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Novel Inverse-Electron-Demand Cycloadditions For Functionalizing Carbohydrates

by

BAOQING LI

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

1999

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THE CITY UNIVERSITY OF NEW YORK

Abstract

Novel Inverse-Electron-Demand Cycloadditions For Functionalizing Carbohydrates

by

Baoqing Li

Advisor: Professor Richard W. Franck

Two sorts of carbohydrate linkages have been prepared by using novel inverse-electron-demand cycloadditions. Our generalized glycosidation method for introducing oxygen and nitrogen to the anomeric carbon demonstrated an alternative approach to a variety of interesting 2-deoxy-O and 2-deoxy-N glycosides e.g. **4.67** which exist in many natural products, such as aureolic acids **2.23** and glycopeptides **3.2**. The stereoselectivity of the cycloadducts **2.48**, **4.59**, and **4.61** can be controlled by choosing the suitable sugar-based dienophiles (e.g. tri-O-benzyl-D-glucal **1.15** and tri-O-benzyl-D-allal **1.17**). Also, the assignment of the stereoselectivity of the cycloadduct **4.46** was based on the analysis of 1D, 2DNMR, and X-ray crystallography.

Acknowledgments

First and foremost, I would like to thank Professor Richard W. Franck for his invaluable guidance, kindness, and encouragement throughout my whole Ph.D. study.

Great thanks to my committee members Professor W. Berkowitz and Professor K. Grohmann, who provided invaluable suggestions, which benefited my research progress; Dr. M. Blumenstein for his help in the NMR experiments; Dr. G. Quigley and Miss M. Noto for providing the X-ray structure; Professor D. Mootoo and Dr. C. Soll for their kind help.

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To my wife Cuijian Yang and my son Jeffrey Li,
who endured it all, with my deepest love.

Table of Contents

List of Tables

List of Figures

Chapter 1

General Considerations for the Inverse-Electron-Demand Diels-Alder Reaction

Introduction

An inverse-electron-demand Diels-Alder cycloaddition has been developed as a novel method for the synthesis of important, or potentially important, glycosidic linkage types including 2-deoxy-O (found in many antibiotics[1]) and 2-deoxy-N.[2] The research to be described was undertaken to develop an alternative approach to the important glycosidic linkage found in many natural materials. Although a comprehensive literature exists where the construction of both alpha and beta O-glycosidic linkages are described,[3,4] each approach is centered around two concepts: (1) by use of an inherent participating group in the glycosyl donor,[5] usually at C-2 to direct the formation of the glycosidic bond, as shown in figure **1**.

(2) the temporary introduction of a participating group with an equatorial C-2 heteroatom substituent (e.g., -Br,[6] -SAr,[7] -SePh,[8] and 1,2-epoxyl[9]) on the glycosyl donor in order to direct the stereochemistry of the glycosidic linkage, and reductive removal of these substituents after the glycosylation event, as shown in figure **2**.

Figure 1. General mechanism for construction of an O-glycosidic bond by using an inherent participating group

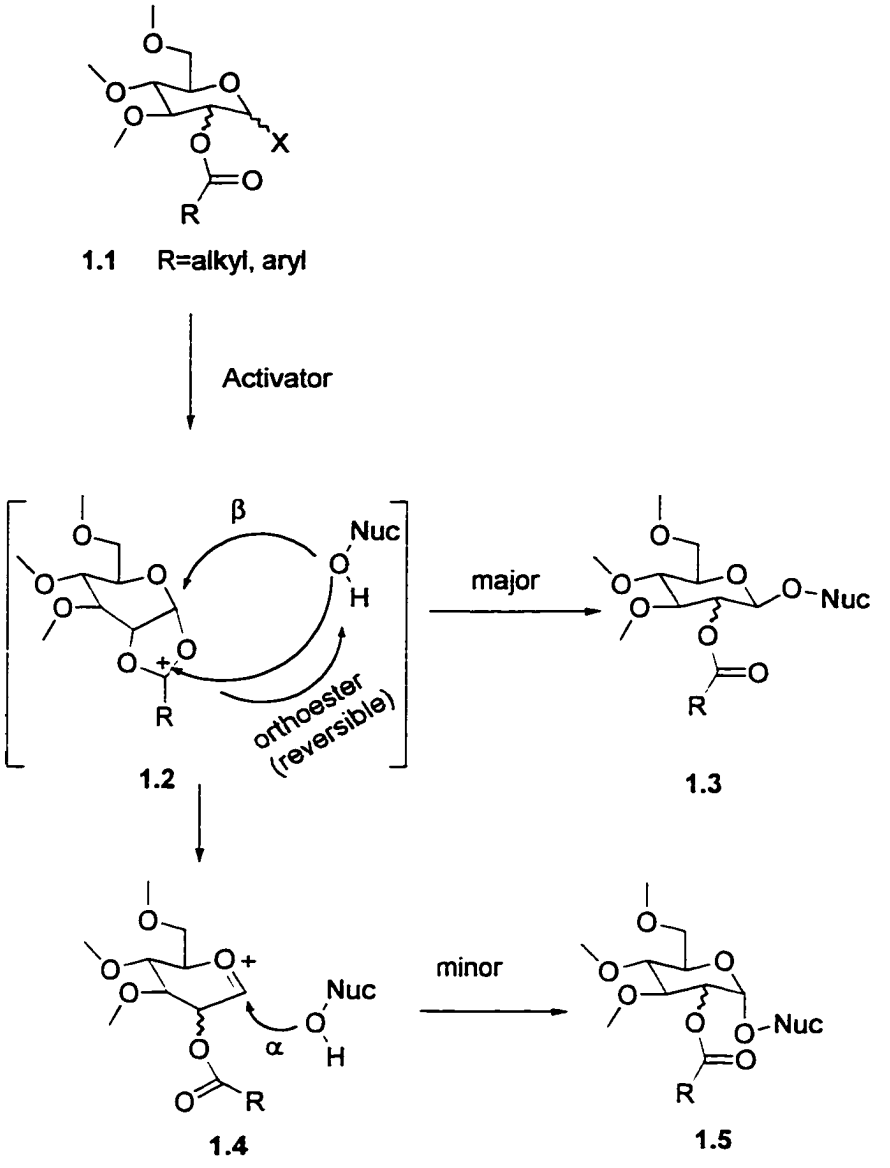
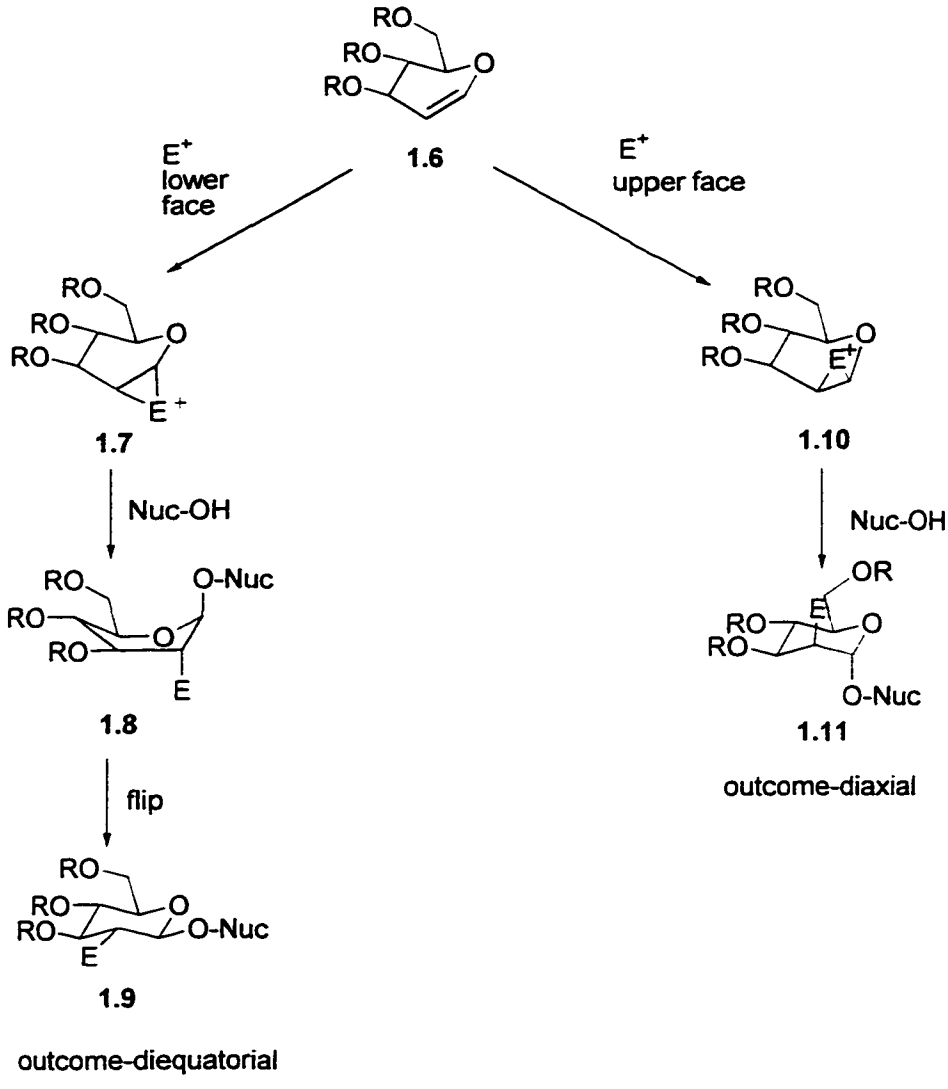


Figure 2. General reaction of glycals with electrophiles in the formation of 2-deoxy-glycosides

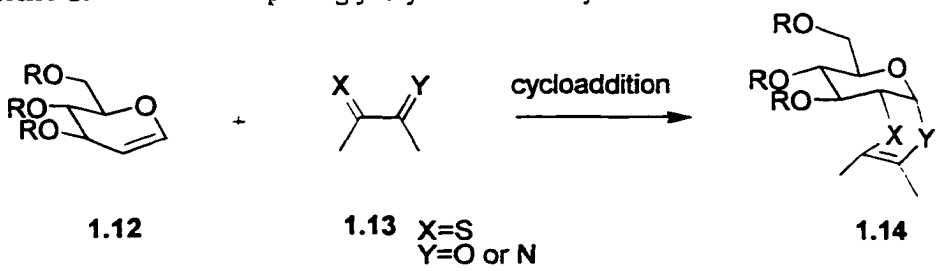


But the fact that so many methods exist and are in broad use clearly signals that the competing reaction (and degradation) pathways summarized in figure 1 and 2 have transition-states of very similar energies (**1.2** and **1.4** in figure 1 and **1.7** and **1.10** in figure 2). This means that one is not able to predict in a new case what the outcome of a glycosylation reaction will be with certainty. A simple change from a hexose to fluorodeoxy hexose or a deoxy hexose can have a disastrous consequence on glycosylation yield and even anomeric configuration, as can a simple change of protecting group even when these are far removed from the glycosylation center. *It is*

extremely important to invent truly new and different glycosylation strategies that will not require a bimolecular reaction to occur between a developing oxocarbonium ion and a sterically-hindered lowly-nucleophilic alcohol.[10]

Our method develops heterocycloaddition for group transfer.[11] The principles of our concept can be illustrated in the general equation below where sugar dienophile **1.12** would undergo cycloaddition with heterodiene **1.13** to afford adduct **1.14** (Scheme 1).

Scheme **1.** Novel concept for glycosyl transfer via cycoladdition

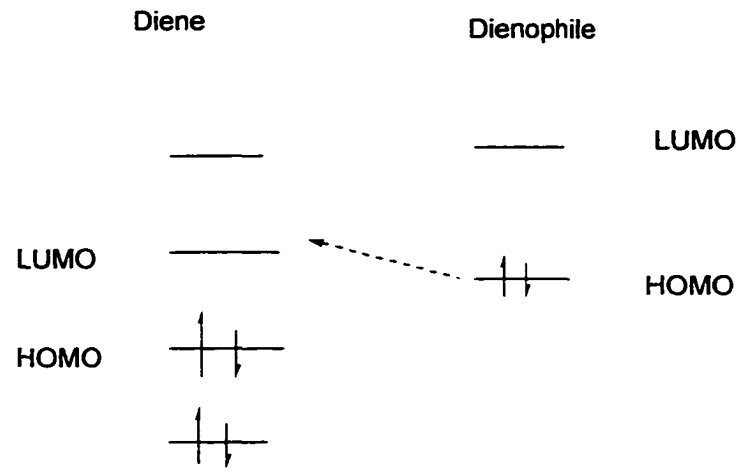


1.12 **1.13** X=S, Y=O or N **1.14**

1.1. The inverse-electron-demand Diels-Alder reaction

One of the important processes for the strategic formation of a new ring from two reacting molecules is the Diels-Alder reaction. There is a strong electronic substituent effect in the Diels-Alder cycloaddition.[12] In most common cases, the dienophile bears an electron-withdrawing substituent which will lower the energy of its LUMO and the diene has an electron-releasing one which will raise the energy of its HOMO. The strongest interaction is then between the HOMO of the diene and the LUMO of the dienophile. It is significant that if a relatively electron-poor diene is utilized, the preference is reversed and electron-rich alkenes are the best dienophiles. Such reactions are called inverse-electron-demand Diels-Alder reactions. In this case, the strongest interaction is between the HOMO of dienophile and the LUMO of diene because of the substituent effects as illustrated in figure 3.

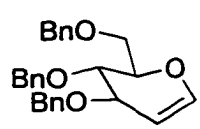
Figure 3. Frontier orbital interaction in inverse electron demand Diels-Alder reaction



1.1.1. The inverse-electron-demand Diels-Alder reaction: dienophiles

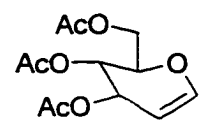
Examples of some alkenes that exhibit reactivity as dienophiles are collected in Table 1. All of these are sugar-based electron-rich dienophiles. Among the dienophiles, the benzyl-protected sugars are much more reactive than the acetyl-protected sugars. Also, the galactal series are more reactive than the glucal series according to the AM1 calculation of their HOMOs.[1]

Table 1. Sugar-based dienophiles and their energies of HOMOs



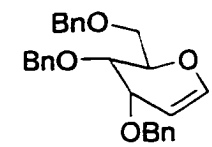
-9.53 ev

1.15



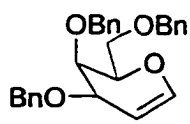
-9.74 ev

1.16



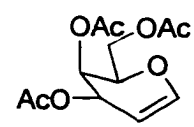
-9.50 ev

1.17

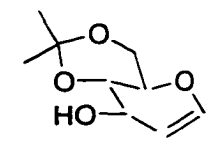


-9.17 ev

1.18



1.19



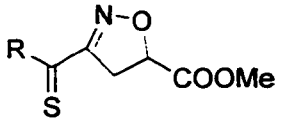
-9.53 ev

1.20

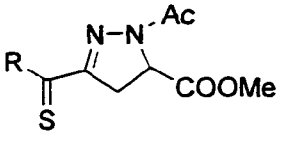
1.1.2. The inverse-electron-demand Diels-Alder reaction: dienes

Unstable thio-oxo heterodienes (Table 2), which act as dienes in the inverse-electron-demand Diels-Alder reactions can be generated *in situ* from their precursors: phthalimidosulfenyl compounds. Basic conditions cause elimination of phthalimide to form the dienes which are then trapped with dienophiles[14] (see scheme 3).

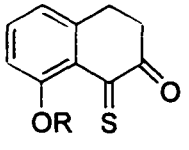
Table 2. Thio-oxo heterodienes and the energies of their LUMOs



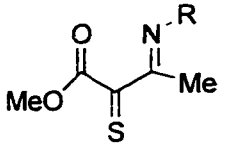
1.21, R=COOMe(-2.06 ev)
1.22, R=CN(-2.35 ev)



1.23, R=COOMe(-1.87ev)
1.24, R=CN(-2.12 ev)



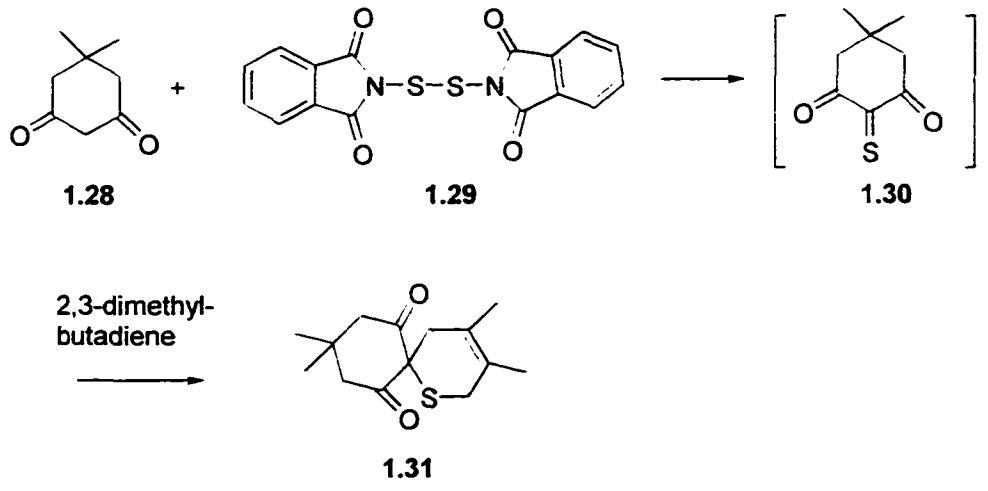
1.25. R=Ac(-1.51ev)
1.26. R=Tf(-1.62 ev)



1.27. R=OMe(-1.71 ev)

Cava et al.[13] first showed the existence of thio-oxo species. They discovered that the diketo thione **1.30** was elusive and its presence could only be detected by trapping with 2,3-dimethylbutadiene to give the adduct **1.31** (Scheme 2).

Scheme 2. Direct thiation of dimedone using dithiobisphthalimide

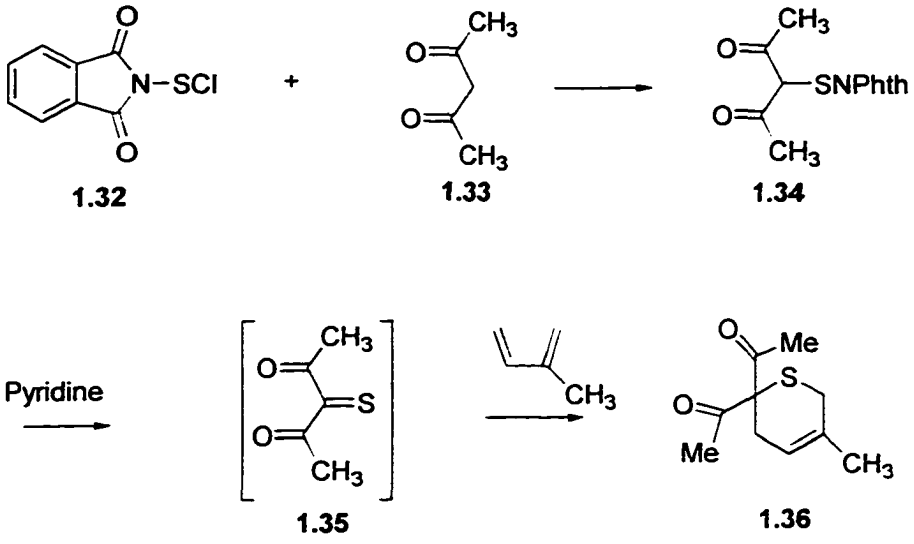


1.28 1.29 1.30

1.31

The use of phthalimidosulfenyl chloride **1.32** as a direct thiation reagent of enolizable dicarbonyl compounds e.g. **1.33** was reported by Cappozi et al.,[14] where the thione portion of a diacylthione **1.35** was trapped as a dienophile (Scheme 3). Their methodology was adopted to prepare the precursors as the highly reactive thio-oxo heterodiene system **1.35** which we required for our novel concept for glycosyl transfer.

Scheme 3. The use of phthalimidosulfenyl chloride as direct thiation reagent to generate their dienophile reported by Cappozi et al.[14]

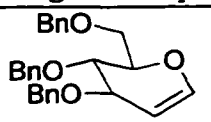
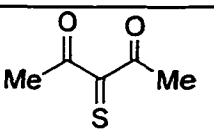
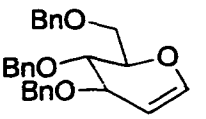
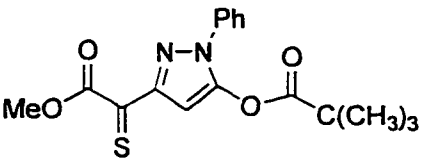


1.2. Calculation of the HOMO-LUMO gap between dienes and dienophiles

It is well known[15] that Diels-Alder reactions depend on the energy gap between the HOMO of the diene and the LUMO of the dienophile. In cases where the energy gap is too large to favor cycloaddition, temperature and/or pressure, Lewis acid catalysis can be adjusted to facilitate cycloaddition.

The AM1 method was used to compute the requisite orbital for every diene and dienophile in our inverse-electron-demand cycloaddition. It can be seen that when the energy gap of HOMO and LUMO is greater than 7.9 ev, the reaction fails (Table 3). At a gap of 7.9 ev, the reaction goes quite slowly, and as the energy difference decreases, the rate of the reaction increases.

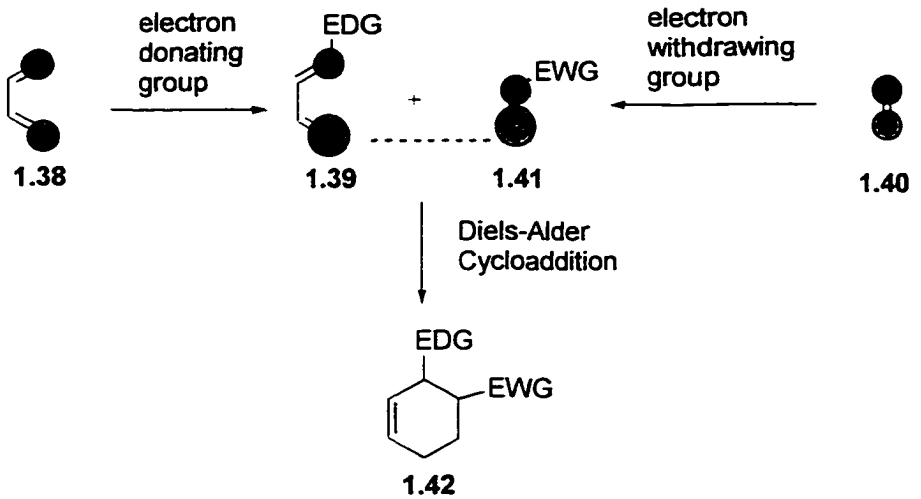
Table 3. The HOMO and LUMO energy values used to determine the occurrence of a cycloaddition

Sugar dienophile	Diene	HOMO-LUMO gap	Cycloaddition
 **1.15**	 **1.35**	7.91 ev	yes
 **1.15**	 **1.37**	8.2 ev	no

1.3. The regiochemistry of the cycloaddition

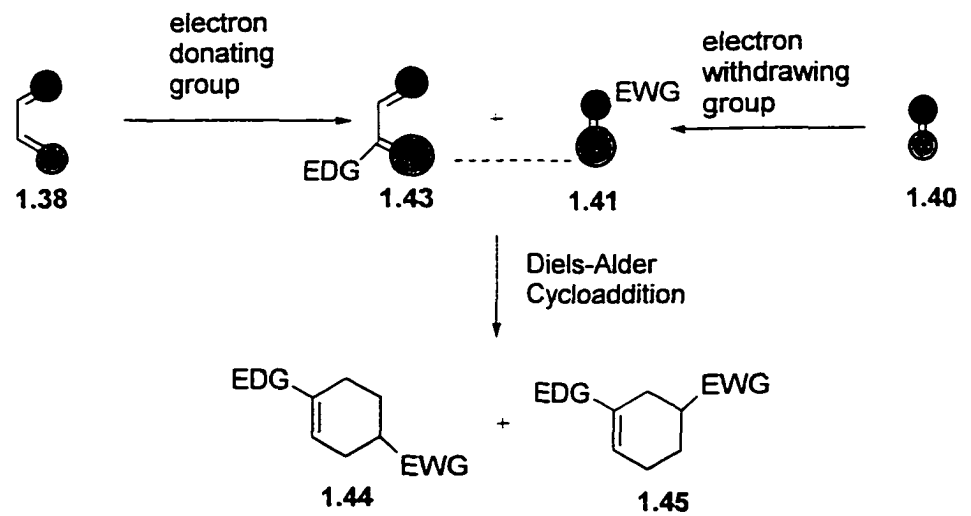
In Diels-Alder reactions, the regiochemistry of the cycloadducts is directed by the effects of substituents on the orbital coefficients at the atoms involved in the bond forming process.[16] In an unsubstituted butadiene, the orbital coefficients at carbons 1 and 4 of the HOMO are equivalent. When an electron donating substituent is introduced at the 1-position of the diene **1.38**, the orbital coefficients at carbons 1 and 4 of the HOMO are no longer equivalent; The orbital coefficient at the 4-position is much greater than the orbital coefficient at the 1-position in **1.39**. Similarly, for the ethylene dienophile **1.40**, the orbital coefficients on the LUMO are equivalent until the introduction of an electron withdrawing group which increases the orbital coefficient at the 2-position in **1.41**. Anh and coworkers[17] have demonstrated that the C-C bond formation occurs at the carbon with the largest orbital coefficients (Figure 4).

Figure 4. The regiochemistry of the Diels-Alder reaction being directed by electron coefficients at the carbons in the bond-forming process.



In the case where the electron donating group is at the 2-position of butadiene **1.38**, because the orbital coefficient around the carbons have changed, the regioselectivity of the reaction favors the *para* product **1.44** over the *meta* product **1.45** (Figure 5).

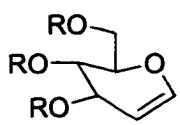
Figure 5. The regiochemistry of the Diels-Alder reaction being directed by electron coefficients at the carbons in the bond-forming process.



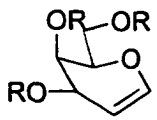
Based on the above theory, we believe that the regiochemistry of cycloaddition reactions in our system are governed by the orbital coefficients at C-1 and C-2 of the HOMO of the

glycal dienophile **1.12** and by the orbital coefficient of LUMO of the sulfur and the ketonic oxygen in the heterodiene **1.13** (Scheme **1**). For the dienophiles e.g.: **1.46** and **1.47**, the orbital coefficients at carbon 1 and 2 were calculated for 2-unsubstituented glycals and it was clear that C-2 possessed a greater orbital coefficient than C-1 for each glycal (Table **4**).

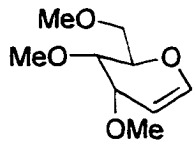
Table **4**. The electron coefficient for C-1 and C-2 for the C-2 unsubstituented glycals



1.46 R=Me
1.16 R=Ac



1.47 R=Me
1.48 R=Ac

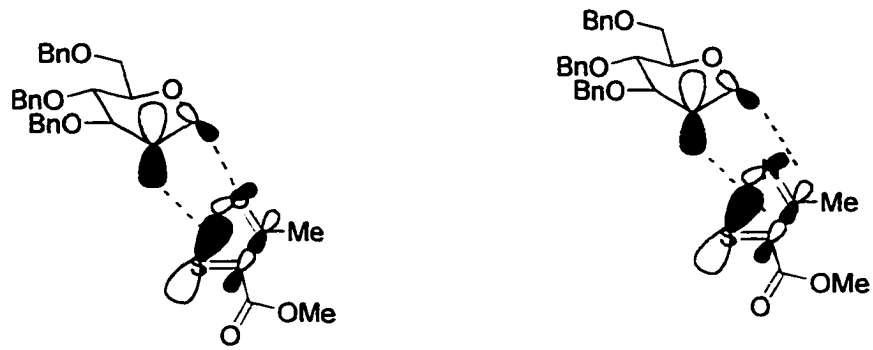


1.49

Glycal	C-1	C-2
1.46	0.334	0.493
1.16	0.336	0.486
1.47	0.352	0.510
1.48	0.346	0.492
1.49	0.343	0.530

As for the heterodienes **1.13**, sulfur has a greater orbital coefficient than oxygen, according to Anh's predictions, sulfur should form a bond with the carbon (C-2) of the dienophile **1.12**, whereas, oxygen forms a bond with C-1 of the dienophile as shown in figure **6**.

Figure 6. The electron coefficients for the diene and tribenzylglucal directing the regiochemistry of the cycloaddition



1.50 **1.51**

1.4. The facial selectivity of the cycloaddition

In the case of tri-O-benzyl-D-glucal, the cycloaddition occurred preferentially from bottom face attack of the double bond to provide the below-plane (α-face) cycloadduct. The facial selectivity of the cycloadduct is also somehow effected by the choice of solvents.[18] For the case of the galactal series with an axial group at C-4 position which will block the upper face, only the below-plane cycloadduct can be obtained (e.g. compound **4.60** in scheme **60**). But in the case of allal series, the axial group at the C-3 position cleanly inverts the stereochemistry of cycloaddition, and affords only the above-plane (β-face) cycloadduct (e.g. compound **4.61** in scheme **60**). The stereochemistry in both the α and β face adducts has been confirmed by X-ray crystallography.

In principle, our generalized glycosidation method uses chemistry that is benign towards essentially every common blocking group found in the aglycones which might be coupled to sugars. It is our goal to invent a variety of reagents that will demonstrate the generality of our idea, and where possible to develop highly stereoselective transfer processes that are simple and easy to carry out. Two sorts of carbohydrate linkages that are prepared by our methodology and will be described in this thesis are found in aureolic acids and glycopeptides.

Part 1.

Chapter 2

A Cycloaddition Approach to Aureolic Acids

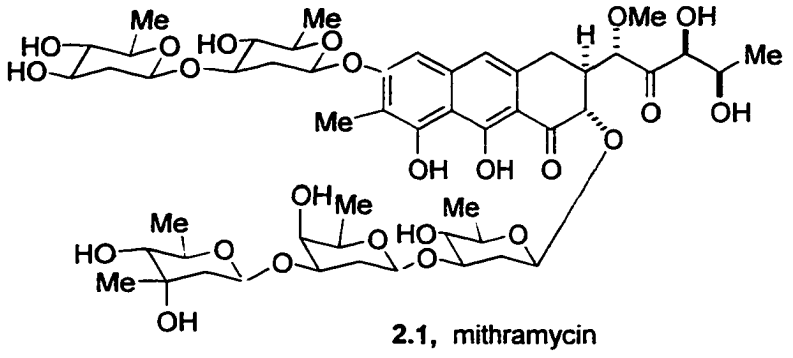
Introduction

The aureolic acid antitumor antibiotic family, including the olivomycins **2.2**, chromomycins **2.3** (Figure 7), and aureolic acid **2.23** (Scheme **13**), has been a challenge for organic chemists since their isolation. Aureolic acid, from which the group name derives, was isolated from unidentified *streptoymces* species in 1953 at Abbott Laboratories.[19,20]

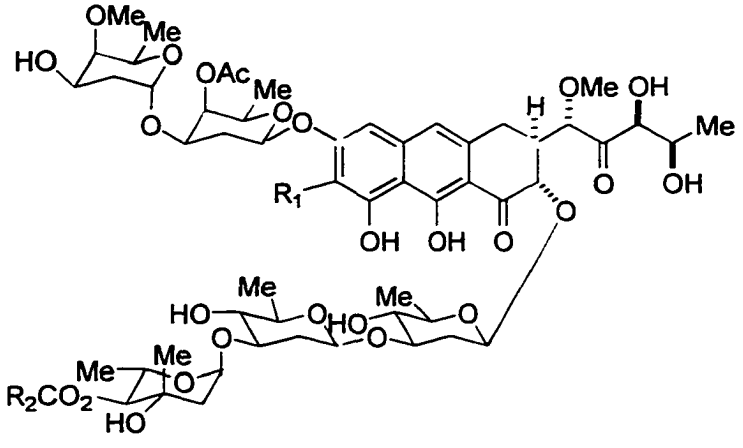
Structures of aureolic acid group compounds are based upon two aglycones, chromomycinone and olivin, which differ only by a methyl group at position 7 (**2.4** in Scheme **4**). These aglycones are tetrahydroanthracene derivatives with phenolic hydroxyl groups at position 6, 8, and 9.

The aglycones are linked at their 2- and 6-positions to chains of two or three sugars. These glycosides are responsible for the difference among the individual antitumor antibiotics.

Figure 7. Aureolic acid family

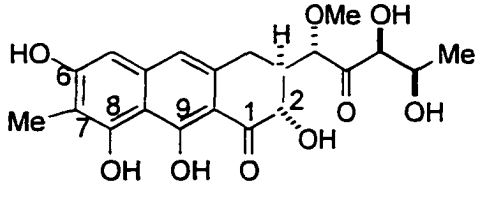


2.1, mithramycin



2.2, olivomycin A (R_1=H, R_2=i-Pr)
2.3, chromomycin A_3 (R_1=R_2=Me)

Scheme 4. Aglycones of the aureolic acid group



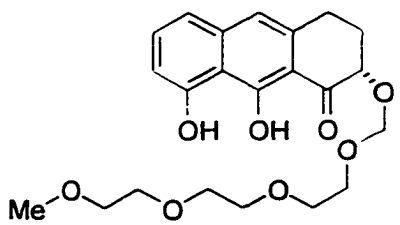
2.4

R=H, olivin
R=CH_3, chromomycinone

Biological studies demonstrated that aureolic acids inhibit RNA synthesis in virus, bacteria, and animal cells.[21,22] They all show partial cross-resistance in bacterial and

tumor cells.[23] A number of investigators have examined the exact nature of the binding with DNA. Studies have shown that chromomycin A_3(CRA_3) binds tightly to GC-rich regions of DNA in the presence of Mg^{2+}, inhibiting the action of DNA and RNA polymerases. It was also shown that sequential removal of the sugars from CRA_3 causes a progressive decrease in the DNA binding. The aglycone of CRA_3, chromomycinone (CRN), does not bind to DNA at all. These studies established that the two intact oligosaccharide chains are essential for DNA binding and biological activity.[24,25] In 1989, Gao and Patel[26,27] reported the NMR study of a CRA_3-Mg^{2+}-DNA complex showing that CRA_3 binds in the minor groove of DNA as a dimeric complex linked by Mg^{2+}. Moreover, Kahne[28] has shown that the intact C-D-E trisaccharide is required for formation of the 2:1 complex with Mg^{2+}. Kahne[29] has also demonstrated that the simplified TEG-chromophore conjugate **2.5** formed 2:1 complexes with Mg^{2+}, and has indicated that the $[\mathbf{2.5}]_2Mg^{2+}$ complex interacts with DNA (Scheme **5**).

Scheme **5.**



2.5

Although the aureolic acids have been used as chemotherapeutic agents, they are highly toxic and have found limited application. Also, the highly complex structures of aureolic acid and its analogs present very difficult targets for total synthesis. In order to develop less toxic analogs and understand the role of the oligosaccharides in the DNA binding and recognition events, several groups have accepted the challenge for synthesis of the target compounds.

2.1. Development of the glycosidation of aglycones

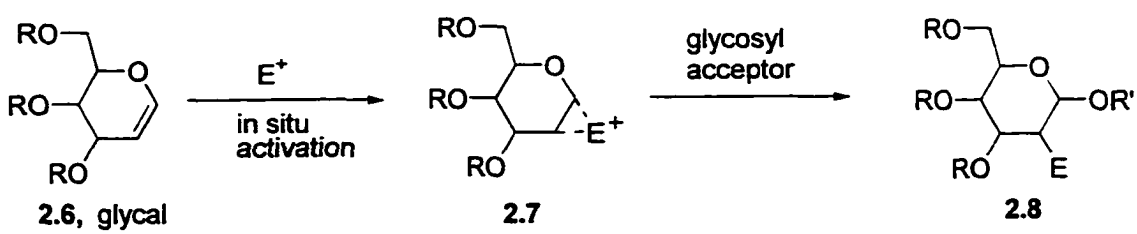
The synthesis of the aureolic acid antibiotics is a formidable challenge, particularly in view of the oligosaccharide substructures: three out of the five glycosidic linkage are β in olivomycin **2.2**, chromomycin **2.3**, whereas all five of the glycosidic bonds are β in mithramycin **2.1** (Figure 7).

So far, the synthesis of the fully deprotected form of the aglycone has been completed.[30] As for the oligosaccharide, Thiem[31] has reported stereostructure assignments and pioneering synthesis of the A-B disaccharide and C-D-E trisaccharide. Many other groups[32] have also made important contributions toward the synthesis of the A-B and C-D-E oligosaccharides. Concerning the connections of the oligosaccharides to the natural aglycone, there are several methods for a stereocontrolled construction of 2-deoxyglycosides of acyloins.

2.1.1. Using glycals as glycosyl donors

The possibility of ultilizing glycals as glycosyl donors in disaccharide synthesis had been demonstrated in the pioneering research of Lemieux[33] and Thiem[34] by halonium mediated coupling to suitably disposed acceptors. Glycal is a very versatile synthetic intermediate especially in the synthesis of 2-deoxy glycosides.[35] When glycals are used as glycosyl donors, the nucleophilic double bond of the glycal **2.6** is reacted with a variety of eletrophilic reagents E^+ to generate an intermediary oxonium species **2.7** (Scheme **6**).

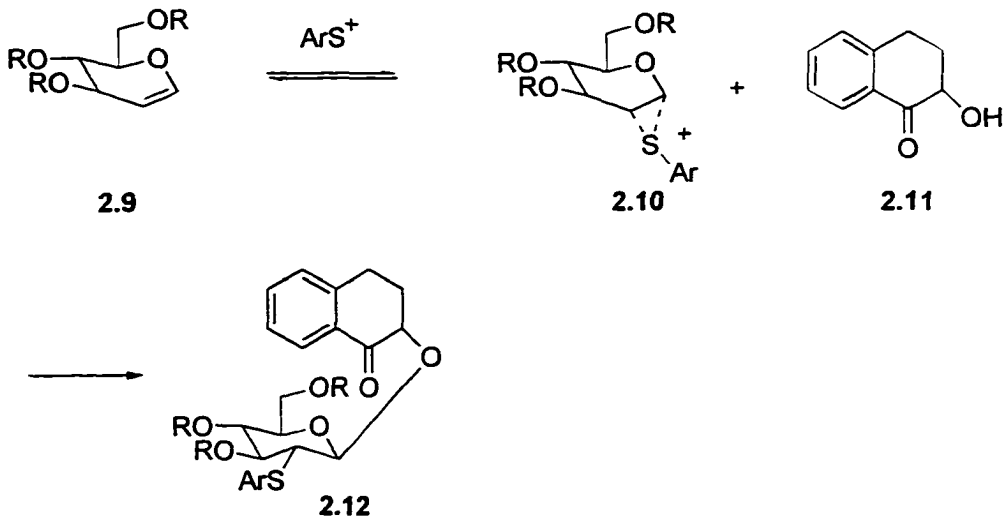
Scheme 6. Glycals as glycosyl donors



2.6, glycal **2.7** **2.8**

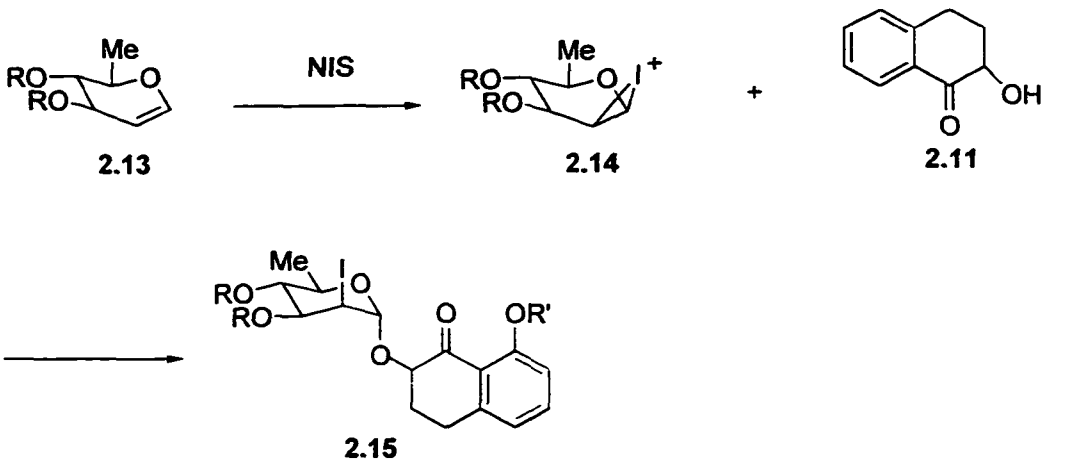
In most cases, the electrophilic agent undergoes addition to the glycal via a below-plane approach to yield the α onium ion. Iodine and sometimes selenium were the exception to this rule and approached to the glycal from the upper-plane to provide the β onium ion.[36] Nucleophilic ring opening of the α-oxonium intermediate yielded the β-glycoside. On the other hand, the β-oxonium intermediate provided the α-glycoside. It was proposed that the stereochemistry of the oxonium species directed the stereochemistry of the glycosidation reaction and subsequently the anomeric configuration of the glycoside. A 2-deoxy glycosidic bond can be easily achieved by removal of the temporary substituent at C-2. Franck[37] developed a selective route to 2-deoxy-β-glycoside **2.12** via the reaction of glycals **2.9** with electrophilic sulfonium salt reagent (Scheme 7).

Scheme 7. Sulfonium salts undergo electrophilic addition to glycals in the presence of alcohols



In contrast, Thiem[38] prepared 2-deoxy-α-glycoside **2.15** selectively via electrophilic addition of glycals **2.13** with 2-hydroxytetralone **2.11** in the presence of NIS (Scheme 8).

Scheme 8. Iodonium salt mediated coupling of glycals

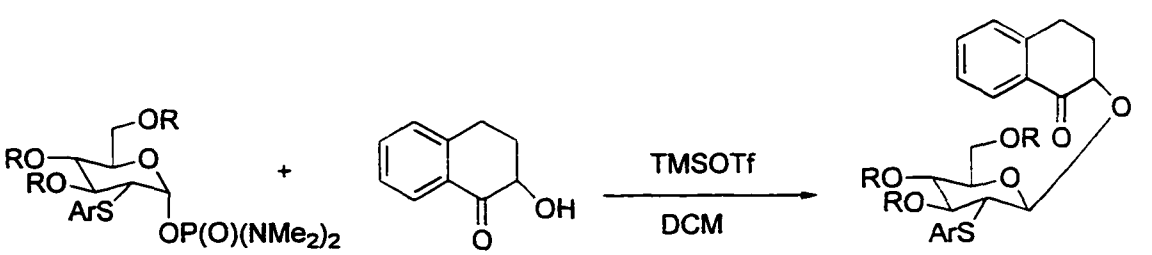


2.13 2.14 2.11 2.15

2.1.2. 2-Deoxy-2-[(p-methoxyphenyl)thio]glycopyranosyl N,N,N',N'-tetramethylphosphoroamidates as glycosyl donor

Hashimoto[39] has achieved 2-deoxy-β-glycoside **2.17** by developing a salient 1,2-trans-glycosidation method with 2-deoxy-2-[(p-methoxyphenyl)thio]glycopyranosyl N,N,N',N'-tetramethylphosphoroamidates **2.16** as glycosyl donor which was effectively activated by TMSOTf, followed by reductive removal of the p-methoxyphenylthio group with Raney nickel (Scheme 9).

Scheme 9. Glycosyl transfer by using phosphate derivative

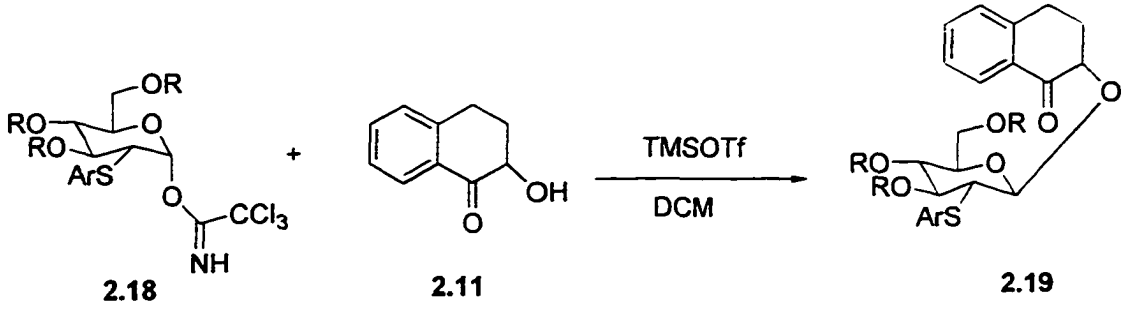


2.16 2.11 2.17

2.1.3. Using glycosyl imidate as glycosyl donor

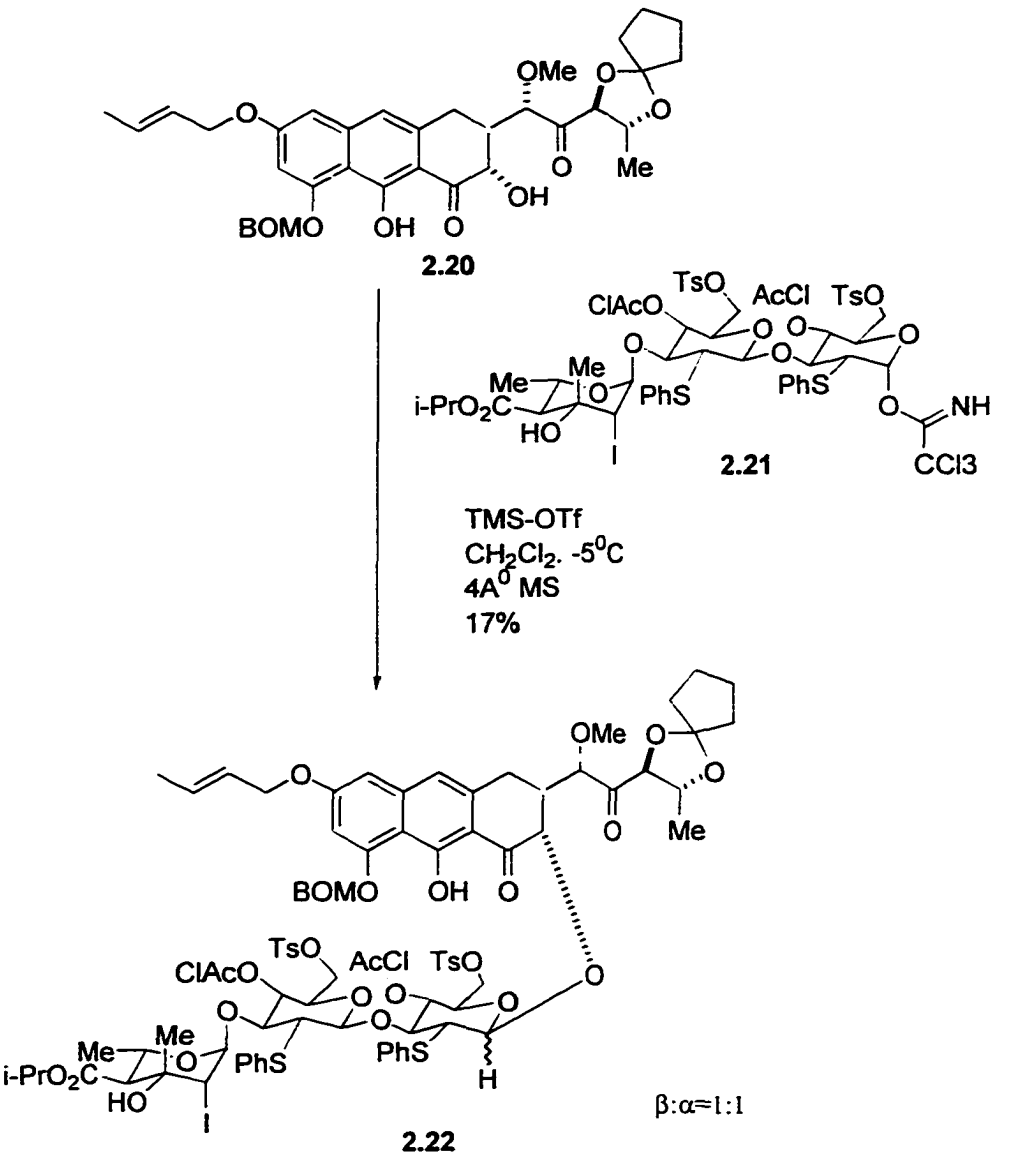
Another elegant method[40, 41] is contributed by using glycosyl imidate **2.18** as glycosyl donor. The imidate can be easily synthesized from the corresponding 1-hydroxy sugar by treatment with trichloroacetonitrile in the presence of a base such as K_2CO_3, NaH, or DBU. The glycosylation reaction was smoothly promoted by a catalytic amount of TMSOTf under mild condition (Scheme **10**). This method has also been applied to a system very close to the natural aureolic acid system (Scheme **11**).

Scheme **10.** Glycosyl transfer by using trichlorimidate as glycosyl donor



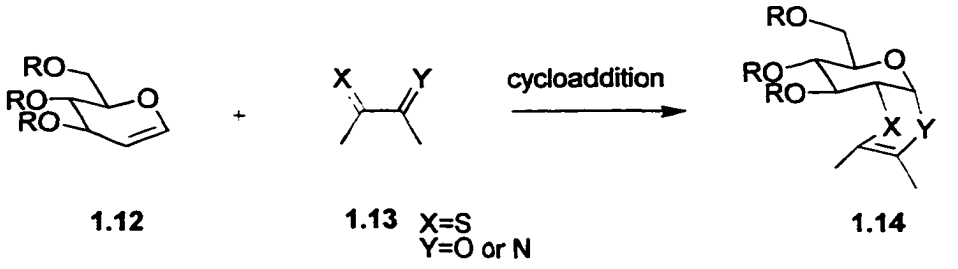
All of the methods for glycosyl transfer shown above involve the formation of an electron-deficient anomeric carbon by electophilic activation of a leaving group at C-1 position of the glycosyl donor. However, the efficient glycosylation of a 2-deoxy sugar, especially β-selective glycosylation, has been a long-standing problem in this field. The main reasons are the lack of stereodirecting anchimeric assistance from the C-2 position and the low stability of a glycosidic bond of a 2-deoxy sugar in acidic conditions due to the lack of an electron-withdrawing C-2 substituent.

Scheme 11.



Our lab has put forward the new concept for glycosyl transfer via cycloaddition which has been well-developed in simple cases (Scheme 12); We planned to apply this methodology to the direct synthesis of 2-deoxy-β-glycosides, as occurs between the C-D-E trisaccharides and the aglycons in all of the aureolic acids.

Scheme 12.

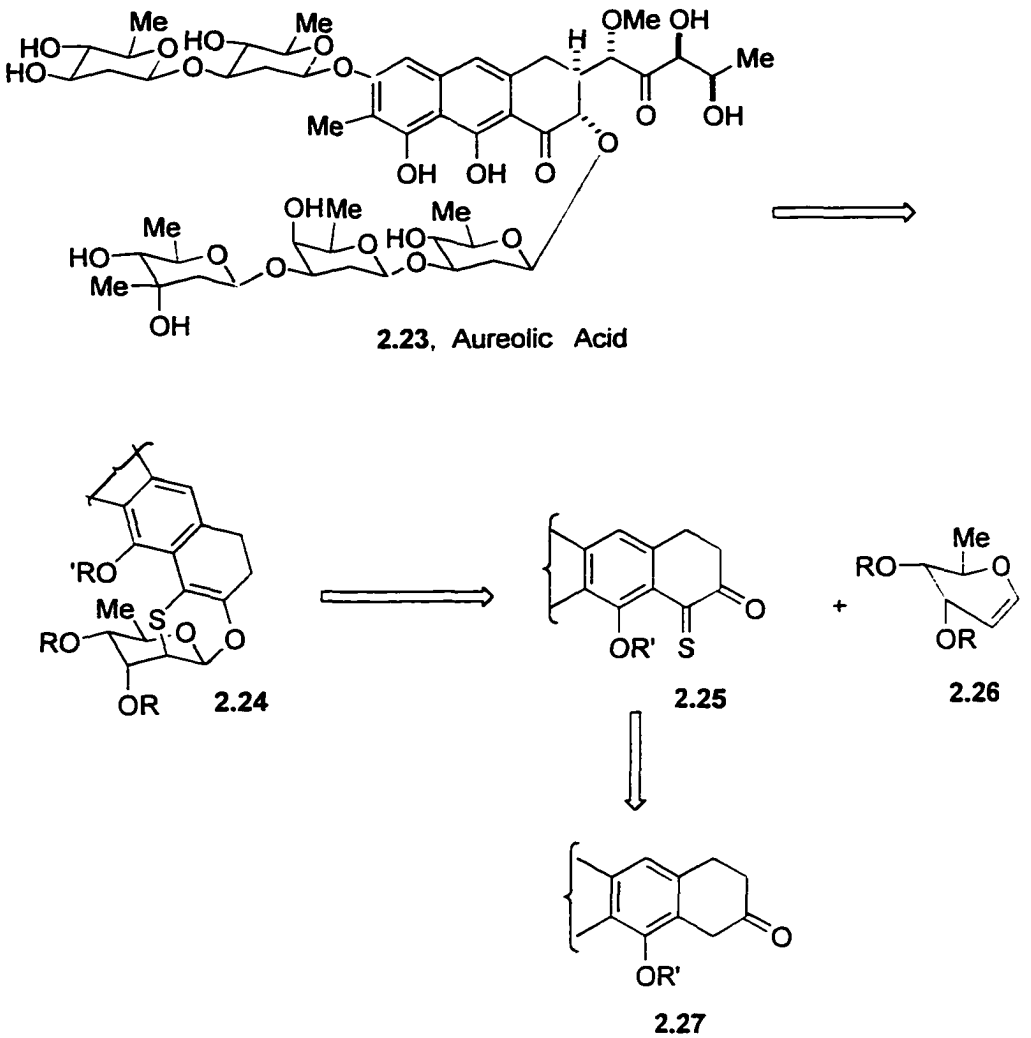


1.12 1.13 X=S Y=O or N 1.14

2.2. Retrosynthetic analysis

Our retrosynthetic disconnections for aureolic acid are outlined in scheme **13**. Cycloaddition of heterodiene **2.25** with dienophile **2.26** should give the above-plane (β-face) cycloadduct **2.24**, which has the same stereochemistry as occurs between the C-D-E trisaccharides and the aglycones in aureolic acids. Thio-oxo heterodiene **2.25** can be achieved from phthalimidosulfenylation of 2-tetralone **2.27**, followed by treatment with base.

Scheme 13.



2.3. Result and Discussion

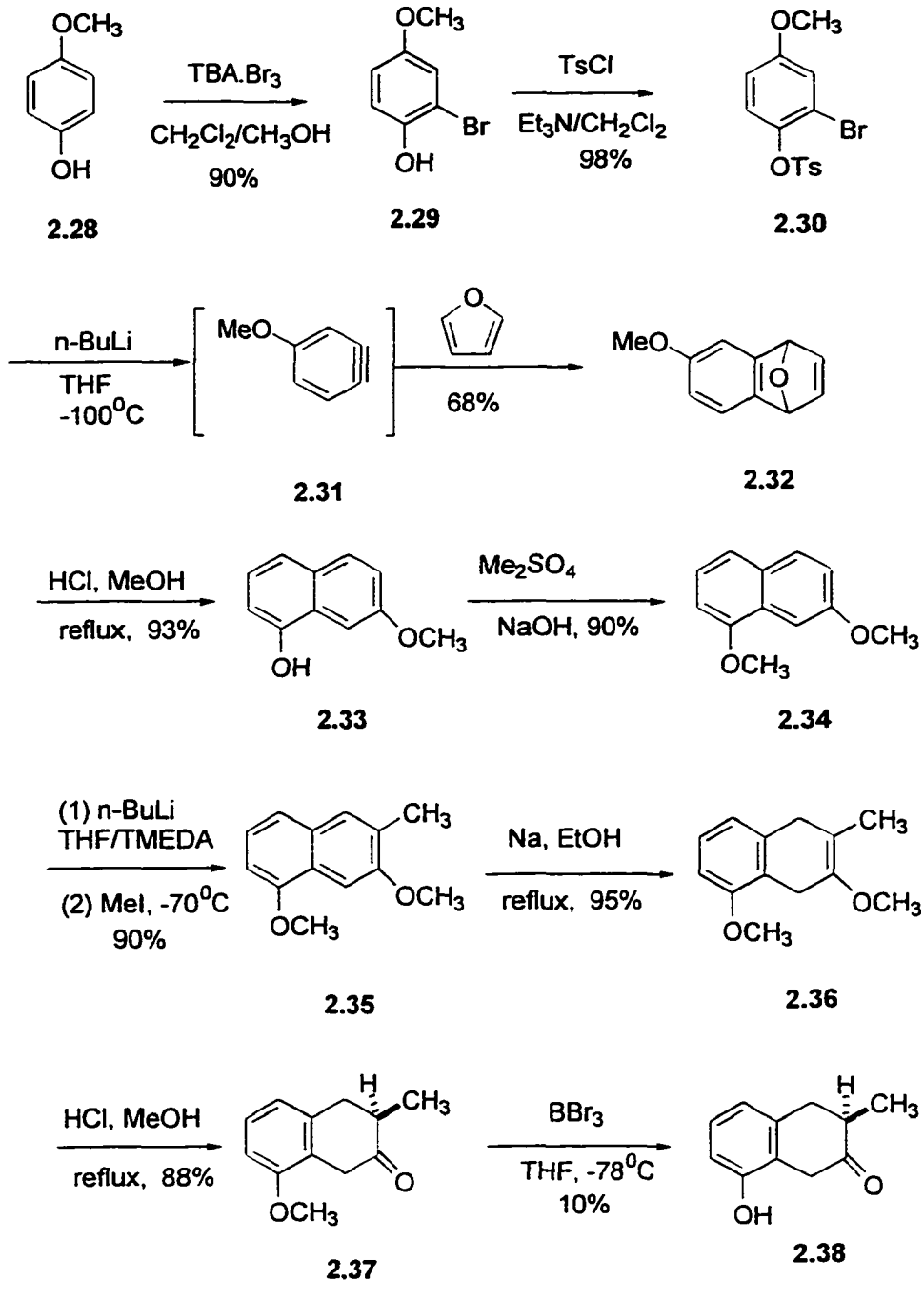
2.3.1. Preparation of 2-tetralones

2-Bromo-4-methoxyphenyl toluene-p-sulfonate **2.30**[42] was readily prepared by tosylation of 2-bromo-4-methoxyphenol **2.29** in 98% yield, which was obtained by selective bromination of 4-methoxyphenol **2.28** by using of tetrabutylammonium tribromide(TBA·Br_3) in 90% yield.[43] Treatment of **2.30** with n-BuLi in the presence of furan at -100^{0}C gave the cycloadduct **2.32** in 68% yield, which on acid-induced ring-opening afforded the known 7-methoxynaphthalen-1-ol **2.33** in the yield of 93%. 1,7-

Dimethoxynaphthalene **2.34** was readily obtained in 93% yield by base-promoted methylation of 7-methoxynaphthalen-1-ol **2.33**. Regioselective methylation of the lithium anion of 1,7-dimethoxynaphthalene **2.34** generated with n-BuLi and TMEDA in THF at 25^0C with CH_3I produced 3,5-dimethyl-2-methylnaphthalene **2.35** in 90% yield. Sodium reduction of compound **2.35** in ethanol produced the more substituted enol ether **2.36** in 95% yield. Acidic hydrolysis of enol ether **2.36** in methanol afforded 8-methoxy-3-methyl-2-tetralone **2.37** in 88% yield[44] (Scheme **14**).

In order to meet the requirement of the HOMO-LUMO energy gap for the cycloaddition in scheme **16**, the methoxy group C-8 in the tetralone **2.37** must be replaced by an electron-withdrawing group, such as the acetyl or triflate group. As for demethylation of the methyl aryl ether **2.37**, treatment of the methyl aryl ether **2.37** with 1.1 eq of BBr_3 caused 10% conversion to **2.38**,[45] whereas 1.1 eq of Me_3SiI left the ether **2.37** unaffected[46] (Scheme **14**).

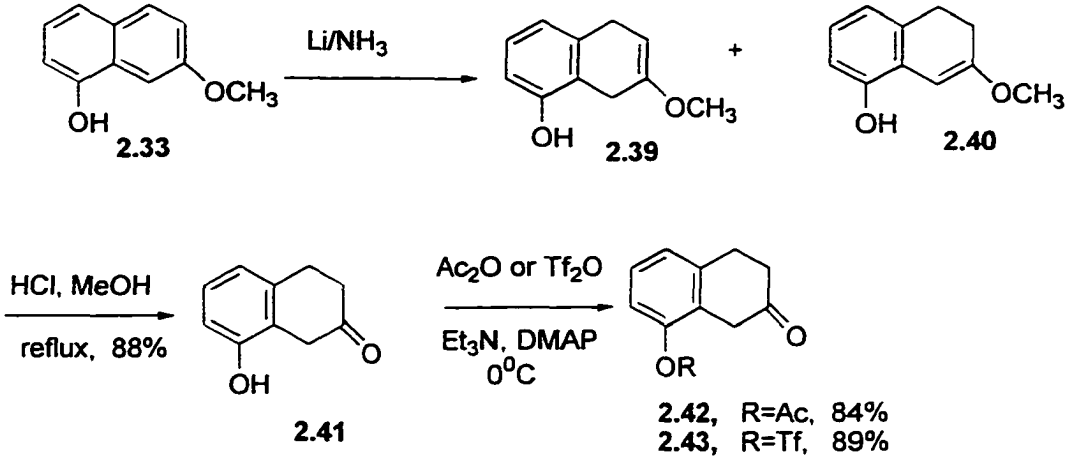
Scheme 14.



Because of the difficulties of the cleavage of the methyl aryl ether **2.37**, we decided to reduce 7-methoxynaphthalen-1-ol **2.33** by Lithium directly. Birch reduction[47] of 7-methoxynaphthalen-1-ol **2.33** afforded the mixture of enol ether **2.39** and **2.40** (ratio: 5:3). Acidic hydrolysis of enol ether **2.39** and **2.40** in methanol afforded tetralone **2.41** in 87% yield. Acetylation of tetralone **2.41** by acetic anhydride or triflic anhydride in

CH_2Cl_2 by means of triethylamine as base and DMAP as catalyst, gave compound **2.42** and **2.43** in 84% and 89% respectively[48] (Scheme **15**).

Scheme **15**.



Treatment of **2.42** and **2.43** with PhthN-S-Cl in CH_2Cl_2 at 0°C gave the phthalimidosulfenyl derivatives **2.44** and **2.45** in quantitative yield (Scheme **16**).

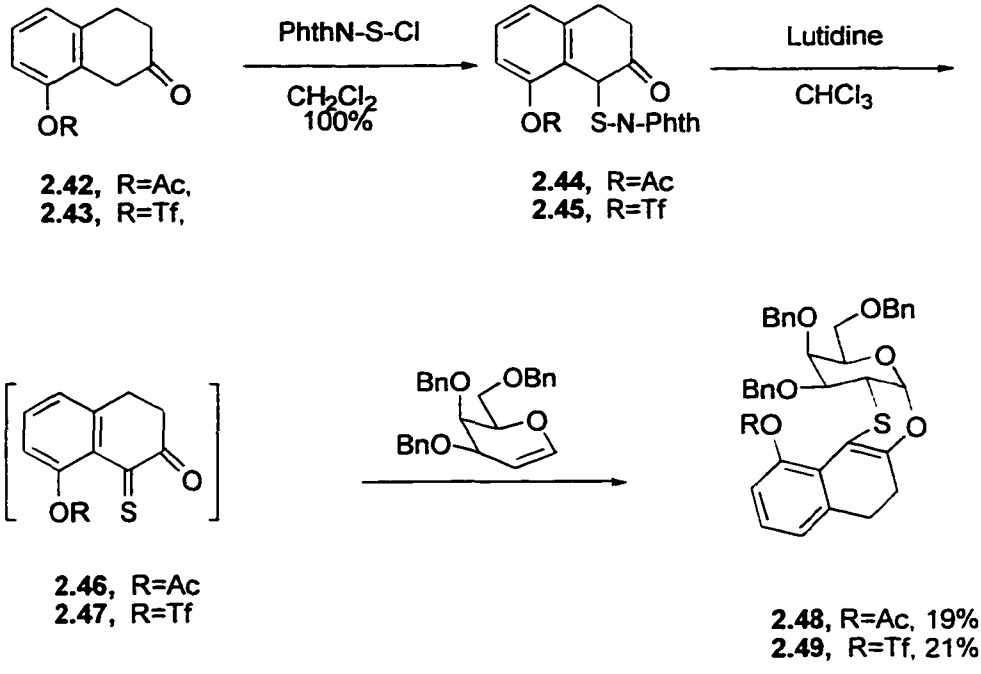
2.3.2. The cycloaddition

In a typical cycloaddition between glycals and the phthalimidosulfenyl precursor to oxothione, lutidine was added to a chloroform solution of glycal and phthalimidosulfenyl derivative **2.44** or **2.45** and the reaction mixture was stirred at room temperature. After the glycal was consumed, the reaction mixture was quenched with ammonium chloride and extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated. Purification of the crude product by a silica gel column chromatography provided the cycloadducts.

Application of the standand cycloaddition method gave the cycloadducts **2.48** and **2.49** (Scheme **16**) in the yield of 19% and 21% respectively. The key chemical shifts of the cycloadducts **2.48** and **2.49** are the anomeric protons at 5.72 ppm (doublet, J=2.4 Hz) and

5.74 ppm (doublet, J=2.7 Hz) respectively. This suggested an axial-equatorial relationship between H-2' and H-1' in both products.

Scheme 16.



2.42, R=Ac,
2.43, R=Tf,

2.44, R=Ac
2.45, R=Tf

2.46, R=Ac
2.47, R=Tf

2.48, R=Ac, 19%
2.49, R=Tf, 21%

2.3.3. Preparaton of 8,9-dihydroxytetrahydroxyanthracen-2-one

A key conclusion from the successful cycloaddition (Scheme **16**) was that heterodienes **2.46** and **2.47** did not aromatize via enolization to form **2.51** (Scheme **17**). Encouraged by these results, we attempted this approach using tricyclic model compound **2.60** (Scheme **19**), which is even closer to the natural aglycone (see compound **2.4** in scheme **4**).

Scheme 17.

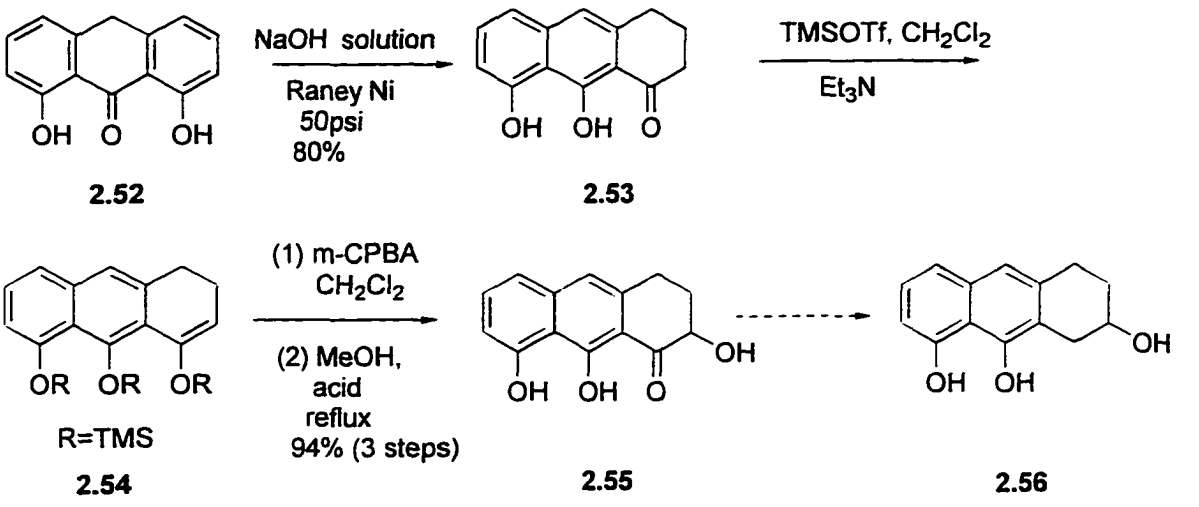
2.46, R=Ac
2.47, R=Tf

2.50

2.51

The tricyclic ketone **2.53** was readily prepared from the commercially available anthralin **2.52** by hydrogenation over Raney Ni in 80% yield. Ketone **2.53** was converted to its trimethylsilyl enol ether **2.54** and then oxidized by m-CPBA in CH_2Cl_2 to give the crude epoxide, which was used directly for the next step. Hydrolysis of the crude epoxide in methanol under the catalyst of citric acid, afforded α-hydroxy ketone **2.55** in 94% for the 3 steps.[49] Attempts to reduce the carbonyl group in α-hydroxy ketone **2.55** by hydrogenation with different kinds of catalysts in ethanol did not give any useful results[50] (Scheme **18**).

Scheme **18**.

