Synthesis of Calix[4]naphthalenes and Their Properties

by

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Abstract

The calixarenes **2-4** are well-known and well-studied cyclic oligomers formed by the base-induced condensation of formaldehyde with *p-tert*-butylphenol. They are potentially a very versatile class of host molecules.

This thesis describes the syntheses and some properties of the calixnaphthalenes, which are a new class of cyclic formaldehyde-naphthol tetramers which are analogous with the calixarenes. These calixnaphthalenes were prepared by either one-pot or convergent procedures.

Calixnaphthalenes offer some advantages over the calixarenes. For example, since the naphthalene unit is larger than benzene the cavity of "cone conformations" of the corresponding calixnaphthalenes should be deeper. Also, the presence of a B ring in naphthalene provides a site for the addition of different functional groups, which allow calixnaphthalenes to be modified. Furthermore, due to the low symmetry of 1-naphthol and 3-hydroxy-2-naphthoic acid, some calixnaphthalenes can be inherently chiral. They therefore have potential applications as chiral hosts, or chiral ligands.

Calix[4]naphthalenes **10-12** were synthesized first by the direct condensation of 1-naphthol and formaldehyde under basic conditions. Due to the difficulty in the separation and purification of these compounds, a convergent approach was used to synthesize these compounds as well as **13** in larger amounts for further investigations. The calix[4]-naphthalenes are conformationally flexible at room temperature even after their

derivatization as tetraester derivatives.

In order to synthesize calixnaphthalenes which are closer to calixarenes in the location of the hydroxyl groups within the lower rim of the calixnaphthalene basket, a retrosynthetic analysis of compounds **57** and **62** showed that 3-hydroxy-2-naphthoic acid (**9**) would be a suitable starting material. Syntheses of compounds **57** and **62** were effected by self-condensation reactions of 3-(hydroxymethyl)-2-naphthol and 6-*tert*-butyl-3-(hydroxymethyl)-2-naphthol, respectively, using $TiCl_4$/dioxane conditions.

Variable temperature ^1H NMR analyses showed that compounds **57** and **62** are conformationally flexible at room temperature, but the methylene protons are split into doublets at -10 °C and the molecules are locked in the cone conformation as its preferred conformation at -20 °C. X-ray analysis showed that in the solid state **57** adopted a "pinched-cone" conformation.

In order to modify calixnaphthalenes **57** and **62**, they were converted into their ester derivatives by reaction with ethyl bromoacetate. Calix[4]naphthalene **57** produced two tetraester derivatives in the cone and partial-cone conformations, **70b** and **70a**, respectively. Calix[4]naphthalene **62** produced mono- and diester derivatives **62a** and **62b**, respectively. ^1H NMR and molecular modeling analyses revealed that **62b** exists preferrentally in the 1,3-alternate conformation.

Using a modified oxidation procedure, the hydroxyl groups of **57** and **62** were oxidized to produce bis(spirodienone) derivatives. Compound **57** afforded only one

isomer, **78**, having C_2 symmetry as revealed by NOED experiments and confirmed by x-ray analysis. Compound **62** produced two isomers, **81** and **80**, having C_i and C_2 symmetries, respectively. Mild oxidation of **62** produced one monospirodienone isomer.

Dithiadihomocalix[4]naphthalenes **82** and **83** were synthesized from 1-naphthol and 3-hydroxy-2-naphthoic acid using procedures commonly employed in cyclophane chemistry. These compounds are found to be conformationally flexible at room temperature. Photolytic sulfur extrusion of **83** produced the corresponding dihomocalix[4]naphthalene **83a** while such conditions employed with **82** did not produce the corresponding **82a**.

In order to enlarge the annulus of calix[4]naphthalenes derived from 3-hydroxy-2-naphthoic acid, approaches to the tetrahomocalix[4]naphthalene isomers **85a** and **91a-93a** were attempted. The synthetic approach employed was the base-mediated coupling of **97** and **98** to produce, in principle, tetrathianaphthalenophanes **91-94**, which are potential precursors of the corresponding tetrahomocalix[4]naphthalenes after sulfur extrusion. Instead, four isomeric dithianaphthalenophanes **99-102** were produced from the above coupling reaction. Photolysis of these dimers produced two isomeric tetrahydrodibenzo-pyrenes, **107** and **108**, instead of [2.2](1,3)naphthalenophanes, **111** and **112**. This type of sulfur extrusion with concomitant transannular cyclization appears to be general one, which could offer some advantages for the synthesis of tetrahydropyrenes and tetrahydrodibenzopyrenes.

Acknowledgements

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List of Symbols, Abbreviations, and Acronyms

Ac	aetyl
APT	attached proton test
BTMA Br_3	benzyltrimethylammonium tribromide
br	broad
Bu	butyl
COSY	correlated spectroscopy
DMF	N,N-dimethylformamide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMSO	dimethyl sulfoxide
DNP	dinitrophenylhydrazine
equiv.	equivalent
FAB	fast atom bombardment
HETCOR	hetero atom correlation
I.R	infrared (spectroscopy)
LAH	lithium aluminum hydride
m.p.	melting point
MS	mass spectrometry
min	minute
NOED	nuclear Overhauser effect difference
NOBA	*p*-nitrobenzyl alcohol

NMR	nuclear magnetic resonance
PTMATB	phenyltrimethylammonium tribromide
p-	*para*
PLC	preparative thin layer chromatography
rt	room temperature
tert	tertiary
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TLC	thin-layer chromatography
TMS	trimethylsilyl
U.V.	ultraviolet
VT	variable temperature

To my parents and family

Chapter 1

Introduction

1.1. Introduction.

Living cells utilize mechanisms in which particular ions may be taken up or released. One of these mechanisms involves ion-transport with the help of molecular vehicles such as ionophores. Although they vary in chemical composition and molecular size, these ionophores all function using similar principles. They all bind the metal ion in an internal cavity by virtue of polar ligating groups and create a lipid envelope around the ion, which makes the resulting complex soluble in lipid media.[1]

An examination of the receptor sites of biological molecules such as e.g. enzymes ("hosts") reveal them to have concave surfaces to which substrates ("guests") bind to produce complexes as a result of electrostatic forces other than those of full covalent or ionic bonds. These biochemical phenomena have provided inspiration for much of the work in chemical molecular recognition, also often referred to as supramolecular chemistry. For example, the early work of Pedersen on the crown ethers (hosts)[2] for their complexation and selectivity towards metal ions (guests) provided the chemists an entry into the field of host-guest complexation chemistry. Also, inspired by the enforced concave surfaces of naturally-occurring biological compounds, Cram *et.al.*[3] were able to design and synthesize organic molecules with enforced concave surfaces having active binding sites such as spherands, cavitands, carcerands, and carceplexes.

As a result of Cram's extensive investigations,[3] and those of others[4,5] in the field of host-guest complexation chemistry, it was found that for a carrier molecule or ligand to behave as an ionophore it must meet the following requirements:[6]

a. It should contain both polar and non-polar groups.

b. It should be able to assume a stable conformation that provides a cavity, surrounded by polar groups that are suitable for the uptake of ions, most often a cation, while the non-polar groups form a lipophilic shell around the coordination sphere. These groups must ensure sufficiently high lipid solubility for the ligand and complex.

c. Among the polar groups of the ligand sphere, there should be preferably 5 to 8, but not more than 12 coordination sites, such as for example, oxygen atoms.

d. High selectivities are achieved by locking the coordination sites into rigid arrangements around the cavity.

e. Notwithstanding requirement (d), the ligand should be flexible enough to allow a sufficiently fast ion exchange. This is possible only with a stepwise substitution of the solvent molecules by the ligand groups. Thus, a compromise between stability (d) and exchange rate has to be found.

Currently, many different types of supramolecular compound are under investigation. One of these types of supramolecular compounds is the calixarenes.[7,8]

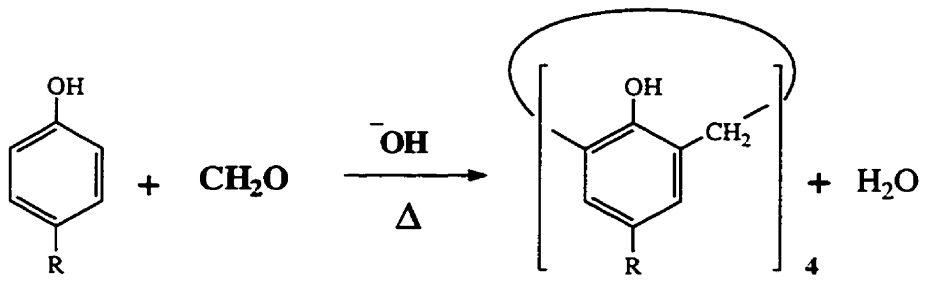
1.2. Synthesis of Calixarenes

Macrocyclic calixarenes can be obtained from the condensation of certain *para*-substituted phenols and formaldehyde by one of the procedures outlined below.

1.2.1. One-pot procedure

The formation of macrocyclic calixarenes was first demonstrated by Zinke and Ziegler in 1941.[9] They treated *p*-alkyl phenols with formaldehyde in the presence of base at high temperatures and obtained high melting point substances to which they assigned cyclic tetrameric structures as shown in Scheme 1.1.

Scheme 1.1.

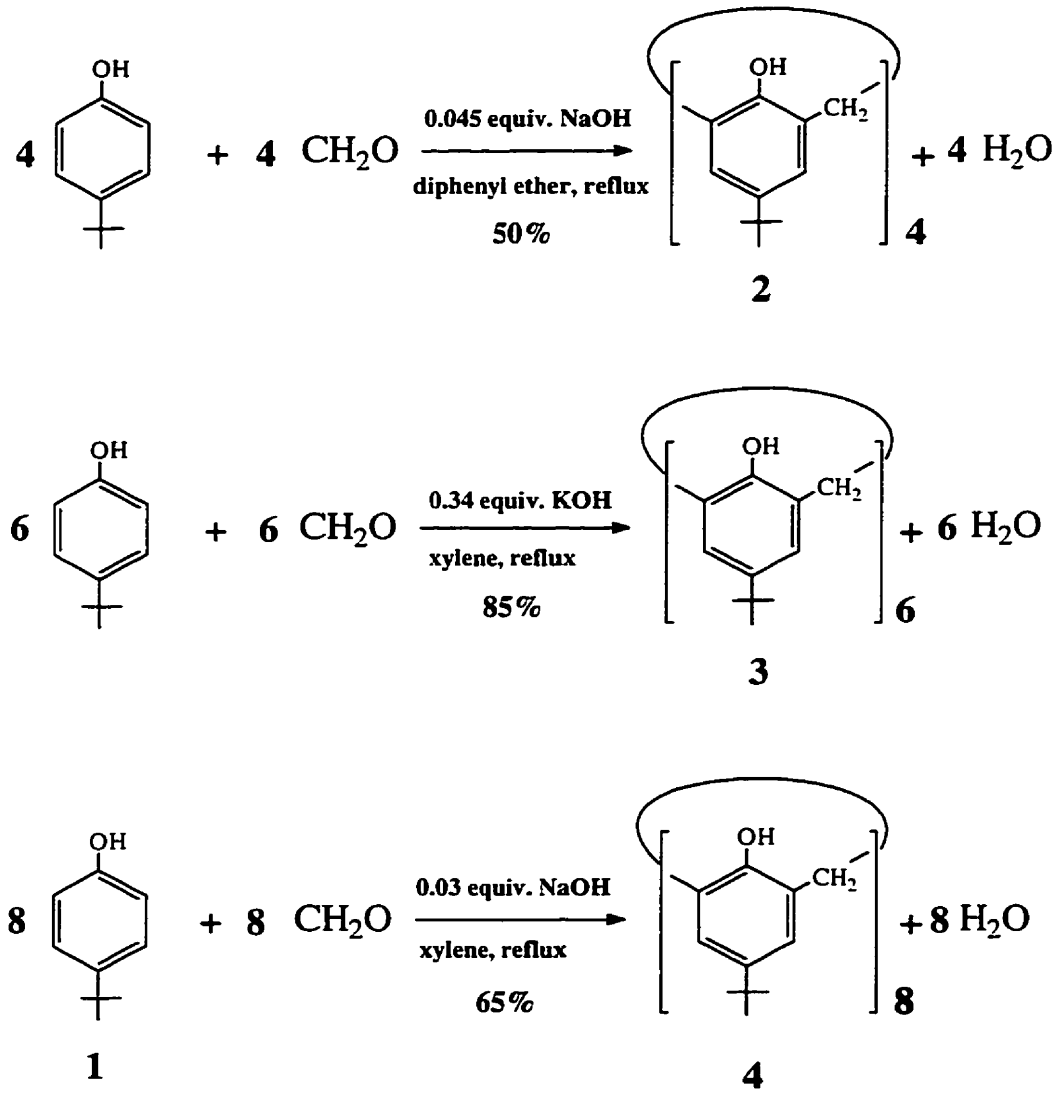


R = methyl, cyclohexyl, *tert*-butyl, phenyl, isobutyl, ...etc.

However, these products proved to be mixtures whose yields were not very reproducible. Also, Zinke and Ziegler did not appreciate the conformational properties of their products and their potential as candidates for molecular substances appropriate for building enzyme mimics.

In the early 1970's, Gutsche became interested in Zinke's cyclic tetramers as potential candidates for enzyme mimics, which led him to re-investigate the one-pot procedure in order to find a synthetically useful method.[10]

Scheme 1.2.



Changes involving solvents, bases, reactant ratios and other variables resulted in recipes that now permit the cyclic tetramer, hexamer, and octamer to be prepared easily in good yield, from *p-tert*-butylphenol. Some optimized conditions are shown in Scheme 1.2.[11]

Gutsche also perceived a similarity between the shape of a type of Greek vase called a "Calix Crater" and a space-filling model of the non-planar form of the cyclic tetramer in which all of the aryl moieties are oriented in the same direction. He assigned the name calix[n]arenes to these compounds ("arene", specifying the incorporation of aryl residues in the macrocyclic array and "n" indicating the number of aryl residues). These calixarenes have different positions that can be functionalized: the phenolic oxygens at the "lower" rim, and the aromatic *para*-positions at the "upper rim". With regard to the *para*-substituent alkyl group of phenol, it was found that the *tert*-butyl group is the best alkyl group, giving the best yields and the most tractable products.

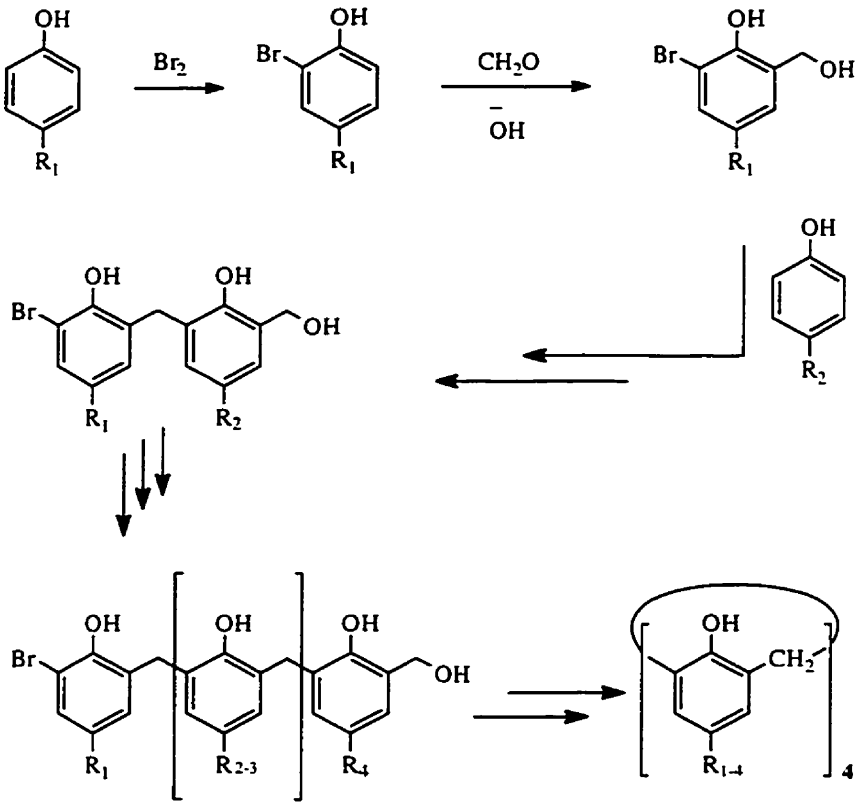
1.2.2. Stepwise procedure

The calixarenes obtained from a one-pot procedure necessarily have the same substituent in all the *para*-positions. Calixarenes with different *para*-substituents can be obtained by stepwise synthesis. Two strategies have been employed.

1.2.2.a. Non-convergent stepwise synthesis[12]

This type of synthesis starts from an *o*-bromo-*p*-alkylphenol and uses a series of alternating hydroxymethylation and condensation steps to build up a linear oligomer with a hydroxymethyl group at one end. This can then be cyclized under high dilution conditions after the other *o*-position has been de-blocked by dehalogenation. (Scheme 1.3). The yields obtained in the cyclization step are generally very good, but because of the large number of steps, the synthesis is long, and the overall yield is low.

Scheme 1.3.

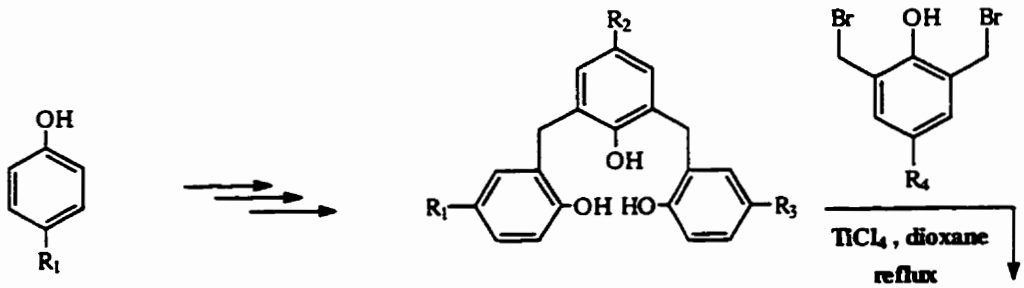


1.2.2.b. Fragment condensation

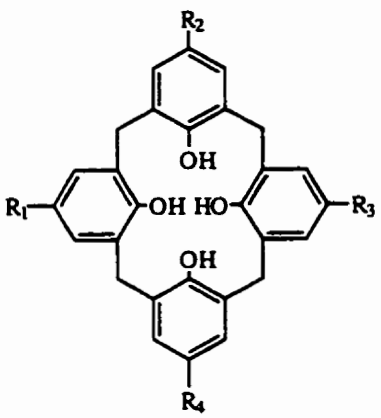
The last step in the non-convergent approach involves the cyclization of a single linear fragment molecule in a final intramolecular reaction step. Calix[4]arenes can also be prepared from two (or more) fragments. In this case the cyclization step is preceded by an intermolecular condensation step. Böhmer's group has effected condensations using [3+1],[13,14] [2+2],[15] and [2x1+2x1][16] processes using mostly $TiCl_4$/dioxane conditions to synthesize of a wide range of calix[4]arenes having different substituents present in the *p*-positions. (Scheme 1.4).

Scheme 1.4.

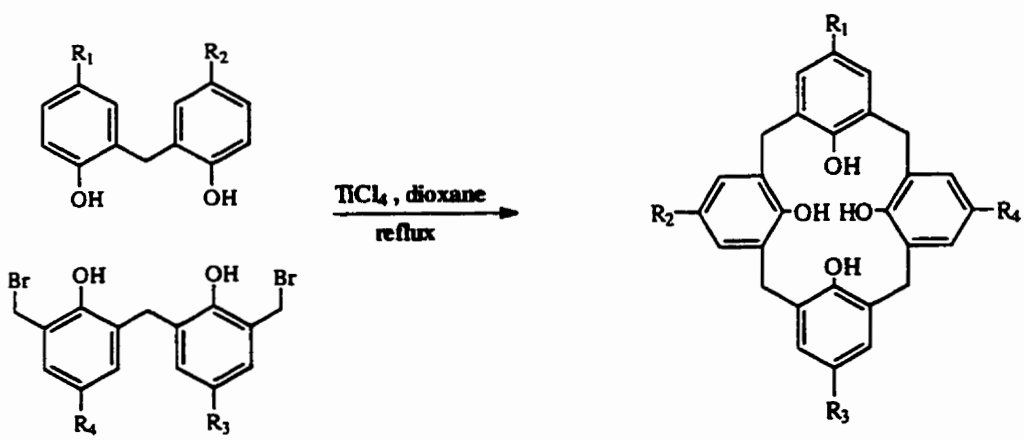
[3+1] Condensation



$R_1(R_3)$	R_2	R_4
tert-Bu	*tert*-Bu	CH_3
tert-Bu	*tert*-Bu	Cl
CH_3	Br	*tert*-Bu
CH_3	*tert*-Bu	Br
CH_3	Br	CH_3
CH_3	NO_2	CH_3



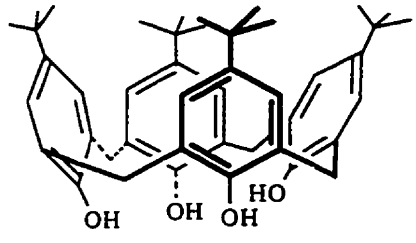
[2+2] Condensation



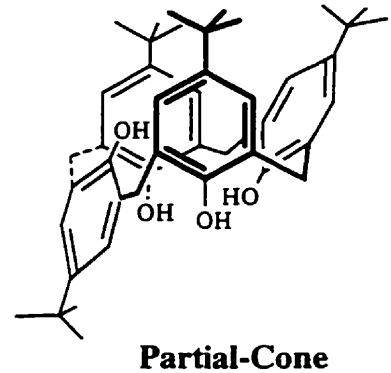
1.3. The conformations of calixarenes

All of the calixarenes containing free phenolic hydroxyl groups are conformationally mobile in solution at room temperature. That calix[4]arenes possess the potential for conformational isomerism was recognized by Cornforth and his coworkers.[7] Gutsche has designated these isomers as cone, partial-cone, 1,2-alternate and 1,3-alternate (Figure 1.1). These conformational isomers result from the free rotation of the σ–bonds of the methylene bridges.

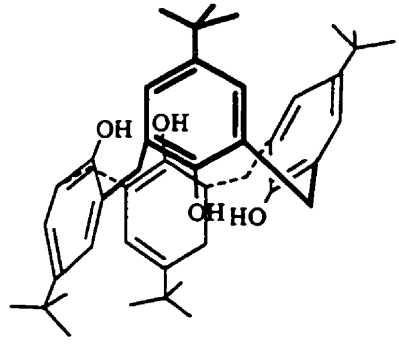
Figure 1.1. Conformational isomers of calix[4]arenes.



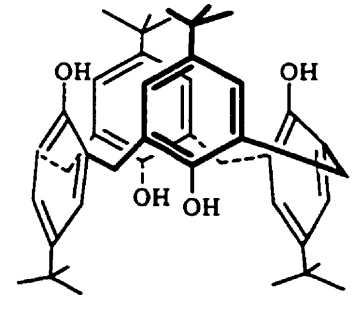
Cone



Partial-Cone



1,2-Alternate

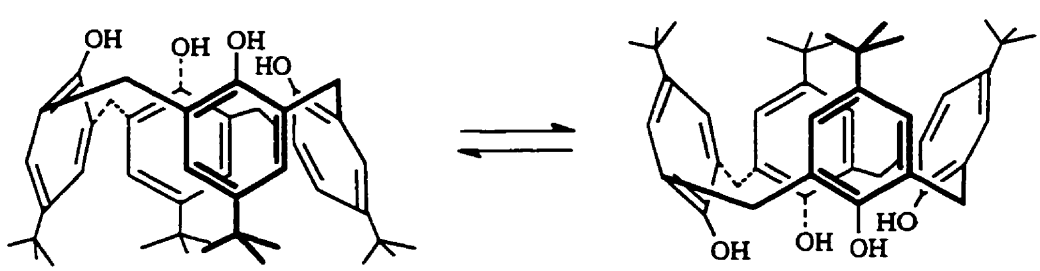


1,3-Alternate

All crystal structures of calix[4]arenes having free hydroxyl groups which have so far been reported,[17] including those of compounds containing different phenolic units,[18] have shown that the calix[4]arenes adopt the cone conformation in the solid state. In this conformation there is stabilization by intramolecular hydrogen bonding between the hydroxyl groups.

Calix[4]arenes also exist in the cone conformation in solution, as shown by ^1H NMR spectroscopy. In the case of *tert*-butylcalix[4]arenes, singlets are expected for the hydroxyl, the aromatic and the *tert*-butyl groups. The two protons of each methylene group, however, are nonequivalent in the cone conformation, and at temperatures at or below 20 °C in a nonpolar solvent such as $CDCl_3$, a pair of doublets is indeed observed with a coupling constant of 12-14 Hz, which is typical for non-equivalent geminal protons. These signals become broader when the temperature is increased, but collapse to form a sharp singlet at temperatures higher than 60 °C. This can best be explained in terms of a rapid exchange (Figure 1.2) between the two opposite (but identical) cone

Figure 1.2. A rapid exchange between the two opposite cone conformations



conformations, in which the hydroxyl groups pass through the interior of the macrocycle,

the equatorial protons which were originally equatorial becoming axial, and *vice versa*. The ^{1}H NMR spectrum therefore shows only an averaged signal.

It was shown that a substituent in the *p*-position has a small effect on the barrier to interconversion process. Thus, in $CDCl_3$ solution the free energy of activation for *p-tert*-butylcalix[4]arenes is 15.7 kcal/mol and for *p-tert*-pentylcalix[4]arenes is 14.5 kcal/mol. The energy barrier for interconversion, however, decreases when a nonpolar solvent such as $CDCl_3$ or benzene-d_6 is replaced by a more polar solvent. This is because interconversion requires that the hydroxyl groups pass through the ring, so that the cyclic arrangment of the hydrogen bonds is temporarily interrupted. Solvents which can break hydrogen bonds will therefore lead to a decrease in the energy barrier. For example, the inversion barrier for *p-tert*-butylcalix[4]arenes falls from 15.7 kcal/mol in $CDCl_3$ to 13.4 kcal/mol in pyridine.[19,20]

1.4. Synthesis of functionalized calixarenes

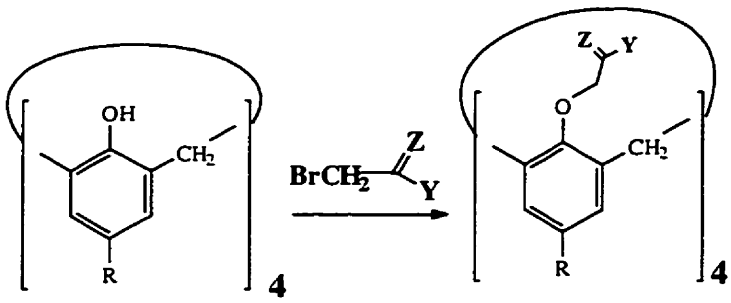
One of the primary motives that chemists have for building molecular "baskets" is the hope that such compounds will have enzyme-like properties and possess the ability to catalyze reactions in specific ways. For this to be possible, it is necessary that the baskets carry one or more functional groups that can take part in the chemical reactions required for the catalytic process. Two main procedures have been used for introducing functional groups into the calixarene basket.

1.4.1. Lower rim functionalization

The hydroxyl groups of the lower rim provide obvious sites for the attachment of

other functional groups. Useful synthetic methods involve reactions with excess α–halocarbonyl reagents to give tetraesters, amides, thioamides and ketones (Scheme 1.5).

Scheme 1.5.



Y	Z
OH	O
OR	O
NH_2	O or S
NHR	O or S
NR_2	O or S
CH_3	O

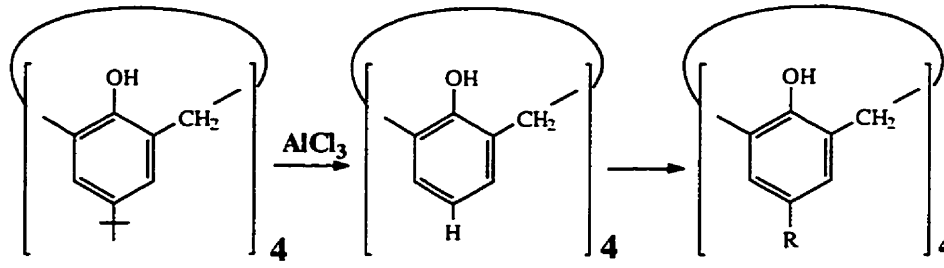
A convenient method for introducing alkyl groups involves treatment of calixarenes with an alkyl halide in THF-DMF solution, in the presence of sodium hydride. Methyl, ethyl, allyl and benzyl ethers have all been prepared in high yields.[22] A series of polyalkoxy ethers have been synthesized with the tosylate of the alkylating agent in the presence of potassium *tert*-butoxide.[23]

1.4.2. Upper rim functionalization

A variety of procedures has been employed for introducing groups into the *p*-positions subsequent to removal of the *tert*-butyl groups by Lewis acid catalysis such as $AlCl_3$. These procedures include electrophilic substitution (*i.e.*, bromination,[24] iodination,[25] nitration,[26] sulfonation,[27] chlorosulfonation,[28] acylation,[29] diazo coupling,[30] formylation[31]), the Claisen rearrangment of *o*-allyl to *p*-allyl,[32] the Mannich reaction,[33]

chloromethylation,[34] and mercuration (Scheme 1.6).[35]

Scheme 1.6.



R = Br, I, NO_2, NH_2, CH_2NR_2, CH_2NH_2, N_2Ar, CN, $CH_2CH_2NH_2$, CO_2H, CH_2CO_2H $CH_2CH_2CO_2H$, CH_2OH, CH_2SH, SO_3H, SO_2Cl, CHO, $COCH_3$, COC_6H_5

These chemical modifications not only permit the synthesis of new host molecules by the introduction of additional groups, but also permit the following:

1.4.a. Enhancement of the selectivity and efficiency of the complexation properties of calix[n]arenes

Derivatives of calixarenes which contain esters, amides or ketones have been studied in detail, and several general rules can be formulated:[36-41]

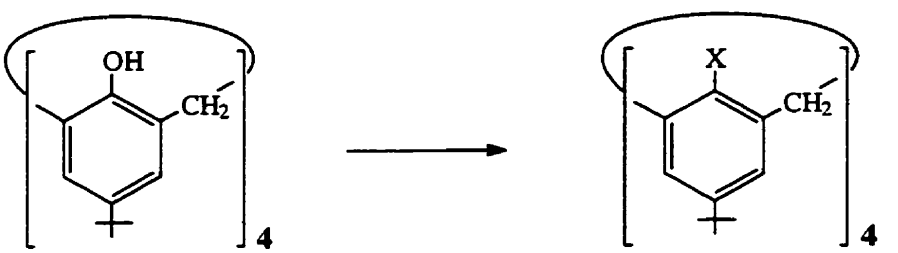
1. Both ester and ketone derivatives complex alkali metal ions more strongly than alkaline earth metal ions.
2. The ion selectivity depends on the conformation.
3. Tetraesters in the cone conformation are selective for Na^+, while the other conformations favour K^+.
4. Fine tuning of selectivities is possible by varying the alkoxy groups.
5. Tetraamides bind alkali metal ions more strongly than do the corresponding esters.

Also, in contrast to ester and ketone derivatives, amides are stronger complexing agents for alkaline earth metal ions.

1.4.b. Lower rim functionalization control of calixarene conformers by hindering conformational inversion

Since larger substituents (acetyl, propyl or larger) cannot pass through the macrocycle (annulus), it is possible to fix all the conformations and to isolate them as stable conformers. For example, acetylation of *tert*-butylcalix[4]arene yields tetraacetate **5a** (Scheme 1.7) that is frozen in the partial-cone conformation.[22]

Scheme 1.7.



