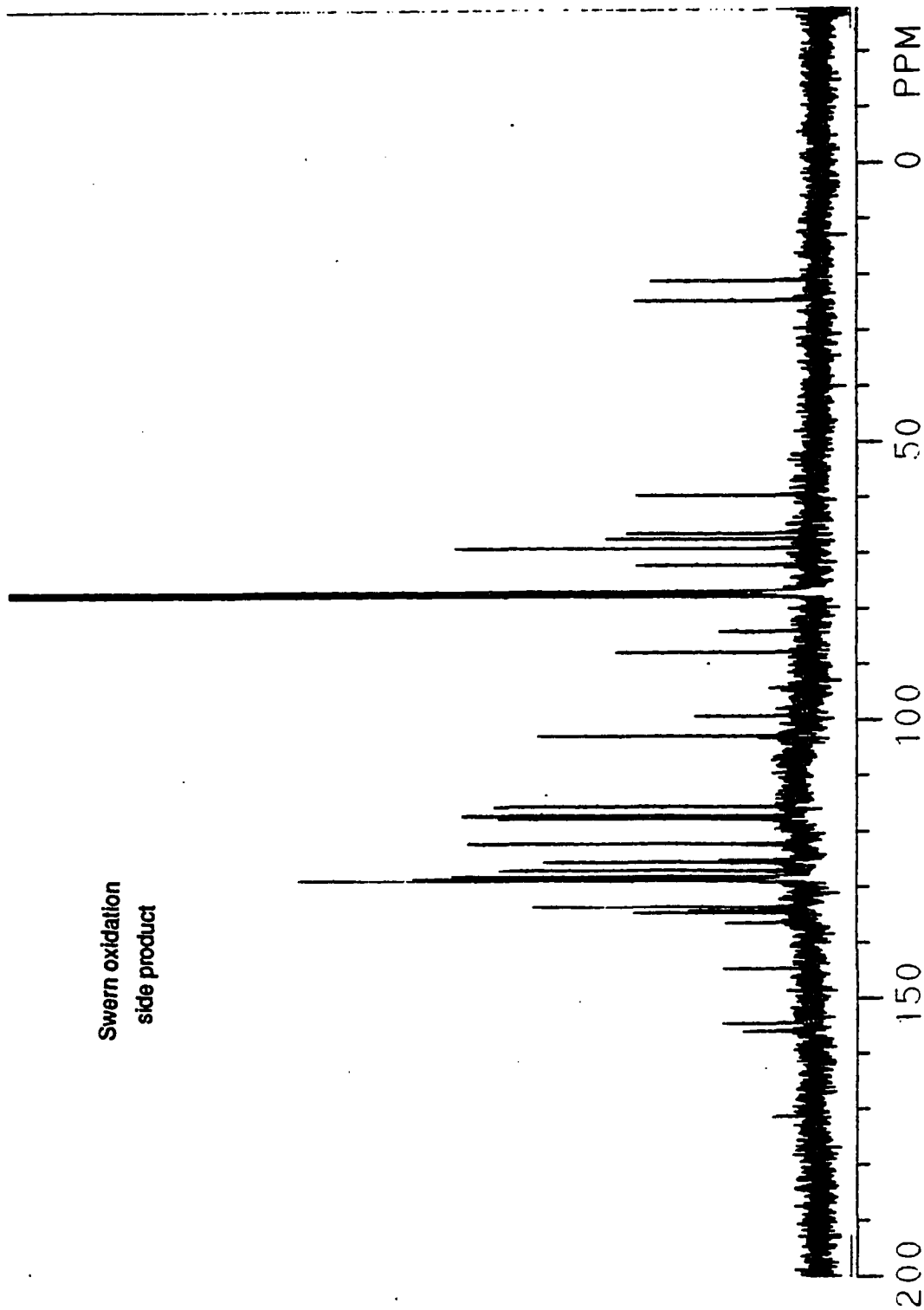