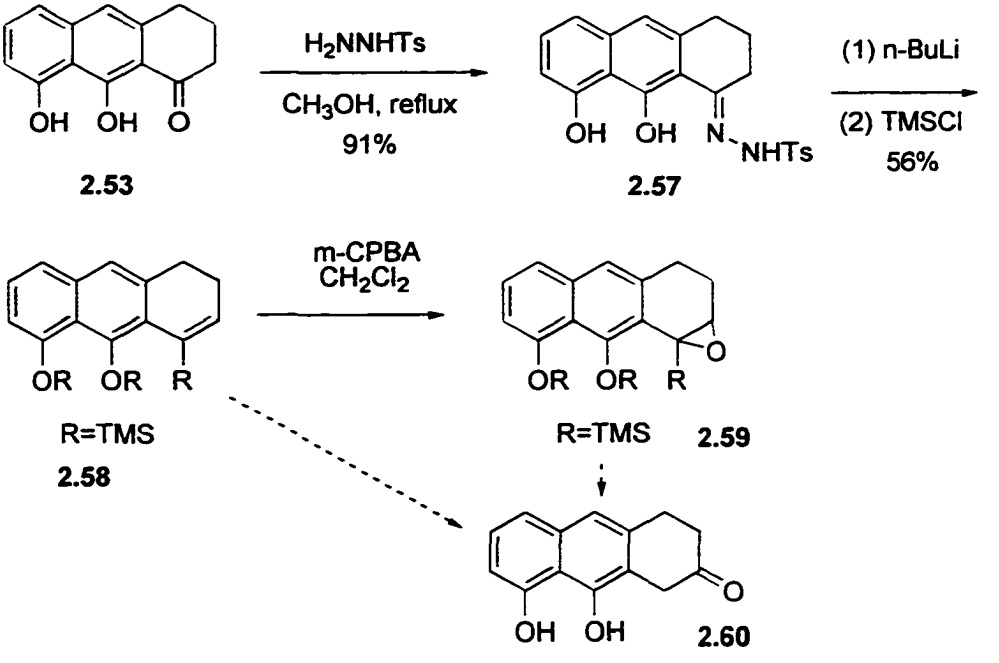


2.3.3.1. Applying vinylsilanes as intermediates

In order to make the 2-tetrahydroanthracene **2.60** (Scheme **19**), we attempted a 1,2-carbonyl transposition of the tricyclic ketone **2.53** by applying the Shapiro reaction.[51] First, the tricyclic ketone **2.53** condensed readily with (p-tolysulfonyl)hydrazine to give tosylhydrazone **2.57** in 91% yield; Then sequential treatment with n-BuLi and TMSCl in anhydrous tetramethylethylenediamine proceeded regiospecifically to afford the more substituted vinylsilane **2.58** in 56% yield. On reaction with mCPBA, the derived epoxide

2.59 was formed. Ring opening with $LiAlH_4$ followed by acidic sodium dichromate oxidation did not give the desired product **2.60**[52] (Scheme **19**).

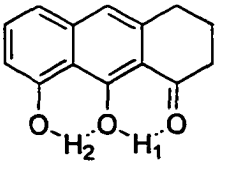
Scheme **19**.



2.3.3.2. Acid-catalyzed rearrangement of epoxides

In order to get alkene **2.63** (Scheme **22**), ketone **2.53** was reduced with different reagents (e.g. $NaBH_4$, and $LiAlH_4$). Unfortunately, no reaction took place in any case.

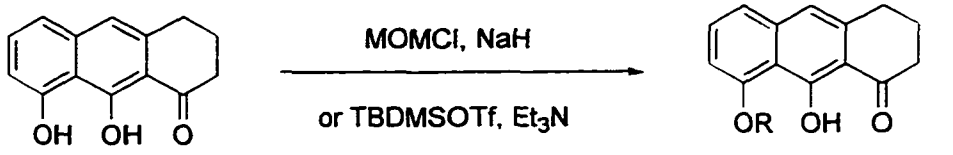
Scheme **20**.



2.53

When we reexamined the structure of the tricyclic ketone **2.53**, we found that there is strong intramolecular hydrogen bonding between H_1 and the oxygen of carbonyl. This was detected by the chemical shift of H_1 which is 16.18 ppm (Scheme **20**). Also trying to protect the free hydroxyl groups by MOM or TBDMS[53], only one of the hydroxyl was protected. After protection of one hydroxyl group, the chemical shift of H_1 shifted to 13.4 ppm (Scheme **21**).

Scheme **21**.

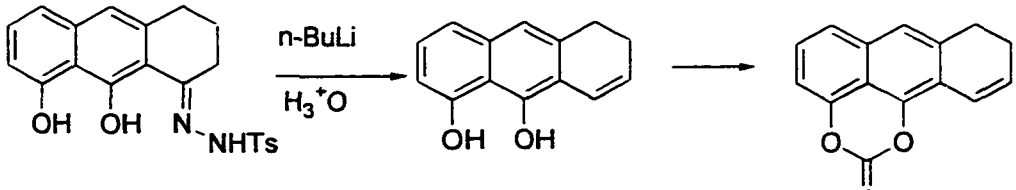


2.53

2.61, R=MOM
2.62, R=TBDMS

In a return to the original Shapiro reaction, the hydrazone **2.57** was treated with n-BuLi in TMEDA at -50°C, then the reaction was quenched by adding aqueous NH_4Cl instead of TMSCl to afford alkene **2.63**. Protection of the hydroxyl group by triphosgene gave carbonate **2.64**,[54] but it was unstable. Some difficulties were met during purification of the compound and the reaction with m-CPBA for the next step (Scheme **22**), and the approach was discontinued.

Scheme **22**.



2.57 **2.63** **2.64**

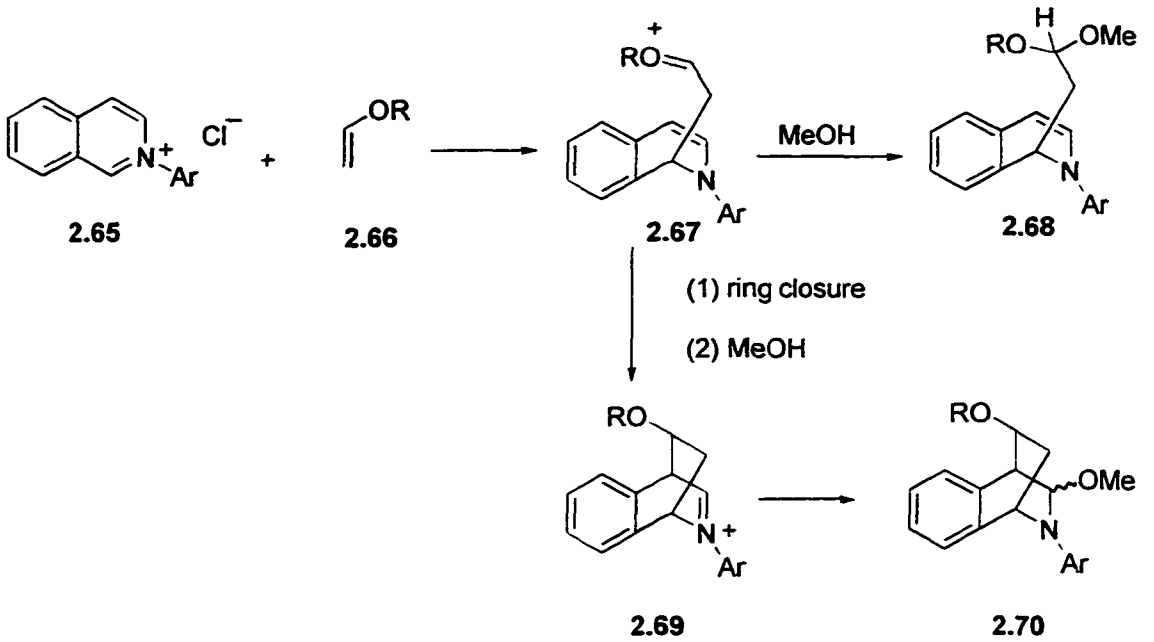
2.3.4. Isoquinoline chemistry approach to 2.60 analogs

In the face of the difficulties of preparing a 2-tetrahydroanthracene such as **2.60** from **2.53** (Scheme **19**), we turned to isoquinoline chemistry.

The Franck group[55] has demonstrated the synthetic and mechanistic aspects of the inverse-electron-demand Diels-Alder reaction of 2-(2,4-dinitrophenyl)isoquinolium chloride **2.65** with vinyl ether **2.66**. The most important finding is the evidence for the mechanism of the cycloaddition reaction being a two step process. The conclusion was based on the isolation and characterization of one-bond products derived from the partitioning of the intermediate oxocarbonium ion via solvent trapping and cycloadditoin.

In every cycloaddition, when the reaction was worked up prior to acid treatment, there could be isolated a one-bond product **2.68**. The proposal of an oxocarbonium ion **2.67** which is the intermediate for both the observed one-bond **2.68** and tricyclic adduct **2.70** explained the observation. In fact, this is the proof that the cycloadditon goes via two steps. Retention of configuration of the dienophile is used as an evidence for a two step process, with the second step being faster than any possible epimerization (Scheme **23**).

Scheme 23.

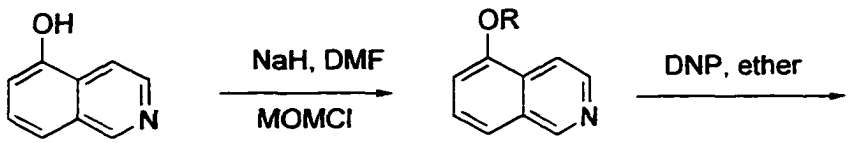


Hydroxyl-protected 5-hydroxyisoqunolines **2.72**, **2.73** and **2.74**[53] were prepared from 5-hydroxyisoquinoline **2.71** by reacting with methoxymethyl chloride, methyl iodide and ethyl carbonate in the yield of 99%, 94%, and 62% respectively. The isoquinolium salt dienes such as, **2.75**, **2.76** and **2.77** were prepared by refluxing an equimolecular mixture of hydroxyl-protected 5-hydroxyisoquinolines **2.72**, **2.73** and **2.74** and 2,4-dinitrochlorobenzene in dry ether for 1-3 days. The salts precipitated out from the reaction mixture. They were filtered and washed with cold ether till the reddish color disappeared. The yellow crystal salts were dried under vacuum (Scheme **24**).

For the typical cycloaddition:[56] the salt was dissolved in a minimum amount of dry methanol and 1-3 equivalents of dienophile was added, followed by the addition of anhydrous $CaCO_3$ (600 mg per each millimole of the substrate). The resulting mixture was stirred at room temperature. The completion of the reaction was monitored by TLC. The suspended $CaCO_3$ was filtered through Celite. The cycloadduct-containing filtrate was concentrated under reduced pressure. Treatment of the crude cycloadducts with

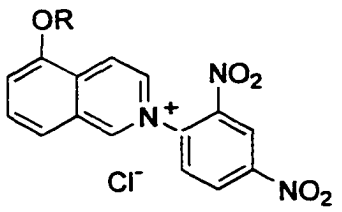
Amberlyst-15 in THF-H_2O afforded an aldehyde, which was then aromatized to a naphthaldehyde via elimination by K_2CO_3 in methanol and water at 65^{0}C.

Scheme **24.**



2.71

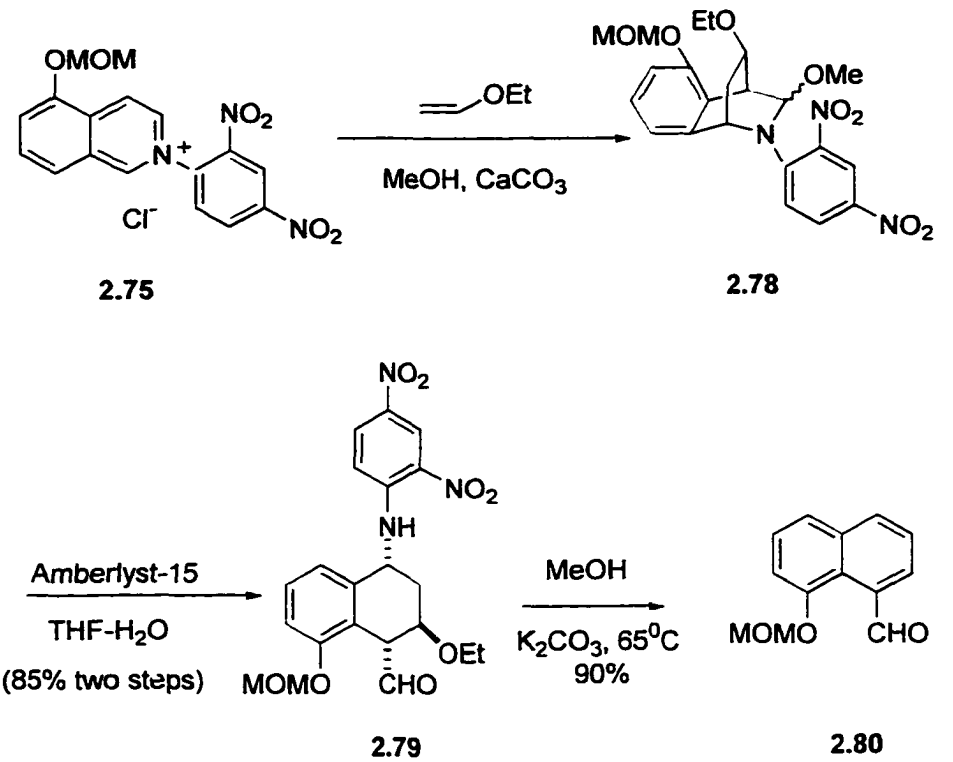
2.72, R=MOM, 99%
2.73, R=CH_3, 94%
2.74, R=$CO_2CH_2CH_3$, 62%



2.75, R=MOM, 77%
2.76, R=CH_3, 82%
2.77, R=$CO_2CH_2CH_3$, 36%

Ethyl vinyl ether was chosen as the first dienophile for the IED reaction. The crude product **2.78** was prepared from the reaction of salt **2.75** and ethyl vinyl ether. Without purification, treatment of it with Amberlyst-15 in THF-H_2O afforded the aldehyde **2.79** in the yield of 85% (two steps). Elimination of ethanol and 2,4-dinitroaniline from aldehyde **2.79** with K_2CO_3 in methanol and water at 65^{0}C gave 1-naphthaldehyde **2.80** as expected in the yield of 90% (Scheme **25**).

Scheme **25.**



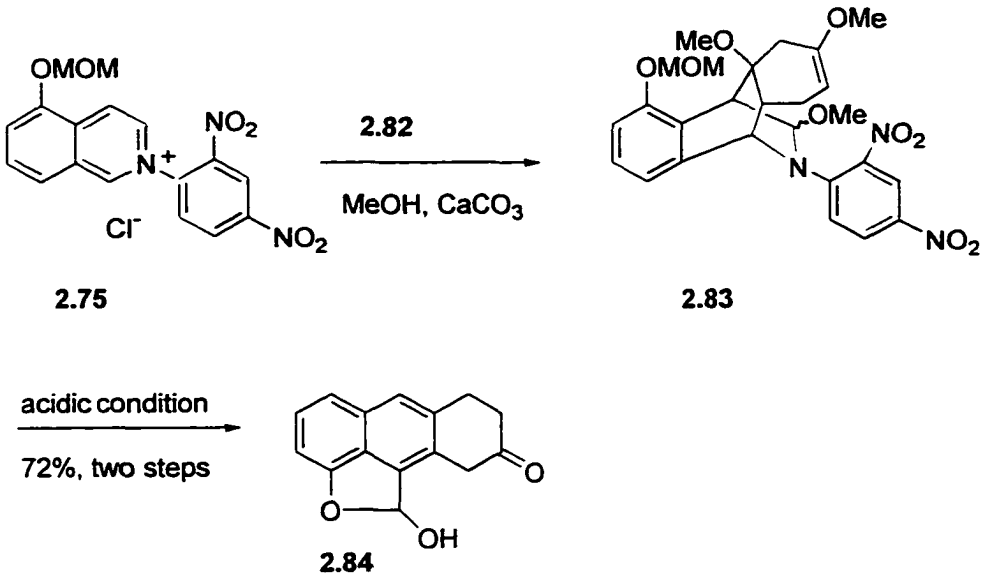
2.75 **2.78** **2.79** **2.80**

Scheme **26.**

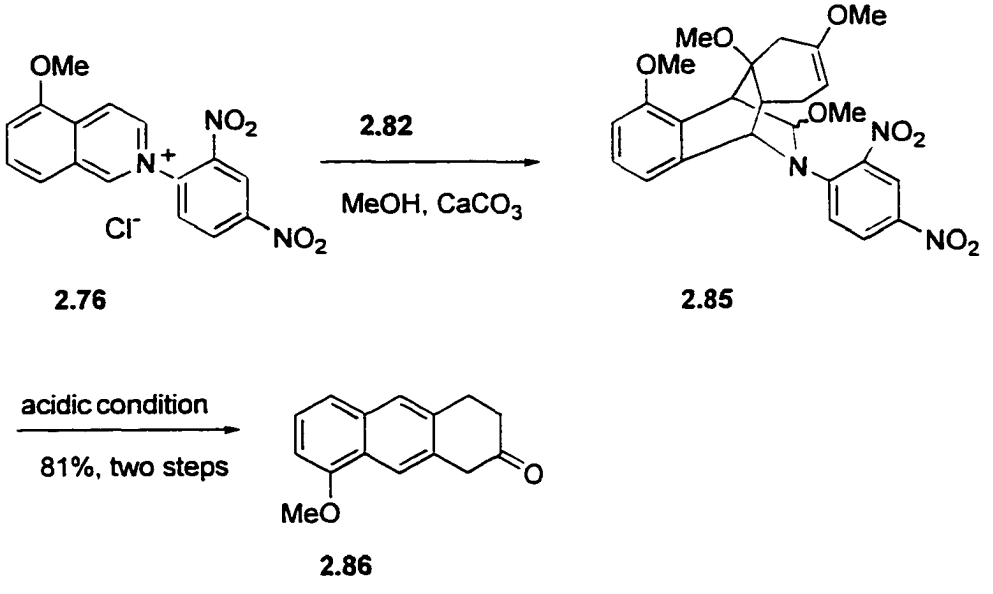
2.81 **2.82**

Cycloaddition of salts **2.75** and **2.76** with dienophile **2.82** which was obtained by Birch reduction of 1,3-dimethoxy benzene[57] (Scheme **26**) gave the crude adducts **2.83** and **2.85**. These were treated with a variety of solvents and acidic catalysts, e.g. CH_3CN-H_2O with concentrated HCl, 3N HCl, 1N HCl and TsOH at 40°C and 60°C; THF-H_2O with Amberlyst-15 or TsOH at 40°C and 60°C; Compounds **2.84** and **2.86** were detected in the yield of 72% and 81% respectively (Scheme **27** and **28**).

Scheme 27.

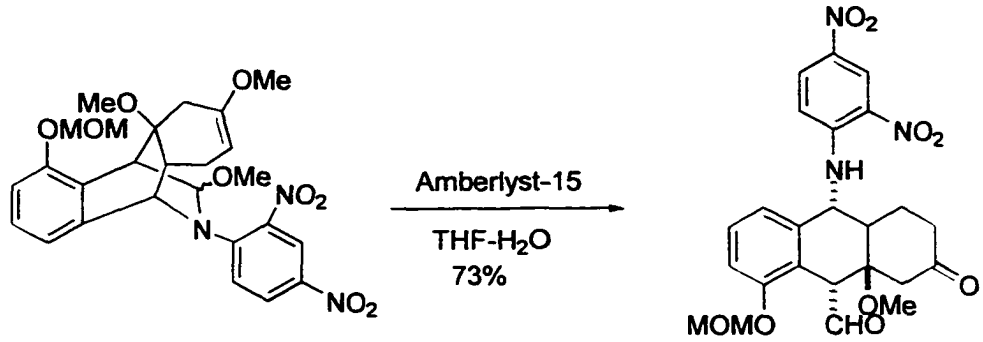


Scheme 28.



When the crude adduct **2.83** was carefully treated with Amberlyst-15 in THF-H_2O at room temperature, ring-opening aldehyde **2.87** was obtained in the yield of 73% (Scheme **29**).

Scheme **29**.

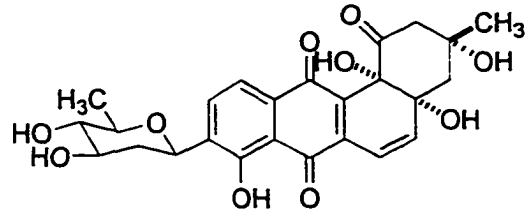


2.83 **2.87**

2.4. Isoquinoline chemistry approach the tetracyclic benz[*a*]anthrance frame in angucycline group antibiotics

Our success in isolating highly functionalized aldehydes (such as **2.87**) led us to prepare a vinyl substituted cycloadduct as a possible precursor to angularly fused systems such as aquayamycin **2.88** (Scheme **30**).

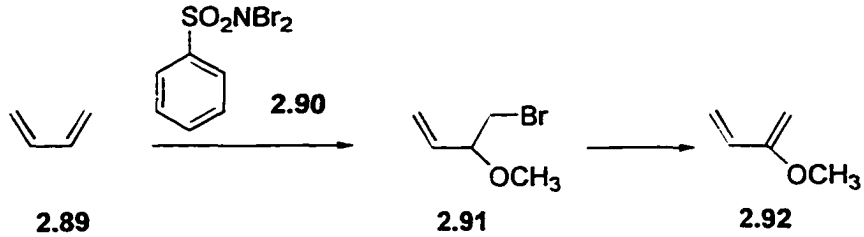
Scheme **30.**



2.88 Aquayamycin

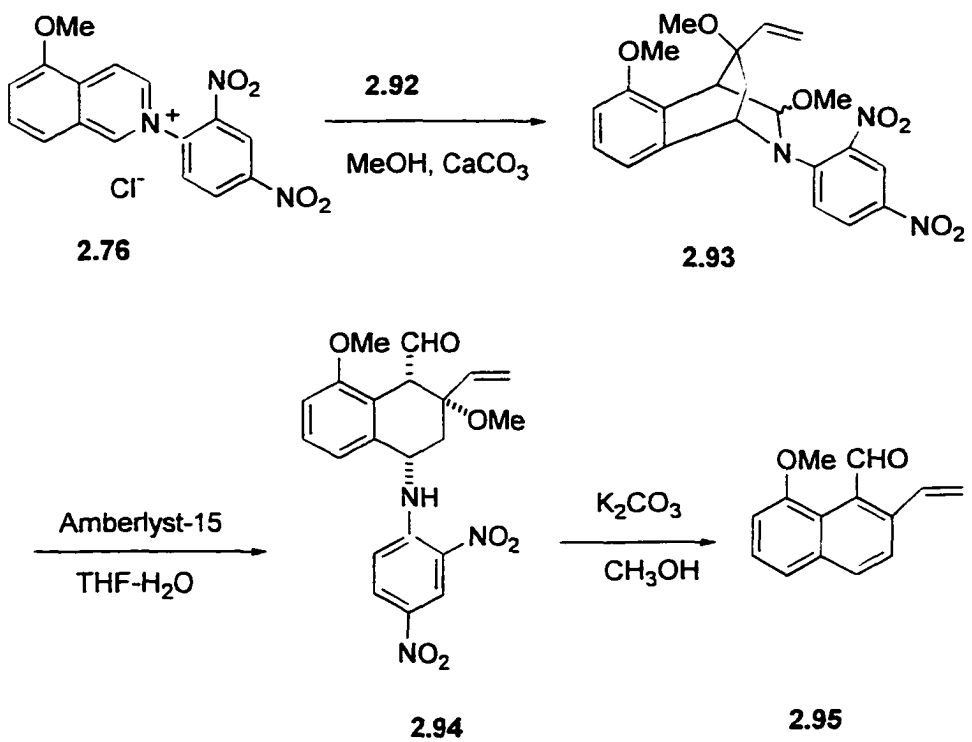
The dienophile 2-methoxy butadiene **2.92** was prepared via bromination of 1,3-butadiene **2.89** with N,N-dibromobenzenesulfonamide **2.90** in methanol at -10^{0}C, followed by elimination under basic condition at 130^{0}C in diethylene glycol.[58] Preparation of N,N-dibromobenzenesulfonamide **2.90** was carried out by reaction of benzenesulfonamide with bromine by using $NaHCO_3$ as base[59] (Scheme **31**).

Scheme 31.



Tetralin adduct **2.93** was prepared using the IED reaction of salt **2.76** with 2-methoxy-1,4-butadiene **2.92**. Treatment of the crude product **2.93** with Amberlyst-15 in THF-H_2O gave aldehyde **2.94**. Aldehyde **2.95** can be obtained through elimination of the aldehyde **2.94** under basic conditions in the yield of 73% (three steps) (Scheme **32**).

Scheme 32.



In fact, both **2.94** and **2.95** are important intermediates for the synthesis of angucycline group antibiotics[60] (Scheme **32**).

Conclusion

Based on the new concept for the glycosyl transfer via inverse electron demand cycloaddition, the model study described above demonstrated a promising avenue toward the 2-deoxy glycosides which occurs in aureolic acids. We observed excellent diasteroselectivity, and we showed that oxothiones have a sufficient lifetime for the cycloaddition since no aromatization products were detected.

Part 2.

Chapter 3

Evaluation of the Synthesis of N-Glycopeptides

Introduction

The construction of glycopeptides continues to represent a challenging goal in organic synthesis.[61] Glycopeptides are partial structures of the connecting regions of glycoproteins. Glycoproteins, which contain covalently bonded carbohydrate, are ubiquitous in nature, where they fulfill vital functions as enzymes, antibodies, toxins, and other components. Glycoproteins are not only widely distributed but also decisive factors in biological selectivity, especially in biological recognition.[62] Moreover, glycopeptides have proved to be an important source of antibiotics.[63] Some of the specific functions of glycoproteins are mediated by their oligosaccharide chains, which show an enormous range of structures. Many types of oligosaccharide chains can be attached covalently to proteins. Proteins of all types (e.g., enzymes, hormones, structure proteins, and transport proteins) may be glycosylated.

The presence of one or more oligosaccharide chains on a protein can alter both its physical and biological properties. Various physical properties[64] that may be altered include overall size, solubility, heat stability, conformation, tendency to aggregate, and resistance to protease. Biological properties that may be altered include the rate of secretion, half-time in circulation, activity, and immunogenicity.[65] In a few cases, specific roles of oligosaccharide chains of glycoproteins have been identified. Ashwell et al.[66] have found that the copper-transport glycoprotein, ceruloplasmin, has a biological half-life of 54 h in rabbit serum. However, after removing the terminal N-acetylneuraminic acid (sialic acid) residue from the oligosaccharide chain of

ceruloplasmin with neuraminidase and thereby uncovering a galactose unit, they found that the resulting asialoceruloplasmin had a half-time of less than 5 min. in rabbit serum. They were able to show that this dramatic biological effect is caused by the recognition of the now terminal galactose residue by a specific receptor in the liver cells of the rabbit, a selection mechanism that holds for many analogous glycoproteins and for mammals in general. This galactose-specific receptor in the hepatocyte membrane, which acts as a lectin, and is itself a glycoprotein.[67]

The carbohydrate side chain of a glycoprotein also serves as a recognition signal for the directed transport of lysosomal enzymes into the lysosomes of fibroblasts. In this case, terminal mannose-6-phosphate residues are recognized by specific receptors in the membrane which are glycoproteins.[68]

The carbohydrate side chain of a glycoprotein plays roles in many biological processes, including the clearance of certain proteins from the plasma, the spread of cancer cells and certain aspects of inflammation.[69]

3.1. There are three major classes of glycoproteins

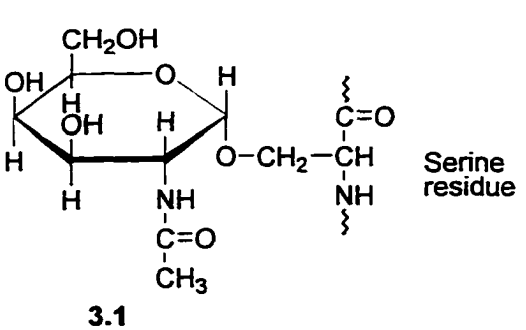
Despite the large number of natural glycoproteins, the types of covalent bonds between the protein and the saccharide part show relatively little variation.[64] Based on the nature of the linkage between their polypeptides and the carbohydrates, glycoproteins can be divided into three major classes: O-linked glycoproteins **3.1**, N-linked glycoproteins **3.2** (Figure 8), and phosphatidylinositol-glycan-linked glycoproteins.

In most O-linked glycoproteins, a GalNAc residue is attached via an O-glycosidic linkage to a serine or threonine residue. The α-O-glycosidic linkage between N-acetylgalactosamine and serine or threonine was first found in the mucous glycoproteins (mucins). Mucins, major members of the O-linked class of glycoproteins, are generally of high molecular weight and often contain as much as 80% carbohydrate, in many oligosaccharide chains. They usually contain high amounts of NeuNAc and sulfate attached to specific sugars. The α-O-glycosidic linkage is characteristic of many other

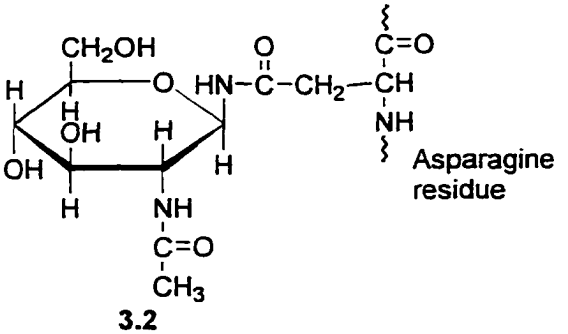
serum and membrane glycoproteins,[70] including the blood-group glycoproteins, human glycoproteins, epiglycanin, and the glycoproteins of the tumor-associated TN and T antigens.

The second important type of connection between the carbohydrate and peptide portion of glycoproteins is the N-glycosidic linkage. In N-linked glycoproteins, a GlcNAc residue is linked to an asparagine residue via an N-glycosidic linkage. The structures of the N-linked carbohydrates fall into three basic types: high-mannose, complex, and hybrid carbohydrates.[71] Each of these three types contains a common core pentasaccharide ($GlcNAc_2Man_3$), attached by its innermost GlcNAc residue via β-N-glycosyl linkage to an asparagine residue. Furthermore, the N-glycoproteins are characterized by a common sequence in the connecting region: the next but one C-terminal amino acid following the N-glycosylated asparagine is always serine or threonine. Until recently it was assumed that in nature the type of β-N-glycosidic linkage occurred exclusively. Nakanishi et al.,[72] however, have shown that a nephritogenic glycopeptide has been isolated from the glomerular basal membrane of rats in which an α-N-glycosidic bond exists between glucose and the peptide part. Glucosamine has been suggested as the binding partner.[73]

Figure 8. Comparison of an O-glycosidic linkage and an N-glycosidic linkage. (1) N-Acetylgalactosamine-serine linkage, the major O-glycosidic linkage found in glycoproteins. (2) N-Acetylglucosamine-asparagine linkage which characterizes N-linked glycoproteins. The O-glycosidic linkage is α, whereas the N-glycosidic linkage is β.



3.1



3.2

The third major class of glycoproteins includes proteins linked to surface membrane via phosphatidylinositol-glycan structures,[64] also referred to as glycosyl phosphatidylinositol (GPI) membrane anchors, or "sticky feet". These glycoproteins,

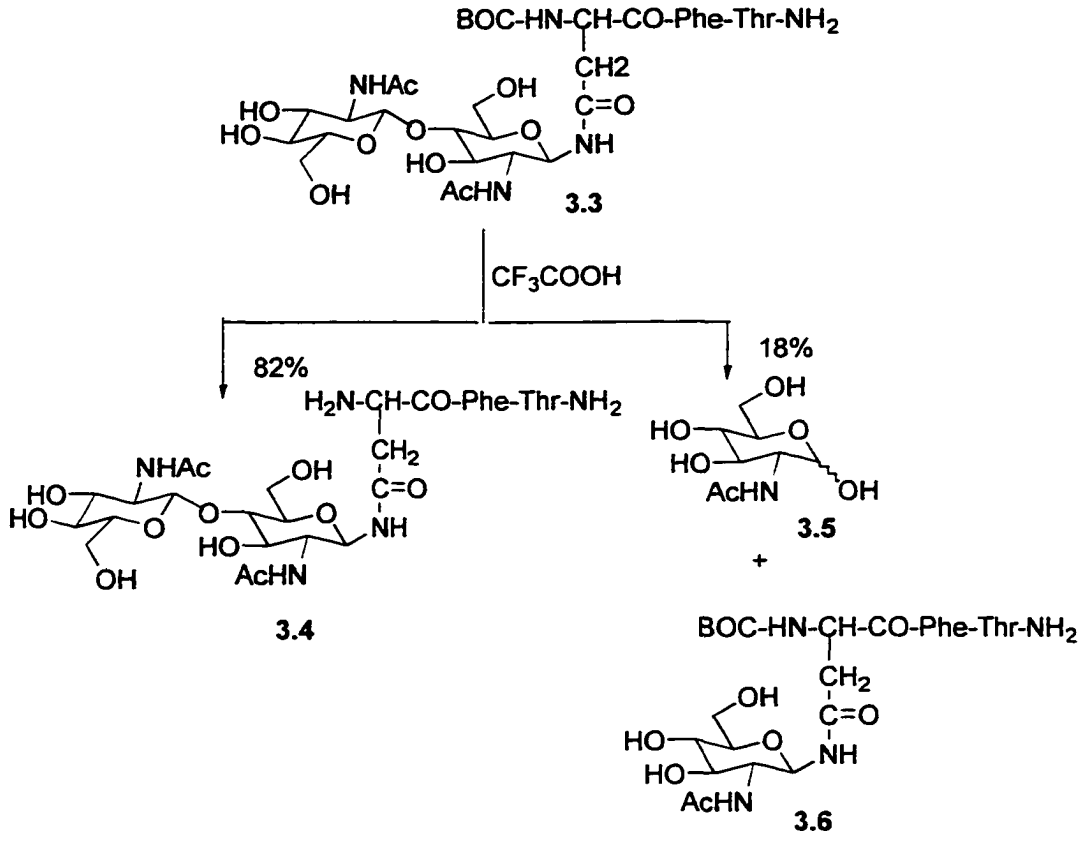
recognized quite recently, have been identified only in eukaryotic organisms and include certain cell-adhesion molecules and some enzymes.

Members of the O- and N-linked classes of glycoproteins are found in many locations, such as, in cell membranes and in blood plasma, whereas members of phosphatidylinositol-glycan-linked glycoproteins appear to be confined to the extra cellular surface of plasma membranes. An individual glycoprotein may contain both O-linked and N-linked oligosaccharides; For instance, glycophorin A, a major constituent of the membrane of human red blood cells, contains 1 N-linked and 15 O-linked oligosaccharide chains. The length of the oligosaccharide chains among O-and N-linked glycoproteins varies, in some cases, the number of sugars can be 30 or more.

3.2. The lability of glycosidic linkage

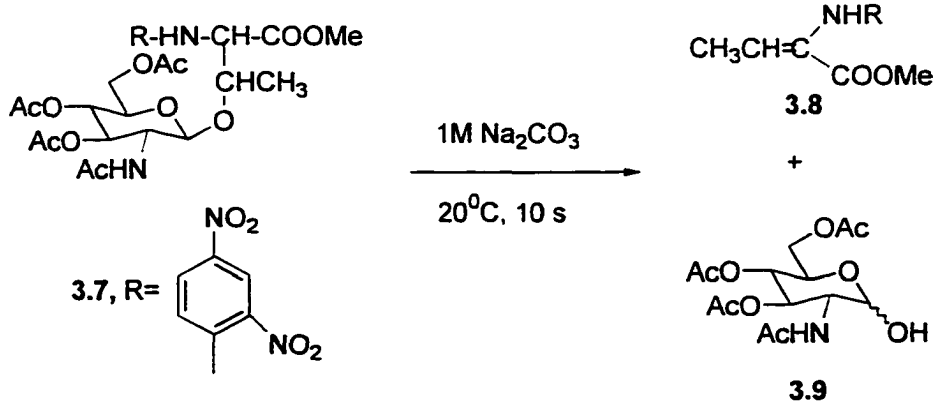
The glycosidic bond of the glycopeptides, being an acetal-like bond, is always more or less acid-sensitive. The most acid-stable glycosidic bonds are the N-glycosides and the glycosyl derivatives of δ-hydroxylysine.[74] More recent work showed that the lability of the O-glycosidic bond appears to depend on the structure of the glycopeptide. Sinaÿ et al.[75] were able to remove the t-BOC of O-glycopeptides selectively with trifluoroacetic acid without cleavage of the glycosidic bond. However, weakly nucleophilic trifluoroacetic acid can also cleave the glycosidic linkage, e.g., in the chitobiosyl tripeptide **3.3**. Together with the desired **3.4**, which represents a partial structure of the human complement factor B, **3.5** and **3.6**, the products of cleavage, were obtained in a ratio of 2:9[76] (Scheme **33**). Analogues of **3.6** with acetyl-protected carbohydrate portions were not attacked by trifluoroacetic acid at that glycosidic bond (Scheme **33**). These different results show clearly that the acidic hydrolysis of protective groups in glycopeptide synthesis should be checked in each individual case.

Scheme 33.



The rate of the β-elimination to α-aminoacrylic acid derivatives, such as **3.8**, depends on the structure of the glycoconjugate and especially on the substituents on the amino and carbonyl functions of the amino-acid portion. Esters and amides undergo elimination at room temperature at pH 9[77] (Scheme **34**).

Scheme 34.



The base lability and the potential acid lability of the glycopeptides make it necessary, in the synthesis of these compounds, to use protective groups that can be removed under mild and if possible, neutral conditions.

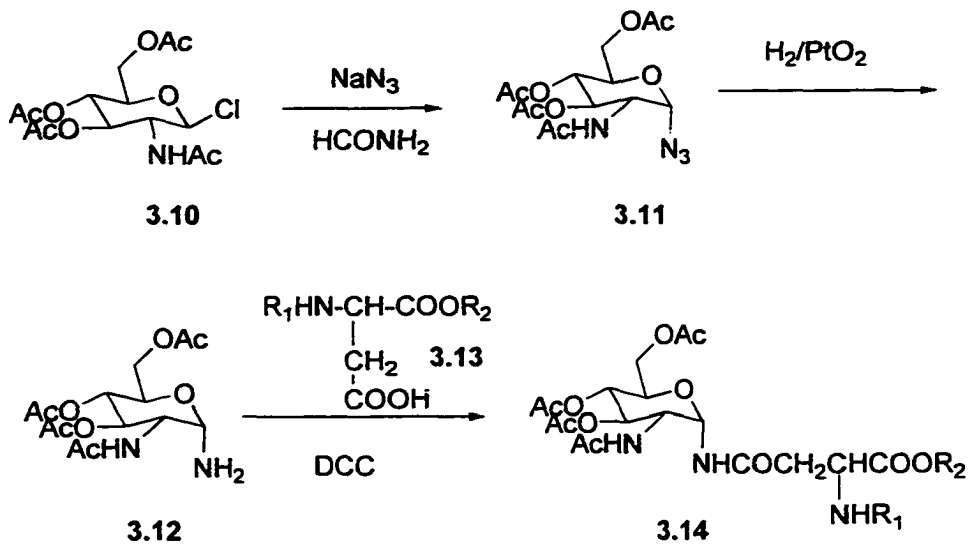
3.3. Comparison of glycopeptide and peptide synthesis

In comparison with peptide synthesis, glycopeptide synthesis requires the protection of many more functional groups, reversibly and with maximum selectivity. More important in the compounds is the presence of the glycosidic linkage, which must both be formed stereoselectively and be retained unchanged during the course of the synthesis.[78]

3.4. N-Glycopeptide synthesis

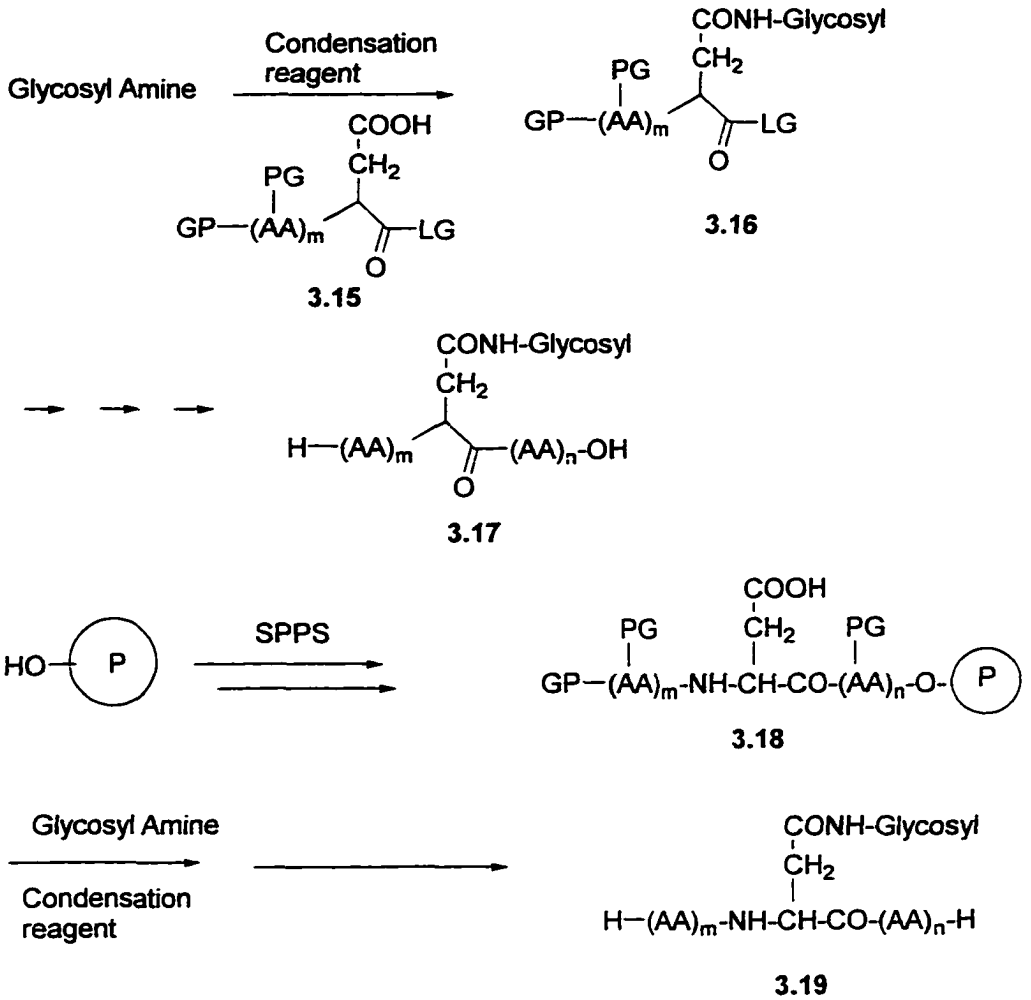
With the increased understanding of the biological functions of glycoproteins as recognition signals for various phenomena, the state of art for synthesis of glycopeptides and glycoproteins has improved dramatically within the last decade.[79] Targeted synthesis of glycopeptides requires stereoselective formation of the glycosidic bonds between the carbohydrate and the peptide parts. The standard chemical approach proceeds via stereoselective preparation of glycosyl azide **3.11**, then reduction to a sensitive glycosylamine **3.12** and finally to amidation **3.14**.[80] However, in practice the reduction of glycosyl azide **3.11** leads to α and β mixtures of glycosylamines **3.12** (Scheme **35**).

Scheme 35. The standard chemical approach to the synthesis of glycopepetides



The assembly of the glycopeptides can be performed either by stepwise elongation of the peptides or by convergent fragment condensation in solution or on a solid phase as illustrated in figure 9. The carbohydrate may be introduced at the end of the synthesis by selective N-glycosylation or sequentially as a glycosylated amino acid building block. Although the convergent fragment condensation approach may be the best choice with biologically isolated and very rare complex-type glycosylamines for optimal formation of N-linked glycopeptide, where the key reaction is relatively easy formation of an amide bond, it is not the best choice for the more difficult generation of O-glycosidic bonds. Here the nature of the peptide and the reaction conditions needed for a successful outcome are often incompatible. Furthermore there are problems with regioselectivity and anomeric selectivity. On the contrary, the stepwise strategy, in which the selectivity problem is solved before peptide assembly, is much more versatile and general and has been successfully employed for the synthesis of a large variety of both N- and O-linked glycopeptides.

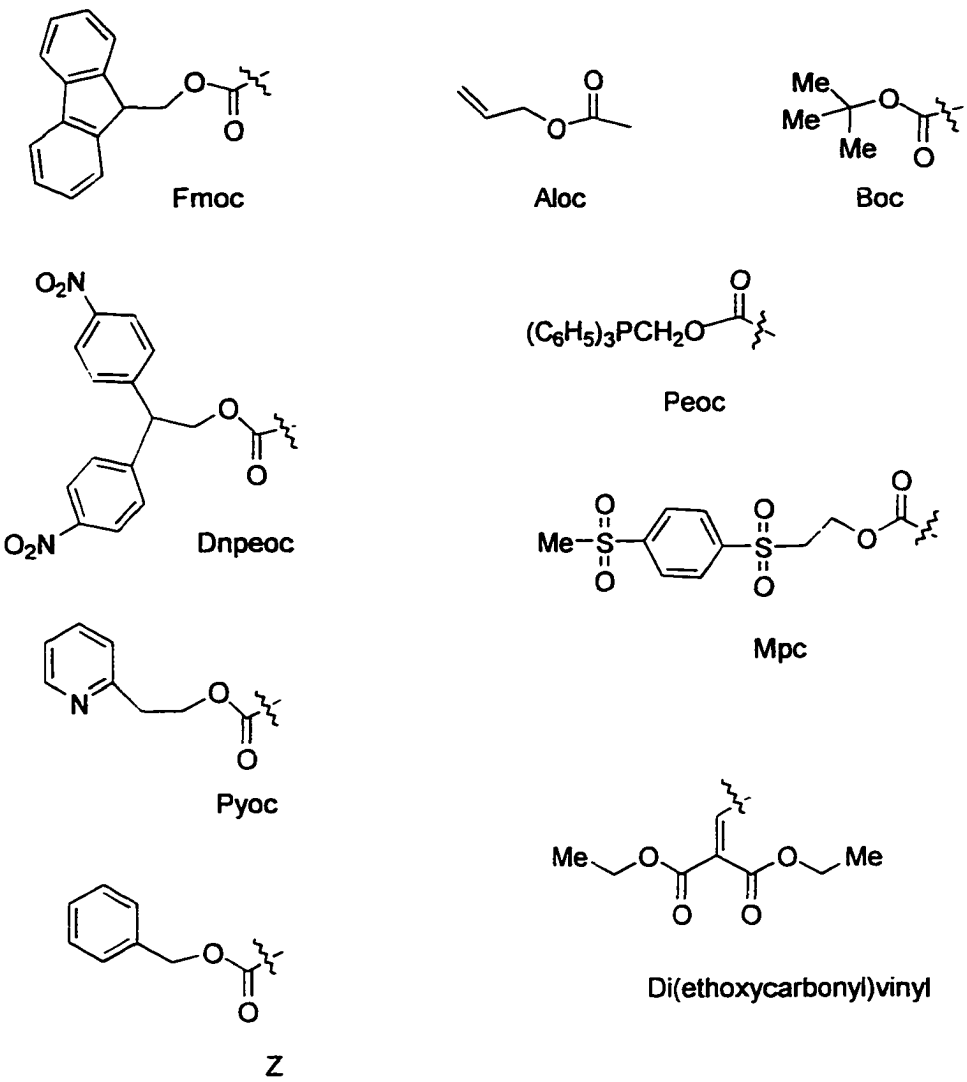
Figure 9[81], Two different general approaches to the synthesis of glycopeptides. SPPS, solid-phase peptide synthesis; P, polymer; AA, amino acid; PG, protecting group; LG, leaving group.



3.4.1. Stepwise approach to N-glycopeptides

Synthesis of N-glycopeptides has been carried out most often by stepwise approach,[82] in which glycosyl amine is coupled to a suitably-protected Asp derivative **3.15** to give an Asp(Sug) derivative **3.16**, which is then deprotected and elongated to give the desired glycopeptides **3.17** (Figure 9).

Figure 10. Most used protecting groups used for amino protection in glycopeptide synthesis



Most of the stepwise approach methods have been performed by solid phase techniques[83] where it is important that the building blocks can be easily and selectively converted into a C-terminal, highly active derivative for coupling on the solid phase. N-protecting groups, such as the 2-triphenylphosphonioethoxycarbonyl (Peoc) group,[84] can be removed from the amino group even under very mild condition and have allowed the targeted synthesis of N-glycopeptides when combined with either the C-terminal benzyl or the tert-butyl group. Owing to the high stability of the Peoc group toward acids, the Peoc amino acid chlorides, which are stable at room temperature, can be used for chain

extension. The neutral Fmoc protective group is somewhat less labile than the Peoc residue.

Condensation reagents used in glycopeptide synthesis[81] are presented in figure 11. These reagents form very reactive mixed anhydride intermediates and it is important to be aware of the possible side reactions, in particular when they are used in difficult and slow coupling with glycosylamino acid derivatives and in fragment condensations. The prevailing use of these reagents may be due to the ease of purification of the product.

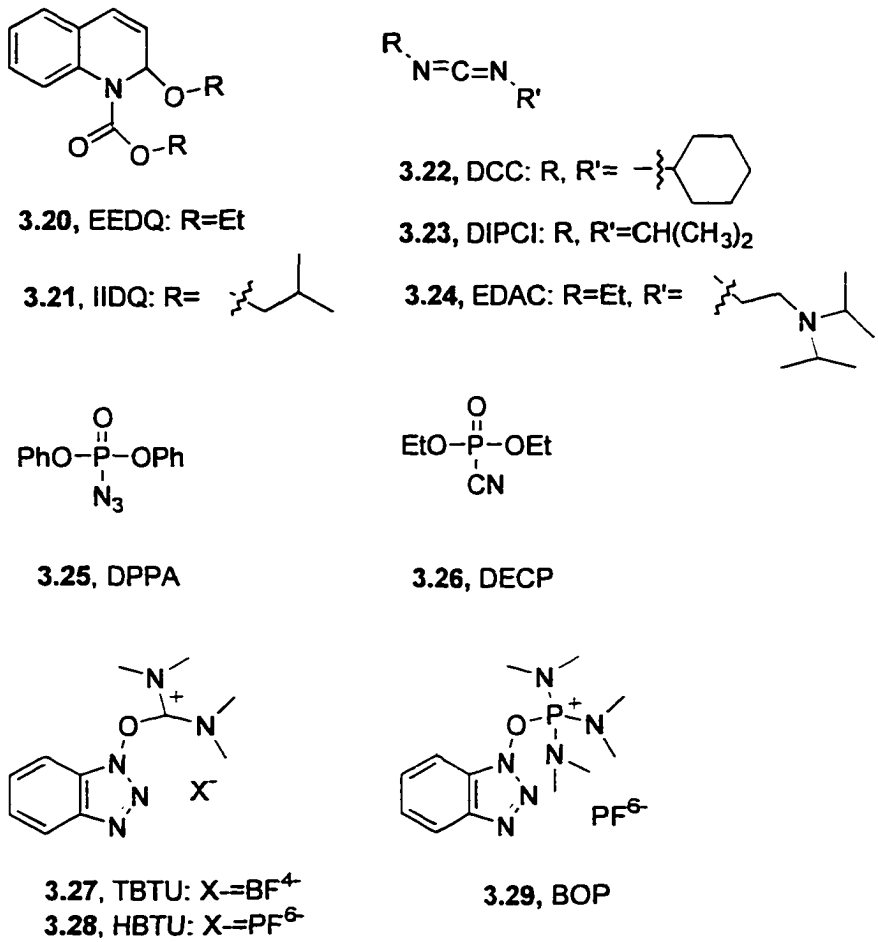
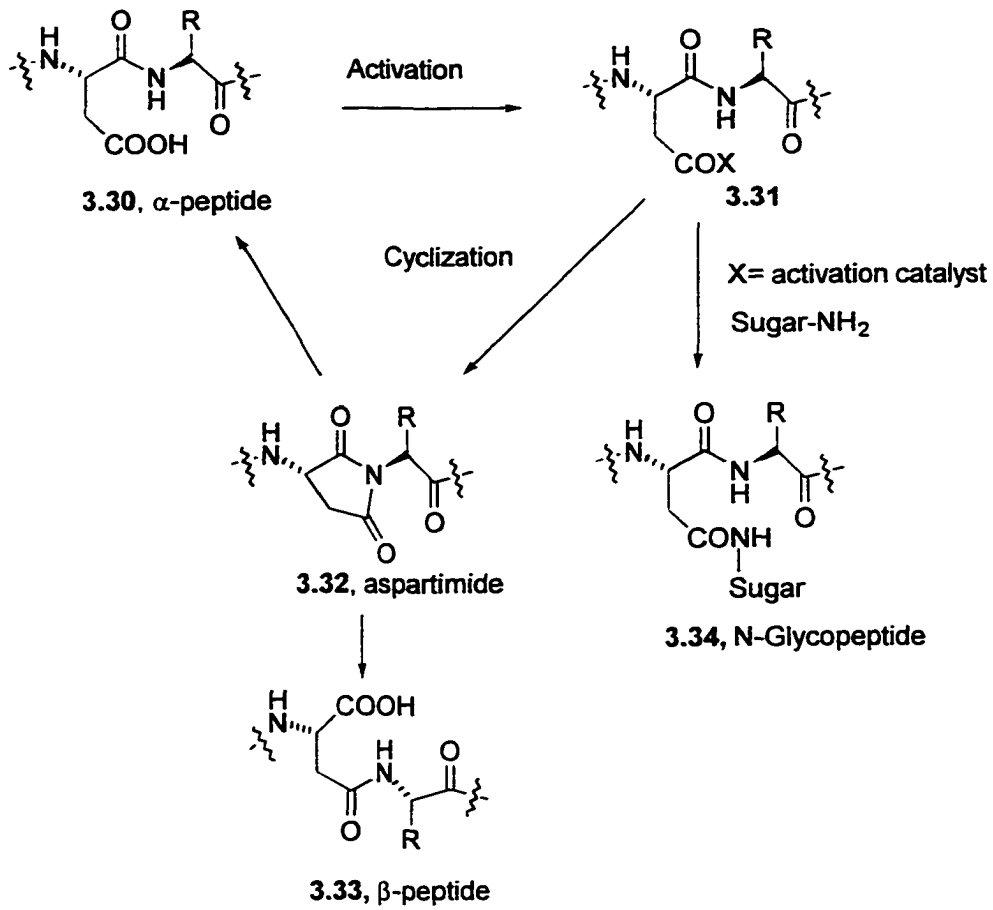


Figure 11. Reagents that have been used as condensation reagents in glycopeptide synthesis. Most popular are N-ethoxylcarbonyl-2-ethoxyl-1,2-dihydroquinoline [EEDQ], N,N'-dicyclohexylcarbodiimide [DCC], and in situ coupling reagents 2-[1H-benzotriazo-1-yl]-1,1,3,3-tetramethyluronium tetrafluoroborate [TBTU] and benzotriazol-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate [BOP].

3.4.2. Convergent approach N-glycopeptides

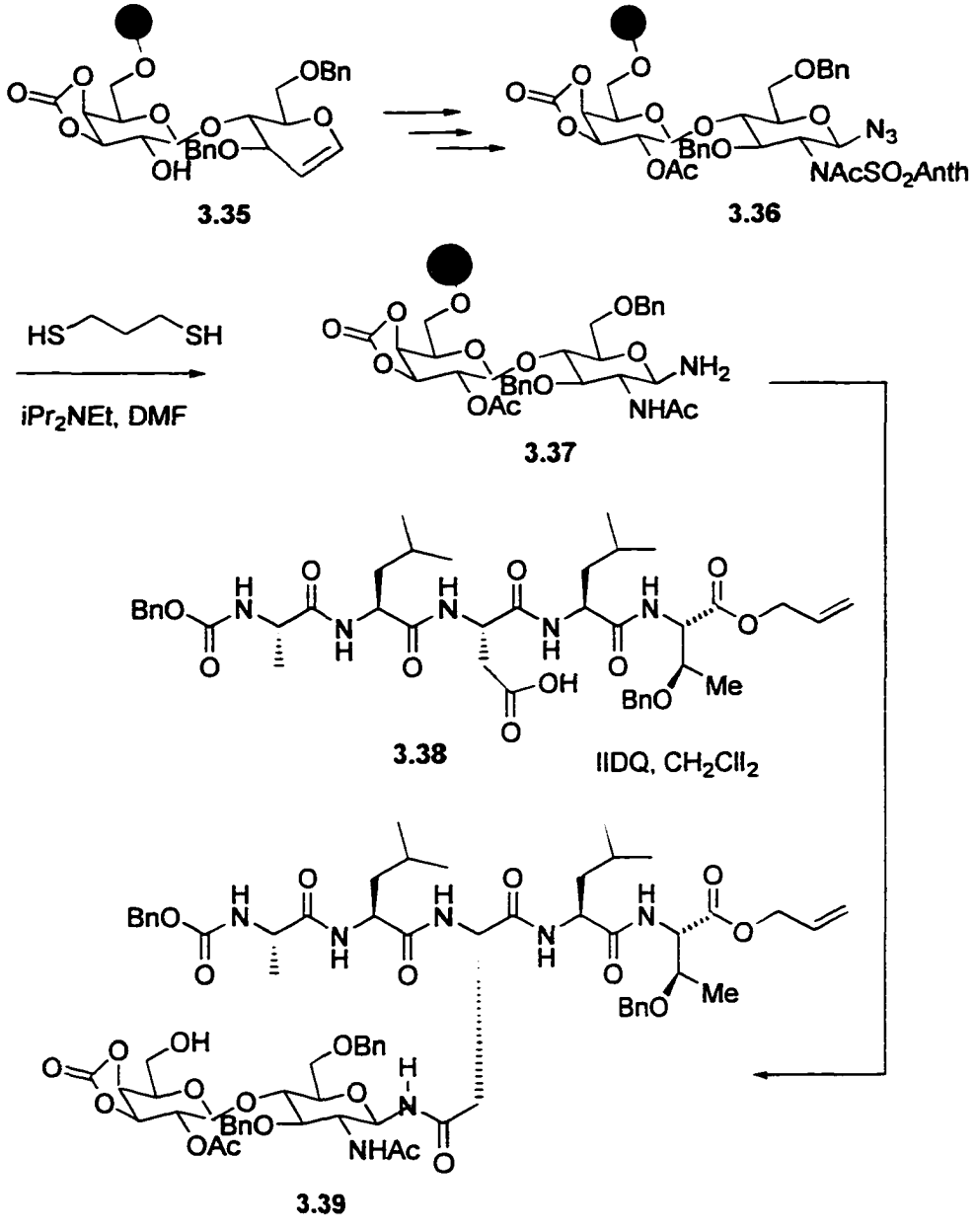
Lansbury[85] and Danishefshy[86] have demonstrated the feasibility of accomplishing a convergent union of carbohydrate and peptide domains based on the coupling of a glycosylamine **3.37** to a fully protected peptide containing an active aspartic acid side-chain either **3.38** in solution or on a solid-phase (scheme 37). An orthogonal side-chain protected group compatible with the fluoren-9-ylmethoxycarbonyl (Fmoc) methodology was required during peptide assembly for the aspartyl β-carboxy group. The protecting group was selectively removed to obtain the free β-carboxy group which could be activated and subsequently coupled with a simple glycosylamine to give the desired N-glycopeptide. The major problem[85] which has not been solved efficiently yet is the intramolecular aspartimide **3.32** formation with the C-terminal to a small residue like glycine or alanine. This side-reaction competes with glycosidation and partially limits the efficacy of the convergent approach to very small glycan structures (scheme **36**).

Scheme 36. Aspartimide formation during convergent N-glycopeptide synthesis. This side-reaction is dependent on the chemical structure of the adlacent amino acid in the C-terminal direction. For large oligosaccharides, aspartimide formation is predominant.



The advantage of the convergent approach is that it allows the synthesis of a series of glycopeptides containing different oligosaccharides, without the need to resynthesize the peptide for each individual case.

Scheme 37. Danishefsky's convergent synthesis of N-linked glycopeptide on a solid support

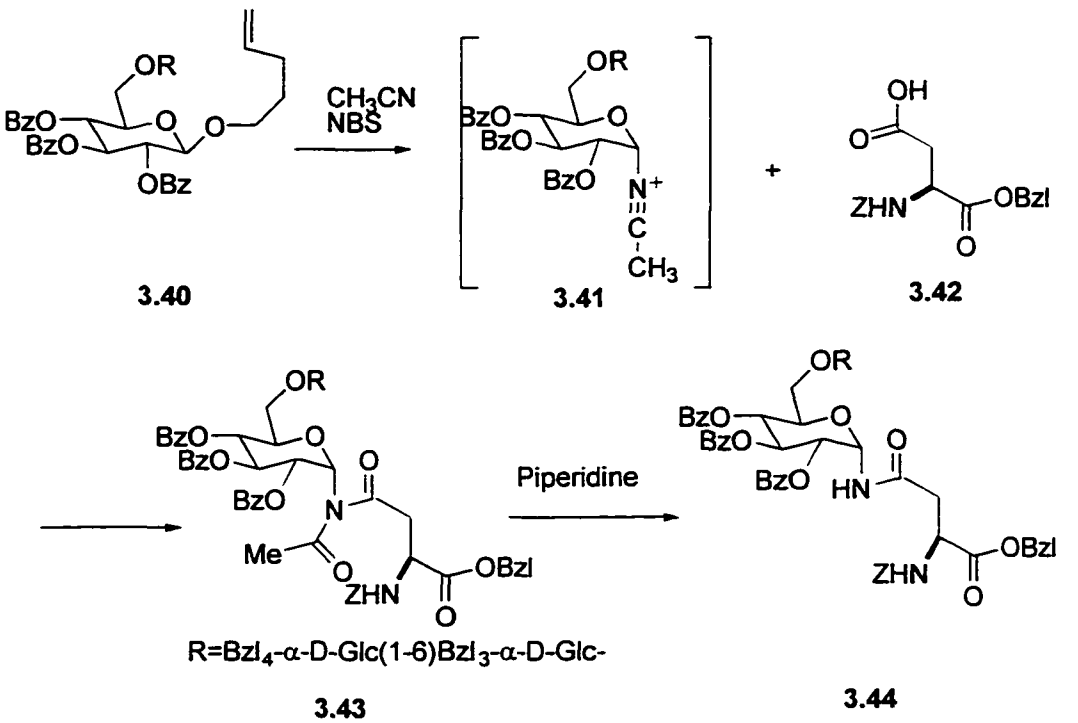


3.4.3. Ritter reaction approach to N-glycopeptides

One exception is the modified Ritter reaction described by Fraser-Reid.[87] During activation of pentenyl glycosides **3.40** with N-bromosuccinimide (NBS) in acetonitrile, the kinetically formed α-acetonitrilium ion **3.41** may be trapped by the presence of a carboxylic acid **3.42**. The intermediate rearranges and loses an acetyl group originating

from the acetonitrile on treatment with piperidine (Scheme **38**). This method has been improved and perbenzylated Z-Asn[α-D-Glc(1-6)β-D-Glc(1-6)α-D-Glc]OBz] was obtained in 74% yield by NBS/trifluoromethanesulfonic acid (TfOH) activation of the ethyl thioglycosides in propionitrile at low temperature.[88]

Scheme **38.** Approaching to α-N-linked glycopeptide via Ritter reaction

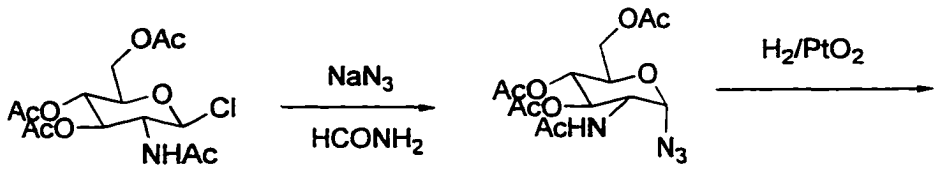


3.5. Synthesis of glycosylamines

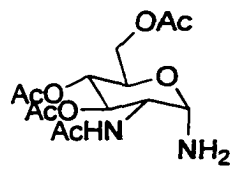
Efficient introduction of an anomeric amino sugar has long been an unsolved problem in glycopeptide synthesis.[89] In the preparation of asparagine carrying the α-linkage glucose present in the rat basement membrane, the α-glycosyl azide **3.11** was reduced by sodium borohydride or hydrogen sulfide or by catalytic hydrogenation over platinum oxide or Lindlar's catalyst;[90] The latter gives the best yield of the α-glycosylamine **3.12** in the presence of triethylamine (Scheme **39**). In order to get β-glycosylamine, protected glycosylamines have been prepared by the catalytic hydrogenation of β-glycosyl azides

which were derived from a glycosyl halide. For the conversion of the glycosyl halide into the β-glycosyl azides.[91] sodium azide in formamide is more suitable than silver azide, which was formerly used exclusively. In the more complex chitobiose series, on the other hand, this method was unsuccessful. The unpleasant silver azide, could be replaced, however, by a method involving phase-transfer catalysis with sodium azide in chloroform/water. In contrast to the reduction of other carbohydrate azides, the hydrogenation of β-glycosyl azides in the N-acetylglucosamine series has only been satisfactorily accomplished with platinum catalysts. It is accompanied by the formation of bisglycosamine as by-products.

Scheme **39.**



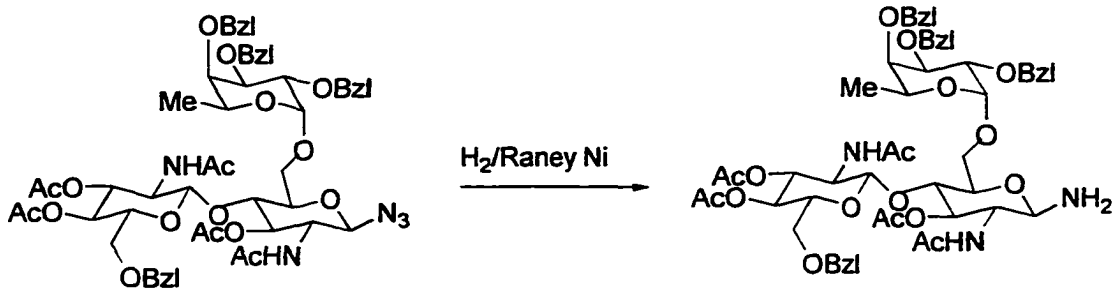
3.10 **3.11**



3.12

Kunz[62] has showed that this hydrogenation also proceeds very well with Raney Ni. This method has the advantage that benzylic protecting groups are not attacked. In this way, the selective reduction of the azido function in the complex, fully protected trisaccharide **3.45** was achieved with the nearly quantitative formation of the amine **3.46** (Scheme **40**). A new method for the synthesis of 2-deoxy-2-tosylamidoglucosyl azides from D-glucal derivatives has been described.[92]

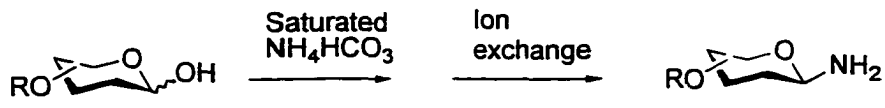
Scheme **40.**



3.45 **3.46**

The introduction of an amino group at the reducing end of an oligosaccharides may also be carried out by equilibration of the nonprotected carbohydrate with aqueous or methanolic solutions containing ammonia in one form or another. The ammonium bicarbonate method,[93] in which the free sugar **3.47** is treated with a saturated solution of ammonium hydrogen carbonate in water with adjustment to pH 8.5 with ammonia at 37^{0}C can afford 40-80% of the glycosylamine **3.48**. The reaction is, however, not clean and often diglycosylamines are present in the crude product. Pure compounds **3.48** can be obtained by cumbersome ion-exchange chromatography (Scheme **41**).

Scheme **41**. Formation of glycosylamines from the reducing oligosaccharides



3.47 **3.48**

Chapter 4

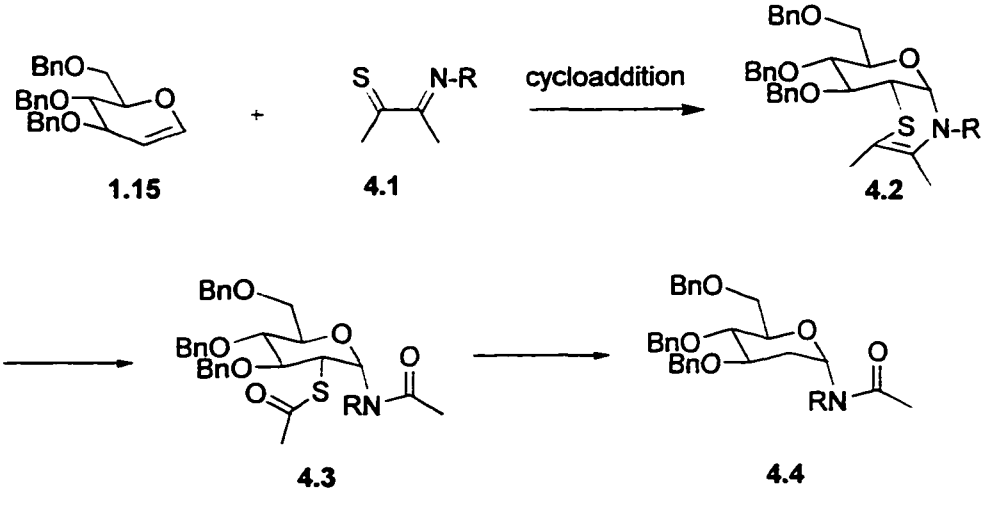
Synthesis of N-Glycosides

Introduction

It is not surprising that a key step in N-glycopeptide syntheses involves the stereoselective introduction of a new carbon-nitrogen bond between the anomeric carbon in the carbohydrate and a peptide fragment.