2

5 a x = $OCOCH_3$
b x = OCH_2CHCH_2
c x = $OCH_2C_5H_6$
d x = $OSi(CH_3)_3$
e x = $CH_2CO_2C_2H_5$
f x = CH_2CH_2OR

Conversion of *tert*-butylcalix[4]arenes to the tetraallyl **5b**, tetrabenzyl **5c**, or trimethylsilylether **5d** locks the respective calixarene in the cone conformation. In general, it appears that acetylation and alkylation with simple alkyl halides favor the partial-cone conformation. Benzylation and trimethylsilylation favor the cone

conformation. The formation of the cone conformation often appears to be favored by a template effect of the metal ions present such as Na^+. Thus, when *tert*-butylcalix[4]arenes react with ethylbromoacetate in acetone in the presence of Na_2CO_3, the cone isomer **5e** is formed quantitatively.[36,40] Ethers of type **5f** in the 1,3-alternate conformation were obtained by alkylation with the corresponding tosylates in DMF with Cs_2CO_3 as a base with selectivity up to 100% and isolated yields up to 75%,[42] whereas, in the presence of NaH, the cone conformation was preferentially formed.[43]

1.4.c. Enhancement of the solubility of calixarenes

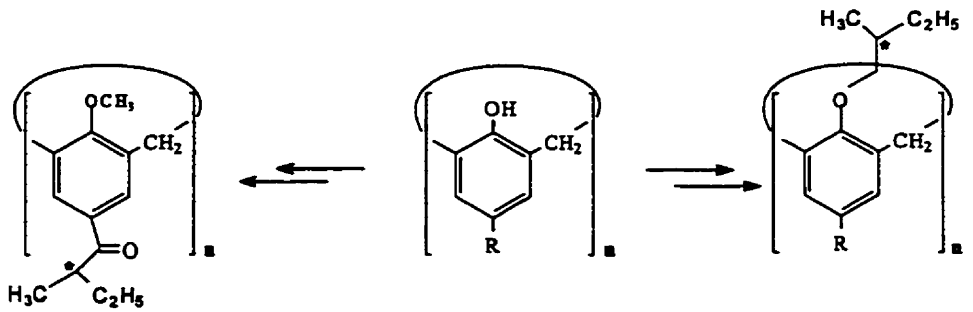
Calixarenes are sparingly soluble in several organic solvents but are insoluble in water. Lower rim functionalization with ester, alkyl or amide groups enhances their solubility in organic solvents, and upper rim functionalization with sulfonato groups produces water soluble sulfonated calixarenes.[27]

1.4.d. Synthesis of chiral calixarenes

Two general possibilities exist for the production of chiral calix[4]arenes:

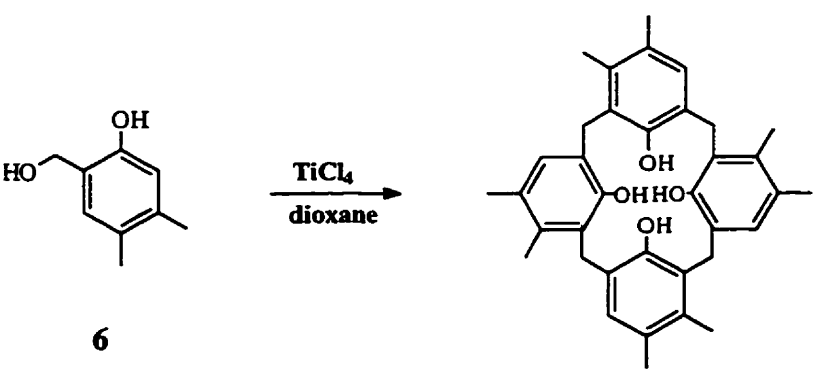
1. Derivatives with chiral substituents: Calixarenes have been converted into chiral derivatives by the introduction of a chiral substituent either at the phenolic OH groups or at the *p*-positions (Scheme 1.8).[43]

Scheme 1.8.



2. Dissymmetric calixarenes: A more interesting possibility is to make the calixarene itself inherently chiral by introducing substituents at *meta* positions in addition to the *para*-position. Calixarenes with C_4 symmetry have been obtained with yields in the cyclization step of up to 30% (Scheme 1.9).[44]

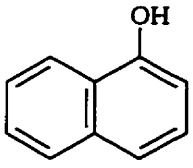
Scheme 1.9.



6 **7**

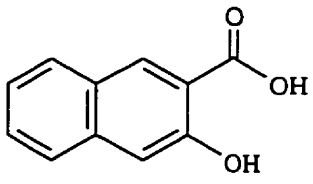
1.5. Calix[n]naphthalenes.

The calixarenes discussed to this point have been confined to those containing only benzene rings. In the present work other common aromatic compounds, namely naphthalenes such as 1-naphthol (**8**) and 3-hydroxy-2-naphthoic acid (**9**), were considered as building blocks for calixnaphthalenes, which are calixarene analogues.



1-naphthol

8



3-hydroxy-2-naphthoic acid

9

Since naphthalene is larger than benzene, the cavity of calixnaphthalenes should be deeper. This deeper cavity in a calixnaphthalene, particularly in a 1,3-alternate conformation, can provide a potential tube-shaped π-bond-based cavity, which might enhance its complexation properties by cation–π interaction phenomena.[45] Not only do the B rings of the naphthalenes increase the depth of the calixnaphthalene cavity but they also provide sites for the addition of different functional groups, which allow calixnaphthalenes to be modified. As opposed to most calixarenes, many calixnaphthalenes can be inherently chiral. They therefore have potential applications as chiral hosts or chiral ligands.

This thesis describes some synthetically useful convergent routes for synthesizing all four isomeric calix[4]naphthalenes that are derived from 1-naphthol using either $TiCl_4$- or TFA-mediated coupling reactions to achieve the cyclization steps. The synthesis of inherently chiral calix[4]naphthalenes and their conformational properties using variable temperature (VT) ^1H NMR is also described. Oxidation of these chiral calixnaphthalenes into their corresponding bis(spirodienones) is also presented. New routes for the synthesis of precursors which could easily be converted into pyrenes and dibenzopyrenes is also presented.

Chapter 2

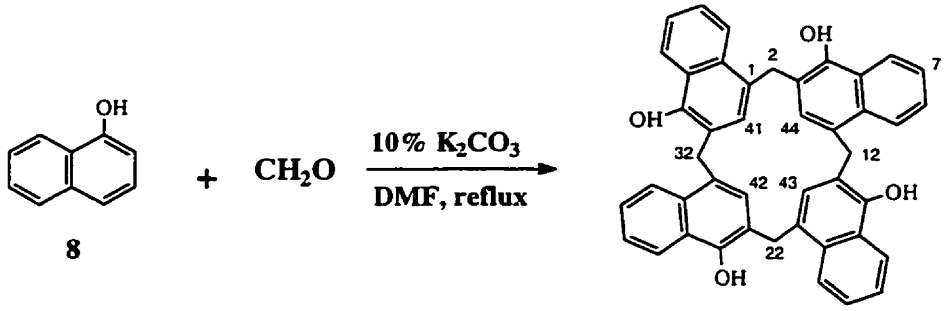
Calix[4]naphthalenes Derived from 1-Naphthol

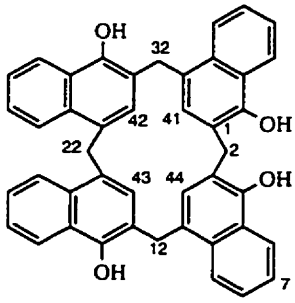
2.1. Introduction

The 1- and 2-naphthols are more reactive than phenols, and they resemble resorcinol rather than phenol in many of their reactions.[46] The complexity of the reaction of 1-naphthol with formaldehyde is well known,[47] and it has been assumed that cross-linked polymers are formed since reaction can occur at both C-2 and C-4. The acid- and base-catalyzed reactions between 1-naphthol and formaldehyde have been studied since 1892. Breslauer and Pictet obtained an amorphous product when they reacted 1-naphthol with formaldehyde and potassium carbonate and obtained a solid product whose empirical formula was found to be $C_{23}H_{16}O_3$.[48] When Abel heated 1-naphthol in 50% acetic acid with formaldehyde and a small quantity of hydrochloric acid, he obtained a brown brittle resin that was alkali-soluble.[49] Niether Abel nor Breslauer elucidated the structures of the products of these reactions.

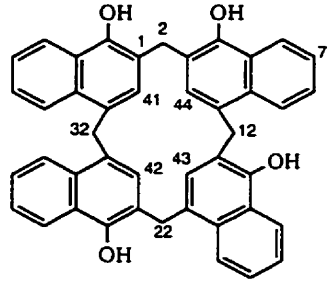
In 1993, Georghiou and Li[50] reported the synthesis of three cyclic tetrameric compounds from the base-induced reaction of formaldehyde with 1-naphthol in DMF solution (Scheme 2.1). These cyclic tetrameric compounds were the first members of a new class of compounds, which were named calix[4]naphthalenes by analogy with the calixarenes.

Scheme 2.1

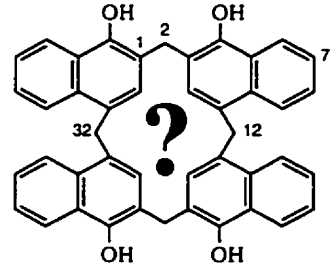




11 (C-23, C_S)



12 (C-44, C_1)



13 (C-12, C_{2v})

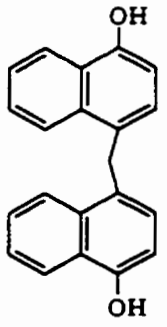
For simplicity and using symmetry considerations, these compounds were designated as "C-11", "C-12", "C-23" and "C-44". These terms refer to the number of carbon signals expected in the ^{13}C NMR spectra. The C-12 is included as a possible structure but was not obtained by Georghiou and Li from their base-catalyzed reaction.

The yields of C-11, C-23 and C-44 were relatively low, and the limited solubility of the crude reaction mixture in the usual organic solvents required tedious separation and purification of these compounds from the crude reaction product. Also, since no C-12 was formed, a convergent synthetic approach was necessary to synthesize in larger amounts all of the four isomeric calix[4]naphthalenes (**10-13**) derived from 1-naphthol

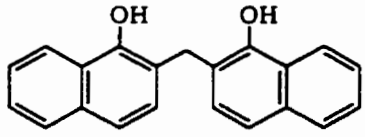
for further investigations.

For purposes of synthetic considerations, the C-11, C-12, C-23 and C-44 compounds can be seen to be formed by subsequent condensation of formaldehyde with various combinations of the following first condensation products, as depicted in Figure 2.1.

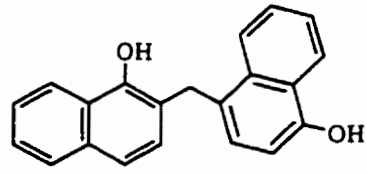
Figure 2.1. Three condensation products of 1-naphthol with formaldehyde



14



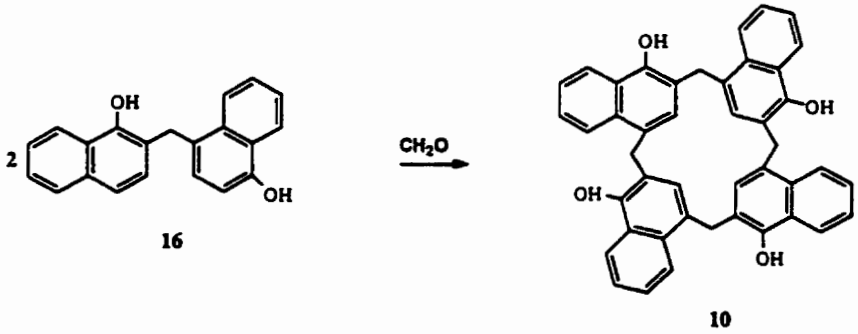
15



16

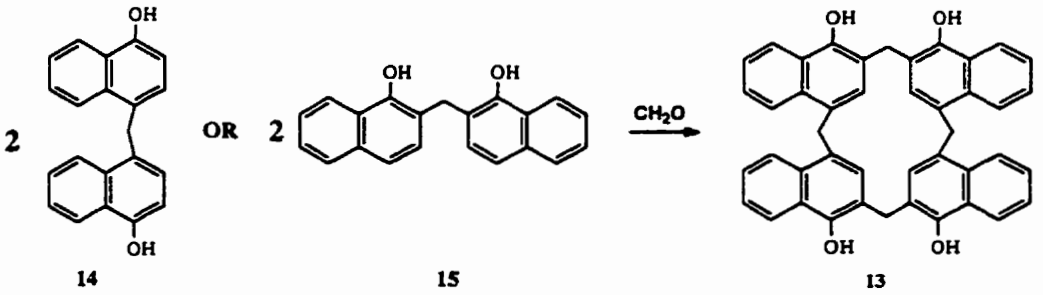
In principle, the C-11 product can be seen to be formed by condensation of two molecules of formaldehyde between two molecules of **16** (Scheme 2.2).

Scheme 2.2.



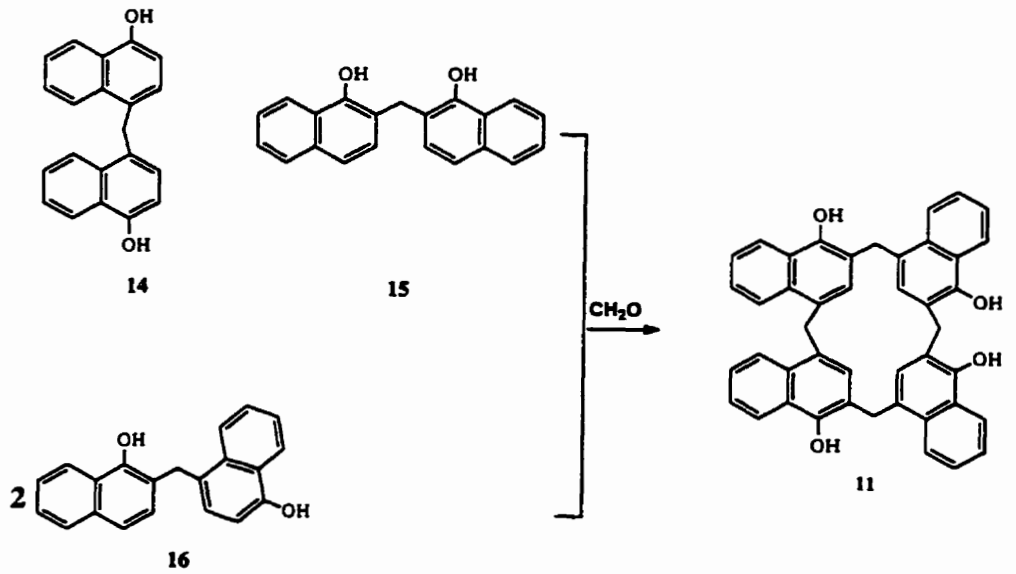
The C-12 product can in principle also be seen to be formed by condensation of two molecules of formaldehyde between two molecules of **14**, or two molecules of **15** (Scheme 2.3).

Scheme 2.3.



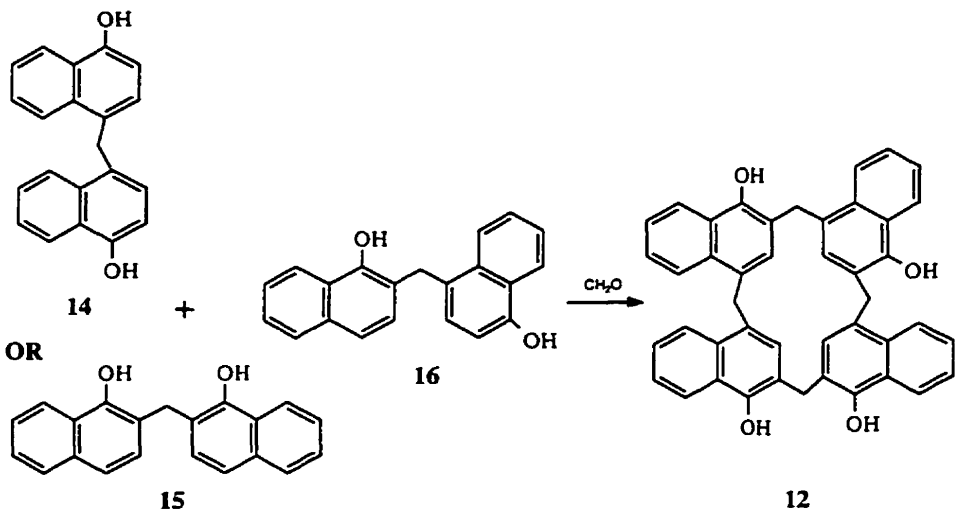
The product C-23 can be seen to be formed by condensation of two molecules of formaldehyde between two molecules of **16**, or between molecules of **14** and **15** (Scheme 2.4)

Scheme 2.4.



Finally, the C-44 product can be seen to be formed by condensation of two molecules of formaldehyde between two molecules of **14** and **16**, or **15** and **16** (Scheme 2.5).

Scheme 2.5.



The complexity of the reaction of 1-naphthol with formaldehyde is well known,[47] since reaction can occur at both C-2 and C-4 positions. Thus, none of compounds **14-16** could be synthesized directly from 1-naphthol and formaldehyde. In order to direct the condensation of formaldehyde between two molecules of 1-naphthol selectively, the classical approach was explored of using a blocking group which is added to protect one of the reactive sites, and then removed later on to reopen that site to reaction.

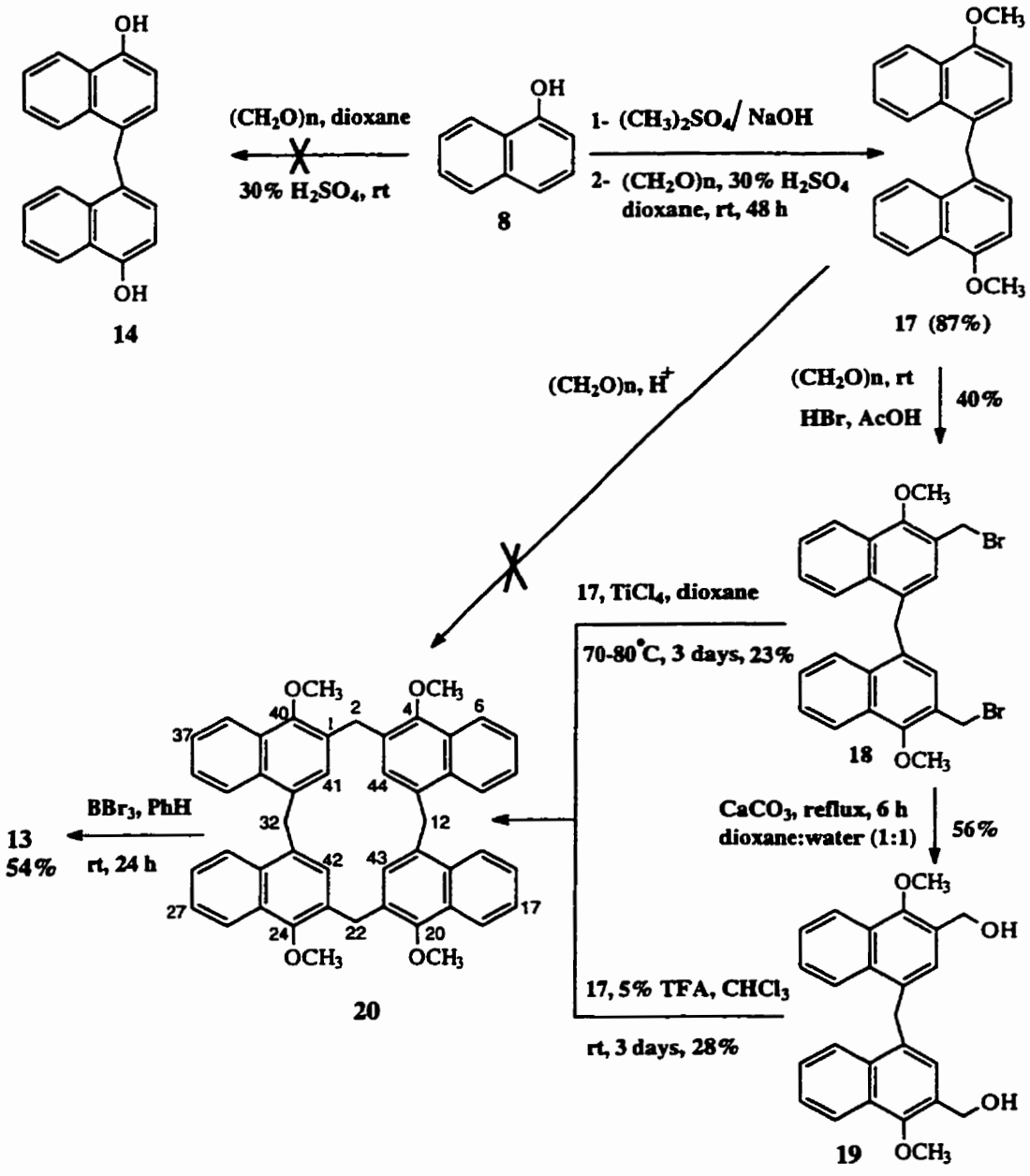
Initially, the *tert*-butyl group was chosen as the blocking group. It had been reported[51] that the $ZnCl_2$-catalyzed reaction of 1-naphthol with *tert*-butyl chloride afforded a 42% yield of 4-*tert*-butyl-1-naphthol. It had also been reported [52] that the H_2SO_4-

catalyzed reaction of 1-naphthol and *tert*-butyl alcohol afforded an unspecified amount of 2,4-di-*tert*-butyl-1-naphthol and 20% of 2-*tert*-butyl-1-naphthol. Employing these alkylation reaction conditions did not afford any 2- or 4-*tert*-butyl-1-naphthols. Several other variations of $ZnCl_2$- or H_2SO_4-catalyzed reactions were employed, but in no case was any 2- or 4-*tert*-butyl-1-naphthol observed. The results of the re-investigation of *tert*-butylation of 1-naphthol using several *tert*-butylating agents and several acid catalysts will be the subject of a forthcoming chapter. However, we found that **14** and **15** could be synthesized via their corresponding dimethoxy derivatives using a convergent synthetic approach.

2.2. Synthesis of calix[4]naphthalene C-12 isomer: [2+2] condensation

A convergent synthesis of calix[4]naphthalene **13** was achieved by the route depicted in Scheme 2.6. It was reported[53] that the dimethoxy derivative of **14**, namely bis(4-methoxy-1-naphthyl)methane (**17**), could be synthesized in good yield by an acid-catalyzed reaction of paraformaldehyde with 1-methoxynaphthalene. Employing these reaction conditions with 1-naphthol itself did not produce **14** and yielded only an intractable resinous product. Under a variety of different conditions the direct condensation of **17** with formaldehyde could not be effected. However, the corresponding bis-bromomethyl **18**, namely bis(3-bromomethyl-4-methoxy-1-naphthyl)methane, could be obtained in 40% yield by reacting **17** with paraformaldehyde in HBr/AcOH. Using Böhmer's[13-16] $TiCl_4$-catalyzed coupling conditions in dry dioxane,

Scheme 2.6.


OH
OH
14
(CH2O)n, dioxane
30% H2SO4, rt
OH
8
1- (CH3)2SO4/ NaOH
2- (CH2O)n, 30% H2SO4
dioxane, rt, 48 h
OCH3
OCH3
17 (87%)
(CH2O)n, H+
(CH2O)n, rt
HBr, AcOH
40%
OCH3
Br
Br
18
OCH3
17, TiCl4, dioxane
70-80°C, 3 days, 23%
CaCO3, reflux, 6 h
dioxane:water (1:1)
56%
OCH3
OH
OH
19
OCH3
17, 5% TFA, CHCl3
rt, 3 days, 28%
OCH3
OCH3
40
1
2
4
6
37
41
44
32
12
42
43
27
17
24
22
20
OCH3
OCH3
20
BBr3, PhH
13
54%
rt, 24 h

17 and **18** coupled to afford the C_{2v} symmetrical tetra-methoxycalix[4]naphthalene **20**, in 23% yield. A more convenient alternative synthesis of **20** was achieved by first converting **18** to the corresponding bis-hydroxymethyl compound **19**, and then coupling **19** with **17** using 5% trifluoroacetic acid (TFA) in chloroform.[54] The product, **20**, which was obtained in 28% yield, was easier to isolate from the crude reaction mixture than when $TiCl_4$ was used. Demethylation of **20** using BBr_3 produced the elusive calix[4]naphthalene **13** in 54% yield. The ^1H NMR and ^{13}C NMR spectra aided by 2-D (HETCOR, APT) and NOED experiments were consistent for structures **13** and **20**, which possess C_{2v} symmetry. The HETCOR and APT ^{13}C NMR spectra of **20** in $CDCl_3$ clearly indicated five methine aromatic carbon signals, two aliphatic methylene carbon signals and the methoxy carbon signal. Only four of the five quaternary aromatic carbon signals were clearly resolved.

The ^1H NMR spectrum of **20** (Figure 2.2) shows a relatively high field aromatic signal as a four-proton singlet at 6.43 ppm due to the four intraannular naphthalene protons (H-41, H-42, H-43, H-44). The methylene protons (on C-2, C-12, C-22, C-32) appear as two singlets at 4.24 and 4.59 ppm with relative intensities in the ratio of 1:1.

The ^{13}C-NMR (DMSO-d_6) spectrum of the demethylated product **13** shows all twelve carbon signals, consisting of five quaternary aromatic carbon signals, five methine aromatic signals and two aliphatic methylene carbon signals clearly resolved. The ^1H-NMR spectrum of **13** (Figure 2.3) shows also a relatively high-field aromatic signal which is a four-proton singlet at 6.64 ppm due to the four intraannular naphthalene

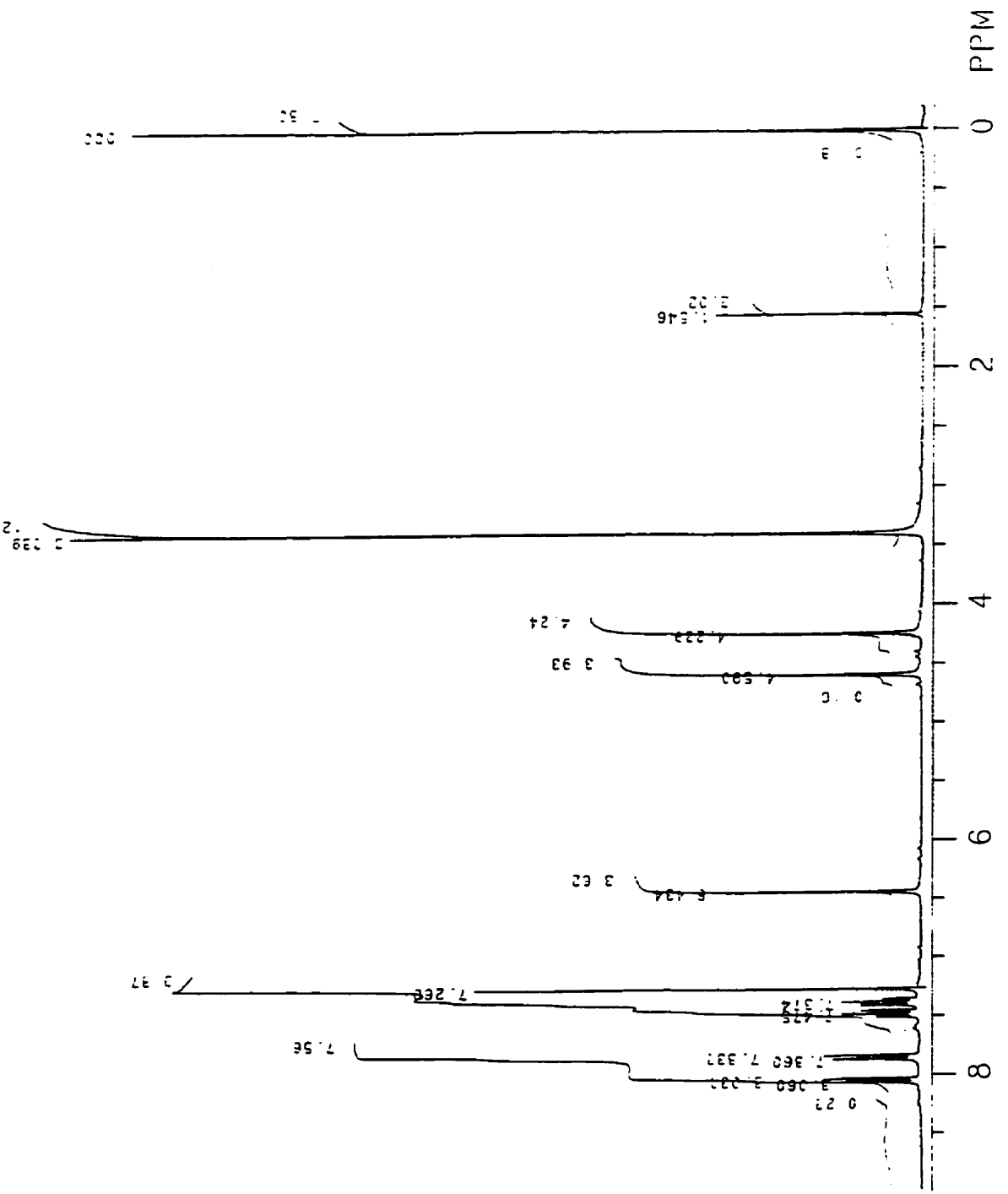


Fig. 2.2. ^{1}H NMR Spectrum of Calix[4]naphthalene 20 in $CDCl_3$.

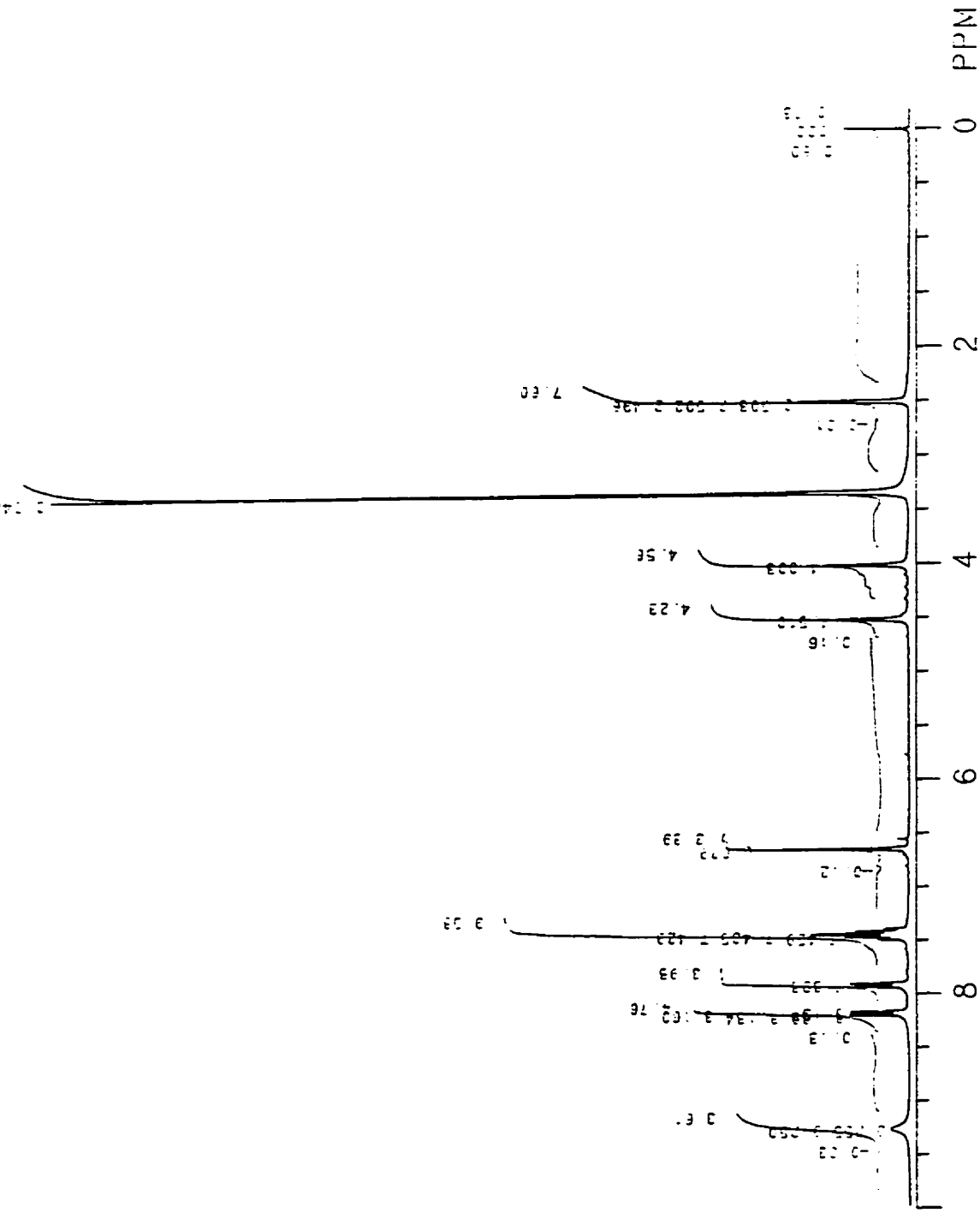
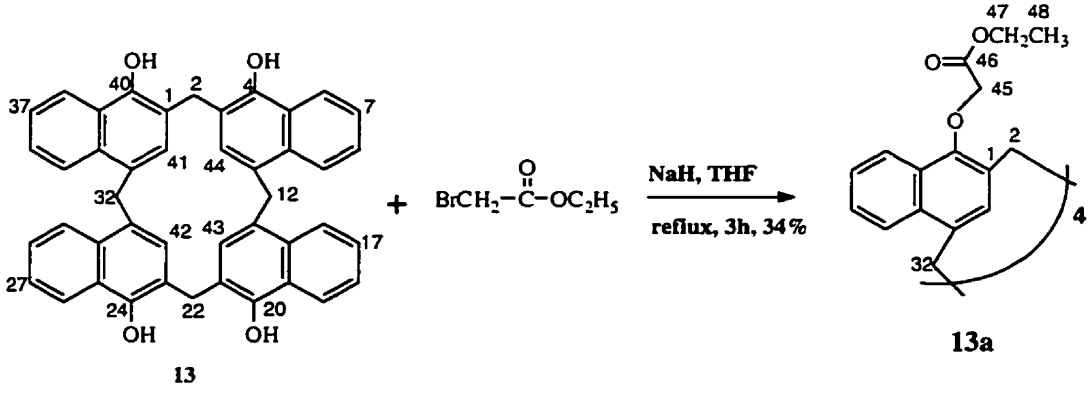


Fig. 2.3. ^{1}H NMR Spectrum of Calix[4]naphthalene 13 in Acetone-d_6.

protons. The methylene protons appear as two singlets at 4.01 and 4.51 ppm. The higher-field aromatic signals in **13** and **20** can be accounted for by examination of molecular models, which reveal that the intra-annular protons are situated in the shielding region of the naphthalene ring. That the methylene protons appear as a singlet at ambient temperature indicates that the compound has a flexible structure with interchanging sites.