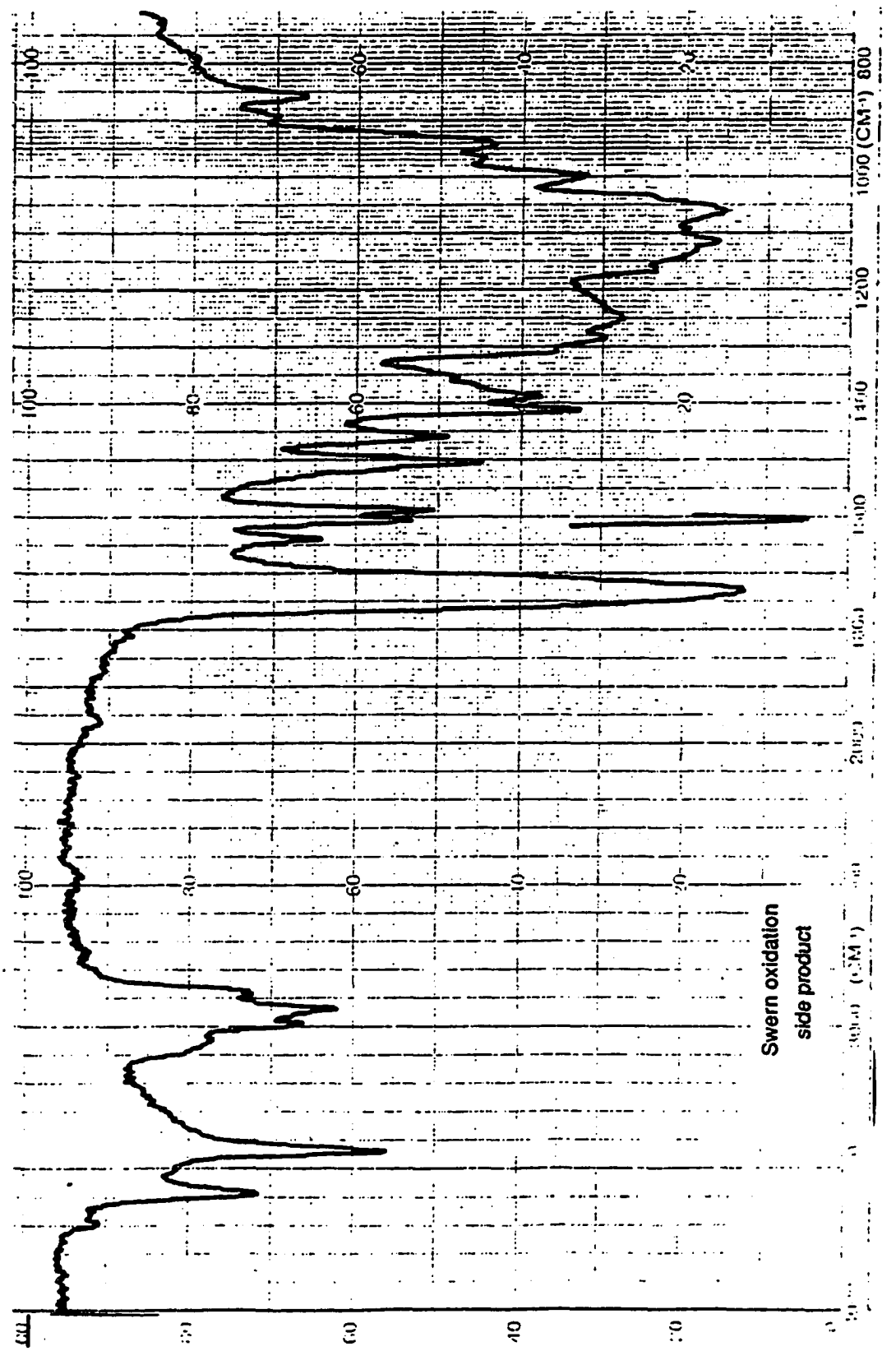

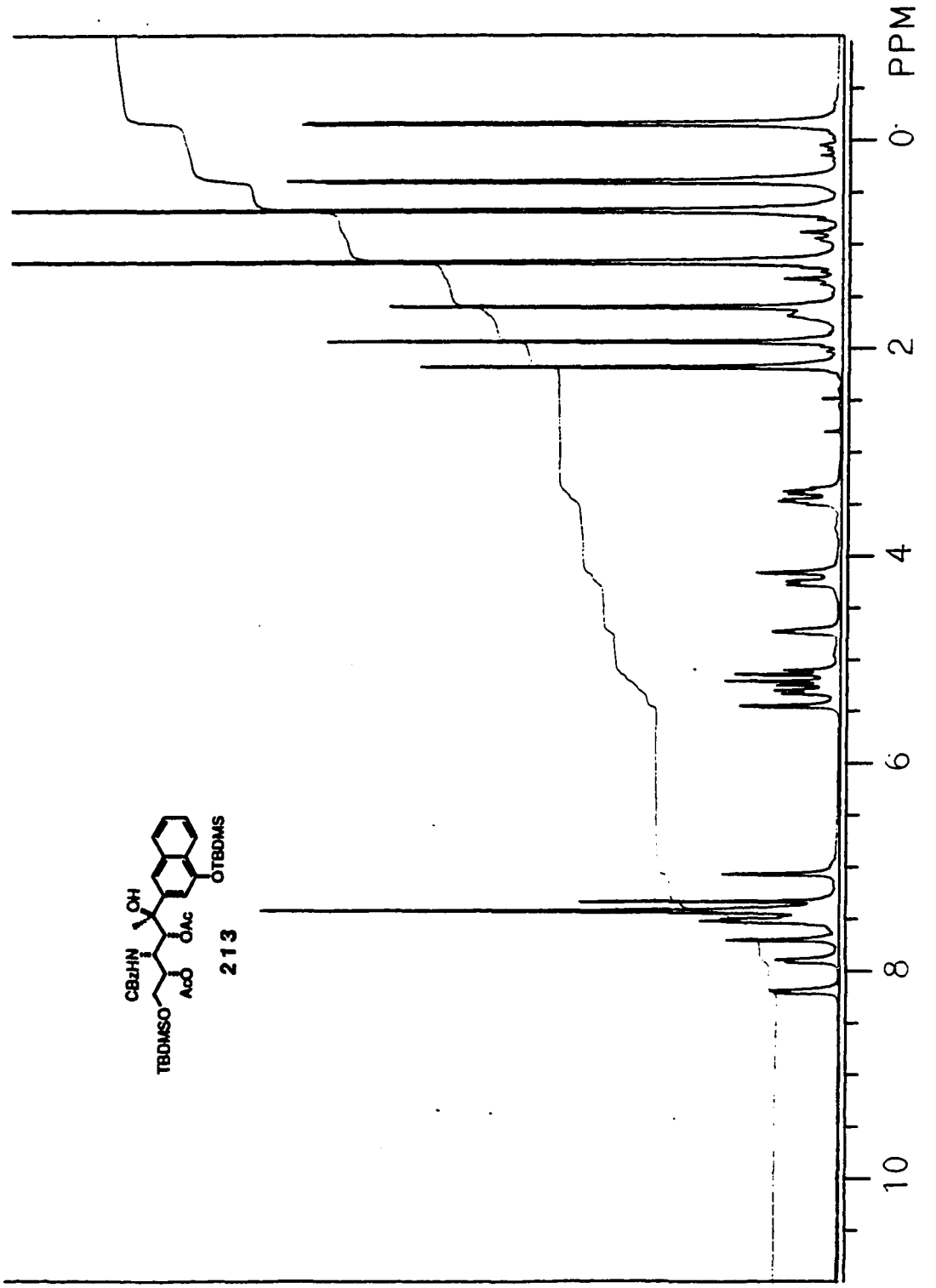