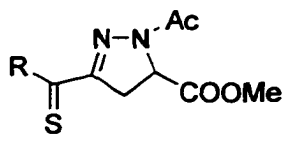
We envisioned that sugar dienophile **1.15** would undergo cycloaddition with heterodiene **4.1** to afford adduct **4.2**. Then, oxidative cleavage of the double bond in bicyclic species **4.2** will give **4.3** and reduction cleavage of the C-S bond from **4.3** will produce 2-deoxy-N-glycoside **4.4** as model of N-glycopeptide (Scheme 42).

Scheme 42. General approach to N-glycoside via cycloaddition

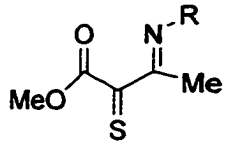


During screening via AM1 computation for likely iminothione candidates, it was shown that the imino N should have an electron-withdrawing group attached in order to produce a suitable energy gap between the LUMO of the heterodiene and the HOMO of the dienophile. For the related structures, ester **1.23**, nitrile analog **1.24** and ester **1.27** (Scheme **43**), were found to have reasonable LUMO energies for the cycloaddition.

Scheme 43.



1.24, R=COOMe(-1.87ev)
1.25, R=CN(-2.12 ev)

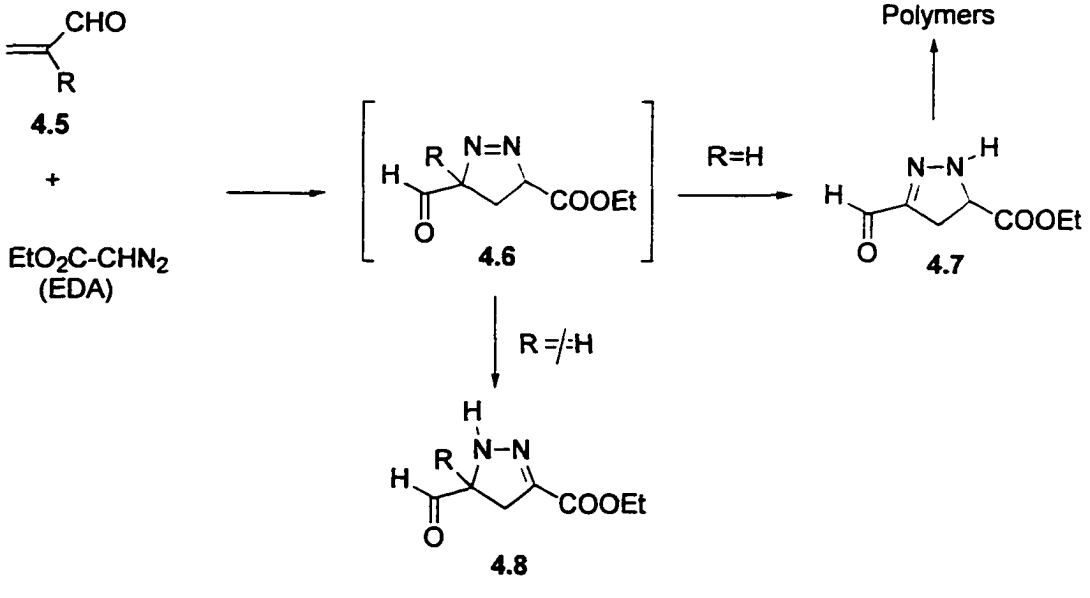


1.28. R=OMe(-1.71 ev)

4.1. Preparation of nitrile analog

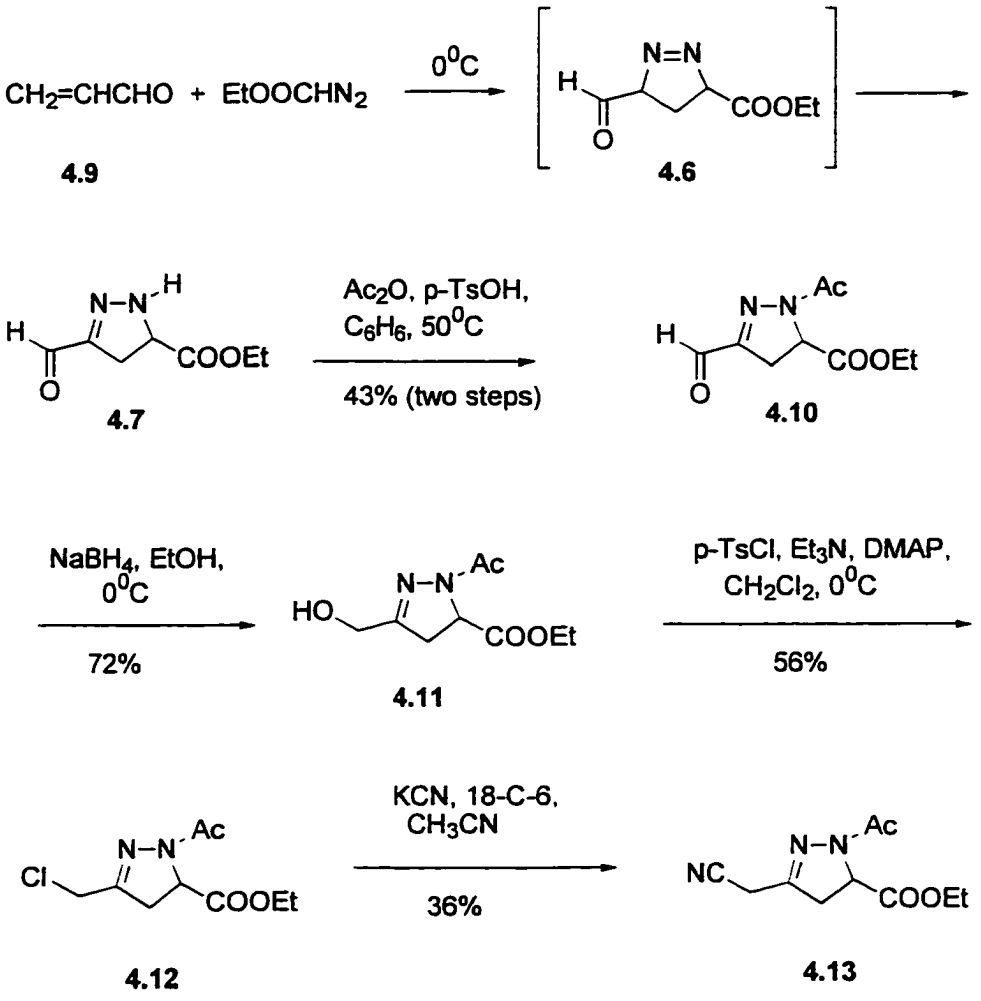
When EDA is added in equimolecular amount to acrolein **4.9** in an apolar solvent, such as hexane, a precipitate immediately forms. However, the oily liquid **4.7** was unstable, and quickly evolved nitrogen at room temperature, so all operations have to be carried out in the cold to minimize what appeared to be an oligomerization processes. In fact, the 1-pyrazoline **4.6** itself was never observed, it was very rapidly rearranged to the more stable **4.7** even below room temperature. At room temperature, isolated **4.7** can give polymers. Interestingly, **4.6** exclusively isomerized to **4.7**, and no ester-conjugated **4.8** was ever detected when R=H (Scheme **44**)[94].

Scheme 44.



In order to avoid the oligomerization during the purification, the crude product **4.7** was used directly to prepare the N-acetyl derivative **4.10** (43 % overall yield for the two steps), which is very stable. Reduction of aldehyde **4.10**[95] with $NaBH_4$ in C_2H_5OH at 0^0C afforded alcohol **4.11** in the yield of 72%. Alcohol **4.11** was converted smoothly into the corresponding chloride **4.12** with p-toluenesulfonyl chloride in the presence of Et_3N and catalytic amount of DMAP in 56 %. Displacement of the activated function by a cyano group[96] added catalysis of 18-crown-6 in CH_3CN gave **4.13** in 36 % yield (Scheme **45**).

Scheme **45.**

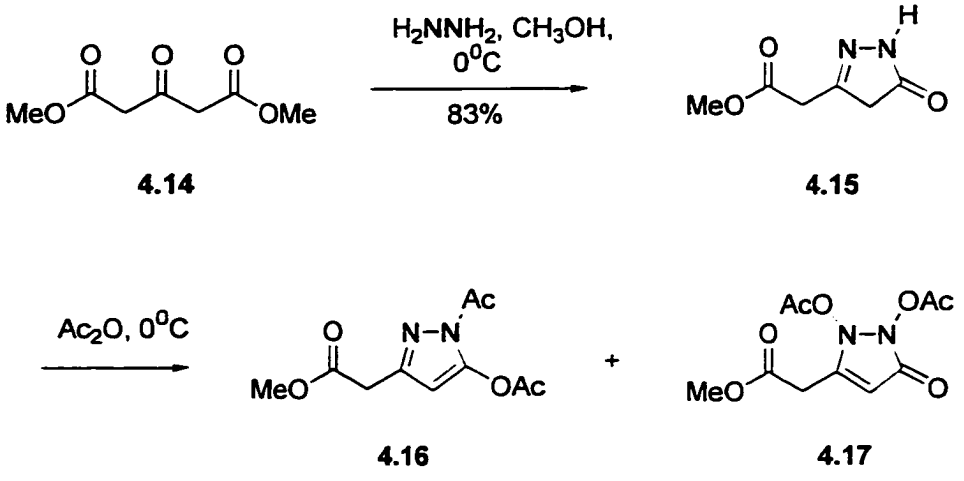


However, from the starting material EDA and acrolein **4.9**, the overall yield is relatively low. In order to get reasonable yield of the starting material **1.24** for the

heterocycloaddition, heterocylic compound **4.19** (scheme **47**) which is similar to the nitrile **4.13** was prepared as following.

Condensation[97] of dimethyl acetone dicarboxylate **4.14** with hydrazine in CH_3OH at 0^0C gave **4.15** in 83 % yield. Acetylation of **4.15** with acetic anhydride afforded a mixture of the isomers **4.16** and **4.17** (ratio=1:1) (Scheme **46**).

Scheme **46.**

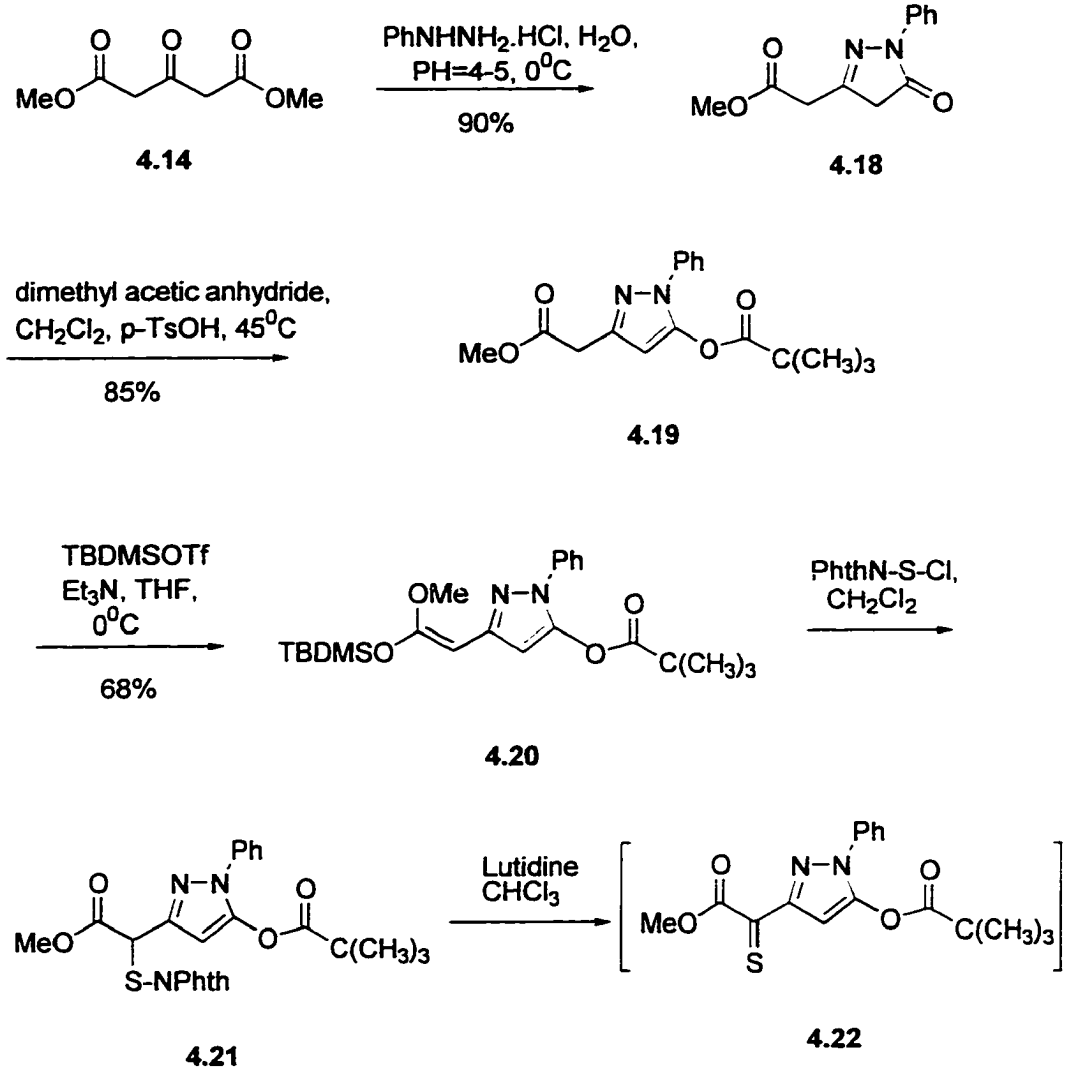


In order to prevent the isomerization, the condensation was performed at pH=4-5 aqueous solution by using phenyl hydrazine instead of hydrazine. Compound **4.18** was obtained in 90% yield. Acetylation of **4.18** with trimethyl acetic anhydride via catalysis of p-TsOH in CH_2Cl_2 afford **4.19** in 89% yield (Scheme **47**).

Silylation[98] of compound **4.19** with TBDMSOTf in the presence of Et_3N in THF at 0^0 C afforded ketene silyl acetal **4.20** in the yield of 68%. Phthalimidosulfenylation of compound **4.20** with Phth-N S-Cl afforded **4.21** smoothly. Unfortunately, when it was treated with different strength bases, e.g. 2,6-lutidine, Et_3N, $(i\text{-}Pr)_2EtN$ and NaH, in the presence of tri-O-benzyl-glucal, there was no desired cycloadduct detected even though the starting material was consumed (Scheme **47**). The calculated energy gap between the LUMO of the heterodiene and the HOMO of the dienophile: tri-O-benzyl-D-glucal was 8.2 ev. All of the early successful cycloadditions in our lab had a computed energy gap of less

than 8 ev. So it is not a complete surprise that our diene **4.22** did not react with tri-O-benzyl-glucal under the standard cycloaddition conditions.

Scheme **47.**

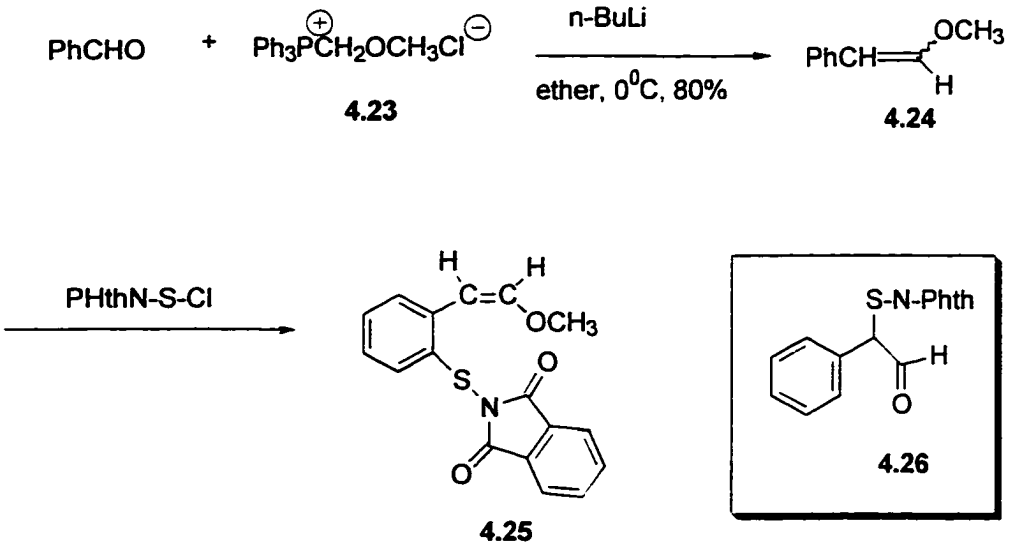


4.2. Wittig reaction approach to ester analogs

Because of the above difficulties, we tried to approach the ester **1.23** based on Wittig reaction of aldehyde **4.10** which was prepared from the cycloaddition of EDA and acrolein **4.9** (Scheme **45**).

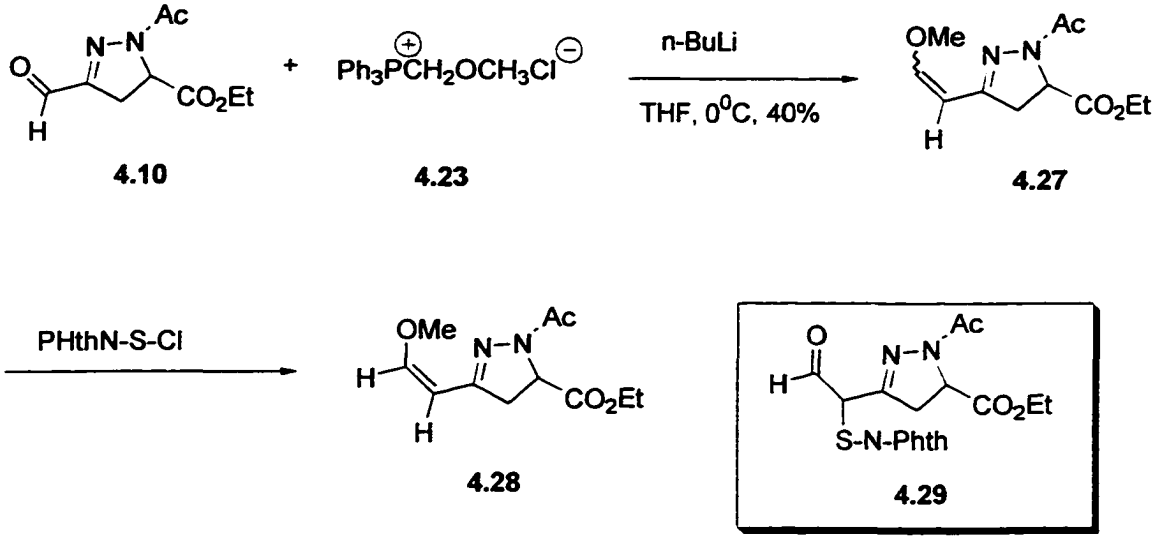
The model reaction sequence began with benzoaldehyde which was reacted with (methoxymethyl)triphenylphosphonium chloride **4.23** in the presence of n-BuLi in ether at 0°C to afford the *trans* and *cis* (ratio 3:2) of enol ether **4.24** in 80% yield.[99] Treatment of the enol ether **4.24** with PhthN-S-Cl in CH_2Cl_2 at 0°C did not give the desired phthalimidosulfenylated aldehyde **4.26**, however, only the *cis* enol ether **4.25** was detected (Scheme **48**).

Scheme **48.**



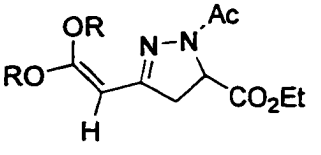
Wittig olefination of aldehyde **4.10** also gave the enol ether **4.27** (*trans/cis*=2:1) in 40% yield, and when the enol ether **4.27** was treated with PhthN-S-Cl in CH_2Cl_2, only rearrangement *cis* enol ether **4.28** was obtained instead of the desired aldehyde **4.29** (Scheme **49**).

Scheme 49.



Although the phthalimidosulfenylation of the enol ether **4.27** could not give the desired product **4.29**, acetal ketene ether, such as **4.30** (scheme **50**), may be a good substitute for the starting material of ester **1.24**, because it is more reactive than the enol ether **4.27**.

Scheme 50.

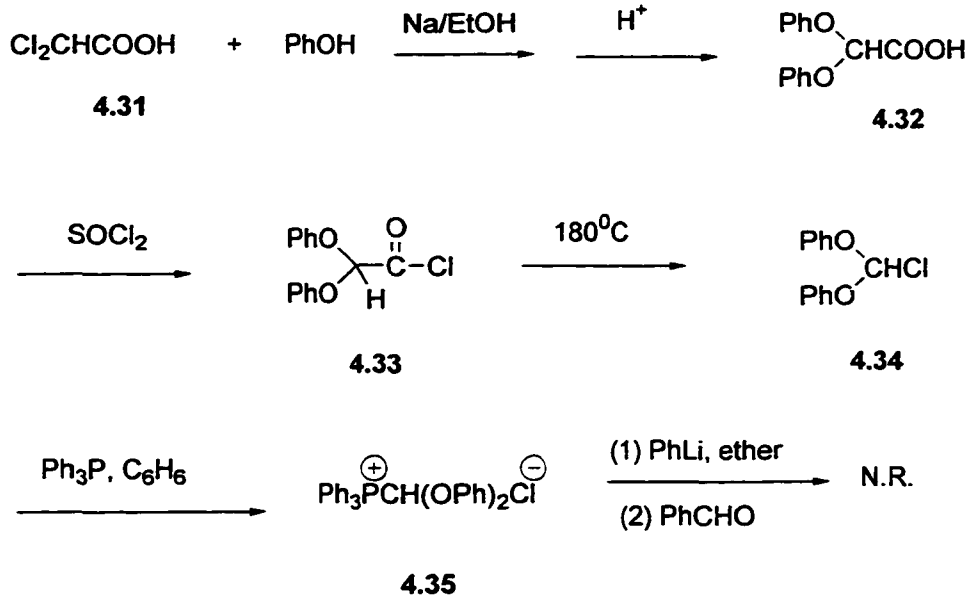


4.30

Acetal ketene ether **4.30** could be prepared, in principle, from Wittig reaction of aldehyde **4.10** with (diphenoxy methyl)triphenylphosphonium chloride **4.35**[100] under standard Wittig reaction conditions. Diphenoxy methyl chloride **4.34** was prepared by reaction of dichloroacetic acid **4.31** with phenol under basic conditions,[101] followed by reaction of diphenoxy acetic acid **4.32** with SO_2Cl_2 in benzene to form diphenoxyacetyl chloride **4.33**. Decarbonylation[102] of diphenoxyacetyl chloride **4.33** by heating at 180°C under reduced pressure was reported to form diphenoxymethyl chloride **4.34**. Although diphenoxymethyl chloride **4.34** was confirmed by NMR and MS, the reaction of benzylaldehyde with the

Wittig reagent **4.35** prepared from diphenoxymethyl chloride **4.34** and Ph_3P in refluxing benzene, did not take place under the standard Wittig reaction conditions (Scheme **51**).

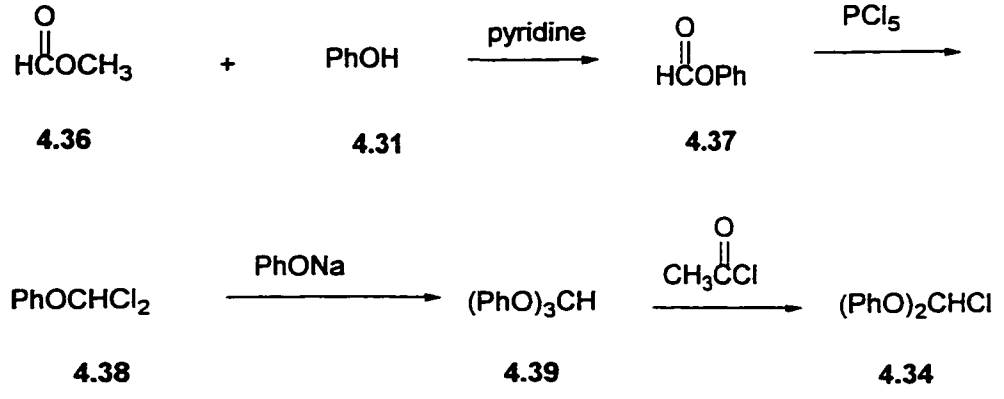
Scheme **51.**



4.31 **4.32** **4.33** **4.34** **4.35**

Diphenoxymethyl chloride **4.34** was also prepared as described in scheme **52.**[103]

Scheme **52.**

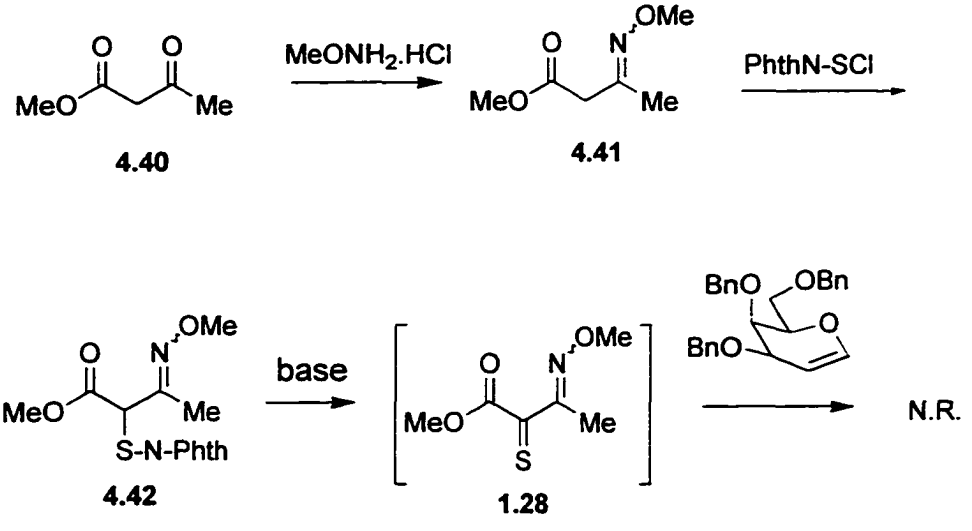


4.36 **4.31** **4.37** **4.38** **4.39** **4.34**

4.3. Analogs of 1.28

Simple precursor **4.42** attracted our interest; It was easily obtained by reaction of methyl acetoacetate with methoxy amine in methanol at room temperature,[104] followed by treatment with PhthN-S-Cl in CH_2Cl_2 at 0°C. Another advantage of this compound **4.42** is numerous other N-substituents instead of methoxy group would give suitable LUMOs of the heterodienes. Unfortunately, when **4.42** was treated with different strength bases, e.g. 2,6-lutidine, Et_3N, $(i\text{-}Pr)_2EtN$ and NaH, in the presence of tri-O-benzyl-glucal, there was no cycloadduct detected even thought the starting material **4.42** was consumed (Scheme **53**).

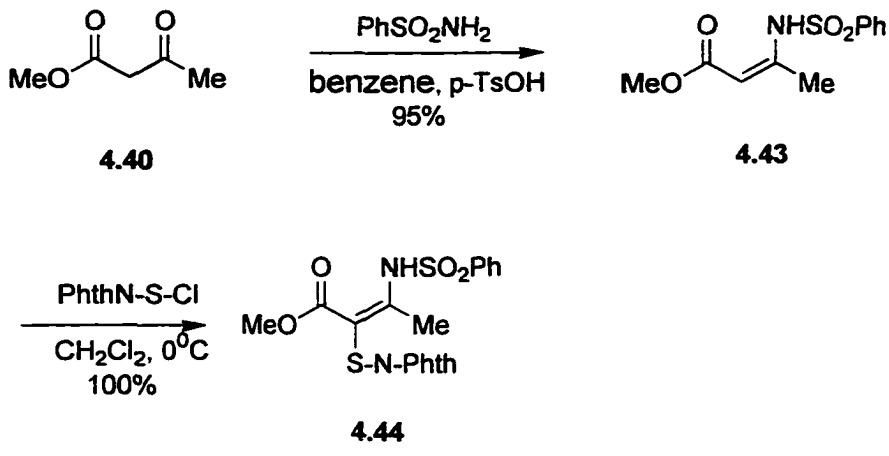
Scheme **53.**



As predicted via AM1 computation for likely iminothione candidates related to diene **1.27**, we can simply switch the N-methoxy group in diene **1.28** for an electron-withdrawing group, e.g. sulfonyl groups, which could give suitable LUMO's for the inverse-electron demand cycloaddition.

Condensation of methyl acetoacetate **4.40** with benzenesulfonyl amide under the catalysis of p-toluenesufonic acid afforded sulfonyl enamine **4.43** in 95 % yield.[105] Reaction of **4.43** with PhthN-S-Cl in dichloromethane at 0^0C gave the phthalimidosulfenylated compound **4.44** in quantitative yield (Scheme **54**).

Scheme **54.**

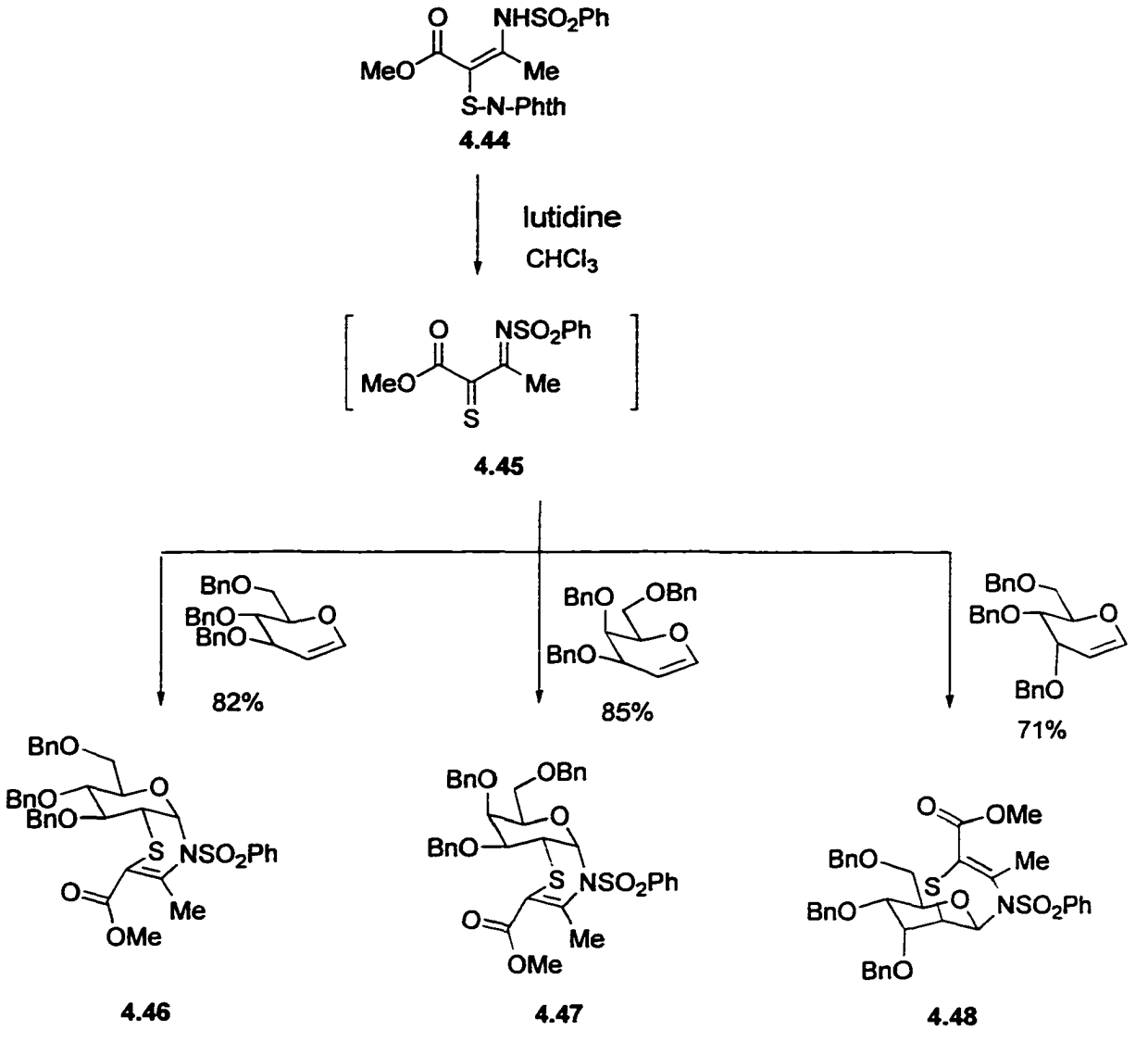


4.40 **4.43** **4.44**

In a typical cycloaddition reaction between glycals and the phthalimidosulfonyl imine, lutidine was added to a chloroform solution of glycal and phthalimidosulfonyl imine and the reaction mixture was stirred at room temperature. After the glycal was consumed, the reaction mixture was quenched by adding ammonium chloride and extracting with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated. Purification of the crude product by a silica gel column chromatography provided the cycloadducts.

Cycloadducts **4.46, 4.47** and **4.48** were obtained with tri-O-benzyl-glucal, tri-O-benzyl-galactal and tri-O-benzyl-allal in chloroform in the yields of 82%, 85% and 71% respectively (Scheme **55**). Oxidation of cycloadduct **4.47** using m-CPBA gave sulfone **4.49** in 91% yield (Scheme **56**).

Scheme 55.



Scheme 56.

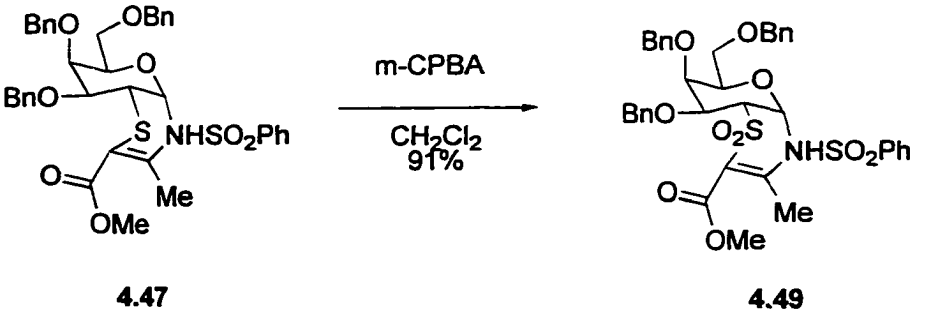
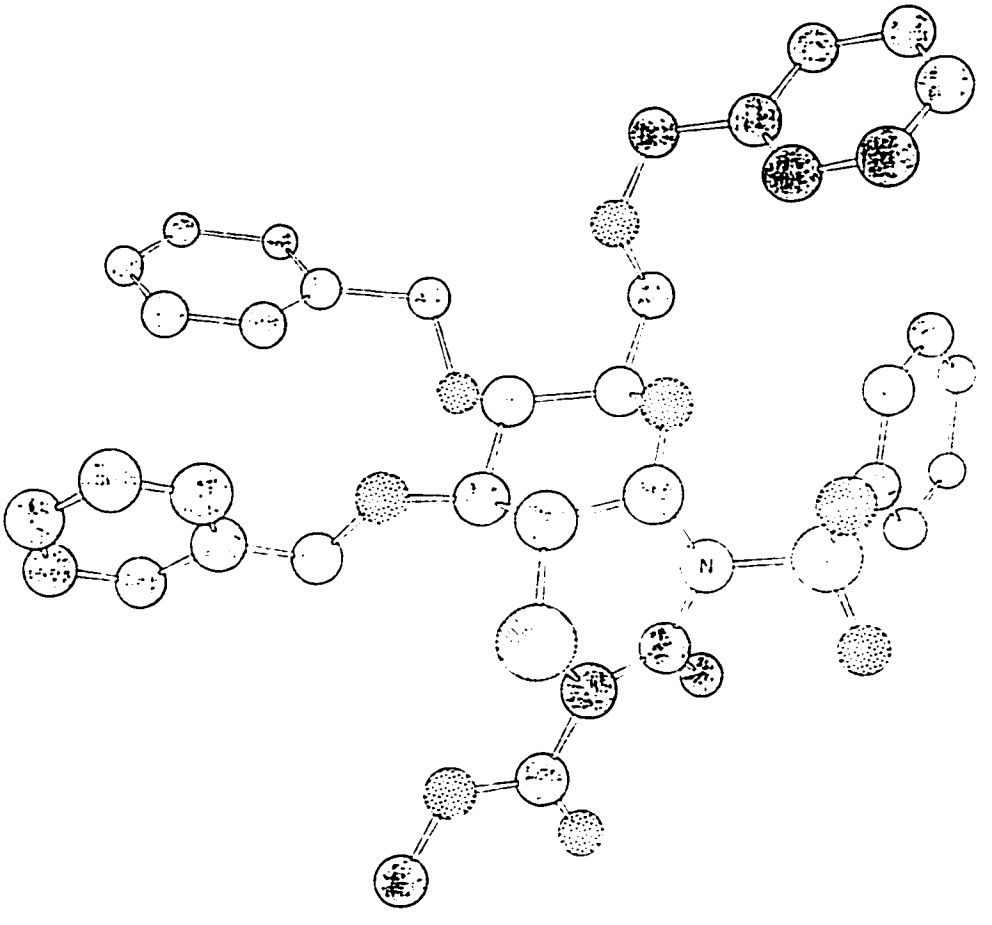
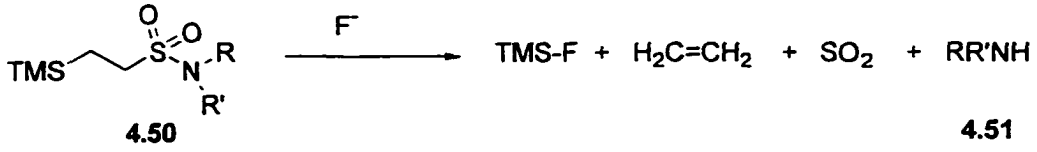


Figure 12. The X-Ray structure of cycloadduct **4.46**.



It proved difficult to produce the NH species by removal of the phenyl sulfonyl group in the cycloadducts **4.46, 4.47** and **4.48**. However, 2-trimethylsilyethanesulfonyl-protected amines **4.50** have been shown to be stable compounds which can be readily cleaved by a fluoride source to generate the parent amines **4.51**[106] (Scheme 57).

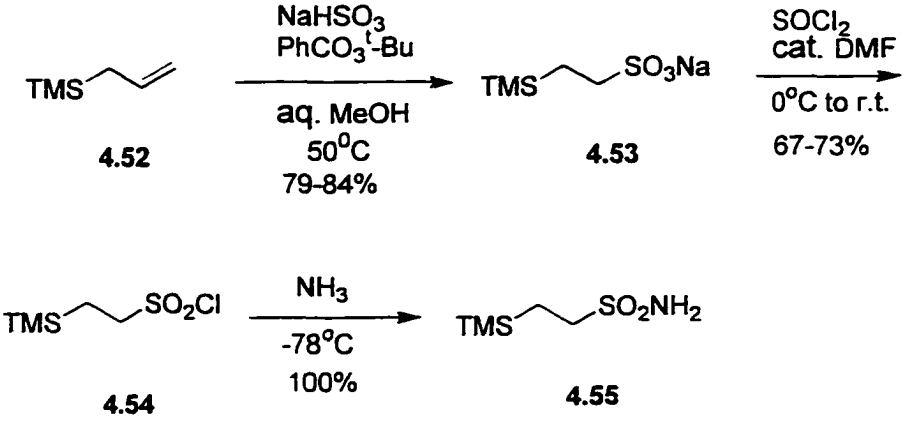
Scheme **57.**



4.50 **4.51**

2-Trimethylsilyethanesulfonyl chloride **4.54** was obtained according to Weinreb's method,[107] starting from vinyltrimethylsilane **4.52** in two steps. 2-Trimethylsilyethanesulfonyl amide **4.55** was prepared in quantitative yield by reaction of 2-trimethylsilyethanesulfonyl chloride **4.54** with liquid ammonia in THF at -78°C (Scheme **58**).

Scheme **58.**

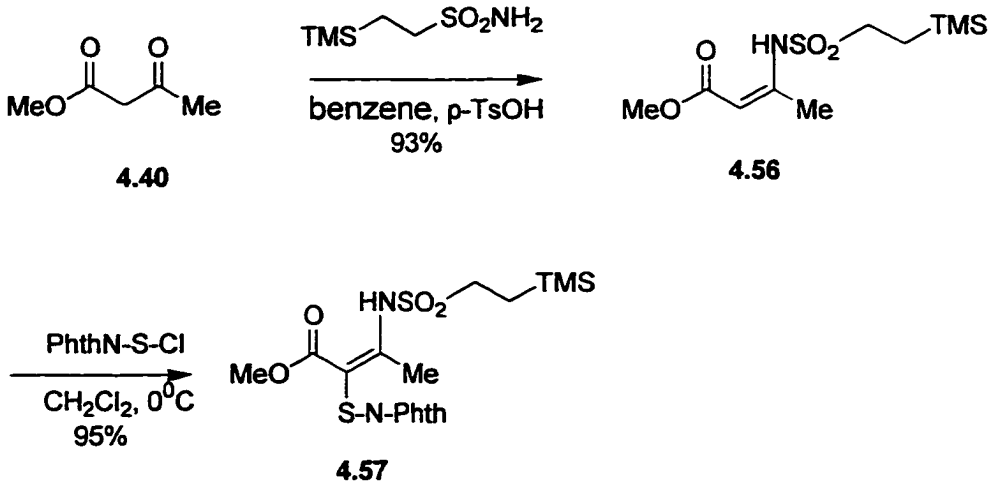


4.52 **4.53** **4.54** **4.55**

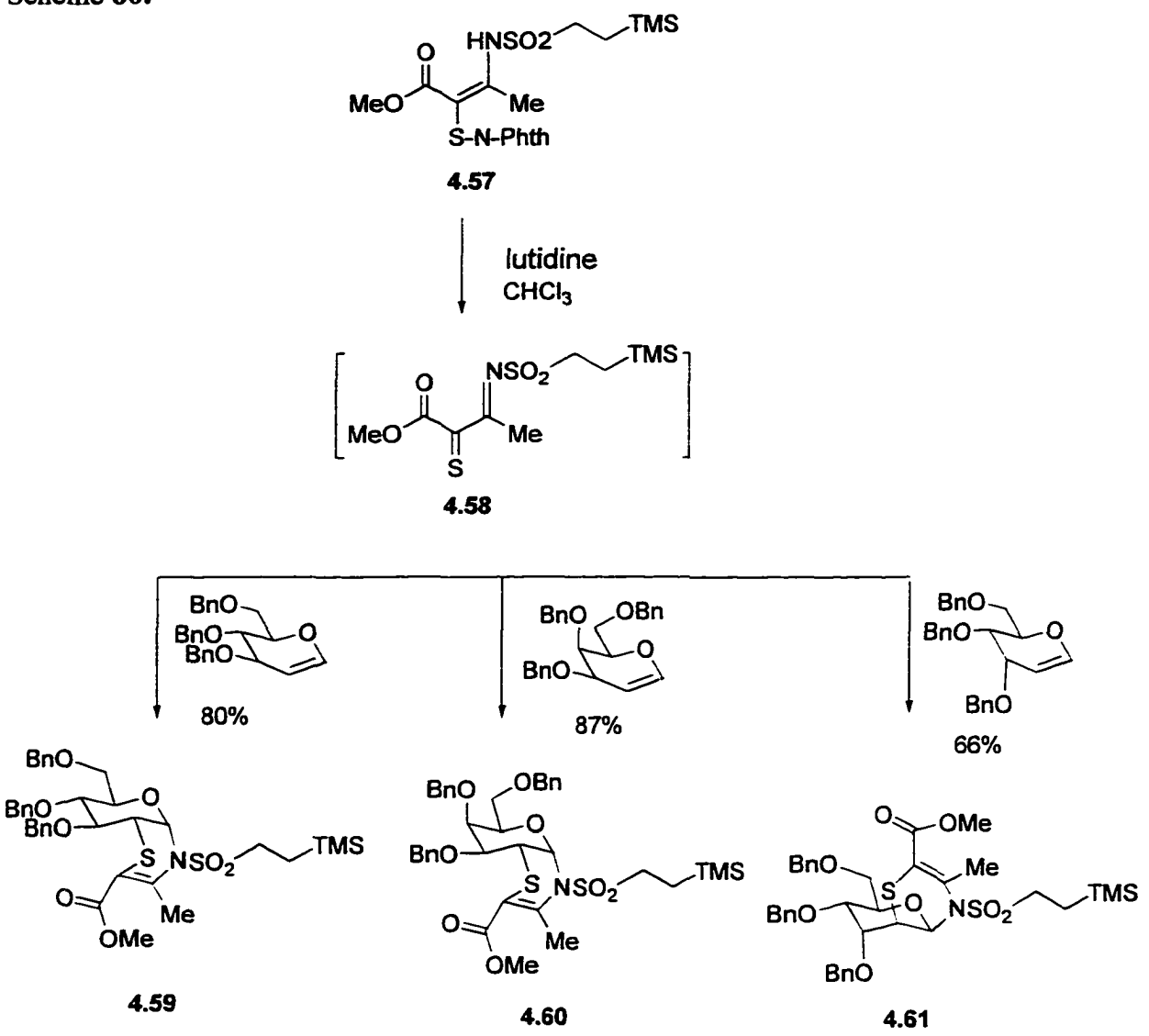
Then, condensation of methyl acetoacetate **4.40** with 2-trimethylsilyethanesulfonyl amide **4.55** with the catalysis of p-toluenesulfonic acid in refluxing benzene gave sulfonyl enamine **4.56** in 93% yield [105] (Scheme **59**). Treatment of **4.56** with PhthN-S-Cl in dichloromethane at 0°C, followed by adding a catalytic amount of 2,6-lutidine to the solution of tri-O-benzyl-glucal, tri-O-benzyl-galactal and tri-O-benzyl-allal in chloroform

produced cycloadducts **4.59**, **4.60**, and **4.61** of 80%, 87% and 66% yield respectively (Scheme **60**).

Scheme **59**.

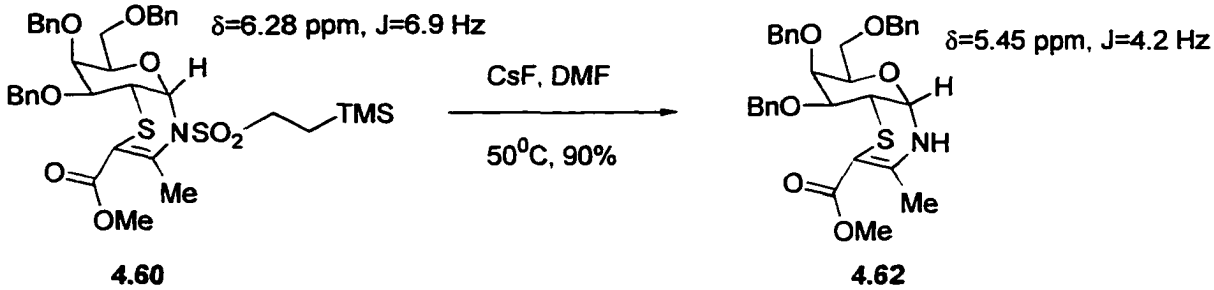


Scheme **60.**



Deprotection of cycloadduct **4.60** proceeded smoothly with CsF in DMF to give the NH species **4.62** in 90% yield (Scheme **61**). Once the cycloadduct **4.60** was converted to **4.62**, the chemical shift of the anomeric proton changed from 6.28 ppm (d, J=6.9 Hz) to 5.45 ppm (d, J=4.2 Hz).

Scheme **61.**

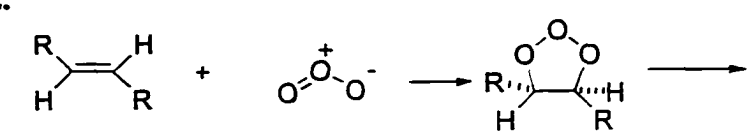


4.60 **4.62**

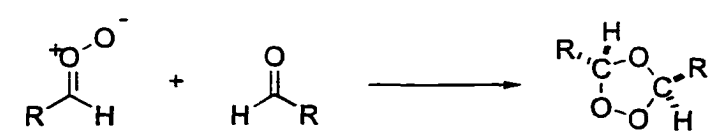
4.4. The cleavage of the carbon-carbon double bond by ozonolysis

The reaction of alkenes with ozone constitutes an important method of cleaving carbon-carbon double bonds. The first step of the reaction is a cycloaddition to give the 1,2,3-trioxolane **4.64**. This is followed by a fragmentation and recombination to give the isomeric 1,2,4-trioxolane **4.66** (Scheme **62**). The mechanistic pattern of the first step is that of a 1,3-dipolar cycloaddition reaction. Ozone is expected to be a very electrophilic 1,3-dipole because of the accumulation of electronegative oxygen atoms in the ozone molecule.

Scheme **62.**



4.63 **4.64**



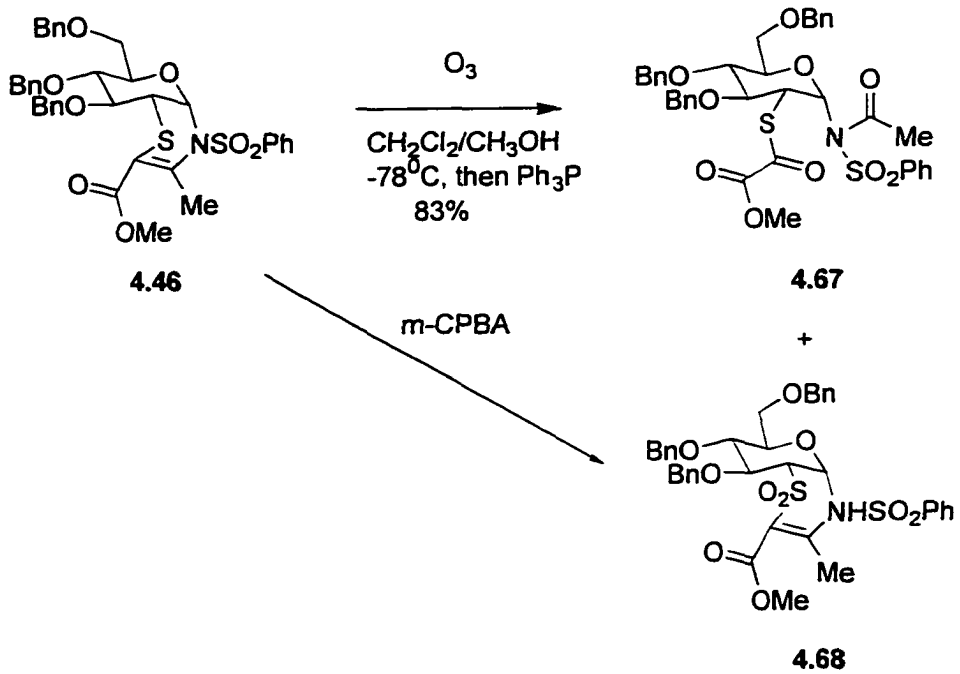
4.65 **4.66**

The actual products isolated after ozonolysis depend upon the conditions of workup.[108] It is usually preferable to include a mild reducing agent that is capable of reducing peroxidic products.

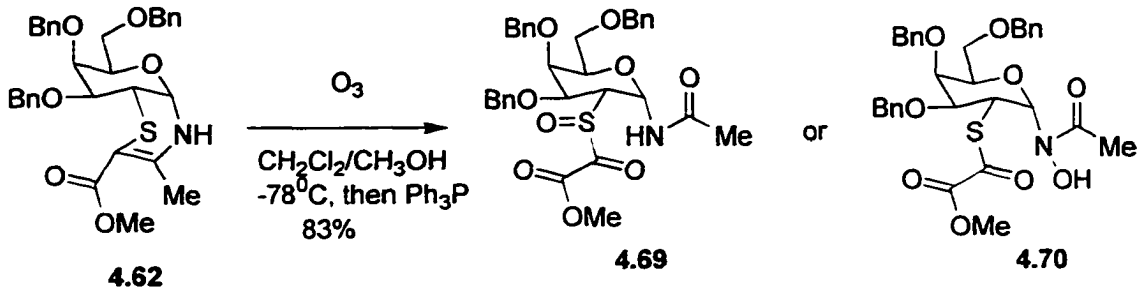
Treatment of cycloadduct **4.46** with ozone at -78^{0}C, followed by Ph_3P work-up, afforded the cleaved product **4.67** in 83% yield,[108] along with a small amount of oxidized product **4.68** which can also be obtained by oxidation of the cycloadduct **4.60** with m-CPBA (Scheme **63** and **56**).

For the deprotected cycloadduct amine **4.62**, according to the elemental analysis, one more oxygen was detected than expected for the product of the ozonolysis. There are two possibilities for the position of the extra oxygen, either a partially oxidized sulfur **4.69**, or an oxidized nitrogen as in hydroxylamine **4.70** (Scheme **64**).

Scheme **63.**



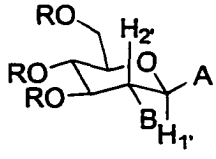
Scheme **64.**



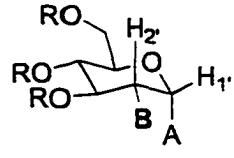
4.5. Assignment of structure

The stereochemistry of the anomeric carbon of pyranoid derivatives can be assigned by proton NMR analysis.[109] In pyranoid glycosides, β-glycosides are usually identified by a $J_{H1'-H2'}$ coupling constant which is between 8-12 Hz, indicating a *trans* diaxial coupling between H-1' and H-2' as shown in scheme **65.** α-Glycosides usually exhibit a $J_{H1'-H2'}$ coupling constant which is between 1 to 3 Hz, indicating a *cis* axial-equatorial coupling between H-2' and H-1' as shown in scheme **65.**

Scheme **65.** Relation between H-1' and H-2' of α- and β-pyranosides



β-glycoside diaxial coupling between $H_{1'}$ and $H_{2'}$



α-glycoside axial-equatorial coupling between $H_{2'}$ and $H_{1'}$

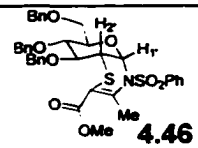
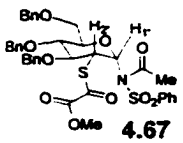
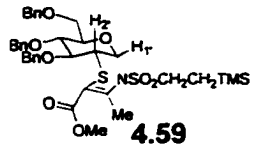
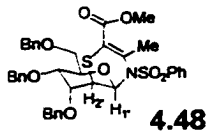
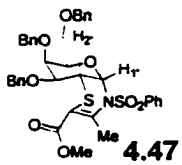
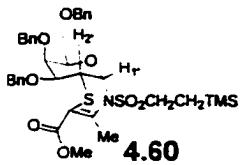
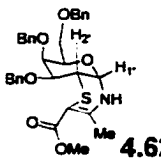
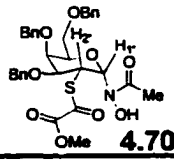
For the cycloadducts **4.46** (7.2 Hz), **4.47** (6.8 Hz), **4.59** (6.6 Hz), and **4.60** (6.9 Hz), measured J values indicated an equatorial-axial coupling between H-1' and H-2'. After comparing the coupling constants and the anomeric configuration assignment with the

similar compounds which have been prepared in our laboratory, we concluded that H-1' was equatorially oriented, and H-2' was axially oriented in these cycloadducts. The chemical shifts of the pyranoid protons were ascertained on the basis of ^{1}H-^{1}H connectivity derived from COSY experiments. For the below-plane (α-face) cycloadduct **4.46**, the equatorially oriented anomeric proton was expected to resonate at lower field than the analogous anomeric proton of the β-face cycloadducts **4.48** and **4.61** which were oriented in axial position. In the case of cycloadduct **4.46**, the equatorially oriented anomeric proton resonated as a doublet at 6.33 ppm with J=7.2 Hz. This suggested an equatorial-axial relationship between H-1' and H-2'.

For the upper-plane (β-face) cycloadducts **4.48** and **4.61**, the anomeric protons were axially oriented and resonated as doublets at 6.08 and 5.72 ppm with J=3 and 2.9 Hz respectively, which were more upfield and smaller coupling constants than the equatorially oriented H-1' of the α-face cycloadduct **4.46**. Furthermore the configuration of cycloadduct **4.46** has been confirmed by X-ray crystallography (Figure **12**). From the X-ray structure, we concluded that the nitrogen at C-1 was not perfectly axial, nor the sulfur at C-2 perfectly equatorial. These small distortions possibly due to the N-sulfonyl group, are assumed to cause the small change in the H_1-H_2 dihedral angle (53.3^0) which resulted in a change of the J value.

Also, when the sulfonyl protective group in cycloadduct **4.60** was removed, as in **4.62** the anomeric proton H-1' was shifted upfield to 5.45 ppm (compared with chemical shift of H-1' at 6.28 ppm in cycloadduct **4.60**) and the coupling constant (J=4.2 Hz) became more reasonable for the equatorial-axial coupling than its parent cycloadduct **4.60** (6.6 Hz).

Table 5. Determination of the anomeric configuration by using the chemical shift and the coupling constant

	H-1', ppm	H-2', ppm	$J_{H1'-H2'}$, Hz
 **4.46**	6.33	3.38	7.2
 **4.67**	6.53	3.51	4.8
 **4.59**	6.30	3.55	6.6
 **4.48**	6.08	3.51	3.0
 **4.47**	6.31	3.72	6.8
 **4.60**	6.28	3.31	6.9
 **4.62**	5.45	3.56	4.2
 **4.70**	5.63	3.52	4.5

After cleavage the double bond in cycloadduct **4.46** by ozonolysis, the bicyclic framework is removed. As a result, compound **4.67** featured an anomeric proton as a doublet at chemical shift 5.3 ppm with J=2.1 Hz. NMR reveals H-2' as having equatorial-axial coupling to H-1'. Hence we have an α-glycoside. This is additional evidence that α-face cycloadduct was obtained in **4.46**.

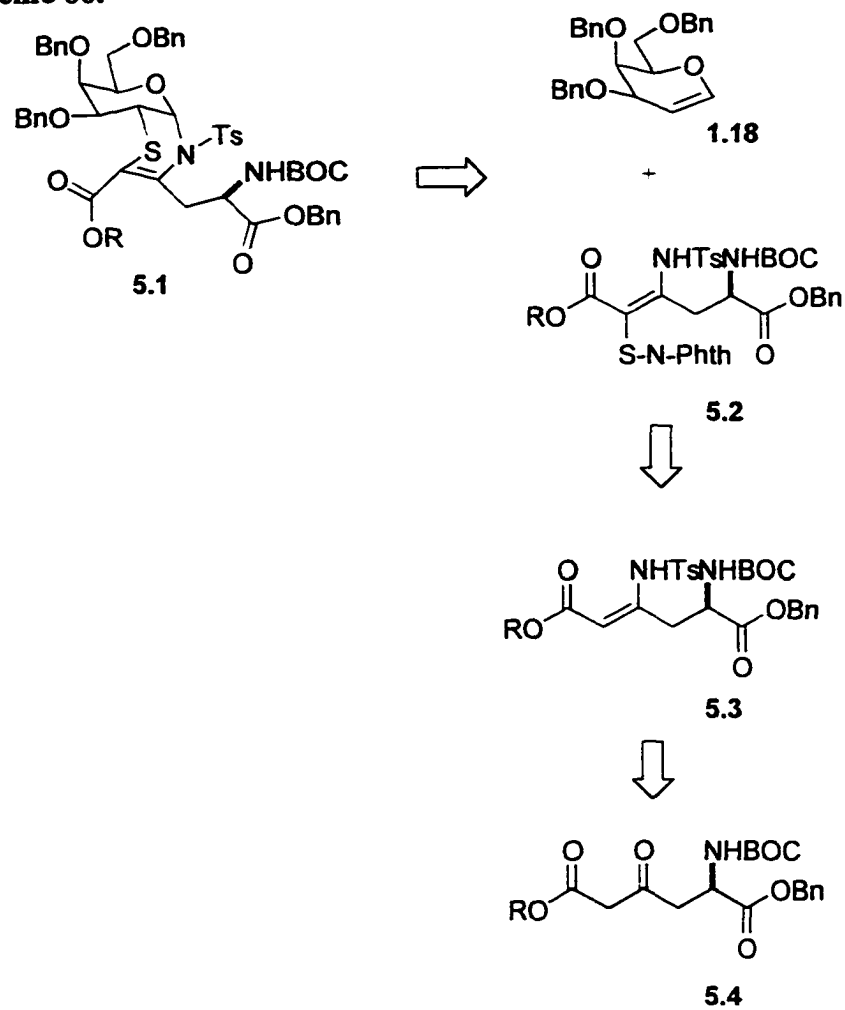
Chapter 5

Synthesis of N-Glycopeptides

Introduction

With an efficient route in hand to build the C-N bond stereoselectively, we next attempted to prepare glycopeptide analog **5.1** by using our cycloaddition route for glycosyl transfer to a model peptide. Our retrosynthetic disconnections for the cycloadduct are outlined in Scheme **66**. Generation of N-sulfonyl imines **5.3** could be achieved from amino-keto-ester **5.4**. Phthalimidosulfenylation of N-sulfonyl imines **5.3**, followed by treatment with base in the presence of tri-O-benzyl-galactal via cycloaddition, would give the desired cycloadduct **5.1** (Scheme **66**).

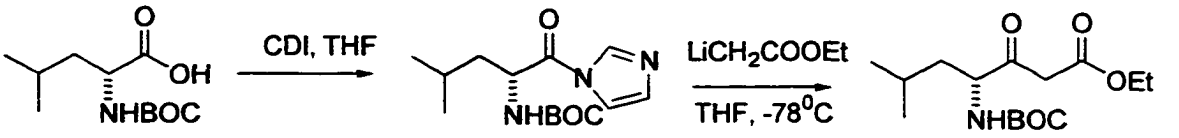
Scheme 66.



5.1. Synthesis of amino-keto-esters

As precursors of γ-amino-β-hydroxy acids,[110] an important class of compounds which exist in many natural products,[111] γ-amino-β-keto acids have been synthesized by several methods. Activation of carboxyl groups **5.5** as the imidazolide **5.6** followed by C-C bond formation with lithioacetate, afforded γ-amino-β-keto-esters **5.7**[112] (Scheme **67**).

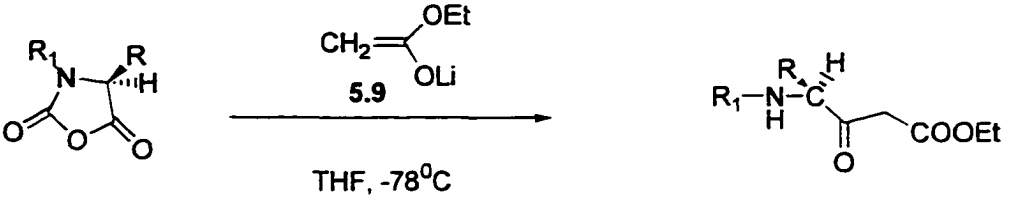
Scheme **67.**



5.5 **5.6** **5.7**

Also, reactions of urethane N-protected-N-carboxyanhydrides (UNCAS) **5.8** with the lithium enolate of ethyl acetate **5.9**[113] and enolate acylation with N-carboxyanhydrides previously formed from β-lactams[114] gave γ-amino-β-keto-esters **5.10** (Scheme **68**).

Scheme **68.**



5.8 **5.10**

R_1= benzyloxycarbonyl; tert-BOC

The published methods proved unsuitable for our purpose, especially for the synthesis of δ-amino-β-keto-esters since products were obtained in unsatisfactory yield or starting materials were not readily available.[113,114] We therefore considered the condensation of amino acids with Meldrum's acid. The acylation of Meldrum's acid is well established as a synthesis for β-keto-esters,[115] but apparently has never found use in the synthesis of amino-keto-esters.[116]

Condensations of commercially available amino acids **5.11** (Scheme **69**) and **5.26** (Scheme **70**) with Meldrum's acid **5.12** were examined by using diethyl phosphorocyanidate (DEPC)[117] and isopropenyl chloroformate (IPCF)[118] as activating agents in the presence of different bases (e.g. DMAP, Et_3N), with only IPCF affording compounds **5.13** and **5.27** in satisfactory yield. Without purification, compounds **5.13** and **5.27** were refluxed with alcohols in benzene to give γ-amino-β-keto-esters **5.14**

(Scheme 69) and δ-amino-β-keto-esters **5.28** (Scheme 70) in good yield[119] (Tables 6 and 7).

Scheme 69. Synthesis of γ-amino-β-keto-ester from α-amino acids

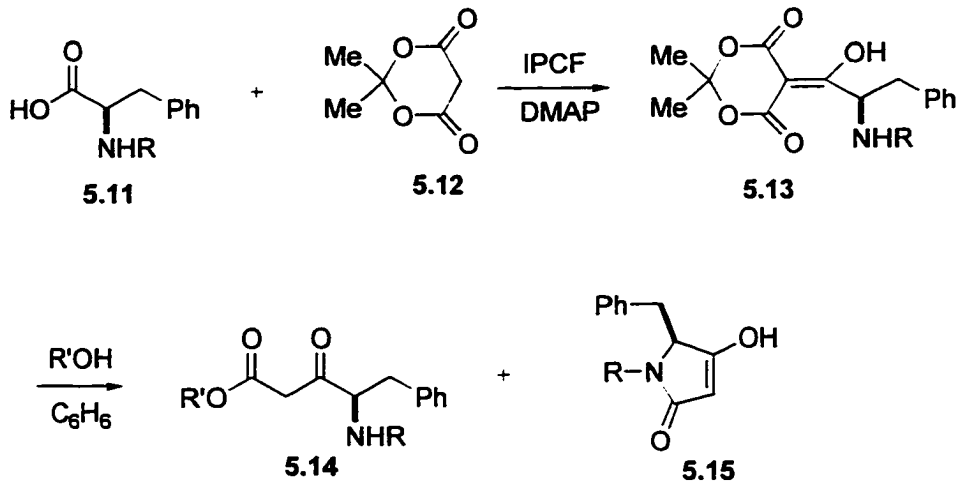


Table 6. Preparation of γ-amino-β-keto-esters **5.14** from α-amino acids **5.11**

Compound	Amino acids	R	R′	Ratio of **5.14** and **5.15**	Yield (%)
5.16	Phe-OH	BOC	Bn	1:3	82
5.17	Phe-OH	BOC	Et	1:2	90
5.18	Phe-OH	BOC	i-Pr	2:5	78
5.19	Phe-OH	BOC	t-Bu	1:3	83
5.20	Phe-OH	CBZ	Bn	1:4	75
5.21	Phe-OH	CBZ	Et	1:2	81
5.22	Phe-OH	CBZ	i-Pr	1:3	77
5.23	Phe-OH	CBZ	t-Bu	1:3	85
5.24	Gly-OH	Phth	Et	Only **5.14**[120]	78
5.25	ALL-OH	BOC	Et	1:6	76

The reaction of intermediate compounds **5.13** and **5.27** were reacted with some representative alcohols and the results are summarized in table **6** and **7**. For the α-amino acids, along with the desired γ-amino-β-keto-esters **5.14**, we obtained the easily separated cyclization products (N-protected tetramic acid derivatives) **5.15**,[118] with the exception of the N-phthaloylglycine. There were no cyclization products

detected in the case of the aspartic acid, presumably because the 6-member ring is formed less easily than the 5-membered examples.