As stated before, one of the methods to lock calixarenes into one of their four conformations at ambient temperature is to replace the hydroxyl groups with larger moieties, such as ester groups. Employing this strategy, calix[4]naphthalene **13** was converted into its tetraester derivative **13a** (Scheme 2.7).

Scheme 2.7.



As shown in Figure 2.4, the simple tetraester derivative **13a** is conformationally labile at ambient temperature as demonstrated by the fact that the methylene bridge protons appear as a sharp singlets at 4.31 and 4.6 ppm, and not as an AB quartet.

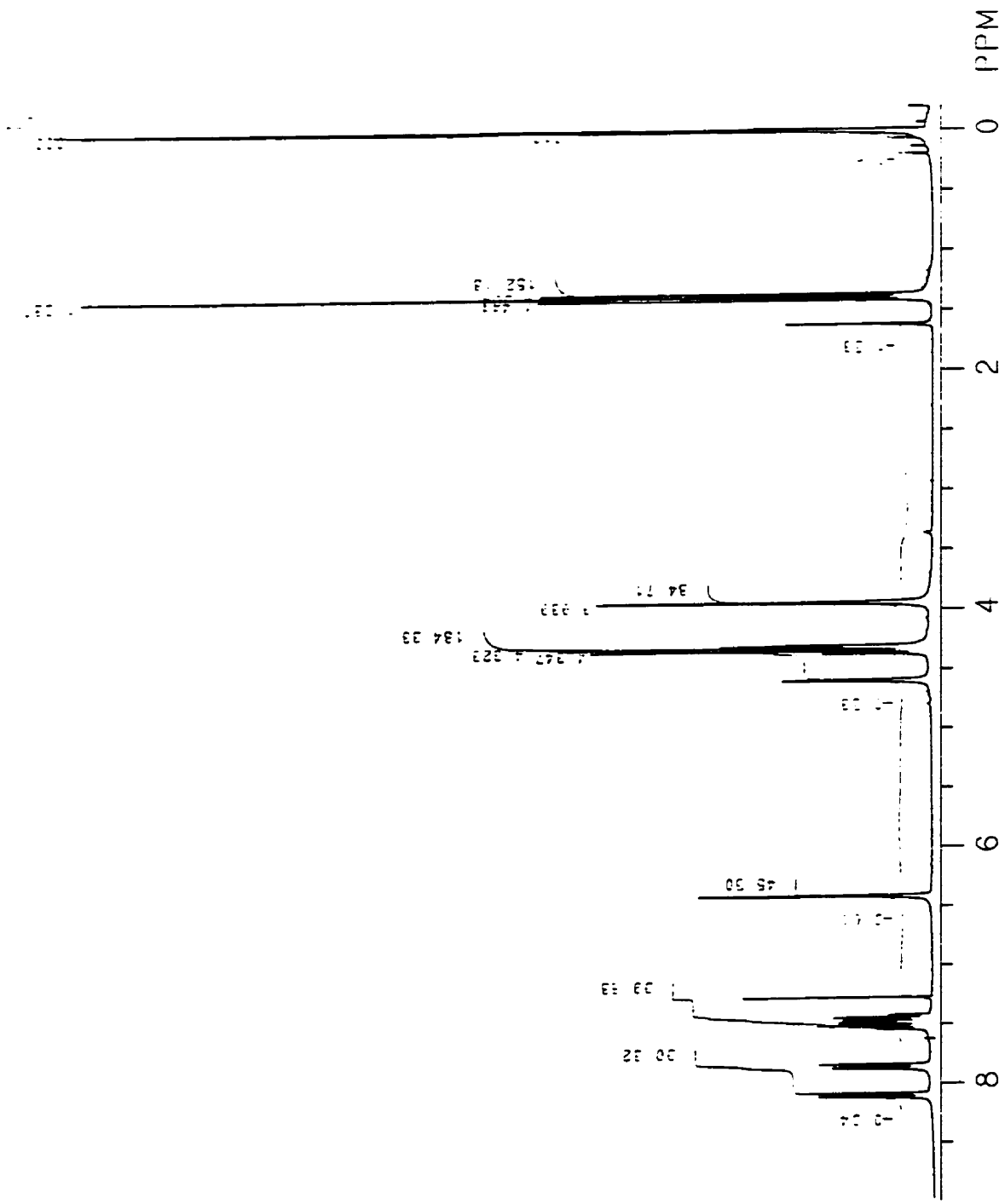
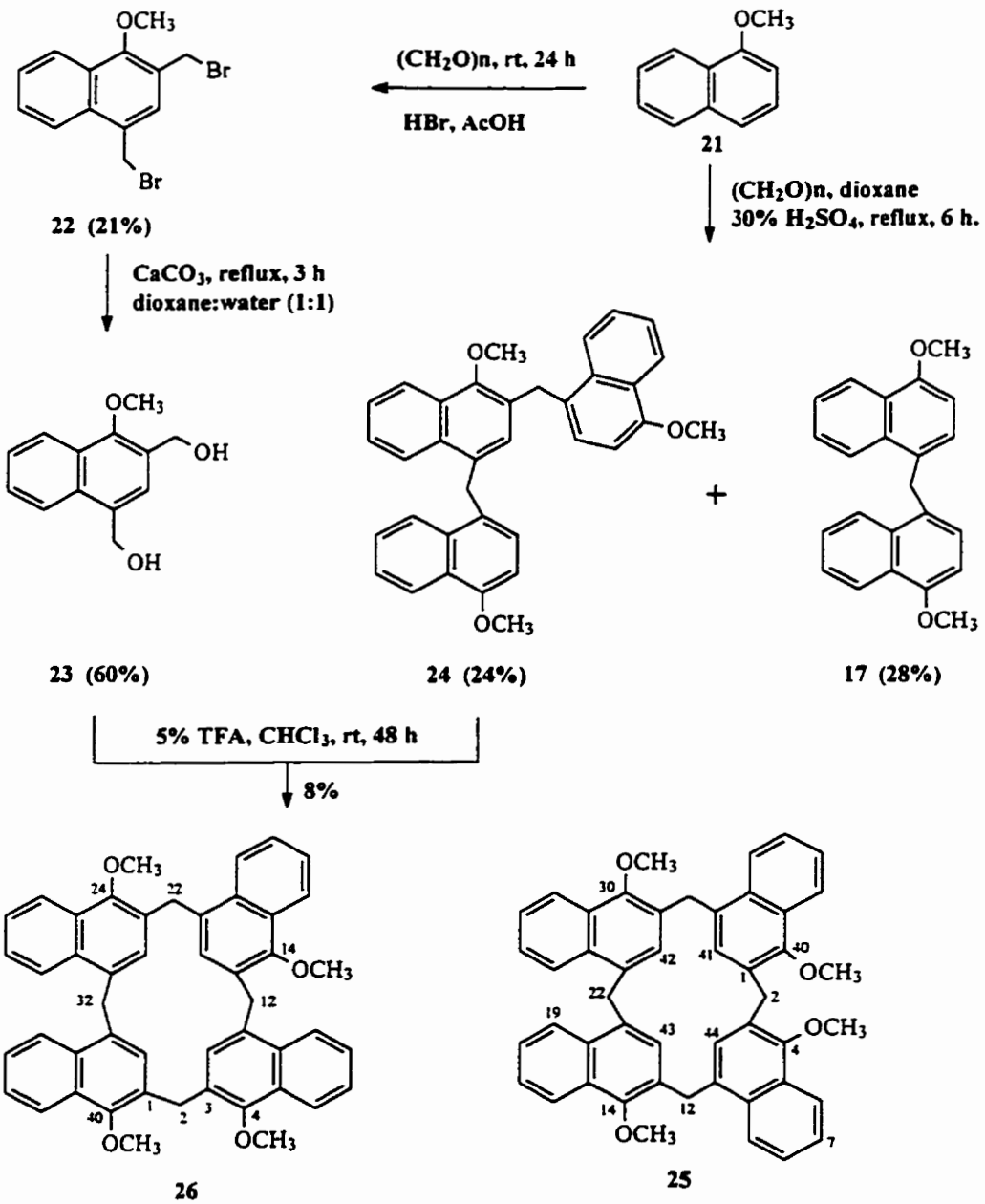


Fig. 2.4. ^{1}H NMR Spectrum of tetraester derivative 13a in $CDCl_3$.

Scheme 2.8


OCH3
Br
Br
22 (21%)
(CH2O)n, rt, 24 h
HBr, AcOH
OCH3
21
(CH2O)n, dioxane
30% H2SO4, reflux, 6 h.
CaCO3, reflux, 3 h
dioxane:water (1:1)
OCH3
OH
OH
23 (60%)
OCH3
OCH3
OCH3
24 (24%)
+
OCH3
OCH3
17 (28%)
5% TFA, CHCl3, rt, 48 h
8%
OCH3
OCH3
OCH3
OCH3
26
OCH3
OCH3
OCH3
OCH3
25

2.3. Synthesis of C-23 and C-44 Tetramethoxycalix[4]naphthalenes

2.3.a. [3+1] Condensation

A convergent synthesis of the C-23 and C-44 tetramethoxycalix[4]naphthalenes **25** and **26**, respectively, was achieved by the route depicted in Scheme 2.8. Refluxing 1-methoxynaphthalene (**21**) for 6 h with paraformaldehyde in 30% sulfuric acid afforded a mixture which contained linear oligomers including dimer **17** and trimer **24**. The structure of **24** was established on the basis of its spectroscopic properties, including 2-D ^{1}H and ^{13}C NMR experiments and NOED correlations. When **24** was reacted with the bis(hydroxymethyl)naphthyl derivative **23** using TFA-catalyzed conditions, a 3:1 mixture of **26** and **25** was obtained in 8% overall yield. Compound **23** was synthesized from the corresponding bis-bromomethyl precursor **22**, which, in turn, was obtained from the reaction of 1-methoxynaphthalene with paraformaldehyde in HBr/AcOH.

The ^{1}H-NMR spectrum of **25** (Figure 2.5) shows the higher field aromatic signals as two (two-protons) singlets of equal intensity at 6.50 and 6.58 ppm for the intra-annular protons. The methylene protons appear as three singlets, at 4.30, 4.40 and 4.51 ppm with relative intensities in the ratio of 1:2:1. Also, the two singlets at 3.90 and 3.91 ppm are due to two sets of equivalent methoxy groups. This ambient temperature ^{1}H NMR spectrum of **25** indicates conformational mobility, since all signals including the methylene protons are sharp and well-defined. Also, the two singlets due to two sets of equivalent methoxyl groups and three singlets due to three sets of methylene protons

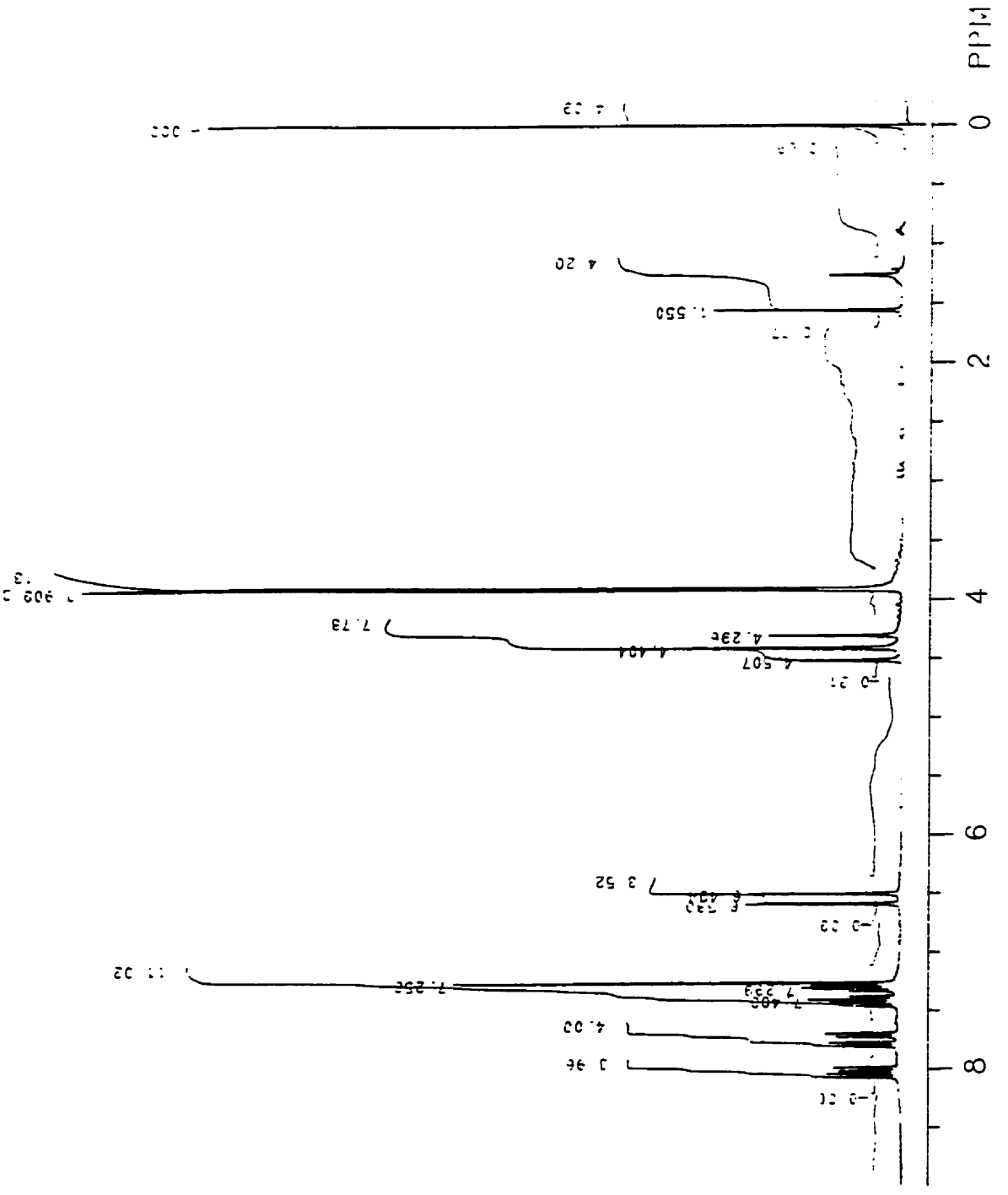


Fig.2.5. ^{1}H NMR Spectrum of Calix[4]naphthalene 25 in $CDCl_3$.

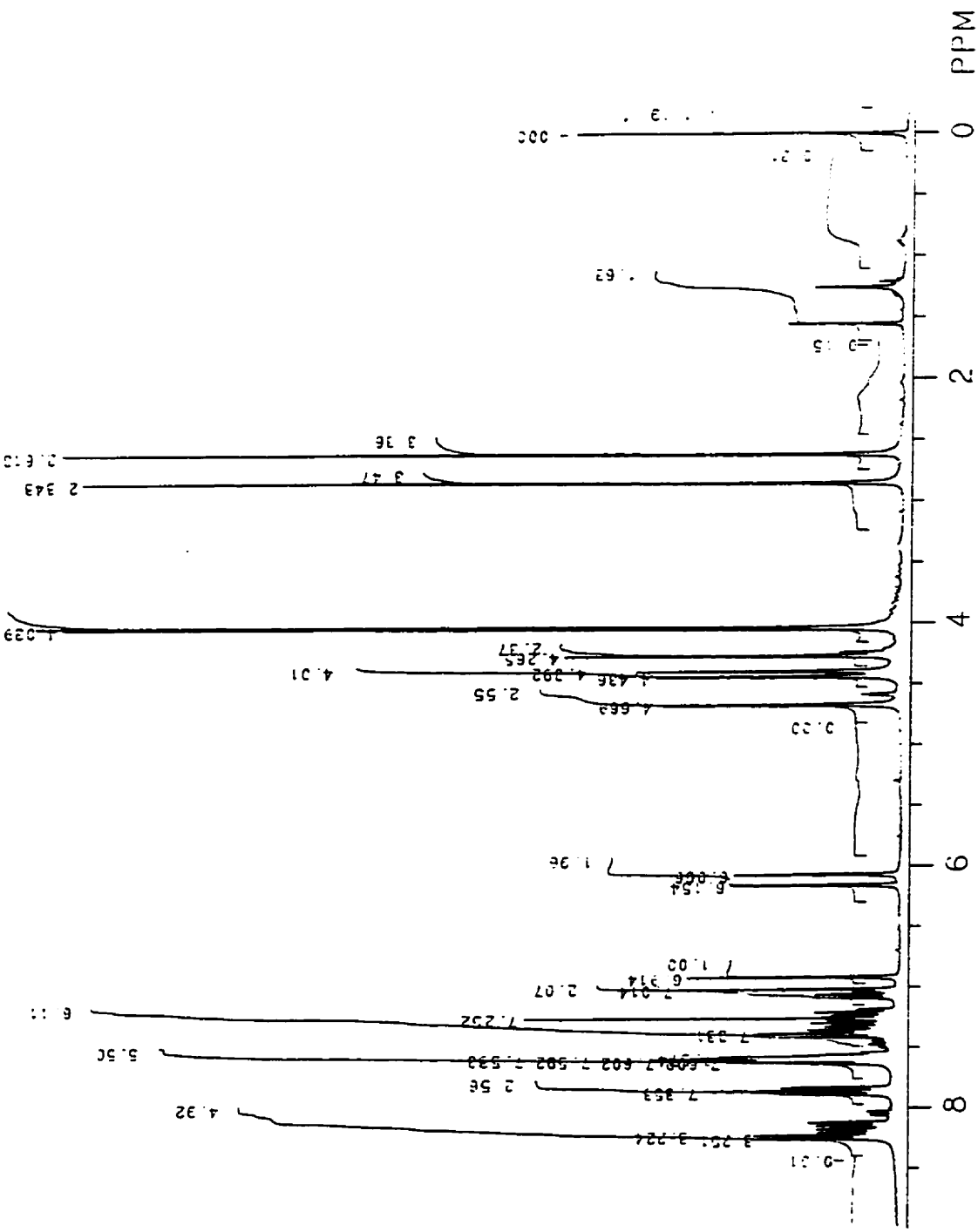
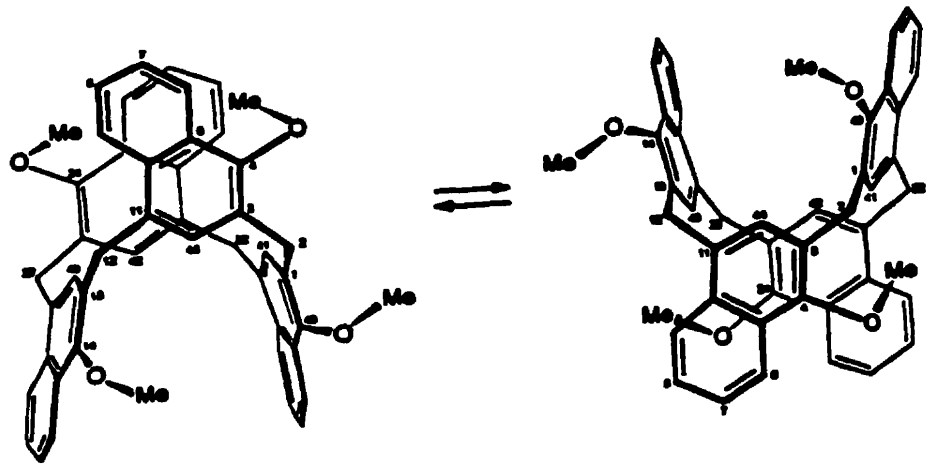


Fig.2.6. ^{1}H NMR Spectrum of Calix[4]naphthalene 26 in $CDCl_3$.

indicate that the molecule has C_s symmetric. The two possible C_s symmetric conformations are 1,2-alternate and "crown". The lower field shift of the two sets of methoxy groups suggests that the molecule possesses a crown-like conformation in solution.

The ^{1}H NMR spectrum of **26** (Figure 2.6) shows the intra-annular naphthalene protons as four, four-proton singlets of equal intensity at 6.10, 6.15, 6.91 and 7.01 ppm. The methylene protons appear as four singlets at 4.27, 4.39, 4.44 and 4.67 ppm with relative intensities in the ratio 1:1:1:1. The methoxy protons appear as four singlets of equal intensities in the ratio 1:1:1:1 at 2.61, 2.85, 4.03 and 4.04 ppm. An unusual feature of the ^{1}H NMR spectrum of **26** is that the chemical shifts of the two methoxy methyl groups at 2.61 and 2.85 ppm are situated at relatively high fields. These clearly indicate that these two methyl groups are shielded by the naphthalene rings. The two other methoxy methyl groups have more typical chemical shifts. There appears to be a dynamic equilibrium between two 1,3-alternate type of conformations (Figure 2.7). In these conformations, the methoxy methyl groups situated on C4 and C24 are shielded by the opposing naphthalene rings. The methoxy methyl groups at C14 and C40 are not similarly situated with respect to their opposing naphthalene rings and are therefore not shielded. Rapid interconversion must be occurring at ambient temperature since all four methylene protons appear as singlets and not as AB quartets.

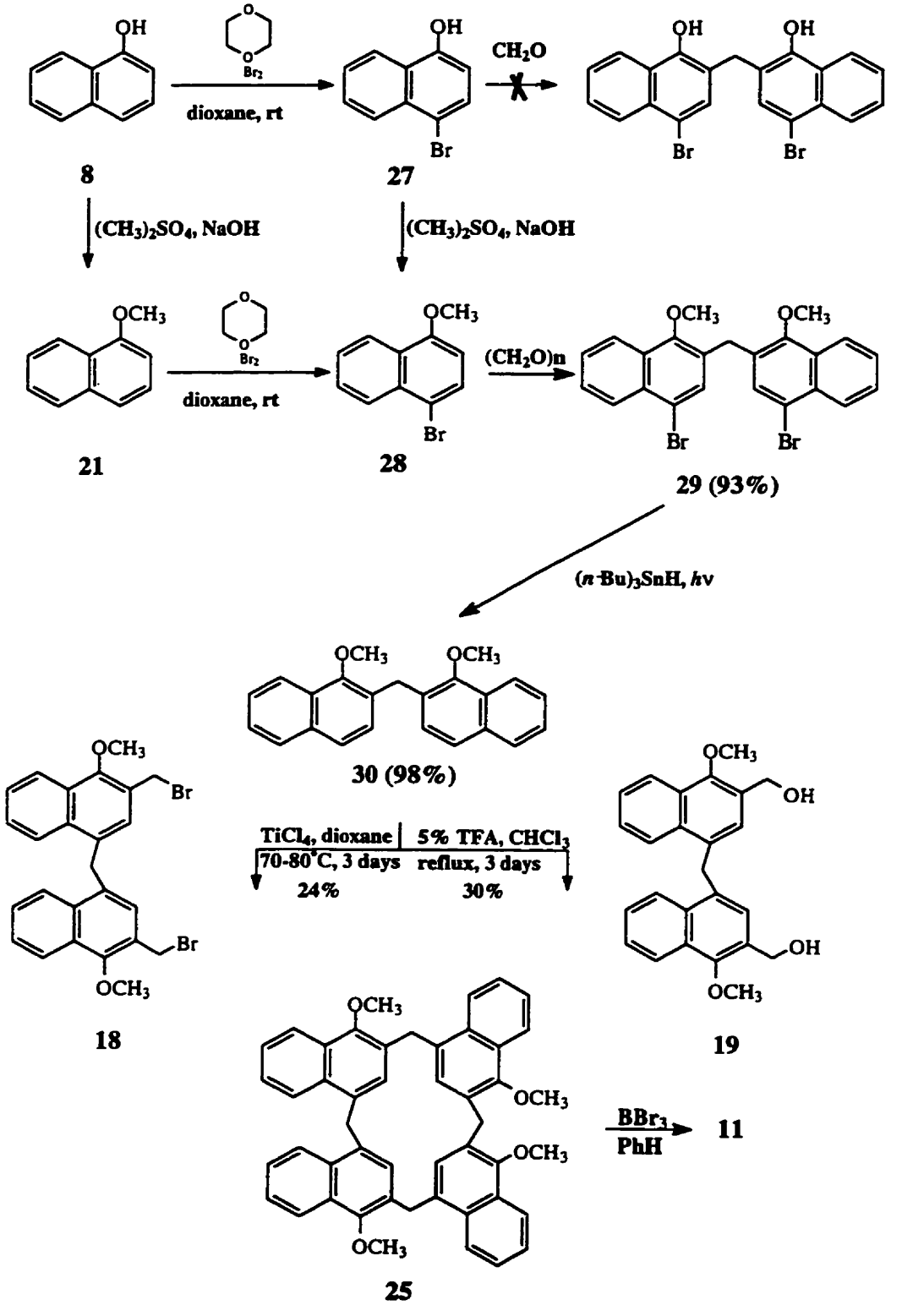
Figure 2.7. Dynamic equilibrium between 1,3-alternate conformations of calix[4]naphthalene, 26.



2.3.b. [2+2] Condensation

Since the yield of **25** by [3+1] condensation was low, [2+2] condensation was used as shown in Scheme 2.9. The *para* position of 1-naphthol was blocked using bromine to give 4-bromo-1-naphthol (**27**). Attempts at the direct condensation of **27** with formaldehyde were unsuccessful, but when **27** was first converted to its methoxy derivative **28**, the *ortho,ortho* methylene-coupled, bis-bromonaphthyl **29** was obtained in good yield. Removal of both bromine atoms with light-initiated reduction using tri-*n*-butyltinhydride[55] gave a quantitative yield of **30**, the dimethoxy derivative of **15**. Coupling of **30** with **18** using $TiCl_4$/dioxane conditions gave **25**, the C_{2v} symmetrical tetra-methoxycalix[4]naphthalene derivative of **11** in 11% yield. This compound could also be synthesized more conveniently in 30% yield by the TFA-catalyzed coupling of **30** with bis-hydroxymethyl compound **19**. Demethylation of **25** using BBr_3 produced the

Scheme 2.9

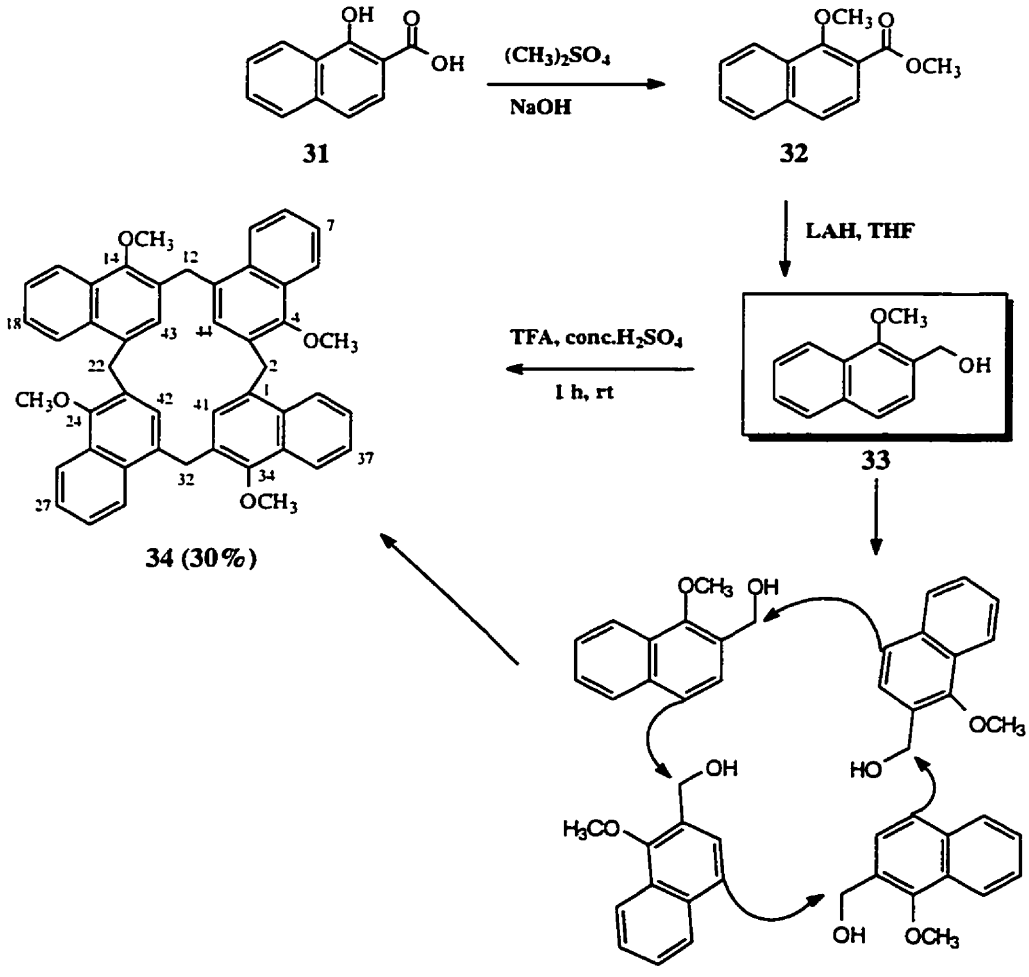

OH
Br2
dioxane, rt
CH2O
Br
8
27
(CH3)2SO4, NaOH
OCH3
21
28
(CH2O)n
29 (93%)
(n-Bu)3SnH, hv
30 (98%)
TiCl4, dioxane
70-80°C, 3 days
24%
5% TFA, CHCl3
reflux, 3 days
30%
18
19
25
BBr3
PhH
11

calix[4]naphthalene **11** in 89% yield.

2.4. Synthesis of C-11 tetramethoxycalix[4]naphthalene: self-condensation of 2-hydroxymethyl-1-methoxynaphthalene

Synthesis of **34** was achieved using the reaction depicted in Scheme 2.10.

Scheme 2.10



The starting material chosen for this sequence of reactions was 1-hydroxy-2-naphthoic acid (**31**), which was converted to 2-(hydroxymethyl)-1-methoxynaphthalene (**33**) via LAH reduction of methyl 1-methoxy-2-naphthoate (**32**). When **33** was treated with sulfuric acid as catalyst in TFA as solvent, tetramethoxycalix[4]naphthalene **34** was obtained in 30% yield.