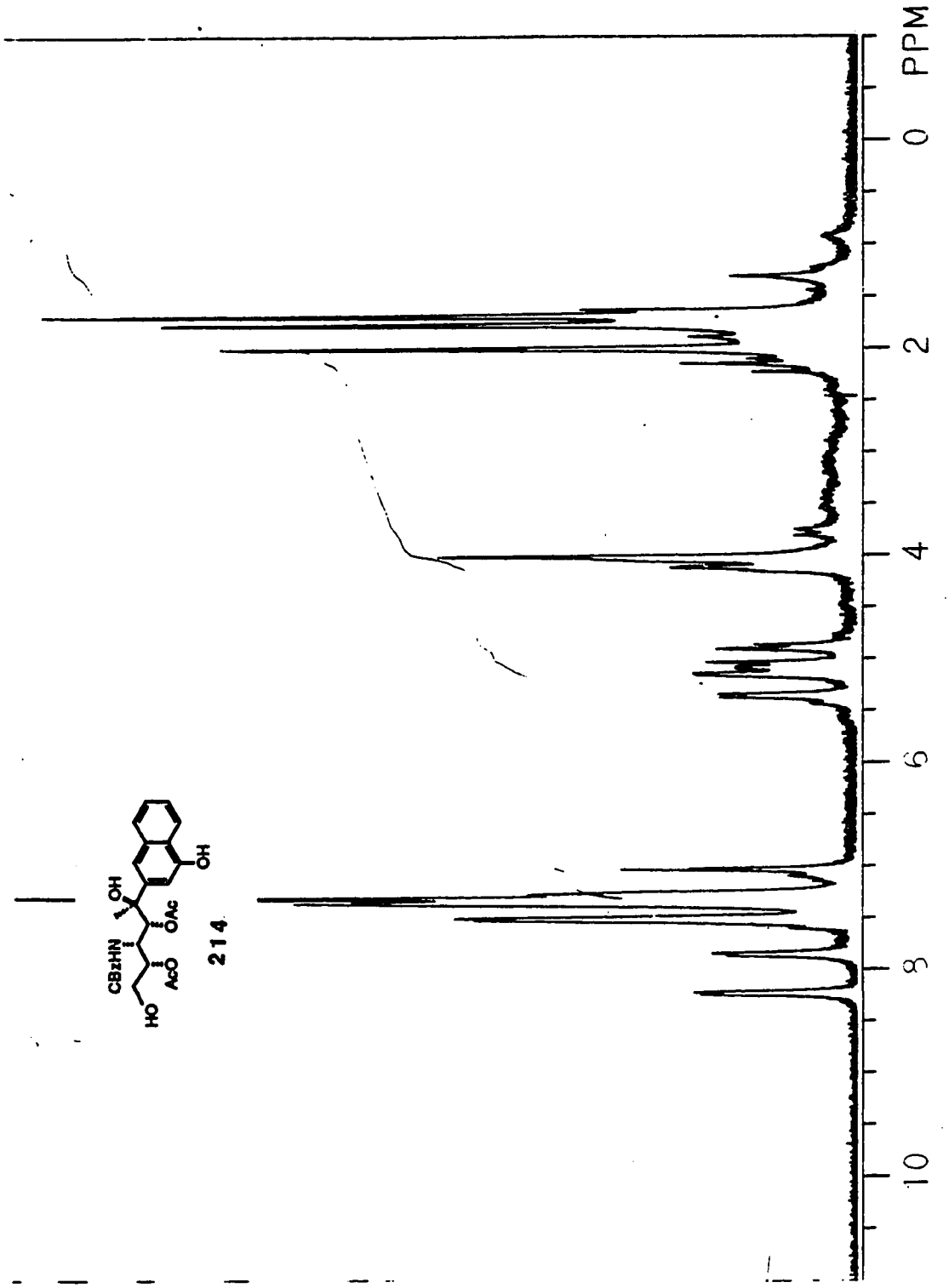