Scheme 70. Synthesis of δ-amino-β-keto-esters **5.28** from β-amino acids **5.26**

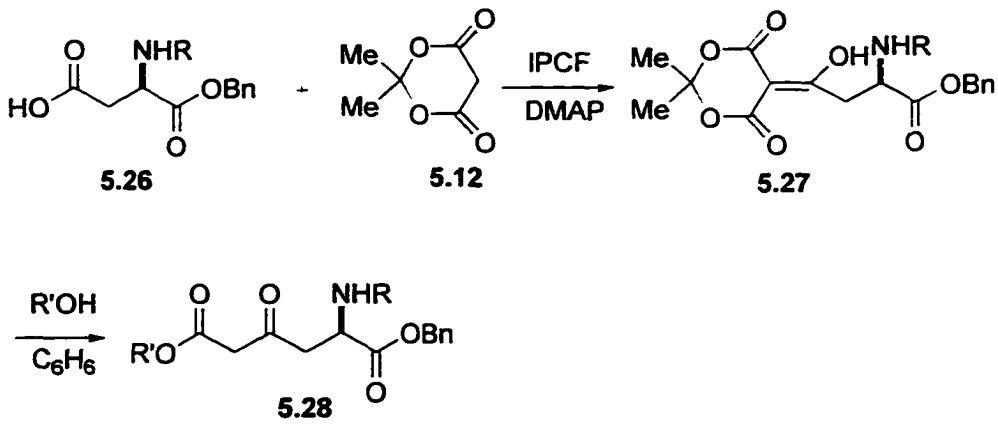


Table 7. Preparation of δ-amino-β-keto-esters **5.28** from β-amino acids **5.26**

Compound	Amino acid	R	R'	Yield (%)
5.29	Asp-OBn	BOC	Bn	86
5.30	Asp-OBn	BOC	Et	92
5.31	Asp-OBn	BOC	i-Pr	90
5.32	Asp-OBn	BOC	t-Bu	72
5.33	Asp-OBn	CBZ	Bn	77
5.34	Asp-OBn	CBZ	i-Pr	70

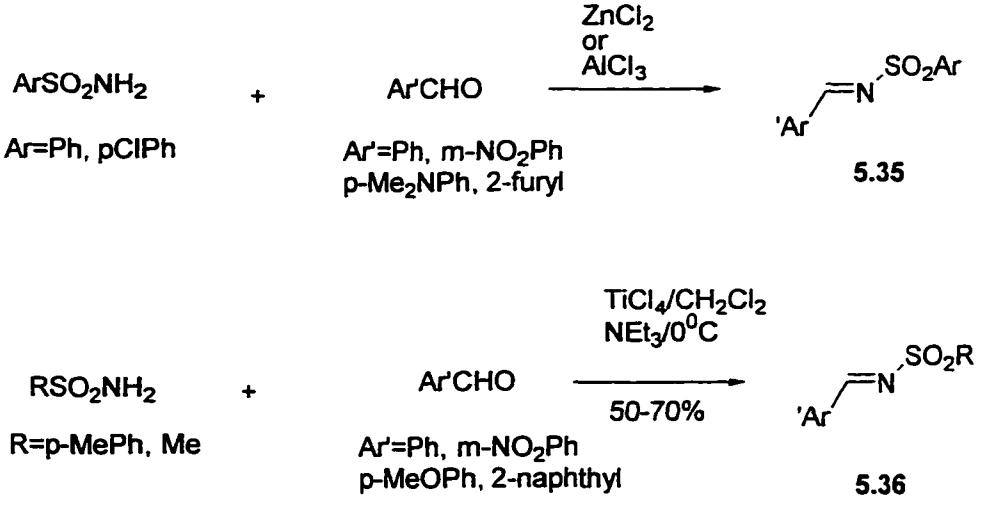
5.2. Preparation of N-sulfonyl imines

Once amino-keto-esters became readily available, we began to investigate the synthesis of N-sulfonyl imines. N-sulfonyl imines can often be produced *in situ* from more stable precursors such as α-alkyoxy or α-hydroxyl sulfonamides. However, a number of good procedures now exist for direct synthesis of N-sulfonyl imines, particularly those derived from non-enolizable aldehydes, e.g. oxidation of N-sulfenylimines, sulfonylation of NH imines or N-silyl imines, and free radical rearrangement of oximes. It might be noted that there is still a lack of good procedures for synthesizing N-sulfonyl imines from enolizable aldehydes and ketones.[121]

5.2.1. Direct formation from primary sulfonamides and aldehydes/ketones

The earliest procedure described for synthesis and isolation of N-sulfonyl imines **5.35** of aryaldehydes utilized $ZnCl_2$ as a catalyst.[122] A related procedure published shortly thereafter by a Russian group[123] using $AlCl_3$ seems to produce somewhat higher isolated yields of the ary N-sulfonyl imines **5.35** (Scheme **71**).

Scheme **71.**



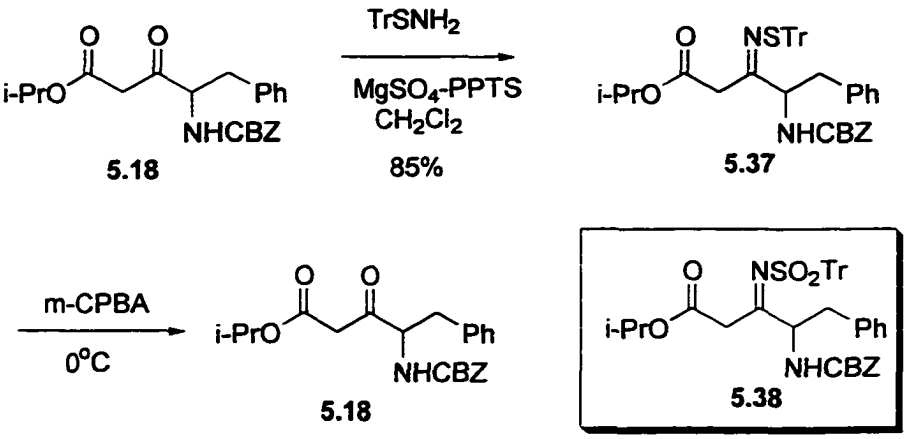
Another method which has been utilized for condensing benzaldehyde and p-toluenesulfonamide involves azeotropic distillation of water in the presence of an acid

ion exchange resin and $4A^0$ molecular sieves. Condensation of methyl acetoacetate **4.40** with benzenesulfonyl amide or 2-trimethylsilyethanesulfonyl amide **4.55** in refluxing benzene in the presence of an acid catalyst worked very well in our hand (see chapter **4** scheme **54** and **59**). However the similar condensation of amino-keto-esters **5.28** with benzenesulfonyl amide or 2-trimethylsilyethanesulfonyl amide **4.55** when performed in refluxing benzene in the presence of an acid catalyst or in dichloromethane using a Lewis acid, such as, $TiCl_4$ as catalyst,[124] (e.g. scheme 71) did not give any desired N-sulfonyl imine products. It seems that our initial synthetic route for the preparation of N-sulfonyl imines is problematic in more complex cases. We decided to adopt an alternative synthetic pathway to obtain N-sulfonyl imines.

5.2.2. Oxidation of sulfenamides

As for the oxidation of N-sulfenylimines, Branchaud[125] has reported that carbonyl compounds react with stable, crystalline triphenylmethanesulfenamide ($TrSNH_2$) under mild conditions to form tritylsulfenimines. Amino-keto-ester **5.18** reacted with stable, crystalline triphenylmethanesulfenamide ($TrSNH_2$) under mild condition ($MgSO_4$ as drying agent-catalyst and pyridinium p-toluenesulfonate (PPTS) as a catalyst in dichloromethane at room temperature) to form tritylsulfenimine **5.37** in a yield of 85%. But tritylsulfenimine **5.37** was hydrolyzed back to keto ester **5.18** upon treatment with m-CPBA in dichloromethane at 0^0C (Scheme 72).

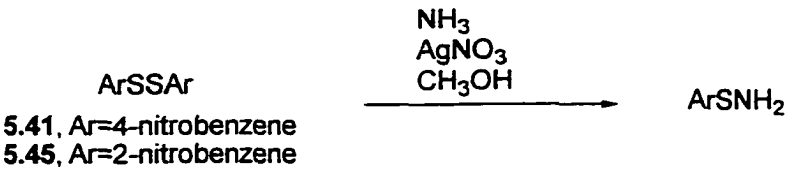
Scheme 72.



In fact, studies[125] have shown that treatment of the tritylsulfenimine with various oxidizing reagents, such as: $AgNO_3$, $HgCl_2$, $FeCl_3$, and $HClO_4$ led to the corresponding carbonyl compound.

In order to prevent hydrolysis during the oxidation, different arenesulfenamides were prepared. Good yields of arenesulfenamides, such as: 4-nitrobenzenesulfenamide **5.41** were obtained from the reaction of silver nitrate, aromatic disulfides and ammonia[126] when the disulfides contained electron-withdrawing groups more powerful than a 4-chlorophenyl group. Both phenyl and 4-chlorophenyl gave the corresponding bis(arenesulfen) imide **5.42** and **5.43** as the only isolated product (Scheme 73).

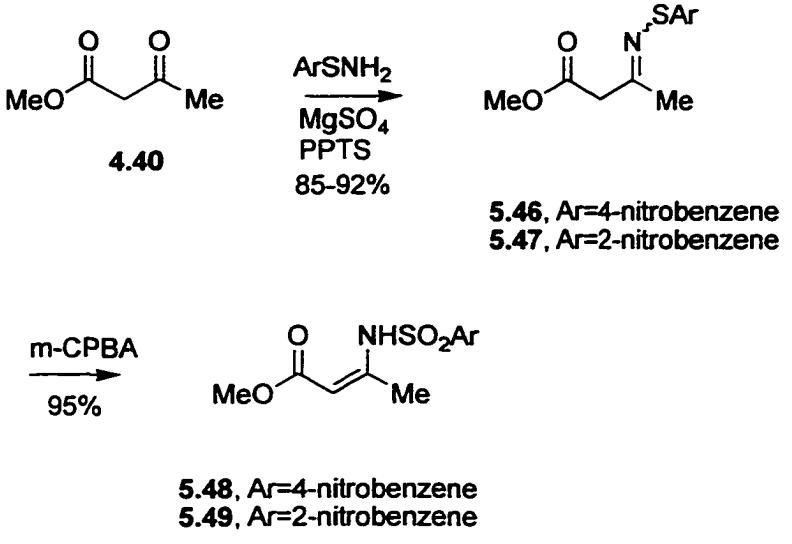
Scheme 73.



$YY\text{-}C_6H_3S\text{-}NH_2$	$(XY\text{-}C_6H_3S)_2NH$
5.39, X=Y=3,4-Cl_2	**5.42**, X=Y=H
5.40, X=H; Y=3-NO_2	**5.43**, X=H; Y=4-Cl
5.41, X=H; Y=4-NO_2	**5.44**, X=H; Y=3-NO_2

Treatment of methyl acetoacetate **4.40** with 4-nitro and 2-nitrobenzenesulfenamides **5.41** and **5.45** in the presence of $MgSO_4$ as drying agent-catalyst and pyridinium p-toluenesulfonate (PPTS) as a catalyst in dichloromethane at room temperature, followed by oxidation by m-CPBA, gave the desired arenesulfonamides **5.48** and **5.49** (Scheme 74). Unfortunately, the sequence failed when applied to the more complex amino-keto-esters.

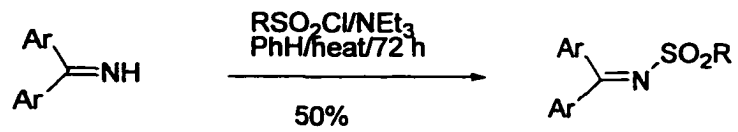
Scheme 74.



5.2.3. Sulfonylation of imines and N-silyl imines

The direct N-sulfonylation of simple NH imines has not been studied to any significant degree despite the availability of these precursors. In a rare use of this approach, Hudson and coworkers have reported two examples of N-sulfonylation of ditolyl imine **5.50** to afford the N-sulfonyl imines **5.51** and **5.52** in reasonable yields[127] (Scheme 75).

Scheme 75. Direct sulfonylaton of imines

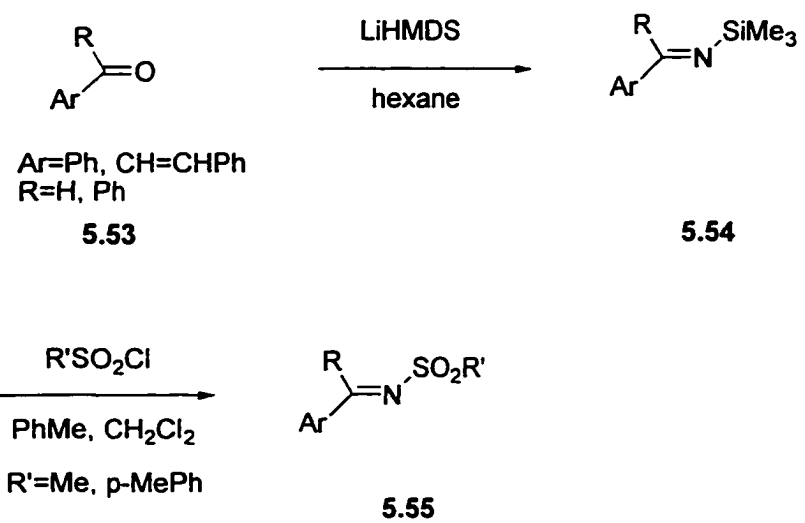


5.50, Ar=p-MePh

5.51, R=Me
5.52, R=Ph

Georg et al.[128] have found that N-trimethylsilyl imines **5.54** of aromatic non-enolizable aldehydes and ketones **5.53**, prepared by the methodology of Hart, can be converted to the corresponding N-sulfonyl imines **5.55** using aryl or alkyl sulfonyl chlorides (Scheme **76**). Unfortunately, the procedure is not applicable to forming N-sulfonyl imines from enolizable aldehydes and ketones.

Scheme 76. Sulfonylation of N-silyl imines

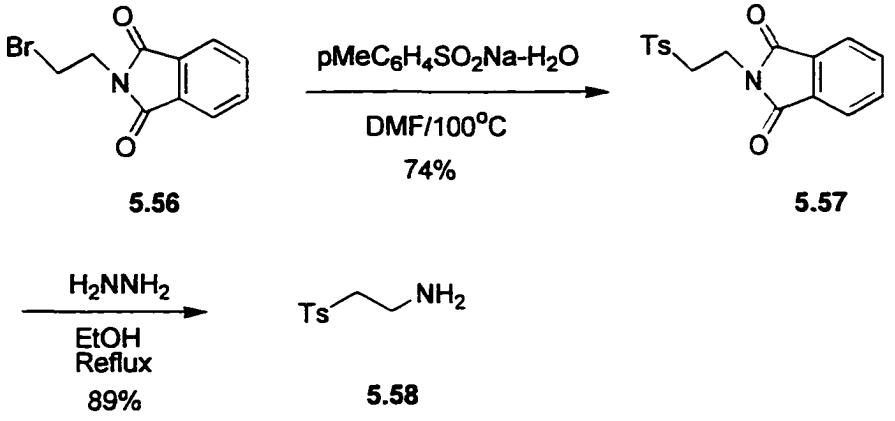


In order to synthesize NH imines or N-silyl imines, two of the four different methods which have been investigated are shown as follows.

(1). The stable crystalline β-tosylethylamine **5.58** can be easily prepared via an efficient modification of the reported route[129] as shown in scheme 77. Thus, commercially available N-(2-bromoethyl)phthalimide **5.56** was combined with sodium p-

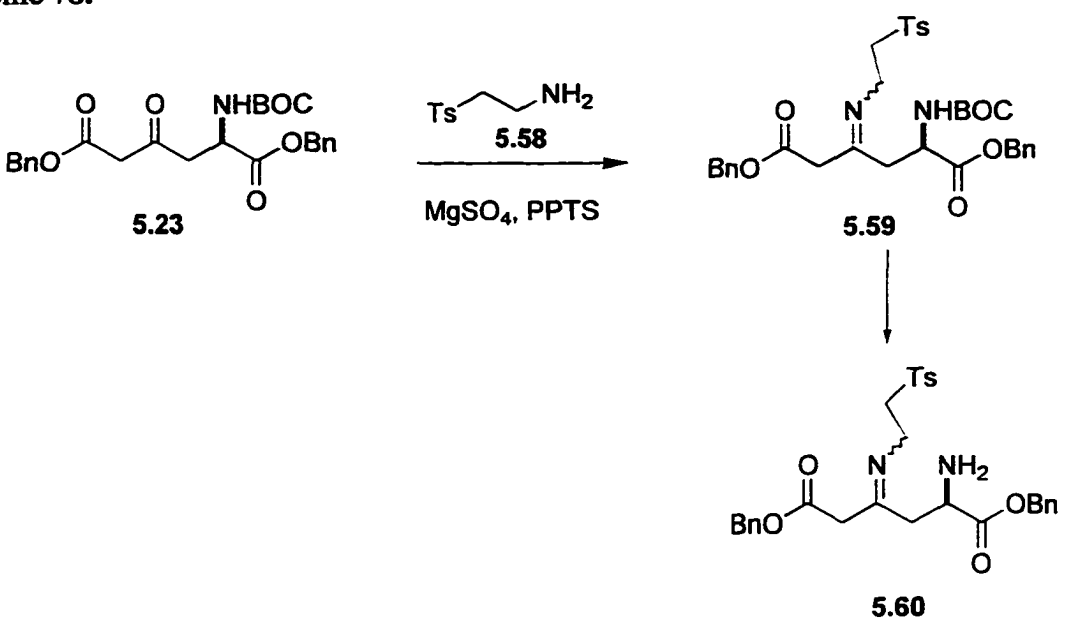
toluenesulfinate to afford sulfone **5.57**. Hydrazinolysis of the phthlimido group of compound **5.57** provided β-tosylethylamine **5.58** in good overall yield. β-tosylethylamine **5.58** can be used to synthesize N-tosylethyl (TSE) protected amide, which can be deprotected under mild conditions with potassium t-butoxide.

Scheme 77.



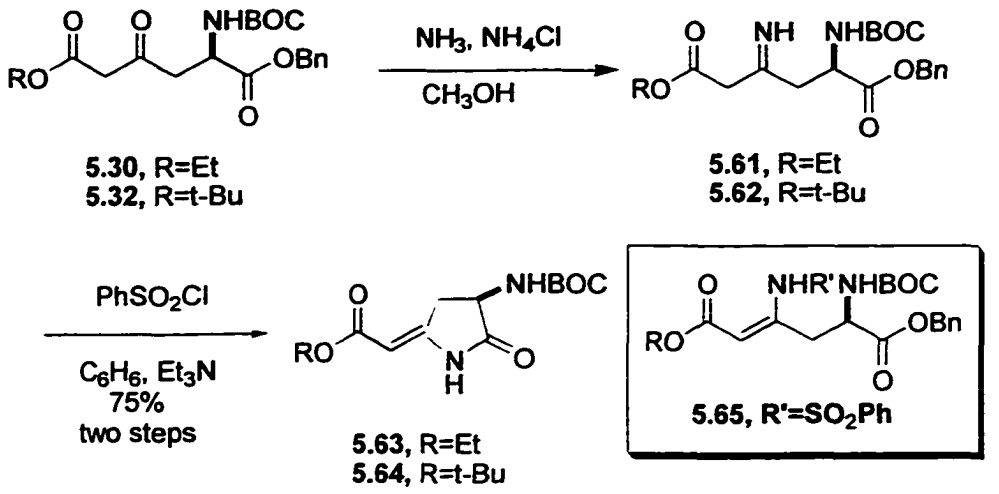
N-TSE protected amides **5.59** were prepared by adding β-tosylethylamine **5.58** to the blocked amino-keto-esters **5.19** and **5.23** in the presence of $MgSO_4$ in dichloromethane at room temperature, but no imine only compound **5.60** was obtained when compound **5.59** was treated with potassium t-butoxide in THF (Scheme 78).

Scheme 78.



(2). The old fashioned method for synthesis of imines using liquid ammonia[130] was revisited. The amino-keto-esters **5.30** and **5.32** were treated with ammonia under the catalysis of ammonium chloride in methanol at 0^0C for about 30 min., then the mixture was allowed to stir at room temperature for overnight. Removal of solvent afforded the crude products **5.61** and **5.62**. Sulfonylation[131] of the imines **5.61** and **5.62** were performed by reacting with benzensulfonyl chloride under basic catalyst. Surprisingly, cyclized products **5.63** and **5.64** were obtained instead of the predicted N-sulfonyl enamide **5.65**. These heterocycles should have enough activity for the cycloaddition with tri-O-benzyl-glactal since the nitrogen was attached to an electron-withdrawing group: carbonyl group (Scheme **79**).

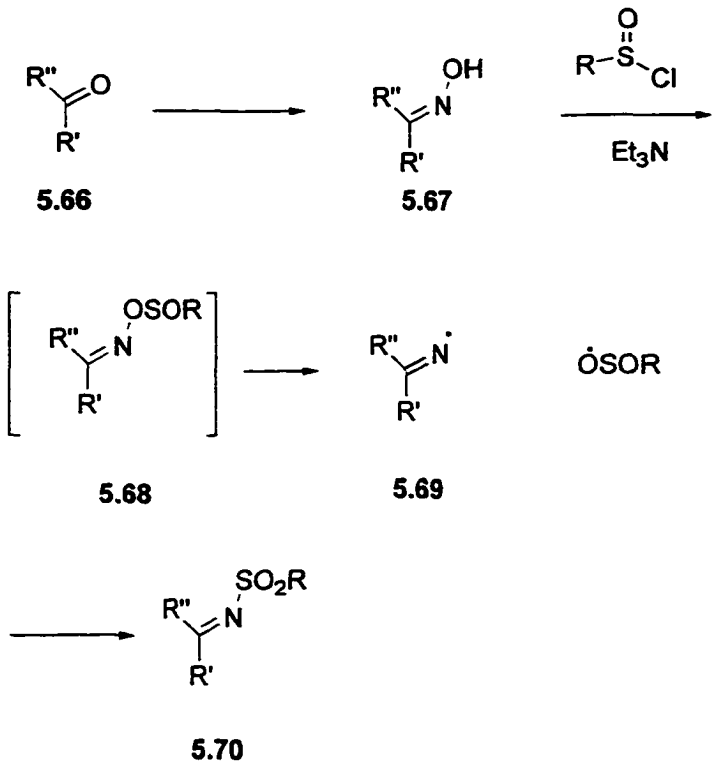
Scheme 79.



5.2.4. From oximes

Even though N-sulfonyl enamides such as **5.63** and **5.64** can be prepared successfully from amino-keto-esters by use of liquid ammonia, we still wanted to investigate the method of the free radical process via the oximes. Studies by Hudson and coworkers have demonstrated that N-sulfonyl ketimines **5.70** can be prepared from the corresponding ketoximes **5.67**; Thus, treatment of the ketoximes **5.67** with a sulfinyl chloride initially afforded the O-sulfinylated oximes **5.68**. Upon warming, the sulfonyloximes rearranged via a free radical process into N-sulfonyl ketimines **5.70** (Scheme **80**). However, the use of the unstable and reactive sulfinyl chloride reagents detracts from the technical convenience of this procedure.

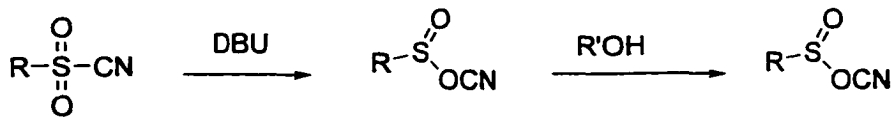
Scheme **80.**



5.66 **5.67** **5.68** **5.69** **5.70**

Boger and Corbett have describe a convenient modification of the original Hudson methodology.[132] They demonstrated the preparation of N-sulfonylimines **5.77** based on the preparation and *in situ* rearrangement of oxime O-sulfinates **5.76** employing readily available and stable sulfonyl cyanides **5.71** as reagents (Scheme **82**). Barton and co-workers have described the preparation of sulfinates **5.73** from alcohols upon treatment with methanesulfonyl cyanide or p-toluensufonyl cyanide (TsCN) **5.71** in the presence of DBU or DAB CO through a process of base-catalyzed rearrangement of the sulfonyl cyanide **5.71** to the corresponding sulfinyl cyanate **5.72** (Scheme **81**).

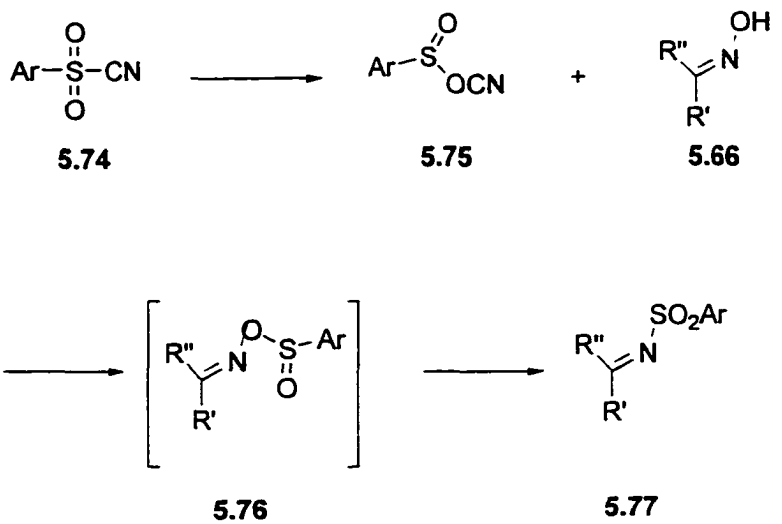
Scheme **81.**



5.71 **5.72** **5.73**

On the basis of these observations, treatment of an oxime **5.66** with commercially available toluenesulfonyl cyanide **5.74** generates the corresponding sulfinyl cyanate **5.75** *in situ*, which leads to the O-sulfinylated oxime **5.76** and then to the N-tosyl imine **5.77** (Scheme **82**). This methodology avoids the use of reactive, often unstable sulfinyl chlorides.

Scheme **82.**

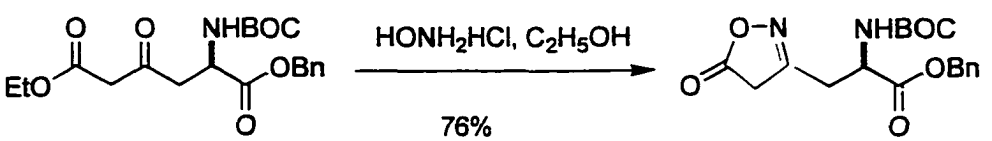


5.74 **5.75** **5.66**

5.76 **5.77**

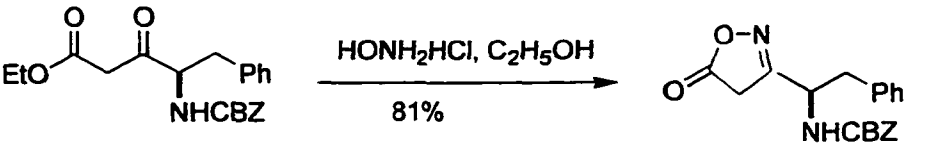
In order to prepare the oximes from amino-keto-esters, hydroxyl amine hydrochloride was added to a solution of amino-keto-esters **5.30** and **5.21** in methanol at room temperature and stirred overnight to afford the cyclized compounds **5.78** and **5.79** in the yield of 76% and 81% respectively instead of the desired ketoximes **5.82** and **5.84** (Scheme **83** and **84**).

Scheme **83.**



5.30 **5.78**

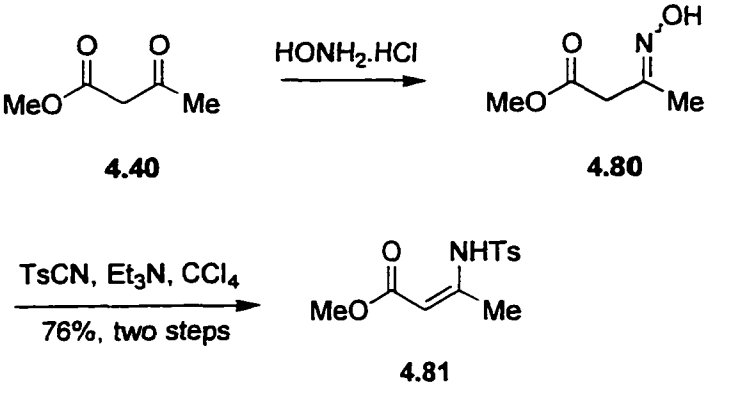
Scheme **84.**



5.21 **5.79**

To prevent cyclization in the preparation of ketoximes, the reaction mixture was buffered with 1 molar equivalent of Na_2CO_3. The desired ketoximes **5.80**, **5.82** and **5.84** were obtained after stirring in ethanol at room temperature for 5h. Treatment of the ketoximes **5.80**, **5.82** and **5.84** with commercially available toluenesulfonyl cyanide in the presence of 5 molar equivalents of triethylamine in CCl_4 gave the N-tosyl enamides **5.81**, **5.83** and **5.85** in the yield of 76%, 60%, and 65% respectively (Scheme **85**, **86**, and **87**).

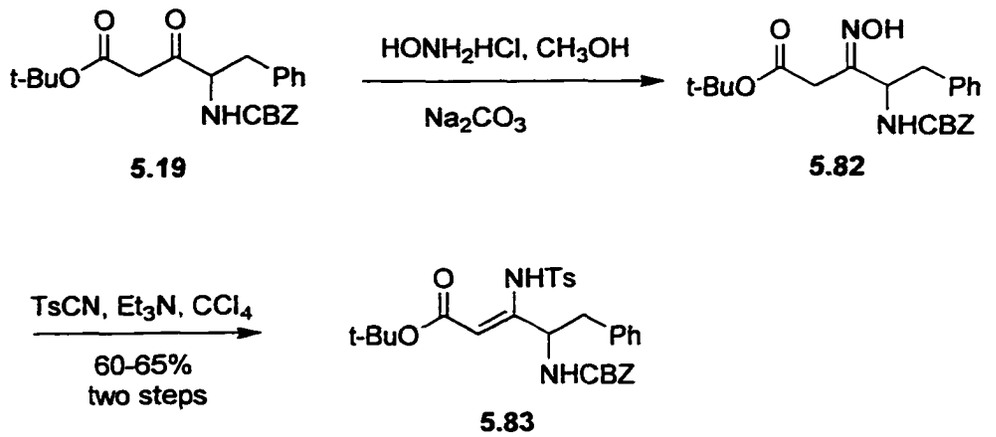
Scheme **85.**



4.40 **4.80**

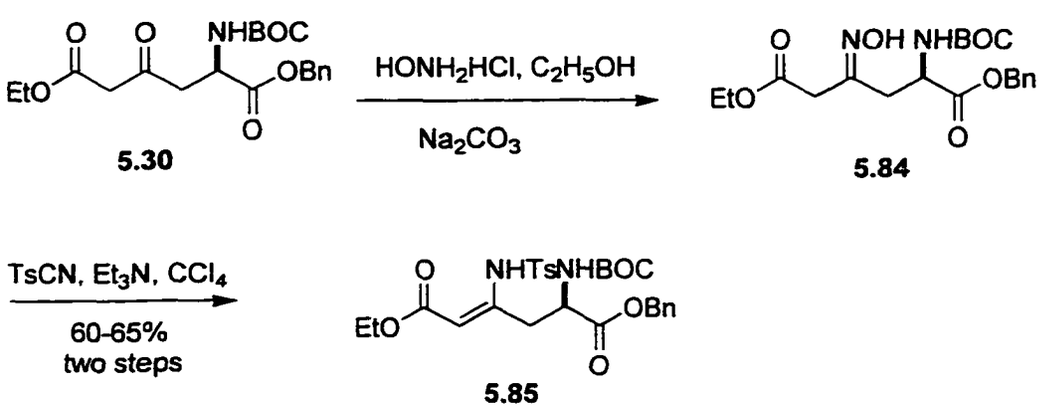
4.81

Scheme **86.**



5.19 **5.82** **5.83**

Scheme **87.**

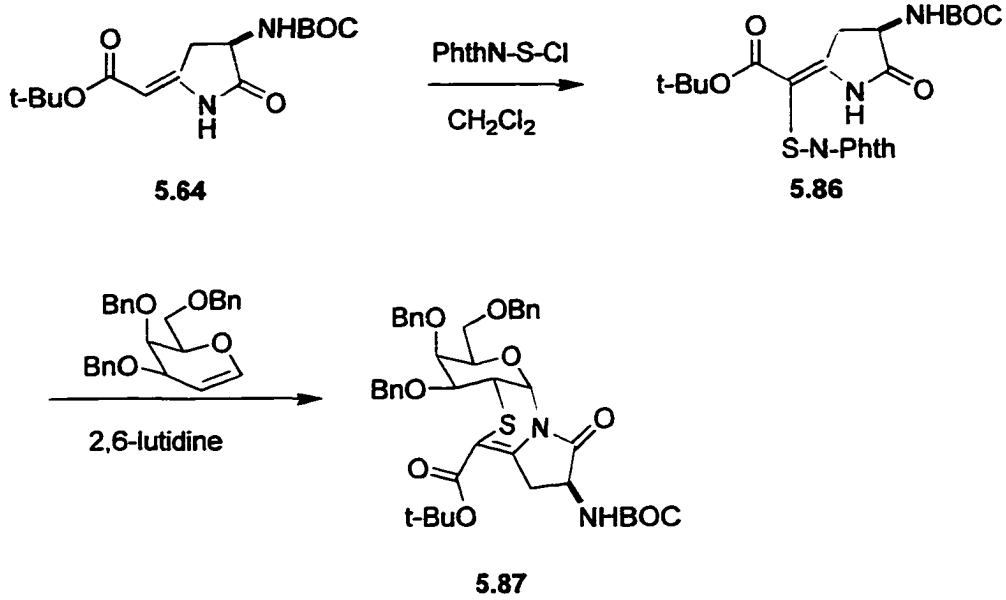


5.30 **5.84** **5.85**

5.3. Synthesis of glycopeptides via cycloaddition

Treatment of the cyclized product **5.64** with PhthN-S-Cl in dichloromethane at 0^0C, gave the phthalimidosulfenylated product **5.86** in quantitative yield. Cycloaddition was undertaken by treatment of the phthalimidosulfenylated product **5.86** with base in the presence of tri-O-benzyl-galactal. Cycloadduct **5.87** were obtained in 45% yield (Scheme **88**).

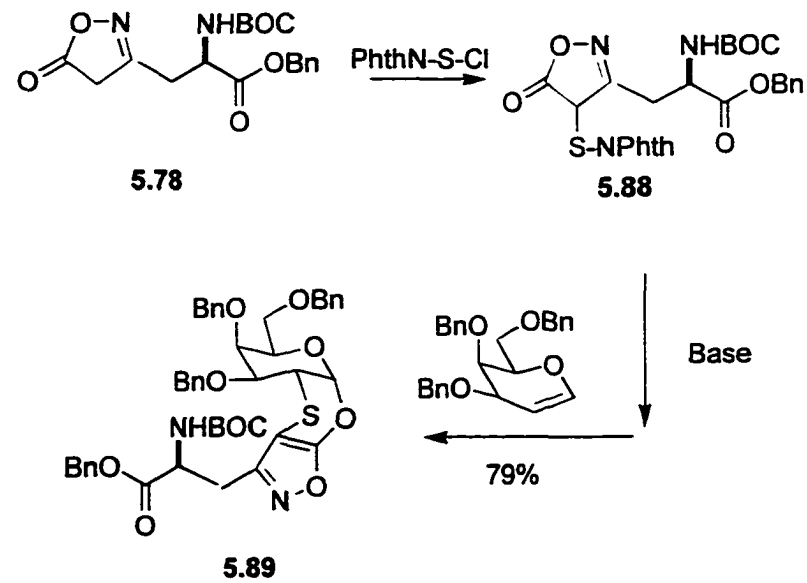
Scheme **88.**



5.64 **5.86** **5.87**

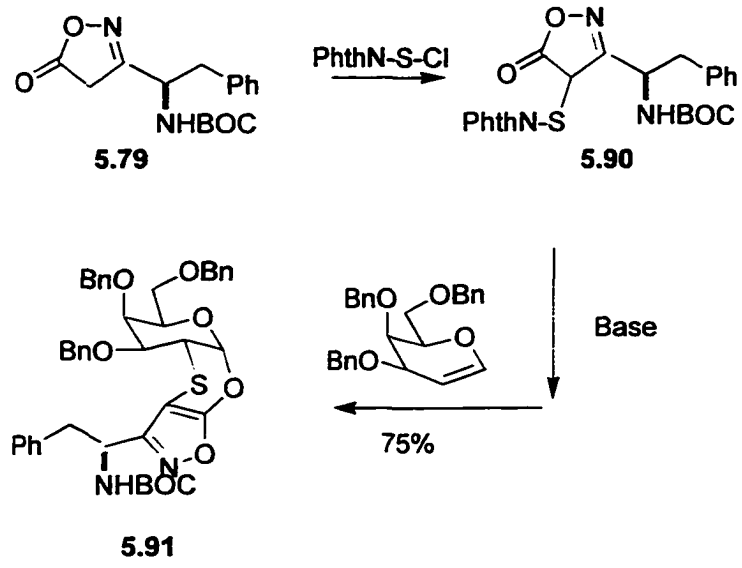
Similarly, treatment of **5.78** and **5.79** with PhthN-S-Cl in CH_2Cl_2, followed by adding base and tri-O-benzyl-galactal in chloroform at room temperature, afforded O-glycosyl cycloadducts **5.89** and **5.91** in the yields of 79% and 75% respectively (Scheme **89** and **90**).

Scheme **89.**



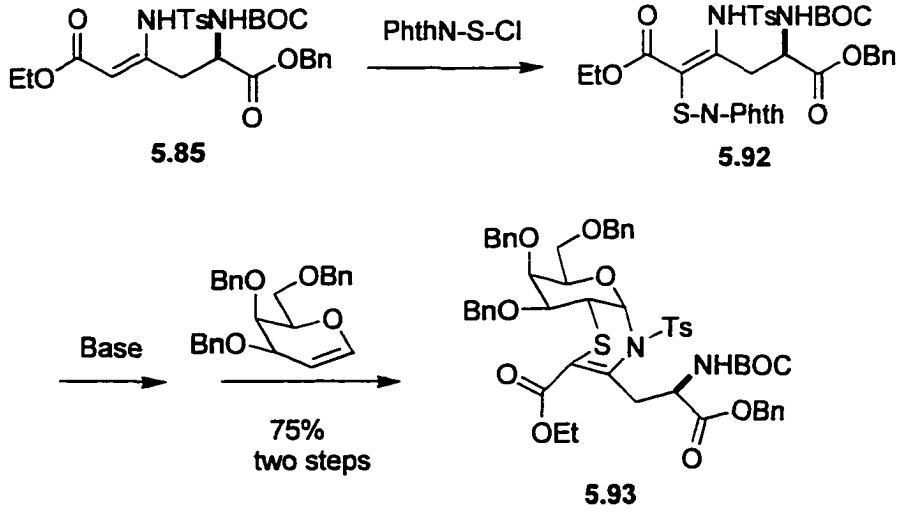
5.78 **5.88** **5.89**

Scheme **90.**



Finally, the phthalimidosulfenylation of N-tosyl imine **5.85**, followed by treatment with a catalytic amount of 2,6-lutidine in the presence of tri-O-benzyl-galactal in chloroform at room temperature, afforded the desired N-glycosyl cycloadduct **5.93** in 75% (Scheme **91**). The key chemical shift of cycloadduct **5.93** is the anomeric proton at 5.13 ppm (doublet, J=6.9 Hz).

Scheme **91.**



Conclusion

By using our unique method for introducing functionalized nitrogen to the anomeric carbon, a variety of interesting analogs of natural N-glycopeptides can be prepared. Also, by choosing the suitable sugar-based dienophile, we can get the right stereoselectivity of the cycloadducts.

EXPERIMENTAL SECTION

All reactions were carried out under a dry argon or nitrogen atmosphere at ambient temperature unless otherwise stated. Low temperatures were recorded as bath temperatures. Chromatography was carried out on silica gel 60, 230-400 mesh, using flash chromatography techniques. Analytical thin-layer chromatography (TLC) was performed on E. Merck precoated silica 60 F_{254} plates. Petroleum ether, hexane, pentane, dichloromethane, and ethyl acetate used as eluants were ACS reagent grade solvent. The following reaction solvents were purified by distillation: dichloromethane and chloroform (from P_2O_5), diethyl ether (from benzophenone and sodium, N_2), benzene (from CaH_2, N_2) and THF (from benzophenone and sodium, N_2), triethylamine (from CaH_2, N_2), acetonitrile (from P_2O_5). NMR spectra were measured with a GE QE 300 MHz instrument. Chemical shifts are reported in δ units, coupling constants in Hz. TMS (δ=0.0) was used as internal reference for spectra measured in $CDCl_3$. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrophotometer.

2-Bromo-4-methoxyphenol (2.29)[43]

To a stirred solution of 4-methoxyphenol (1.5 g, 12.1 mmol) in dichloromethane (90 ml)-methanol (60 ml) was added dropwise tetrabutylammonium tribromide at room temperature. The mixture was stirred for 1 hour until no more starting material was detected by TLC. The solvent was removed under vacuum and the obtained residue was treated with water. The mixture was extracted with ether (4×). The ether layer was dried over sodium sulfate and evaporated in vacuum to afford a residue which was purified by a silica gel column (20% ethyl acetate in petroleum ether) affording **2.29** in 2.2 g (90%). m.p. 114-115°C (lit.[43] 115-116°C). ^{1}HNMR ($CDCl_3$): δ 6.78-7.01 (m, 3H, ArH), 5.13 (s, 1H, OH), and 3.75 (s, 3H, Me).

2-Bromo-4-methoxyphenyl-toluene-p-sulfonate (2.30)[42]

A stirred solution of 2-bromo-4-methoxyphenol (2.0 g, 9.85 mmol) and triethylamine (1.7 ml) in dichloromethane (13 ml) was treated dropwise at 0°C with a solution of p-toluenesulfonyl chloride (2.25 g, 1.2 eq) in dichloromethane (20 ml). Stirring was continued at room temperature for 2 hours. The solution was diluted with dichloromethane, and washed with water, saturated sodium bicarbonate, and brine. The organic phase was dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded the crude product. The crude product was purified by flash chromatography with 10% ethyl acetate in petroleum ether as eluent which gave the tosylate (3.47 g, 90%), which was crystallized from dichloromethane-hexane as prisms. m.p. 74-75°C (lit.[42] 73.5-75°C). ^{1}HNMR ($CDCl_3$): δ 7.30 and 7.74 (AABB, 4H, ArH), 7.19 (d, $J_{6,5}$=8.9, 1H, 6-H), 7.01 (d, $J_{3,5}$=3.0, 1H, 3-H), 6.78 (dd, $J_{5,6}$=8.9, $J_{5,3}$=3.0, 1H, 5-H), 3.76 (s, 3H, Me), and 2.44 (s, 3H, Me).

1,4-Dihydro-6-methoxy-1,4-epoxynaphthalene (2.32)[42]

A stirred solution of tosyl ester (2.88 g, 8.1 mmol) in THF (36 ml)-furan (30 ml) was cooled to -100°C under argon and a solution of butyllithium (2.5 M) in hexane (3.4 ml) was added slowly by syringe. The solution was stirred for 10 min at -100°C and was then allowed to warm to room temperature during 2 hours. The reaction was quenched by adding water slowly and was then extracted with ethyl acetate. The crude product was purified by a silica gel column with 10% ethyl acetate in petroleum ether as eluent which afforded the desired adduct product 0.98 g in 68% yield. The adduct was crystallized from dichlomethane-hexane as needles. m.p. 63-65°C (lit.[42] 63-64°C). ^{1}HNMR ($CDCl_3$): δ 7.13 (d, J=7.8, 1H), 7.00 (m, 2H), 6.90 (d, J=3.9, 1H), 6.40 (dd, J=9.9, 1H), 5.66 (d, J=4.2, 2H), and 3.77 (s, 3H).

7-Methoxynaphthalen-1-ol (2.33)

A solution of 1,4-dihydro-6-methoxy-1,4-epoxynaphthalene (1.338 g) in methanol (35 ml) was heated under reflux with conc. HCl (5 drops) for 1 hour under argon. Some of the methanol was removed under reduced pressure and the residue was diluted with water. The crude product was isolated by extraction with ethyl acetate. The solvent under reduced pressure and the residue was then purified by a silica gel column with 5% ethyl acetate in petroleum ether as eluent to afford 7-methoxynaphthalen-1-ol 1.244 g (93%). The product was crystalllized from dichloromethane-hexane as prisms. m.p. 103-105°C (lit.[42] 100-102°C). ^{1}HNMR ($CDCl_3$): δ 7.70 (d, $J_{5,6}$=7.6, 1H, 5-H), 7.04-7.50 (m, 4H, 3-, 4-, 6-, and 8-H), 6.77 (dd, $J_{2,3}$=7.2, $J_{2,4}$=1.3, 1H, 2-H), 5.21 (s, 1H, OH), and 3.95 (s, 3H, OMe); ^{13}CNMR ($CDCl_3$): δ 156.68, 150.01, 129.87, 128.86, 124.84, 122.99, 119.99, 118.68, 108.81, 99.64, 54.88.

1,7-Dimethoxynaphthalene (2.34)

7-methoxynaphthalen-1-ol (0.402 g, 2.3 mmol) was added to a 2M NaOH solution (9 ml) which had been previously purged with N_2. Dimethyl sulfate (1 ml) was carefully added to the above stirred solution. After 1 hour, additional portions of 5M NaOH (3 ml) and dimethyl sulfate (0.3 ml) were added. Throughout, the reaction temperature was kept between 17 and 21°C by adjusting the rate of dimethyl sulfate addition and by use of an ice bath. After 1 hour at room temperature, the reaction mixture was heated to reflux for 1 hour. The cooled mixture was extracted with ether. The combined ether extracts were washed with 5M NaOH and water. The ether extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified with a silica gel column with 20% ethyl acetate in petroleum ether, affording 0.40 g of 1,7-dimethoxynaphthalene in 93% yield. ^{1}HNMR ($CDCl_3$): δ 7.69 (d, $J_{5,6}$=7.6, 1H, 5-H), , 7.60-7.06 (m, 4H, 3-, 4-, 6-and 8-H), 6.80 (d, $J_{2,3}$=7.5, 1H, 2-H), 4.01 (s, 3H, OMe), and 3.94 (s, 3H, OMe).

3,5-Dimethoxy-2-methylnaphthalene (2.35)[44]

To a stirred solution of 1,7-dimethoxynaphthalene (0.40 g, 2.13 mmol) in dry THF (5 ml) kept at -100°C under nitrogen was added a 2.5 M solution of butyllithium in hexane (1 ml, 2.5 mmol) followed by tetramethylethylenediamine (0.7 ml, 4.4 mmol). After being stirred at room temperature for 20 hours, the mixture was cooled to -70°C, and CH_3I (0.138 ml, 2.2 mmol) was added. After 1 hour, a saturated solution of NH_4Cl (5 ml) was added to the cold reaction mixture. Ether was added, and the ether layer was separated and concentrated. The residue was diluted with ether and extracted with 2 M HCl. The ether layer was dried, filtered, and concentrated to afford the crude product which was purified by a silica gel column with 10% ethyl acetate in petroleum ether. Colorless needles of 3,5-dimethoxy-2-methylnaphthalene were obtained 0.387 g (90%). m.p. 73-74°C (lit.[44] 72-73°C). ^{1}HNMR ($CDCl_3$): δ 7.68-7.05 (m, 4H), 6.83-6.75 (m, 1H), 3.96 (s, 3H, Me), 3.93 (s, 3H, Me), and 2.37 (s, 3H, Me); ^{13}CNMR ($CDCl_3$): δ 156.7, 154.3, 129.8, 128.6, 128.5, 125.1, 123.3, 119.4, 102.7, 99.0, 55.3, 54.2, 17.0.

1,4-Dihydro-3,5-dimethoxy-2-methylnaphthalene (2.36)[44]

To a stirred solution of 3,5-dimethoxy-2-methylnaphthalene (40 mg, 0.2 mmol) in dry EtOH (5 ml) kept at gentle reflux under N_2, were added thin slices of sodium (0.5 g) during 1.5 hours. The heating was interrupted, and water (2 ml) and NH_4Cl (0.2 g) were added. After evaporated of the EtOH, water and ether were added to the semisolid residue. The ether layer was separated, dried, filtered, and concentrated to give 37 mg (90%) of white crystals. m.p. 57-61°C (lit.[44] 58-61°C). ^{1}HNMR ($CDCl_3$): δ 7.22-7.00 (m, 1H), 6.81-6.55 (m, 2H), 3.89 (s, 3H, Me), 3.60 (s, 3H, Me), 3.37 (s, 4H), and 1.73 (s, 3H, Me); ^{13}CNMR ($CDCl_3$): δ 156.8, 145.5, 135.3, 123.0, 126.4, 120.0, 110.7, 106.6, 56.2, 55.0, 35.8, 24.2, 14.7.

8-Methoxy-3-methyl-2-tetralone (2.37)

A solution of 1,4-dihydro-3,5-dimethoxy-2-methylnaphthalene (38 mg), 12N HCl (7 drops), and methanol (3 ml) was refluxed under N_2 for 3 hours. The volatiles were evaporated under reduced pressure, and the residue was partitioned between water and ether. The ether layer was separated, dried, filtered, and concentrated to give 8-methoxy-3-methyl-2-tetralone in 88% yield. ^{1}HNMR ($CDCl_3$): δ 7.28-6.66 (m, 3H, ArH), 3.81(s, 3H, OMe), 3.52 (d, J=9, 2H), 3.25-2.38 (m, 3H,), and 1.16 (d, J=6.3, 3H, Me); ^{13}CNMR ($CDCl_3$): δ 211.9, 156.7, 137.0, 127.2, 122.2, 120.1, 108.0, 55.3, 42.6, 37.8, 37.3, 14.5.

Birch reduction of 7-methoxynaphthalen-1-ol

A three-necked flask, equipped with a dry-ice condenser was charged with 7-methoxynaphthalen-1-ol (75 mg, 0.43 mmol). The stirrer was started, and to the rapidly stirred solid, was added 5 ml of liquid ammonia as rapidly as possible. When 7-methoxynaphthalen-1-ol had dissolved, 0.2 g of lithium metal was added in small pieces. After addition of the lithium metal, the solution was stirred for an additional 5 min. and was then treated with 10 ml of absolute C_2H_5OH, which was added dropwise during 5 min. The condenser was removed, and the ammonia was evaporated. The residue was dissolved in 10 ml of water, extracted with ether. The aqueous phase was carefully acidified with concentrated HCl. The resulting mixture was then extracted with ether (4×). The combined ether phase was dried over Na_2SO_4, then the solvent was removed to afford the crude product **2.39** and **2.40** in the ratio of 5:3 (83 mg).

8-Hydroxy-2-tetralone (2.41)

A solution of the Birch reduction products **2.39** and **2.40** (80 mg), 12N HCl (0.5 ml), and methanol (10 ml) was refluxed under N_2 for 2 hours. The volatiles were

evaporated under reduced pressure, and the residue was partitioned between water and ether. The ether layer was separated, dried, filtered, and concentrated to give 106 mg of crude 8-hydroxy-2-tetralone which was purified by means of a silica gel column (20% of ethyl acetate in petroleum ether as fluent) to afford 8-hydroxy-2-tetralone 65 mg (87%). ^{1}HNMR ($CDCl_3$): δ 7.06 (t, 1H), 6.82 (d, J=7.2, 1H), 6.67 (d, J=8.1, 1H), 4.74 (Broad, 1H, OH), 3.55 (s, 2H), 3.09 (t, J=6.6, 2H), and 2.58 (t, J=6.6, 2H); ^{13}CNMR ($CDCl_3$): δ 210.72, 152.62, 137.54, 126.88, 119.66, 112.75, 38.32, 37.46, 28.30.

8-Acetoxy-2-tetralone (2.42)

To a solution of 8-hydroxy-2-tetralone (63 mg, 0.39 mmol), pyridine (0.1 ml, 5 eq) in CH_2Cl_2 (2 ml) was added acetic anhydride (1 eq) at 0°C. The resulting solution was allowed to warm up to room temperature. After stirring the solution at room temperature for 3 hours, there was no starting material detected by TLC. The reaction mixture was diluted with CH_2Cl_2, washed with water, $NaHCO_3$ solution, and brine, dried over Na_2SO_4. Removal of the solvent afforded the crude product. The crude product was purified on a silica gel column (10% of ethyl acetate in petroleum ether as fluent) to give 8-acetoxy-2-tetralone (66 mg, 84%). FTIR: 1746, 1716, 1467, 1208; ^{1}HNMR ($CDCl_3$): δ 7.22 (m, 3H), 7.15 (d, J=7.5, 1H), 6.98 (d, J=7.5, 1H), 3.4 (s, 2H), 3.11 (t, J=6.6, 2H), 2.59 (t, J=6.6, 2H), and 2.32 (s, 3H, Me); ^{13}CNMR ($CDCl_3$): δ 209.28, 169.28, 148.70, 138.48, 127.72, 126.15, 125.76, 120.62, 38.62, 28.90, 21.04.

8-Trifloxy-2-tetralone (2.43)

To a solution of 8-hydroxy-2-tetralone (25.1 mg, 0.15 mmol), Et_3N (0.1 ml, 5 eq) and DMAP (3 mg) in CH_2Cl_2 (2 ml) was added triflic anhydride (31.5 μl, 1.2 eq) at 0°C. The reaction was completed within 15 min., and ice water was added to the reaction

mixture. The resulting solution was extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded the crude product, which was purified on a silica gel column, affording the desired product 27.5 mg (89%). ^{1}HNMR ($CDCl_3$): δ 7.2-7.26 (m, 3H), 3.62 (s, 2H), 3.18 (t, J=6.8, 2H), and 2.60 (t, J=6.8, 2H).

Phthalimidosulfenylation of 8-acetoxy-2-tetralone and 8-trifloxy-2-tetralone

To a solution of 8-acetoxy-2-tetralone (47.6 mg, 0.23 mmol) or 8-trifloxy-2-tetralone (40 mg, 0.15 mmol) in chloroform was added PhthN-S-Cl[103] (1.2 eq) in portions at 0^0C during a period of 15 min. The reaction mixture was stirred at such temperature for an additional 20 min., allowed to warm up to room temperature in 30 min. Cold n-pentane was added. A white precipitate formed which was filtered and washed with cold n-pentane to afford the desired product.

2.44 (88% yield): FTIR: 1773, 1744, 1716, 1607, 1467, 1280, 1195; ^{1}HNMR ($CDCl_3$): δ 8.06- 7.75 (m, 4H), 7.40-7.08 (m, 3H), 5.02(s, 1H), 3.8(m, 1H), 3.2 (m, 2H), 2.6 (s, 3H, Me), and 2.3-2.5 (m, 1H); ^{13}CNMR ($CDCl_3$): δ 203.1, 170.0, 167.8, 150.1, 140.2, 135.3, 135.1, 134.6, 132.5, 130.3, 126.3, 124.6, 124.3, 123.9, 121.9, 50.5, 35.6, 28.0, 20.1.

2.45 (80% yield): ^{1}HNMR ($CDCl_3$): δ 8.10-7.75 (m, 4H), 7.42-7.10 (m, 3H), 5.1 (s, 1H), 3.8(m, 1H), 3.1(m, 2H), and 2.4(m, 1H).

General procedure for cycloaddition of 1-phthalimidosulfenyl-8-acetoxy-2-tetralone 2.44 or 1-phthalimidosulfenyl-8-trifloxy-2-tetralone 2.45 with tri-O-benzyl-D-galactal.

To a mixture of the heterodiene precursors **2.44** (50 mg, 0.13 mmol) or **2.45** (55 mg, 0.11 mmol) and tri-O-benzyl-D-galactal[103] (1.2 eq) in 2 ml of $CHCl_3$ was added a catalytic amount of 2,6-lutidine and the solution was stirred at room temperature for 2

days. The syrupy solution was dissolved in CH_2Cl_2 and washed with saturated ammonium chloride (2×) and brine once, then dried over Na_2SO_4. Removal of the solvent gave the crude products. The crude products were purified on a silica gel column, affording the desired products.

2.48 (19% yield): ^{1}HNMR ($CDCl_3$): δ 7.4-6.9 (m, 18H), 5.72 (d, J=2.4, 1H), 5.00-4.47 (m, 6H), 4.03 (m, 1H), 3.69-3.59 (m, 5H), 2.32 (s, 3H), 2.60-2.05 (m, 4H).

2.49 (21% yield): ^{1}HNMR ($CDCl_3$): δ 7.8-6.85 (m, 18H), 5.74 (d, J=2.7, 1H), 4.95-4.48 (m, 6H), 3.80-3.60 (m, 5H), 2.74-2.07 (m, 4H)

Preparation of the vinylsilane (2.58)

To the solution of the arenesulfonylhydrazone **2.57** (90 mg, 0.23 mmol) in 4 ml of TMEDA was added 1.2 ml of n-BuLi M in hexane, 13 eq) via syringe at -45°C. The resulting solution was stirred at -45°C for 20 min. and at 0°C for 3 hr, at which point, 4 eq of TMSCl was added. After 4 hr, water was introduced, and the mixture was extracted with pentane. The organic layer was washed with water, copper sulfate solution and brine. The dried solution was concentrated, afforded the product. ^{1}HNMR ($CDCl_3$): δ 7.29-7.14(m, 2H), 6.88(d, J=9.9, 1H), 6.78(d, J=6.6, 1H), 6.04 (m, 1H), 2.86 (t, 2H), 2.3 (m, 2H), and 0.12 (s, 27H).

General procedure for the preparation of 5-substituted isoquinoline.

To a suspension of NaH (1.4 eq, 60% in mineral oil) in DMF was added 5-hydroxyl isoquinoline (500 mg, 90% purity, 3.44 mmol) in DMF dropwise at 0^0C. After the resulting mixture was stirred at room temperature for 40 min., RX (1.2 eq) was added to the mixture at 0^0C. The mixture was stirred at room temperature for 4 h until it was quenched by adding ice-water to the reaction mixture. The aqueous solution was extracted with ethyl acetate three times. The combined organic phase was dried over

Na_2SO_4. Removal of the solvent afforded the crude product. The crude product was purified by a silica gel affording the desired 5-protected isoquinoline product.

5-Methoxymethyl isoquinoline (2.72)

This compound was prepared according to the above general procedure from 5-hydroxyisoquinoline (0.561g, 90% purity, 3.48 mmol). Yield: 99%; ^{1}HNMR ($CDCl_3$): δ 9.22 (s, 1H), 8.54 (d, J=5.7, 1H), 8.01 (d, J=6, 1H), 7.60 (d, J=7.2, 1H), 7.50 (t, J=7.2, 1H), 7.31 (t, J=7.2, 1H), 5.40 (s, 2H), 3.55 (s, 3H); ^{13}CNMR ($CDCl_3$): δ 174.6, 151.9, 142.7, 129.4, 128.5, 127.3, 120.4, 114.8, 111.6, 94.7, 56.2.

5-Methoxyisoquinoline (2.73)

This compound prepared according to the above general procedure for compound **2.72** from 5-hydroxyisoquinoline (1.20 g, 90% purity, 7.44 mmol). Yield: 94%; ^{1}HNMR ($CDCl_3$): δ 9.20 (s, 1H), 8.53 (d, J=6, 1H), 7.9 (d, J=6, 1H), 7.48 (m, 2H), 6.98 (m, 1H), 4.0 (s, 3H); ^{13}CNMR ($CDCl_3$): δ 153.9, 151.3, 142.2, 128.9, 127.9, 126.9, 118.8, 114.5, 107.1, 55.1.

5-Ethoxycarbonyloxy isoquinoline (2.74)

This compound was prepared according to the above general procedure for compound **2.72** from 5-hydroxyisoquinoline (0.50 g, 90% purity, 3.1 mmol). Yield: 62%; ^{1}HNMR ($CDCl_3$): δ 9.30 (s, 1H), 8.59 (d, J=6, 1H), 7.88 (dd, J=1.8, 6.4, 1H), 7.78 (d, J=6.4, 1H), 7.61 (m, 2H), 4.41 (q, J=7.2, 2H), 1.45 (t, J=7.2, 3H).

General procedure for the preparation of 2-(2,4-dinitrophenyl)-5-substituted isoquinolinium chloride.

The isoquinolium salts were prepared by refluxing an equimolecular mixture of hydroxyl-protected 5-hydroxyisoquinolines and 2,4-dinitrochlorobenzene in dry ether

for 1-3 days. The salts precipitated out from the reaction mixture. They were filtered and washed with cold ether till the reddish color disappeared and the yellow crystalline salts remained on the filter paper. The salts were dried under vacuum.

2-(2,4-Dinitrophenyl)-5-methoxymethylisoquinolinium chloride (2.75)

This compound was prepared according to the above general procedure from 5-methoxymethyisoquinoline (0.373 g, 1.97%). Yield: 14%; ^{1}HNMR ($CDCl_3$): δ 11.39 (s, 1H), 10.12 (d, J=2.1, 1H), 9.94 (d, J=8.7, 1H), 9.78 (m, 2H), 8.62 (d, J=8.7, 1H), 8.40 (m, 1H), 7.92 (m, 2H), 5.54 (s, 2H), 3.61 (s, 3H).

2-(2,4-Dinitrophenyl)-5-methoxyisoquinolinium chloride (2.76)

This compound was prepared according to the above general procedure for compound **2.75** from 5-methoxyisoquinoline (0.85 g, 5.34 mmol). Yield: 65%; ^{1}HNMR ($CDCl_3$): δ 11.40 (s, 1H), 9.21 (d, J=2.1), 9.11(d, J=8.1, 1H), 8.82 (dd, J=2.1, 7.2, 1H), 8.71 (d, J=7.2, 1H), 8.43 (d, J=7.5, 1H), 8.20 (d, J=7.2, 1H), 8.02 (t, J=7.2, 1H), 7.59 (d, J=7.2, 1H), 4.19 (s, 3H).

2-(2,4-Dinitrophenyl)-5-ehtoxycarbonyloxyisoquinolinium chloride (2.77)

This compound was prepared according to the above general procedure for compound **2.75** from 5-ethoxycarbonyloxyisoquinoline (0.21 g, 0.99 mmol). Yield: 38%; ^{1}HNMR ($CDCl_3$): δ 11.49 (s, 1H), 9.09 (d, J=1.8, 1H), 8.74 (m, 3H), 8.54 (m, 1H), 8.22 (d, J=7.5, 1H), 7.90 (m, 2H), 3.51 (q, 2H), 1.18 (t, 3H).

Preparation of the naphthaldehyde (2.80)

Ethyl vinyl ether was added in excess to the mixture of 2-(2,4-dinitrophenyl)-5-(methoxymethyl)isoquinolinium chloride **2.75** (30 mg, 0.077 mmol) and $CaCO_3$ (6 eq) in 1 ml of dry methanol. The mixture was stirred at room temperature for 24 h.

The reaction mixture was filtered over Celite which was further washed with CH_2Cl_2. A reddish material was obtained following the removal of the solvent in vacuum.

The crude adduct was dissolved in 3 ml of THF/H_2O (8:1), followed by adding Amberlyst 15, and stirred at room temperature for 1 day. The resin was filtered. the solvent was removed by vacuum. The crude product was purified by a silica gel column to give the desired compound **2.79**. ^{1}HNMR ($CDCl_3$): δ 9.81 (s, 1H), 9.19 (d, J=2.7, 1H), 8.91(d, J=8.7, 1H), 8.30 (dd, J=2.7, 8.7, 1H), 7.32-7.01 (m, 4H), 5.23 (s, 2H), 5.20 (m, 1H), 4.36 (m, 1H), 4.21 (m, 1H), 3.62 (q, J=7.2, 2H), 3.48 (s, 3H), 2.55 (m, 1H), 1.86 (m, 1H), 1.23 (t, J=7.2, 3H).

The above product was treated with K_2CO_3 solution in methanol and water at 60°C for 5 min.. The reaction mixture was diluted with ethyl acetate which was then washed with water and brine, dried over Na_2SO_4. After removal of the solvent, the desired product **2.80** was obtained by the purification on a silica gel column (14.8 mg, 89% yield for the three steps). ^{1}HNMR ($CDCl_3$): δ 11.06 (s, 1H, CHO), 7 .94-7.19 (m, 6H), 5.33 (s, 2H), and 3.46 (s, 3H).

1,5-Dimethoxy-1,4-cyclohexadiene[57] (2.82)

Ammonia (700 ml) was collected in a three-necked flask equipped with a dry-ice condenser. Sodium (30.0 g, 1.3 mol) was added over a period of 30 min., and the resultant dark blue solution was stirred for an additional 30 min. A solution of m-dimethoxybenzene (32.7 g, 0.237 mol) in a mixture of anhydrous ether (100 ml) and anhydrous ethanol (62.5 g, 1.36 mol) was added slowly over a period of 2 h. The mixture was stirred for an additional 1.5 h. The reaction mixture was quenched by addition of 75 ml of 1:1 ethanol-water , followed by water until a colorless mixture was obtained. The condenser was removed from the flask and the ammonia was allowed to evaporate. The remaining solution was diluted with brine and extracted with 1:1 mixture of ether and petroleum ether. The combined extracts were washed

with brine and dried over Na_2SO_4. Removal of the solvent , followed by distillation, afforded the product in 95 % yield. ^{1}HNMR ($CDCl_3$): δ 4.66 (m, 2H), 5.57 (s 6H), 2.83 (m, 4H); ^{13}CNMR ($CDCl_3$): δ 151.6, 90.2, 53.7, 30.6, 24.5.

Preparation of the 2-benzotetralones (2.84 and 2.86)

1,5-Dimethoxy-1,4-cyclohexadiene **2.82** was added to the mixture of 2-(2,4-dinitrophenyl)-5-(methoxymethyl)isoquinolinium chloride or 2-(2,4-dinitrophenyl)-5-(methoxy)isoquinolinium chloride and $CaCO_3$ (6 eq) in 2 ml of dry methanol. The mixture was stirred at room temperature for 2 days. The reaction mixture was filtered over Celite, washed with CH_2Cl_2. A reddish materials **2.83** and **2.85** were obtained following the removal of the solvent in vacuum.

The crude adducts were dissolved in 5 ml of THF/H_2O (8:1), followed by adding concentrated HCl (4 drops). After stirred at 65°C for 50 min., the reaction was quenched by adding water. The combined organic phase was washed with brine, dried over Na_2SO_4. Removal of the solvent afforded the crude products. Purification of the crude products on a silica gel gave compounds **2.84** and **2.86**.

2.84: (69% yield); ^{1}HNMR ($CDCl_3$): δ 7.96 (s, 1H), 7.68 (s, 1H), 7.39 (d, J=7.5, 1H), 7.30 (t, 1H), 6.78 (d, J=7.5, 1H), 5.40 (s, 1H), 3.81 (s, 2H), 3.20 (t, 2H), and 2.59 (t, 2H).

2.86: (82% yield); ^{1}HNMR ($CDCl_3$): δ 8.02 (s, 1H), 7.66 (s, 1H), 7.37 (m, 2H), 6.80 (m, 1H), 4.00 (s, 3H), 3.79 (s, 2H), 3.20 (t, 2H), and 2.60 (t, 2H).

Ring-opening of cycloadduct 2.83 with Amberlyst-15 (2.87)

The crude adduct **2.83** was dissolved in 5 ml of THF/H_2O (8:1), followed by the addition of Amberlyst-15. After being stirred at 40°C for 24h., the reaction was quenched by adding water. The combined organic phase was washed with brine, then dried over Na_2SO_4. Removal of the solvent afforded the crude product. After

purification, compound **2.87** was obtained in 69% yield. FTIR: 1721.9, 1614.3, 1587.8, 1521.9; ^{1}HNMR ($CDCl_3$): δ 9.64 (s, 1H), 9.20 (m, 1H), 9.19 (d, J=5.7, 1H), 8.34 (dd, J=11.7, 1H), 7.32(m, 3H), 6.99 (d, J=9, 1H), 5.18 (s, 2H), 5.02 (dd, J=8.4, 1H), 3.85 (m, 1H), 3.54 (m, 1H), 3.47 (s, 3H), 3.28 (s, 3H), 2.75 (m, 2H), 2.48 (m, 3H), 2.23 (m, 1H).

Cycloaddition of 2-methoxy-1,4-butadiene with 2-(2,4-dinitrophenyl)-5-methoxyisoquinolinium chloride (2.93)

2-Methoxy-1,4-butadiene (0.209 g, 6 eq) was added to the mixture of 2-(2,4-dinitrophenyl)-5-methoxyisoquinolinium chloride (0.15 g, 0.42 mmol) and $CaCO_3$ (6 eq) in 8 ml of dry methanol. The mixture was stirred at room temperature for 2 days. The reaction mixture was filtered over Celite which was then washed with CH_2Cl_2. A reddish material **2.93** was obtained following the removal of the solvent in vacuum. ^{1}HNMR ($CDCl_3$): δ 8.62 (d, J=2.7, 1H), 8.19 (dd, J=2.7, 9.3, 1H), 7.32 (m, 2H), 6.98 (d, J=7.2, 1H), 6.82 (d, J=8.4, 1H), 5.53 (q, J=17.7, 1H), 5.30 (d, J=2.4, 1H), 5.02 (d, J=9.9, 1H), 4.93 (d, J=17.4, 1H), 4.23 (d, J=2.4, 1H), 3.82 (s, 3H), 3.31 (s, 3H), 3.07 (s, 3H), 2.33 (dd, J=2.8, 17.4, 1H), 1.96 (dd, J=2.8, 17.4, 1H).