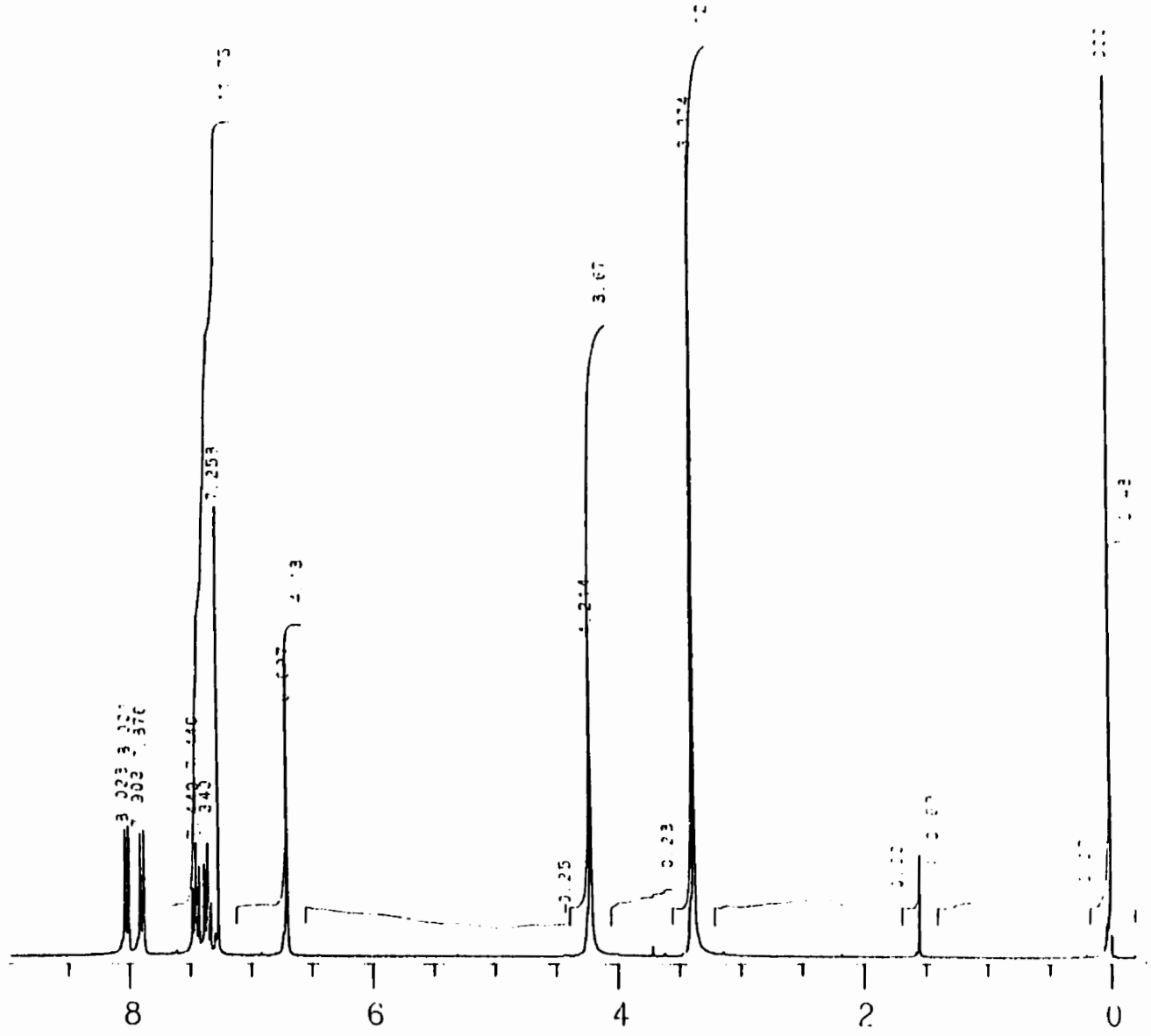
The ^{13}C NMR ($CDCl_3$) spectrum of **34** shows twelve signals consisting of five quaternary aromatic carbon signals, five methine aromatic carbon signals, a single aliphatic methylene carbon signal and a single methoxy carbon signal.

The ^1H NMR spectrum of **34** (Figure 2.8) includes a relatively high-field aromatic signal, which is a four-proton singlet at 6.69 ppm due to the four intra-annular naphthalene protons (H-41, H-42, H-43, H-44). The methylene protons (on C-2, C-12, C-22, C-32) appear as an eight-proton singlet at 4.21 ppm. The methoxyl protons appear as a singlet at 3.37 ppm. These data are consistent for structure **34**, which possesses C_4 symmetry.

2.5. Experimental

General Methods: All reactions were performed under N_2 or Ar. Organic solutions were concentrated on a rotary evaporator. All of the compounds were purified by either flash chromatography using Merck silica gel (230-400) mesh or preparative thin layer chromatography (PLC) plates, which were made from Aldrich silica gel (TLC standard grade, 2-25 μ) with 14% calcium sulphate. Thin-layer chromatography (TLC) was

Fig. 2.8. ^{1}H NMR Spectrum of Calix[4]naphthalene 34 in $CDCl_3$.



performed on precoated silica gel 60 F_{254} plates (Merck, Darmstadt, FRG).

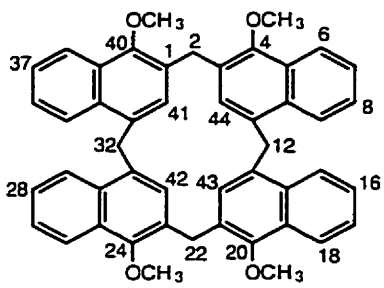
Materials: Chemical reagents and solvents were purchased from Aldrich or Fluka. Anhydrous CH_2Cl_2 and $CHCl_3$ were obtained by distillation of ACS grade dichloromethane and chloroform from calcium hydride. Anhydrous THF was obtained by drying ACS grade over Na and distilling it from purple sodium benzophenone under N_2. Dioxane was purified by first refluxing one litre of dioxane with 14 mL of concentrated HCl and 100 ml water for 6-12 h, followed by treating the cold solution with excess of solid KOH to remove the water. The decanted solvent was refluxed over an excess of sodium metal under N_2 to afford anhydrous dioxane.

Instrumentation: Melting points (m.p.) were determined on a Fisher-Johns apparatus and are uncorrected. Infrared (I.R.) spectra were recorded on a Mattson Polaris FT instrument. Low resolution and high resolution mass (HRMS) spectral data were obtained using a V.G. Micromass 7070HS instrument. MS data were presented as follows: *m/z*, intensity. Fast atom bombardment (FAB) MS were obtained with a Kratos MS5OTC spectrometer at the Department of Chemistry, U.N.B., Fredericton, N.B. using the following operating conditions: Vacc = 4,000 volts; FAB gun set at 7.0-7.5 Kv, using xenon as FAB gas; resolution = 1500; accelerating voltage = 6 Kv. ^{1}H NMR spectra were recorded on a GE GN-300NB spectrometer at 300.117 MHz, and chemical shifts are relative to internal TMS. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet), coupling constant (*J*, Hz), integration and assignment (H#). The assignments are based on ^{1}H-^{1}H

COSY, ^{13}C-^{1}H HETCOR and NOED experiments. ^{13}C NMR spectra were recorded at 75 MHz and were obtained from zero-filled 16K data tables to which a 1-2 Hz exponential line broadening function had been applied. Chemical shifts for ^{13}C NMR spectra are relative to the solvent (δ 77.0 ppm for $CDCl_3$; 53.8 ppm for CD_2Cl_2; 128 for C_6D_6). The assignments are based on CH HETCOR and APT. The conformation of products was determined from NOE data obtained from a set of interleaved ^{1}H experiments (16K) of 8 transients cycled 16 to 32 times through the list of irradiated frequencies. The decoupler was gated on continuous-wave mode for 4 seconds with sufficient attenuation to give a 70-90% reduction in intensity of the irradiated signal. Frequency changes were preceded by a 60 second delay. Four scans were used to equilibrate spins before data acquisition but a relaxation was not applied between scans of the same frequency. Proton nuclear Overhauser effect difference (NOED) spectra were obtained from zero-filled 32K data tables to which a 1-2 Hz exponential line-broadening function had been applied. A set of four dummy scans was employed to equilibrate the spins prior to data acquistion. No relaxation delay was applied between successive scans of a given frequency. Data collection for x-ray structure was made on a Rigaku AFC6S diffractometer at 298 K.

Calix[4]naphthalene (20). (a) $TiCl_4$-catalyzed conditions

To a solution of **17** (64 mg, 0.19 mmol) and **18** (100 mg, 0.19 mmol) in 5.0 mL of dioxane was added $TiCl_4$ (93 mg, 0.05 mL, 0.49 mmol) at rt. The temperature was raised to 70-80 °C, and the reaction mixture was maintained at this temperature with stirring for 72 h. The solvent was removed under vacuum. The residue was dissolved in 5 mL of



20

CH_2Cl_2 and 2 g of silica gel was added to the solution. After evaporation of the CH_2Cl_2 on a rotary evaporator, the crude product-silica gel mixture was extracted overnight with CH_2Cl_2 using a Soxhlet apparatus. The extract was concentrated to approximately 3 mL, and it was chromatographed by PLC using CH_2Cl_2-petroleum ether (80:20) to give 30 mg (23%) of the tetramethoxy compound **20**, m.p. >300 °C dec.; ^{1}H NMR ($CDCl_3$) δ = 3.39 (s, 12H, 4OCH_3), 4.24 (s, 4H, H-2, H-22), 4.59 (s, 4H, H-12, H-32), 6.43 (s, 4H, H-41, H-42, H-43, H-44), 7.37 (dt, J = 8.1, 0.6 Hz, 4H, H-8, H-16, H-28, H-36), 7.46 (dt, J = 8.1, 0.6 Hz, 4H, H-7, H-17, H-27, H-37), 7.85 (dd, J = 8.1, 0.6 Hz, 4H, H-9, H-15, H-29, H-35), 8.06 (dd, J = 8.1, 0.6 Hz, 4H, H-6, H-18, H-26, H-38); NOE (%): **OCH_3***/ H-2(H-22)(3), H-41 (H-42, H-43, H-44)(4), H-6(H-18, H-26, H-38)(9); **H-2 (22)**/ H-OCH_3 (2), H-41 (H-42, H-43, H-44)(6); **H-12 (H-32)**/ H-41 (H-42, H-43, H-44)(11), H-9 (H-15, H-29, H-35)(19); **H-41 (H-42, H-43, H-44)**/ H-2 (H-22)(2), H-12 (H-32)(3); **H-8 (H-16, H-**

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*The ^{1}H NMR signal of the protons indicated in **boldface** type was saturated.

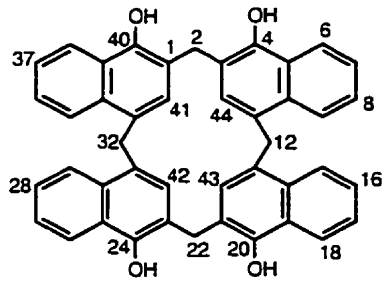
26, H-36)/ H-9 (H-15, H-29, H-35)(6); **H-7(H-17, H-27, H-37)**/ H-6(H-18, H-26, H-38) (7.86); **H-9 (H-15, H-29, H-35)**/ H-8 (H-16, H-28, H-36)(6.70), H-12 (H-32)(5.24); **H-6 (H-18, H-26, H-38)**/ H-7 (H-17, H-27, H-37)(7), OCH_3(1.33); ^{13}C NMR ($CDCl_3$) δ = 27.9 (C-2, C-22), 35.1 (C-12, C-32), 61.4 (C-OCH_3), 122.5 (C-6, C-18, C-26, C-38), 124.3 (C-9, C-15, C-29, C-35), 125.6 and 125.7 (C-8, C-16, C-28, C-36 and C-7, C-17, C-27, C-37), 127.8 (C-5, C-19, C-25, C-39 or C-10, C-14, C-30, C-34), 128.9 (C-41, C-42, C-43, C-44), 131.9 (C-1, C-3, C-21, C-23), 132.1 (C-11, C-13, C-31, C-33), 152.9 (C-4, C-20, C-24, C-40); MS *m/z* (%) 680 (M^+, 100), 665 (5), 650 (3), 619 (3), 649 (2), 340 (35), 326 (7), 171 (91), 141 (41); HRMS $M^+/2$ 340.1483, calcd for $C_{48}H_{40}O_4/2$ 340.1464.

Calix[4]naphthalene (20). (b) Trifluoroacetic acid (TFA)-catalyzed conditions

To a solution of **17** (85 mg, 0.26 mmol) and **19** (100 mg, 0.26 mmol) in 5.0 mL of $CHCl_3$ was added 5.0 mL of a solution of 10% TFA in $CHCl_3$. The mixture was stirred at rt for 48 h. Work-up was effected by evaporation of both the $CHCl_3$ and the TFA under vacuum. The residue was dissolved in 2 mL of $CHCl_3$ and chromatographed by PLC using CH_2Cl_2-petroleum ether (60:40) to afford 50 mg (28%) of **20** as a crystalline product, m.p. >300 °C, with spectroscopic properties are identical with those described above.

Demethylation of 20 to give 13

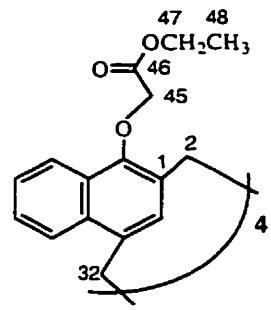
To a suspension of **20** (160 mg, 0.231 mmol) in anhydrous benzene (20 mL) was added BBr_3 (0.43 mL, 4.3 mmol) at rt. The reaction was left stirring at rt for 24 h. The



13

reaction was worked-up by adding 5 mL of H_2O followed by saturated aqueous $NaHCO_3$. The solution was extracted with 30 mL portions of diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was washed with diethyl ether to give **13** as a light brown solid (76 mg, 54%), m.p. >300 °C dec.; ^{1}H NMR (DMSO-d_6) δ = 4.01 (s, 4H, H-2, H-22), 4.51 (s, 4H, H-12, H-32), 6.64 (s, 4H, H-41, H-42, H-43, H-44), 7.43 (m, 8H, H-7, H-8, H-16, H-17, H-27, H-28, H-36, H-37), 7.91 (dd, J = 7.8, 1.5 Hz, 4H, H-9, H-15, H-29, H-35), 8.17 (dd, J = 7.8, 1.5 Hz, 4H, H-6, H-18, H-26, H-38); ^{13}C NMR (DMSO-d_6): δ = 29.9 (C-2, C-22), 33.2 (C-12, C-32), 120.9, 122.5 (C-6, C-18, C-26, C-38), 123.6 (C-9, C-15, C-29, C-35), 124.6 (C-8, C-16, C-28, C-36), 125.5 (C-7, C-17, C-27, C-37), 125.5, 127.7, 128.8 (C-41, C-42, C-43, C-44), 131.2, 147.8 (C-4, C-20, C-24, C-40); MS *m/z* (%) 624 (M^+, 100), 620 (10), 466 (1), 451 (3), 450 (1), 437 (2), 312 (23), 311 (24), 310 (36), 309 (18), 300 (15), 298 (22), 296 (30), 295 (48), 282 (27), 281 (54), 265 (19), 252 (20), 239 (12), 172 (30), 171 (16); HRMS M^+ 624.2303, calcd for $C_{44}H_{32}O_4$ 624.2301.

Tetraester Derivative of C-12 Calix[4]arene, (13a)

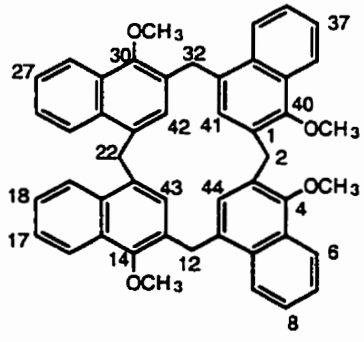


13a

To a solution of **13** (230 mg, 0.37 mmol) in anhydrous THF (15 mL) was added NaH (150 mg, 3.7 mmol) as one portion at rt. The reaction mixture was stirred at rt for 10 minutes, then an excess of ethyl bromoacetate (0.41 mL, 3.7 mmol) was added. The temperature was raised, and the mixture was refluxed for 4 h. The reaction mixture was cooled to rt then diluted with 50 mL of $CHCl_3$ followed by the addition of coled tap water. The organic layer was separated and dried over anhydrous $MgSO_4$. Evaporation the solvent gave a crude product, which was washed with methanol to yield **13a** as a colorless solid (0.12 g , 34%), m.p. 243-245 °C; I.R. ($CHCl_3$, cm^{-1}): 3069, 2981, 2935, 2908, 1756 (CO), 1599, 1524, 1443, 1386, 1208, 1105, 1052, 764; ^1H NMR ($CDCl_3$) δ = 1.39 (t, J = 7.1 Hz, 12H, CH_3), 3.94 (s, 8H, -CH_2CO), 4.31 (s, 4H, H-2, H-22), 4.33 (q, J = 7.1 Hz, 8H, OCH_2CH_3), 4.60 (s, 4H, H-12, H-32), 6.41 (s, 4H, H-41, H-42, H-43, H-44), 7.48 (m, 8H, H-7, H-8, H-16, H-17, H-27, H-28, H-36, H-37), 7.85 (d, J = 8.1 Hz, 4H, H-9, H-15, H-29, H-35), 8.10 (d, J = 8.1 Hz, 4H, H-6, H-18, H-26, H-38); NOE (%)

CH_2CO/ H-2 (H-22)(1), H-41 (H-42, H-43, H-44)(3); OCH_2CH_3/ OCH_2CH_3 (2), **CH_2CO** (1.4), H-41 (H-42, H-43, H-44)(4); **H-12 (H-32)/** H-41 (H-42, H-43, H-44)(7), H-9 (H-15, H-29, H-35)(15); **H-41 (H-42, H-43, H-44)/** H-12 (H-32)(2); **H-7 (H-8, H-16, H-17, H-27, H-28, H-36, H-37)/** H-9 (H-15, H-29, H-35)(4), H-6 (H-8, H-26, H-38)(7); **H-9 (H-15, H-29, H-35)/** H-7 (H-8, H-16, H-17, H-27, H-28, H-36, H-37)(3), H-12 (H-32)(4); **H-6 (H-8, H-26, H-38)/** H-7 (H-8, H-16, H-17, H-27, H-28, H-36, H-37)(3), CH_2CO (1.3); ^{13}C NMR ($CDCl_3$) δ = 124.2 (C-48, C-48', C-48", C-48"), 28.2 (C-2, C-22), 35.2 (C-12, C-32), 61.3 (C-47, C-47', C-47", C-47"), 70.3 (C-46, C-46', C-46", C-46"), 122.2 (C-6, C-18, C-26, C-38), 124.2 (C-9,C-15, C-29, C-35), 126.3 and 126.4 (C-7, C-8, C-16, C-17, C-27, C-28, C-36, C-37), 127.4, 127.7, 128.6 (C-41,C-42, C-43, C-44), 132.0, 132.6, 151.0 (C-4, C-20, C-24, C-40), 168.7 (C-46, C-46', C-46", C-46"); +FAB MS (matrix: 3-nitrobenzylalcohol): *m/z* (%) 991 (M^++Na^+, 4), 968 (M^+, 13), 902 (8), 880 (15), 879 (15), 791 (7), 617 (11), 601 (12), 242 (82).

Calix[4]naphthalene (25). (a) $TiCl_4$-catalyzed conditions



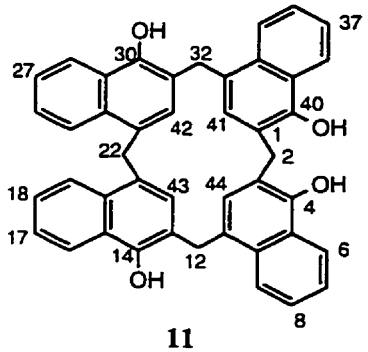
25

To a solution of **30** (64 mg, 0.19 mmol) and **18** (0.10 g, 0.19 mmol) in 5.0 mL of dioxane was added $TiCl_4$ (93 mg, 0.05 mL, 0.49 mmol) at rt. The reaction was conducted and worked up exactly as described above for **20**. The tetramethoxy **25**, m.p. >300°C dec. was obtained in 15 mg (11%) yield; ^1H NMR ($CDCl_3$) δ = 3.89 (s, 6H, $2OCH_3$ at C-4, C-40), 3.90 (s, 6H, $2OCH_3$ at C-14, C-30), 4.29 (s, 2H, H-2), 4.40 (s, 4H, H-12, H-32), 4.50 (s, 2H, H-22), 6.49 (s, 2H, H-42, H-43), 6.59 (s, 2H, H-41, H-44), 7.30 (m, 4H, H-8, H-18, H-26, H-36), 7.41 (m, 4H, H-7, H-17, H-27, H-37), 7.70 (dd, J = 8.1, 0.6 Hz, H-19, H-25), 7.78 (dd, J = 8.1, 0.6 Hz, H-9, H-35), 7.99 (dd, J = 8.1, 0.6 Hz, H-6, H-38), 8.04 (dd, J = 8.1, 0.6 Hz, H-16, H-28); NOE (%): **H-42 (H-43)/** H-22 (3), H-12 (H-32)(1.2); **H-41 (H-44)/** H-12 (H-32)(1.3); **H-2 (2.64); H-18 (26)/** H-19 (H-25)(5); **H-8 (H-36)/** H-9 (H-35)(5); **H-7 (370/** H-6 (H-38)(8); **H-17 (27)/** H-16 (H-28)(6); **H-19 (H-25)/** H-18 (H-26)(2), H-22 (5); **H-9 (H-35)/** H-8 (H-36)(5), H-12 (H-32)(3); **H-6 (H-38)/** H-7 (H-37)(4), OCH_3 (at C-4, C-40)(2); **H-16 (28)/** H-17 (H-27)(4), OCH_3 (at C-14, C-30)(2); ^{13}C NMR ($CDCl_3$) δ = 29.3 (C-2), 32.5 (C-12, C-32), 34.7 (C-22), 61.9 (OCH_3 at C-4 C-14, C-30, C-40), 122.3 (C-6, C-38 or C-16, C-28), 123.9 (C-19, C-25), 124.1 (C-9, C-35), 125.5 (C-18, C-26 or C-8, C-36), 125.6 (C-7, C-37 or C-17, C-27), 127.5, 127.8, 128.6 (C-41, C-44), 129.3 (C-42, C-43), 132.0, 152.2 (C-14, C-30), 152.6 (C-4, C-40); MS *m/z* (%) 680 (M^+, 25), 665 (0.5), 650 (0.6), 340 (10), 171 (14), 84 (100); HRMS $M^+/2$ 340.144, calcd, for $C_{48}H_{40}O_4/2$ 340.1464.

Calix[4]naphthalene (25). (b) TFA-catalyzed conditions

To a solution of **30** (85 mg, 0.26 mmol) and **19** (100 mg, 0.26 mmol) in 5.0 mL $CHCl_3$ was added 5.0 mL of a solution of 10% TFA in $CHCl_3$. The mixture was refluxed for 72 h. After cooling to rt, work-up was effected by evaporation both the $CHCl_3$ and TFA on a rotary evaporator. The residue was dissolved in 2 mL of $CHCl_3$ and chromatographed by PLC using CH_2Cl_2 to afford 51 mg (30%) of a solid product with m.p. and spectroscopic properties identical with those of **25** described above.

Demethylation of 25 to give 11

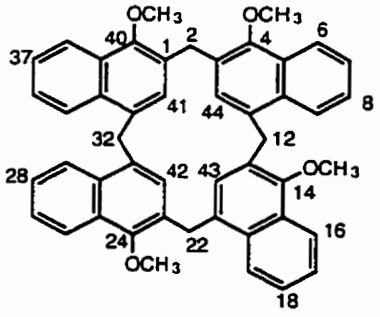


11

To a suspension of **25** (168 mg, 0.25 mmol) in anhydrous benzene (25 mL) was added BBr_3 (0.47 mL, 4.9 mmol) at rt. The reaction was left stirring at rt for 24 h. The reaction was worked-up by adding 5 mL of H_2O followed by saturated aqueous $NaHCO_3$. The solution was extracted with 30 mL portions of diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was washed with diethyl ether to give **11** as a light brown solid (137 mg, 89%), m.p. 260-265 °C dec.; I.R. (KBr, cm^{-1}): 3404 (br, OH), 1690, 1600, 1500, 1404; ^1H NMR (DMSO-

d_6) δ = 4.08 (s, 2H, H-22), 4.29 (s, 4H, H-12, H-32), 4.40 (s, 2H, H-2), 6.72 (s, 2H, H-41, H-44), 6.83 (s, 2H, H-42, H-43), 7.40 (m, 8H, H-7, H-8, H-17, H-18, H-26, H-27, H-36, H-37), 7.78 (d, 2H, H-7, H-35), 8.08 (m, 2H, H-19, H-25), 8.18 (m, 2H, H-16, H-28), 8.31 (d, J = 9.3 Hz 2H, H-6, H-38); ^{13}C NMR (DMSO-d_6) δ = 31.6 (C-12, C-32), 33.6 (C-22), 36.7 (C-2), 120.3 (C-1, C-3), 120.9 (C-13, C-31), 122.2 (C-16, C-28), 122.8 (C-6, C-38), 123.7 (C-5, C-37), 123.9 (C-19, C-25), 124.6, 124.8 (C-7, C-8, C-36, C-37), 125.3, 125.4 (C-17, C-18, C-26, C-27), 125.9 (C-15,C-29), 127.6 (C-5, C-39), 127.7 (C-20, C-24), 128.5 (C-41, C-44), 128.7 (C-10, C-34), 129.4 (C-42, C-43), 131.2 (C-21, C-23), 131.4 (C-11, C-33), 147.3 (C-14, C-30), 147.8 (C-4, C-40); MS *m/z* (%) 624 (M^+, 18), 606 (4), 480 (3), 468 (3), 313 (7), 312 (10), 311 (3), 282 (10), 281 (16), 144 (100).

Calix[4]naphthalenes (25) and (26)



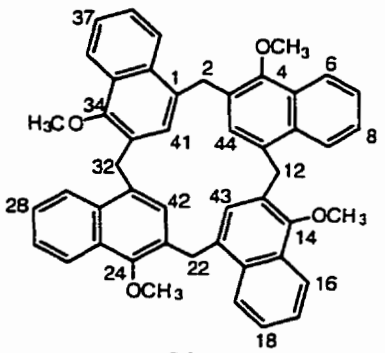
26

To a solution of **24** (203 mg, 0.40 mmol) and **23** (89 mg, 0.41 mmol) in 5.0 mL of $CHCl_3$ was added 5.0 mL of a solution of 10% TFA in $CHCl_3$. The mixture was stirred at rt for 48 h. Work-up was effected as was done for **25**. The residue was dissolved in

$CHCl_3$ and chromatographed by PLC using CH_2Cl_2-petroleum ether (80:20) to afford, in order of increasing polarity: **26** (16 mg) and **25** (5 mg). Calix[4]naphthalene **26** is a solid, m.p. >300 °C dec.; ^{1}H NMR ($CDCl_3$) δ = 2.61 (s, 3H, OCH_3 at C-24), 2.85 (s, 3H, OCH_3 at C-4), 4.03 (s, 3H, OCH_3 at C-14), 4.04 (s, 3H, OCH_3 at C-40), 4.27 (s, 2H, H-2), 4.44 (s, 2H, H-12), 4.67 (s, 2H, H-32), 6.07 (s, 1H, H-43), 6.15 (s, 1H, H-41), 6.91 (s, 1H, H-44), 7.01 (s, 1H, H-42), 7.06 (m, 1H), 7.21 (m, 1H), 7.30 (m, 1H), 7.50 (m, 1H), 7.60 (m, 5H), 7.85 (m, 1H), 7.87 (m, 1H), 8.13 (m, 1H), 8.19 (m, 1H), 8.23 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 27.9, 31.4, 33.0, 35.1, 61.4, 61.5, 122.3, 122.5, 122.6, 123.5, 123.6, 124.3, 125.2, 125.3, 125.4, 125.6, 125.7, 125.9, 126.0, 126.5, 126.8, 127.3, 127.7, 128.1, 128.4, 128.6, 130.9, 131.1, 131.5, 131.6, 131.8, 132.0, 132.5, 132.6, 132.6, 132.8, 152.4, 153.5; MS *m/z* (%): 681 (M^++1, 13), 680 (M^+, 25), 665 (1.5), 650 (1.6), 340 (8), 171 (10), 86 (62), 84 (100); HRMS M^+/2 340.1460, calcd for $C_{48}H_{40}O_4$/2 340.1464.

Calix[4]naphthalene (34)

To a solution of **33** (106 mg, 0.60 mmol) in 2.0 mL of TFA at rt, was added 4-6 drops of concentrated H_2SO_4. The mixture was stirred for 1 h and then worked-up by the addition of 15 mL of water and solid $NaHCO_3$ until the mixture became basic. The mixture was then extracted with three 30 mL of CH_2Cl_2. The organic layers were combined and worked-up in the usual manner to give a solid product which was washed several times with diethyl ether to give calix[4]naphthalene **34**, 30 mg (30%), m.p. 285-290 °C dec.; ^{1}H NMR ($CDCl_3$) δ = 3.37 (s, 12H, 4OCH_3), 4.21 (s, H-2, H-12, H-22, H-

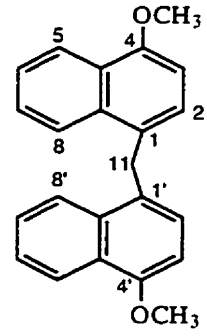


34

32), 6.70 (s, 4H, H-41, H-42, H-43, H-44), 7.35 (dt, J = 8.4, 0.6 Hz, 4H, H-8, H-18, H-28, H-38), 7.40 (dt, J = 8.4, 0.6 Hz, 4H, H-7, H-17, H-27, H-37), 7.89 (dd, J = 8.4, 0.6 Hz, 4H, H-9, H-19, H-29, H-39), 8.01 (dd, J = 8.4, 0.6 Hz, 4H, H-6, H-16, H-26, H-36); ^{13}C NMR ($CDCl_3$) δ = 32.1 (C-2, C-12, C-22, C-32), 61.8 (C-4, C-14, C-24, C-34), 122.5 (C-6, C-16, C-26, C-36), 124.3 (C-9, C-19, C-29, C-39), 125.8 (C-7, C-17, C-27, C-37 or C-8, C-18, C-28, C-38), 127.2, 128.2, 128.7 (C-41,C-42, C-43, C-44), 132.1, 132.5, 152.1 (C-4, C-14, C-24, C-34); NOE (%): **OCH_3/** H-2 (H-12, H-22, H-32)(1.2), H-41(H-42, H-43, H-44)(2), H-6 (H-16, H-26, H-36)(9); **H-2 (H-12, H-22, H-32)/** H-OCH_3 (2), H-41 (H-42, H-43, H-44)(14), H-9 (H-19, H-29, H-39)(18); **H-41 (H-42, H-43, H-44)/** H-OCH_3 (0.66), H-2 (H-12, H-22, H-32)(2); **H-8 (H-18, H-28, H-38)/** H-9 (H-19, H-29, H-39)(5); **H-7 (H-17, H-27, H-37)/** H-6, (H-16, H-26, H-36)(8); **H-9 (H-19, H-29, H-39)/** H-8 (H-18, H-28, H-38)(7), H-2 (H-12, H-22, H-32)(2), H-OCH_3 (0.35); **H-6 (H-16, H-26, H-36)/** H-7(H-17, H-27, H-37)(6), H-OCH_3 (1.4); MS *m/z* (%): 680 (M^+, 100), 185

(23), 171 (32), 141 (16), 128 (15); HRMS $M^+/2$ 340.1466, calcd for $C_{48}H_{40}O_4/2$ 340.1464.

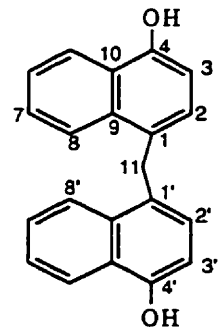
Bis(4-methoxy-1-naphthyl)methane (17)



17

To a solution of 1-methoxynaphthalene (12.0 g, 75.9 mmol) and paraformaldehyde (2.76 g, 92.0 mmol) in 80 mL of dioxane was added 15 mL of 30% H_2SO_4 dropwise at rt. The mixture was stirred at rt, for 48 h. The resulting white precipitate was filtered, washed with several portions of petroleum ether, and dried under vacuum to give 10.8 g (87%) of colorless solid **17**, m.p. 149-150 °C (lit. m.p. 150.5-152 °C)[53]; ^{1}H NMR ($CDCl_3$) δ = 3.97 (s, 6H, OCH_3), 4.71 (s, 2H, H-11), 6.67 (d, J = 7.8 Hz, 2H, H-3, H-3'), 6.97 (d, J = 7.8 Hz, 2H, H-2, H-2'), 7.49 (m, 4H, H-6, H-6', H-7, H-7'), 8.0 (m, 2H, H-5, H-5'), 8.34 (m, 2H, H-8, H-8'); ^{13}C NMR ($CDCl_3$) δ = 34.8 (C-11), 55.4 (C-12), 103.4 (C-3, C-3'), 122.5 (C-5, C-5'),123.8 (C-8, C-8'), 124.9 (C-6, C-6' or C-7, C-7'), 125.8 (C-9, 9-6' or C-10, C-10'), 126.5 (C-7, C-7' or C-6, C-6'), 126.8 (C-2, C-2'), 128.2 (C-1, C-1' or C-9, C-9'), 133.0 (C-9, C-9' or C-1, C-1'), 154.3 (C-4, C-4').