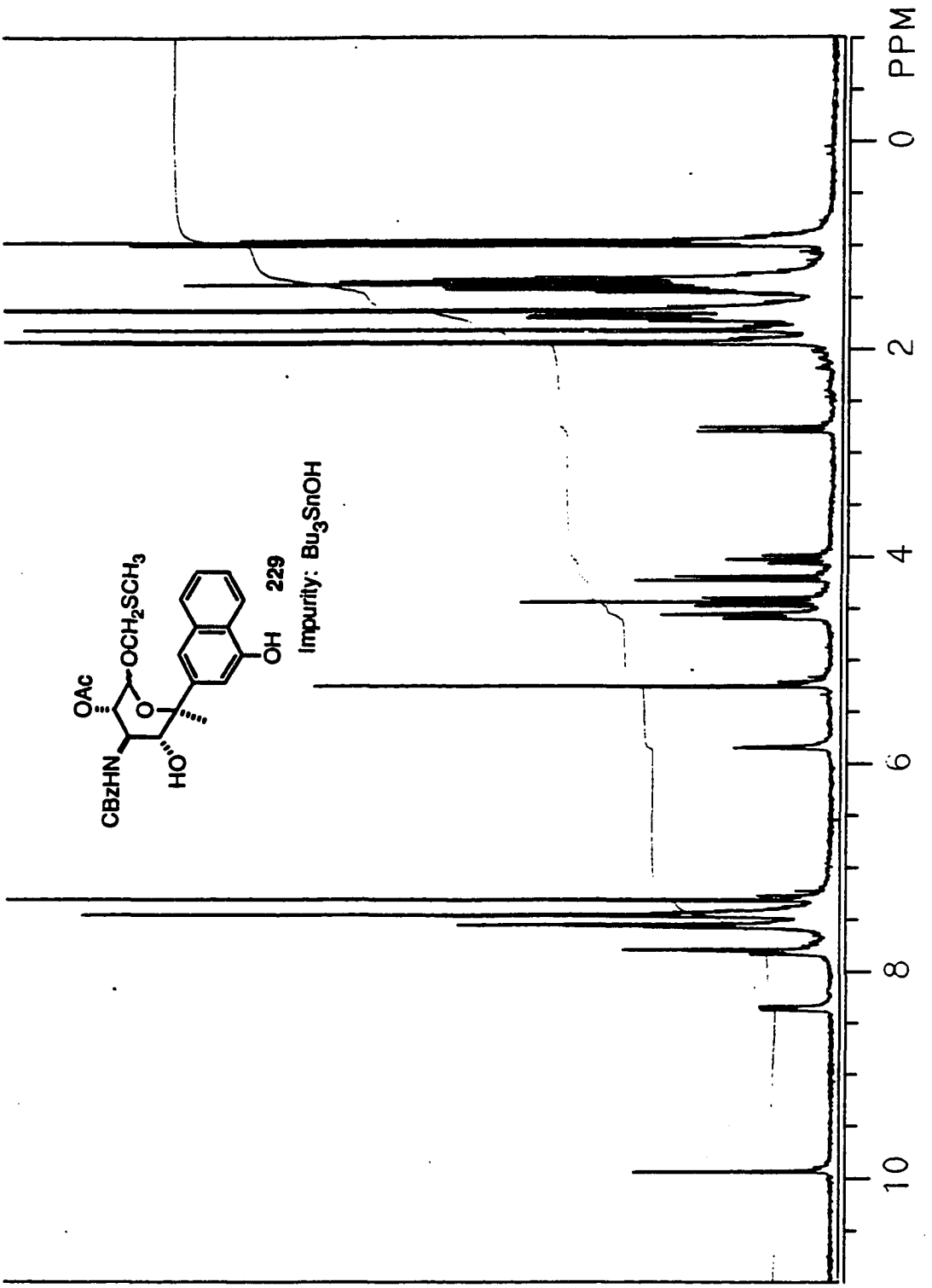

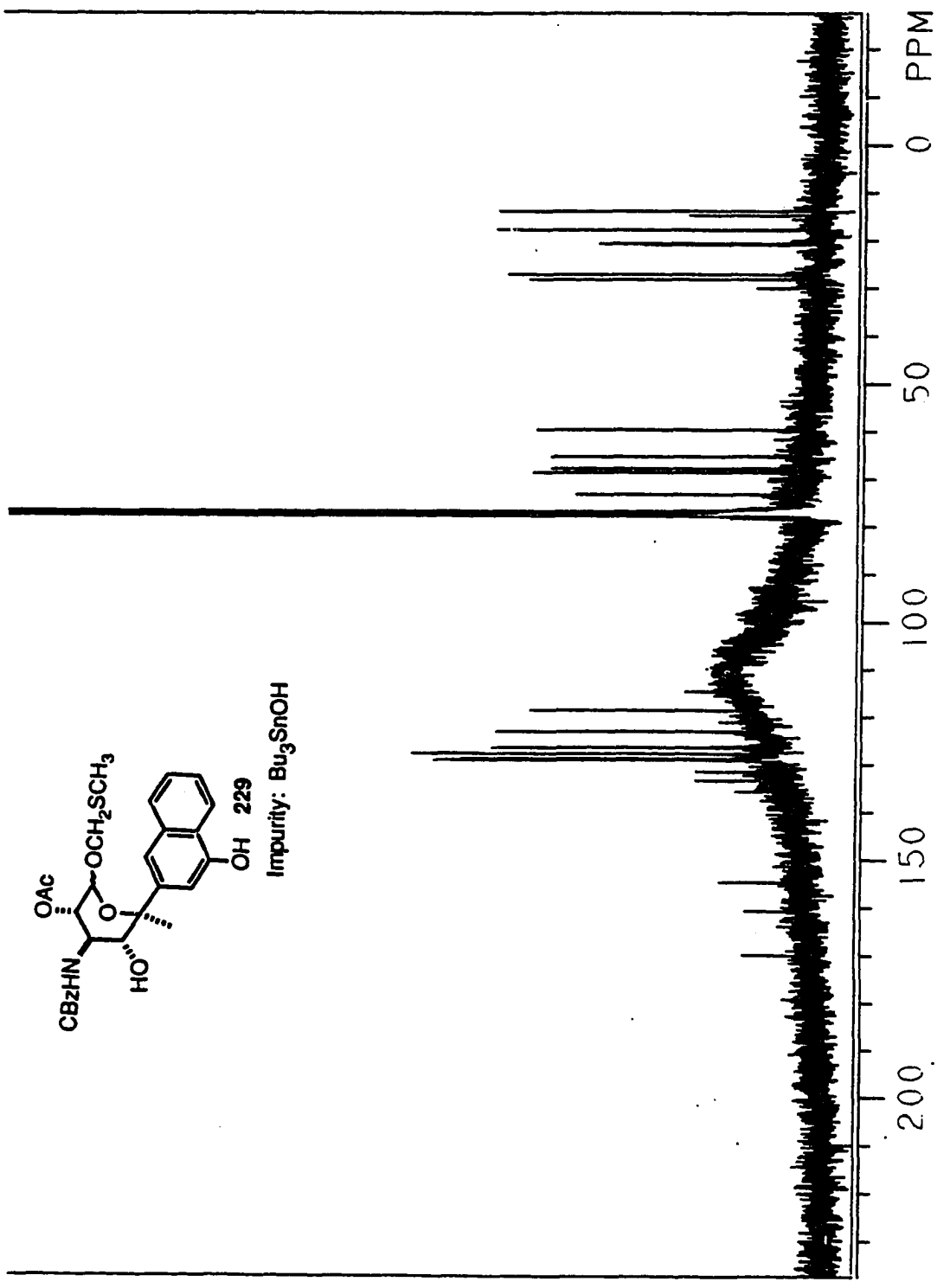