Hydrolysis of the cycloadduct 2.93 of 2-methoxy-1,4-butadiene with 2-(2,4-dinitrophenyl)-5-methoxyisoquinolinium chloride (2.94)

The crude adduct **2.93** was dissolved in 4 ml of THF/H_2O (3:1), followed by adding TsOH (50 mg). After being stirred at room temperature overnight, the reaction was quenched by adding water. The combined organic phase was washed with brine, dried over Na_2SO_4. Removal of the solvent afforded the product **2.94**(175 mg, 100%). FTIR: 3351, 1724, 1615, 1588, 1522, 1335; ^{1}HNMR ($CDCl_3$): δ 9.79 (d, J=2.7, 1H), 9.17 (d, J=2.7, 1H), 9.07 (d, J=8.4, 1H), 8.26 (dd, J=2.4, 9.3, 1H), 7.26 (m, 1H), 7.18 (d, J=9.3, 1H), 6.95 (d, J=7.5, 1H), 6.86 (d, J=8.1, 1H), 5.93 (q, J=17.7, 1H), 5.43 (d,

J=10.2, 1H), 5.20 (d, J=17.7, 1H), 4.94 (m, 1H), 4.41 (m, 1H), 3.84 (s, 3H), 3.30 (s, 3H), 2.34 (q, J=17.4, 1H), 2.28 (q, J=17.4, 1H); ^{13}CNMR ($CDCl_3$): δ 199.4, 156.6, 147.0, 137.7, 135.8, 135.4, 130.3, 129.9, 128.8, 124.1, 124.0, 120.4,118.5, 118.4, 113.9, 77.4, 55.2, 50.9, 50.7, 50.2, 33.9.

Preparation of the aldehyde (2.95)

The above product **2.94** was treated with K_2CO_3 solution in methanol and water at 60°C for 5 min.. The reaction mixture was diluted with ethyl acetate, then washed with water and brine, dried over Na_2SO_4, and the solvent was removed. The desired product **2.95** was obtained by the purification of the crude product on a silica gel column (20.1mg, 90% yield for three steps); ^{1}HNMR ($CDCl_3$): δ 10.82 (s, 1H), 7.84 (dd, J=8.7, 27, 2H), 7.41 (t, J=8.7, 1H), 7.07 (dd, J=8.7, 18.2, 2H), 6.90 (d, J=1.5, 1H), 5.85 (d, J=17.1, 1H), 5.42 (d, J=10.5, 1H), 3.96 (s, 3H).

5-Ethoxycarbonyl-3-formyl-2-pyrazoline[94] (4.7)

To a solution of acrolein (1.8 ml, 0.03 mol) in hexane (10 ml) was slowly added a solution of EDA (2.1 ml, 0.02 mol) in hexane (3 ml). The mixture was stirred at 20^0 C for 2 hr, and the solution siphoned off by means of a capillary. The remaining yellow thick oil was then purified with a silica gel column, first by benzene to eliminate the reactants in excess, then by 4:1 mixture of ether-pentane at 2^{0}C. The desired product (1.651 g) was obtained in 49% yield. FTIR: 3403, 1732, 1664, 1549; ^{1}HNMR ($CDCl_3$): δ=9.7 (s, 1H, COH), 7.0 (broad, 1H, NH), 4.6-4.4 (m, 1H, CH-CO_2Et), 4.3-4.2 (q, 2H, CH_2-CH_3), 1.25(t, 3H).

N-Acetyl-5-ethoxycarbonyl-3-formyl-2-pyrazoline[94] (4.10)

To the crude **4.7** (obtained from 0.03 mol of acrolein) in benzene (10 ml) was added Ac_2O (2.5 ml) and p-TsOH (10 mg). The red solution was then heated for 12 hr at 50^0

C, and the crude product was purified on a silica gel column (EtOAc : PE=30:70) affording 1.792 g (43%) product. FTIR: 1739, 1672, 1661, 1570; ^{1}HNMR ($CDCl_3$): δ=9.8 (s, 1H, COH), 4.9 (q, 1H), 4.2 (q, 2H, CH_2-CH_3), 3.35 (q, J_{AX}=12.2, 1H), 3.1 (q, J_{BX}=6.5, 1H), 2.4 (s, 3H, CH_3 acetyl), 1.3 (t, 3H, CH_3-CH_2-).

N-Acetyl-5-ethoxycarbonyl-3-hydroxylmethyl-2-pyrazoline (4.11)

$NaBH_4$ (0.640 g, 0.017 mol) was added to the solution of N-acetyl-5-ethoxycarbonyl-3-formal-2-pyrazoline **4.7** (2.50 g, 0.013 mol) in C_2H_5OH (45 ml) at 0^0C over 30 min. Stirring was continued at 0^0C for 1 hr, then the solution was allowed to warm up to room temperature during 2 hr. The solvent was removed by rotary evaporator. The residue was treated with cold water (50 ml) and extracted with CH_2Cl_2 (4×15 ml). The organic phase was dried by Na_2SO_4, and evaporated to afford the crude product. Purification of crude product on a silica gel column (PE:EtOAc=1:3) gave 1.56 g (62%) of the desired product. ^{1}HNMR ($CDCl_3$): δ= 4.9 (q, 1H, CH-CO_2Et), 4.4 (s, 2H, CH_2-OH), 4.15 (q, 2H, CH_2-CH_3), 3.4-2.9 (m, 2H, CH_2), 2.35 (s, 3H, CH_3 acetyl), 1.6 (broad, 1H, OH), 1.25(t, 3H, CH_3-CH_2-).

N-Acetyl-5-ethoxycarbonyl-3-chloromethyl-2-pyrazoline (4.12)

A solution of p-TsCl (1.21g, 0.006 mol) in CH_2Cl_2 (2 ml) was added to a mixture of **4.11** (1.06g, 0.005 mol), Et_3N (3 ml, 0.023 mol) and DMAP (55 mg) in.CH_2Cl_2 (6 ml) at 0^0 C. After stirring at 0^0 C for 2 hr, the solution was allowed to warm up to room temperature. The excess p-TsCl was hydrolyzed with ice (10 g). After stirring at room temperature for 1 hr, the mixture was extracted with CH_2Cl_2 (5 ×10 ml). The organic phase was washed with brine, and dried over Na_2SO_4. Removal of the solvent afforded the crude product. The crude product was purified on a silica gel column (PE: EtOAc=1:3). It gave 0.649 g (56%) pure product. ^{1}HNMR ($CDCl_3$):

δ=4.8 (q, 1H, CH=CO_2Et), 4.2 (q, 2H, CHCl), 4.18 (q, 2H, -CH_2CH_3), 3.4-2.9 (m, 2H, CH_2), 2.27 (s, 3H, CH_3 acetyl), 1.2 (t, 3H, CH_3-CH_2-).

N-Acetyl-5-ethoxycarbonyl-3-cyanomethyl-2-pyrazoline (4.13)

To the mixture of **4.12** (90 mg, 0.4 mmol) and 18-crown-6 (160 mg) in CH_3CN (4 ml) was added KCN (50 mg, 10 mmol) at room temperature. After being stirred for 1 hr, no more starting material was found on TLC.

The reaction mixture was filtered, and evaporated to ca. 1/3 volume. Distilled water was added, and the solution was extracted with CH_2Cl_2 (3×4 ml). The combined CH_2Cl_2 was dried over Na_2SO_4. Removal of the solvent gave the crude product. The crude product was purified by silica gel (PE: EtOAc=1:3) affording the desired product 33 mg (36%). FTIR(NaCl neat): 2250 (C=N), 1740 (C=O ester), 1570 (C=N). ^{1}HNMR ($CDCl_3$): δ=4.9 (q, 1H, CH-CO_2Et), 4.23 (q, 2H, CH_2-CH_3), 3.5 (s, 2H, CH_2-CN), 3.4-2.9(m, 2H, CH_2), 2.35 (s, 3H, CH_3 acetyl), 1.25 (t, 3H, CH_3-CH_2-).

Condensation of dimethyl 1,3-acetonedicarboxylate with hydrazine (4.15)

Hydrazine (1.6 ml, 0.0051 mol) in CH_3OH (5 ml) was added to the solution of dimethyl 1,3-acetonedicarboxylate (7.4 ml, 0.05 mol) in CH_3OH (12 ml) at 0^{0}C. After stirring at 0^{0}C for 2 hr, the white solid that formed was filtered off by suction and washed several times with cold CH_3OH. After drying under vacuum, white crystals were obtained (6.5 g, 83%). m.p.: 80^{0}C; ^{1}HNMR ($CDCl_3$): δ= 5.6 (s, 1H, NH), 3.79 (s, 4H, 2 -CH_2), 3.7 (s, 3H, CH_3).

Condensation of dimethyl 1,3-acetonedicarboxylate with phenyl hydrazine (4.18)

Dimethyl 1,3-acetonedicarboxylate (2 ml,13.6 mmol) was added to a solution of phenyl hydrazine (2.1445 g, 14.8 mmol) in water (25 ml, pH~ 4) at 0^{0}C. After

stirring at 0^0C for 2 hr, the mixture was allowed to warm up to room temperature, After the mixture was stirred at room temperature for an additional 2 hr, a lot of white precipitate was formed. The white solid was filtered by suction, washed with cold water. It afforded 2.8495 g (90 %) of product. ^{1}HNMR ($CDCl_3$): δ= 7.9-7.2 (m, 5H, phenyl), 3.8 (s, 3H, CH_3), 3.6 (s, 4H, 2 -CH_2).

Acetylation of compound 4.15 by using trimethylacetic anhydride (4.19)

To a solution of **4.18** (0.152 g, 2.23 mmol) in benzene (15 ml) was added trimethylacetic anhydride (1.5 ml, 13.0 mmol), and 65 mg of p-TsOH. The mixture was heated to reflux. After refluxing for 4 hr, the mixture was washed with $NaHCO_3$ solution and brine, dried over Na_2SO_4. Removal of the solvent gave the crude product. The crude product was purified by means of a silica gel column (PE : E_tOAc = 80: 20) giving 0.583 g of product (83 %). ^{1}HNMR ($CDCl_3$): δ=7.6-7.3 (m, 5H, phenyl), 6.3 (s, 1H,CH=C), 3.74 (s, 3H, CH_3), 3.73 (s, 2H, CH_2), 1.2 (s, 9H, t-butyl).

Preparation of the silyl enol ether (4.20)

To a stirred, cold (0^0C) solution of 0.5860 g (0.002 mol) of **4.19** in THF (6 ml), 7 ml (50.4 mmol) of Et_3N and 0.65 g (0.002 mol) of TBDMSOTf was added sequentially. The mixture was allowed to warm up to room temperature over 30 min. After stirring at room temperature for 3 hr, the mixture was diluted with EtOAc (20 ml), washed with $NaHCO_3$ solution and brine, dried over Na_2SO_4. Removal of the solvent afforded the crude product. The crude product was purified on a basic alumna column (PE:EtOAc =90: 10), giving 0.4238 g of product (53 %). (79 % based on the recovered starting material). ^{1}HNMR ($CDCl_3$): 7.6-7.2 (m, 5H), 6.47 (s, 1H), 4.83 (s, 1H), 3.66 (s, 3H), 1.23 (s, 9H), 0.97 (s, 9H), 0.25 (s, 6H).

Phthalimidosulfenylation of the enol ether (4.25)

To the solution of the enol ether **4.24** (100 mg, 0.75 mmol) in $CHCl_3$ (2 ml) was added PhthN-S-Cl (160 mg, 0.75 mmol) in portions at 0°C during the period of 15 min. The mixture was stirred at 0°C for an additional 20 min., warmed to room temperature in 30 min. Cold n-pentane was added. A lot of white precipitate formed, which was filtered and then washed with cold n-pentane. The remaining preciptate was the desired product (167.9 mg, 72%). ^{1}HNMR ($CDCl_3$): δ 3.45 (s, 3H), 4.87 (d, J=9.0, 1H), 6.02 (d, J=9.0, 1H), 7.3(m, 4H) and 7.75-7.9 (m, 4H).

Preparation of the enol ether (4.27)

(Methoxymethyl)triphenylphosphonium chloride (1.611g, 4.7 mmol) was suspended in 10 ml of ether and cooled to 0°C. A hexane solution of n-BuLi (2.5M, 1.88 ml, 4.7 mm) was added over 15 min. and the resulting dark red mixture warmed to room temperature, and stirred for an additional 15 min. After recooling to 0°C, a solution of aldehyde **4.10** (0.615 g, 3.62 mmol) in 5 ml of ether was slowly added over 10 min., and the mixture stirred for 45 min. The reaction was quenched by adding NH_4Cl solution and extracted with ether (4×). The organic phase was dried over Na_2SO_4. Removal of the solvent afforded the crude product. Purification by means of a silica gel column gave the product (0.287 g, 40%). ^{1}HNMR ($CDCl_3$): δ 1.28(t, 3H), 2.30 and 2.31(s, 3H), 2.90-3.58 (m, 2H), 3.70 and 3.74 (s, 3H), 4.20 (q, 2H), 4.88 (q, 1H), 5.26 and 5.80 (d, J=6.9, 13.2, 1H) and 6.31 and 6.86 (d, J=6.9, 13.2, 1H).

Phthalimidosulfenylation of the enol ether (4.28)

To the solution of the enol ether **4.27** (100 mg, 0.75 mmol) in $CHCl_3$ (2 ml) was added PhthN-S-Cl (160 mg, 0.75 mmol) in portions at 0°C during the period of 15

min. The mixture stirred at 0°C for an additional 20 min., warmed to room temperature in 30 min. Cold n-pentane was added. A lot of white precipitate formed which was filtered and washed with cold n-pentane to afford the product (182 mg, 82%). ^{1}HNMR ($CDCl_3$): δ 1.25 (t, 3H), 2.32 (s, 3H), 2.95-3.6 (m, 2H), 3.70 (s, 3H), 4.10 (q, 2H), 4.88 (q, 1H), 5.79 (d, J=12.9, 1H) and (d, J=12.9, 1H).

Preparation of diphenoxy acetic acid[101] (4.32)

(1) Preparation of $Cl_2CHCOONa$: To a solution of sodium (0.92 g, 40 mmol) in 12 ml of ethanol was added dichloroacetic acid (5.16 g, 40 mmol), and the mixture was stirred at room temperature for 1 hour to yield solution **A**.

(2) Preparation of PhONa. To a solution of sodium (1.8 g, 80 mmol) in 24 ml of ethanol was added phenol (7.52 g, 80 mmol), and the mixture was stirred for 1 hour at room temperature to give solution **B**.

(3) Solution **A** was slowly added to the solution **B** at room temperature, then the temperature was increased to reflux. After refluxing for 14 hours, the reaction solvent was removed under vacuum. The residue was treated with ice-water, then neutralized by H_2SO_4 (3M). The resulting solution was extracted with ether (4×), dried over Na_2SO_4. Removal of the solvent afforded the crude product.

NH_4OH was added to the crude acid in order to remove the unreacted phenol. The resulting aqueous solution was extracted with ether (6×) until there was no more phenol in ether phase. The aqueous phase was neutralized by H_2SO_4 (3M) again, extracted with $CHCl_3$, dried over Na_2SO_4. Removal of the solvent and recrystallization from CH_2Cl_2/PE gave the desired product in 55% yield. m.p. 88-90^{0}C (lit.[101] 90^{0}C). FTIR: 3100, 1740, 1590, 1490, 1202, 1174, 1062; ^{1}HNMR ($CDCl_3$): δ 9.3 (s, br., 1H), 7.29-7.03 (m, 10H), 6.07 (s, 1H).

Chlorination of diphenoxy acetic acid[101] (4.33)

To a solution of diphenoxy acetic acid (1.75 g, 7.2 mmol) in 10 ml of benzene, was slowly added thionyl chloride (1.05 ml, 14 mmol) at room temperature. The resulting mixture was slowly heated to reflux. After refluxing for 4 hours, solvent was removed, affording the crude diphenoxyacetyl chloride. Yield: 85 %. FTIR: 1799, 1591, 1490, 1197, 1071; ^{1}HNMR ($CDCl_3$): δ 7.42-7.01 (m, 10H), 6.04 (s, 1H); ^{13}CNMR ($CDCl_3$): δ 170.1, 156.2, 131.0, 125.3, 124.7, 119.4, 118.9, 101.8.

Preparation of diphenoxy methyl chloride[102] (4.34)

Diphenoxy acetyl chloride was heated at 180^{0}C in the presence of boiling chips under reduced pressure. After heating for 2.5 h at such temperature, the crude product was purified by distillation under reduced pressure in 45% yield. FTIR: 1588, 1488, 1201, 1066; ^{1}HNMR ($CDCl_3$): δ 7.42-7.11 (m, 11H); ^{13}CNMR ($CDCl_3$): δ 154.5, 130.8, 130.7, 125.7, 124.7, 119.8, 119.3, 110.3.

General procedure for the condensation of methyl acetoacetate with sulfonylamides.

To a solution of methyl acetoacetate (1.2 eq) and sulfonylamides (1 eq) in a convenient amount of benzene was added a catalytic amount of p-toluenesulfonic acid. The resulting solution was refluxed until the reaction was complete (12-14h). The solution was cooled and then concentrated on a rotary evaporator. The resulting residue was purified by a silica gel column using ethyl acetate/petroleum ether as eluant.

Methyl 3-benzenesulfonylamino 2-butenate (4.43)

This compound was prepared according to the above general procedure from benzenesulfonylamide (4.0 g, 25.4 mmol). Yield: 95%; White solid, m.p. 149-150^{0}C; ^{1}HNMR ($CDCl_3$) δ 9.92 (s, 1H), 7.45 (m, 5H), 5.02 (s, 1H), 3.81 (s, 3H), 2.67 (s, 3H).

General procedure for phthalimidosulfenylation of sulfonyl imines.

To a solution of sulfonyl imines in dichloromethane was added PhthN-S-Cl (1.2 eq) in portions at 0^{0}C during a period of 15 min. The reaction mixture was stirred at such temperature for an additional 20 min, allowed to warm up to room temperature in 30 min. Cold n-pentane was added. A lot of white precipitate formed which was filtered and then washed with cold n-pentane to afford the desired product.

Phthalimidosulfenylation of methyl 3-benzenesulfonyl amino 2-butenoate (4.44)

This compound was prepared according to the above general procedure from methyl 3-benzenesulfonyl amino 2-butenoate **4.43** (0.429 g, 2.01 mmol). Yield: 100%; ^{1}HNMR ($CDCl_3$) δ 12.53 (s, 1H), 7.95-7.57 (m, 9H), 3.80 (s, 3H), 2.89 (s, 3H).

General procedure for cycloaddition of phthalimidosulfenyl imines with tri-O-benzyl-D-glucal, tri-O-benzyl-D-galactal, and tri-O-benzyl-D-allal

To a solution of the phthalimidosulfenyl imines (1.2 eq) and tri-O-benzyl-D-glucal, tri-O-benzyl-D-galactal or tri-O-benzyl-D-allal (1 eq) in chloroform was added a catalytic amount of 2,6-lutidine (2 mol %). The resulting solution was stirred at room temperature until the reaction was complete as monitored by TLC. The solution was dissolved in dichloromethane and washed with saturated ammonium chloride and brine, dried over Na_2SO_4. The organic solvent was removed under reduced pressure. The crude materials were purified by a silica gel column to give the desired products.

Sometimes, it is difficult to remove phthalimide, then 20% of NaOH was used to extract the phthalimide after flash chromatography.

Cycloadduct of methyl 2-phthalimidosulfenyl 3-benzenesulfonylamino 2-butenoate 4.43 with tri-O-benzyl-D-glucal (4.46)

This compound was prepared according to the above general procedure from tri-O-benzyl-D-glucal (140 mg, 0.35 mmol). Yield: 82%; FTIR (neat): 1715.3, 1585.4, 1448.2, 1357.6, 1251.5, 1169.1; ^{1}HNMR ($CDCl_3$) δ 7.96 (d, 2H), 7.52 (t, 2H), 7.40-7.16 (m,), 6.33 (d, J=7.2, 1H), 4.82-4.57 (m,), 3.71 (s, 3H), 3.52-3.3 (m, 4H), 2.52 (s, 3H); ^{13}CNMR ($CDCl_3$) δ 165.2, 148.1, 139.2, 137.9, 137.6, 133.1, 128.6, 128.2, 128.0, 127.7, 127.6, 127.5, 117.4, 87.9, 79.0, 77.9, 76.1, 74.9, 73.3, 72.0, 67.5, 52.1, 47.9, 21.4; Anal. Calcd for $C_{38}H_{39}O_8NS_2$: C, 65.03; H, 5.56; N, 2.00. Found: C, 64.47; H, 5.93; N, 2.12.

Cycloadduct of methyl 2-phthalimidosulfenyl 3-benzenesulfonylamino 2-butenoate 4.43 with tri-O-benzyl-D-galactal (4.47)

This compound was prepared according to the above general procedure for **4.46** from tri-O-benzyl-D-galactal (70 mg, 0.17 mmol). Yield: 85%; FTIR (neat): 1749.4, 1715.7, 1352.9, 1250.2, 1167.8, 1089.8, 1254.2; ^{1}HNMR ($CDCl_3$) δ 7.95 (d, 2H), 7.58 (t, 1H), 7.42-7.23 (m,), 6.30 (d, J=6.6, 1H), 4.86-4.52 (q, H=11.4, 2H), 4.57 (s, 2H), 4.39 (s, 2H), 3.95 (d, J=2.4, 1H), 3.73 (s, 3H), 3.57 (m, 1H), 3.48-3.42 (m, 4H), 2.46 (s, 3H); ^{13}CNMR ($CDCl_3$) δ 166.1, 147.2, 140.1, 138.8, 138.3, 134.9, 133.9, 129.5, 129.0, 128.9, 128.6, 128.5, 128.3, 124.2, 117.4, 87.6, 75.3, 75.1, 74.2, 73.9, 73.1, 72.0, 68.3, 52.9, 44.9, 22.0.

Cycloadduct of methyl 2-phthalimidosulfenyl 3-benzenesulfonylamino 2-butenoate 4.43 with tri-O-benzyl-D-allal (4.48)

This compound was prepared according to the above general procedure for **4.46** from tri-O-benzyl-D-allal (70 mg, 0.17 mmol). Yield: 71%; ^{1}HNMR ($CDCl_3$) δ 7.93 (d, J=10.2, 2H), 7.55 (t, J=10.2, 1H), 7.30 (m, 17H), 6.08 (d, J=3, 1H), 4.63 (s, 2H) 4.49-4.45 (m, 3H), 4.23 (m, 2H), 4.17 (dd, J=9.6, 1H), 3.75 (m, 3H), 3.71 (s, 3H), 3.62 (m, 1H), 2.43 (s, 3H).

Oxidation of the cycloadduct of methyl 2-phthalimidosulfenyl 3-benzenesulfonylamino 2-butenoate and tri-O-benzyl-D-galactal with m-CPBA (4.49)

To a solution of the cycloadduct **4.47** (22 mg, 0.03 mmol) and $NaHCO_3$ (1 eq) in 5 ml of dichloromethane was added 3 molar equivalent of m-CPBA (30 mg, 56-80%) in portions at 0^0C. After 30 min., the ice water bath was removed. The reaction mixture was allowed to reach room temperature. No more starting material was detected on TLC after 1 h. The reaction mixture was diluted with dichloromethane, washed with $NaHCO_3$ solution and brine, dried over Na_2SO_4. Removal of the solvent afforded pure product as white solid. Yield: 83%; ^{1}HNMR ($CDCl_3$) δ 8.09 (d, 2H), 7.62 (t, 1H), 7.49 (t, 2H), 7.40-7.08 (m,), 6.38 (d, J=6.9, 1H), 4.75-4.40 (m,), 3.98-3.85 (m, 3H), 3.71 (s, 3H), 3.53 (m, 2H), 2.58 (s, 3H); ^{13}CNMR ($CDCl_3$) δ 163.7, 155.9, 137.9, 137 3, 137.0, 136.7, 133.9, 129.8, 128.9, 128.1, 128.0, 127.8, 127.5, 127.4, 127.3, 115.7, 79.1, 78.9, 77.6, 76.5, 76.1, 74.9, 74.8, 73.3, 72.1, 67.4, 59.9, 52,0, 20.9.

2-Trimethylsilylethanesulfonamide (4.55)

Ammonia was distilled into a solution of of 2-trimethylsilylethanesulfonyl chloride **4.54** (0.9 g, 4.49 mmol) in 20 ml of THF. The resulting solution was stirred at -78^{0}C for 30 min. The bath was removed and the reaction mixture was allowed to reach

room temperature for 1 h. The remaining ammonia was blown out by N_2. The mixture was diluted with ether, washed with water, brine, and dried over Na_2SO_4. Removal of the ether afforded 0.81 g of 2-trimethylsilylethanesulfonamide as solid in the yield of 98%. ^{1}HNMR ($CDCl_3$) δ 4.49 (br, 2H), 3.05 (m, 2H), 1.12 (m, 2H), 0.06 (s, 9H).

Methyl 3-(2-trimethylsilylethylsulfonyl amino) 2-butenoate (4.56)

This compound was prepared according to the above general procedure for compound **9** from 2-trimethylsilylethylsulfonamide **4.55** (0.40 g, 2.21 mmol). Yield: 93%; ^{1}HNMR ($CDCl_3$) δ 10.8 (s, 1H), 5.0 (s, 1H), 3.65 (s, 3H), 3.04 (m, 2H), 2.10 (s, 3H), 1.02 (m, 2H), 0.04 (s, 9H); ^{13}CNMR ($CDCl_3$) δ 169.8, 153.6, 96.3, 52.2, 51.6, 20.4, 10.8, -1.65.

Phthalimidosulfenylation of methyl 3-(2-trimethylsilylethylsulfonyl amino) 2-butenoate (4.57)

This compound was prepared according to the above general procedure for compound **4.44** from compound **4.56** (0.289 g, 1.04 mmol). Yield: 100%; ^{1}HNMR ($CDCl_3$) δ 12.15 (s, 1H), 7.88-7.73 (m, 4H), 3.77 (s, 3H), 3.18 (m, 2H), 3.05 (s, 3H), 1.02 (m, 2H), 0.05 (s, 9H). ^{13}CNMR ($CDCl_3$) δ 169.9, 168.4, 167.9, 165.7, 135.3, 134.9, 134.6, 132.5, 124.7, 124.2, 123.9, 53.1, 52.7, 19.0, 10.7, -1.7.

Cycloadduct of methyl 2-phthalimidosulfenyl 3-(2-trimethylsilylethylsulfon amino) 2-butenoate with tri-O-benzyl-D-glucal (4.59)

This compound was prepared according to the above general procedure for compound **4.46** from tri-O-benzyl-D-glucal (140 mg, 0.35 mmol). Yield: 80%; ^{1}HNMR ($CDCl_3$) δ 7.38-7.22 (m, 15H), 6.31 (d, J=6.8, 1H), 4.8-4.1 (m, 6H), 3.78 (s, 3H), 3.75-3.5 (m, 5H), 3.3-3.0 (m, 2H), 2.61 (s, 3H), 1.13 (m, 2H), 0.05 (s, 9H); ^{13}CNMR ($CDCl_3$) δ

165.1, 147.9, 137.6, 137.2, 128.0, 127.8, 127.6, 127.5, 127.4, 127.2, 115.6, 87.3, 78.6, 77.9, 74.8, 73.1, 71.9, 68.0, 52.4, 51.9, 47.5, 29.2, 21.1, 9.5, -2.5.

Cycloadduct of methyl 2-phthalimidosulfenyl 3-(2-trimethylsilylethylsulfon amino) 2-butenoate with tri-O-benzyl-D-galactal (4.60)

This compound was prepared according to the above general procedure for compound **4.46** from tri-O-benzyl-D-galactal (0.215 g, 0.52 mmol). Yield: 87%; ^{1}HNMR ($CDCl_3$) δ 7.38-7.26 (m, 15H), 6.28 (d, J=6.9, 1H), 4.8-4.52 (dd, J=11.4, 2H), 4.63 (q, J=2.1, 2H), 4.56-4.35 (m, 3H), 3.92 (d, J=2.4, 1H), 3.79 (s, 3H), 3.73-3.44 (m, 5H), 3.3-3.0 (m, 2H), 2.57 (s, 3H), 1.13 (m, 2H), 0.04 (s, 9H); ^{13}CNMR ($CDCl_3$) δ 165.7, 147.0, 138.1, 137.7, 137.5, 128.5, 128.3, 128.2, 128.1, 127.9, 127.2, 115.6, 97.3, 87.3, 76.6, 74.7, 74.5, 73.6, 73.5, 72.6, 71.3, 68.4, 52.7, 52.3, 44.2, 21.3, 9.9, -2.1; Anal. Calcd for $C_{37}H_{47}O_8NS_2Si$: C, 61.2; H, 6.5; N, 1.9; S, 8.8. Found: C, 60.6; H, 6.48; N, 1.94; S, 8.67.

Cycloadduct of methyl 2-phthalimidosulfenyl 3-(2-trimethylsilylethylsulfon amino) 2-butenoate 4.56 with tri-O-benzyl-D-allal (4.61)

This compound was prepared according to the above general procedure for compound **4.46** from tri-O-benzyl-D-allal Yield: 66%; ^{1}HNMR ($CDCl_3$) δ 7.3 (m, 15H), 5.89 (d, J=3, 1H), 4.80-4.42 (m, 6H), 4.25 (s, 2H), 3.74 (m, 4H), 3.82 (s, 3H), 3.27 (m, 2H), 2.60 (s, 3H), 1.12 (m, 2H), 0.05 (s, 9H).

Deprotection of 2-trimethylsilylethylsulfonyl protected cycloadduct amine (4.62)

To a solution of 2-trimethylsilylethylsulfonyl protected cycloadduct amine **4.60** (50 mg, 0.07 mmol) in 5 ml of DMF was added 1.2 molar equivalent of CsF. The resulting solution was heated up to 50^{0}C. After 2 h, the reaction was complete. The reaction mixture was treated with water, and extracted with dichloromethane twice.

The organic phase was washed again with water, brine, and dried over Na_2SO_4. Removal of the solvent afforded the free amine crude product. The crude product was purified by a silica gel column by means of ethyl acetate and petroleum ether as an eluant. Yield: 90%; I.R.: 3325, 2921, 1696, 1683, 1576, 1500, 1247, 1084; ^{1}H-NMR ($CDCl_3$), δ ppm 7.42 (m, 15H), 5.45 (d, J=4.2, 2H), 4.95 (d, J=11.2, 1H), 4.78 (q, J=11.8, 2H), 4.6-4.45 (m, 3H), 3.91 (m, 1H), 3.80 (m, 1H), 3.73 (s, 3H), 3.52 (m, 4H), 2.38 (s, 3H); ^{13}CNMR ($CDCl_3$) δ166.2, 149.9, 137.8, 137.6, 137.3, 128.1, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 82.7, 79.3, 74.1, 73.6, 73.3, 70.7, 69.0, 50.8, 36.4, 21.3.

General procedure for the cleavage of the carbon-carbon double bond of cycloadducts by ozonolysis.

Ozone was bubbled into a solution of cycloadduct (1 eq) in CH_2Cl_2/CH_3OH (3:1 by volume, 4 ml) at -78^{0}C until there was no starting material detected by TLC, Nitrogen was bubbled for 10 min. Methanol (2 ml) and triphenylphosphine (3 eq) were added, and the mixture was allowed to reach room temperature. Concentration in vacuum afforded the crude product which was purified on a silica gel column.

Preparation of the N-glycoside (4.67)

This compound was prepared according to the above general procedure from **4.46** (0.075 g, 0.107 mmol). Yield: 81%; ^{1}HNMR ($CDCl_3$) δ 8.02 (d, J=5.1, 2H), 7.53 (t, J=5.1, 1H), 7.30 (m, 17H), 6.53 (d, J=4.8, 1H), 4.8-4.3 (m, 9H), 3.75 (s, 3H), 3.68-3.5 (m, 3H), 2.3 (s, 3H); ^{13}CNMR ($CDCl_3$) δ 173.3, 140.5, 138.4, 138.3, 133.9, 129.7, 128.8, 128.6, 128.4, 128.3, 128.2, 128.1, 127.9, 80.0, 79.4, 78.1, 76.4, 75.1, 74.5, 73.9, 69.9, 66.7, 55.1, 27.3. Anal. Calcd for $C_{38}H_{39}O_{10}NS_2$: C, 62.21, H, 5.32, N, 1.91, S, 8.73; Found: C, 62.48, H, 5.59, N, 1.88, S, 8.85.

Preparation of the N-glycoside (4.70)

This compound was prepared according to the above general procedure for compound **4.67** from **4.62** (0.048 g, 0.086 mmol). Yield: 81%, ^{1}HNMR ($CDCl_3$) δ 7.7-7.2 (m, 6H), 5.85 (br, 1H), 5.63 (d, J=4.5, 1H), 4.9 (d, J=11.4, 1H), 4.57-4.37 (m, 7H), 3.92-3.87 (m, 3H), 3.79 (s, 4H), 3.59 (m, 2H), 3.27 (dd, J=11.7, 1H); ^{13}CNMR ($CDCl_3$) δ 165.2, 159.6, 137.5, 137.3, 136.3, 128.1, 128.0, 127.9, 127.7, 127.6,127.59, 127.5, 127.4, 74.9, 74.2, 73.8, 73.3, 72.1,71.6, 71.5, 68.9, 51.1, 49.9, 22.4; Anal. Calcd for $C_{32}H_{35}O_9NS$: C, 63.05, H, 5.70, N, 2.29, S, 5.25. Found: C, 62.92, H, 5.81, N, 2.21, S, 5.13.

General procedure for preparation of amino-keto-ester

To a solution of protected amino acid (0.323 g, 1 mmol), DMAP (0.28 g, 1.1 mmol), and Meldrum's acid (0.15 g, 1 mmol) in dichloromethane (5 ml), was added PCF (0.13 ml, 1.1 mmol) in dichloromethane (1 ml) during 20 min at -5^{0}C. The resulting mixture was stirred for a further 1.5 h at this temperature. The mixture was then quenched by adding 10% aqueous potassium hydrogen sulphate. The organic phase was washed with water and brine. and dried over Na_2SO_4. Removal of the solvent gave a white solid (0.55 g). The white solid was treated with alcohol (2 mmol) in refluxing benzene (10 ml) for 4 h. The solvent was removed. Purification of the residue by chromatography over a silica gel gave δ-amino-β-keto-esters and γ-amino-β-keto-esters along with the cyclized by-product.

(5S)-5-Benzyl-4-hydroxy-1-t-butoxycarbonylpyrrol-2(5H)-one (5.15)

This compound[118] was isolated during the preparation of γ-amino-β-keto-esters starting from protected α-amino acids. ^{1}H-NMR ($CDCl_3$), δ ppm 7.1 (m, 5H), 4.68 (m, 1H), 3.5-3.2 (m, 2H), 2.9 (AB q, A part, 1H), 2.2 (AB q, B part, 1H), 1.68 (s, 9H).

Ethyl-4-(carboxyamino)-5-phenyl-3-oxopentanoate 4-tert-butyl ester (5.17)

This compound was prepared according to the above general procedure from N-α-t-BOC-phenylalanine (265 mg, 1 mmol) by using ethanol to workup the Meldrum's acid adduct. Yield: 90%; m.p.: 60-62^{0}C. (Lit.[113] 61-62^{0}C); I.R.: 3376, 2979, 2934, 1715, 1504, 1456, 1393, 1368, 1163; ^{1}H-NMR ($CDCl_3$), δ ppm 7.24 (m, 5H), 5.0 (d, J=8.2, 1H), 4.58 (m, 1H), 4.19 (q, J=7.1, 2H), 3.42 (m, 2H), 3.16 (m, 2H), 1.41 (s, 9H), 1.18 (t, J=7.1, 3H). ^{13}C-NMR ($CDCl_3$), δ ppm: 201.8, 166.8, 136.1, 129.2, 128.7, 128.4, 127.0, 61.4, 60.4, 46.9, 37.0, 29.7, 28.2, 14.0.

Iso-propyl-4-(carboxyamino)-5-phenyl-3-oxopentanoate 4-tert-butyl ester (5.18)

This compound was prepared according to the above general procedure for compound **5.17** from N-α-t-BOC-phenylalanine (265 mg, 1 mmol) by using isopropyl alcohol to workup the Meldrum's acid adduct. Yield: 78%; Oil. I.R. (film): 3363, 2979, 2931, 1714, 1500, 1367. ^{1}H-NMR ($CDCl_3$), δ ppm: 7.22-7.14 (m, 5H), 5.00-4.92 (m, 3H), 4.53-4.45 (q, J=7.1, 1H), 3.58 (m, 2H), 3.12-2.90 (m, 2H), 1.27 (s, 9H), 1.18 (d, J=6.2, 6H). ^{13}C-NMR ($CDCl_3$), δ ppm: 201.5, 165.9, 154.7, 135.7, 128.9, 128.8, 128.2, 128.0, 126.5, 79.7, 76.1, 68.7, 60.0, 46.7, 36.5, 39.2, 27.8, 21.3, 21.2.

Tert-butyl-4-(carboxyamino)-5-phenyl-3-oxopentanoate 4-tert-butyl ester (5.19)

This compound was prepared according to the above general procedure for compound **5.17** from N-α-t-BOC-phenylalanine (265 mg, 1 mmol) by using tert-butyl alcohol to workup the Meldrum's acid adduct. Yield: 78%; ^{1}H-NMR ($CDCl_3$), δ ppm: 7.31-7.16 (m, 5H), 5.03 (d, J=8.3, 1H), 4.53 (m, 1H), 3.42 (q, J=7.1, 2H), 3.21-2.93 (m, 2H), 1.45 (s, 9H), 1.32 (s, 9H); ^{13}C-NMR ($CDCl_3$), δ ppm: 201.5, 165.7, 155.6, 136.1, 135.7, 129.2, 128.6, 128.4, 128.1, 127.9, 127.0, 82., 66.9, 60.7, 48.1, 37.0, 28.2, 27.8.

Benzyl-4-(carboxyamino)-5-phenyl-3-oxopentanoate 4-benzyl ester (5.20)

This compound was prepared according to the above general procedure for compound **5.17** from N-α-t-CBZ-phenylalanine (299 mg, 1 mmol) by using benzyl alcohol to workup the Meldrum's acid adduct. Yield: 75%; ^{1}H-NMR ($CDCl_3$), δ ppm 7.28 (m, 15H), 5.21 (d, J=6.8, 1H), 5.14 (s, 2H), 5.03 (s, 2H), 3.45 (m, 2H), 3.00 (m, 2H).

Ethyl-4-(carboxyamino)-5-phenyl-3-oxopentanoate 4-benzyl ester (5.21)

This compound was prepared according to the above general procedure for compound **5.17** from N-α-t-CBZ-phenylalanine (299 mg, 1 mmol) by using ethanol to workup the Meldrum's acid adduct. Yield: 81%; m.p.: 57-59^{0}C (lit.[113] 57-61^{0}C); FTIR. (film): 3339, 2980, 1718, 1519, 1251; ^{1}H-NMR ($CDCl_3$), δ ppm: 7.39-7.10 (m, 10H), 5.40 (d, J=7.2, 1H), 5.03 (s, 2H), 4.63 (q, J=6.5), 4.18 (q, J=7.1, 2H), 3.41 (m, 2H), 3.20-2.91 (m, 2H), 1.20 (t, J=7.1, 3H); ^{13}C-NMR ($CDCl_3$), δ ppm: 200.9, 166.2, 155.3, 135.6, 135.3, 128.7, 128.3, 128.0, 127.9, 127.8, 127.7, 127.5, 126.7, 66.6, 61.0, 60.3, 46.5, 36.5, 13.5.

Tert-butyl-4-(carboxyamino)-5-phenyl-3-oxopentanoate 4-benzyl ester (5.23)

This compound was prepared according to the above general procedure for compound **5.17** from N-α-t-CBZ-phenylalanine (299 mg, 1 mmol) by using tert-butyl alcohol to workup the Meldrum's acid adduct. Yield: 81%; ^{1}H-NMR ($CDCl_3$), δ 7.38-7.12 (m, 10H), 5.36 (d, J=84., 1H), 5.04 (s, 2H), 4.63 (m, 1H), 3.40 (m, 2H), 3.20-2.95 (m, 2H).

Ethyl-4-(phthalimido)-3-oxobutanoate (5.24)

This compound was prepared according to the above general procedure for compound **5.17** from N-phthaloylglycine (205 mg, 1 mmol) by using ethanol to workup the Meldrum's acid adduct. Yield: 78%; ^{1}H-NMR ($CDCl_3$), δ ppm 7.8 (m, 4H), 4.63 (s,

2H), 4.21 (q, J=7.1, 2H), 3.60 (s, 2H), 1.23 (t, J=7.1, 3H); ^{13}C-NMR ($CDCl_3$), δ ppm 195.3, 167.9, 165.4, 134.8, 132.6, 124.2, 65.2, 51.1, 50.2, 14.4.

Ethyl-4-(carboxyamino)-6-methyl-3-oxopentanoate 4-benzyl ester (5.25)

This compound was prepared according to the above general procedure for compound **5.17** from N-α-t-CBZ-alanine (299 mg, 1 mmol) by using ethanol to workup the Meldrum's acid adduct. Yield: 81%; ^{1}H-NMR ($CDCl_3$), δ 7.38 (m, 5H), 5.38 (d, J=9, 1H), 5.11 (s, 2H), 4.44 (dd, J=3.6, 9, 1H), 3.43 (s, 2H), 1.44 (s, 9H), 1.02 (d, J=6.6, 3H), 0.81 (d, J=6.9, 3H).

N-(tert-butoxycarbonyl)-4-oxo-5-(benzyloxyacetyl)-norvaline (5.29)

This compound was prepared according to the above general procedure for compound **5.17** from N-α-t-BOC-aspartic acid α-benzyl ester (0.323 g, 1 mmol) by using benzyl alcohol to workup the Meldrum's acid adduct. Yield: 86%; m.p.: 54-55^{0}C; ^{1}H-NMR ($CDCl_3$), δ ppm: 7.34-7.25 (m, 10H), 5.51 (d, J=8.1, 1H), 5.15 (m, 4H), 4.55 (m, 1H), 3.45 (s, 2H), 3.44-3.09 (m, 2H), 1.41 (s, 9H); ^{13}C-NMR ($CDCl_3$), δ ppm: 200.1, 170.3, 165.8, 154.9, 134.7, 134.6, 128.0, 127.8, 127.6, 79.5, 66.9, 66.7, 49.0, 48.5, 44.2, 27.7.

N-(tert-Butoxycarbonyl)-4-oxo-5-(ethoxyacetyl)-norvaline (5.30)

This compound was prepared according to the above general procedure for compound **5.17** from N-α-t-BOC-aspartic acid α-benzyl ester (0.323 g, 1 mmol) by using ethanol to workup the Meldrum's acid adduct. Yield: 92%; m.p.: 53-56^{0}C (lit.[113] 54-57^{0}C); FTIR. (film): 3374, 2979, 1738, 1713, 1501, 1367, 1164; ^{1}H-NMR ($CDCl_3$), δ ppm 7.32 (m, 5H), 5.43 (d, J=8.9, 1H), 5.18 (s, 2H), 4.60 (m, 1H), 4.2 (q, J=7.2, 2H), 3.41 (s, 2H), 3.20 (m, 2H), 1.42 (s, 9H), 1.23 (t, J=7.2, 3H). ^{13}C-NMR (

$CDCl_3$), δ ppm: 201.2, 171.3, 166.8, 155.8, 135.6, 128.9, 128.7, 128.5, 80.5, 67.8, 61.2, 49.9, 49.5, 45.1, 28.6, 14.4.

N-(tert-Butoxycarbonyl)-4-oxo-5-(isopropyloxyacetyl)-norvaline (5.31)

This compound was prepared according to the above general procedure for compound **5.17** from N-α-t-BOC-aspartic acid α-benzyl ester (0.323 g, 1 mmol) by using isopropyl alcohol to workup the Meldrum's acid adduct. Yield: 90%; ^{1}H-NMR ($CDCl_3$), δ ppm 7.36 (m, 5H), 5.48 (d, J=8.4, 1H), 5.15 (s, 2H), 5.03 (m, 1H), 4.57 (m, 1H), 3.38 (s, 2H), 3.24 (m, 2H), 1.44 (s, 9H), 1.25 (d, J=3.4, 6H). ^{13}C-NMR ($CDCl_3$), δ ppm: 201.4, 170.2, 165.8, 156.7, 135.6, 133.1, 128.2, 128.1, 127.6, 127.4, 126.3, 79.9, 68.7, 60.1, 46.2, 37.0, 28.3, 27.9, 20.1.

N-(tert-Butoxycarbonyl)-4-oxo-5-(tert-butoxyacetyl)-norvaline (5.32)

This compound was prepared according to the above general procedure for compound **5.17** from N-α-t-BOC-aspartic acid α-benzyl ester (0.323 g, 1 mmol) by using tert-butyl alcohol to workup the Meldrum's acid adduct. Yield: 87%; FTIR. (film): 3376, 2979, 1715, 1503, 1368, 1163; ^{1}H-NMR ($CDCl_3$), δ ppm 7.36 (m, 5H), 5.46 (d, J=8.7, 1H), 5.16 (s, 2H), 4.56 (m, 1H), 3.24 (s, 2H), 3.24 (m, 2H), 1.42 (s, 9H), 1.41 (s, 9H); ^{13}C-NMR ($CDCl_3$), δ ppm: 200.7, 170.5, 165.2, 155.0, 134.9, 128.1, 127.9, 127.7, 81.9, 79.6, 66.9, 50.0, 49.0, 44.2, 27.8, 27.5.

N-(Carbobenzyloxy)-4-oxo-5-(ethoxyacetyl)-norvaline (5.33)

This compound was prepared according to the above general procedure for compound **5.17** from N-α-t-CBZ-aspartic acid α-benzyl ester (0.357 g, 1 mmol) by using benzyl alcohol to workup the Meldrum's acid adduct. Yield: 86%; m.p.: 87-88^{0}C; ^{1}H-NMR ($CDCl_3$), δ ppm: 7.41-7.25 (m, 15H), 5.75-5.72 (d, J=8.4, 1H), 5.12-5.10 (m, 6H), 4.65-4.59 (m, 1H),3.45 (s, 2H), 3.33-3.07 (m, 2H); ^{13}C-NMR ($CDCl_3$), δ ppm:

200.0, 170.0, 165.8, 155.5, 135.7, 134.7, 134.6, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 67.1, 66.9, 66.7, 49.5, 48.6, 44.2.

General procedure for the condensation of methyl acetoacetate or amino-keto-esters with sulfenylamide or β-tosylethylamine.

A solution of sulfenylamide or β-tosylethylamine (1.2 eq), carbonyl compound (1 eq), and PPTS (0.05 eq) in dry dichloromethane was stirred at room temperature over anhydrous $MgSO_4$ (5 eq) until the reaction was completed. Vacuum filtration through Celite followed by removal of volatiles in vacuum produced crude product. The crude product was purified by a silica gel column.

2-Nitrobenzenesulfenamide (5.45)

This compound was prepared according to the literature[126] from 2-nitrophenyl disulfide (0.925 g, 3 mmol). Yield: 70%; ^{1}H-NMR ($CDCl_3$), δ ppm 8.23 (t, J=1.8, 1H), 7.95 (dd, J=8.1, J=1.2, 1H), 7.58 (d, 6.9), 7.48 (t, J=7.2), 2.86 (br, 2H).

Methyl 3-(4-nitrobenzenesulfenamino) 2-butenoate (5.46)

This compound was prepared according to the above general procedure from 4-nitrobenzenesulfenamide **5.41** (0.34 g, 2 mmol). Yield: 81%; ^{1}H-NMR ($CDCl_3$), δ ppm 8.2-7.4 (m, 4H), 5.03 and 4.84 (s, 1H), 3.78 and 3.72 (s, 3H), 2.2 and 2.03 (s, 3H).

Methyl 3-(4-nitrobenzenesulfonamino) 2-butenoate (5.48)

This compound was prepared according to the above general procedure for compound **4.49** from methyl 3-(4-nitrobenzenesulfenamino) 2-butenoate **5.46** (0.268 g, 1 mmol). Yield: 95%; ^{1}H-NMR ($CDCl_3$), δ ppm 10.69 (s, br, 1H), 8.41-7.27 (m, 4H), 5.03 (s, 1H), 3.62 (s, 3H), 2.36 (s, 3H).

Preparation of sulfenyl imine from condensation of iso-propyl-4-(carboxyamino)-5-phenyl-3-oxopentanoate 4-tert-butyl ester with tritylsulfenimine (5.37)

This compound was prepared according to the above general procedure for compound **5.47** from compound **5.18** (52 mg, 0.14 mmol). Yield: 53%; ^{1}H-NMR ($CDCl_3$), δ ppm 7.21 (m, 20H), 5.0 (m, 1H), 4.64 (d, J=7.2, 1H), 4.42 (m, 1H), 3.20 (q, J=16.2, 2H), 2.85 (m, 2H), 1.39 (s, 9H), 1.21 (d, J=5.4, 6H).

Basic hydrolysis of sulfonyl imine 5.59 to generate 5.60

To a solution of sulfonyl imine **5.59** (100 mg, 0.18 mmol) in THF (5 ml) was added t-BuOK (1.2 eq.) at -78°C. The resulting solution was allowed to warm up to room temperature for about 30 min. The reaction was quenched by adding NH_4Cl solution. It was extracted with dichloromethane, dried over Na_2SO_4. Removal of the solution afforded the crude product. Purification of the crude product by a silica gel gave the product with the yield of 91 %. ^{1}H-NMR ($CDCl_3$), δ ppm 7.8 (d, J=8.1, 2H), 7.42 (d, J=8.1, 2H), 7.26 (m, 5H), 5.73 (d, J=2.8, 1H), 5.16 (d, J=7.9, 1H), 4.93 (s, 1H), 3.80 (s, 1H), 3.51 (m, 1H), 3.22 (dd, J=2.8, 8.1 Hz, 1H), 2.85 (m, 3H), 2.43 (s, 3H), 1.54 (s, 9H).

General procedure for the synthesis of cyclized imine 5.63 and 5.64 from amino-keto-esters

To a solution of amino-keto-esters in methanol or ethanol was added a catalytic amount of ammonium chloride. Ammonia was passed through the above solution at 0^0C for 30 min. The reaction mixture was stirred at room temperature for overnight. The solvent was removed to give a residue which was redissolved in ether. The ether solution was washed with water, and dried over Na_2SO_4. Removal of ether gave the imine which was used directly without purification.

The above imine was dissolved in benzene. The resulting solution was treated with triethyl amine (2 eq) and benzenesulfonyl chloride (1 eq) at 0^0C. After 30 min at such temperature, it was allowed to reach room temperature, then, refluxed until the reaction was complete. The solution was diluted with ethyl acetate, washed with water, brine and dried over Na_2SO_4. Removal of the solvent gave the crude product. The crude product was purified by a silica gel column (ethyl acetate and petroleum ether as eluant).

Preparation of the cyclized enamide (5.64)

This compound was prepared according to the above general procedure from N-(tert-butoxycarbonyl)-4-oxo-5-(tert-butoxyacetyl)-norvaline **5.32** (84.2 mg, 0.2 mmol). Yield: 75%; ^{1}H-NMR ($CDCl_3$), δ ppm 9.96 (br, 1H), 5.10 (m, 1H), 4.98 (s, 1H), 4.20 (m, 1H), 3.20 (m, 1H), 2.88 (m, 1H), 1.47 (s, 1.47), 1.45 (s, 9H).

General procedure for preparation of oxime from methyl acetoacetate and amino-keto-esters

To a solution of carbonyl compound (1 eq), and Na_2CO_3 (1.3 eq) in methanol or ethanol was added hydroxylamine hydrochloride (2 eq) at 0^0C. The resulting solution was stirred at room temperature until the reaction was complete. Removal of the solvent under reduced pressure gave a residue. The residue was treated with water, then extracted with ethyl acetate twice. The organic phase was dried over Na_2SO_4. The desired product was obtained upon purification on a silica gel column.

Preparation of the lactone (5.78)

This compound was prepared according to the above general procedure without using Na_2CO_3 from N-(tert-butoxycarbonyl)-4-oxo-5-(ethoxyacetyl)-norvaline **5.30** (0.30 g,

0.76 mmol). Yield: 85%; ^{1}H-NMR ($CDCl_3$), δ ppm 7.39 (m, 5H), 5.34 (m, 1H), 5.20 (m, 2H), 4.62 (m, 1H), 3.60-3.21 (m, 2H), 2.94 (m, 2H), 1.42 (s, 9H).

Preparation of the lactone (5.79)

This compound was prepared according to the above general procedure without using Na_2CO_3 for compound **5.78** from **5.21** (0.19 g, 0.495 mmol). Yield: 84%; FTIR: γ (cm^{-1}) 3327, 1805, 1699, 1533, 1251; ^{1}H-NMR ($CDCl_3$), δ ppm 7.39 -7.12 (m, 10H), 5.43 (d, J=8.4, 1H), 5.05 (s, 2H), 4.80 (m, 1H), 3.40-3.12 (m 4H).

Preparation of the oxime (5.80)

This compound was prepared according to the above general procedure from methyl acetoacetate **4.43** (1.0 g, 90 mmol). Yield: 93%; ^{1}H-NMR ($CDCl_3$), δ ppm 8.2 (br, 1H), 3.65 (s, 3H), 3.34 and 3.16 (s, 2H), 1.91 and 1.90 (s, 3H).

Preparation of the oxime (5.82)

This compound was prepared according to the above general procedure for compound **5.80** from **5.19** (30 mg, 0.078 mmol). Yield: 92%; ^{1}H-NMR ($CDCl_3$), δ ppm 8.40 and 7.9 (s, br, 1H), 7.31 (m, 10H), 5.63 and 5.38 (d, J=8.4, 1H), 5.01 (m, 2H), 5.01 and 4.65 (m, 1H), 3.40-2.90 (m, 4H), 1.41 and 1.39 (s, 9H).

Preparation of the oxime (5.84)

This compound was prepared according to the above general procedure for compound **5.80** from N-(tert-butoxycarbonyl)-4-oxo-5-(ethoxyacetyl)-norvaline **5.30** (0.733 g, 1.87 mmol). Yield: 92%; ^{1}H-NMR ($CDCl_3$), δ ppm 8.04 (br, 1H), 7.33 (m, 5H), 5.62 (d, J=9.0, 1H), 5.16 (s, 2H), 4.60 (m, 1H), 4.11 (q, J=7.2, 2H), 3.34 (m, 2H), 2.84 (m, 2H), 1.28 (s, 9H), 1.20 (t, J=7.2, 3H); ^{13}C-NMR ($CDCl_3$), δ ppm 172.0,

168.9, 155.9, 150.5, 135.6, 128.8, 128.5, 80.3, 67.5, 61.4, 51.2, 36.8, 33.9, 28.5, 14.4, 14.3.

General procedure for the preparation of N-tosylimines from oximes by using p-toluenesulfonyl cyanide.

A solution of oxime (3 mmol, 1 eq) in anhydrous CCl_4 (30 ml, 0.10M) was cooled to 0^0C and treated with triethylamine (4.5 eq). The solution was stirred for 5 min at such temperature before a suspension of p-toluenesulfonyl cyanide (2.5 eq) in 1 ml of CCl_4 was added. The resulting reaction mixture was stirred at 0^0C for 1 h, allowed to warm to room temperature over 30 min. and further stirred at room temperature for 10 h. Concentration of the reaction mixture afforded the crude product. Purification by a silica column afforded the product.

Preparation of the sulfonyl enamine (5.81)

This compound was prepared according to the above general procedure from compound **5.80** (0.16 g, 0.12 mmol). Yield: 60%; ^{1}H-NMR ($CDCl_3$), δ ppm 11.11 (br, 1H), 7.78 (d, J=8.4, 2H), 7.32 (d, J=8.4, 2H), 4.90 (s, 1H), 3.7 (s, 2H), 2.43 (s, 3H), 2.03 (s, 3H); ^{13}C-NMR ($CDCl_3$), δ ppm 169.4, 153.2, 143.5, 138.3, 138.1, 128.5, 127.3, 90.1, 50.2, 21.3, 19.8.

Preparation of the sulfonyl enamine(5.83)

This compound was prepared according to the above general procedure for compound **5.81** from oxime **5.82** (40 mg, 0.104 mmol). Yield: 71%; ^{1}H-NMR ($CDCl_3$), δ ppm 10.91 (s 1H), 7.9-6.84 (m, 14H), 5.20 (m, 1H), 5.04 (s, 1H), 4.90 (m, 3H), 3.41 (m, 1H), 2.90 (m, 1H), 2.42 (s, 3H), 1.40 (s, 9H).

Preparation of the sulfonyl enamine(5.85)

This compound was prepared according to the above general procedure for compound **5.81** from oxime **5.84** (0.2 g, 0.49 mmol). Yield: 56%; ^{1}H-NMR ($CDCl_3$), δ ppm 10.96 (br, 1H), 7.84 (d, J=8.1, 2H), 7.70 (d, 7.9, 1H), 7.38 (m, 6H), 5.64 (d, J=8.1, 1H), 5.20 (m, 3H), 4.8 (m, 1H), 4.14 (m, 2H), 3.65 (m, 1H), 2.40 (s, 3H), 2.30 (m, 3H), 1.42 (s, 9H), 1.32 (m, 3H). ^{13}C-NMR ($CDCl_3$), δ ppm 171.2, 169.0, 152.3, 144.7, 137.5, 135.7, 130.4, 130.2, 129.0, 128.8, 128.7, 127.5, 100.5, 67.8, 60.8, 53.1, 35.0, 30.1, 28.6, 22.0, 14.5.

Cycloadduct of the phthalimido derivative 5.86 with tri-O-benzyl-D-galactal (5.87)

This compound was prepared according to the above general procedure for compound **4.46** from **5.86** (25 mg, 0.08 mmol). Yield: 65%; ^{1}H-NMR ($CDCl_3$), δ ppm 7.30 (m, 15H), 6.62 (d, J=3.6, 1H), 4.9-4.7 (m, 7H), 4.42 (m, 3H), 4.2-3.9 (m, 4H), 3.53 (d, J=6.3, 2H), 1.28 (s, 18H).

Cycloadduct of the phthalimido derivative 5.88 with tri-O-benzyl-D-galactal (5.89)

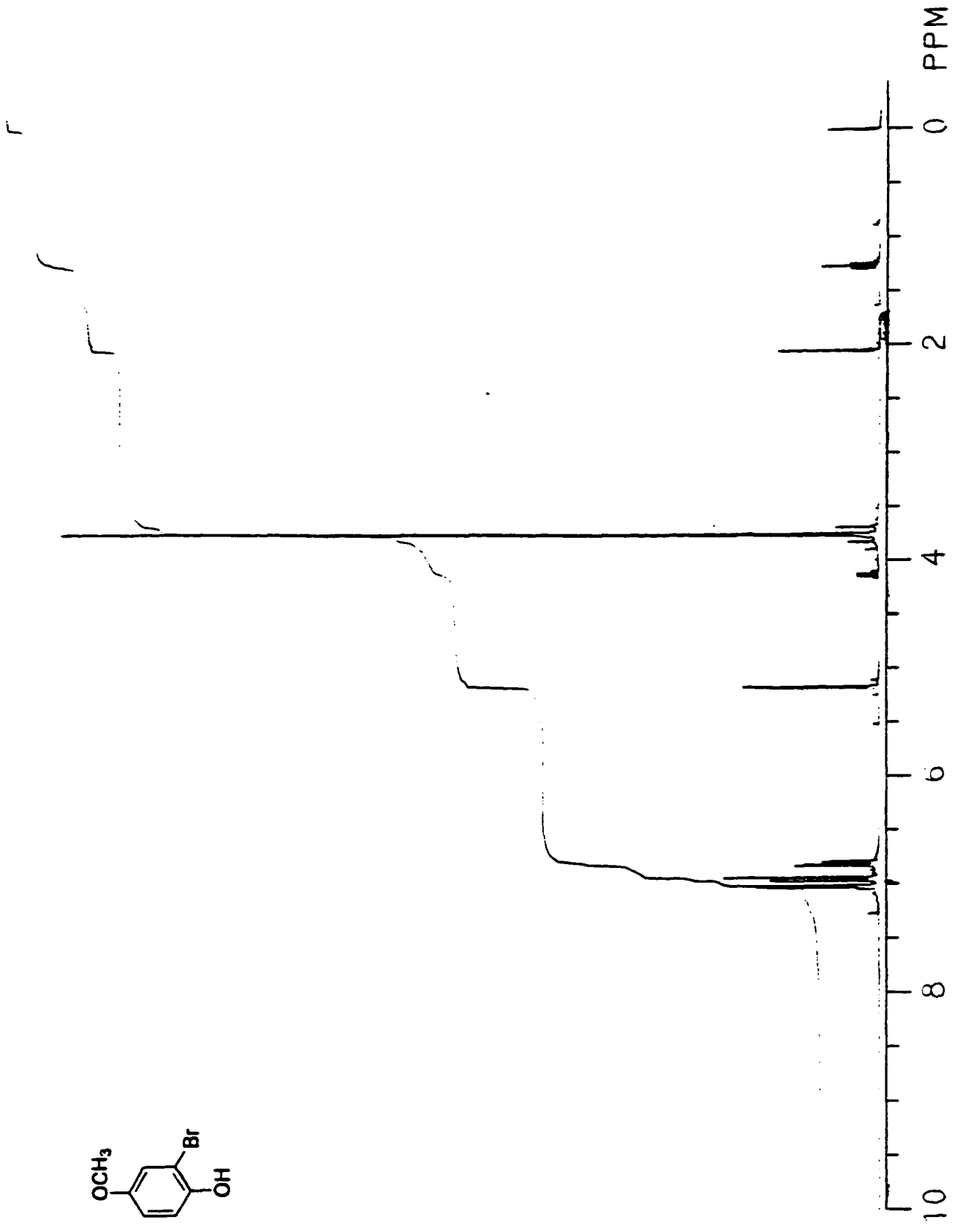
This compound was prepared according to the above general procedure for compound **4.46** from **5.88** (38 mg, 0.069 mmol). Yield: 86%; ^{1}H-NMR ($CDCl_3$), δ ppm 7.32 (m, 20 H), 5.91 (d, J=2.4, 1H), 5.41 (m, 1H), 5.10 (d, J=2.7, 2H), 4.92-4.45 (m, 6H), 4.20 (m, 1H), 3.95 (m, 1H), 3.74 (dd, J=2.4, 11.4, 1H), 3.6 (m, 2H), 3.35-2.96 (m, 4H), 1.42(s, 9H).

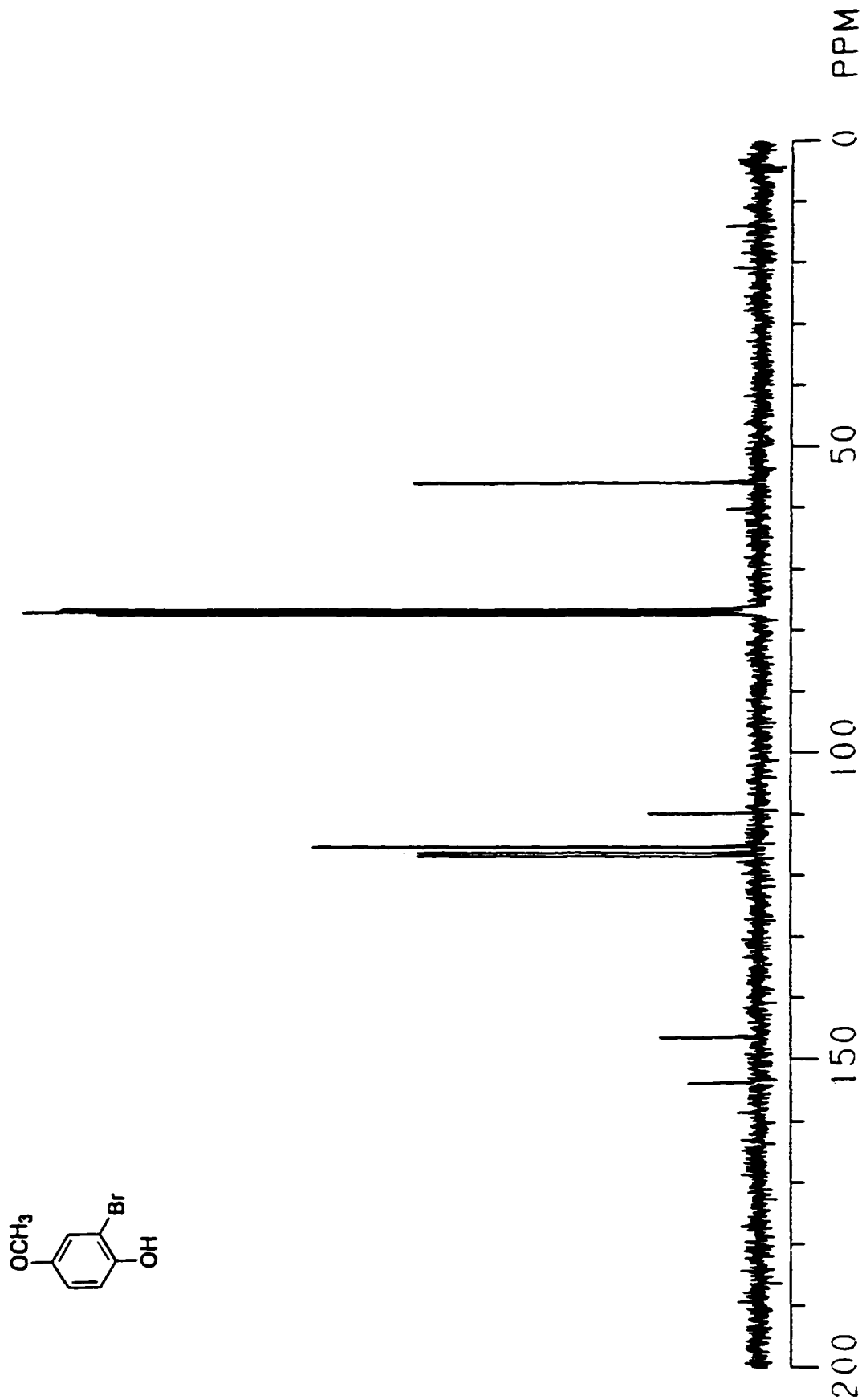
N-Glycopeptide analog (5.93)

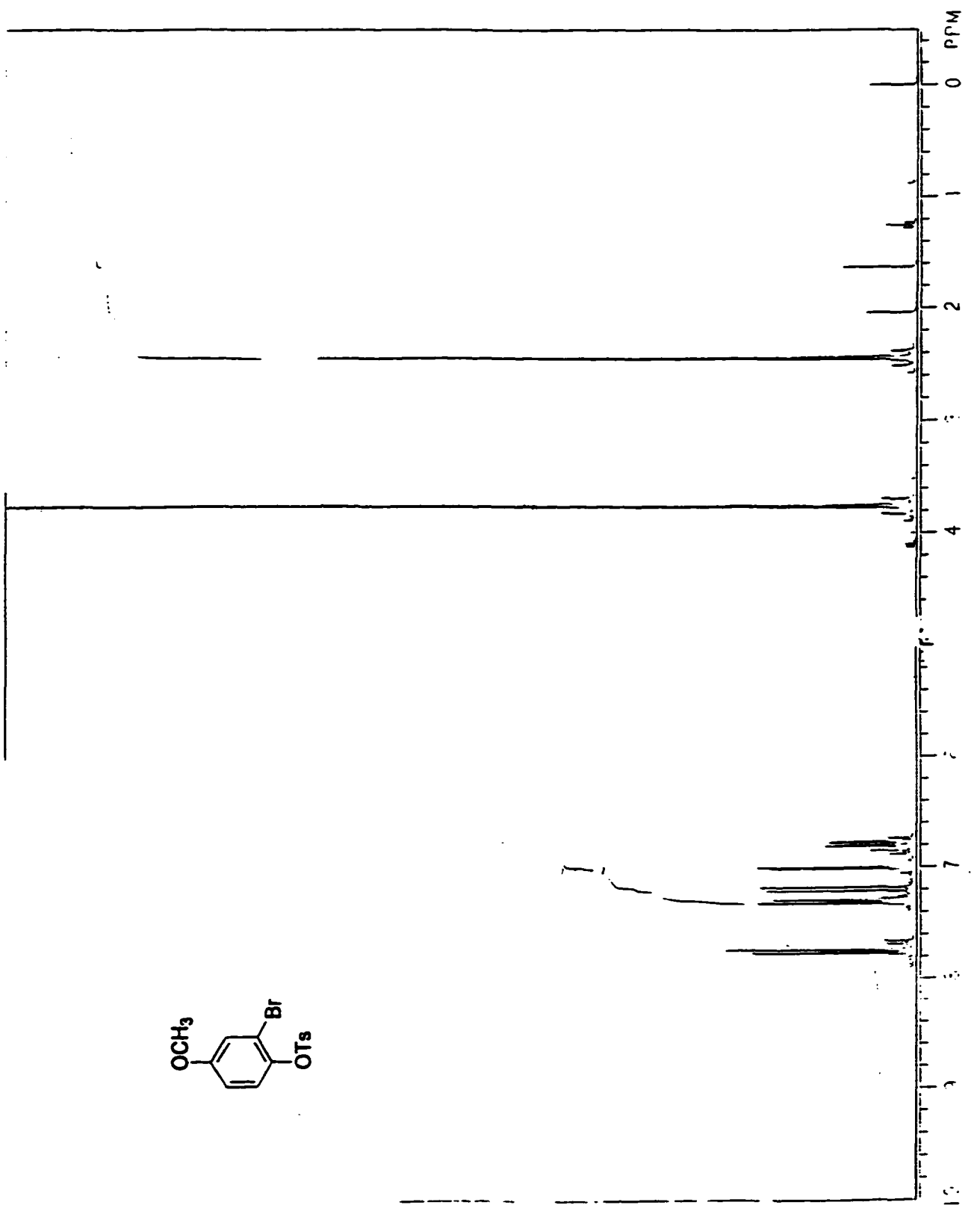
This compound was prepared according to the above general procedure for compound **4.46** from **5.92** (50 mg, 0.09 mmol). Yield: 75%; ^{1}H-NMR ($CDCl_3$), δ ppm 7.83

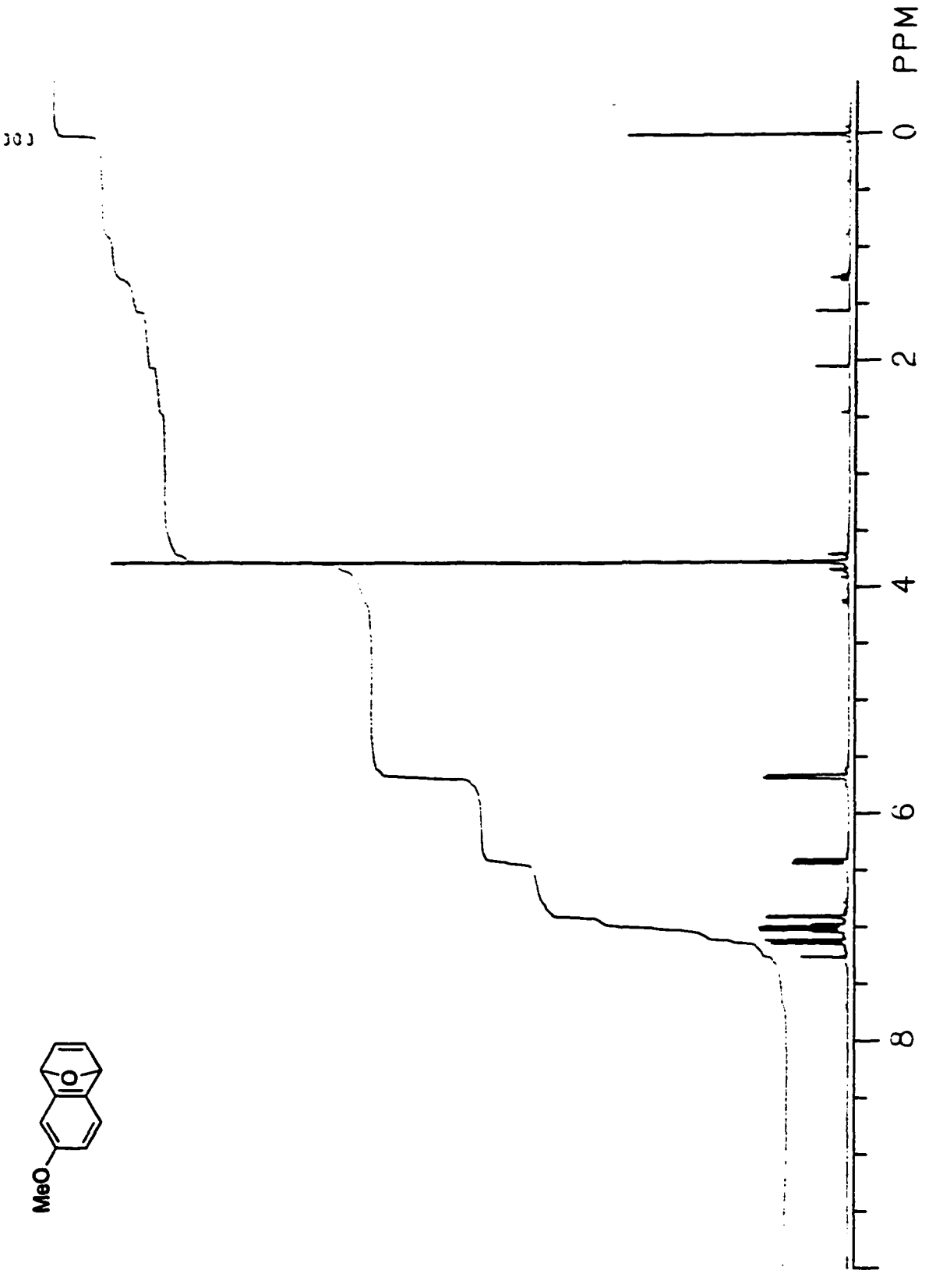
(d, J=11.1, 2H), 7.35 (m, 20H), 6.87 (d, J=11.1, 2H), 6.13 (d, J=6.9, 1H), 6.22 (m, 1H), 5.15 (m, 1H), 4.97 (d, 12.9, 1H), 4.85 (d, J=13.2, 1H), 4.53 (m, 5H), 4.21 (m, 2H), 4.0-3.7 (m, 5H), 3.54 (m, 2H), 3.28 (m, 2H), 2.21 (s, 3H), 1.29 (s, 9H), 1.20 (m, 3H). ^{13}C-NMR ($CDCl_3$), δ ppm 173.1, 167.0, 155.7, 144.2, 138.1, 138.0, 135.6, 129.8, 128.6, 128.3, 128.2, 128.0, 127.8, 127.6, 127.5, 127.2, 119.2, 86.6, 77.7, 77.6, 77.5, 77.2, 74.5, 73.4, 72.7, 67.0, 62.3, 44.7, 44.6, 33.6, 29.7, 28.4, 21.5, 13.9.