Bis(4-hydroxy-1-naphthyl)methane (14)

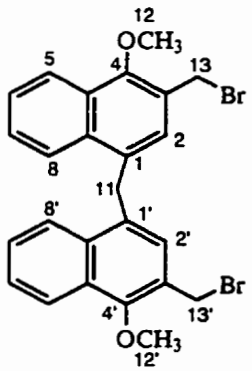


14

To a solution of **17** (106 mg, 0.310 mmol) in 4.0 mL of CH_2Cl_2 at -78 °C was added 0.16 mL (1.75 mmol) of BBr_3 dropwise, with stirring. After 2 h the temperature was raised to -25 °C, and the reaction was maintained at this temperature for 2 h. The temperature was raised and then maintained at rt for another 2h. The reaction was quenched by the addition of aqueous saturated $NaHCO_3$ until the solution became basic. The mixture was extracted with 25 mL of CH_2Cl_2, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The crude product was chromatographed by PLC using ethyl acetate-petroleum ether (30:70) to give **14** (40 mg, 43%), which crystallized from ethanol-water as a colorless solid m.p. 216-218 °C; ^{1}H NMR (acetone-d_6) δ = 4.68 (s, 2H, H-11), 6.75 (d, J = 7.7 Hz, 2H, H-3, H-3'), 6.88 (d, J = 7.7 Hz, 2H, H-2, H-2'), 7.40 (m, 4H, H-6, H-6', H-7, H-7'), 7.95 (m, 2H, H-5, H-5'), 8.33 (m, 2H, H-8, H-8'), 8.36 (s, 2H, OH); ^{13}C NMR (acetone-d_6) δ = 35.2 (C-11), 108.4, 108.5 (C-3), 123.7 (C-5, C-5'), 124.8 (C-8, C-8'), 125.2, and 127.1 (C-6, C-6', C-7, C-7'

), 128.0 (C-4, C-4'); MS *m/z* (%): 300 (M^+, 100), 157 (68), 144 (46); HRMS M^+ 300.1153, calcd for $C_{21}H_{16}O_2$ 300.1149.

Bis[3-(bromomethyl)-4-methoxy-1-naphthyl]methane (18)

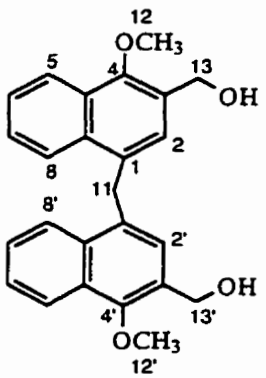


18

To a solution of **17** (500 mg, 1.52 mmol) and paraformaldehyde (220 mg, 7.33 mmol) in 10 mL of glacial acetic acid was added 10 mL of a 15% solution of HBr in glacial acetic acid. The mixture was stirred at rt for 24 h. A colorless precipitate formed which was filtered, washed several times with petroleum ether, and dried under vacuum. The yield of crystalline **18** obtained was 300 mg (38%), m.p.138-140 °C; ^{1}H NMR ($CDCl_3$) δ = 4.09 (s, 6H, OCH_3), 4.65 (s, 4H, H-13, H-13'), 4.75 (s, 2H, H-11), 7.06 (s, 2H, H-2, H-2'), 7.54 (m, 4H, H-6, H-6', H-7, H-7'), 7.98 (dd, J = 7.5, 1.4 Hz, 2H, H-5, H-5'), 8.20 (dd, J = 7.5, 1.4 Hz, 2H, H-8, H-8'); ^{13}C NMR ($CDCl_3$) δ = 28.4 (C-13, C-13'), 35.1 (C-11), 62.6 (C-12, C-12'), 123.2 (C-5, C-5'), 124.4 (C-8, C-8') , 125.9 (C-1, C-1' or C-3, C-3'), 126.2 (C-6, C-6' or C-7, C-7'), 127.0 (C-7, C-7' or C-6, C-6'), 128.1 (C-3, C-3'

or C-1, C-1'), 128.9 (C-2, C-2'), 132.5 (C-10, C-10' or C-9, C-9'), 133.5 (C-9, C-9' or C-10, C-10'), 153.4 (C-4, C-4'); MS *m/z* (%): 514 (M^+, 19), 433 (81), 183 (100), HRMS M^+ 511.9967, calcd for $C_{25}H_{22}Br_2O_2$ 511.9986.

Bis(3-hydroxymethyl-4-methoxy-1-naphthyl)methane (19)

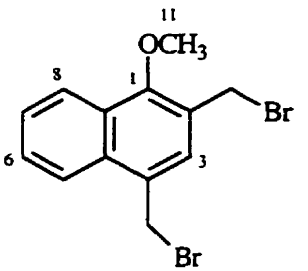


19

A solution of **18** (450 mg, 1.16 mmol) and $CaCO_3$ (878 mg, 8.77 mmol) in 14 mL of aqueous dioxane (1:1) was refluxed for 6 h. The solution was cooled to rt and aqueous 5% HCl was added until the mixture became acidic. The ensuing precipitate was filtered and washed with water. The product crystallized from ethanol-water to give 250 mg (56%) of **19**, m.p. 180-182 °C; ^{1}H NMR (acetone-d_6) δ = 3.95 (s, 6H, OCH_3), 4.10 (t, J = 5.7 Hz, 2H, OH), 4.75 (d, J = 5.7 Hz, 4H, H-13,H-13'), 4.84 (s, 2H, H-11), 7.33 (s, 2H, H-2, H-2'), 7.53 (m, 4H, H-6, H-6', H-7, H-7'), 8.10 (dd, J = 8.7, 1.2 Hz, 2H, H-5, H-5'), 8.18 (dd, J = 8.7, 1.2 Hz, 2H, H-8, H-8'); ^{13}C NMR (acetone-d_6) δ = 35.7 (C-11), 59.4 (C-13, C-13'), 62.9 (C-12, C-12'), 123.5 (C-5, C-5'), 125.3 (C-8, C-8'), 126.5 (C-6, C-6' or

C-7, C-7'), 126.9 (C-7, C-7' or C-6, C-6'), 128.8 (C-2, C-6'), 129.1 (C-3, C-3' or C-1, C-1') , 130.7(C-1, C-1' or C-3, C-3'), 133.2 (C-10, C-10' or C-9, C-9'), 133.8 (C-9, C-9' or C-10, C-10'), 152.9 (C-4, C-4'); MS *m/z* (%): 388 (M^+, 100), 201 (30), 157 (12), 115 (9); HRMS M^+ 388.1649, calcd for $C_{25}H_{24}O_2$ 388.1675.

2,4-Bis(bromomethyl)-1-methoxynaphthalene (22)

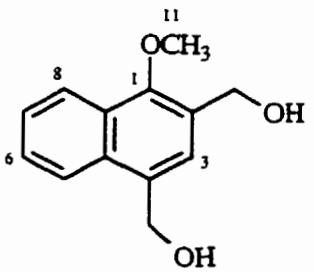


22

To a stirred solution of 1-methoxynaphthalene (1.0 g, 6.3 mmol) in glacial acetic acid (10 mL) was added a 15% solution of HBr in acetic acid (10 mL), dropwise at rt. After stirring for 3 days, the reaction mixture, which had formed a precipitate, was filtered. The solid was washed with petroleum ether to remove any acetic acid and then dried under vacuum to give **18** (102 mg), which was identical to that synthesized above. The filtrate was diluted with water and extracted with two 25 mL of CH_2Cl_2. The organic layer was washed several times with water and saturated aqueous $NaHCO_3$ until the washings were neutral. The crude product was chromatographed on a silica gel column using CH_2Cl_2-petroleum ether (40:60) to give **22** (450 mg, 21%) as a crystalline solid, m.p. 112-114 °C; ^1H NMR ($CDCl_3$) δ = 4.07 (s, 3H, OCH_3), 4.73 (s, 2H, H-12), 4.90 (s, 2H, H-13), 7.53 (s, 1H, H-3), 7.6 (m, 2H, H-6, H-7), 8.11 (m, 1H, H-5), 8.16 (m, 1H, H-

8); ^{13}C NMR ($CDCl_3$) δ = 27.7 (C-12), 31.2 (C-13), 62.7 (C-11), 123.3 (C-8), 124.3 (C-5), 125.9 (C-2 or C-4), 126.7 (C-6 or C-7), 127.4 (C-7 or C-6), 128.5 (C-4 or C-2), 129.8 (C-3), 130.1 (C-10 or C-9), 132.5 (C-9 or C-10), 155.4 (C-1); MS *m/z* (%): 346 (M^+, ^{81}Br, ^{81}Br, 6) 344 (M^+, ^{81}Br, ^{79}Br, 12), 342 (M^+, ^{79}Br, ^{79}Br, 6), 265 (100), 263 (100), 185 (27), 183 (75), 170 (12), 169 (19), 154 (29), 153 (25); HRMS M^+ 341.9244, calcd for $C_{13}H_{12}Br_2O_2$ 341.9255.

2,4-Bis(hydroxymethyl)-1-methoxynaphthalene (23)

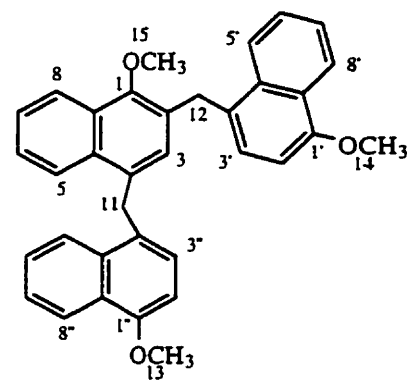


23

To a solution of **22** (380 mg, 1.11 mmol) in aqueous 50% dioxane was added $CaCO_3$ (1.11 g, 11.1 mmol) with stirring and the mixture was refluxed for 3 h. After cooling to rt, the mixture was acidified with aqueous 5% HCl. The mixture was extracted with 25 mL of CH_2Cl_2, and the combined organic extracts were worked-up in the usual manner to give a colorless solid (150 mg, 0.69 mmol). Crystalization from chloroform gave **23** as crystals having m.p. 121-123 °C; ^1H NMR ($CDCl_3$) δ = 3.96 (s, 3H, OCH_3), 4.88 (s, 2H), 5.08 (s, 2H), 7.53 (m, 2H, H-6, H-7), 7.53 (s, 1H, H-3),, 8.10 (m, 1H, H-5), 8.15 (m, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ = 60.7 (C-12), 62.7 (C-11), 63.4 (C-13), 122.8

(C-8), 124.1 (C-5), 126.1 (C-3), 126.4, 126.6, 128.3, 128.4, , 132.5, 132.9, 154.0 (C-1); MS *m/z* (%): 218 (M^+, 100), 201 (14), 187 (14), 171 (26), 159 (11), 157 (21), 145 (13), 144 (13); HRMS M^+ 218.0953, calcd for $C_{13}H_{14}O_3$ 218.0942.

2,4-Bis[(4-methoxy-1-naphthyl)methyl]-1-methoxynaphthalene (24)

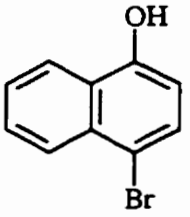


24

To a solution of 1-methoxynaphthalene (210 mg, 1.33 mmol) and paraformaldehyde (184 mg, 6.0 mmol) in 3 mL of dioxane at rt was added aqueous 30% H_2SO_4. The mixture was refluxed for 6 h. After cooling to rt, the reaction mixture was diluted with water and extracted with 15 mL of $CHCl_3$. The combined organic extracts were washed with aqueous saturated $NaHCO_3$ and then with aqueous saturated NaCl. The crude residue thus obtained was chromatographed by PLC using CH_2Cl_2-petroleum ether (30:70) as solvent. Two fractions were isolated to give dimer **17** (62 mg, 28%) and trimer **24** (54 mg, 24%). The trimer **24** was a colorless solid having m.p. 165-167 °C; ^1H NMR ($CDCl_3$) δ = 3.37 (s, 3H, H-13), 3.45 (s, 3H, H-14), 3.68 (s, 3H, H-15), 4.28 (s, 2H, H-11), 4.46 (s, 2H, H-12), 6.18 (d, J = 7.8 Hz, 1H, H-2"), 6.34 (d, J = 8.1 Hz, 1H, H-2'),

6.80 (d, J = 7.8 Hz, H-3"), 7.01 (s, 1H, H-3), 7.01 (d, J = 7.8 Hz, 1H, H-3'), 7.20 (m, 1H), 7.25 (m, 1H), 7.26 (m,1H), 7.27 (m, 1H), 7.36 (m, 1H), 7.40 (m, 1H), 7.71 (d, J = 8.4 Hz, 1H, H-5), 7.89 (dd, J = 8.1, 0.9 Hz, 1H, H-5"), 8.06 (dd, J = 7.5, 0.9 Hz, 1H, H-5'), 8.38 (dd, J = 8.4, 0.9 Hz, 1H, H-8), 8.54 (dd, J = 7.5, 0.9 Hz, H-8'), 8.57 (dd, J = 8.1, 0.9 Hz, 1H, H-8"); ^{13}C NMR (benzene-d_6) δ = 32.4 (C-12), 35.3 (C-11), 54.8 and 54.9 (C-13 and C-14), 61.8 (C-15), 103.4 (C-2'), 103.6 (C-2"), 122.9 (C-8', C-8"), 123.2 (C-8), 124.1 (C-5), 124.4 (C-5'), 125.0 (C-5"), 125.2 (C-7), 126.0 (C-7"), 126.4, 126.6 (C-6'), 126.8 (C-6"), 126.9 (C-6), 127.0 (C-3"), 128.9, 129.1, 130.3, 132.7, 133.2, 133.4, 133.5, 152.8, 152.8, 154.8; MS *m/z* (%): 498 (M^+, 100), 483 (2), 467 (4), 327 (11), 249 (13), 171 (58), 158 (13), 128 (12); HRMS M^+ 498.2193, calcd for $C_{35}H_{30}O_3$ 498.2180.

4-Bromo-1-naphthol (27)



27

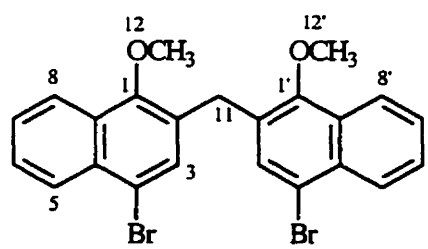
To a solution of 1-naphthol (13.2 g, 0.090 mol) in dioxane (40 mL) was added dropwise, with stirring a solution of dioxane-dibromide (23 g, 0.91 mol) in dioxane (160 mL). After the addition was complete, the reaction mixture was poured into ice-water (200 mL). The reaction mixture was then extracted with three 50 mL of CH_2Cl_2, and the combined organic layers were washed with aqueous saturated NaCl. After drying over

anhydrous $MgSO_4$ and filtering, the CH_2Cl_2 was removed using a rotary evaporator. The product was recrystallized from $CHCl_3$ to give light grey needles, m.p. 129 °C (lit. m.p. 129 °C).[46]

4-Bromo-1-methoxynaphthalene (28)

To an ice-cooled solution of **27** (12 g, 0.05 mol) in aqueous 7% NaOH was added dimethylsulphate (0.7 mL, 8 mmol) dropwise with stirring. The reaction mixture was heated to 80 °C and maintained at this temperature for 2 h. After cooling, the reaction mixture was diluted with $CHCl_3$, and the organic solution washed with aqueous 10% NaOH followed by water until washings were neutral. After drying and work-up, the product was vacuum distilled to give **28** as a golden-yellow oil (10.22 g, 80%), whose spectral characteristics were consistent with **28**.[56] An alternative, more convenient synthesis of **28** was effected by direct bromination of 1-methoxynaphthalene **21** using dioxane-dibromide in the same way as described for **27** above.

Bis(4-bromo-1-methoxy-2-naphthyl)methane (29)

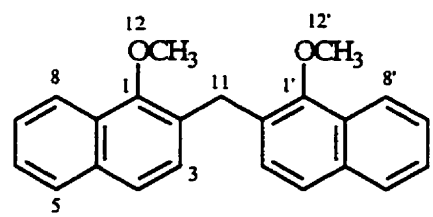


29

To a solution of **28** (0.245 g, 1.03 mmol) and paraformaldehyde (0.13 g, 4.3

mmol) in dioxane (1.6 mL) under N_2 was added $BF_3.Et_2O$ (0.24 mL). The reaction mixture was heated at 80-90 °C for 7-8 h and after cooling to room temperature was extracted with 40-mL portions of CH_2Cl_2. The combined organic layers were washed with aqueous 5% $NaHCO_3$, water, then dried over anhydrous $MgSO_4$. The crude product was chromatographed by PLC using ethyl acetate-hexane (10:90) to give **29** as crystals (0.231 g, 93%) with m.p. 145-146 °C; ^{1}H NMR ($CDCl_3$) δ = 3.94 (s, 6H, OCH_3), 4.35 (s, 2H, H-11), 7.53 (s, 2H, H-3, H-3), 7.57 (m, 4H, H-6, H-7, H-6', H-7'), 8.14 (m, 2H, H-5, H-5'), 8.18 (m, 2H, H-8, H-8'); ^{13}C NMR ($CDCl_3$) δ = 28.8 (C-11), 62.2 (C-12, C-12'), 117.9, 122.5 (C-8, C-8'), 126.9 and 127.1 (C-6 and C-7), 127.5 (C-5), 129.2, 129.4, 131.8 (C-3, C-3'), 132.2, 153.5 (C-1, C-1'); MS *m/z* (%) 488 (M^+, ^{81}Br, ^{81}Br, 50), 486 (M^+, ^{81}Br, ^{79}Br, 100), 484 (M^+, ^{79}Br, ^{79}Br, 49), 439 (11), 361 (19), 359 (19), 296 (13), 280 (13), 268 (10), 252 (10), 250 (12), 239 (26), 237 (21), 235 (20), 221 (14), 219 (15), 187 (16), 171 (50); HRMS M^+ 483.9668, calcd for $C_{23}H_{18}Br_2O_2$ 483.9674.

Bis(1-methoxy-2-naphthyl)methane (30)

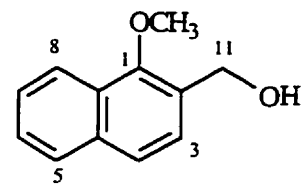


30

A solution of **29** (300 mg, 0.62 mmol) and (n-$C_4H_9)_3SnH$ (0.36 mL) in cyclohexane (6.2 mL) was placed in a quartz tube. The tube was fitted to a condenser,

and the solution was stirred and maintained under an argon atmosphere while being irradiated with 254 nm lamps in a Rayonet photochemical reactor. After 4 h the reaction was terminated by the addition of excess aqueous KF. The resulting white precipitate was filtered off, and the mother liquor was extracted with diethyl ether. The crude product was chromatographed by flash chromatography using ethyl acetate-petroleum ether (10:90) as solvent. The product **30** was obtained (200 mg, 98%) as a colorless solid, m.p. 109-112 °C; ^{1}H NMR ($CDCl_3$) δ = 3.97 (s, 6H, OCH_3), 4.43 (s, 2H, H-11), 7.21 (d, J = 8.7 Hz, 2H, H-4, H-4'), 7.48 (m, 4H, H-6, H-7, H-6', H-7'), 7.50 (d, J = 8.7 Hz, 2H, H-3, H-3'), 7.80 (d, J = 8.1 Hz, 2H, H-5, H-5'), 8.14 (d, J = 8.1 Hz, 2H, H-8, H-8'); ^{13}C NMR ($CDCl_3$) δ = 29.1 (C-11), 61.9 (C-12, C-12'), 118.2, 122.0, 124.1, 125.6, 125.9, 128.0, 128.5, 129.0, 133.9; MS *m/z* (%): 328 (M^+, 100), 297 (26), 282 (11), 281 (35), 265 (10), 252 (12), 157 (32), 149 (12); HRMS M^+ 328.1464, calcd for $C_{23}H_{20}O_2$ 328.1462. An alternative, more convenient synthesis of **30** was affected by adding a THF solution of **29** (127 mg in 2.5 ml anhydrous THF) to a suspention of LAH (40 mg) in 2.5 mL anhydrous THF at rt. The temperature was raised and the mixture was refluxed for 4-6 h. The reaction mixture was worked-up in the usual manner. The crude product was purified by PLC using ethyl acetate-petroleum ether (10:90) to give **30** (65 mg, 76%) as a colorless solid with spectroscopic properties were as above.

2-Hydroxymethyl-1-methoxynaphthalene (33)



33

A solution of methyl 1-methoxy-2-naphthoate (1.0 g, 4.6 mmol) in anhydrous THF (5 mL), was added at rt to a suspension of LAH (0.17 g, 4.6 mmol) in anhydrous THF (10 mL) over 10 minutes. The temperature was raised, and the mixture was refluxed for 6 h. The reaction mixture was cooled to rt and then quenched with aqueous 5% HCl. The mixture was extracted with two 25 mL portions of CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by column using ethyl acetate-petroleum ether (30:70) to give **33** as a light brown solid (0.72 g, 83%), m.p. 68-69 °C; ^{1}H NMR ($CDCl_3$) δ = 3.97 (s, 3H, OCH_3), 4.89 (s, 2H, H-11), 7.50 (m, 3H, H-4, H-6, H-7), 7.62 (d, J = 8.4 Hz, 1H, H-3), 7.83 (d, J = 6.9 Hz, 1H, H-5), 8.10 (d, J = 6.8 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ = 60.8 (C-11), 62.6 (C-12), 122.0 (C-8), 124.4 (C-3), 126.1 (C-4), 126.1 and 126.6 (C-6 and C-7), 128.0 (C-5), 128.9, 133.7, 138.3, 148.0 (C-1); MS *m/z* (%): 189 (M^++1, 13), 188 (M^+, 100), 173 (71), 172 (8), 171 (14), 159 (10), 157 (12) 156 (26), 155 (23), 145 (19), 144 (11), 129 (18), 128 (39), 127 (54), 117 (13), 115 (31); HRMS M^+ 188.0831, calcd for $C_{12}H_{12}O_2$ 188.0837.

Chapter 3

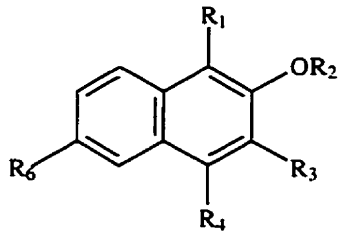
Regioselectivity in the Friedel-Crafts *tert*-Butylation of 1-Naphthol

3.1. Introduction.

It was mentioned previously that the *tert*-butyl group had been considered as a suitable blocking group to produce the putative dimers **14**, **15** and **16**. However, as we later discovered, Friedel-Crafts *tert*-butylation of 1-naphthol was not a trivial matter. On the other hand, the Friedel-Crafts *tert*-butylation of 2-naphthol has been extensively studied. In 1950, Buu-Hoi[57] showed that 2-naphthol reacts with *tert*-butyl chloride and $AlCl_3$ to give a mono-*tert*-butyl derivative having m.p.120 °C, and a di-*tert*-butyl derivative having m.p. 139 °C. He proved that the mono-alkyl derivative was 6-*tert*-butyl-2-naphthol (**35**) and that the di-*tert*-butyl derivative was derived from the mono derivative by further alkylation (Figure 3.1). The dialkyl derivative contained a hydroxyl group which was sterically hindered, and, as a result, the compound was insoluble in aqueous sodium hydroxide.

Arguing by analogy with the alkylation of 2-naphthol with smaller alkyl groups, Buu-Hoi assigned the structure **36** to the di-*tert*-butylated-2-naphthol product . This structural assignment was supported by the failure of the compound to couple with diazonium salts, but later proved to be incorrect. Brady *et al.*[58] found that the autoxidation of the di-*tert*-butylnaphthol was very slow. This would not expected for a such a hindered 1-alkyl-2-naphthol.[59] One of the products from this autoxidation was a red solid to which

Figure 3.1.

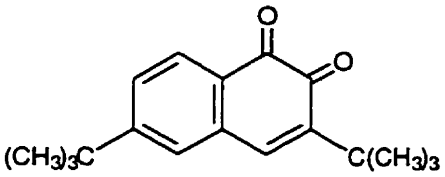


35. $R_1 = R_2 = R_3 = R_4 = H$; $R_6 = tert\text{-Bu}$
36. $R_2 = R_3 = R_4 = H$; $R_1 = R_6 = tert\text{-Bu}$
37. $R_1 = R_2 = R_4 = H$; $R_3 = R_6 = tert\text{-Bu}$
39. $R_3 = R_4 = R_6 = H$; $R_1 = tert\text{-Bu}$; $R_2 = CH_3$
40. $R_1 = Br$; $R_4 = tert\text{-Bu}$; $R_3 = R_6 = H$; $R_2 = CH_3$
41. $R_1 = R_3 = R_4 = H$; $R_6 = tert\text{-Bu}$; $R_2 = CH_3$
42. $R_1 = R_4 = H$; $R_3 = R_6 = tert\text{-Bu}$; $R_2 = CH_3$
43. $R_1 = Br$; $R_3 = R_4 = H$; $R_6 = tert\text{-Bu}$; $R_2 = CH_3$

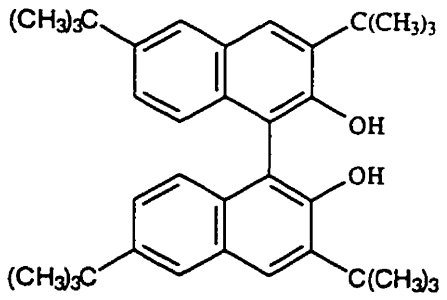
they assigned the structure 3,6-di-*tert*-butyl-1,2-naphthaquinone (**38**) on the basis of U.V. and ^1H NMR spectroscopic analysis. Also, oxidation of the di-*tert*-butyl-2-naphthol with ferricyanide gave a dimer to which they assigned the structure **38a** (Figure 3.2). On the basis of these data they therefore assigned the structure 3,6-di-*tert*-butyl-2-naphthol (**37**) for the di-*tert*-butyl product.

Brady *et al.* also re-investigated the *tert*-butylation of 2-methoxynaphthalene, and 1-bromo-2-methoxynaphthalene, with *tert*-butyl chloride and $AlCl_3$. In contrast to Ferris and Hamer's [60] claim that the first substance gave 1-*tert*-butyl-2-methoxynaphthalene (**39**) and the second gave 4-*tert*-butyl-1-bromo-2-methoxynaphthalene (**40**), Brady *et al.* found that the first substrate gave a mixture of 6-*tert*-butyl-1-methoxynaphthalene (**41**) and 3,6-di-*tert*-

Figure 3.2.



38



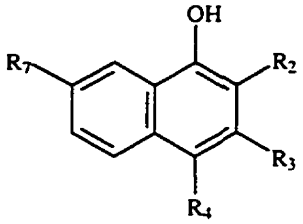
38a

butyl-2-methoxynaphthalene (**42**) and the second gave 6-*tert*-butyl-1-bromo-2-methoxy-naphthalene (**43**). Based on their results, Brady *et al.* concluded that in the Friedel-Crafts alkylation of 2-naphthol with small alkyl groups, electronic factors are more important than steric ones, but that in *tert*-butylation the reverse is true. On electronic grounds the order of reactivity of the position in 2-naphthol is 1> 6> 3> 8, but on steric grounds the order is 6> 3> 8>1.

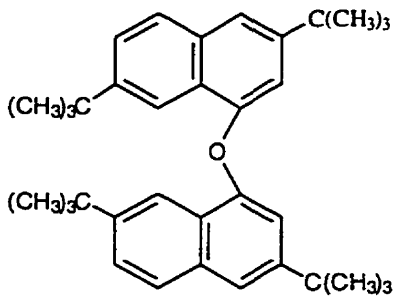
3.2. *tert*-Butylation of 1-Naphthol.

The *tert*-butylation of 1-naphthol has not been as extensively studied. In 1976, Miyata and Hirashima[51] reported that the $ZnCl_2$-catalyzed reaction of 1-naphthol with *tert*-butyl chloride afforded a 42% yield of 4-*tert*-butyl-1-naphthol (**44**). The same authors later also reported[52] that the H_2SO_4-catalyzed reaction of 1-naphthol and *tert*-butyl alcohol afforded an unspecified amount of 2,4-di-*tert*-butyl-1-naphthol (**45**) and 19.5% of 2-*tert*-butyl-1-naphthol (**46**).

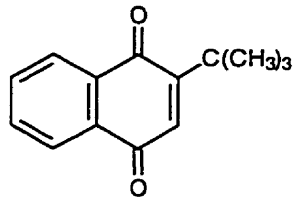
Figure 3.3.



44. $R_2 = R_3 = R_7 = H$; R_4 = *tert*-Bu
45. $R_3 = R_7 = H$; $R_2 = R_4$ = *tert*-Bu
46. $R_3 = R_4 = R_7 = H$; R_2 = *tert*-Bu
47. $R_2 = R_4 = R_7 = H$; R_3 = *tert*-Bu
48. $R_2 = R_3 = R_4 = H$; R_7 = *tert*-Bu
49. $R_2 = R_4 = H$; $R_3 = R_7$ = *tert*-Bu



50



51

As stated before, syntheses of **44** and **46** (Figure 3.3) were of interest to us for the preparation of the dimers **14-16** through the blocking-deblocking strategy. However, the reaction of 1-naphthol with $ZnCl_2$-*tert*-butyl chloride using Miyata's conditions afforded unreacted 1-naphthol (38%) and three other products. Their NMR spectroscopic properties (COSY, HETCOR, APT, and NOED) were consistent with their being 3-*tert*-butyl-1-naphthol (**47**), 7-*tert*-butyl-1-naphthol (**48**), and 3,7-di-*tert*-butyl-1-naphthol (**49**) in 8%, 34% and 20% yields, respectively. There was no evidence for any 2- or 4-*tert*-butyl substituted product being present in the crude reaction mixture. When the reaction was conducted over a 48 h period at ambient temperature, no product formation was observed. An increase in the amount of *tert*-butyl chloride and the reaction period (22 h versus 6 h) resulted in the formation of **49** as the major product (80%) and a small amount (10%) of bis(3,7-di-*tert*-butyl-1-naphthol)ether (**50**, Figure 3.3). Several other variations of Miyata

and Hirashima's conditions employing $ZnCl_2$ were employed (Table 1, run 1-7), but in no case was any **44** or **46** observed. Other experiments were conducted in which *tert*-butyl chloride was used with $AlCl_3$. Heating at 60 °C only resulted in intractable mixtures being formed (Table 1, run 9), but when the reaction was conducted at room temperature for 24 h, a mixture was obtained which consisted of **47** (20%), **49** (35%) and starting material (45%) (Table 1, run 8). When $AlCl_3$ was employed with *tert*-butyl alcohol, the reaction yielded **47** (20%), **49** (28%) and unchanged 1-naphthol (50%) (Table 1, run 10).

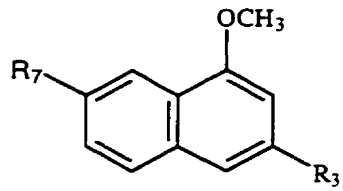
Using Miyata's other conditions, which employed sulfuric acid in glacial acetic acid, a labile, complex reaction mixture was obtained (Table 1, run 12) from which 16% of **46** and 13-15% of a second product, which was shown to be 2-*tert*-butyl-1,4-naphthoquinone (**51**) were isolated. The yield of **46** could not be improved (Table 1, run 11). On standing in air, **46** underwent oxidation to form **51**. In another paper, Miyata and Hirashima[61] reported that **46** was twice as effective as BHT (2,6-di-*tert*-butyl-4-methylphenol) as an antioxidant. These observations are similar to the findings of Brady *et al.* which were stated before.[58]

As mentioned previously, Brady *et al.*[58] have reported that 2-methoxynaphthalene undergoes a similar *tert*-butylation substitution pattern as does 2-naphthol itself. However, no product formation was detected when 1-methoxynaphthalene **52** was treated with $ZnCl_2$/*tert*-butyl chloride.

When **52** (Figure 3.4) was reacted with $AlCl_3$/*tert*-butyl chloride (Table 2, run 14), a mixture was obtained which consisted of 3-*tert*-butyl-1-methoxynaphthalene (**53**) (31%),

3,7-di-*tert*-butyl-1-methoxynaphthalene (**54**) (35%) and starting material (34%). None of

Figure 3.4.



52. $R_3 = R_7 = H$
53. $R_7 = H$; R_3 = *tert*-Bu
54. $R_7 = R_3$ = *tert*-Bu
55. $R_3 = H$; R_7 = *tert*-Bu

the mono substituted 7-*tert*-butyl-1-methoxynaphthalene (**55**) was observed. The NMR spectra of **53** and **54** were similar to those of **47** and **49**, respectively. Reaction of **52** with $AlCl_3$/*tert*-butyl alcohol (Table 2, run 15) afforded 28% of **53**, 53% of **54**, and 18% starting material. Reacting **52** with sulfuric acid/*tert*-butyl alcohol/acetic acid afforded starting material (48%), **55** (39%), and **54** (12%). Longer reaction times served only to increase the yield of **54**. There was no evidence of any 2- or 4-substituted products in the crude reaction mixture.