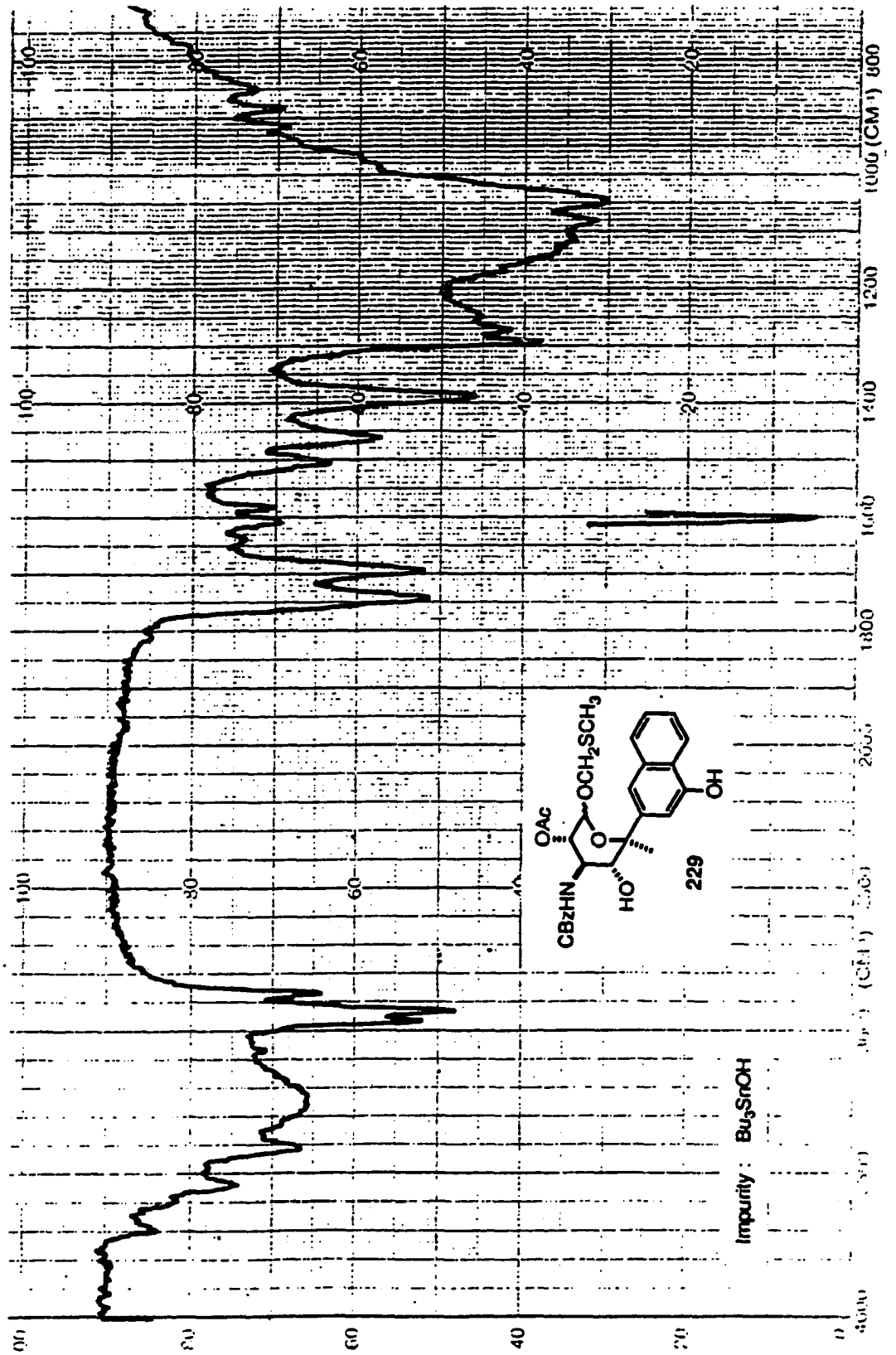