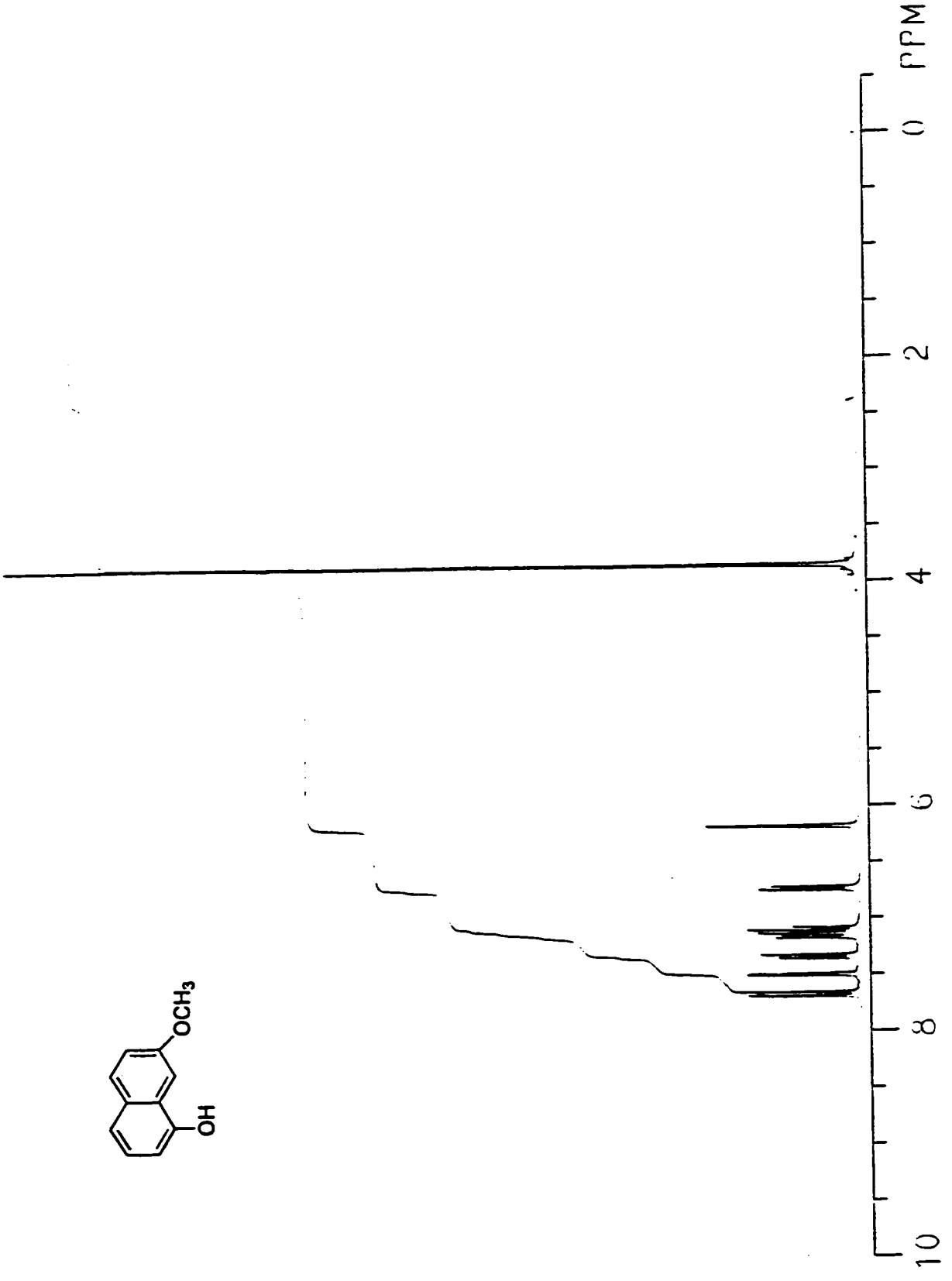
Appendix

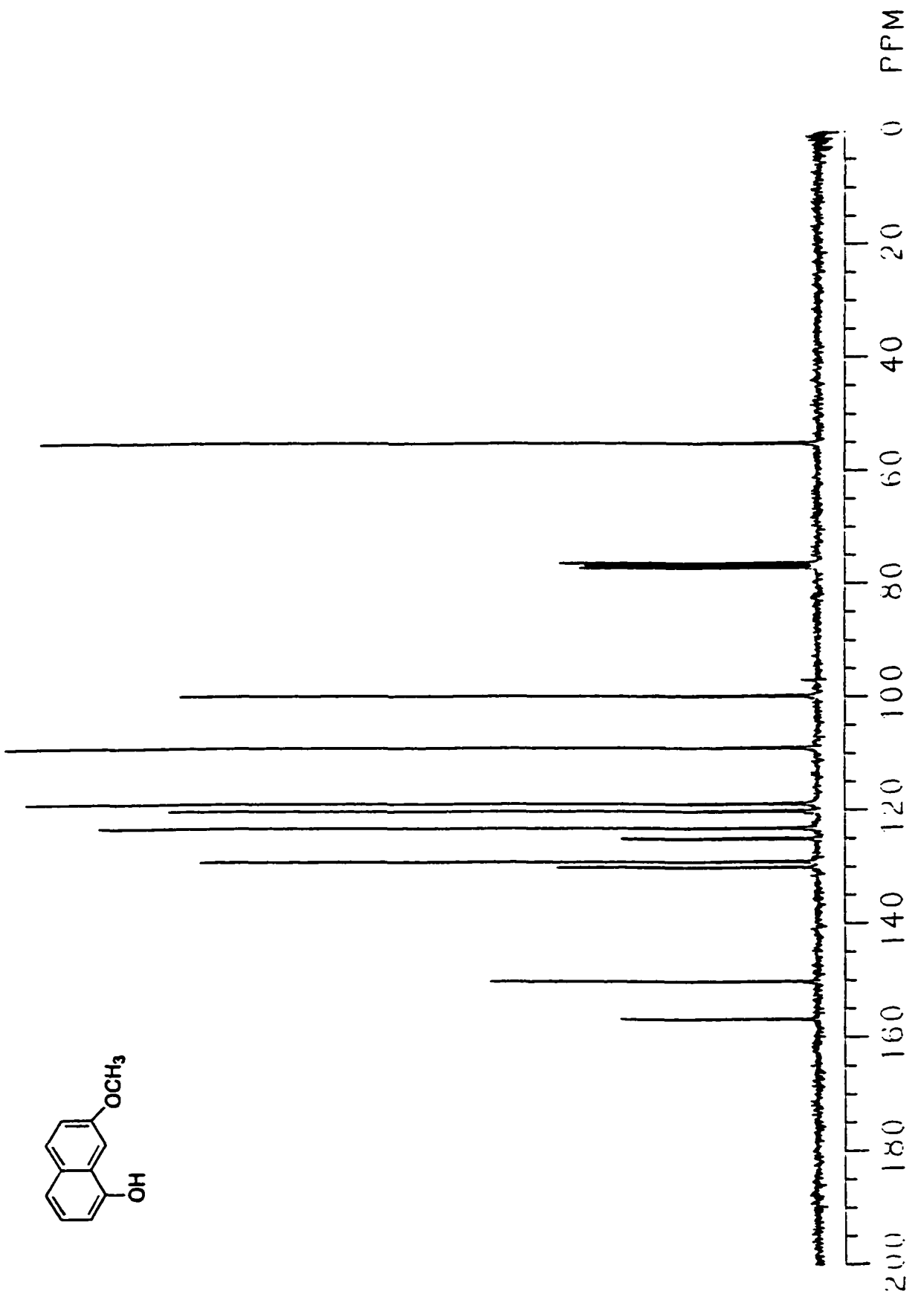


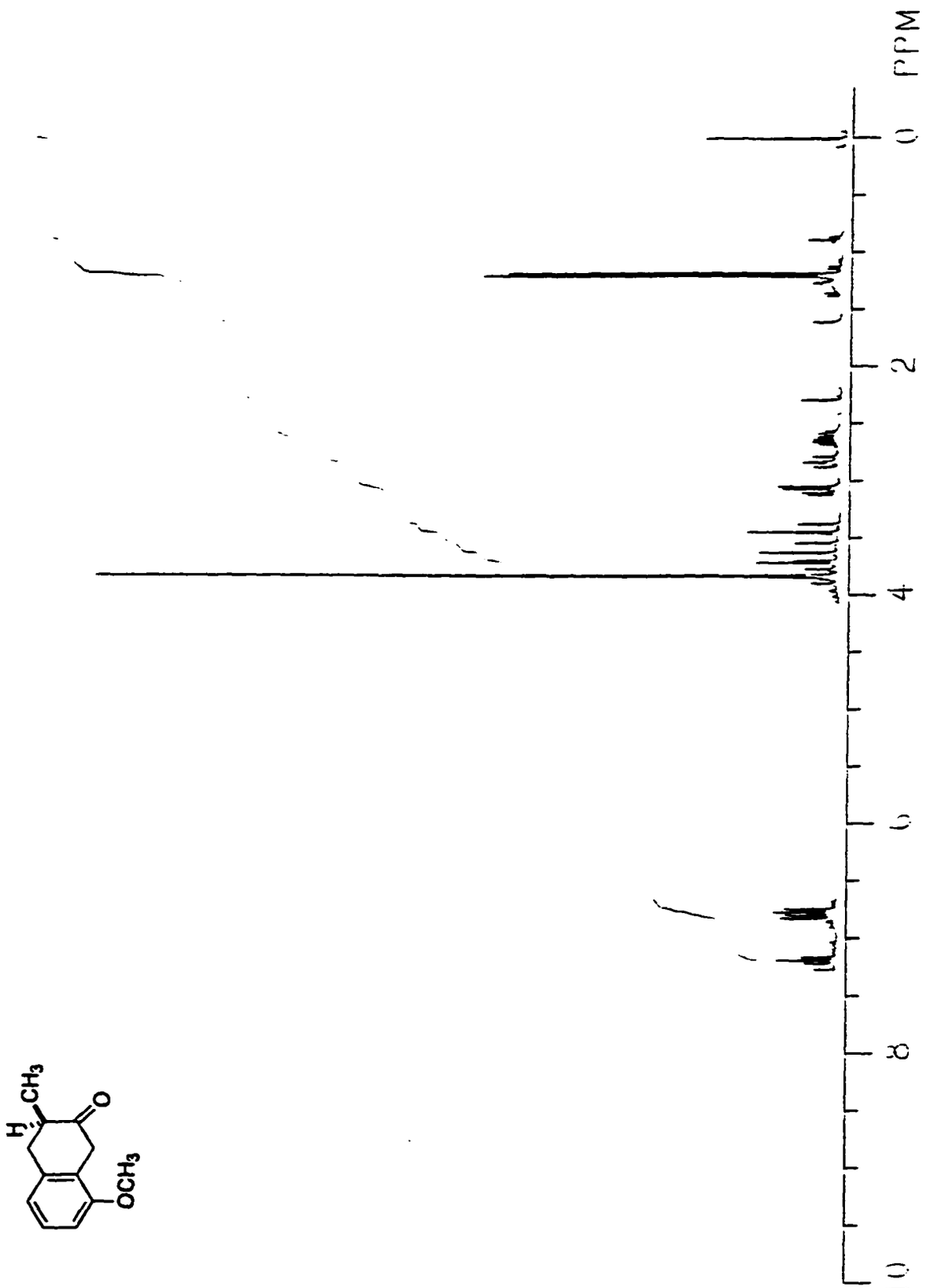


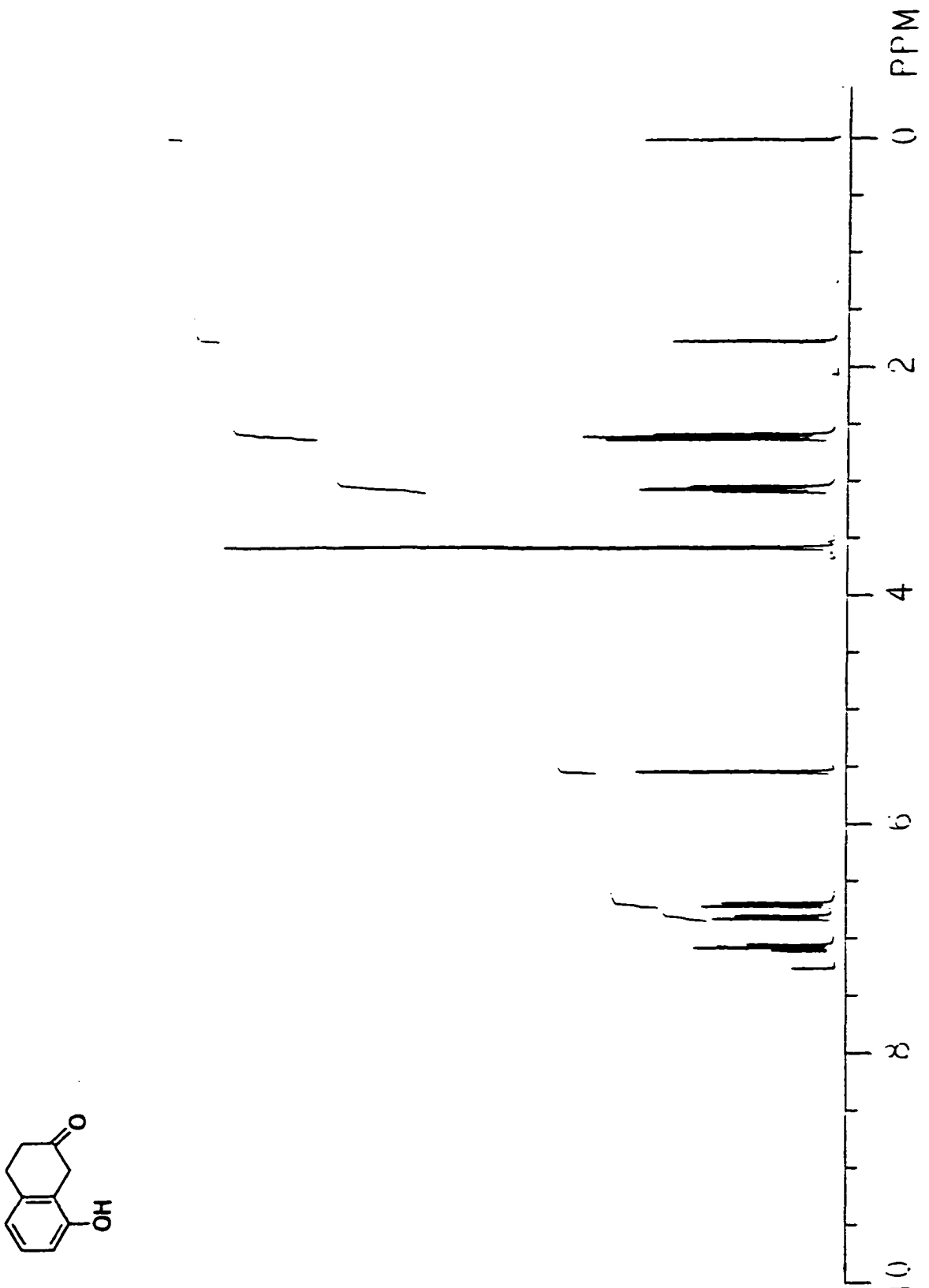


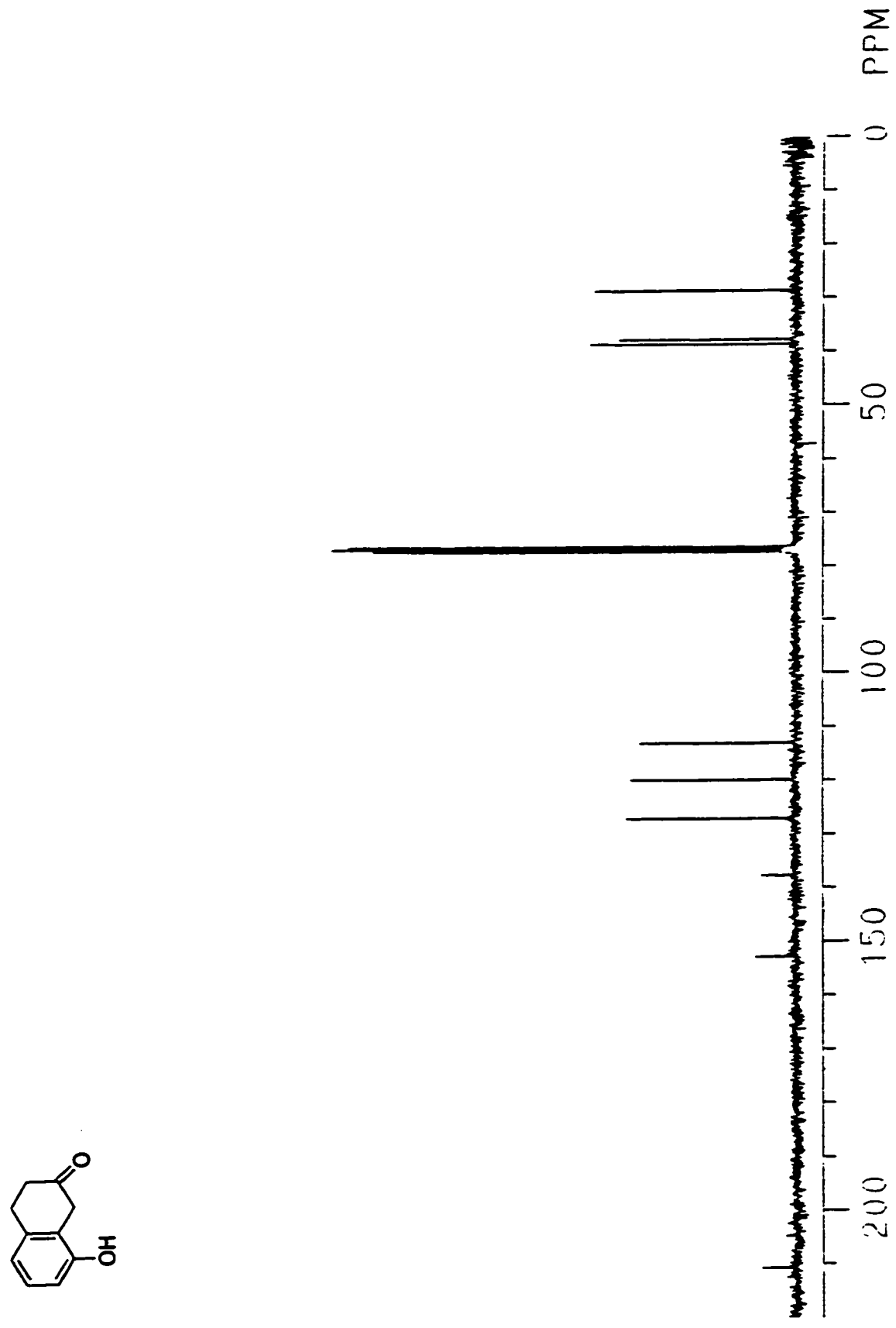


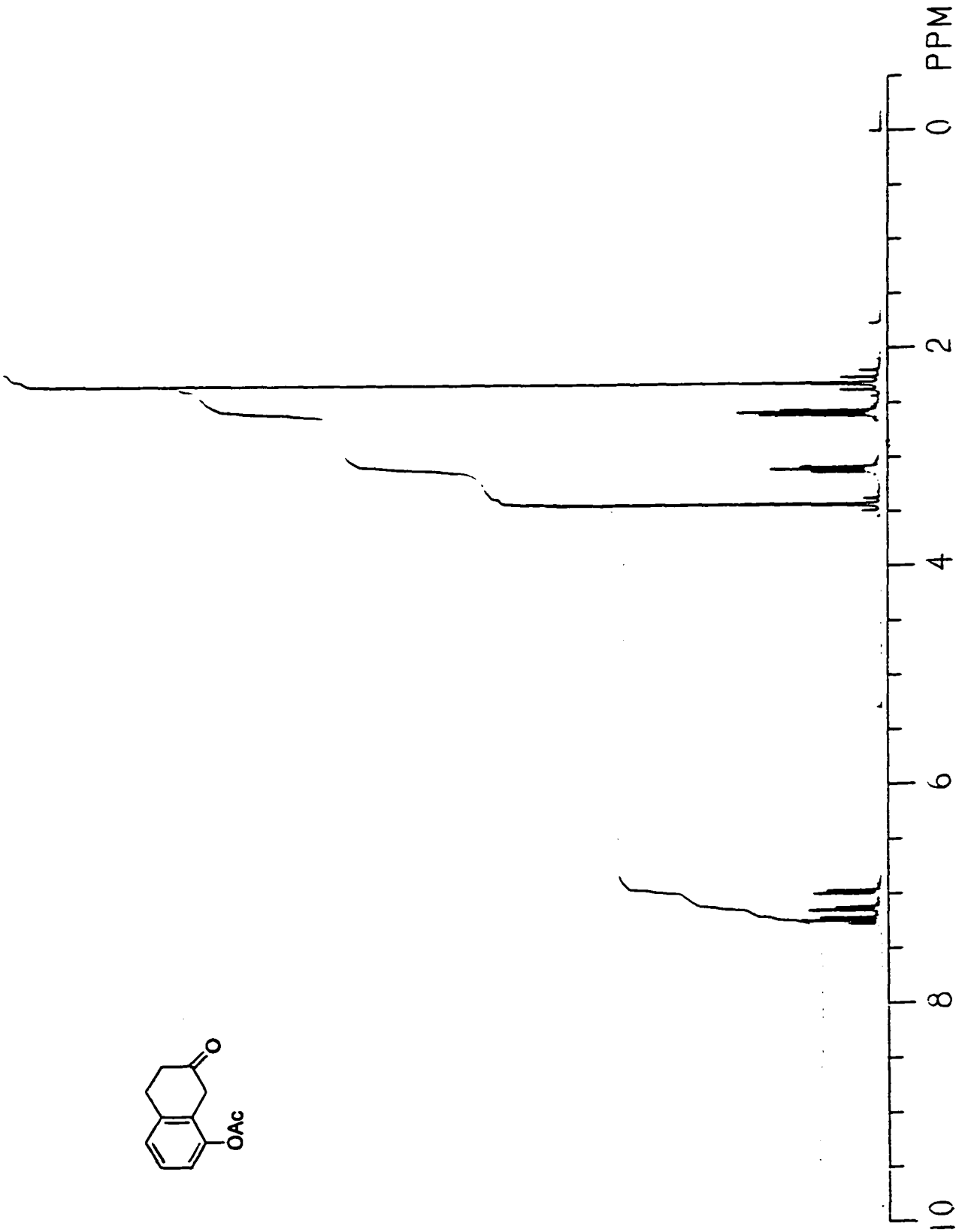


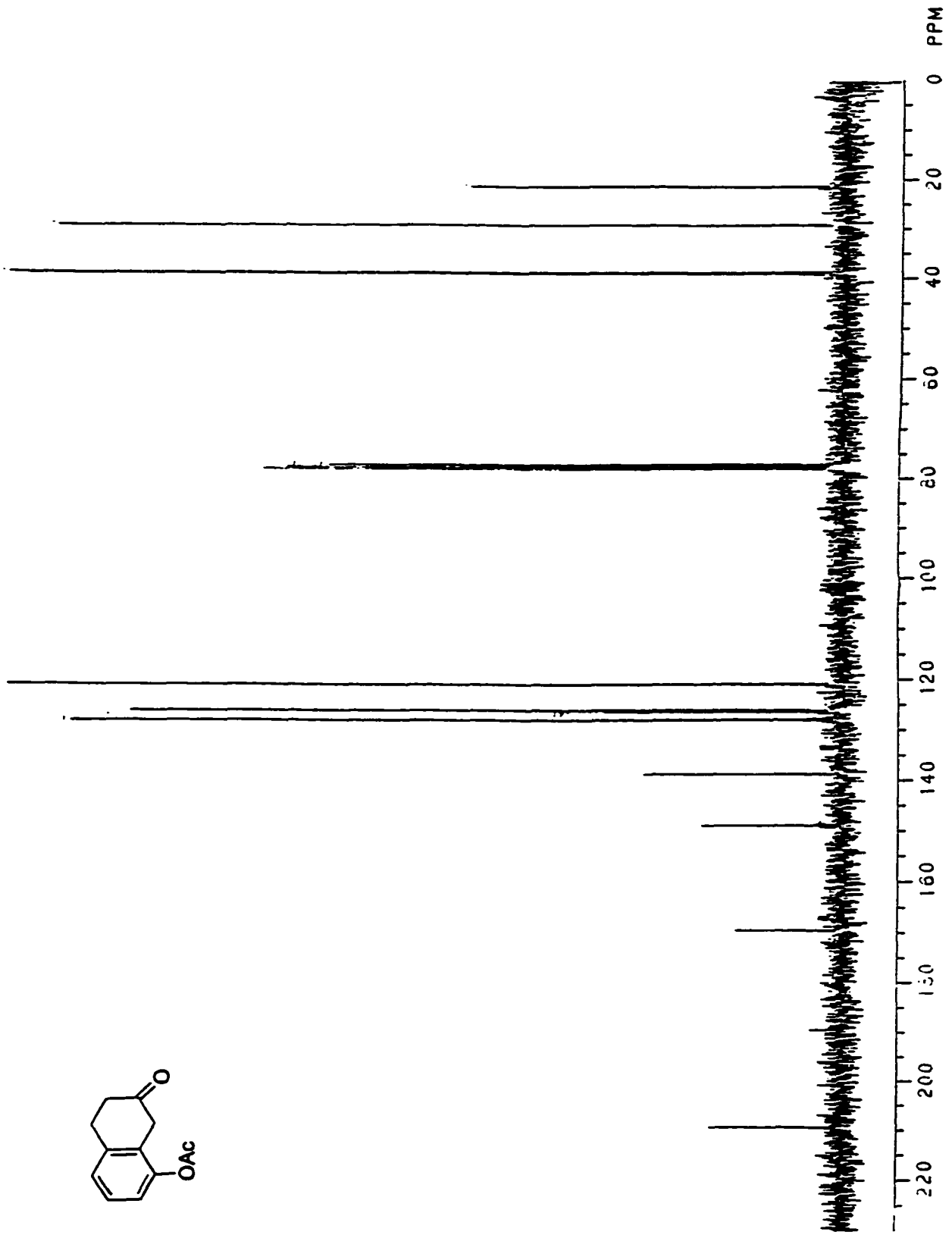


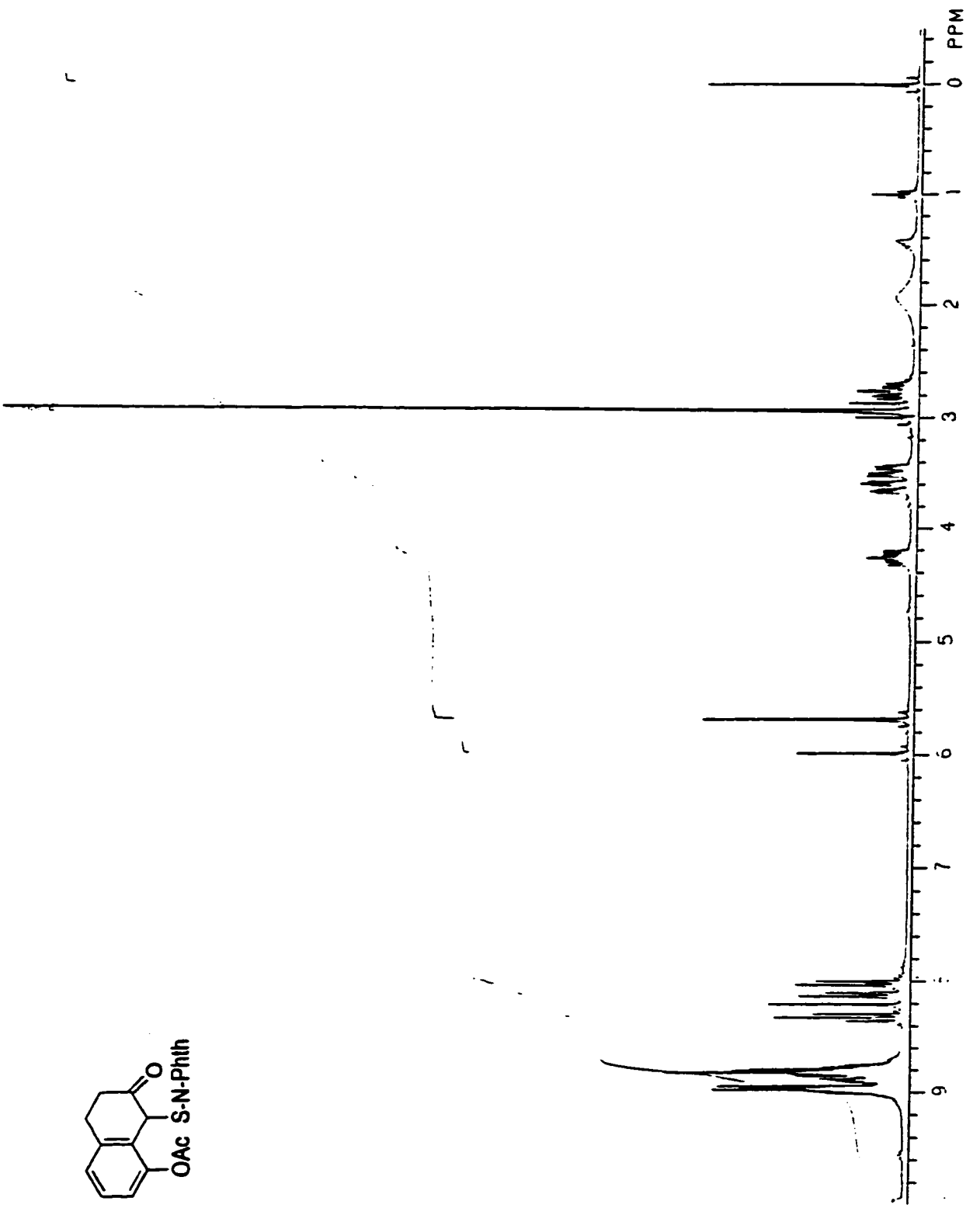


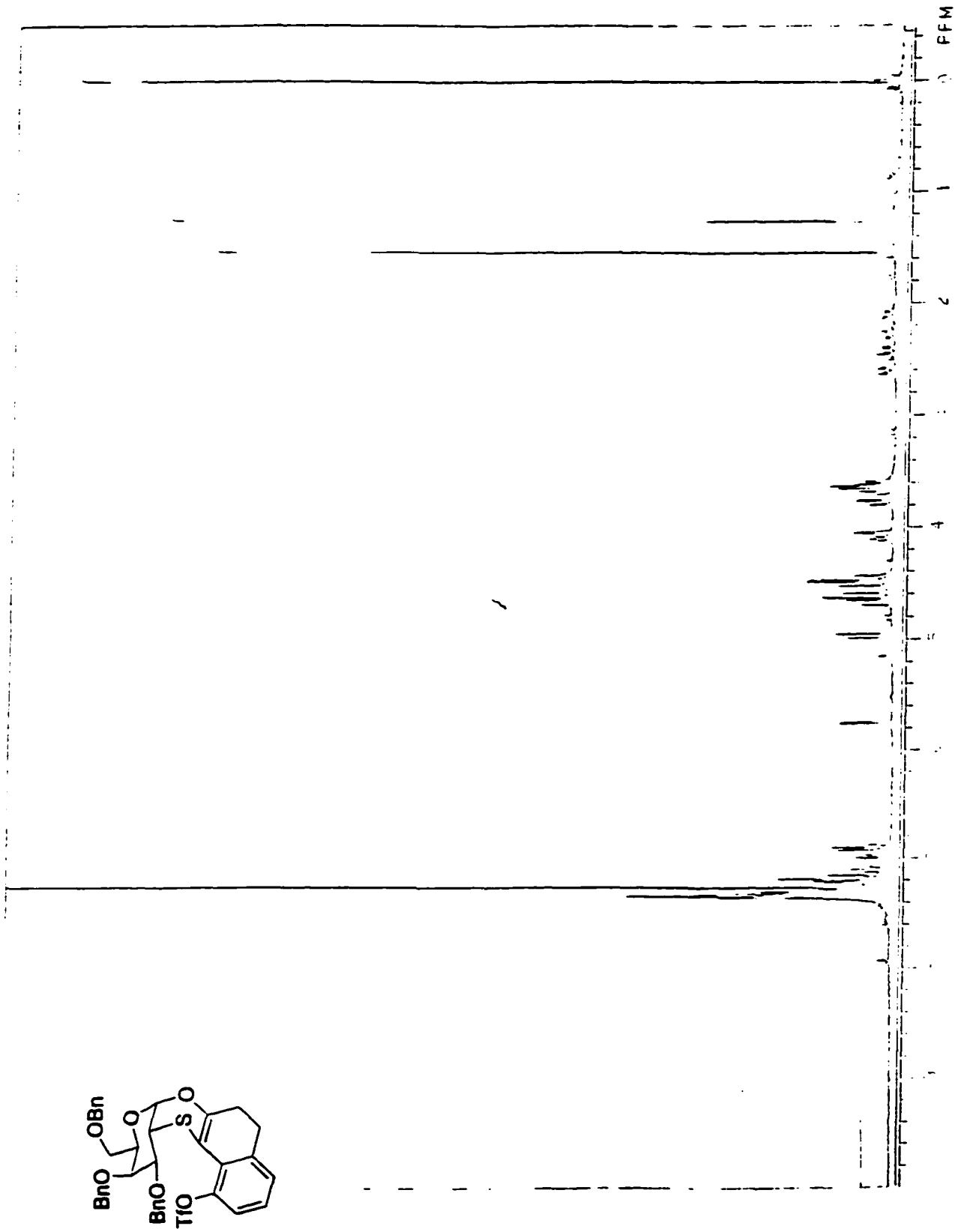


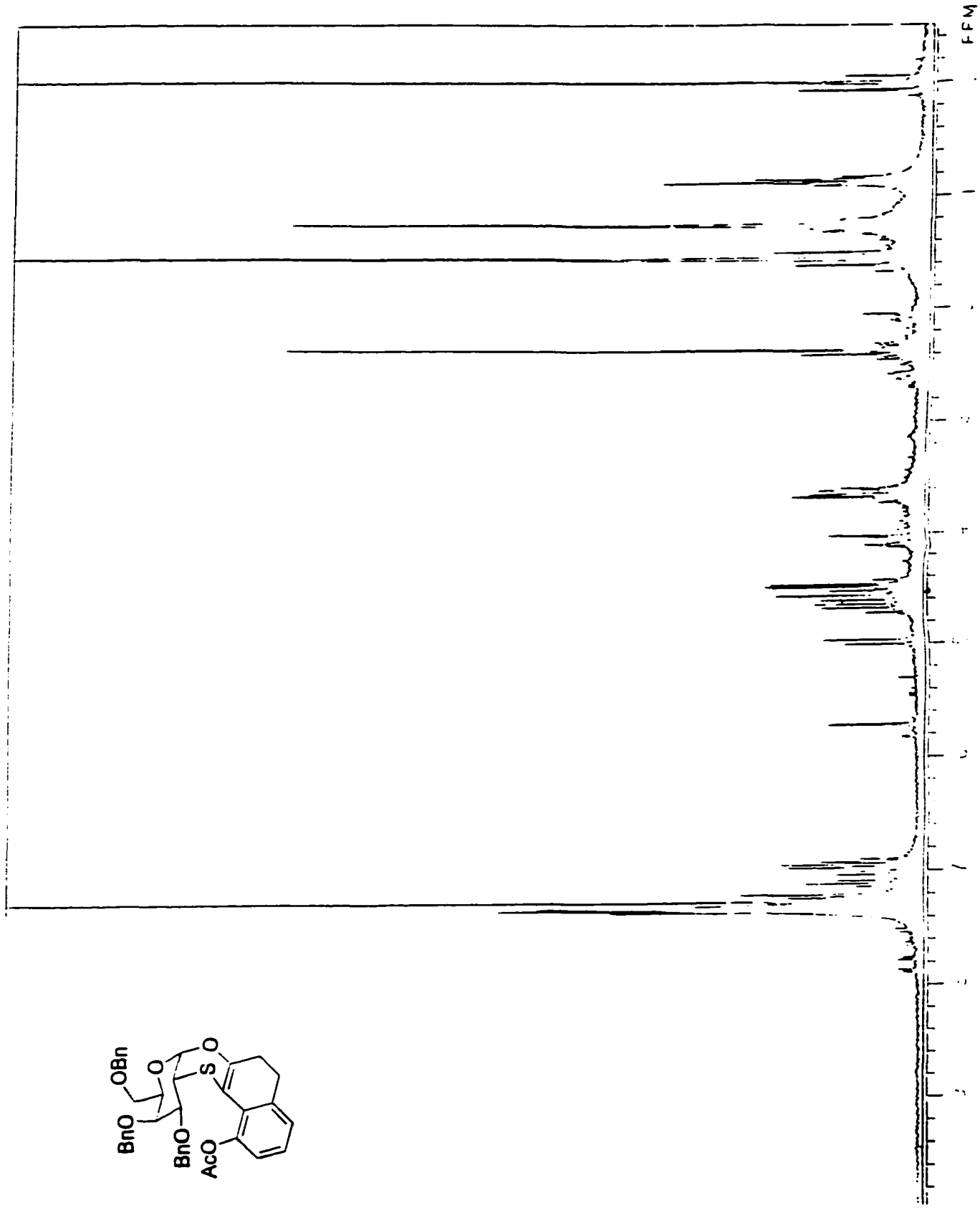


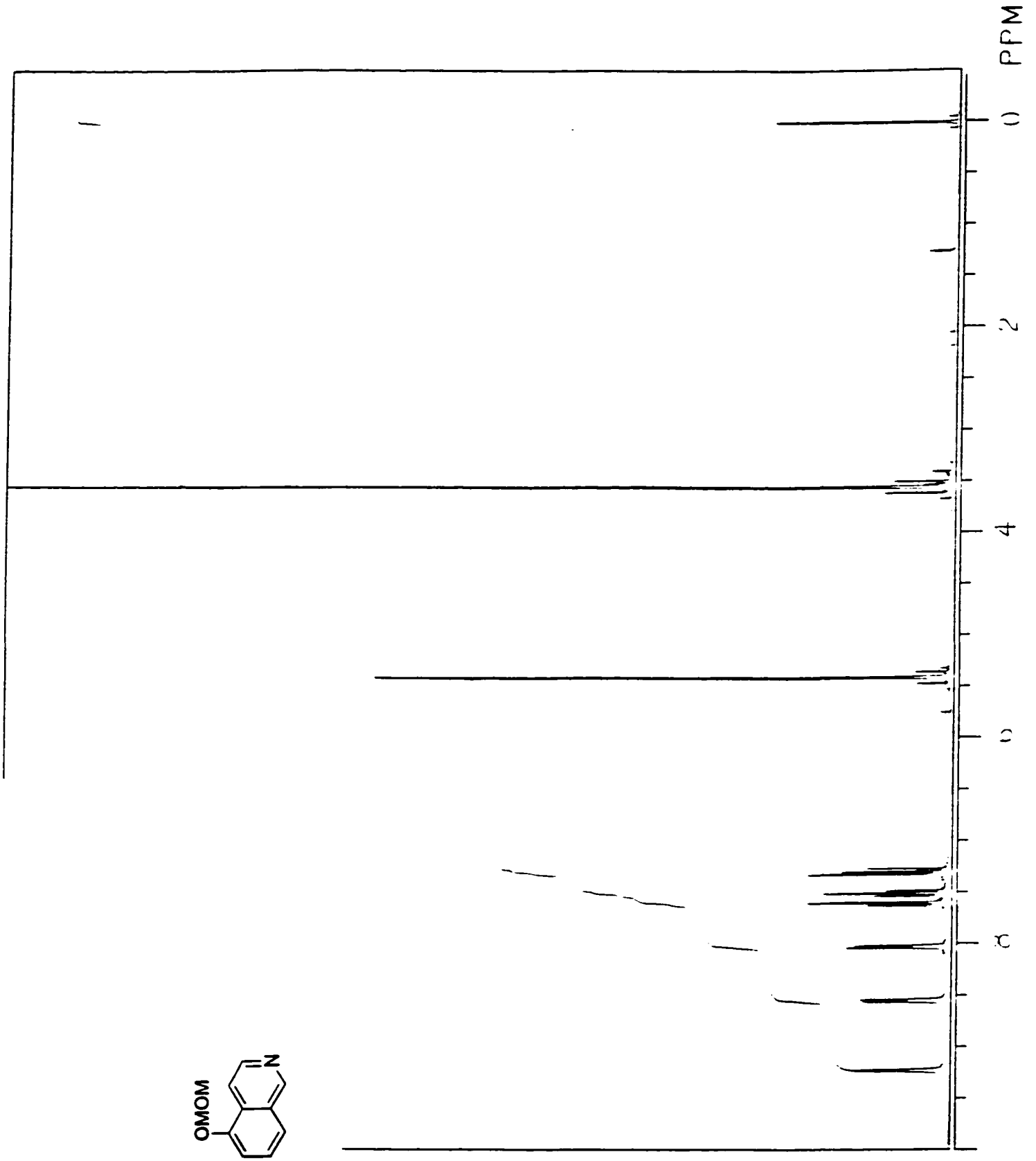


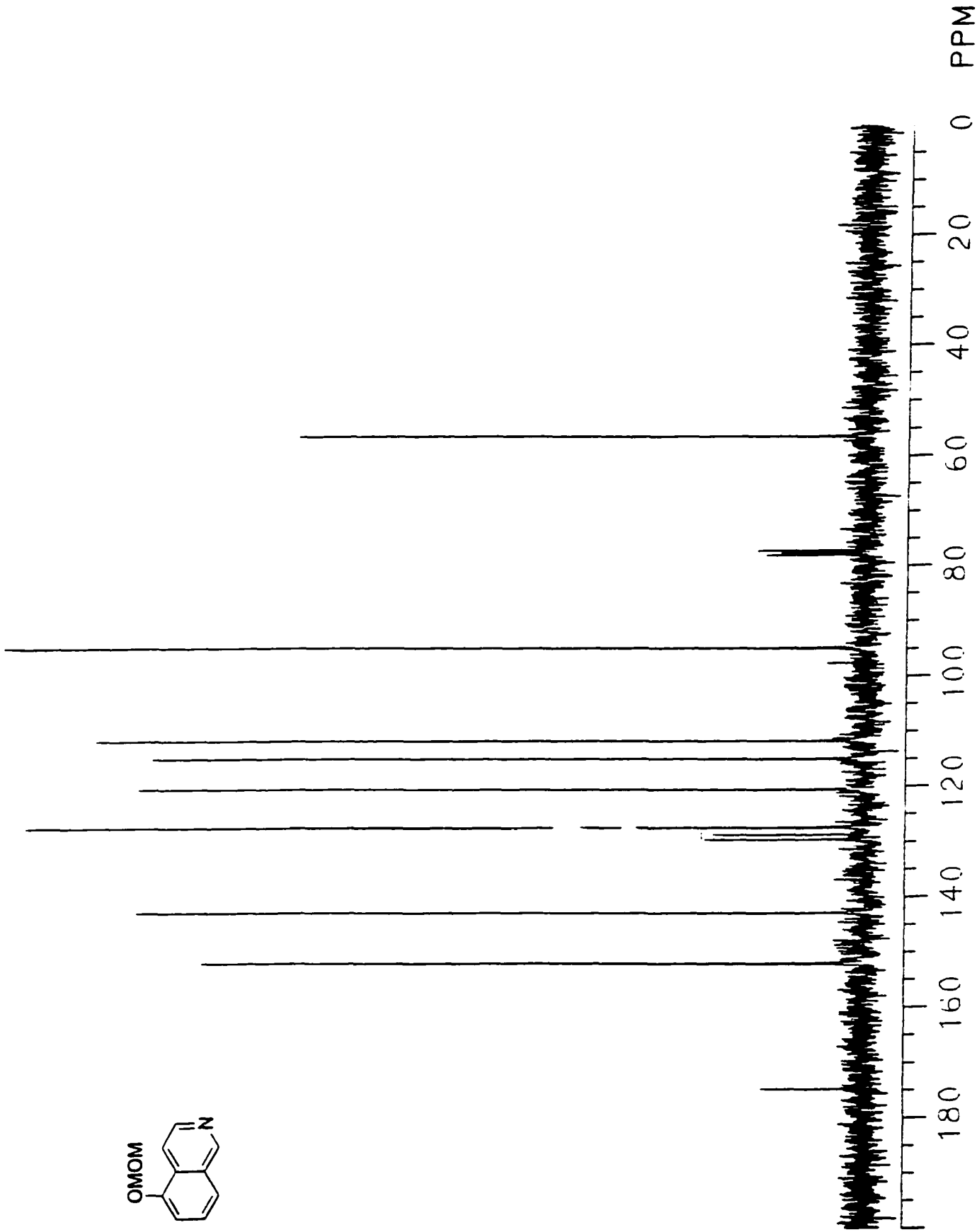


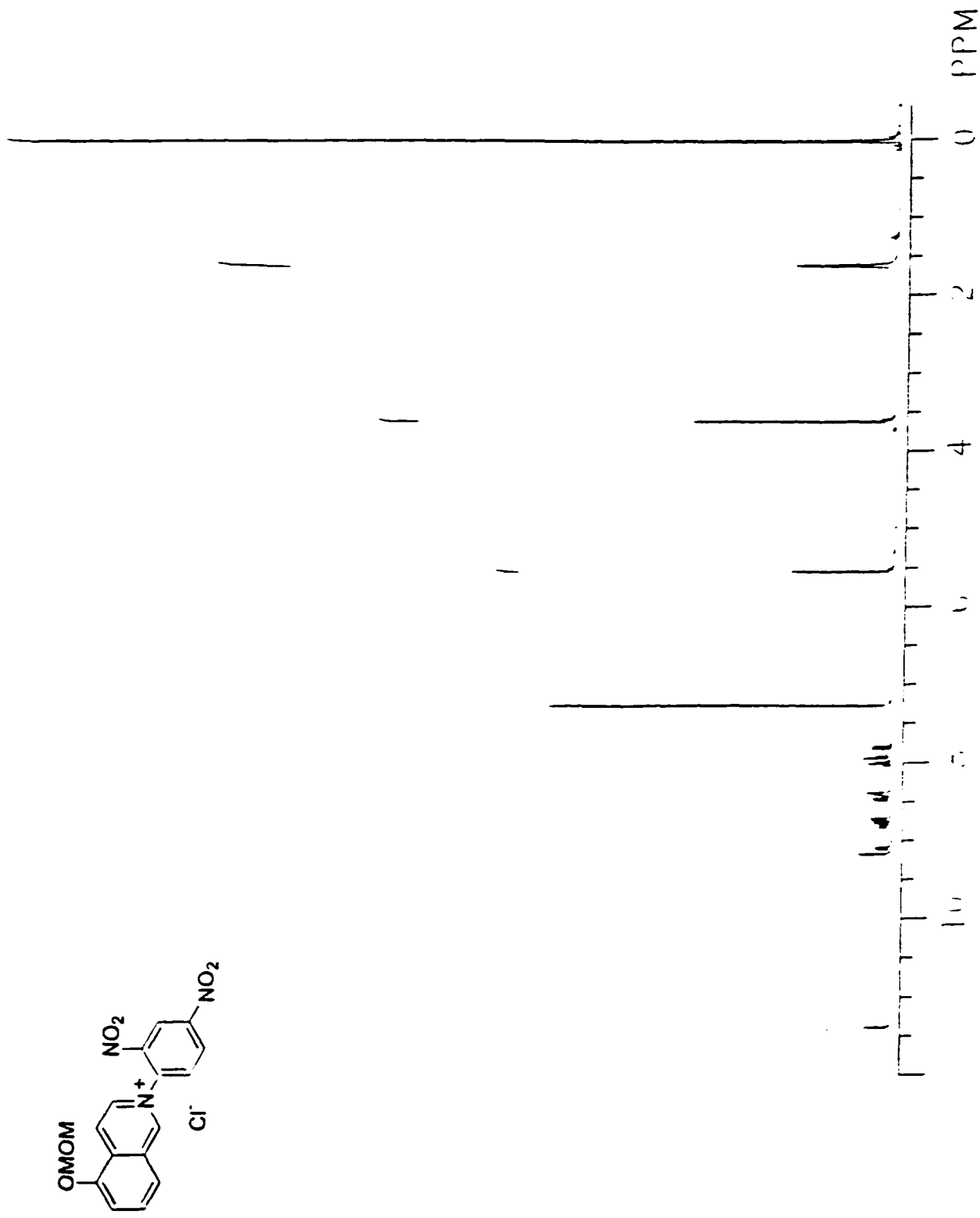


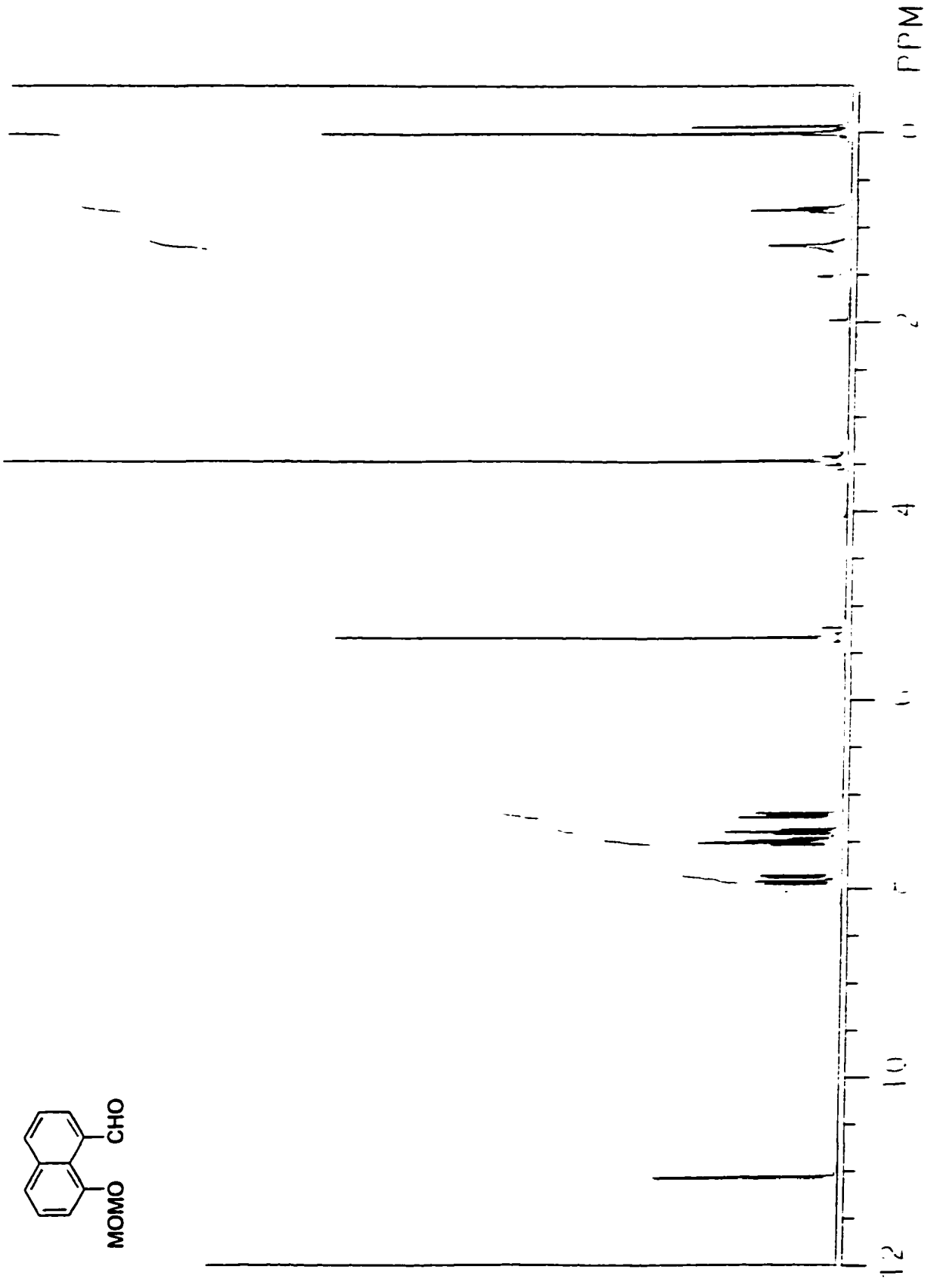


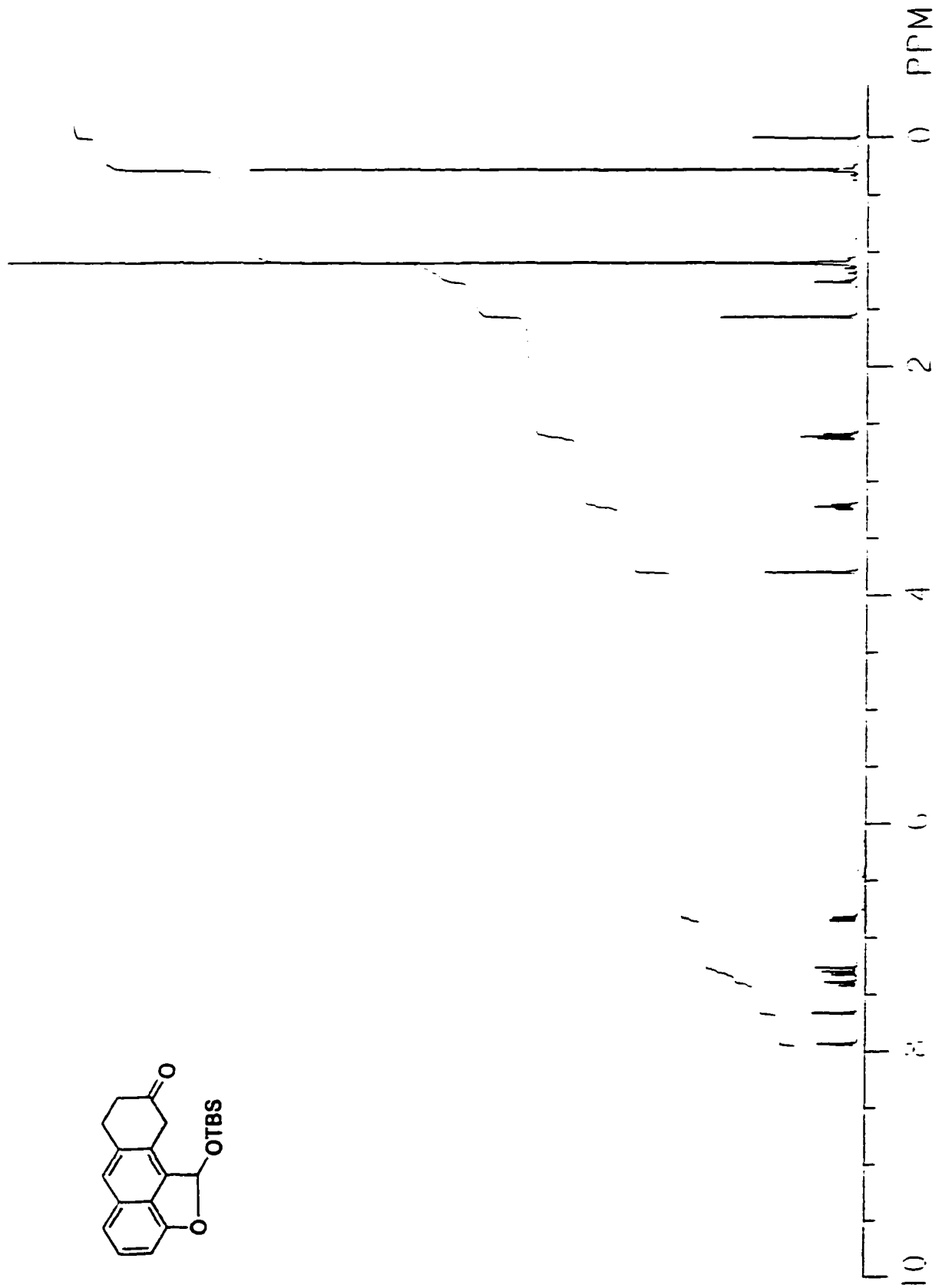


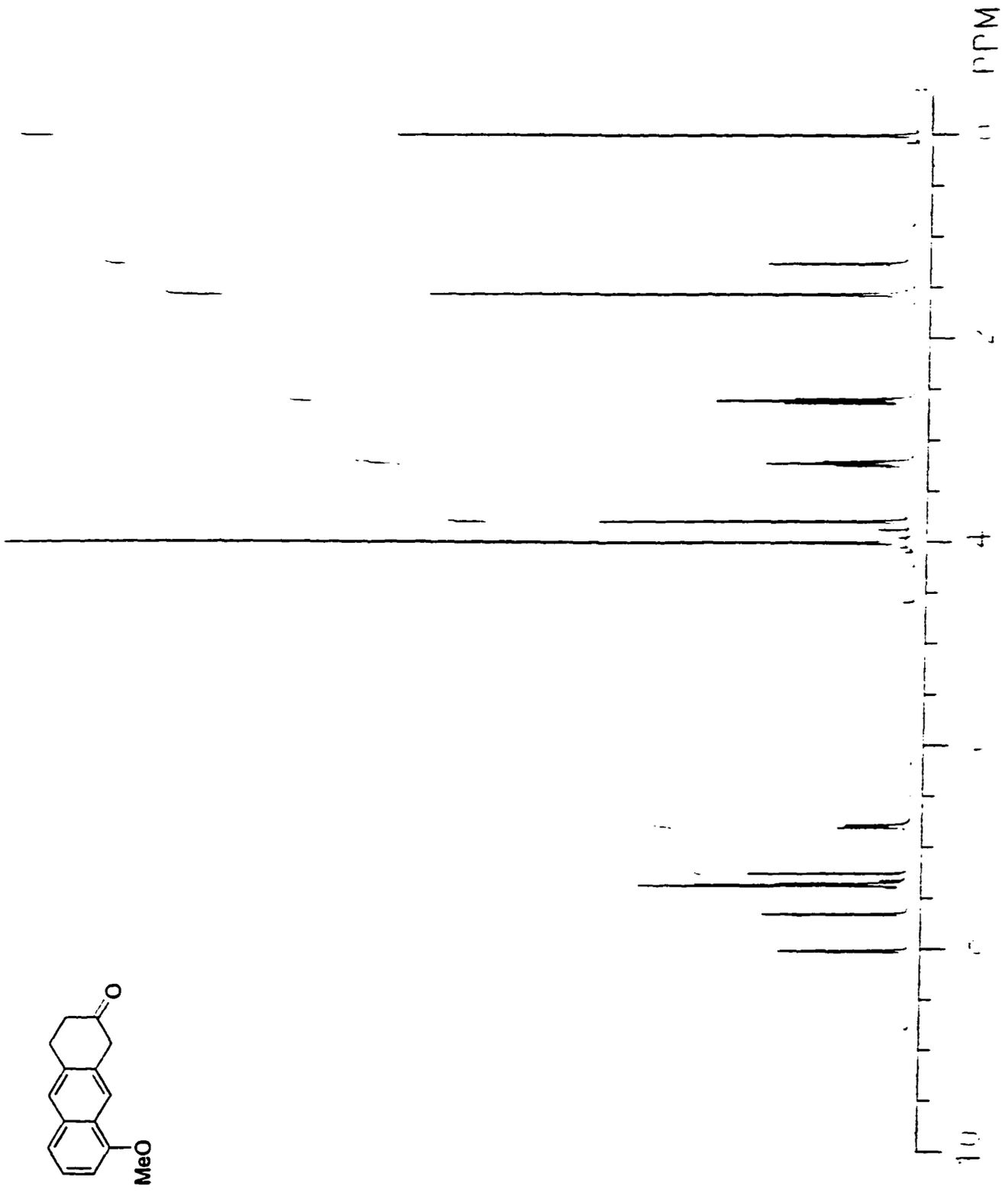


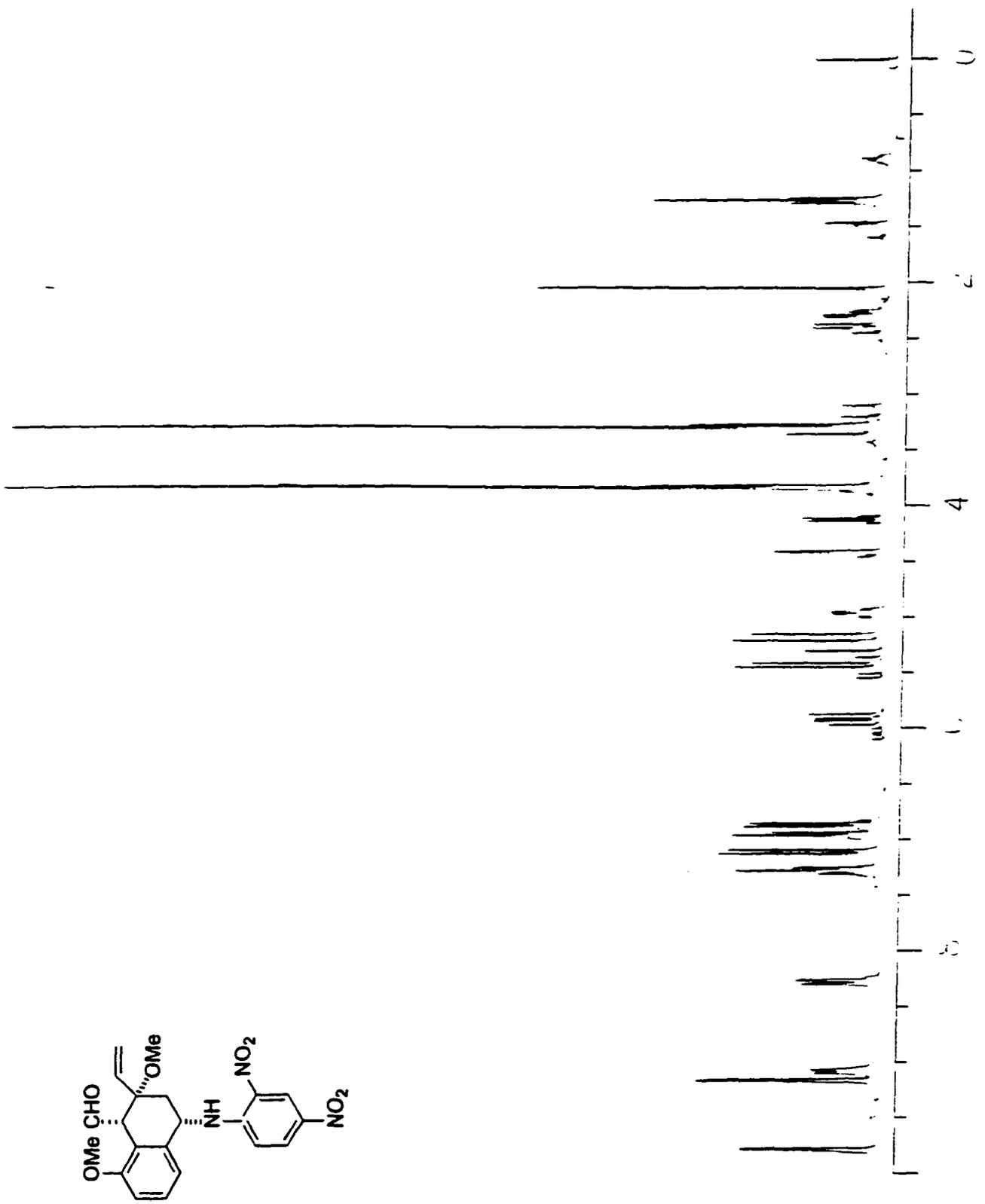


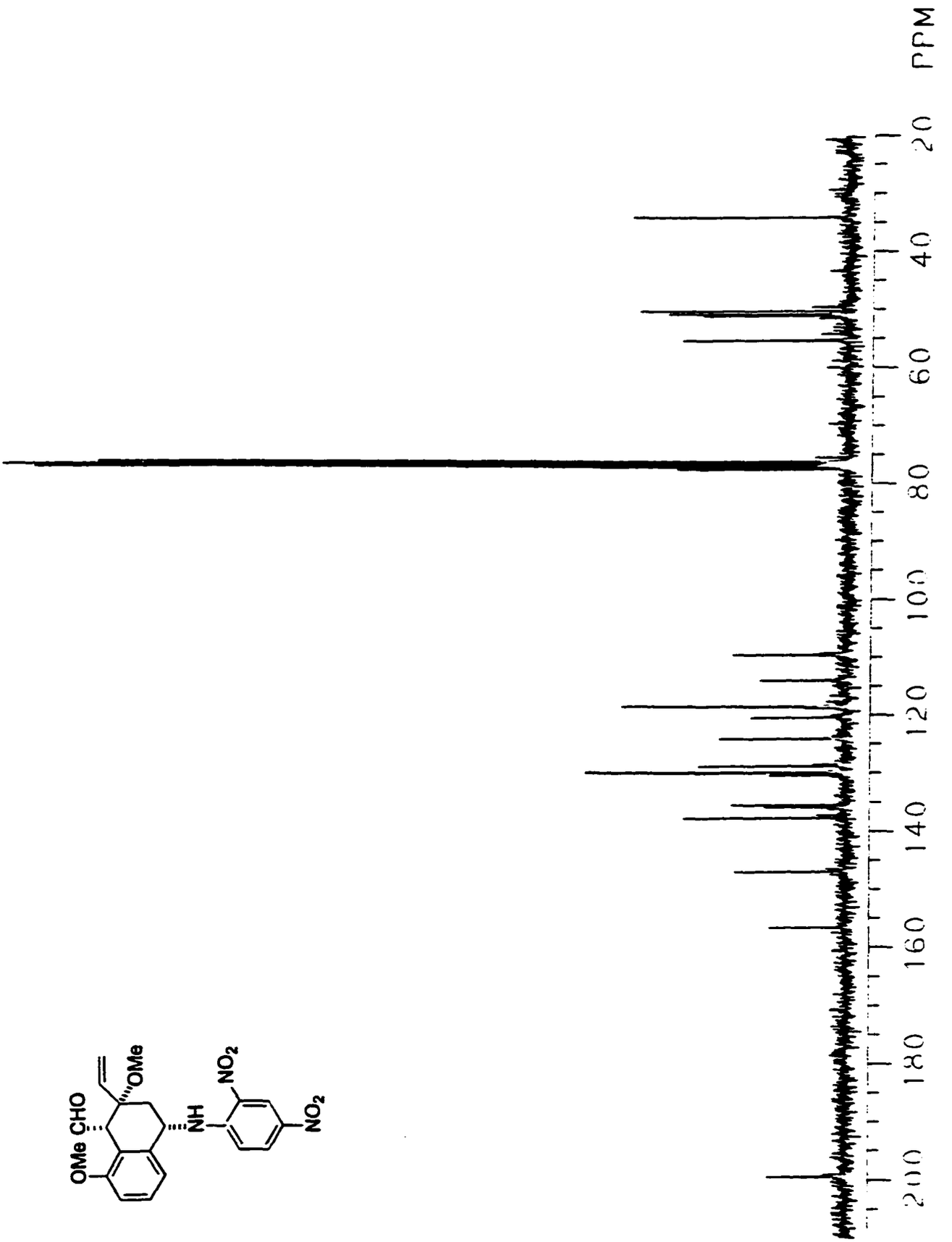


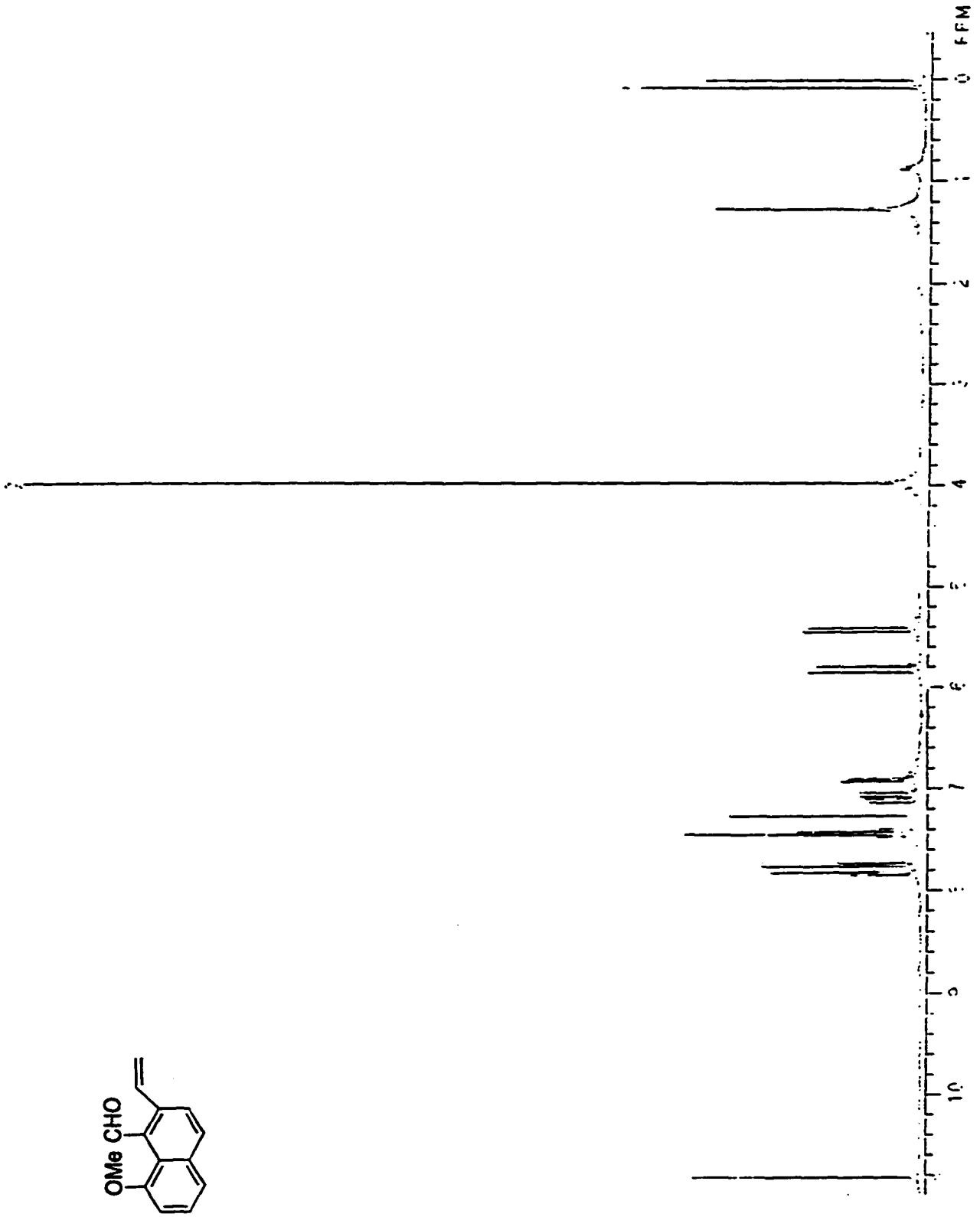


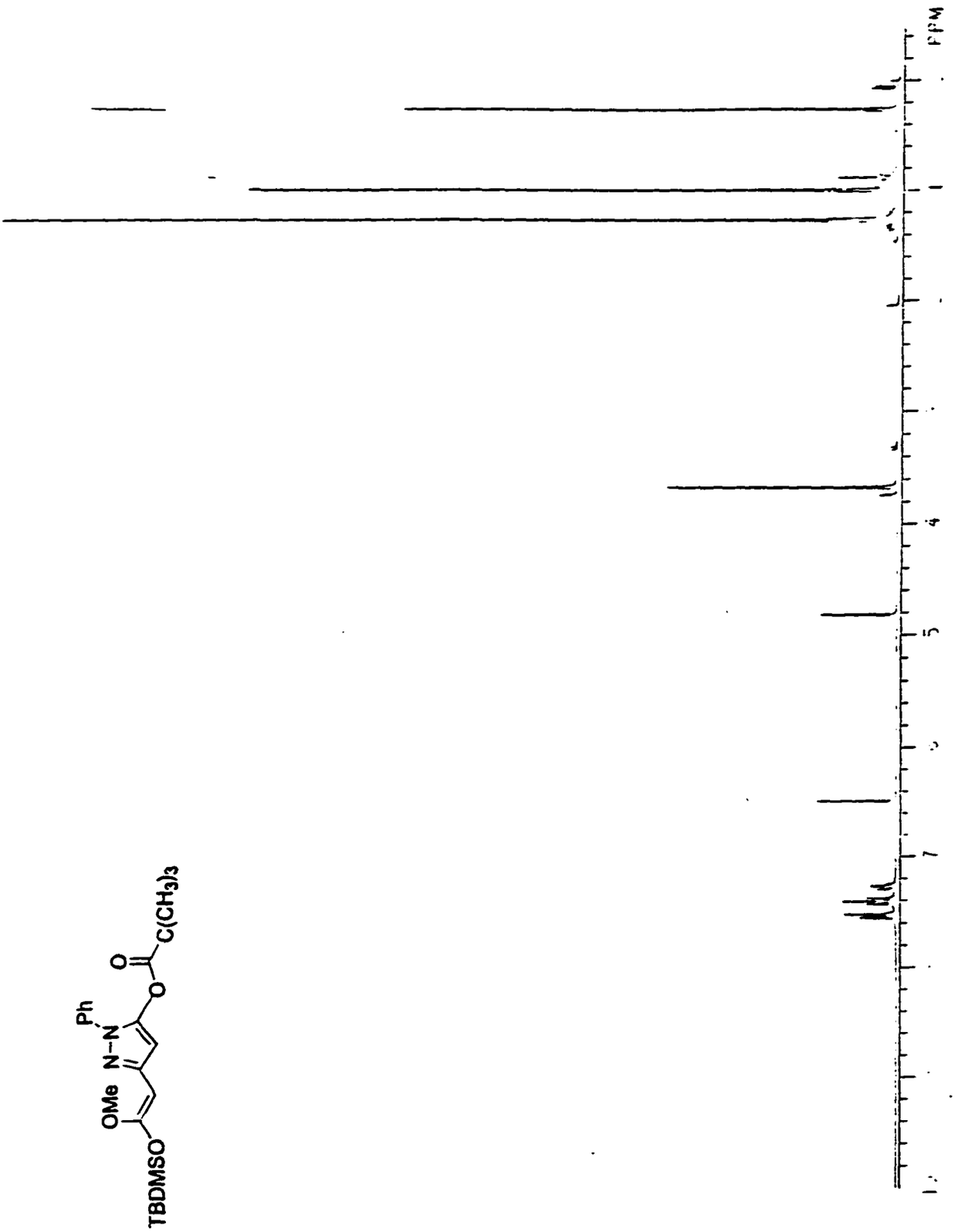


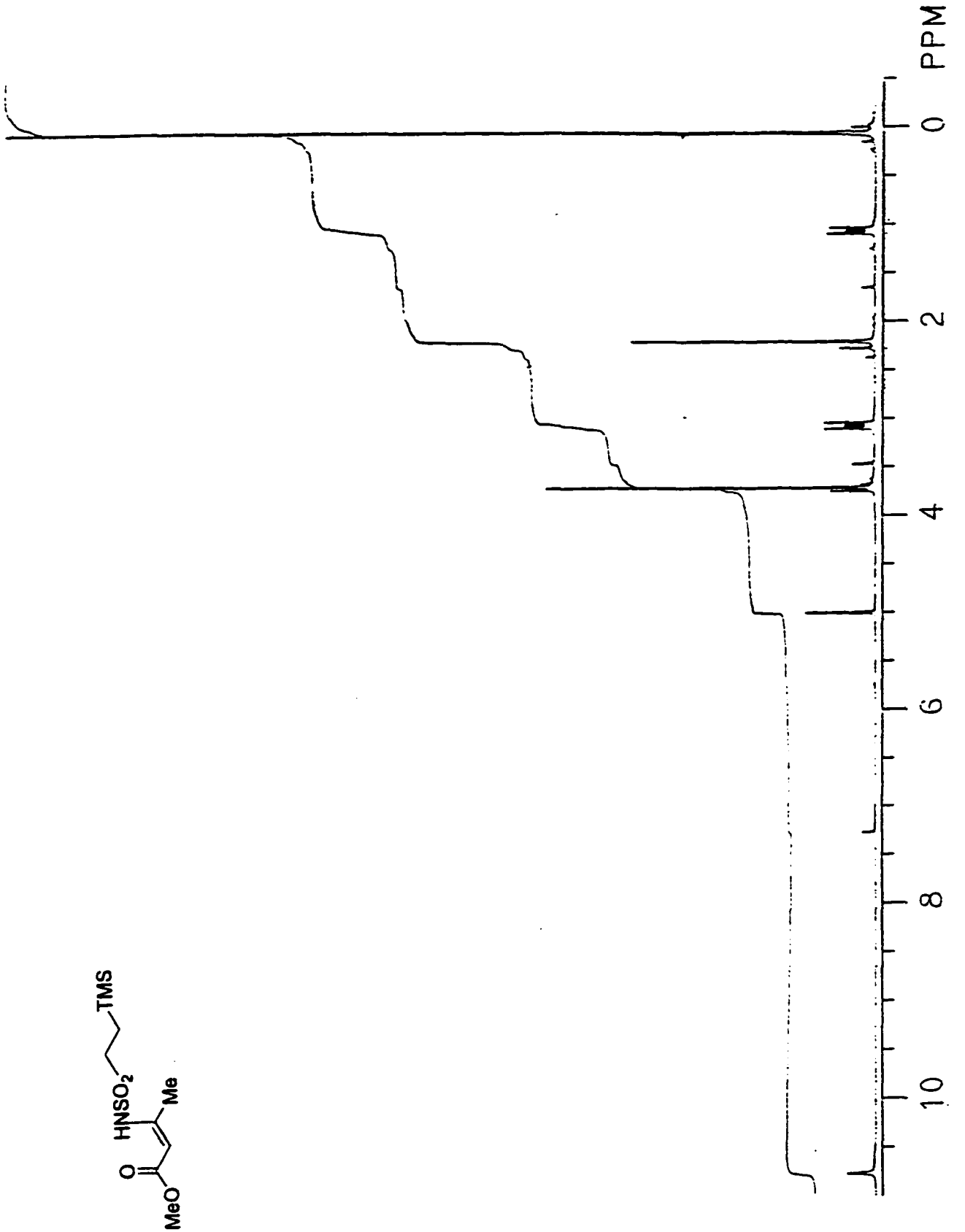


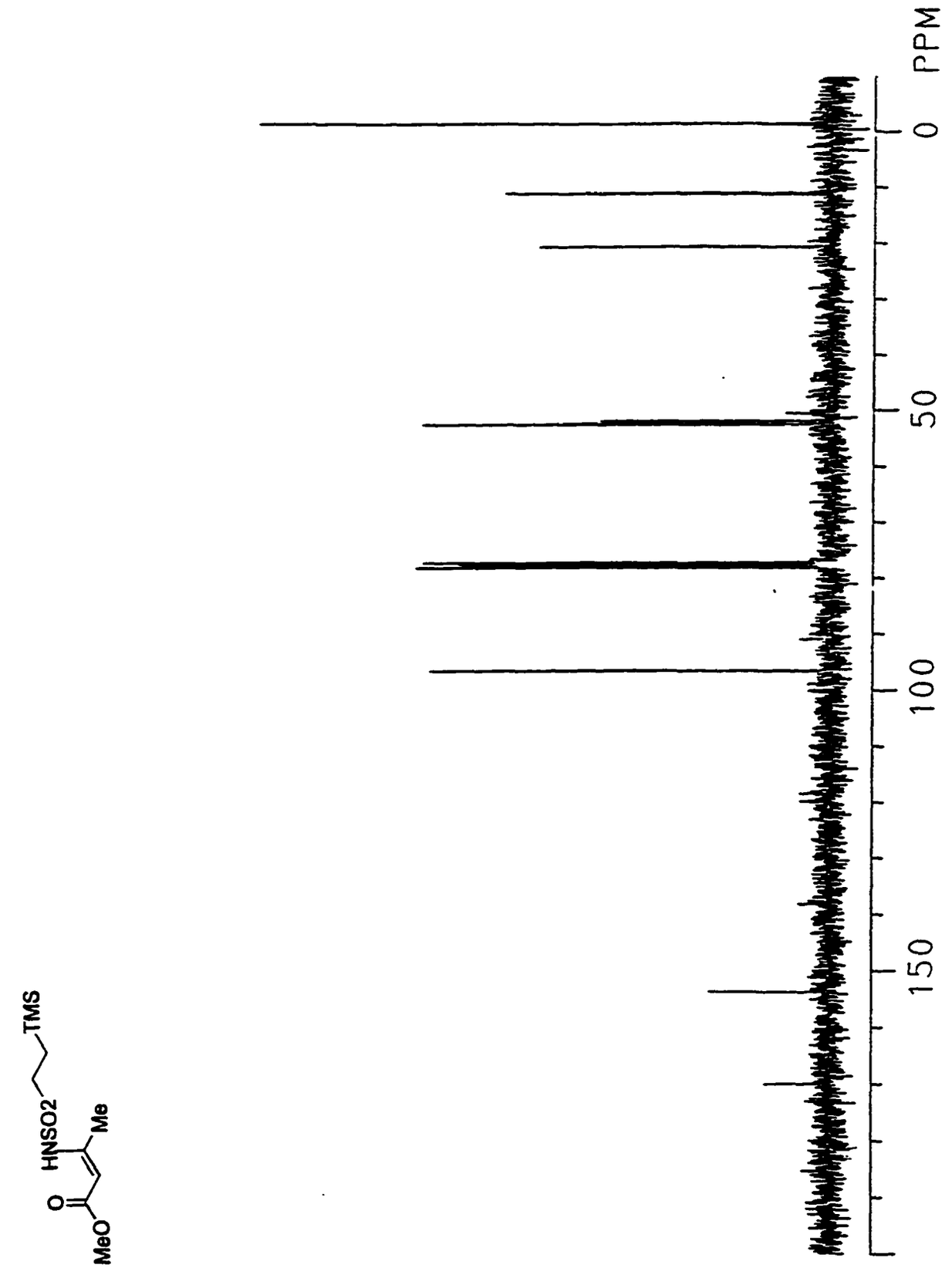