The regioselectivity which was observed in the *tert*-butylation of 1-naphthol and 1-methoxynaphthalene is also consistent with the analysis of Brady *et al.*[58] Electronic effects would have favored substitution at either the 2- or 4-positions, followed by the 5- or 7-positions. Of these positions the 7-position is the most sterically favored. Thus, both electronic and steric effects combined to favor *tert*-butylation at C-7 of 1-naphthol with $ZnCl_2$-*tert*-butyl chloride and at C-7 of **52** with *tert*-butyl alcohol/acid catalysis. For the

second *tert*-butylation, the 3-position is sterically the most favored position. This regioselectivity is reversed when either $AlCl_3$/*tert*-butyl chloride or $AlCl_3$/*tert*-butyl alcohol is employed with either 1-naphthol or **52**. It is only with the sulfuric acid/acetic acid reaction with 1-naphthol that a small amount of the 2-substituted product forms, but it is labile and easily oxidizes to **51**. In comparison, when these same conditions were employed with **52**, the major products formed were once again controlled by steric factors that were operative in the $ZnCl_2$/*tert*-butyl chloride conditions. There is the possibility, that **44** could have been produced in these reactions but that, once formed, the *tert*-butyl group undergoes a rapid 1,2-migration to give **47**, but we did not verify this experimentally.

3.3. Experimental.

Typical conditions for the reaction of 1-naphthol with (a) $ZnCl_2$/*tert*-butyl chloride (Miyata and Hirashima conditions). To a solution of *tert*-butyl chloride (0.81 mL, 7.6 mmol) and 1-naphthol (1.10 g, 7.60 mmol) in 35 mL of 1,1,2,2- tetrachloroethane was added zinc chloride (1.04 g, 7.60 mmol). The mixture was stirred under N_2 at 60 °C for 6 h. The reaction was worked-up by the addition of 15 mL of CH_2Cl_2 followed by washing three times with the aqueous saturated $NaHCO_3$. The organic layer was separated and dried over anhydrous $MgSO_4$. Removal of the solvent left dark oily residue from which 200 mg was removed and chromatographed by PLC using ethyl acetate-petroleum ether (15:85) to give, in increasing order of polarity, 3,7-di-*tert*-butyl-1-naphthol (**49**) (32 mg), 3-*tert*-butyl-1-naphthol (**47**) (13 mg), 7-*tert*-butyl-1-naphthol (**48**) (55 mg) and 1-naphthol (62 mg). The di-*tert*-butyl product **49** was crystalline, m.p. 141-142°C; ^1H NMR ($CDCl_3$) δ = 1.35 (s,

9H, C_4H_9 at C-3), 1.41 (s, 9H, C_4H_9 at C-7), 5.26 (s, OH), 6.88 (d, J = 1.8 Hz, 1H, H-2), 7.33 (br, 1H, H-4), 7.55 (dd, J = 1.8, 8.7 Hz, 1H, H-6), 7.72 (d, J = 8.7 Hz, 1H, H-5), 8.02 (d, J = 1.8 Hz, 1H, H-8); MS *m/z* (%) 256 (M^+, 66), 241 (100), 213 (2), 185 (4), 157 (4); HRMS M^+ 256.1835, calcd for $C_{18}H_{24}O$ 256.1827. The 3-*tert*-butylated product **47** is an oil whose ^1H NMR and MS spectra reveal the presence of a small amount of **49** that could not be separated even after several chromatographic attempts. ^1H NMR ($CDCl_3$) δ = 1.38 (s, 9H), 6.92 (d, J = 1.8 Hz, 1H, H-2), 7.37 (br, 1H, H-4), 7.48-7.39 (m, 2H, H-6, H-7), 7.76 (m, 1H, H-5), 8.18 (m, 1H, H-8); MS *m/z* (%) 200 (M^+, 60), 185 (100), 157 (13) 144 (11); HRMS M^+ 200.1211, calcd for HRMS M^+ $C_{14}H_{16}O$ 200.1200. The 7-*tert*-butylated product **48** is an oil whose ^1H NMR spectrum reveals the presence of a small amount (< 5%) of **47** that could not be separated even after several chromatographic attempts. ^1H NMR ($CDCl_3$) δ = 1.43 (s, 9H), 6.79 (dd, J = 0.9, 7.5 Hz, 1H, H-2), 7.24 (dd, J = 7.5, 8.4 Hz, 1H, H-3), 7.39 (m, J = 8.4 Hz, 1H, H-4), 7.56 (dd, J = 2.1, 8.7 Hz, 1H, H-6), 7.76 (d, J = 8.7 Hz, 1H, H-5), 8.10 (br, 1H, H-8); MS *m/z* (%) 200 (M^+, 50), 185 (100), 157 (13), 144 (7); HRMS M^+ 200.1201, calcd for $C_{14}H_{16}O$ 200.1200.

When the quantity of *tert*-butyl chloride was doubled and the reaction was maintained at 60 °C for 22 h before work-up, as described above, bis(3,7-di-*tert*-butyl-1-naphthyl)ether (**50**) crystallized from a methanol solution of the crude product. On TLC (ethyl acetate-petroleum ether 30:70) **50** was the least polar of the *tert*-butylated products obtained and had m.p. 275 °C (dec.): ^1H NMR ($CDCl_3$) δ = 1.28 (s, 9H), 1.38 (s, 9H), 7.14 (d, J = 1.5 Hz, 1H, H-2), 7.51 (br, 1H, H-4), 7.62 (dd, J = 1.8, 8.7 Hz, 1H, H-6), 7.82 (d, J =

8.7 Hz, 1H, H-5), 8.28 (br, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ = 31.1 (CH_3), 31.3 (CH_3), 34.9 ($C(CH_3)_3$), 35.0 ($C(CH_3)_3$), 111.7 (C-2), 116.6 (C-8), 117.4 (C-4), 124.8 (C-9), 125.4 (C-6), 127.5 (C-5), 132.9 (C-10), 148.0; 148.3 (C-7; C-3), 153.1 (C-1). MS *m/z* (%) 494 (M^+,100), 479 (16), 239 (10), 232 (36), 57 (41). HRMS M^+ 494.3536, calcd for $C_{36}H_{46}O$ 494.3549.

(b) $AlCl_3$/*tert*-butyl chloride. To a solution of *tert*-butyl chloride (0.81 mL, 7.6 mmol) and 1-naphthol (1.1 g, 7.6 mmol) in 3.5 mL of 1,1,2,2-tetrachloroethane, was added $AlCl_3$ (1.04 g, 7.6 mmol). The mixture was stirred under N_2 at room temperature for 24 h. The reaction was worked-up by the addition of 15 ml of CH_2Cl_2 and washing three times with aqueous saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$. A dark oily residue was obtained from which 150 mg was chromatographed by PLC using ethyl acetate-hexane (15:85) to give, in increasing order of polarity, **49** (50 mg), **47** (30 mg), and 1-naphthol (65 mg).

(c) H_2SO_4/acetic acid/*tert*-butyl alcohol. To a solution of 1-naphthol (1.4 g, 10 mmol), and *tert*-butyl alcohol (0.94 mL, 10 mmol) in 10 mL of acetic acid was added 0.27 mL of 98% H_2SO_4. The mixture was stirred under N_2 at room temperature for 17 h. The reaction was worked-up by diluting it with 20 mL of water and extracting it with 20 mL of $CHCl_3$. The organic layer was washed with two 50-mL portions of water. The organic solution was dried over anhydrous $MgSO_4$. A dark oily residue was obtained from which 200 mg was chromatographed on a column of silica gel using $CHCl_3$-petroleum ether (70:30) as solvent. Two major fractions were collected and further purified by PLC using $CHCl_3$-petroleum

ether (50:50) to give 2-*tert*-butyl-1-naphthol (32 mg) (**46**) and 2-*tert*-butyl-1,4-naphthoquinone (**51**) (26 mg). The 2-*tert*-butylated product **46** was a solid, m.p. 45-47 °C, which oxidized on standing in air; ^{1}H NMR ($CDCl_3$) δ = 1.53 (s, 9H), 5.48 (s, OH), 7.41 (d, J = 8.7 Hz, 1H, H-3), 7.48 (d, J = 8.7 Hz, 1H, H-4), 7.50-7.40 (m, 2H, H-6, H-7), 7.79 (m, 1H, H-5), 8.02 (m, 1H, H-8). The naphthoquinone **51** was a solid, m.p. 73-75 °C; ^{1}H NMR ($CDCl_3$) δ = 1.38 (s, 9H), 6.85 (s, 1H, H-3), 7.64-7.67 (m, 2H, H-6, H-7), 8.11-8.82 (m, 2H, H-5, H-8); MS *m/z* (%) 214 (M^+, 100), 199 (41), 171 (22), 159 (14), 157 (11), 128 (18).

Typical conditions for reaction of 1-methoxynaphthalene (52) with (a) $AlCl_3$/*tert*-butyl alcohol. To a solution of *tert*-butyl alcohol (0.54 mL, 0.57 mmol) and **52** (0.79 g, 0.50 mmol) in 2.5 mL of 1,1,2,2-tertachloroethane, was added $AlCl_3$ (1.04 g, 4.9 mmol). The mixture was stirred under N_2 at room temperature for 24 h. The reaction was worked-up by the addition of an aqueous saturated solution of $NaHCO_3$ until the mixture became basic. The mixture was extracted with two 25 mL portions of $CHCl_3$, and the combined organic layers were washed three times with aqueous saturated $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$. A dark oily residue was obtained from which 150 mg was chromatographed by PLC using CH_2Cl_2-petroleum ether (30:70) to give, in increasing order of polarity, 3,7-di-*tert*-butyl-1-methoxynaphthalene (**54**) (70 mg), 3-*tert*-butyl-1-methoxynaphthalene (**53**) (37 mg) and **52** (24 mg). The di-*tert*-butylated product **54** is a solid, m.p. 109-110 °C; ^{1}H NMR ($CDCl_3$) δ = 1.40 (s, 9H), 1.41 (s, 9H), 4.02 (OCH_3), 6.86 (d, J = 1.2 Hz, 1H, H-2), 7.32 (br, 1H, H-4), 7.54 (dd, J = 1.8, 8.7 Hz, 1H, H-6), 7.70 (d, J = 8.7 Hz, 1H, H-5), 8.12 (d, J = 1.8 Hz, 1H, H-8); MS *m/z* (%) 270 (M^+,60), 255 (100), 199

(10), 106 (15), 92 (11), 57 (33); HRMS M^+ 270.1989, calcd for $C_{19}H_{26}O$ 270.1984. The 3-*tert*-butylated product **53** is an oil; ^1H NMR ($CDCl_3$) δ = 1.41 (s, 9H), 4.01 (s, 3H), 6.89 (d, J = 1.5 Hz, 1H, H-2), 7.36 (br, 1H, H-4), 7.41 (m, 2H, H-6, H-7), 7.75 (m, 1H, H-5), 8.18 (m, 1H, H-8); MS *m/z* (%) 214 (M^+, 60), 199 (15), 106 (8); HRMS M^+ 214.1358, calcd for $C_{15}H_{18}O$ 214.1357.

(b) H_2SO_4/acetic acid/*tert*-butyl alcohol. To a solution of **52** (4.6 g, 29 mmol) and *tert*-butyl alcohol (2.8 g, 38 mmol) in 13 mL (0.23 mol) of acetic acid, maintained at 0-2 °C, was added dropwise 20 mL (0.39 mol) of 98% H_2SO_4. The mixture was allowed to warm to 15 °C, and then swirled and the temperature allowed to rise to 20-25 °C. The reaction was worked-up by adding ice to the mixture and diluting it further with approximately 25 mL of water. The mixture was extracted with two 25 mL portions of $CHCl_3$, and the combined organic layers were washed with 25 mL portions of saturated aqueous $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$, and a 200 mg portion of the oily residue was chromatographed by PLC to give, **54** (24 mg), 7-*tert*-butyl-1-methoxy-naphthalene (**55**) (80 mg), and **52** (96 mg). The 7-*tert*-butylated product **55** was an oil; ^1H NMR ($CDCl_3$) δ = 1.42 (s, 9H), 4.20 (s, OCH_3), 6.79 (dd, J = 0.9, 7.5 Hz, 1H, H-2), 7.33 (dd, J = 8.4, 7.5 Hz, 1H, H-3), 7.38 (d, J = 8.4 Hz, 1H, H-4), 7.58 (dd, J = 8.7, 2.1 Hz, 1H, H-6), 7.74 (d, J = 8.7 Hz, 1H, H-5), 8.20 (d, J = 1.8 Hz, 1H, H-8); MS *m/z* (%) 214 (M^+, 60), 199 (15), 106 (15), 92 (11), 57 (33); HRMS M^+ 214.1367, calcd for $C_{15}H_{18}O$ 214.1357.

Table 3.1. Reaction of 1-Naphthol in $Cl_2CHCHCl_2$ as Solvent Except As Noted

Run no.	Reactants (mole ratio based on 1-naphthol)	Conditions (temp ° C; h)	Products (yields (%) based on total material isolated unless otherwise specified)
1	*tert*-BuCl/$ZnCl_2$ (1:1)	60; 6	**47** (8), **48** (34), **49**(20), 1-naphthol (38)
2	*tert*-BuCl/$ZnCl_2$ (2:1)	60; 22	**47** (tr), **48** (5), **49** (80), **50** (10)
3	*tert*-BuCl/$ZnCl_2$ (1:1)	60; 48	**47** (tr), **48** (11), **49** (37), 1-naphthol (27)
4	*tert*-BuCl/$ZnCl_2$ (1:1)	rt; 48	no reaction
5	*tert*-BuCl/$ZnCl_2$ (1:0.01)	60; 6	no reaction
6	*tert*-BuCl/$ZnCl_2$ (1:0.02)	60; 6	no reaction
7	*tert*-BuCl/$ZnCl_2$ (1:0.1)	60; 6	no reaction
8	*tert*-BuCl/$AlCl_3$ (1:1)	rt; 24	**47** (20), **48** (tr), **49** (35), 1-naphthol (45)
9	*tert*-BuCl/$AlCl_3$ (1:1)	60; 24	intractable mixture, products complex, not identified
10	*tert*-BuOH/$AlCl_3$ (1:1)	rt; 24	**47** (20), **48** (tr), **49** (28), 1-naphthol (50)
11	*tert*-BuOH/CH_3CO_2H/ H_2SO_4 (1.0:17.5:0.50)	rt; 17	**46** (16), **51** (13)- yields based on isolated product relative to starting material
12	*tert*-BuOH/CH_3CO_2H/ H_2SO_4 (1.3:7.8:13.50)	0-20; 10 min	Intractable mixture, products complex- not identified.

Table 3.2. Reaction of 1-Methoxynaphthalene in $Cl_2CHCHCl_2$ as Solvent Except As Noted

Run no.	Reactants (mole ratio based on 52)	Conditions (temp °C; h)	Products (yields (%) based on total material isolated unless otherwise specified)
13	*tert*-BuCl/$ZnCl_2$ (1:1)	60; 6	no reaction
14	*tert*-BuCl/$AlCl_3$ (1:1)	rt; 24	**52** (34), **53** (31), **54** (35)
15	*tert*-BuOH/$AlCl_3$ (1:1)	rt; 24	**52** (18), **53** (28), **54** (53)
16	*tert*-BuOH/CH_3CO_2H /H_2SO_4 (1.0:0.175:0.005)	rt; 3	no reaction
17	*tert*-BuOH/CH_3CO_2H /H_2SO_4 (1.0:0.175:0.005)	60; 6	no reaction
18	*tert*-BuOH/CH_3CO_2H /H_2SO_4 (1.0:17.5:0.50)	90; 48	hydrolysis to form 1-naphthol
19	*tert*-BuOH/CH_3CO_2H /H_2SO_4 (1.3:7.8:13.5)	0-20, 10 min	**52** (48), **54** (12), **55** (39)

Chapter 4

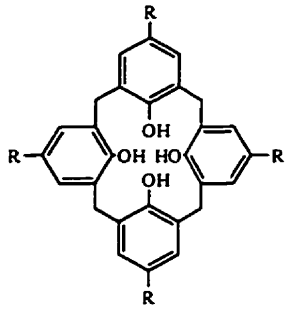
Synthesis of Inherently Chiral Calix[4]naphthalenes and Their Derivatives

4.1. Introduction.

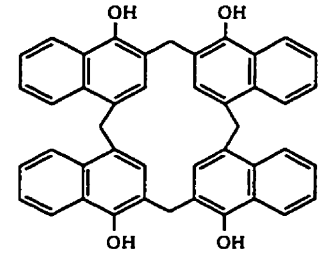
There is a major difference between calix[4]arenes derived from *p-tert*-butylphenol and the calix[4]naphthalenes derived from 1-naphthol which pertains to the location of the hydroxyl groups. In the calixarenes the hydroxyl groups are located at the smaller "lower" rim of the basket, and are in close proximity to one another. This proximity allows for the formation of intramolecular hydrogen bonds which hold the conformation of calixarenes in the cone conformation both in the solid state and in solution, as described in Chapter 1. This cone conformation serves as a "cap" for the cavity of calixarenes so that stable inclusion complexes with guests can be formed. In the calixnaphthalenes derived from 1-naphthol (e.g. **13**), the hydroxyl groups are located outside the cavity at the periphery of the basket which inhibits their complexation and conformation properties (Scheme 4.1). In order to place the hydroxyl groups within the lower rim of the calixnaphthalene basket, a retrosynthetic analysis (Scheme 4.1) shows that 3-hydroxymethyl-2-naphthol (**56**) would be a suitable starting material for compound **57**.

Synthesis of chiral calix[4]arenes is possible by the attachment of chiral residues to the calixarenes at the lower or upper rim. More interesting, however, is the possibility of obtaining inherently chiral calixarenes. Dissymmetric calix[4]arenes may be prepared by

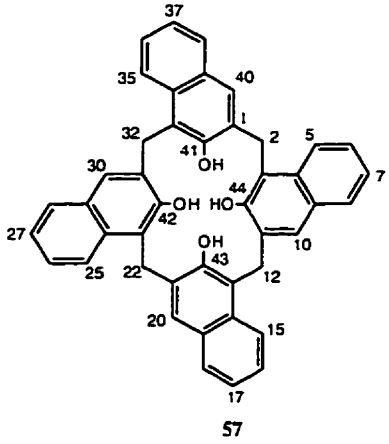
Scheme 4.1.



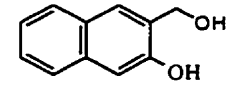
Calix[4]arenes



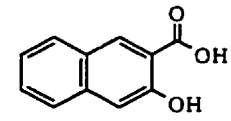
Calix[4]naphthalene 13



57



56



3-Hydroxy-2-Naphthoic Acid

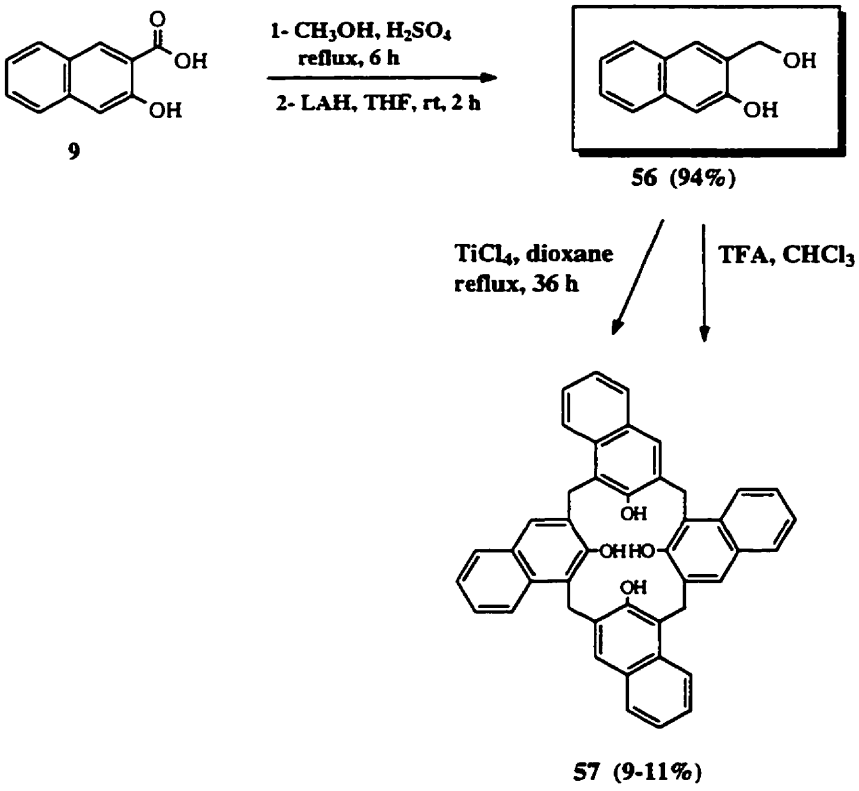
9

the incorporation of a single meta-substituted phenol unit.[62] In present work, due to the substitution pattern of 3-hydroxy-2-naphthoic acid (**9**), the calix[4]naphthalenes **57** and **62** would be inherently chiral.

4.2.a. Synthesis of Inherently Chiral Calix[4]naphthalene 57.

Calix[4]naphthalene **57** was first synthesized by Böhmer *et al.*[62] in 5% yield by self-condensation of 3-(hydroxymethyl)-2-naphthol (**56**) in dioxane, using $TiCl_4$ as a catalyst (and probably as template) as shown in Scheme 4.2. Böhmer *et al.* however, did not fully characterize their product although they did propose a cyclic structure like **57**.

Scheme 4.2.



Re-investigation of the self condensation of **56** using $TFA/CHCl_3$ showed that these

conditions did not yield very consistent results. Modification of the $TiCl_4$/dioxane conditions and the work-up gave improved yields of up to 10-11%. The calix[4]-naphthalene thus formed was easily isolated and purified. After removal of the dioxane by vacuum distillation, the dark crude product was dissolved in excess $CHCl_3$ and was filtered to remove insoluble resinous materials. The chloroform solution was then subjected directly to flash chromatography using CH_2Cl_2-petroleum ether (1:1) to give a light brown solid. In principle, higher members of the calixnaphthalene could be formed also by condensation of 3-(hydroxymethyl)-2-naphthol but **57**, which was unambiguously confirmed by mass spectrometry, was the only isolable cyclic compound. The mass spectrum shows a molecular ion peak at $m/z = 624$. The C_4 symmetrical structure was demonstrated by ^1H NMR and ^{13}C NMR spectra. The ^1H NMR spectrum shows singlets for the hydroxy and methylene protons at 10.96 and 4.58 ppm, respectively (Figure. 4.1). The ^{13}C NMR spectrum revealed eleven carbon signals consisting of five quaternary aromatic carbon signals, five methine aromatic carbon signals and a single aliphatic methylene carbon signal. The calix[4]naphthalene is flexible at room temperature, as demonstrated by the sharp methylene singlet at 4.58 ppm. This signal was broader at 0 °C, and, was split into a doublet at -10 °C with a coalescence temperature of approximately -5 °C. The conformation of the molecule could be fixed at -20 °C into the cone conformation as revealed by the fact that the methylene protons appear as a pair of AB doublets (Figure. 4.2). A colorless single crystal was obtained from toluene solution, which was suitable for

Fig. 4.1. ^{1}H NMR Spectrum of Calix[4]naphthalene 57 in $CDCl_3$.

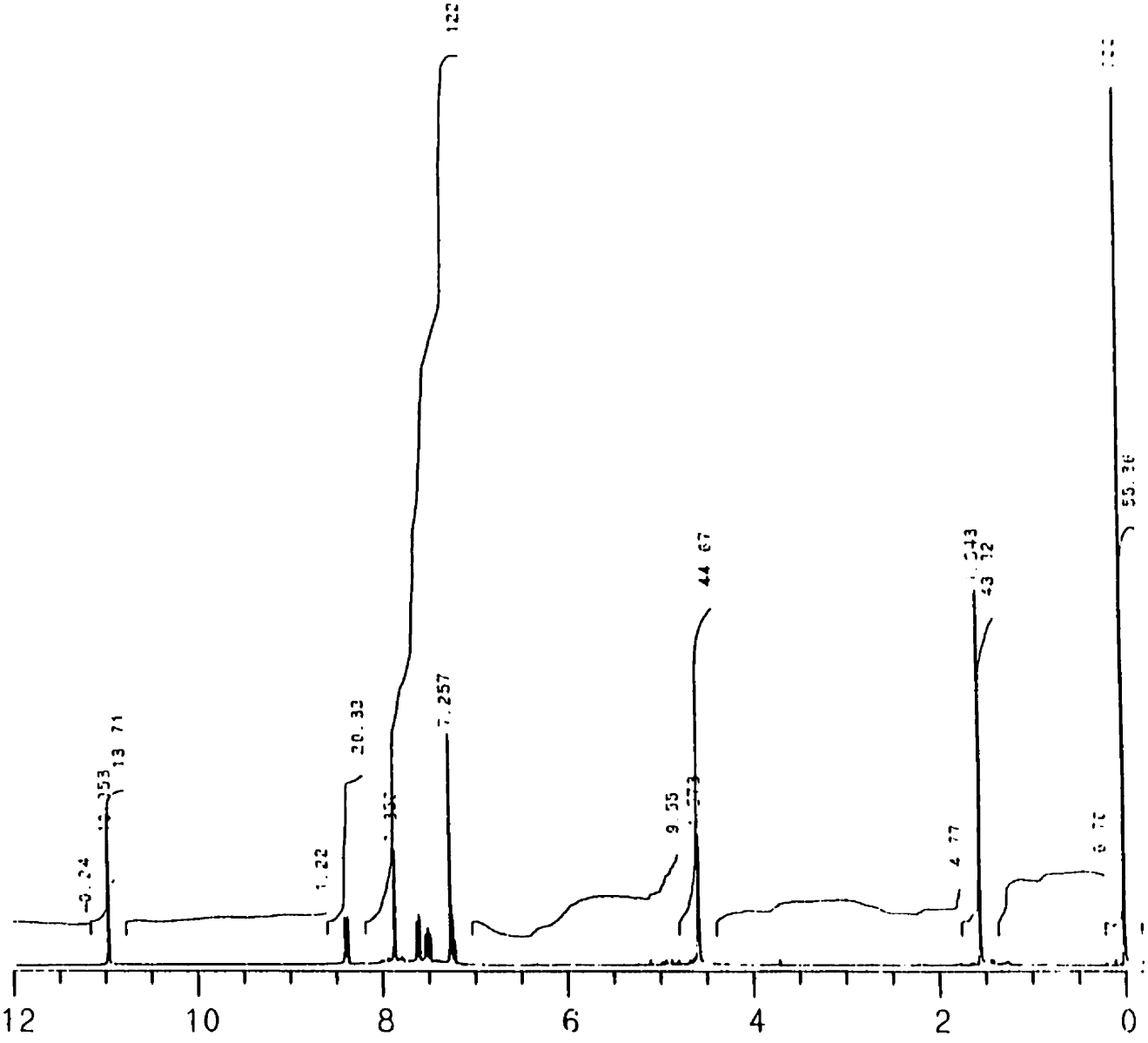
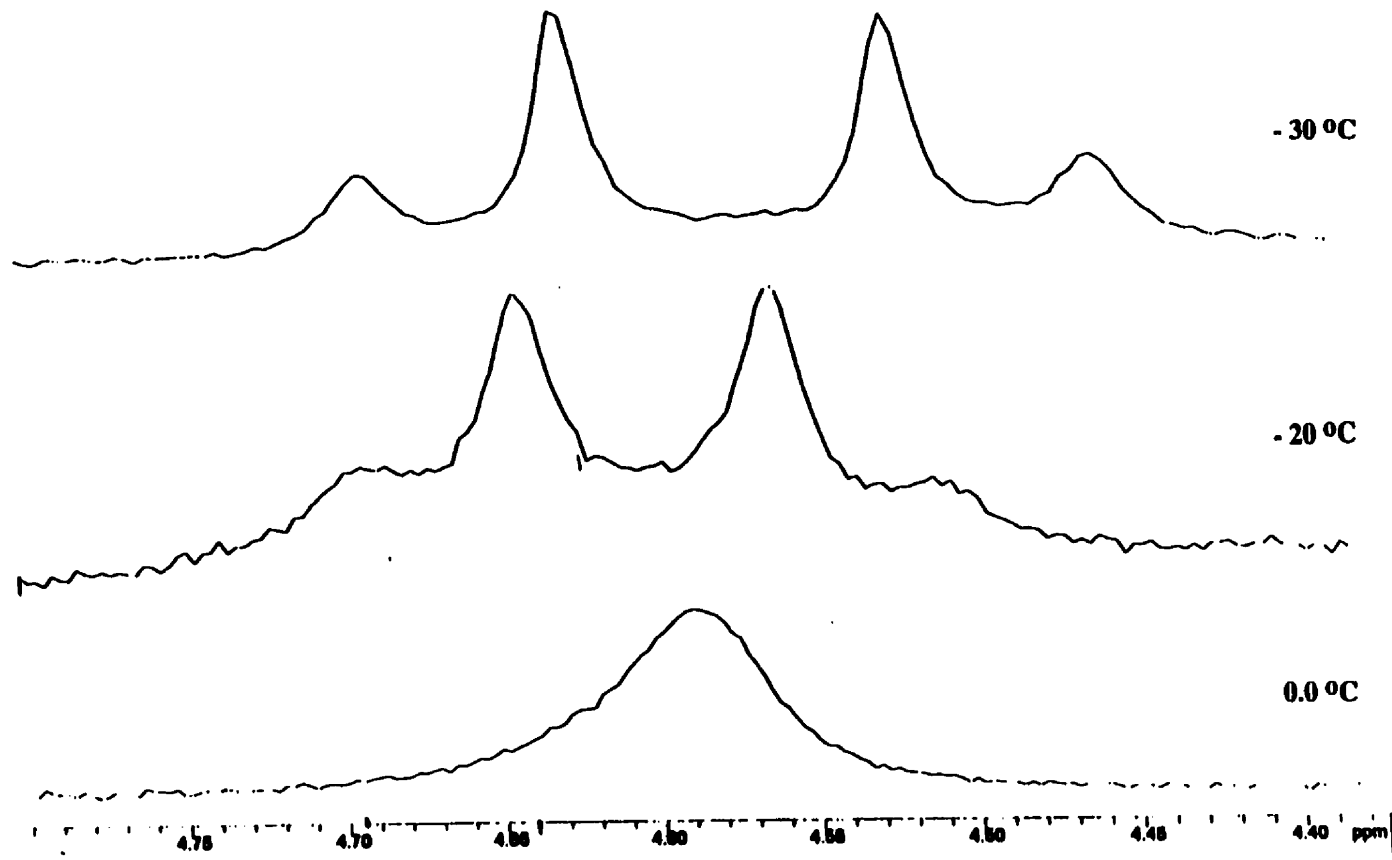


Fig. 4.2. VT ^{1}H NMR Spectra of 57 in $CDCl_3$.



x-ray diffraction analysis. As shown in Figure 4.2a, the compound adopts a "pinched-cone" conformation with C_2 symmetry in the solid state. An interesting finding in the x-ray analysis is that the unit cell contains two molecules, which are packed in such a way that a naphthalene unit of one molecule is situated within the hydrophopic cavity of the second molecule (Figure 4.2b). To our knowledge this behaviour has not been noted in the calixarenes. Three toluene molecules surround the supramolecular dimer.