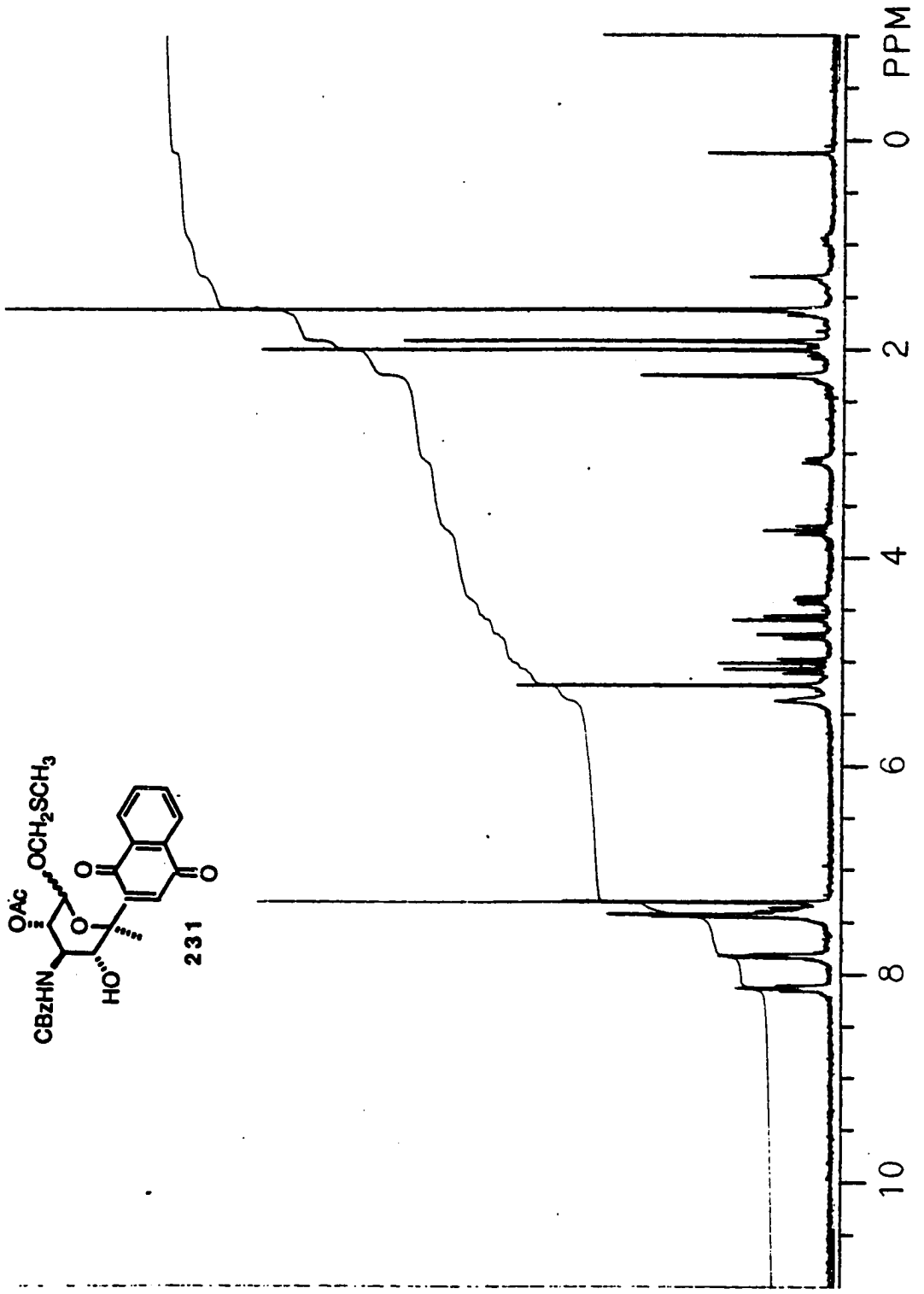