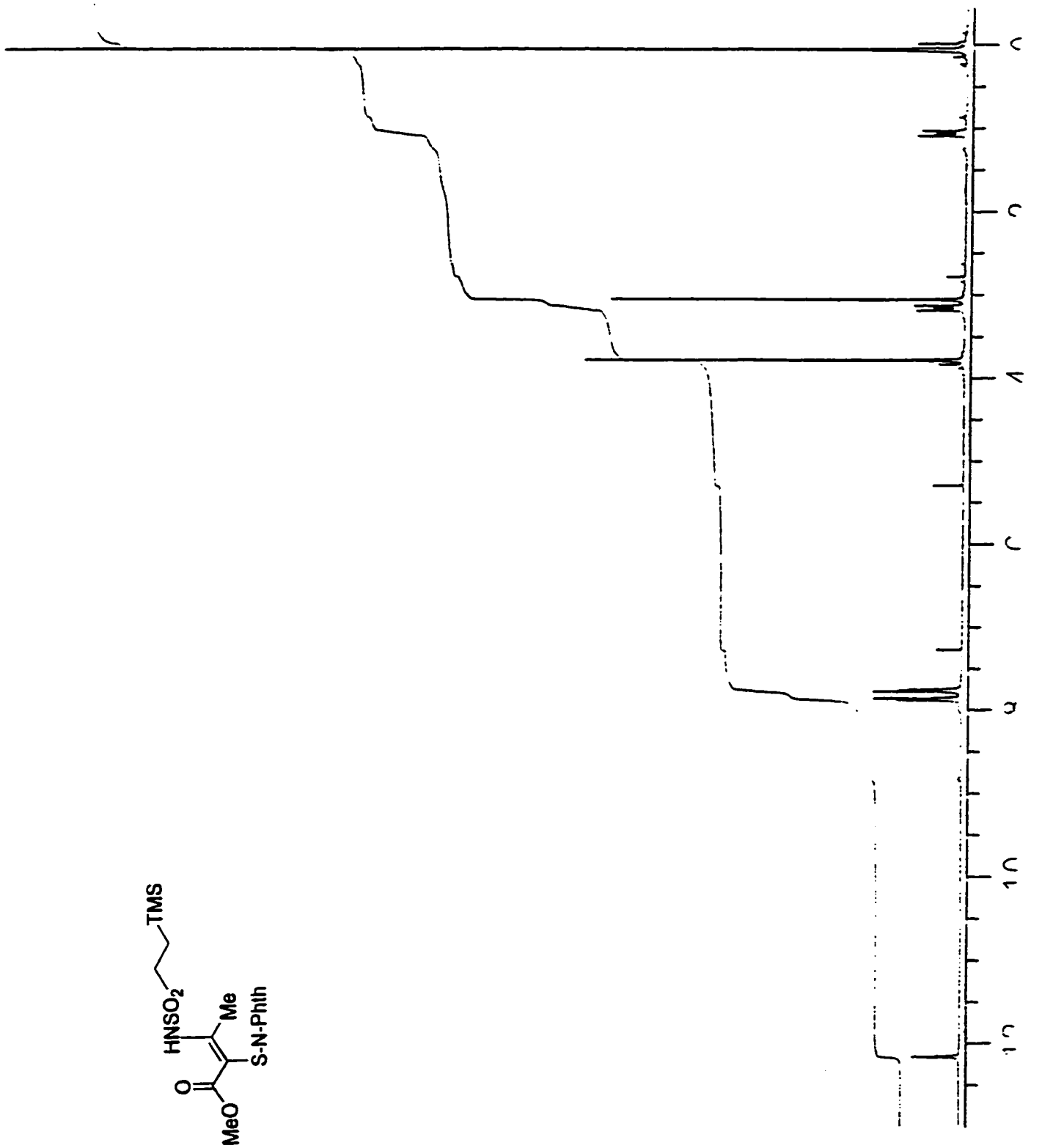


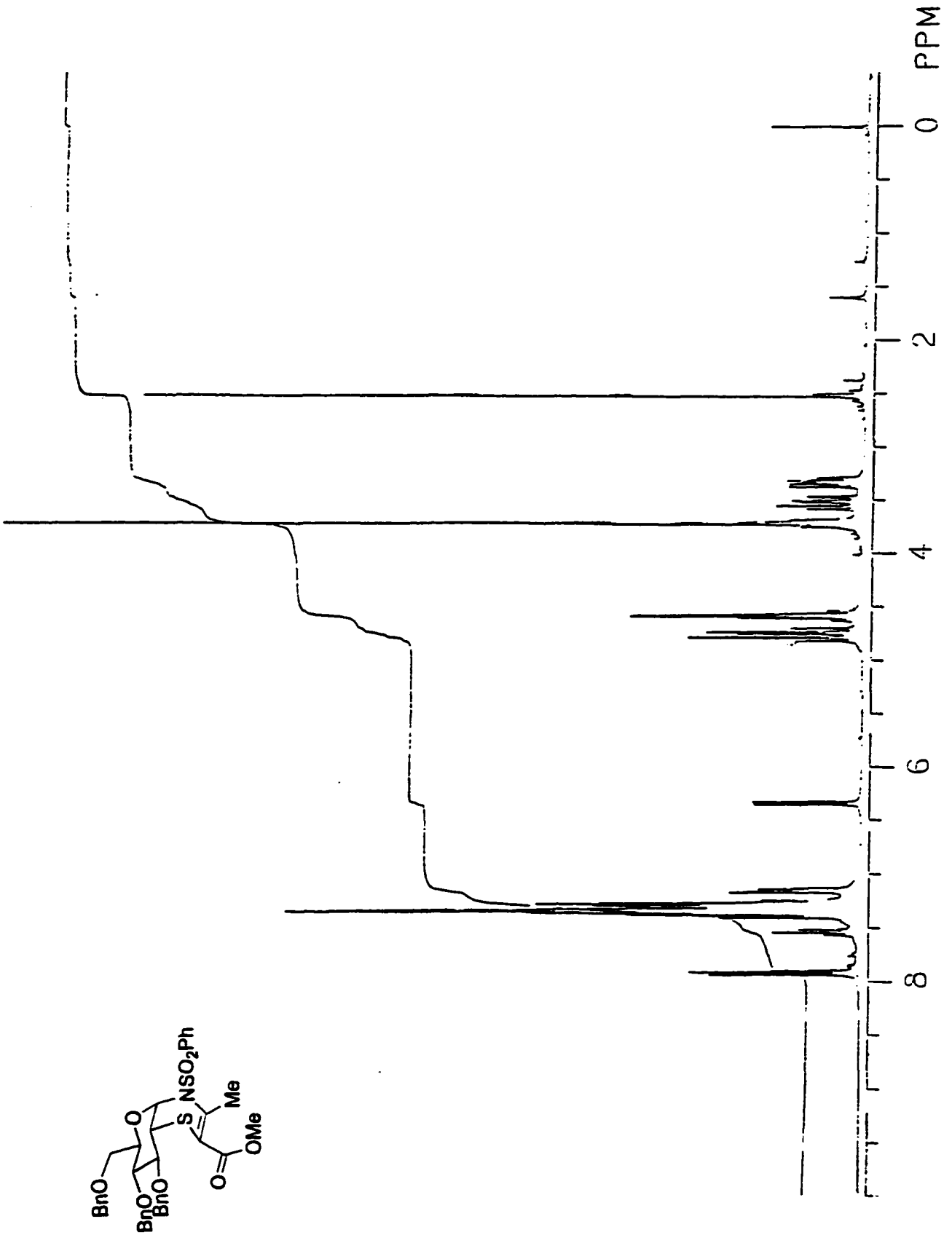


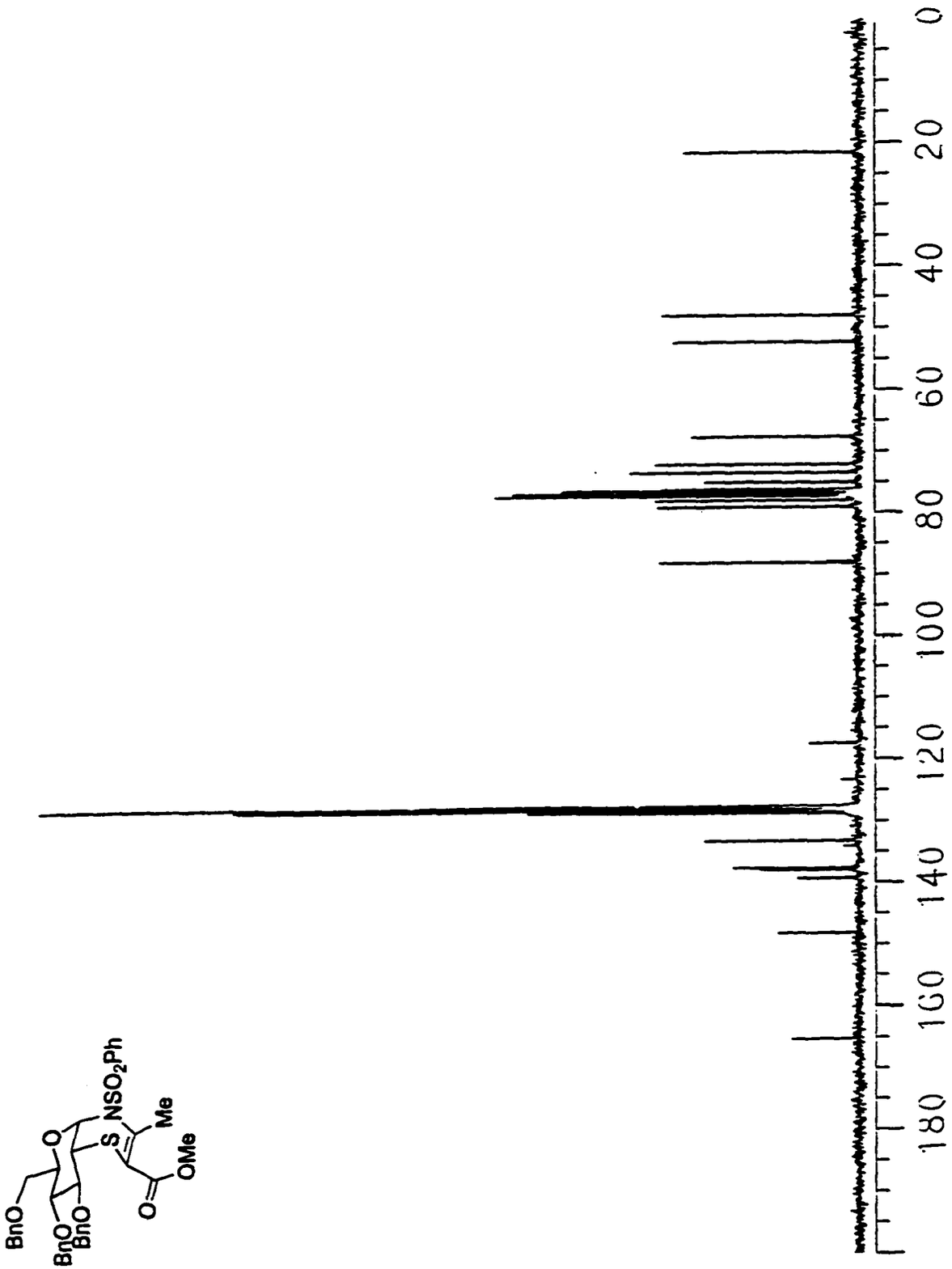


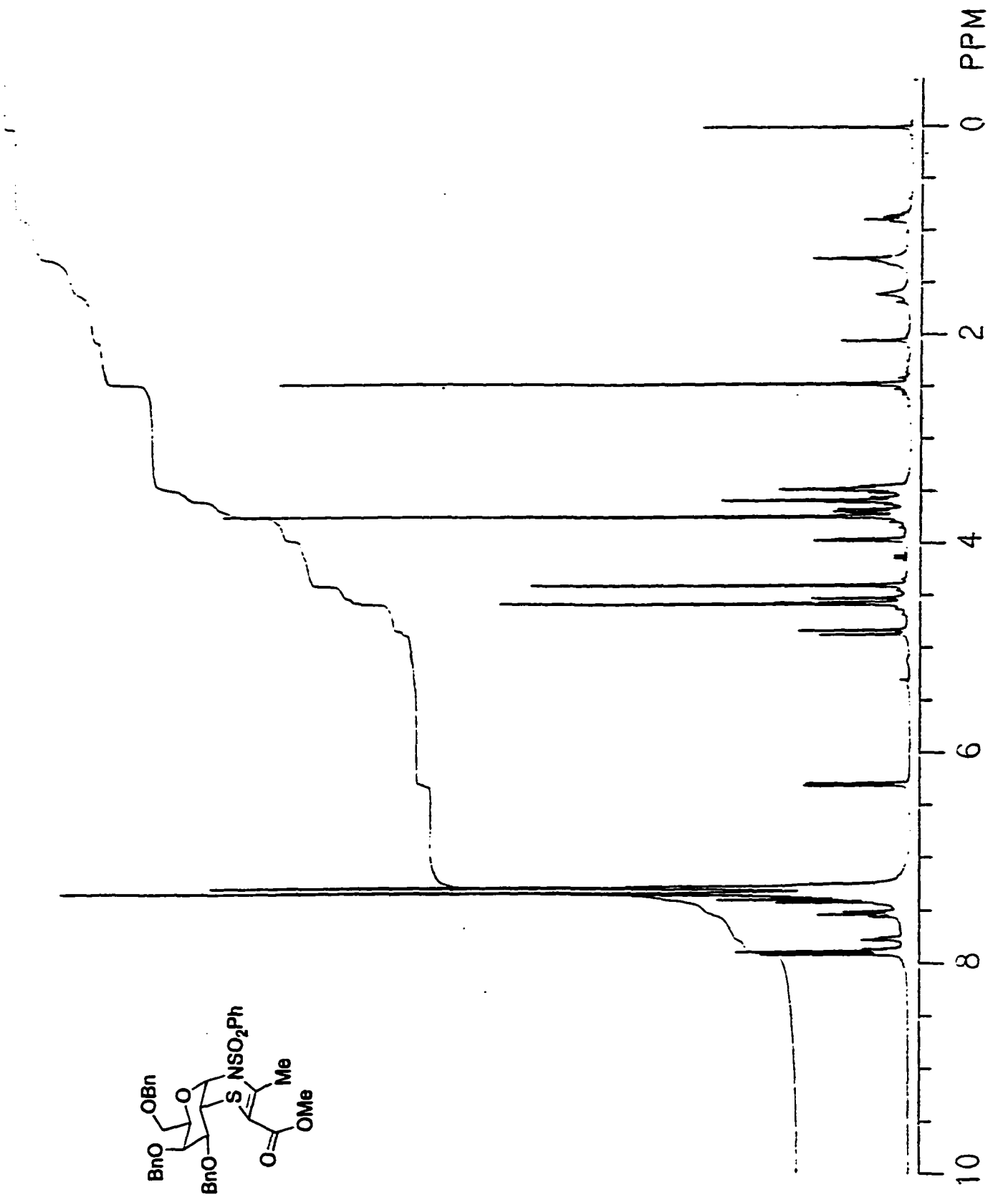


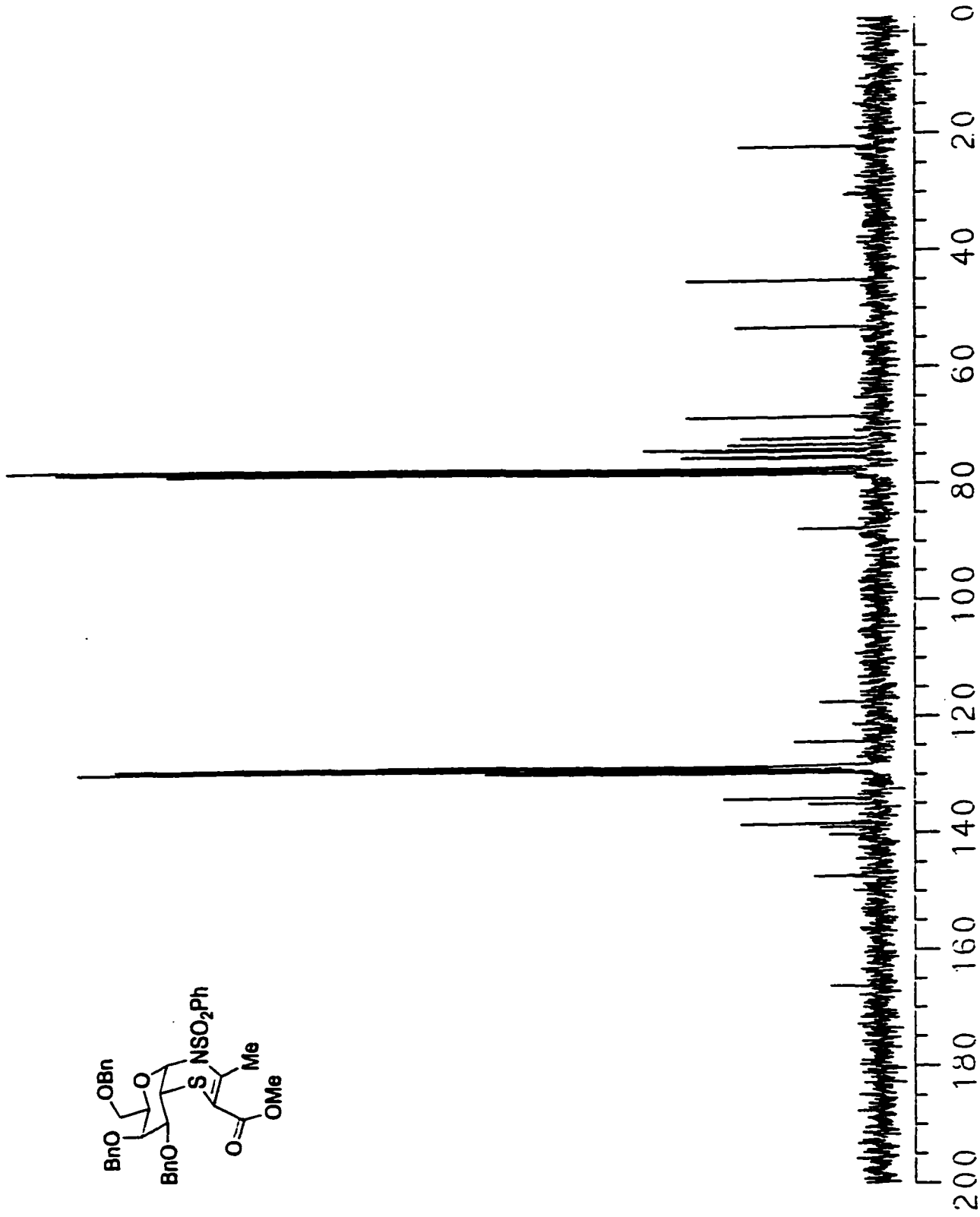


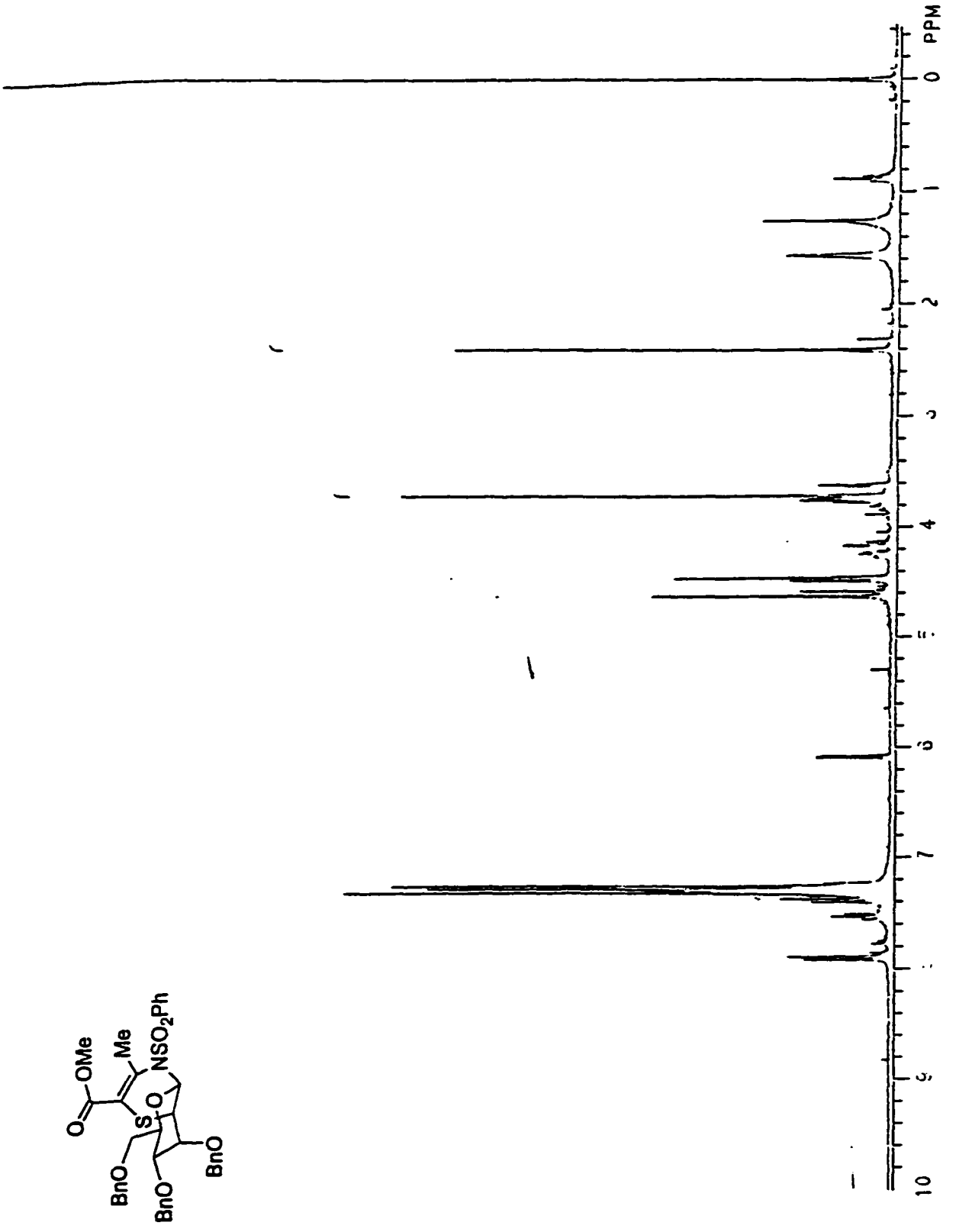


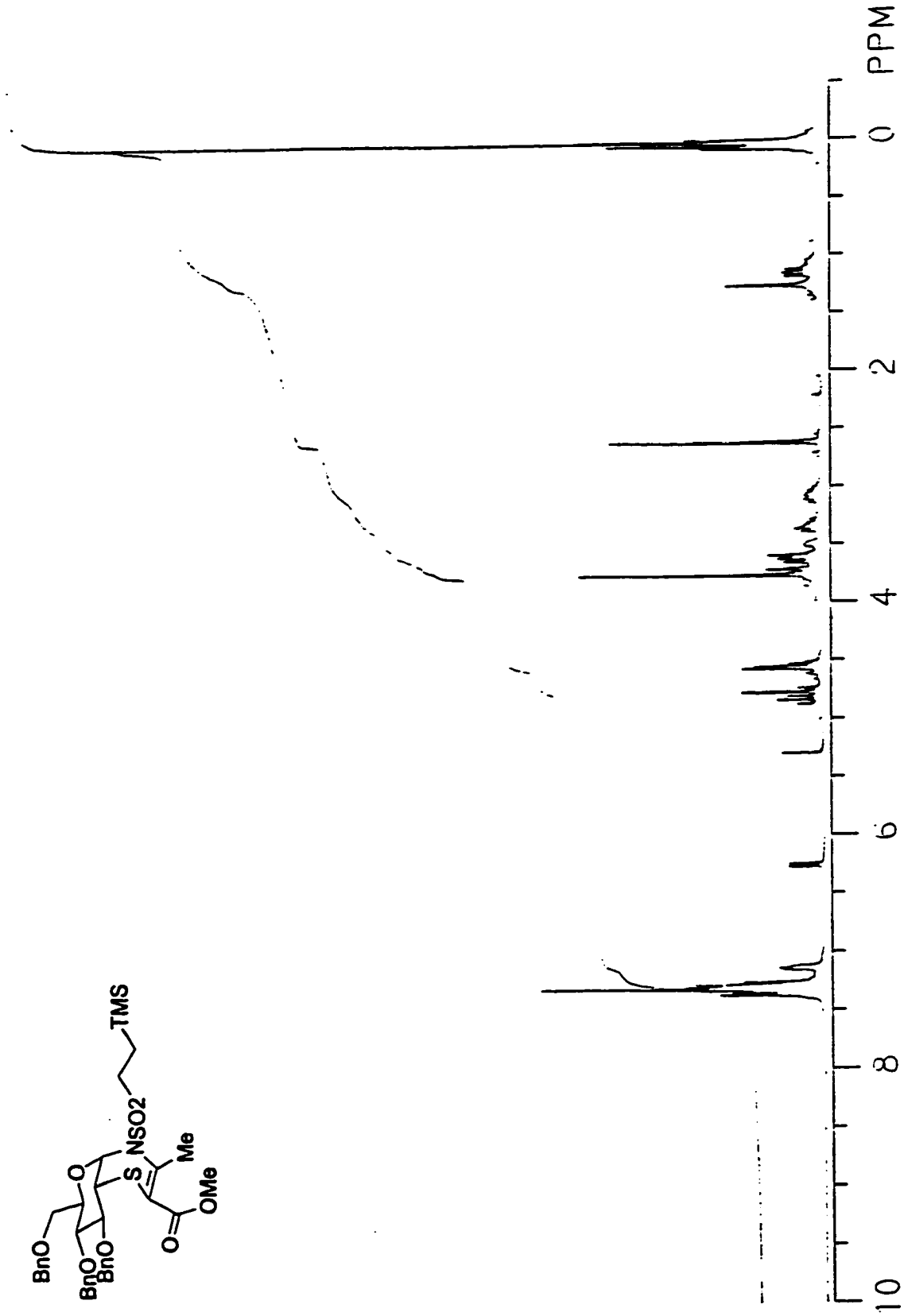


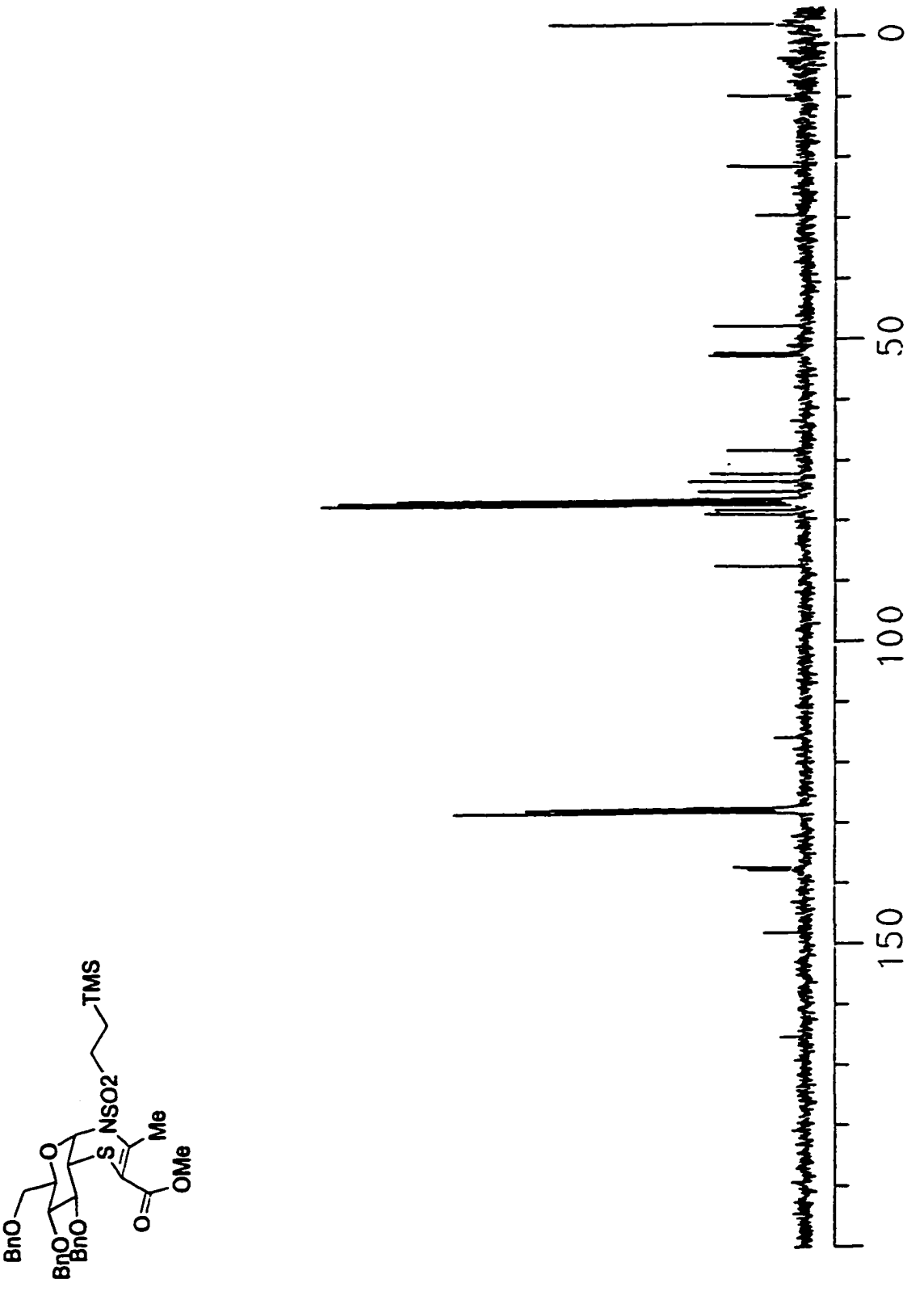


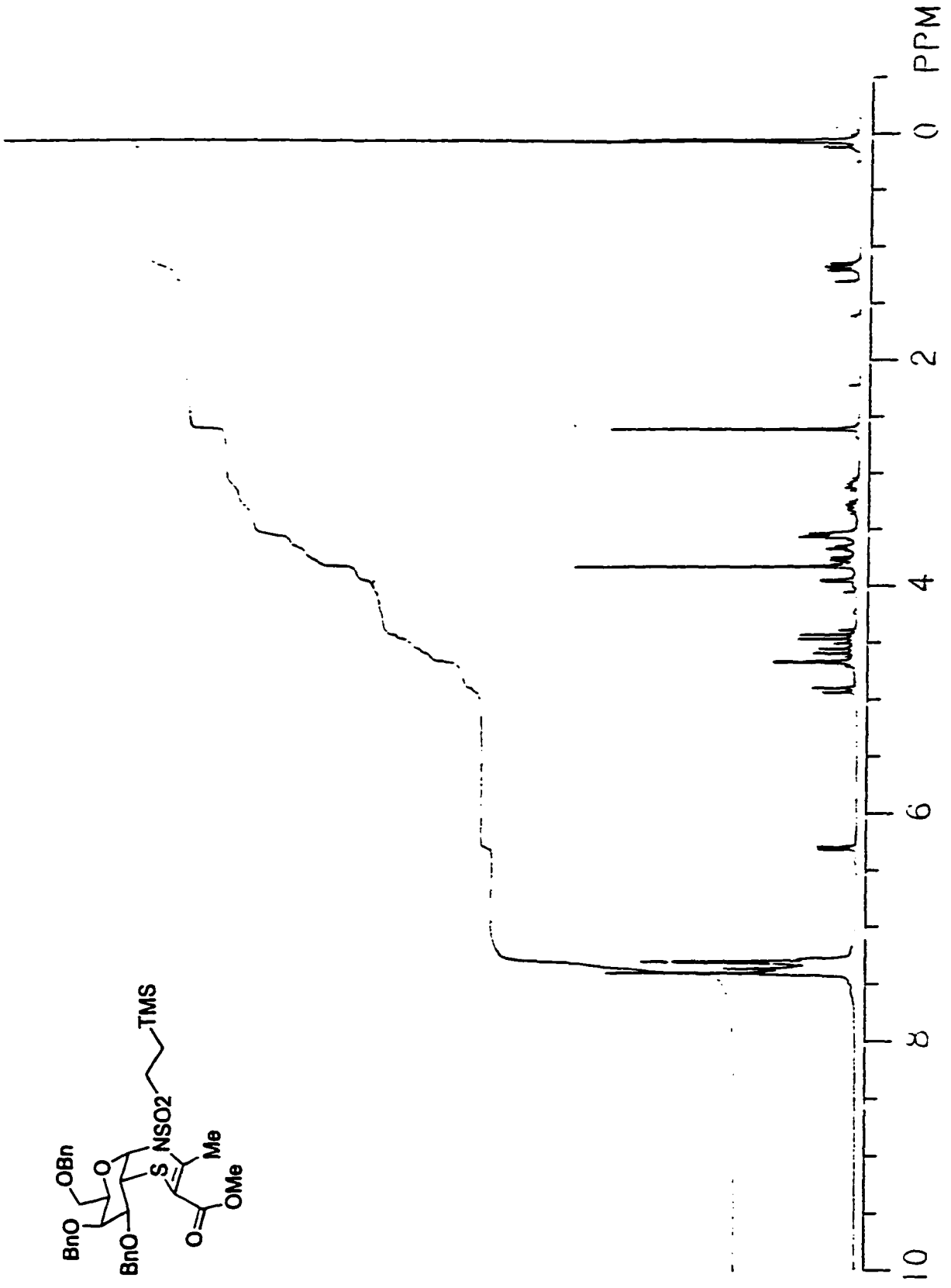


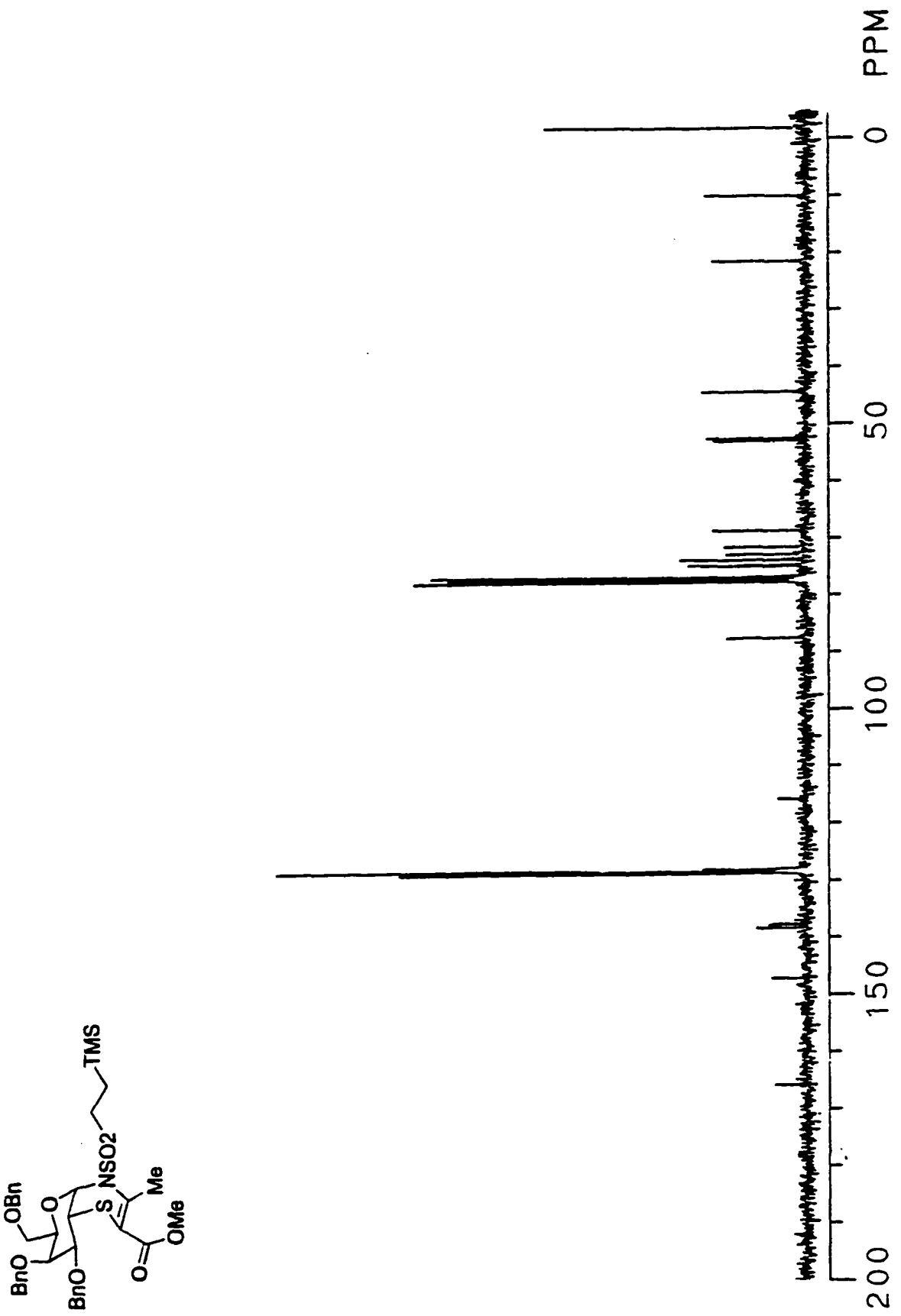


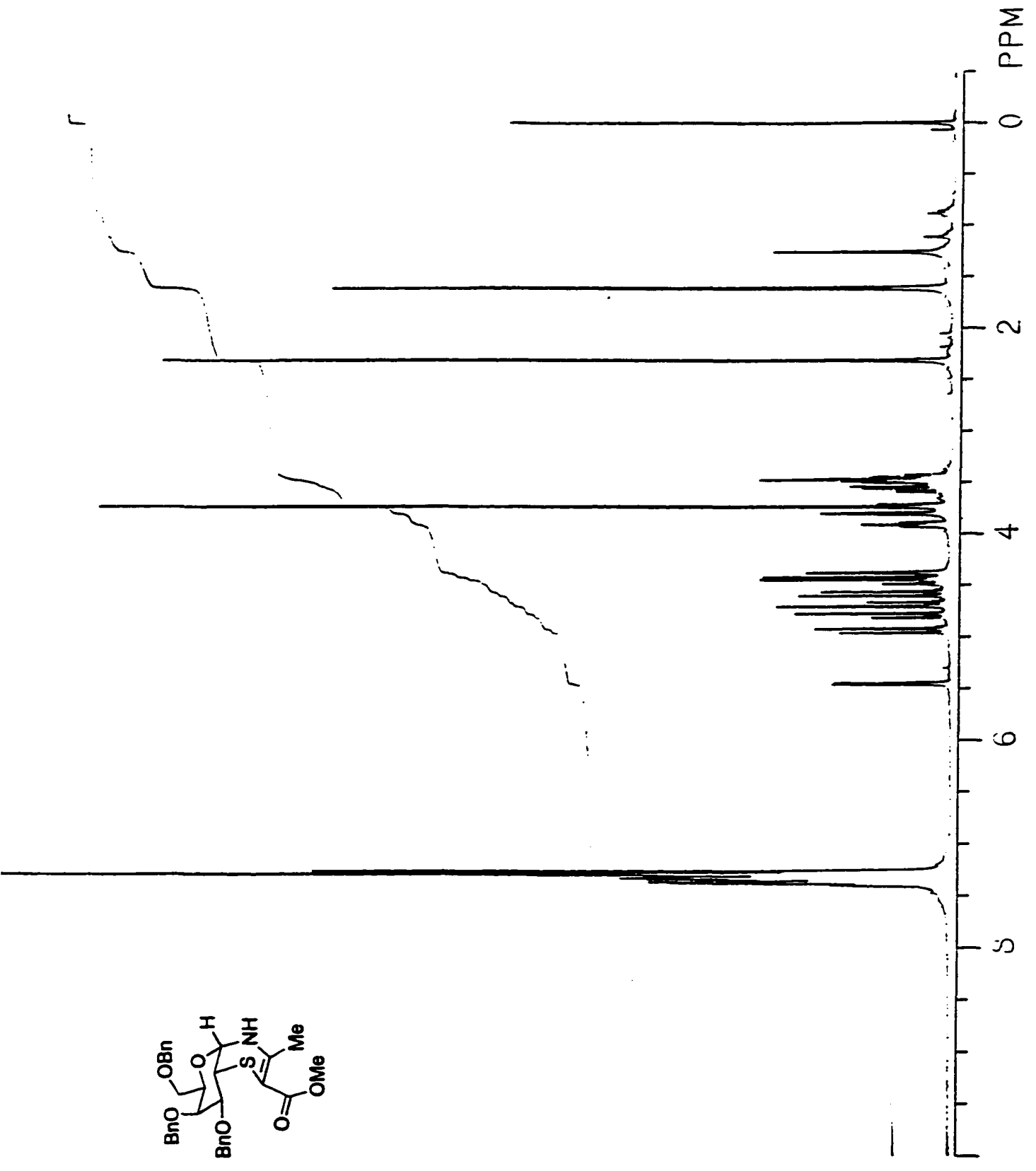


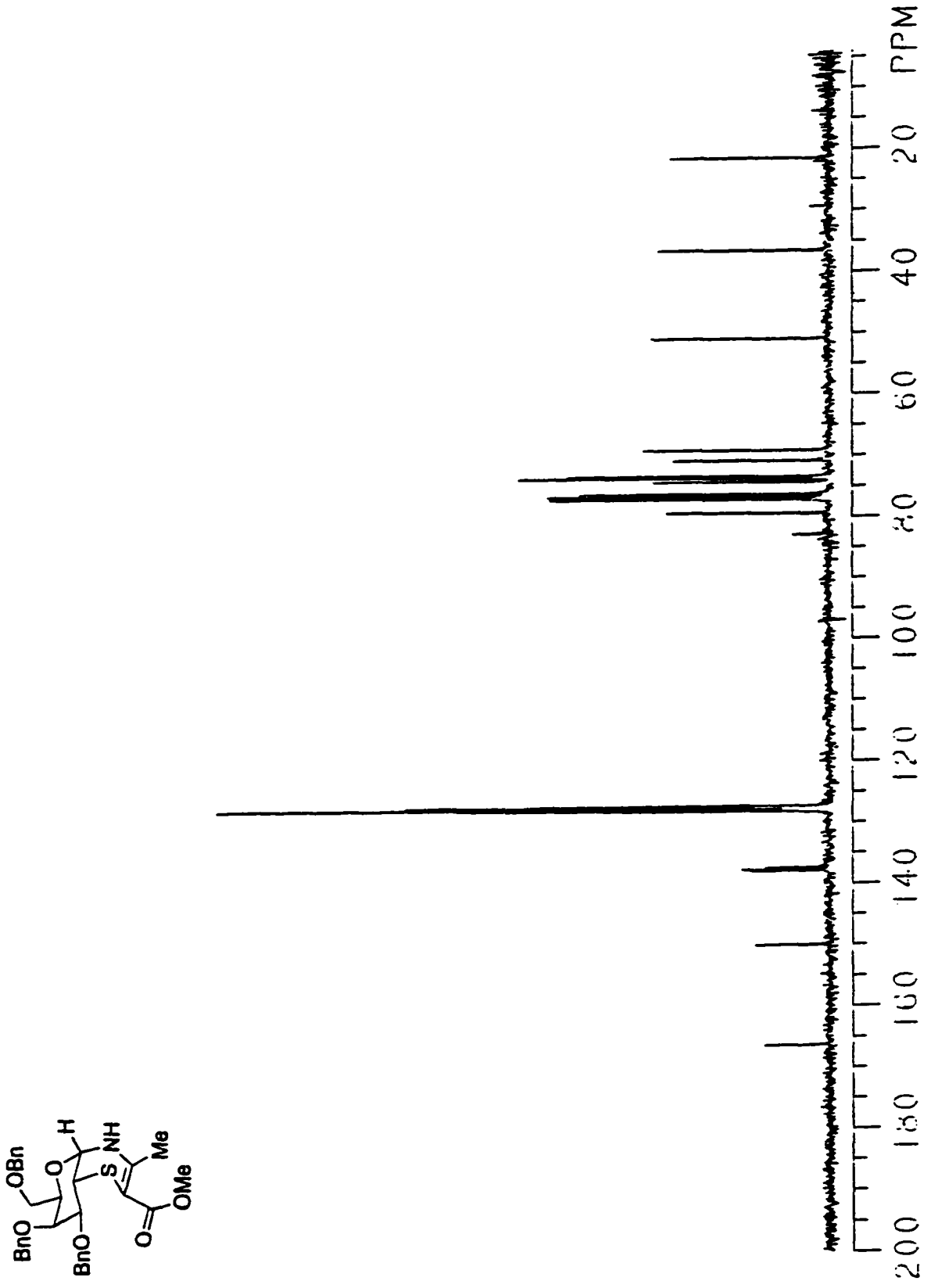


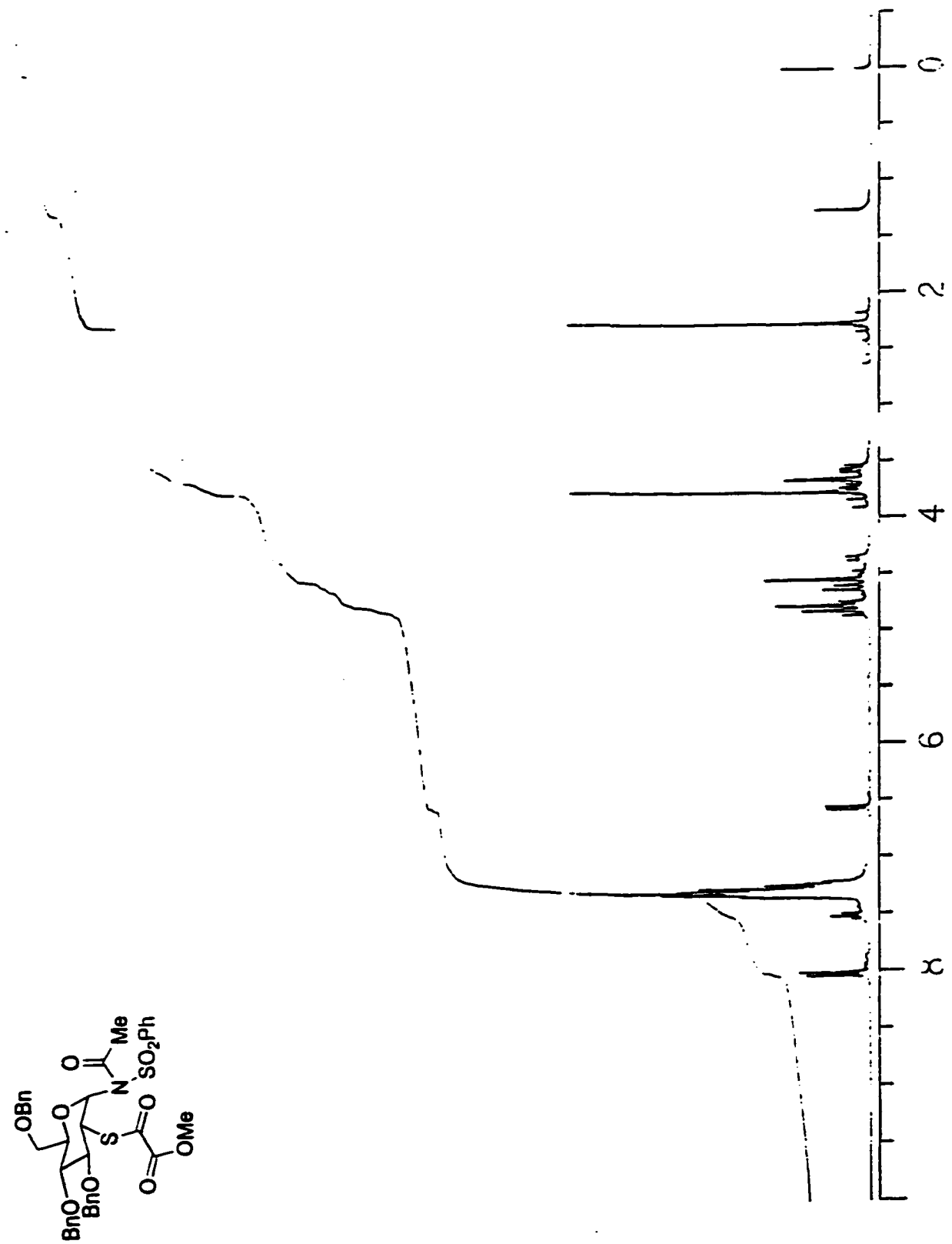


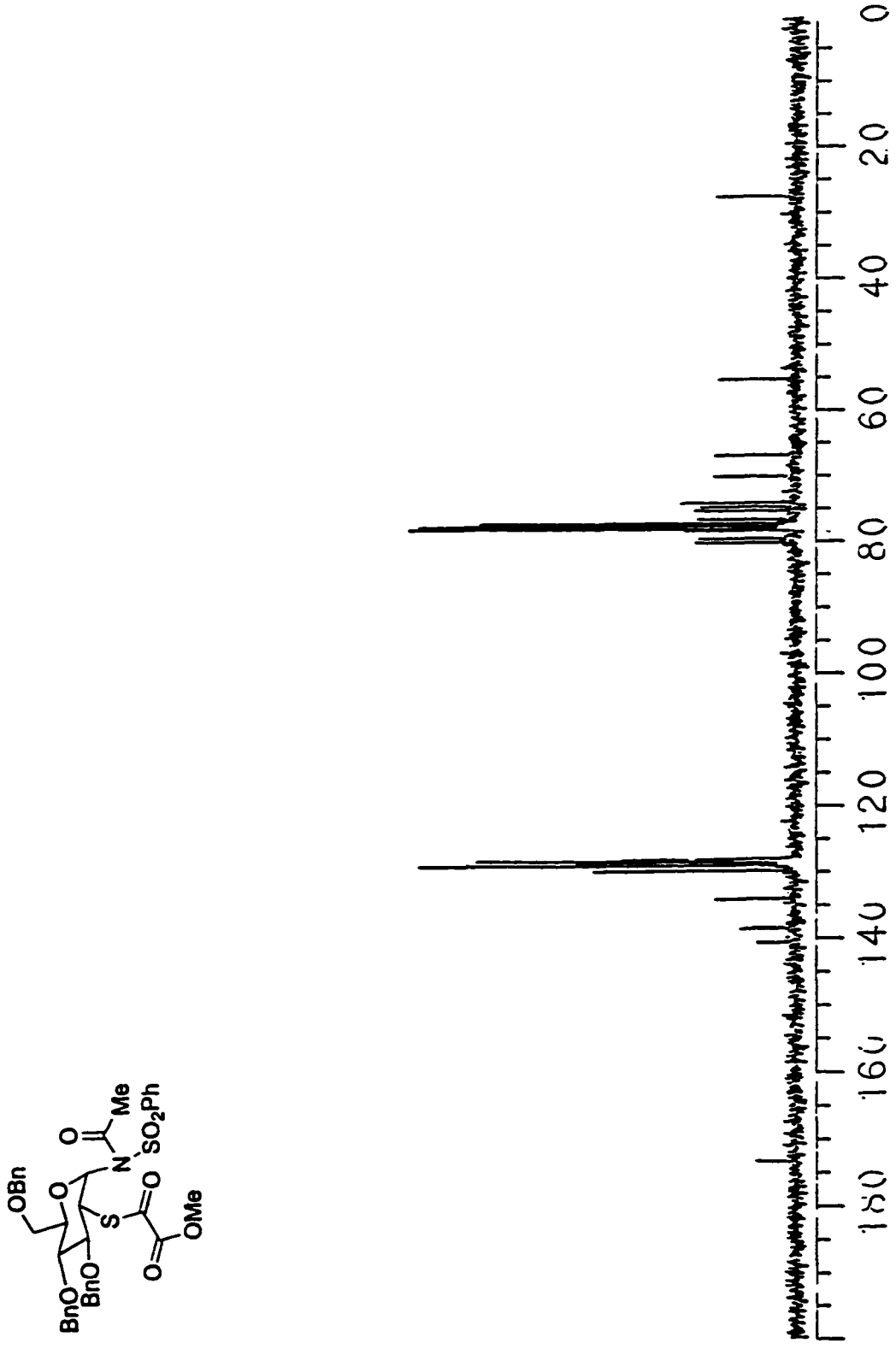


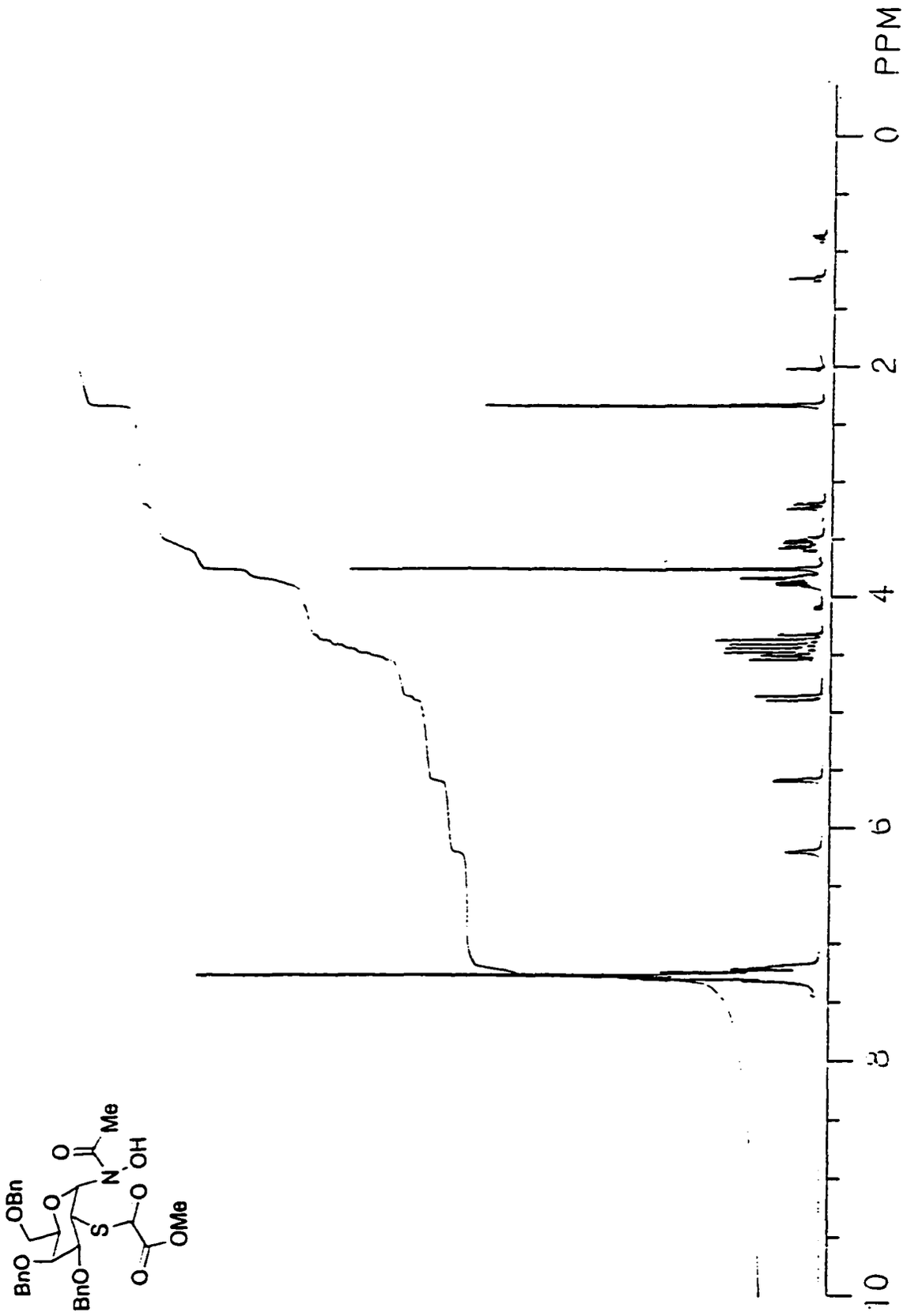


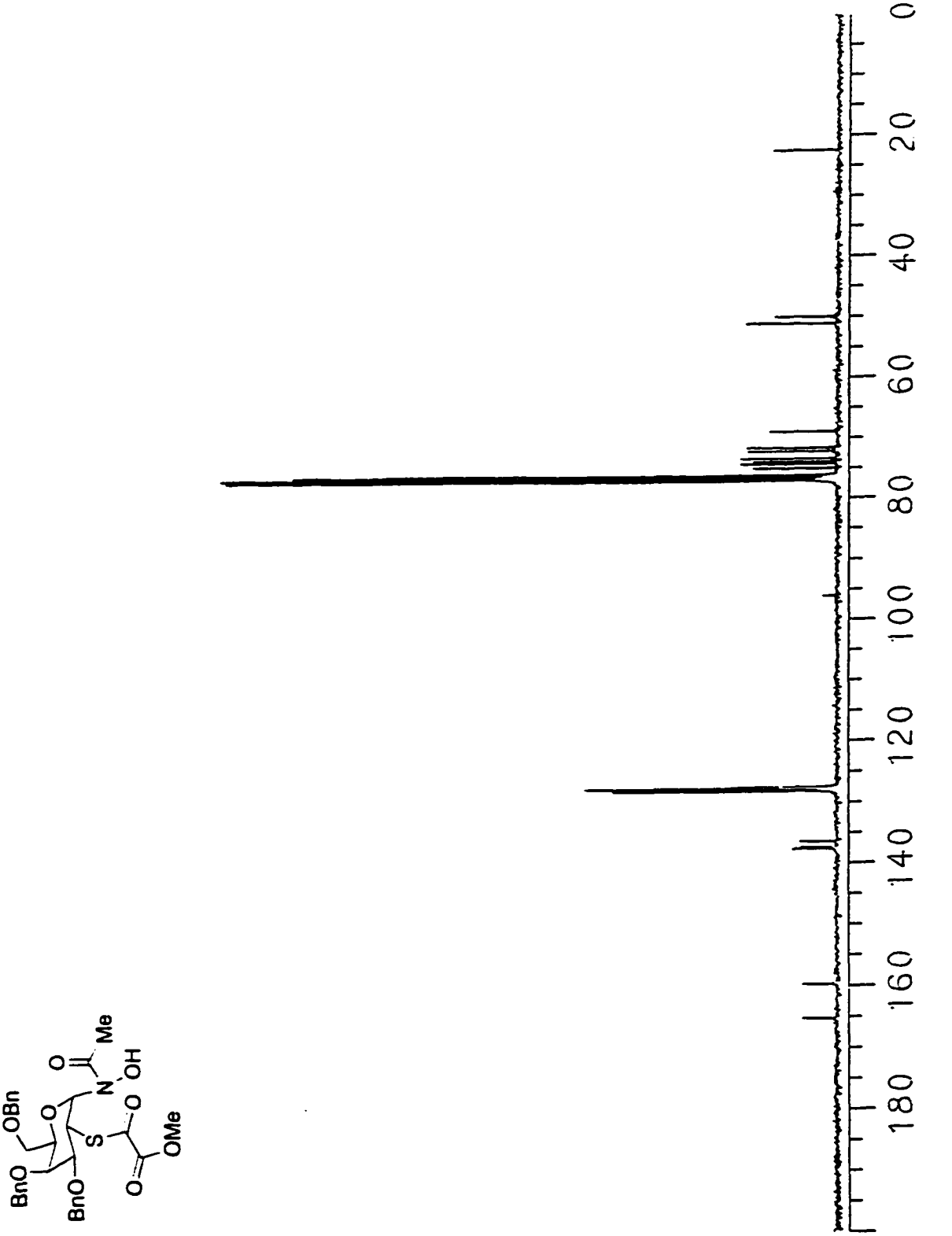


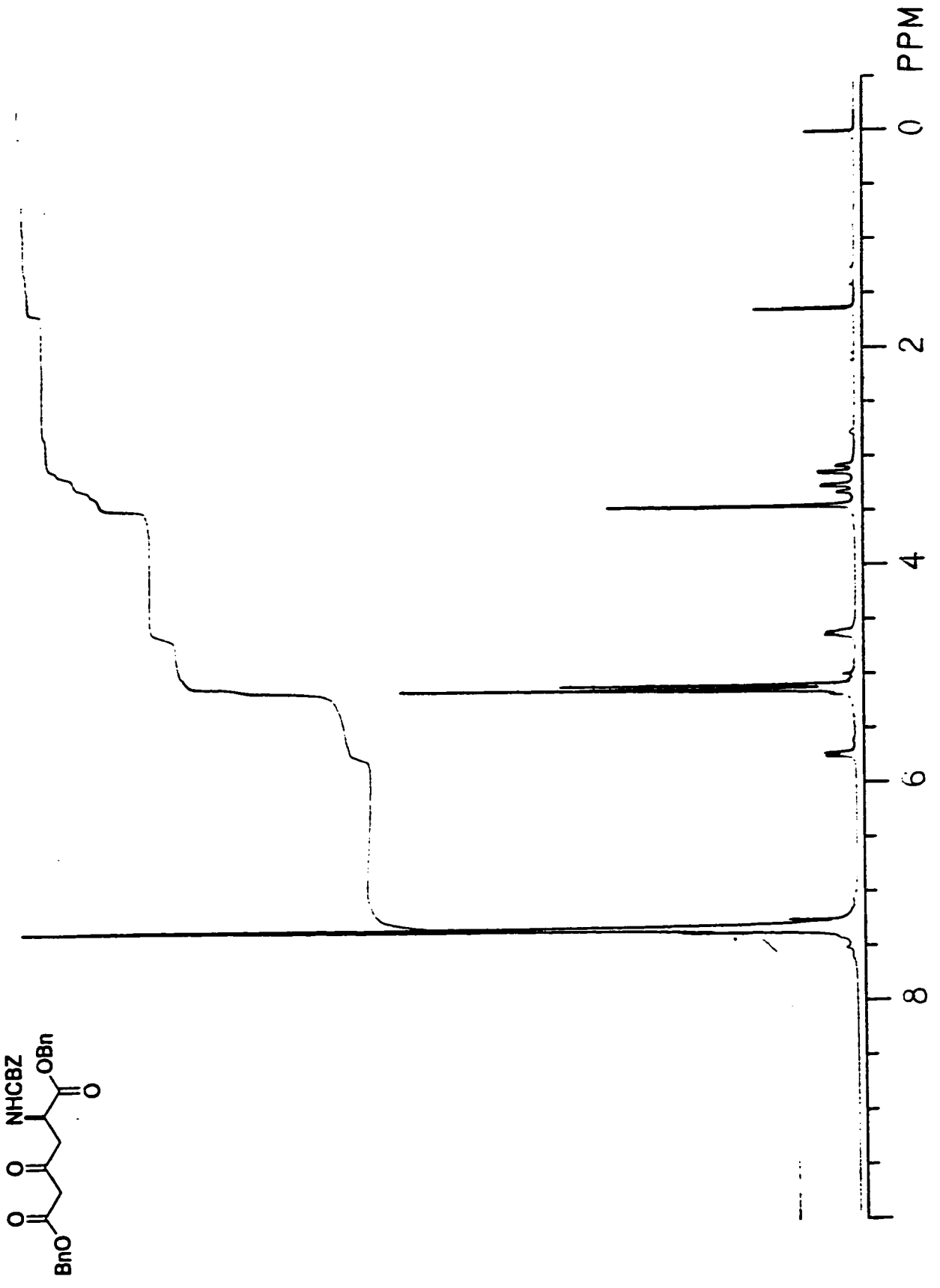


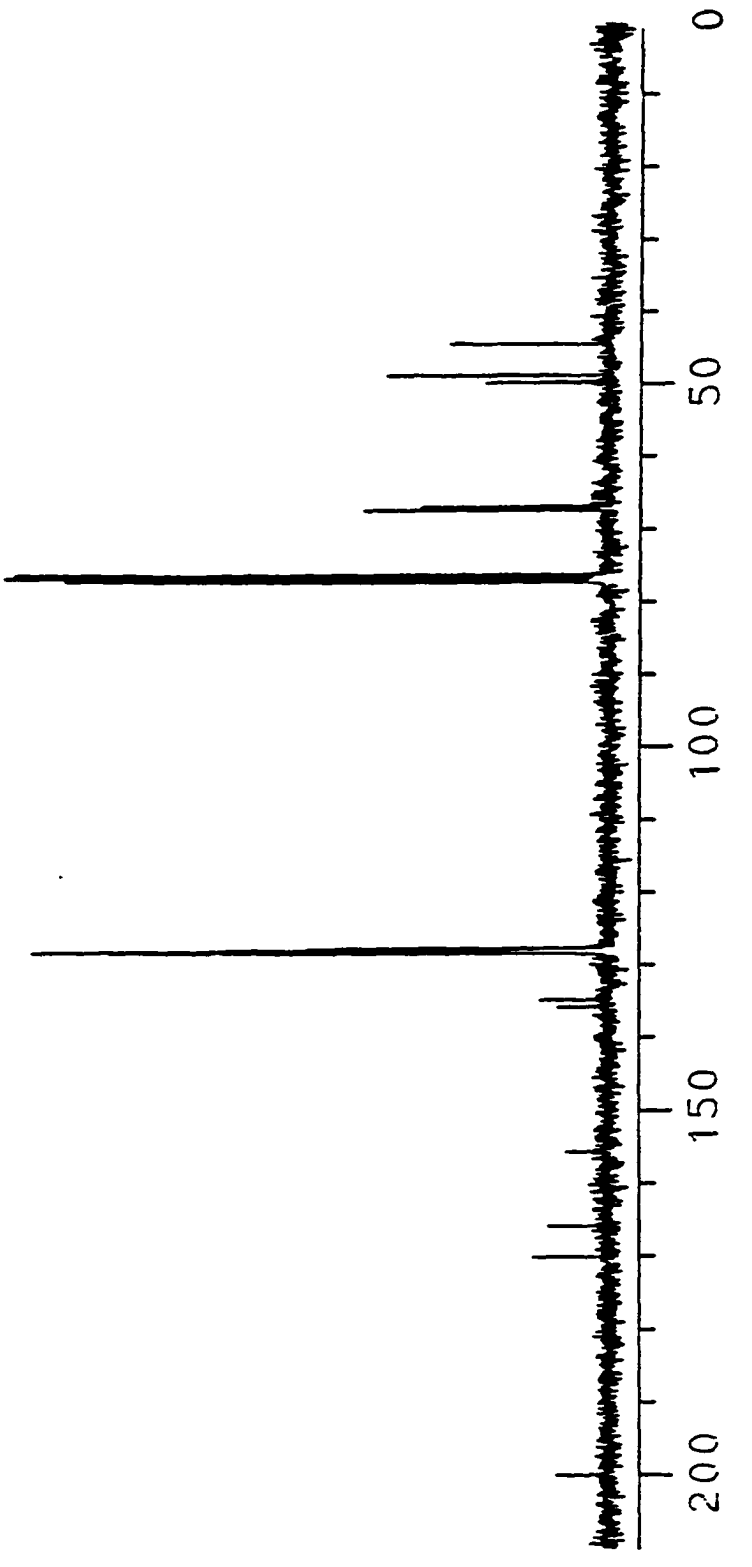


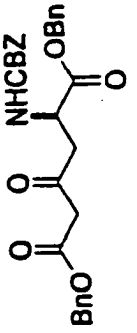


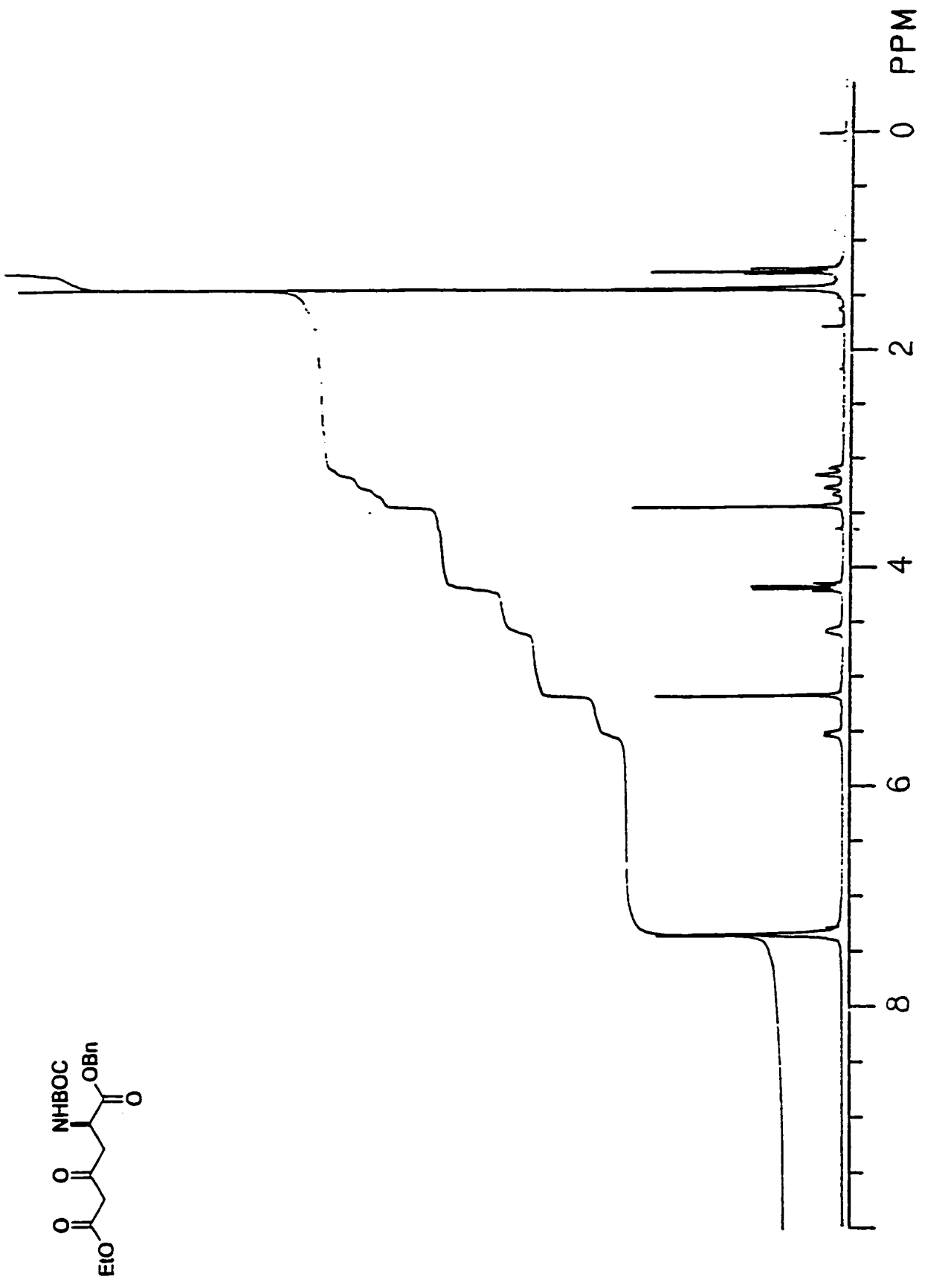


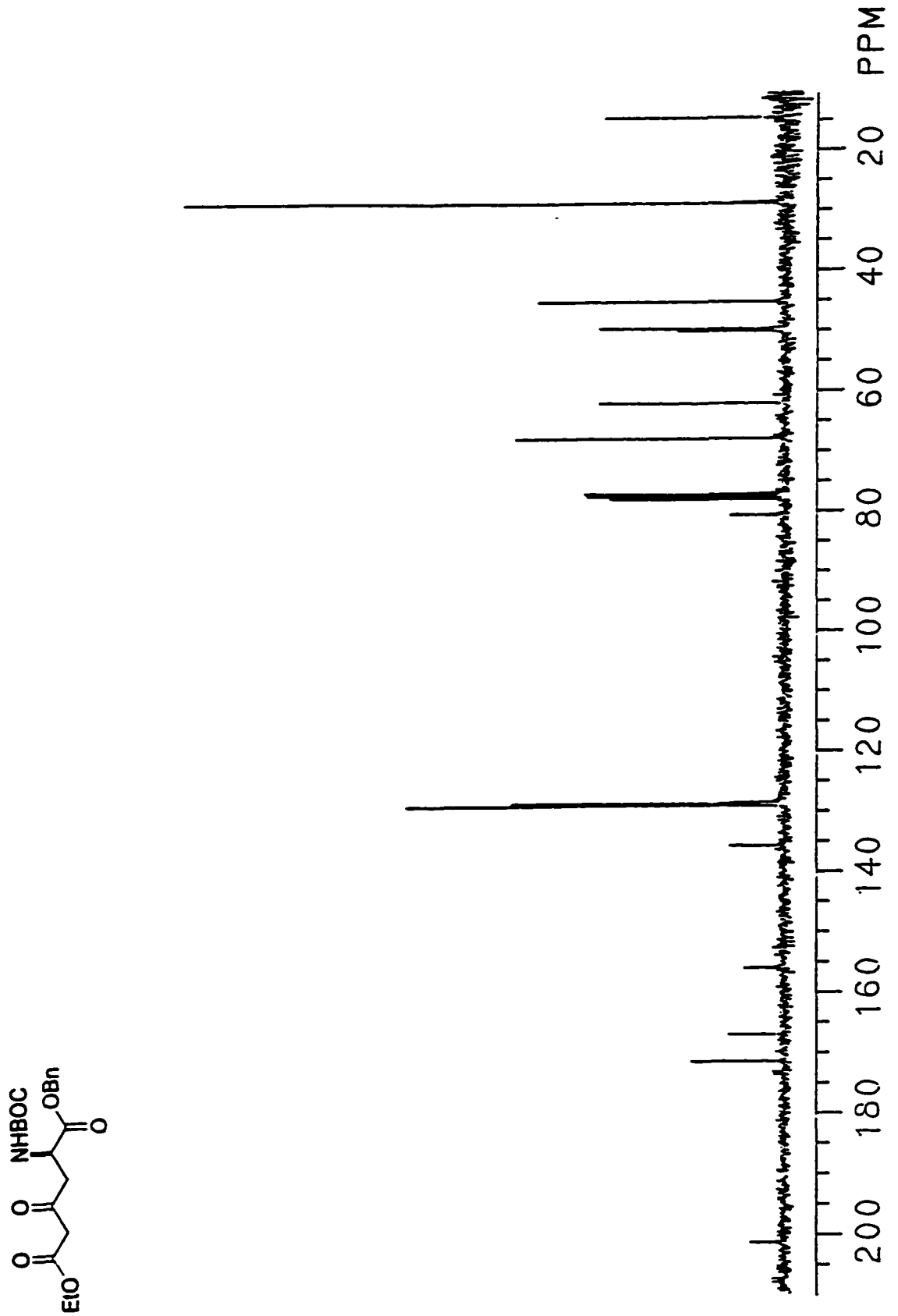