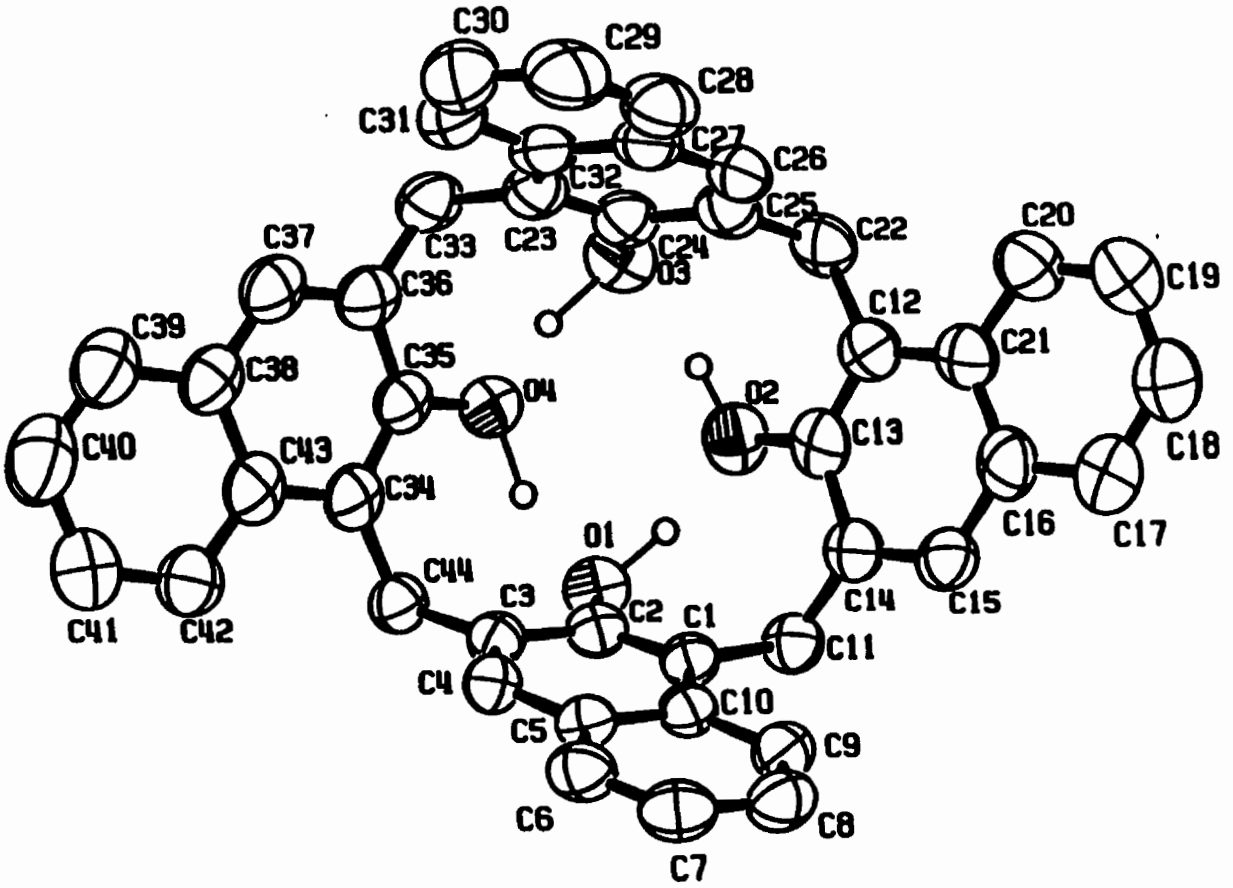
The intramolecular hydrogen bonds in **57** may be stronger than in the *p-tert*-butylcalix[4]arene since the signal for the hydroxyl groups of **57** appears at lower field (10.96 ppm), while in *p-tert*-butylcalix[4]arene it appears at higher field (10.20 ppm).

4.2.b. Synthesis of Inherently Chiral *tert*-Butylcalix[4]naphthalene (62).

As mentioned in Chapter 1, a *tert*-butyl group at the *p*-position of phenol is the alkyl group which gives the best yield and the most tractable calix[4]arene product since the four *tert*-butyl groups apprear to fill and cover the cavity created in the cone conformer.[7] Inspired by this idea, functionalization of ring B of 3-(hydroxymethyl)-2-naphthol (**56**) by a *tert*-butyl group, which could enhance the yield of its self-condensation product, was explored.

The results of the re-investigation of *tert*-butylation of 1-naphthol (Chapter 3), suggested that it would be possible to *tert*-butylate the precursor of **56**, methyl 3-hydroxy-2-naphthoate (**58**), using *tert*-butyl chloride, $AlCl_3$ as catalyst and 1,1,2,2-tetrachloroethane

Fig. 4.2a. X-Ray Crystal Structure of Calix[4]naphthalene 57.



(The numbering used in all X-ray structures reported in this thesis are not the same as those used in the Experimental section.)

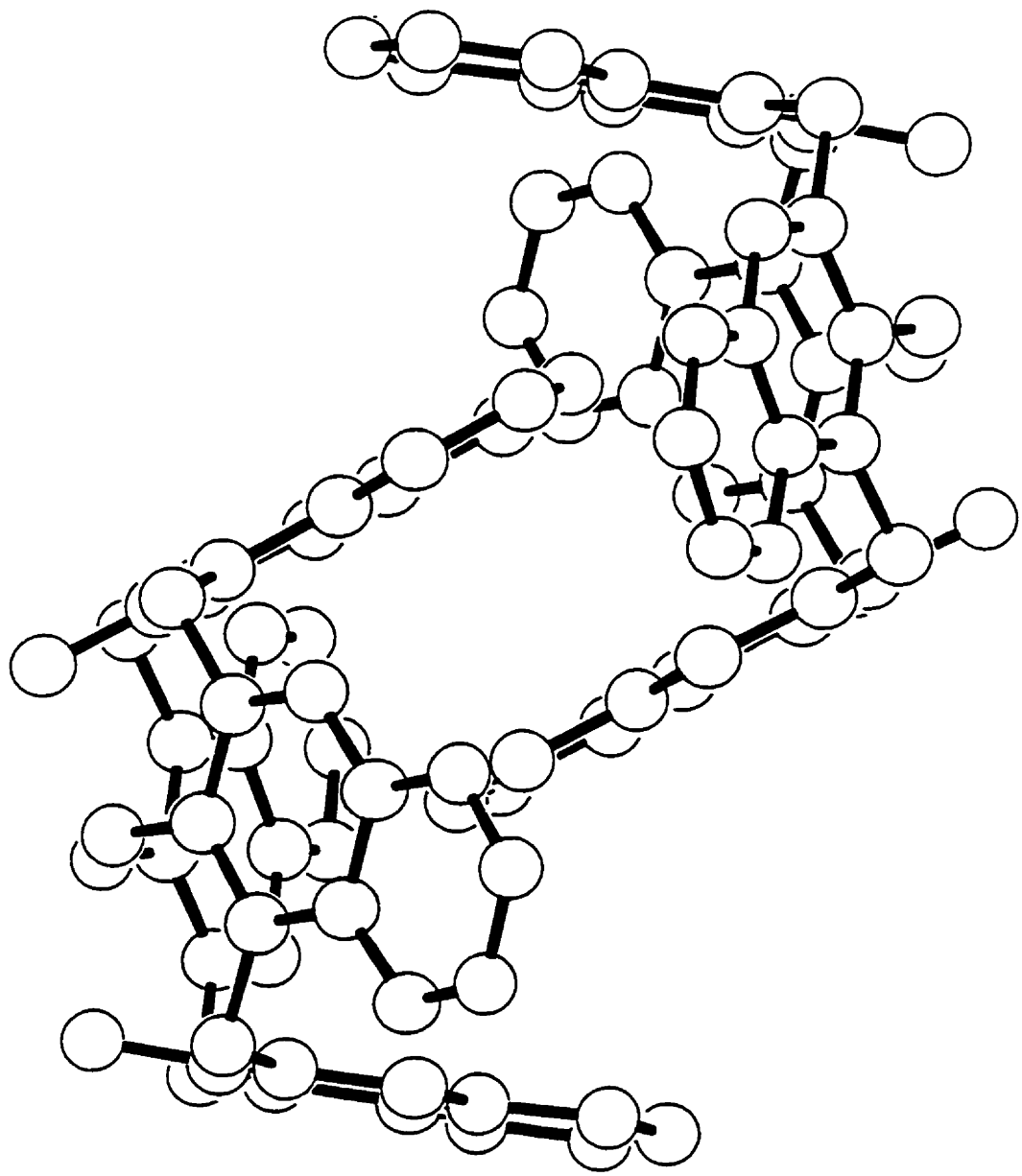
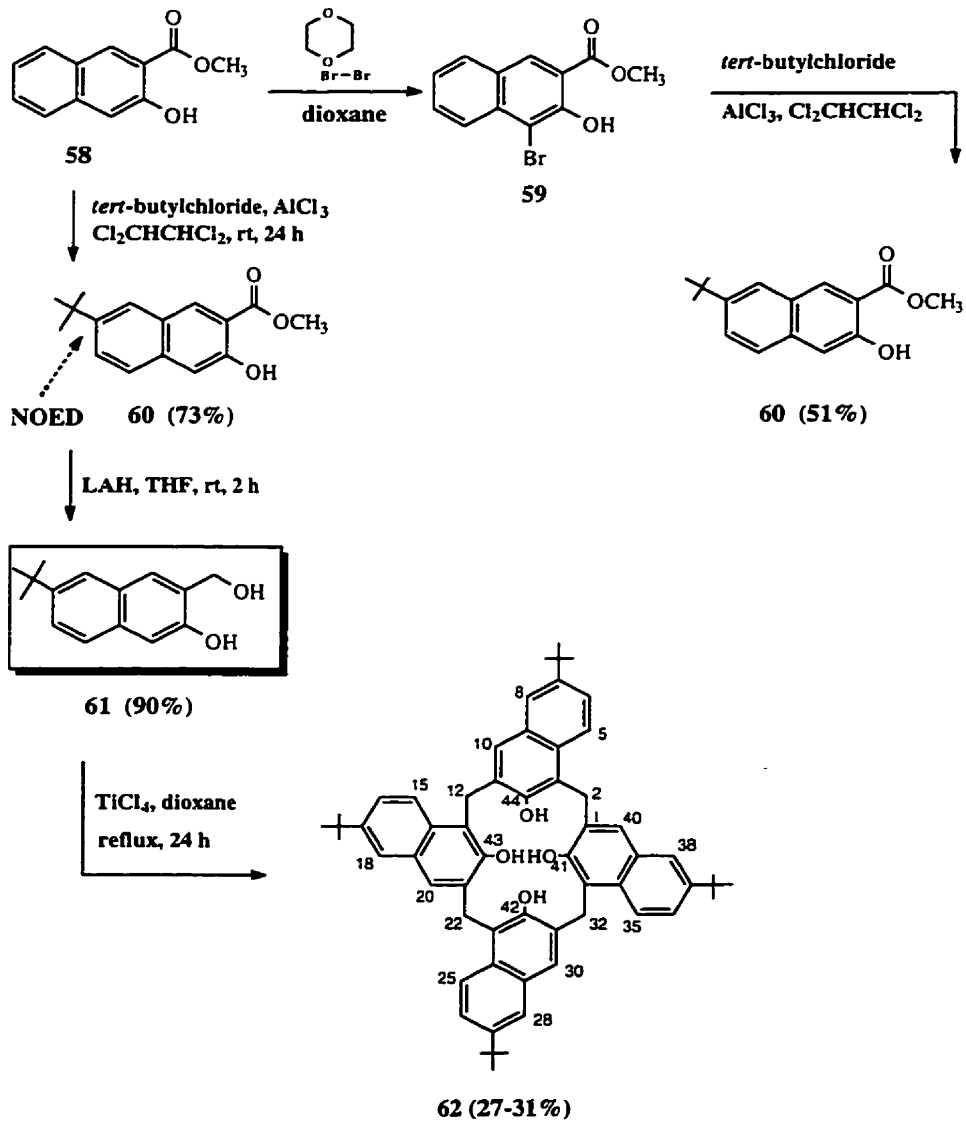


Fig. 4.2b. X-Ray Crystal Structure of Calix[4]naphthalene 57 Dimer.

Scheme 4.3.



as solvent at room temperature, as shown in Scheme 4.3. Position 4 of **58** was first blocked with a bromine atom using dioxane-dibromide to give **59**. It was found that in addition to

tert-butylation of **59** under the above Friedel-Crafts alkylation conditions, the bromine atom was also removed to give methyl 7-*tert*-butyl-3-hydroxy-2-naphthoate (**60**) in 51% yield. It was therefore not necessary to block position 4 of **58** prior to reaction. Indeed, direct treatment of **58** with the above alkylation conditions produced **60**, in 73% yield, which was then reduced by LAH in anhydrous THF to give 6-*tert*-butyl-3-(hydroxymethyl)-2-naphthol (**61**) in 90% yield. NOED experiments confirmed that the *tert*-butylation occurred at position 6. Self-condensation of **61** was conducted, and the reaction was worked-up exactly as described for **56**. The tetra-*tert*-butylcalix[4]naphthalene **62** was obtained in a yield of 27-31% .

The ^{13}C NMR ($CDCl_3$) spectrum of this pure product shows thirteen clearly resolved signals. These signals consist of five quaternary aromatic carbon signals, five methine aromatic carbon signals, a single aliphatic methylene carbon signal, a single quaternary aliphatic carbon signal, and a single methyl carbon signal due to the *tert*-butyl group. The ^1H NMR ($CDCl_3$) spectrum at room temperature is a relatively simple, as shown in Figure. 4.3. The resonances from the *tert*-butyl protons, the methylene protons, and the hydroxyl groups are singlets. These data are consistent for a structure possessing C_4 symmetry. As in the case of calix[4]naphthalene **57**, the methylene singlet signal at 4.52 ppm became broad at 0 °C, split into AB doublets at -10 °C and then freezes in the cone conformation at -20 °C, as revealed by the appearance of a pair of AB doublets for the methylene protons (Figure. 4.4). Also, as shown in Figure 4.3, the intramolecular hydrogen bonds in **62** appear

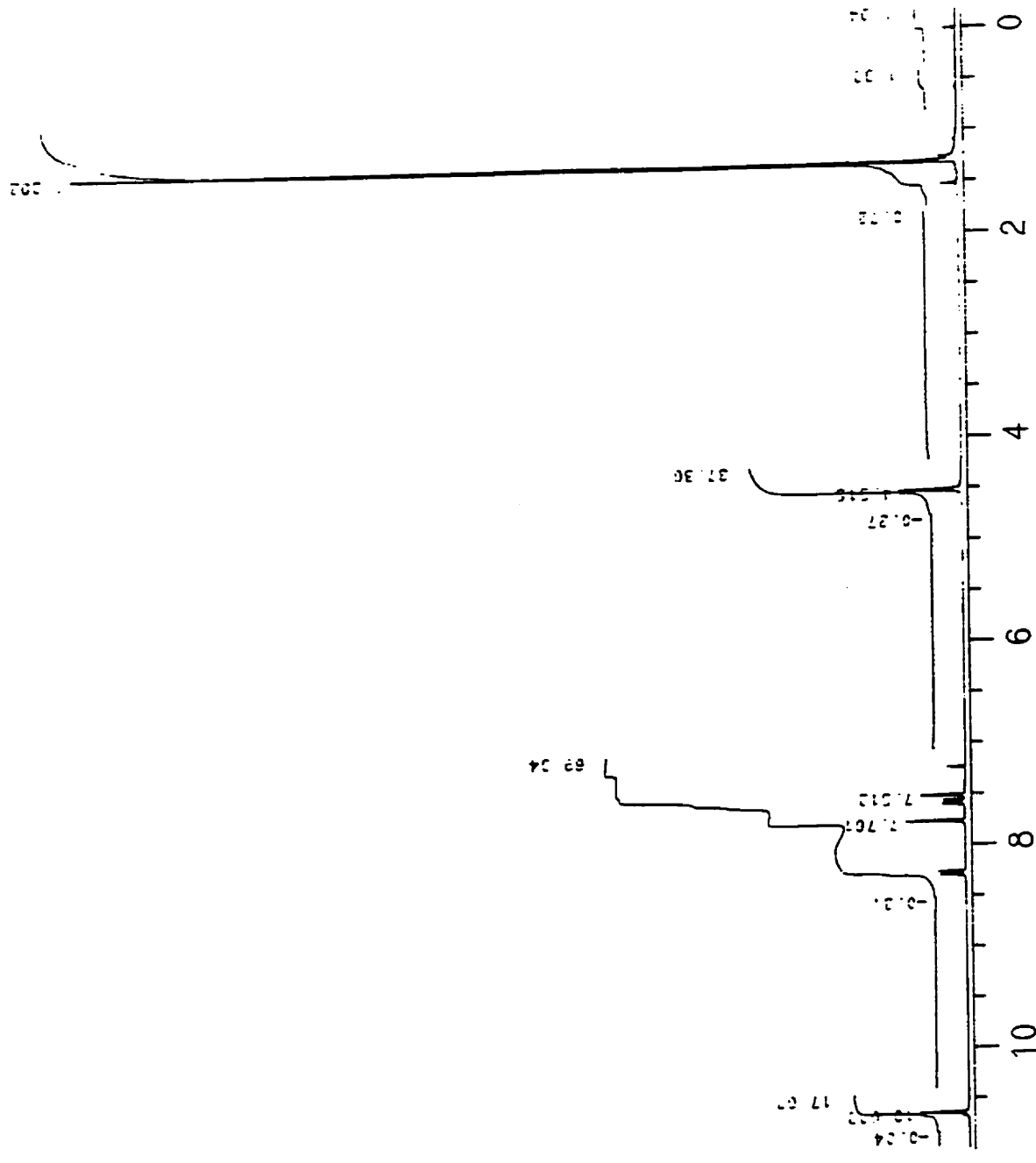
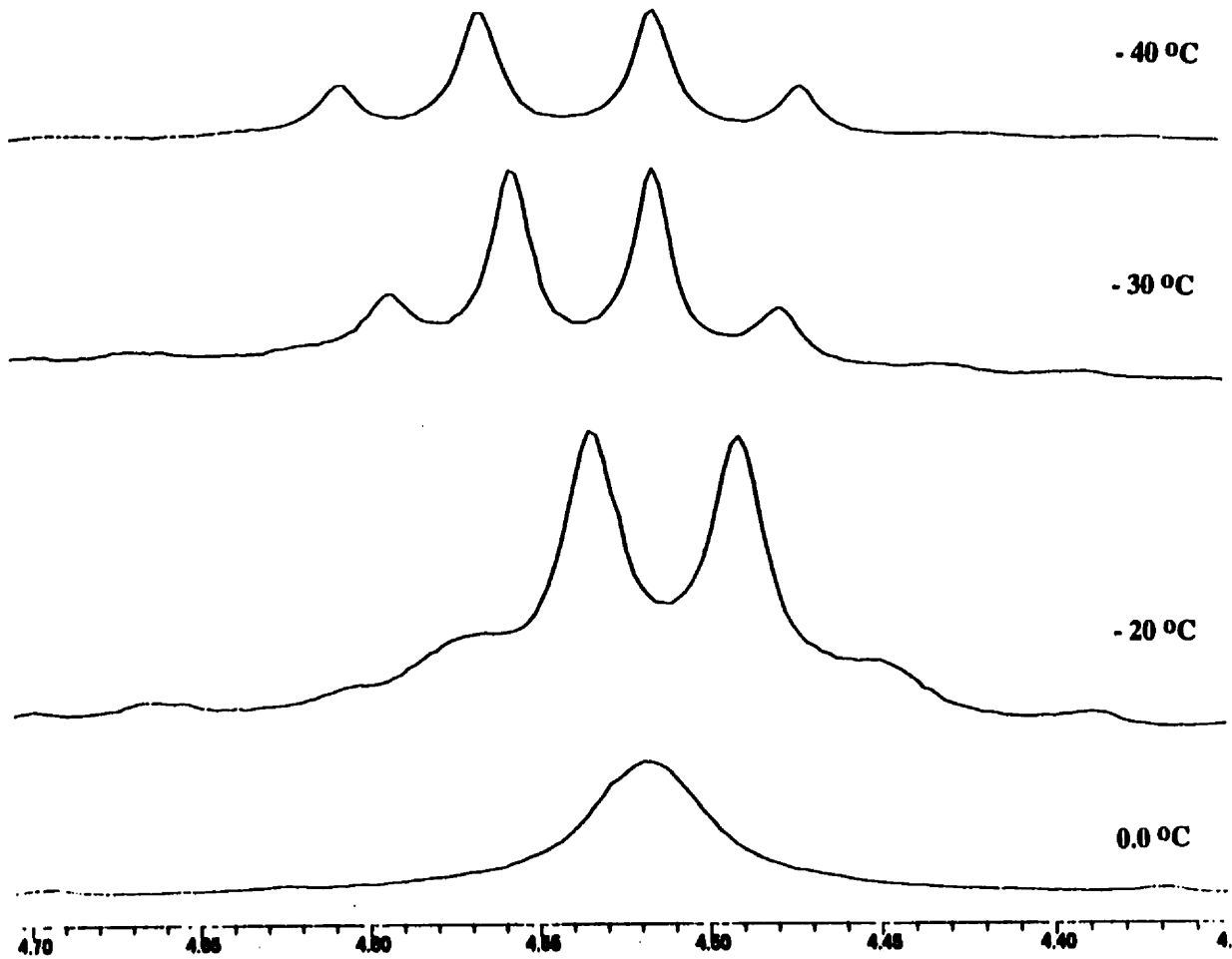


Fig. 4.3. ^{1}H NMR Spectrum of *tert*-butylcalix[4]naphthalene 62 in $CDCl_3$.

Fig. 4.4. VT ^{1}H NMR Spectra of 62 in $CDCl_3$.



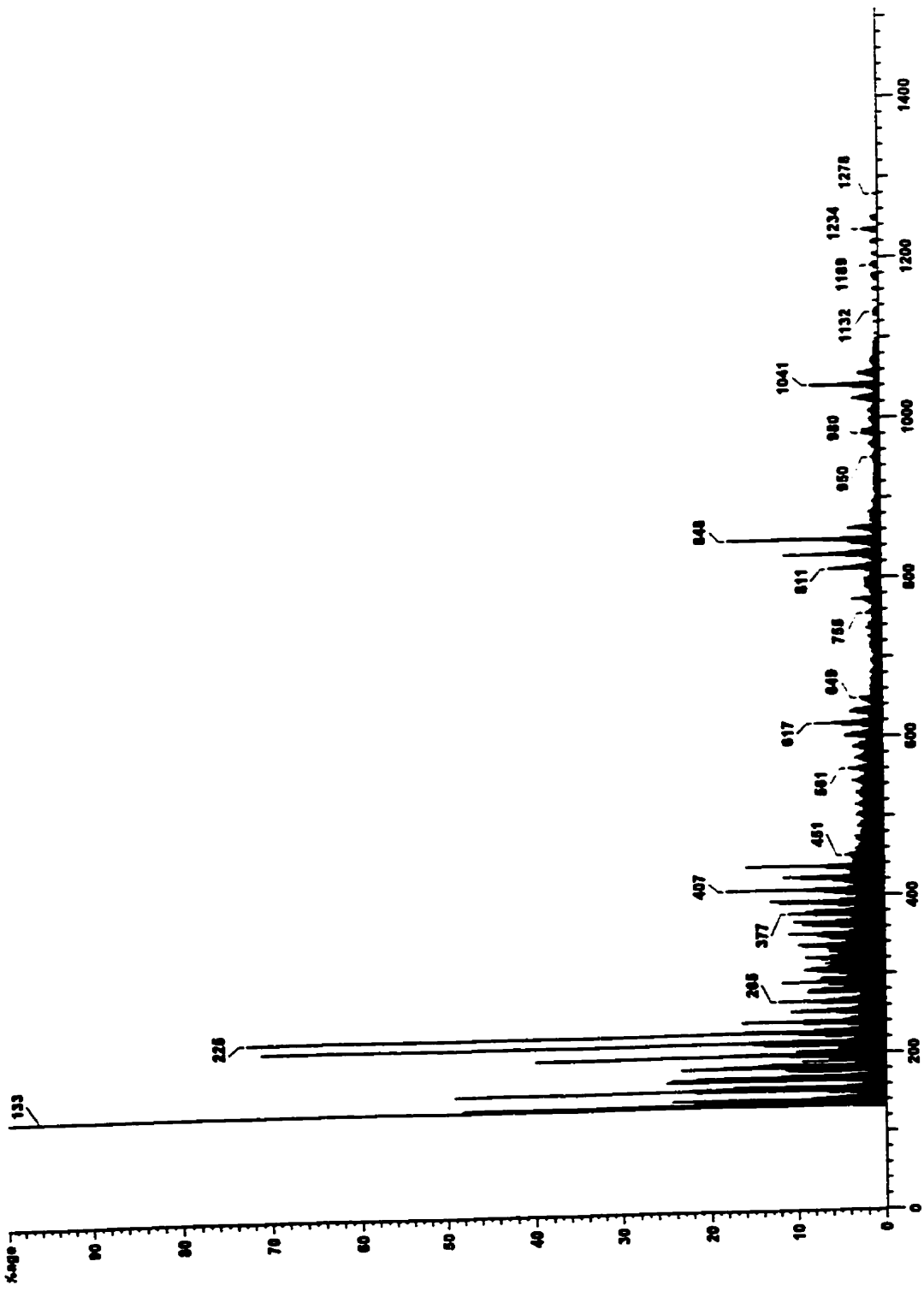


Fig. 4.5. +FAB MS Spectrum of 62.

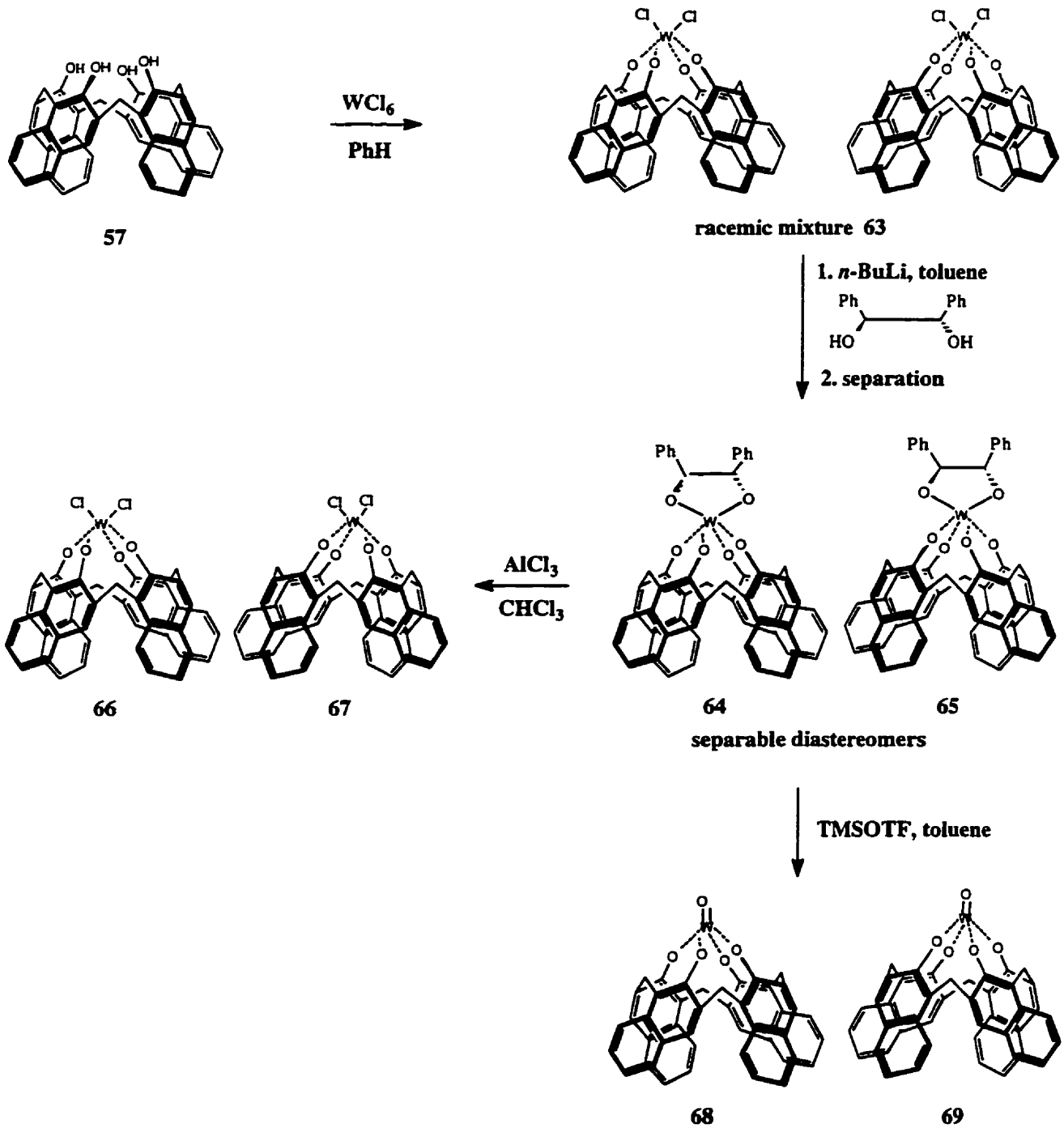
to be stronger than in *tert*-butylcalix[4]arene since the signal for the hydroxyl groups appears at lower field (10.63 ppm) than in *tert*-butylcalix[4]arene (10.20 ppm), but it is very similar to the chemical shift observed for 3,4-dimethylcalix[4]arene (10.61 ppm)[62] although this could be a concentration effect. In spite of the fact that **62** was chromatographically pure, confirmed by its ^{1}H NMR spectrum, the FAB-MS spectrum (Figure 4.5) shows many peaks higher than the molecular ion peak, which appears at $m/z = 848$. These peaks could be due to various unidentified inclusion complexes.

4.3. Chiral Resolution of Dissymmetric Calix[4]naphthalenes 57 and 62.

As stated before, several approaches have been used to design the synthesis of chiral calix[4]arenes because of great interest in using them as potential hosts for enantioselective recognition of suitable guest molecules.[43, 44] In spite of the interest in chiral calix[4]arenes, few resolutions of their enantiomers have been achieved.[63-66] The difficulty in resolving calix[4]arenes is because the rate of conformational interconversion is comparable with that of the NMR time scale. This conformationally dynamic behavior causes a racemization by rapid ring inversion. Resolution by chiral HPLC should be possible providing that ring inversion is sufficiently inhibited. [63-66]

The inherently chiral calix[4]naphthalenes **57** and **62** are conformationally dynamic and thus exist as rapidly equilibrating racemic mixtures. In order to inhibit the conformational mobility of these calix[4]naphthalenes it is possible to use an approach that was recently successfully employed by Swager[67] for chiral resolution of inherently chiral

Scheme 4.4.


WCl6
PhH
racemic mixture 63
1. n-BuLi, toluene
2. separation
AlCl3
CHCl3
TMSOTF, toluene
57
66
67
64
65
separable diastereomers
68
69

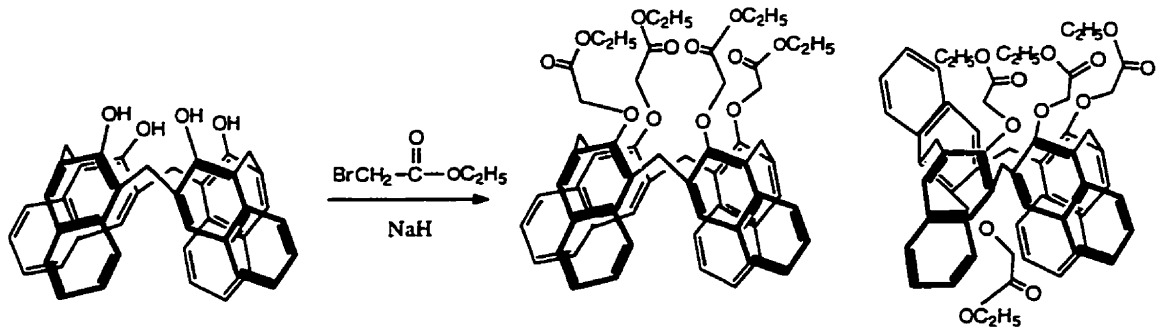
calix[4]arenes by forming transition metal-containing complexes such as with tungsten. This approach or one similar to it could be also employed for the chiral resolution of dissymmetric calix[4]naphthalenes **57** and **62**, as depicted in Scheme 4.4. This first requires that the calix[4]naphthalenes **57** and **62** be fixed in their cone conformations by complexation with the metal to form a non-interconvertible racemic mixture of calix[4]naphthalene complexes. Secondly, the introduction of a chiral auxiliary will provide diastereomers, which, after separation and removal of the chiral auxiliary, could afford resolved enantiomers. To achieve this, reaction of the chiral calix[4]naphthalene **57** with WCl_6 in benzene also could produce the dichlorotungsten (VI) complex **63** as a racemic mixture. Reacting the racemic mixture of **63** with the chiral auxiliary (*S,S*)-(-)-hydrobenzoin will provide a mixture of diastereomers **64** and **65**, which could, in principle, be separated by chromatographic methods. After separation of **64** and **65**, removal of the chiral auxiliary using $AlCl_3$ in $CHCl_3$ should give pure enantiomers of the dichlorotungsten(VI) calix[4]naphthalene complexes **66** and **67**. Also, treatment of **64** or **65** with trimethylsilyltriflate (TMSOTf) in toluene could produce enantiomers of oxotungsten(VI) calix[4]naphthalene complexes **68** and **69**.