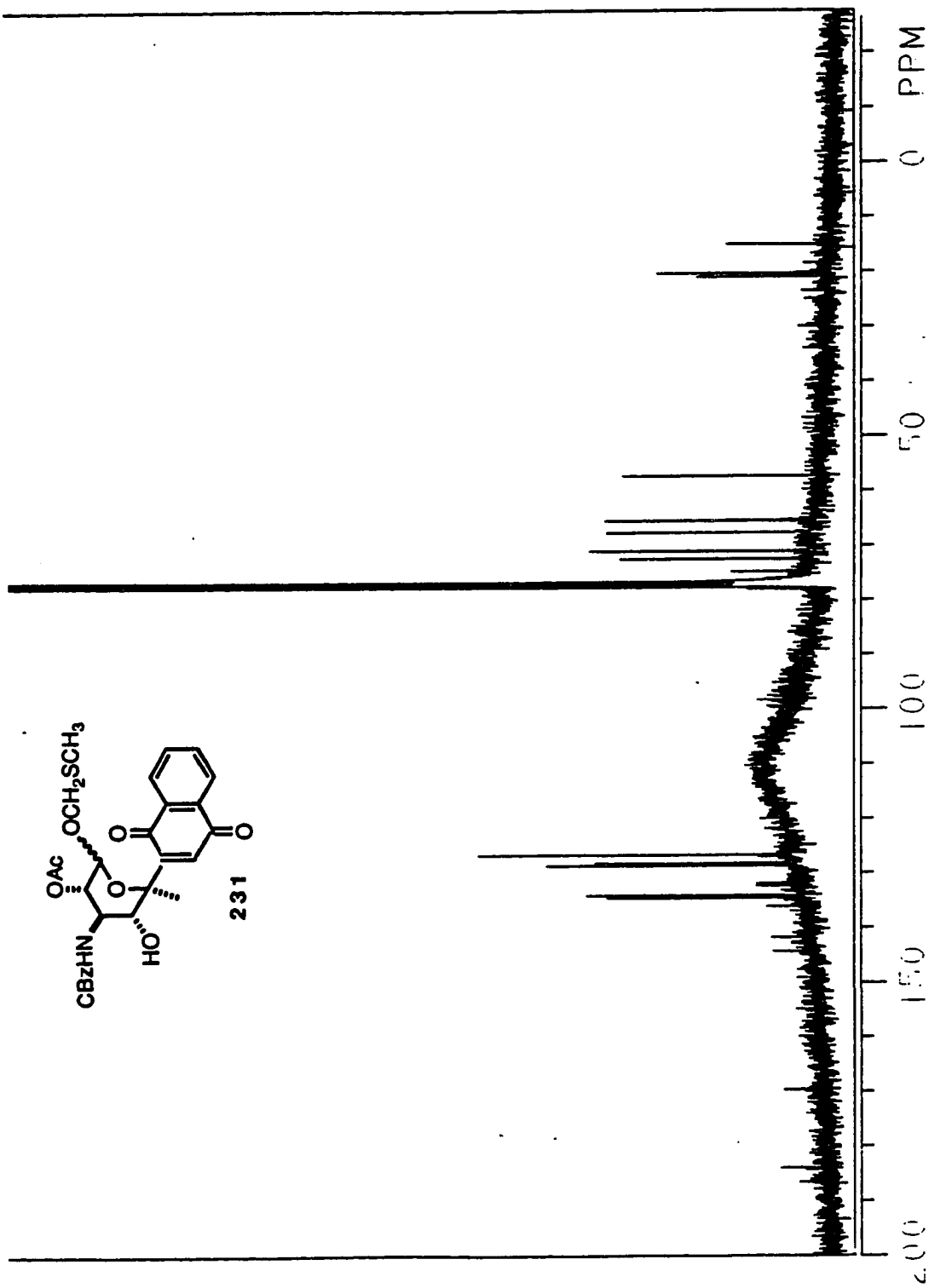

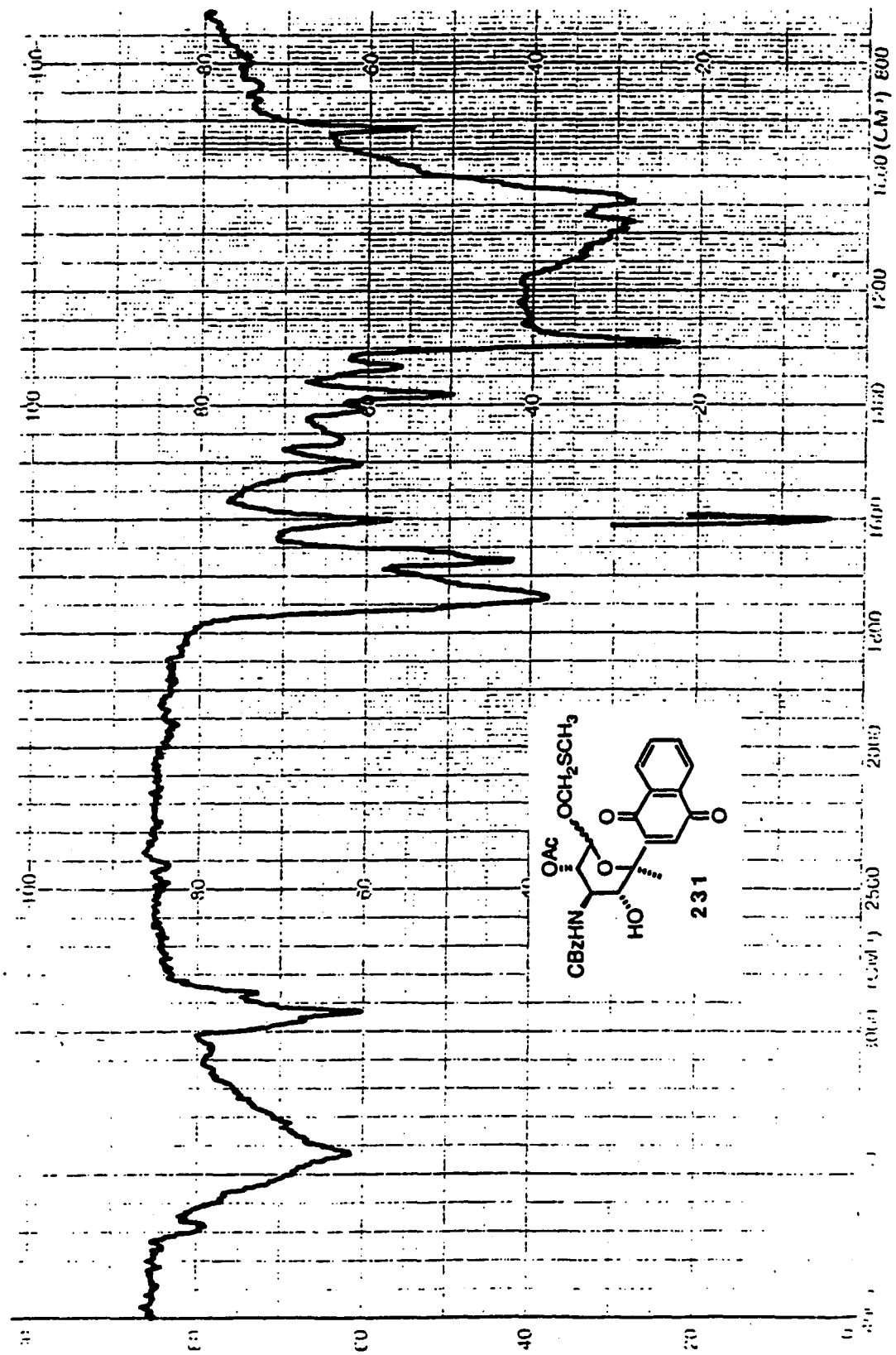

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