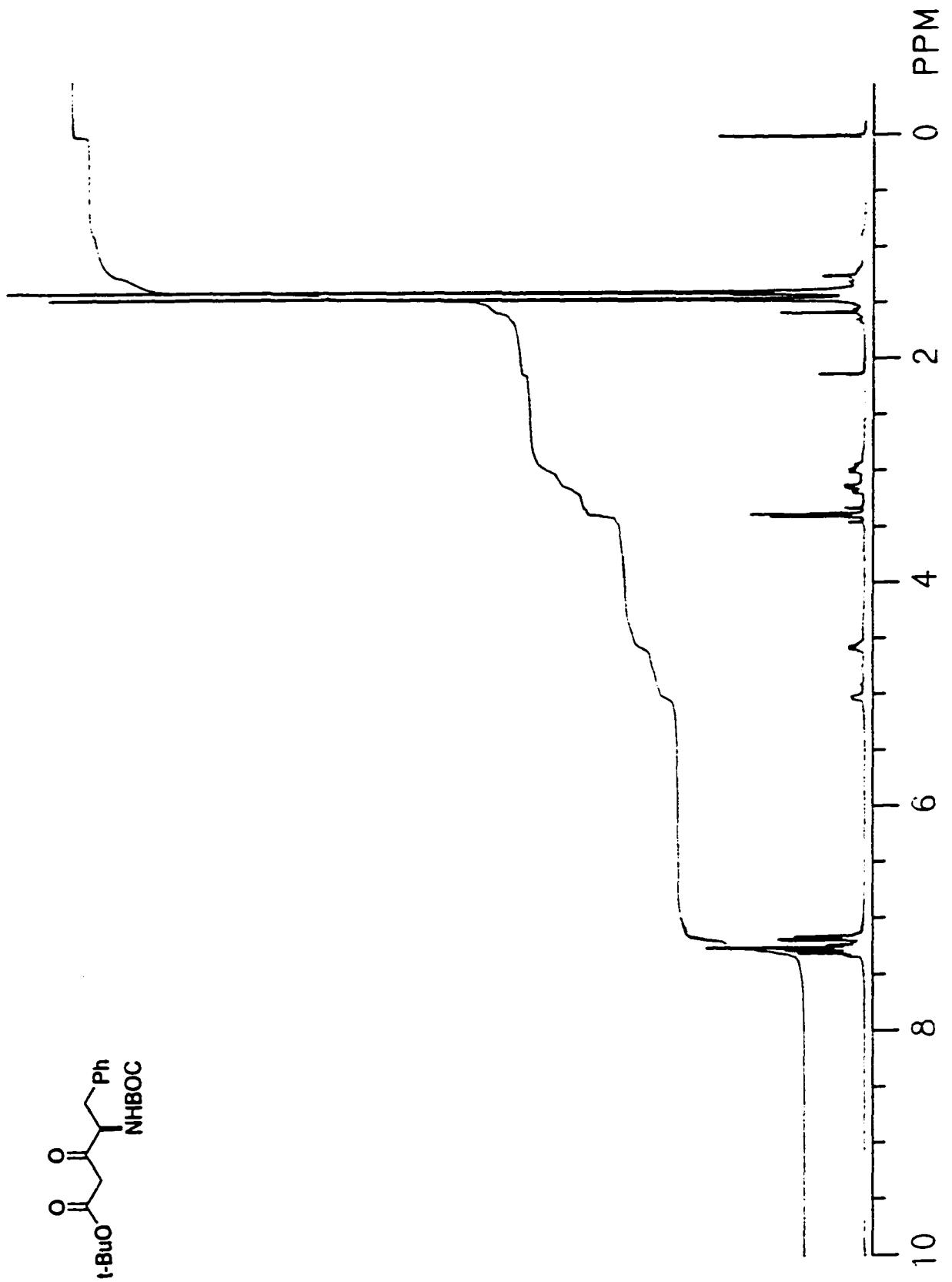


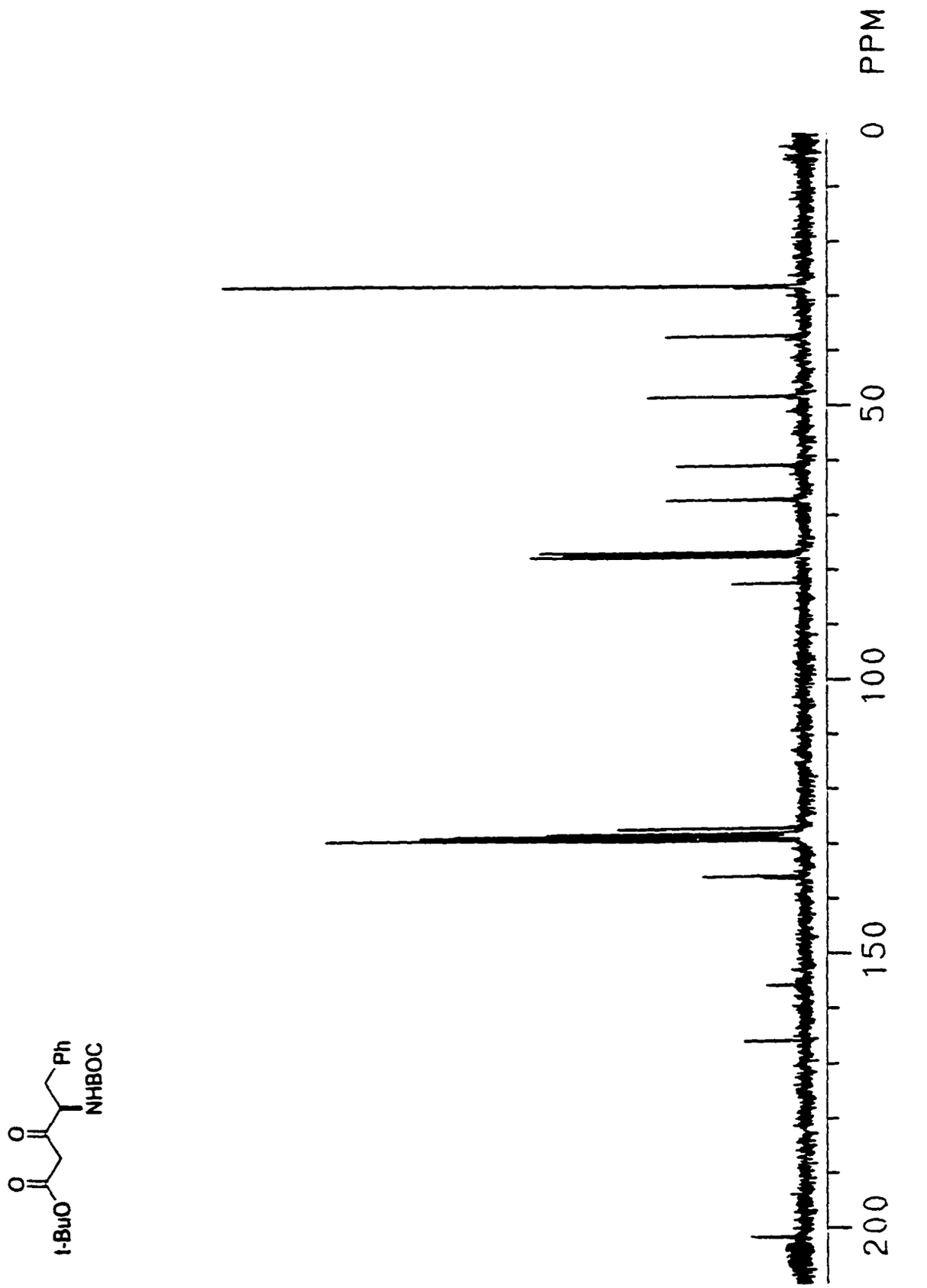


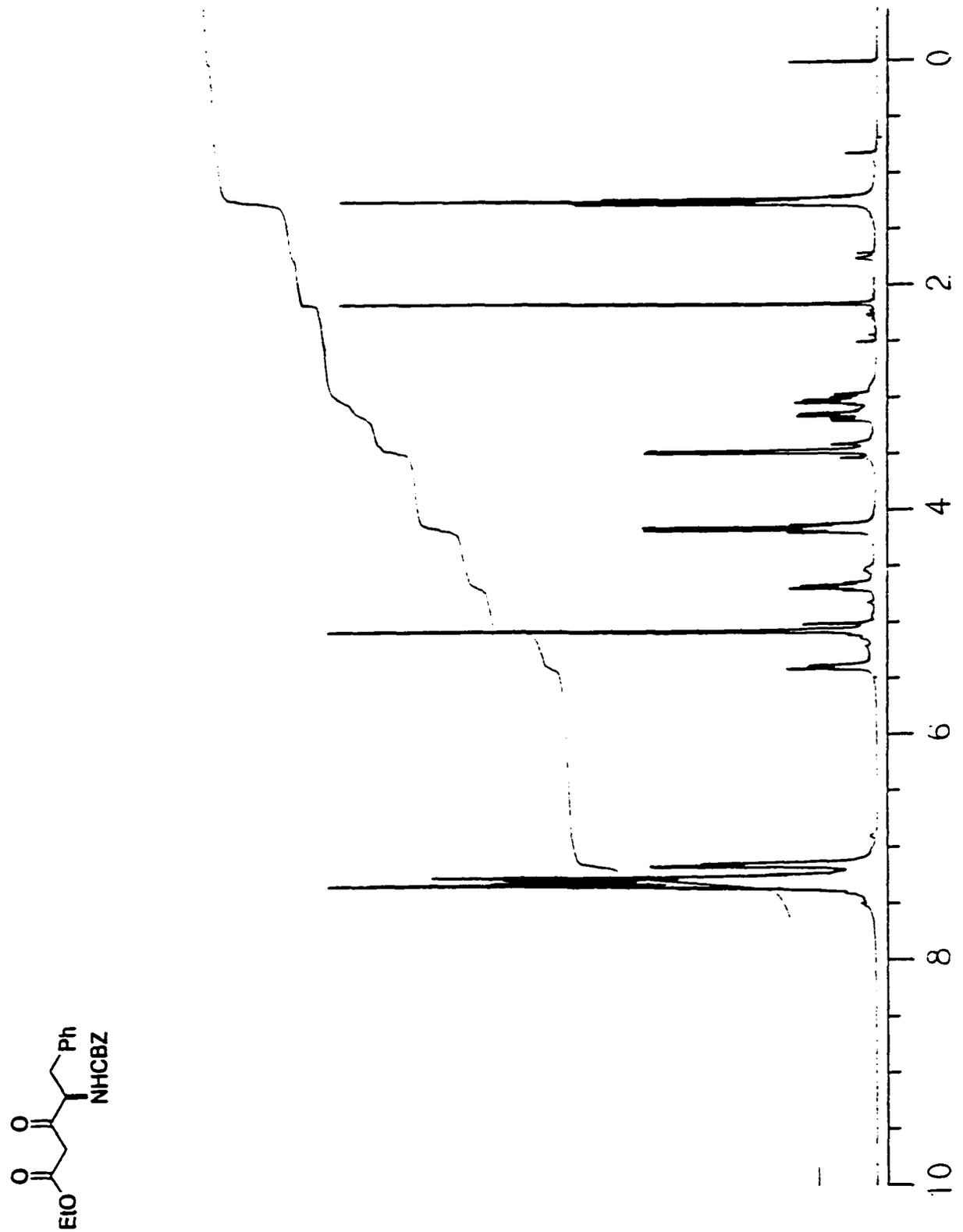


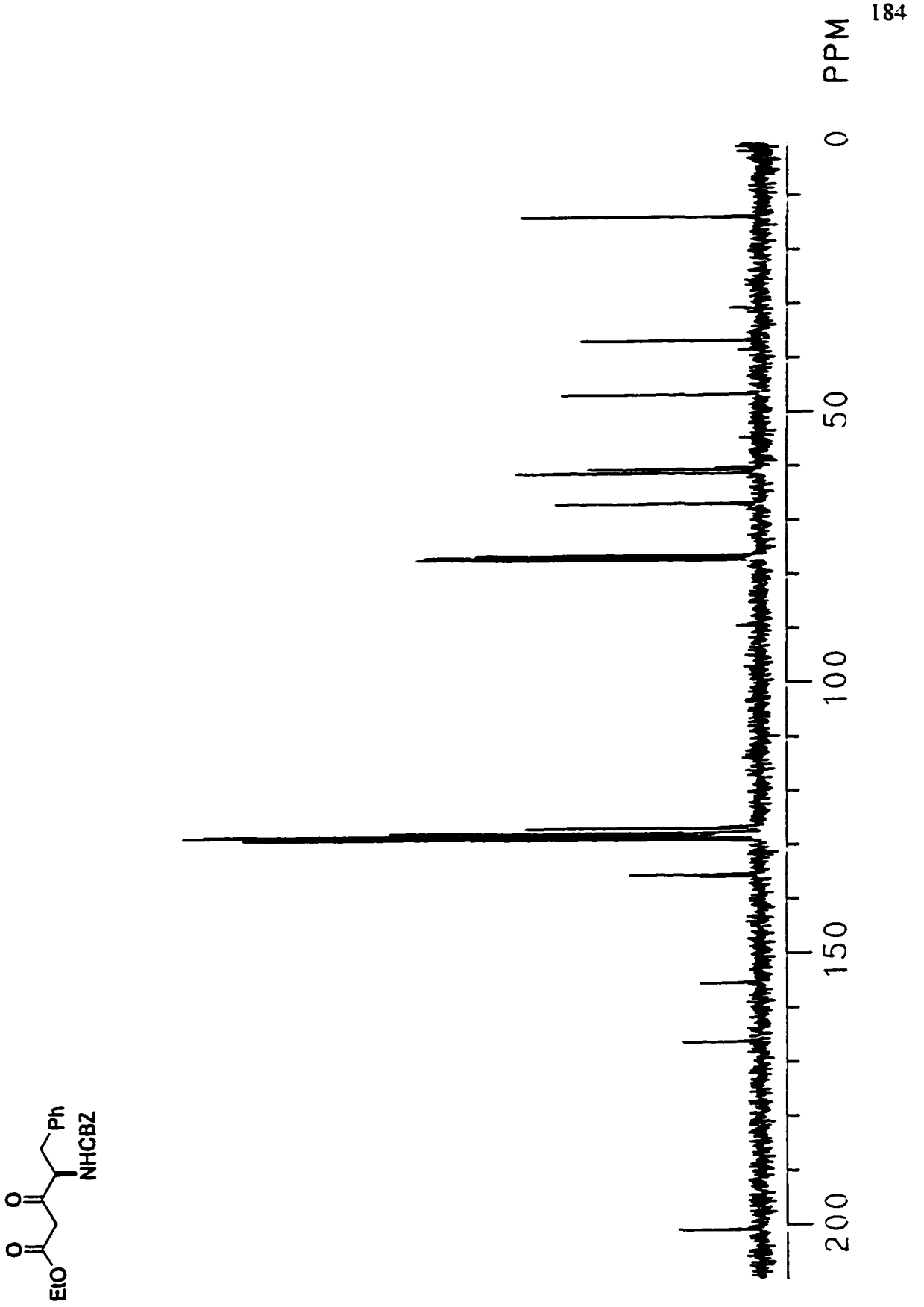


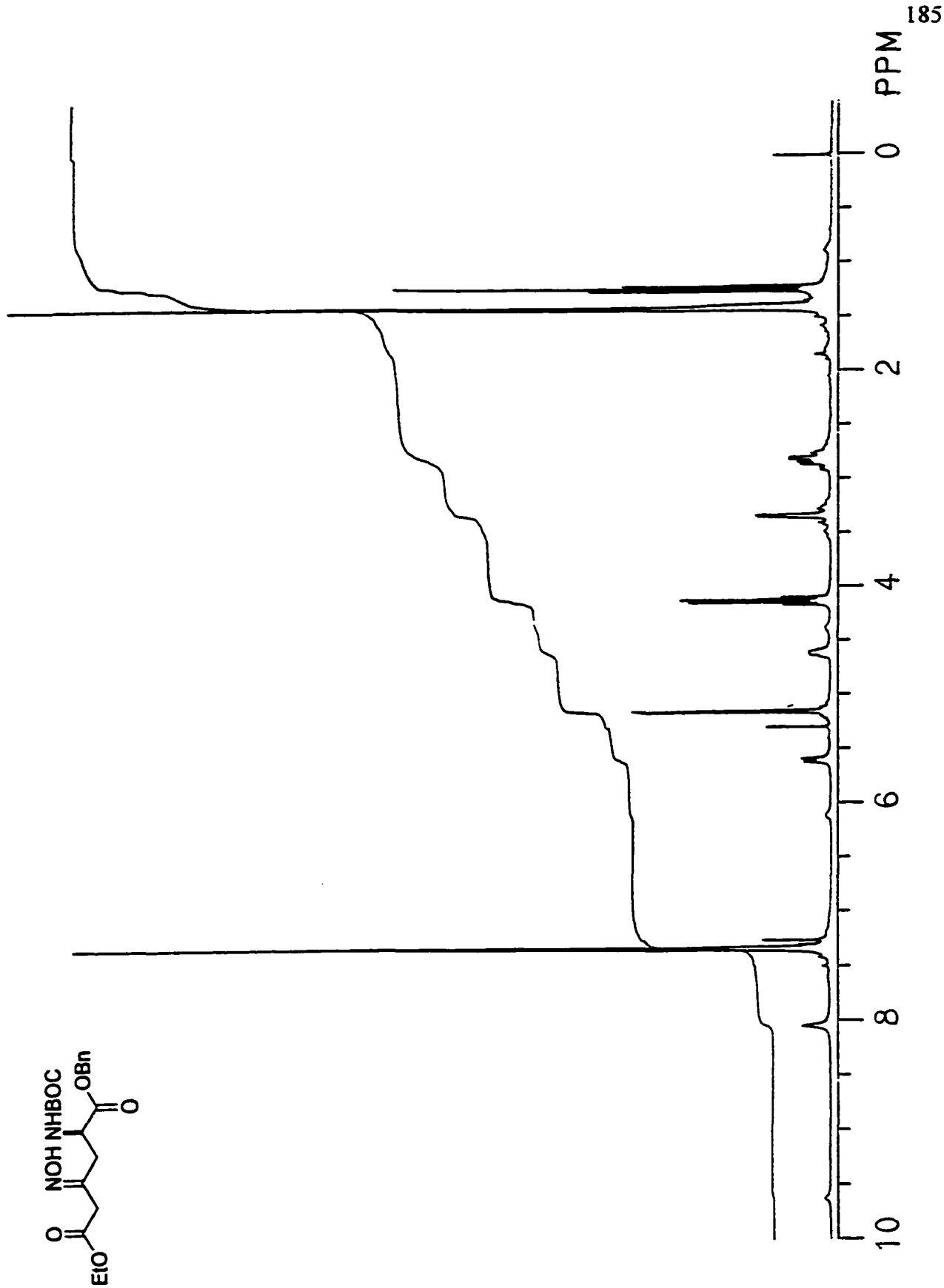


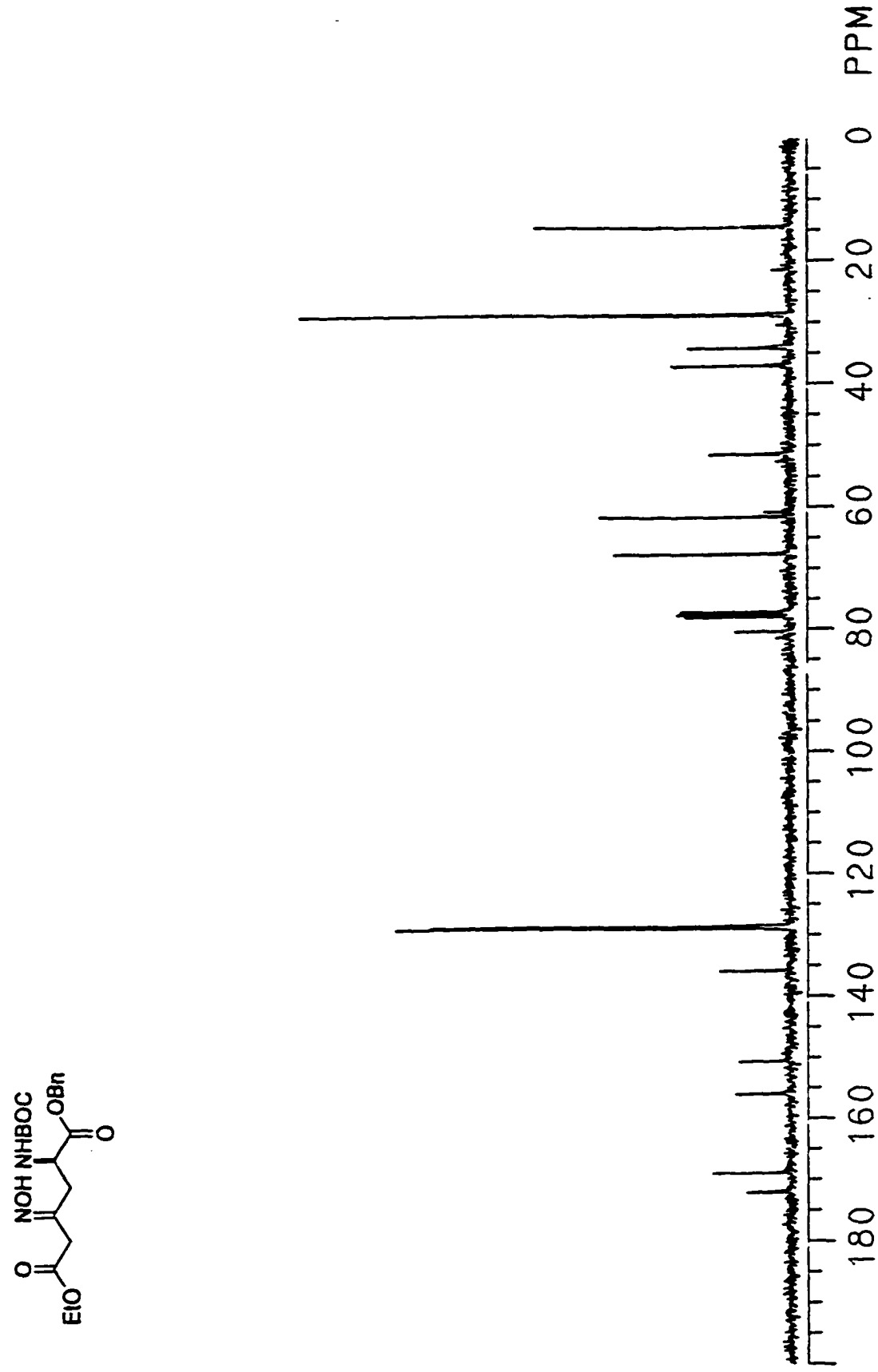


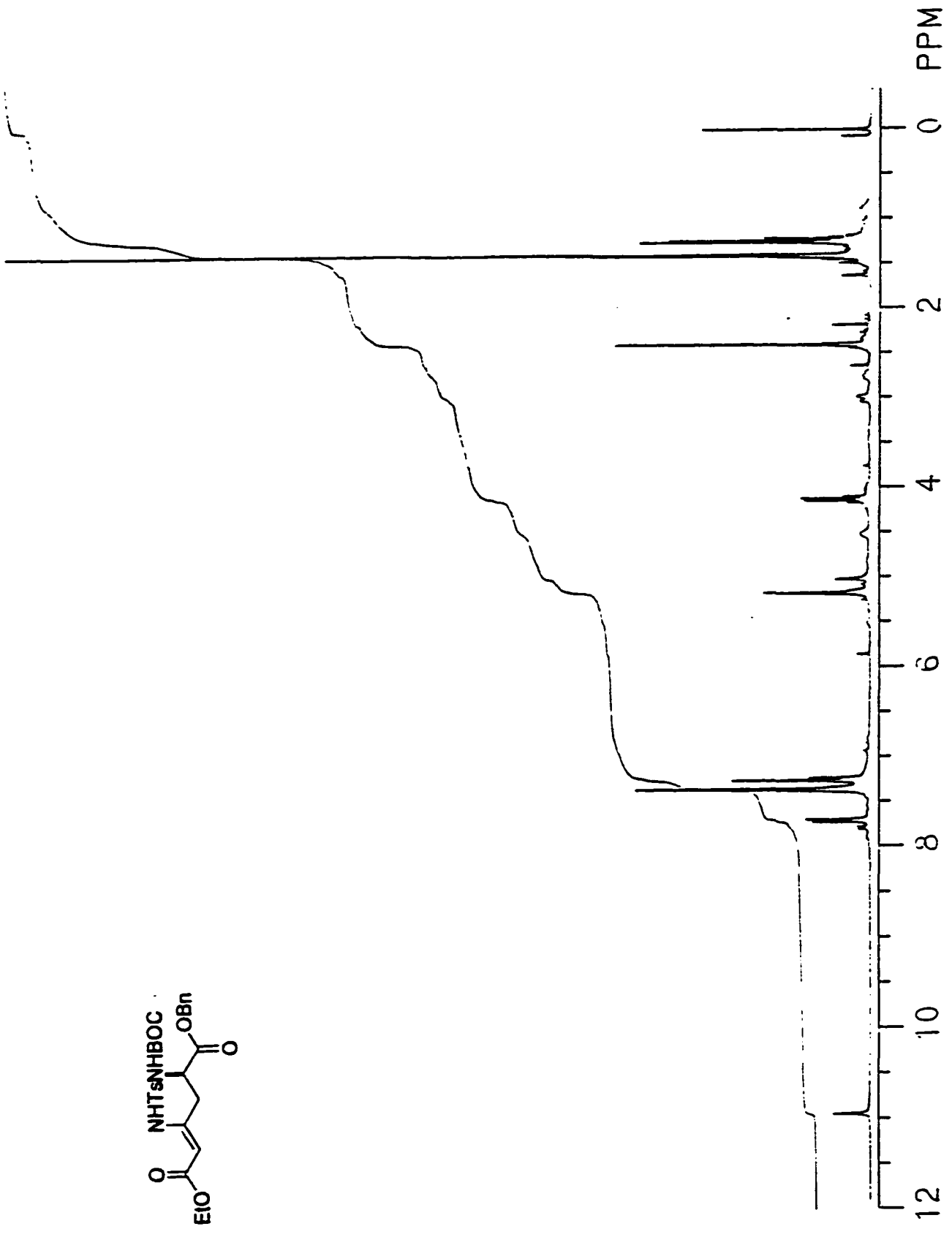


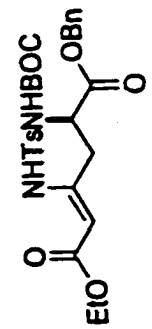


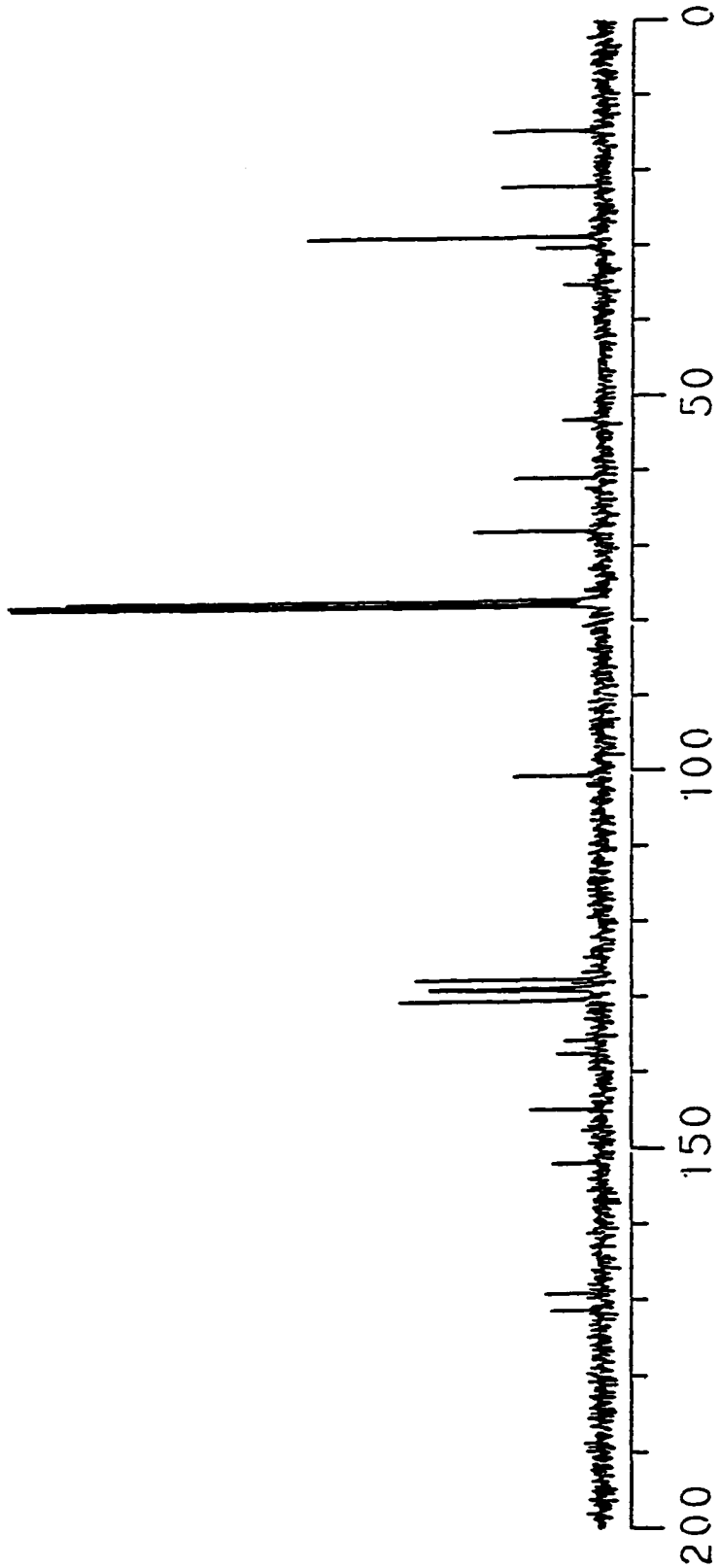


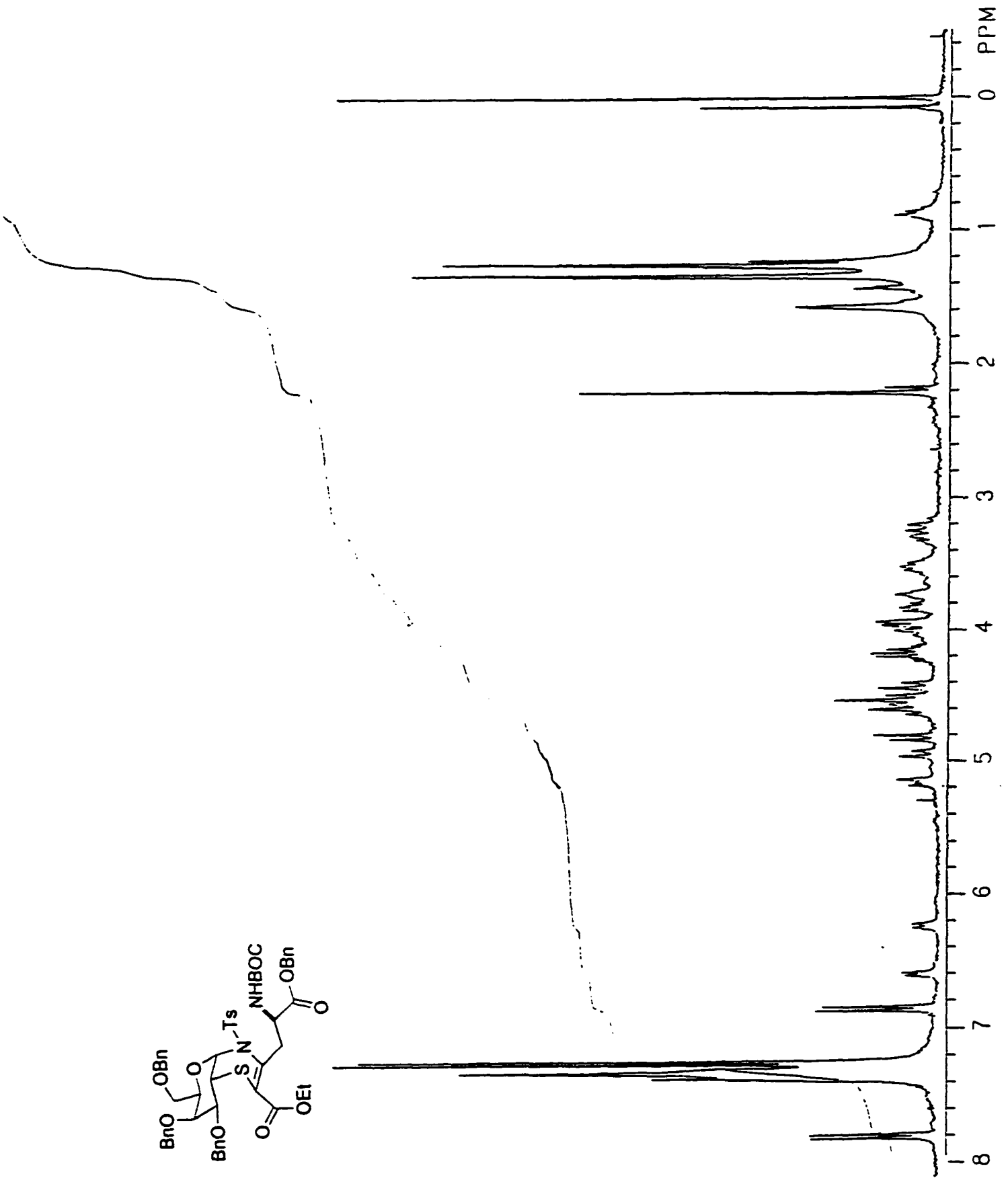


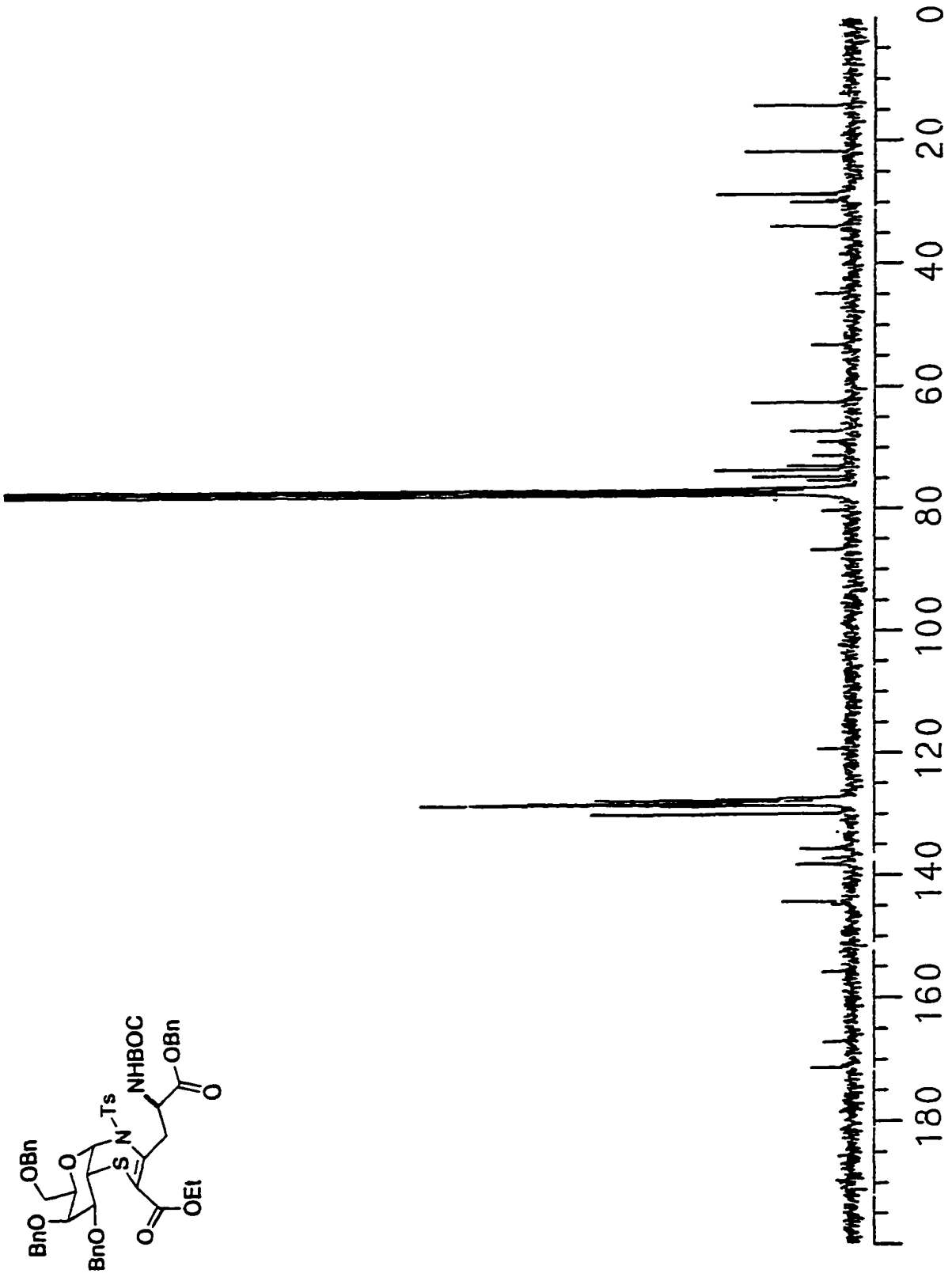












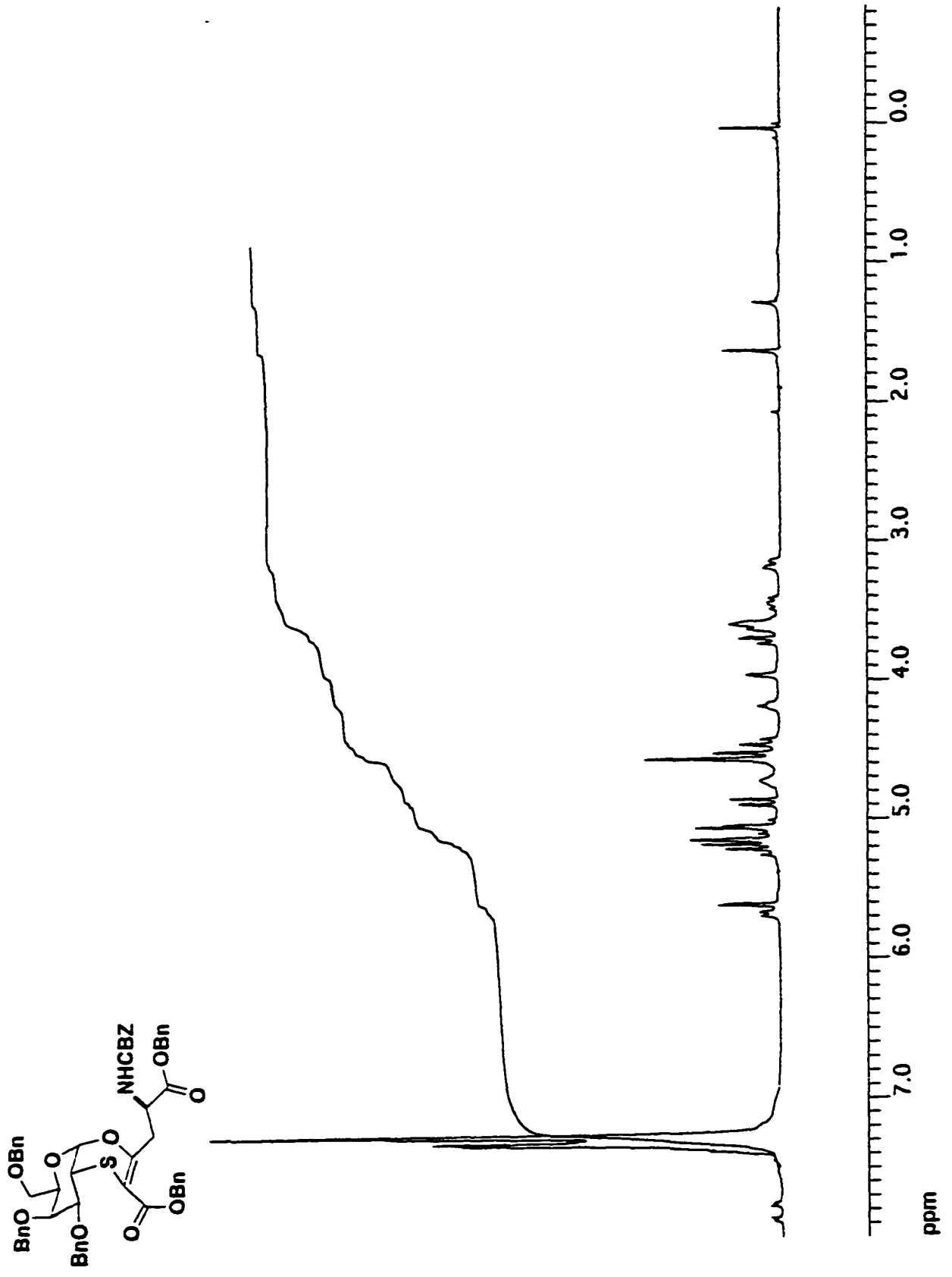


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IMAGE EVALUATION
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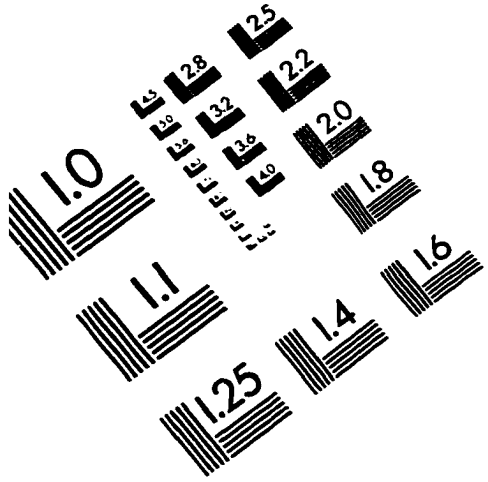

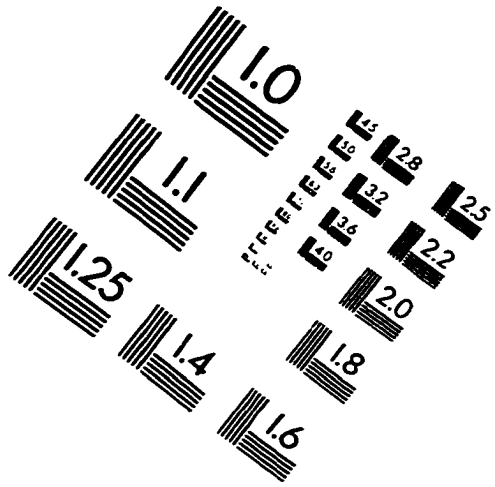

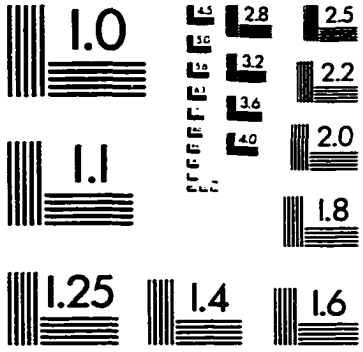

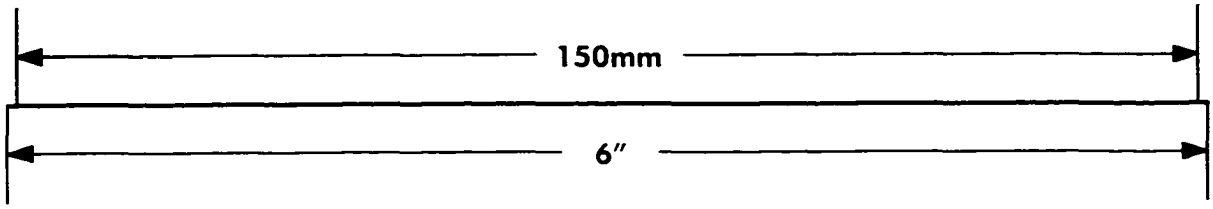

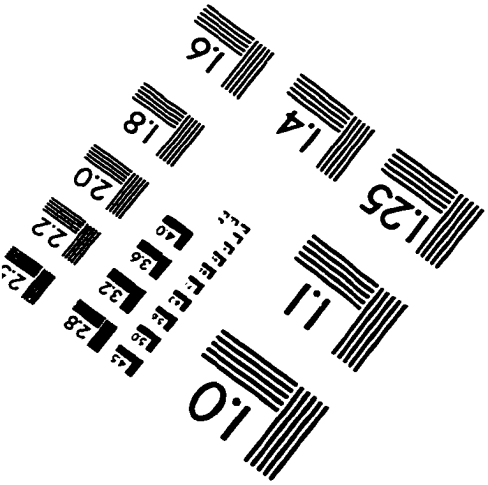

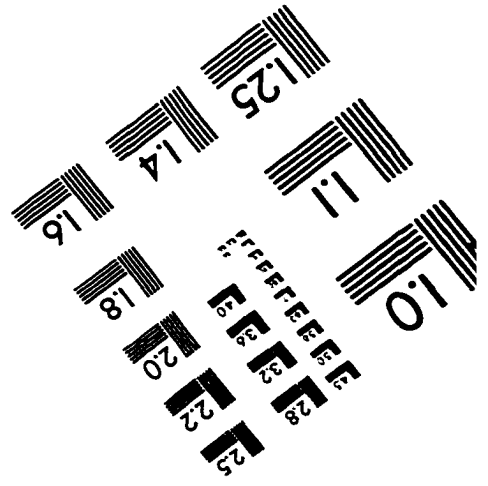

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