4.4.a. Ester Derivative of Calix[4]arenes.

Although the parent *p-tert*-butylcalix[4]arenes form inclusion complexes with small, neutral molecules,[68] they have very little ionophoric activity for alkali metal ions. This is shown by their inability to transport such ions from neutral aqueous solution through a

chloroform membrane.[69] Only when the source phase is the basic metal hydroxide is transport observed, phase transfer then being coupled to phenoxide ion formation. By analogy with the fact that biological receptors are rich in ester-type carbonyl groups, alkyl acetate groups attached to the phenolic groups in *p-tert*-butylcalix[4]arenes result in their having a high degree of phase-transfer affinity for alkali metal cations.[70] This is ascribed to interactions between hard oxygen bases and hard alkali earth metal cations as observed with the crown ethers. In principle, this esterification may fix any of the four possible conformations, provided the residues are bulky enough to inhibit the oxygen-through-the-annulus rotation. It is found that conversion into esters using ethyl bromoacetate in the presence of sodium or potassium ions leads to tetraester derivatives in the cone conformations,[70] while the partial-cone conformation is formed predominantly in the presence of cesium ions.[39] The conformational characteristics of calix[4]arenes and their derivatives can be conveniently estimated by the splitting patten of the methylene protons in their ^{1}H NMR spectra.[7] For tetraester derivatives of calix[4]arenes formed by reacting calix[4]arenes with ethyl bromoacetate, the methyl protons for the ethyl ester groups ($OCH_2\mathbf{CH_3}$) in the cone conformation appear as one triplet, while in the partial-cone conformation they appear as three sets of triplets in the ratio 1:2:1, and in the pinched-cone conformation they appear as two sets of triplets in the ratio of 1:1.[62, 39] This suggests that this feature could be also used as an alternative method for establishing the nature of the conformations of tetraester derivatives of calix[4]naphthalenes.

4.4.b. Synthesis of Tetrakis((ethoxycarbonyl)methoxy)calix[4]naphthalene (70)



57 **70b** **70a**

Acetylation of calix[4]naphthalene **57** was carried out under the same conditions employed for acetylation of calix[4]arenes. Refluxing calix[4]naphthalene **57** with ethyl bromoacetate in THF using NaH as base, produced two products, which were more soluble in $CHCl_3$ than the parent compound.

By analogy with the tetraester derivative of calix[4]arenes, the tetraester derivative of calix[4]naphthalene **70** can in principle adopt one or more conformations of the five types of fixed conformations: cone, partial-cone, 1,2-alternate, 1,3-alternate and pinched-cone conformations.

If **70** adopts the cone conformation, the four bridge methylene groups should be equivalent, but the two protons of each bridge methylene group are chemically non-equivalent and would likely form an AB quartet in the ^1H NMR spectrum. The four OCH_2CO methylene groups are equivalent, but due to the inherent chirality of the molecule,

each of the protons is diastereotopic and should also appear as an AB quartet. All of the protons of each methylene and methyl group in the alkyl moiety of the ethyl ester groups (CH_2CH_3) are equivalent. Therefore, they would appear as one quartet and one triplet, respectively, as is observed for other tetraester derivatives of inherently chiral calix[4]-arenes.[62]

Examination of molecular models showed that the anticipated characteristics of the ^1H NMR signals of tetraester derivative conformers of **70** would be as shown in Table 4.1

Table 4.1. Predicted characteristics of ^1H NMR of conformers of tetraester derivatives of 57.

Conform.	CH_2 bridge	OCH_2CO	OCH_2CH_3	OCH_2CH_3
cone	1 pair doublets	1 pair doublets	1 quartet	1 triplet
partial-cone	4 pairs d (1:1:1:1)	4 pairs d (1:1:1:1)	4 quart. (1:1:1:1)	4 t (1:1:1:1)
1,2-alternate	2 pairs d (1:1)	2 pairs d (1:1)	2 quartets (1:1)	2 t (1:1)
1,3-alternate	1 pair doublets	1 pair doublets	1 quartet	1 triplet
pinched cone	1 pair doublets	2 pairs d (1:1)	2 quartets (1:1)	2 triplets 1:1

d = doublet ; t = triplet ; q = quartet.

At room temperature the ^1H NMR spectrum ($CDCl_3$) of the most polar product is relatively simple, as shown in Figure 4.6. It shows one triplet centered at 1.28 ppm (J = 6.9 Hz), coupled to a quartet centered at 4.2 ppm, and two pairs of doublets. One pair of doublets was centered at 4.12 and 5.31 ppm (J = 14.7 Hz) and the other pair of doublets

was centered at 4.64 and 5.11 ppm (J = 16.2 Hz). COSY and NOED experiments indicate that the pair of doublets at 4.12/5.31 ppm having the larger chemical shift difference is due to the bridge methylene protons, whereas the pair of doublets at 4.64/5.11 ppm is due to the diastereotopic -OCH_2CO- methylene protons. These data suggest either a cone, or 1,3-alternate conformation, as shown from their expected splitting patterns summarized in Table 4.1. However, it is more likely that the molecule adopts the cone conformation since the chemical shift difference between the pair of doublets of the methylene bridge is as large as is observed for the cone conformation of tetraester derivatives of *p-tert*-butylcalix[4]arenes.[39] The ^{13}C NMR spectrum shows only one carbonyl signal at 170.0 ppm, which confirms that all of the carbonyl groups are equivalent. The FAB-MS spectrum shows a signal (7%) at m/z = 986, which is compatable with the molecular mass of the product plus a water molecule.

The ambient temperature ^1H NMR ($CDCl_3$) spectrum (Figure 4.6) shows well-resolved sets of resonances arising from the methyl and methylene protons. Also present is a broad, partially resolved set of resonances arising from the aromatic protons, which correspond to sixteen protons. A new broad aromatic signal centered at 6.83 ppm starts to appear as the temperature was increased to 40 °C which integrated for four protons as shown in Figure 4.7. When the solvent was changed to DMSO-d_6 and the temperature increased gradually to 140 °C, well-resolved aromatic signals were obtained without any major changes to the shapes of the methylene and methyl signals (Figure 4.8). This

Fig. 4.6. ^{1}H NMR Spectrum of Tetraestercalix[4]naphthalene 70b in $CDCl_3$.

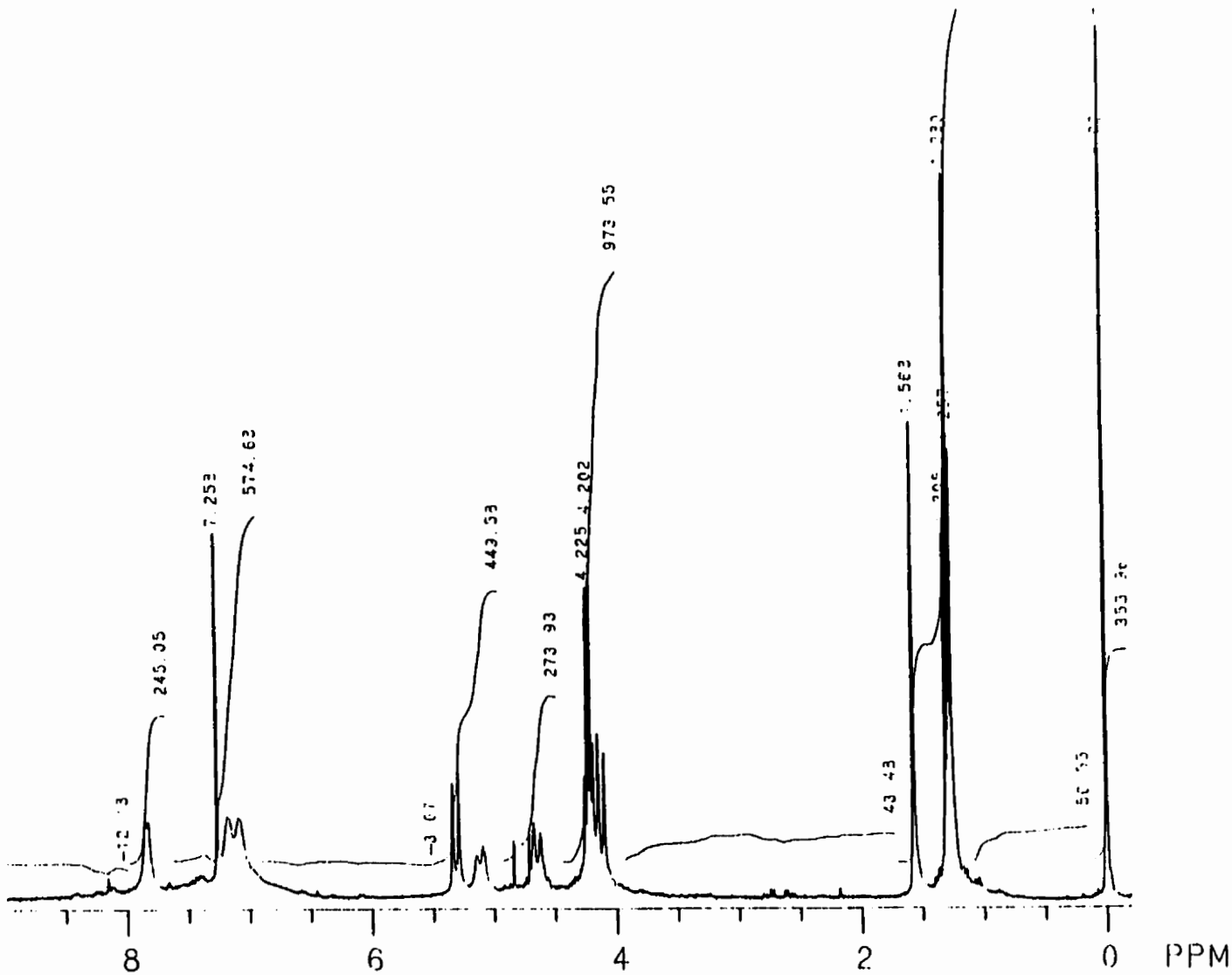
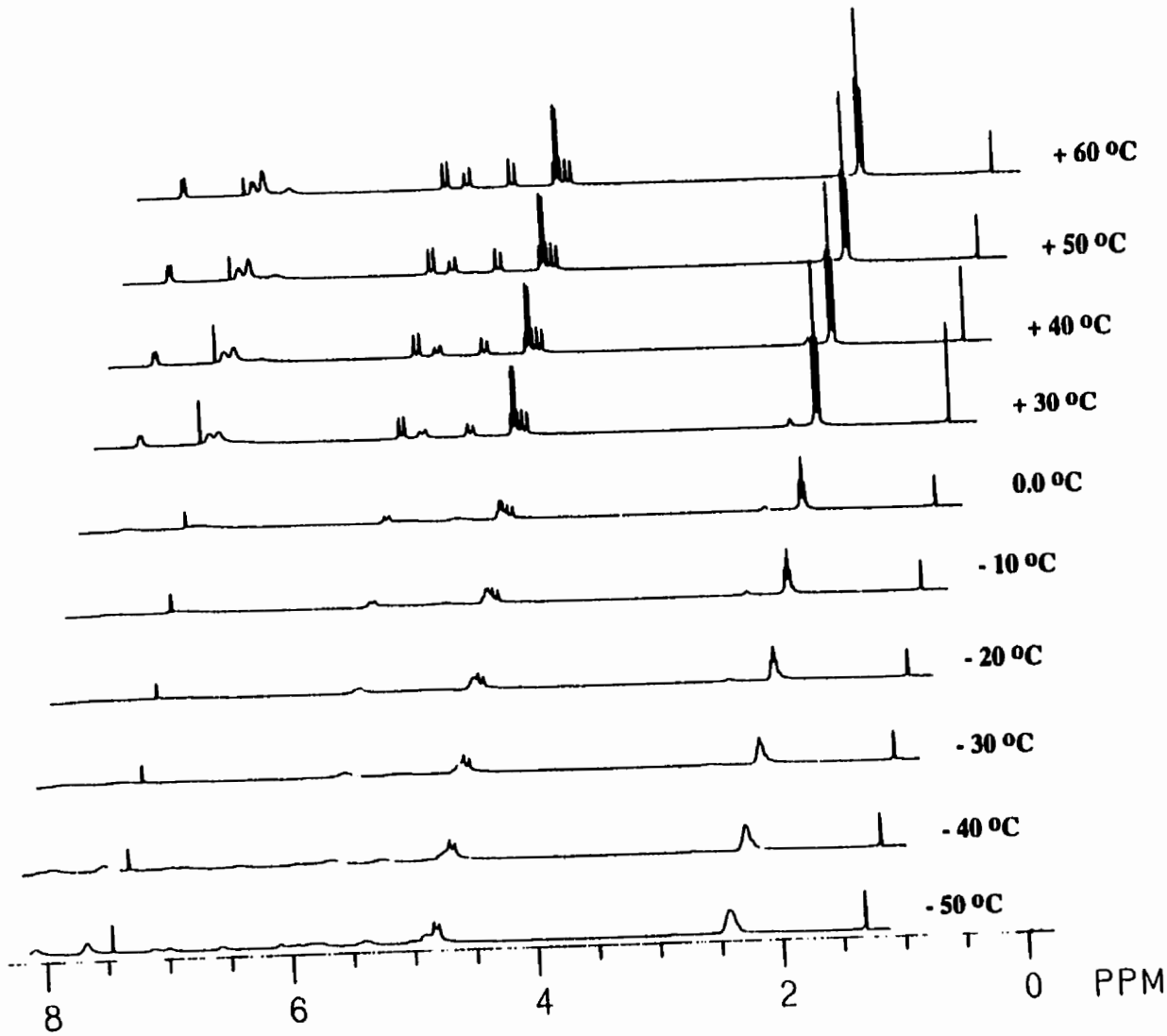


Fig. 4.7. VT ^{1}H NMR Spectra of Tetraestercalix[4]naphthalene 70b in $CDCl_3$.



indicates that the initial conformation (cone conformation) is retained under these conditions. On the other hand, as the temperature was decreased to 0 °C the ^{1}H NMR ($CDCl_3$) spectrum (Figure 4.7) shows that the signals for the aromatic and the diastereotopic methylene protons flattened out. Below 0 °C the signals become broader, particularly at - 20 °C which was therefore was assigned to be the approximate coalescence temperature. At - 50 °C, the ^{1}H NMR spectrum starts to show simple, partially resolved sets of resonances arising from both the aromatic and methylene protons, also compatible with a cone conformation at low temperature (Figure 4.7). These observations (sharp signals at high temperatures, very broad signals at moderate low temperatures and partially resolved signals at very low temperatures) indicate that the molecule fluctuates between the cone and flattened-cone conformations.

The ^{1}H NMR spectrum ($CDCl_3$) of the second product displays four sets of triplets in the ratio of 1:1:1:1, and a very complex splitting pattern in both the methylene (integrated for 24 protons) and aromatic (integrated for 20 protons) regions, as shown in Figure 4.9. Also, its ^{13}C NMR ($CDCl_3$) spectrum shows 58 carbon signals, among them four different carbon carbonyl signals at 168.8, 169.1, 169.2, and 169.9 ppm. These spectra are consistent only with a structure of having C_1 symmetry, i.e., a structure in which all the protons and the carbons of the naphthalene rings, methylene bridges and ester groups are different. On the basis of these data it is most likely that this compound adopts a partial-cone conformation, as can be further discerned from its splitting pattern as predicted from Table

Fig. 4.8. VT ^{1}H NMR Spectra of Tetraestercalix[4]naphthalene 70b in DMSO-d_6.

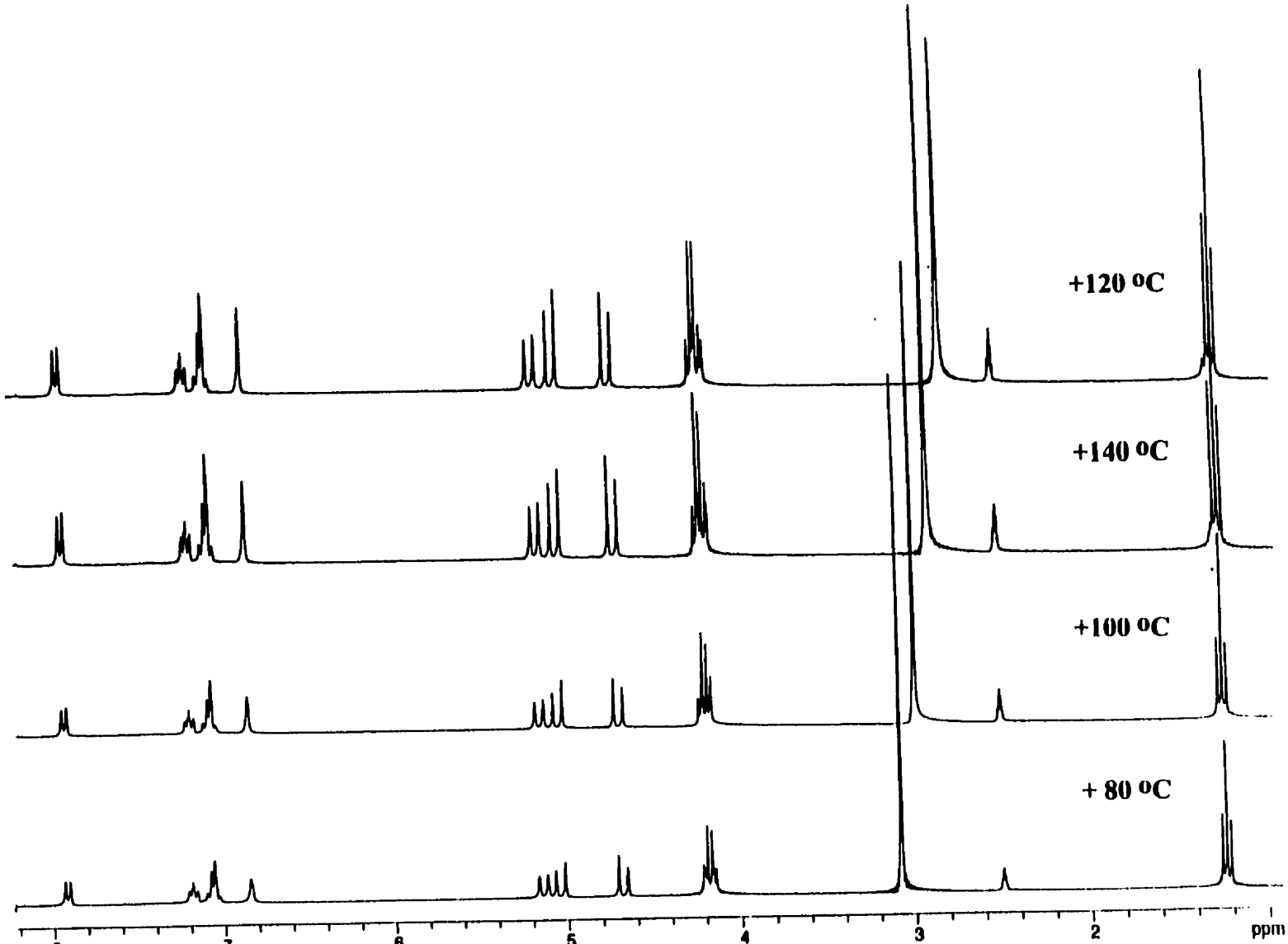
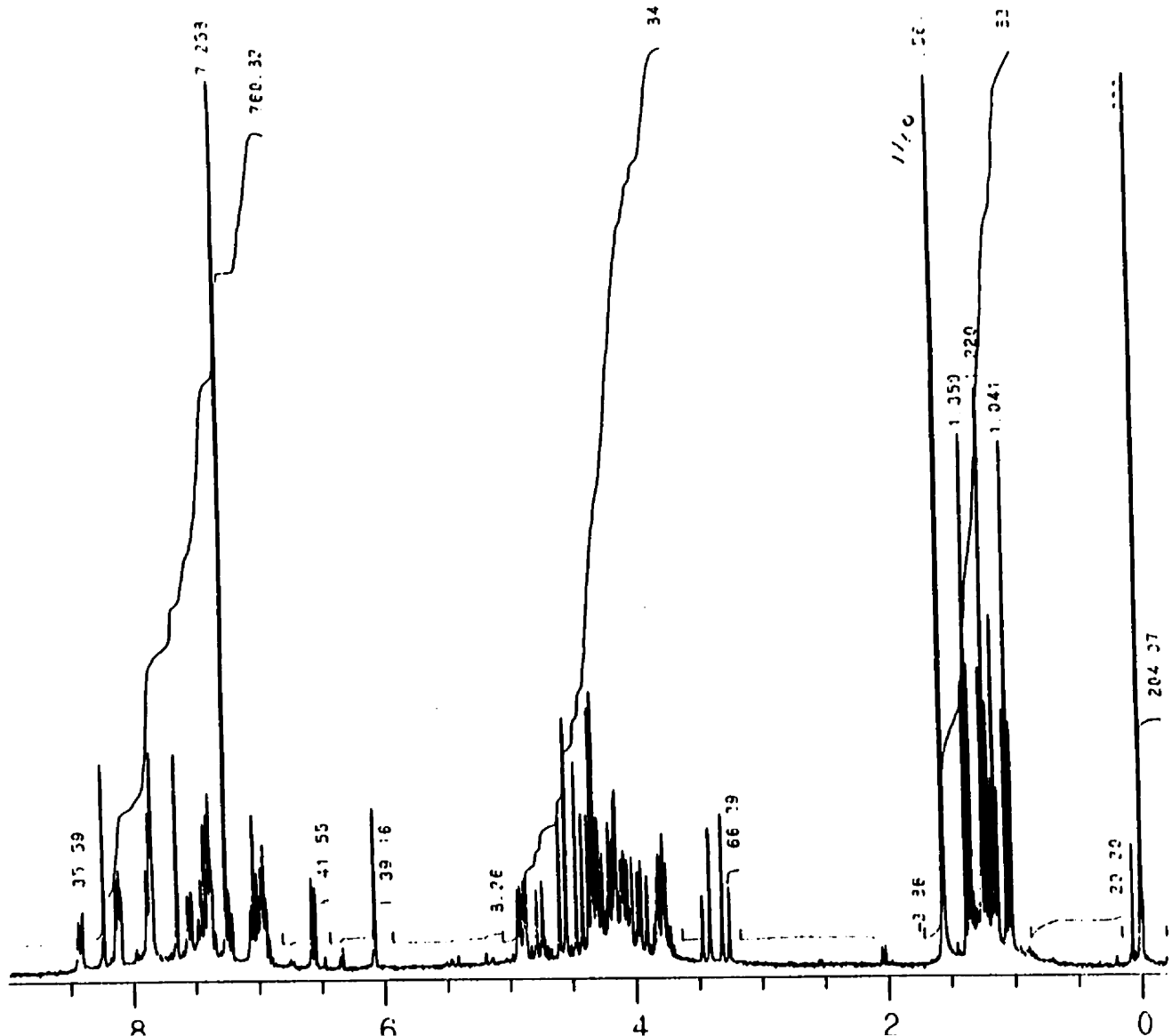
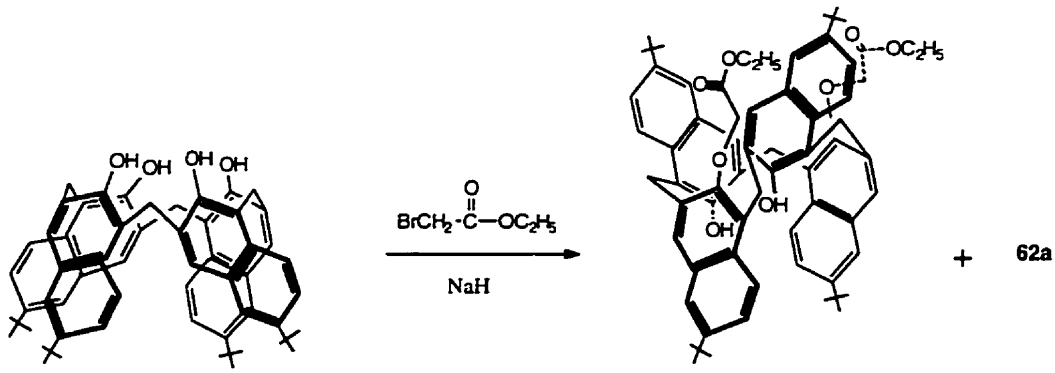


Fig. 4.9. ^{1}H NMR Spectrum of Tetraestercalix[4]naphthalene 70a in $CDCl_3$.



4.1. As in the case for the cone conformer, +FAB MS shows a signal at m/z = 986 (20%), which is compatible with the molecular mass of the molecule plus a water molecule.

4.4.c. Ester Derivatives of *tert*-Butylcalix[4]naphthalene 62



62 **62b**

Acetylation of *tert*-butylcalix[4]naphthalene **62** was carried out under the same conditions as were used for acetylation of calix[4]naphthalene **57**. Treatment of **62** with an excess of ethyl bromoacetate and NaH in refluxing THF for 6 h also resulted in the formation of two products. The less polar one, which formed as the minor product, is the mono-ester derivative **62a**. Attachment of one residue to the phenolic oxygen leads to a totally asymmetric molecule in which all the aromatic units are different. Indeed, the ambient temperature ^{1}H NMR ($CDCl_3$) spectrum of **62a**, besides having three singlets for the hydroxyl groups at 9.10, 9.34 and 9.51 ppm, also shows four singlets for the *tert*-butyl groups at 1.19, 1.22 1.39 and 1.41 ppm, and one methyl group overlaping the later two *tert*-

butyl groups, which integrate for twenty one protons.

The more polar product, formed as the major product, is the di-ester derivative **62b**. In its ^{1}H NMR spectrum, the one set of methyl groups and the methylene region signals integrate for six and sixteen protons, respectively. In principle, the di-ester derivative could be either 1,2-substituted or 1,3-substituted. Also, by analogy with the tetraester derivatives, these two di-substituted derivative, can each adopt one or more of the five possible types of conformations: cone, pinched-cone, partial-cone, 1,2-alternate, and 1,3-alternate. Due to the inherent chirality of calix[4]naphthalene **62**, the two protons of the OC**H**$_2$CO group are diastereotopic and thus appear as two doublets. Based on molecular models, the anticipated splitting patterns for the ArCH$_2$Ar and OCH$_2$CO groups in ^{1}H NMR are summarized in Tables 4.2 and 4.3, respectively.

Table 4.2. Predicted splitting pattern of Ar*CH*$_2$Ar protons of 62b

conformation	**1,3-substituted**	**1,2-substituted**
cone	one pair of doublets	three pairs of doublets
pinched-cone	one pair of doublets	three pairs of doublets
1,2-alternate (symmetrical)* 1,2-alternate (unsymm.)	---------- two pairs of doublets	three pairs of doublets three pairs of doublets
1,3-alternate (symmetrical) 1,3-alternate (unsymm.)	two pairs of doublets ----------	 three pairs of doublets
partial-cone	four pairs of doublets	four pairs of doublets

* symmetrical when the two substituents attached to the phenolic oxygens are in the same direction and *vice-versa*.

Table 4.3. Predicted splitting pattern of OCH_2CO protons of 62b

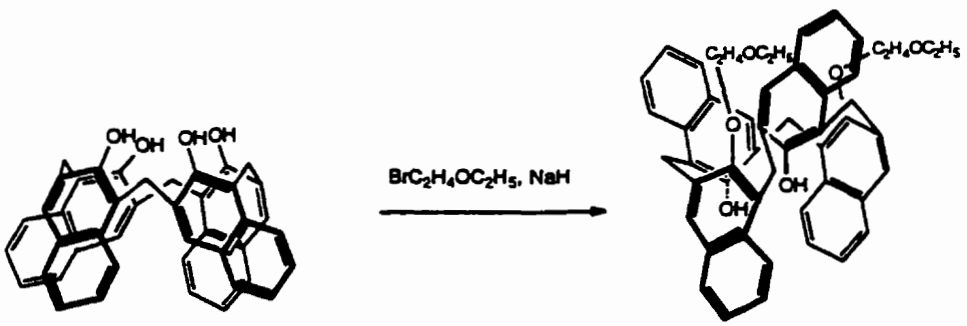
conformation	1,3-substituted	1,2-substituted
cone	one pair of doublets	one pair of doublets
pinched-cone	one pair of doublets	three pairs of doublets
1,2-alternate (symmetrical) 1,2-alternate (unsymm.)*	---------- one pair of doublets	two pairs of doublets two pairs of doublets
1,3-alternate (symmetrical) 1,3-alternate (unsymm.)	one pair of doublets ----------	 one pair of doublets
partial-cone	two pairs of doublets	two pairs of doublets

The ^{1}H NMR (C_6D_6) spectrum of the diester derivative **62b** shows a triplet centered at 1.00 ppm (J = 6.9 Hz), a multiplet centered at 3.99 ppm and six doublets (three pairs) at 4.27 (J = 15.3 Hz), 4.37 (J = 14.7 Hz), 4.43 (J = 13.8 Hz), 4.75 (J = 15.3 Hz), 4.94 (J = 13.2 Hz) and 5.27 ppm (J = 14.1 Hz). Based on these data and the splitting patterns of the $ArCH_2Ar$ and OCH_2CO protons summarized in Tables 4.2 and 4.3, the diester **62b** is most likely the 1,3-substituted diester derivative. Furthermore, the number of signals for the *tert*-butyl groups and the aromatic protons are double those observed with the parent compound **62**, i.e., two *tert*-butyl singlet signals, two singlet signals (H-10, H-20, H-30, H-40), two doublets (J = 9.0 Hz, H-5, H-15, H-25, H-35), two doublets (J = 1.5 Hz, H-8, H-18, H-28, H-38), two double doublets (J = 9.0, 1.5 Hz, H6, H-16, H-26, H-36). This observation is consistent only with a structure which is 1,3-substituted. Examination of Tables 4.2 and 4.3 indicates that two possible conformations for a 1,3-substituted derivative that are consistent

with the observed ^{1}H NMR spectrum, one is 1,3-alternate and 1,2-alternate. The methyl shift of 1.00 ppm, which is typical for the methyl group of ethanol, suggests that they are unshielded by the naphthalene rings, precluding a 1,2-alternate conformation. To confirm this, NOE enhancements of the aromatic singlet signals at 7.45 and 7.95 ppm (corresponding to H-10, H-20, H-30, H-40) were observed when the aromatic doublets centered at 8.04 and 8.40 ppm (corresponding to H-5, H-15, H-25, H-35) were saturated, and *vice-versa*. Examination of molecular models reveals that this NOE could not occur unless the molecule is in the 1,3-alternate conformation.

Based on COSY and NOED experiments, the pair of doublets centered at 5.27 and 4.37 (J = 14.1Hz); 4.94 and 4.43 (J = 13.2 Hz); and 4.75 and 4.27 (J = 15.3 Hz) are clearly coupled. The coupled doublets centered at 5.27 and 4.37, and 4.94 and 4.43 ppm respectively were assigned to the methylene bridge protons, since NOE enhancements were observed for the doublets centered at 4.37 and 4.43 ppm when the aromatic doublets centered at 8.04 and 8.40 ppm (corresponding to H-5, H-15, H-25, H-35) were saturated.

4.5. Bis(2-ethoxyethoxy)calix[4]naphthalene (57a)



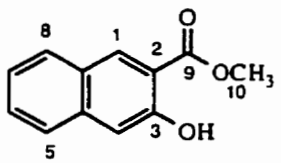
57 **57a**

As mentioned previously, the mobility of the calix[4]arene backbone can be blocked by introducing four substituents that are bulkier than the ethyl group at the lower rim (phenolic oxygen), and the stereochemical outcome is determined by the reaction conditions and the metal ion of the base used. The objective of locking the conformation of a calix[4]arene in one of its conformers is to design receptors (hosts) having steric and electronic features that are complementary to those of the substrates (guests) to be bound. On the basis of these requirements, a great variety of receptor molecules have been designed for the selective recognition of ions and neutral molecules. For example, calix[4]arene was converted into tetrakis(2-ethoxyethoxy)calix[4]arene in the cone conformation upon treatment with $CH_3CH_2OCH_2CH_2Br$ using NaH as base in DMF.[71] Treatment of calix[4]naphthalene **57** with $CH_3CH_2OCH_2CH_2Br$ under these conditions resulted in the formation of only one product. This product was assigned as a dialkyl derivative since in its ^1H NMR (C_6D_6) spectrum the one set of methyl groups centered at 1.2 ppm corresponded to six protons, whereas the signals in the methylene region corresponded to twenty protons assigned to the methylene protons of two alkyl groups (-$CH_2CH_2OCH_2$-) and four methylene bridges. Due to the inherent chirality of calix[4]naphthalene **57**, the methylene protons of the - OCH_2CH_2O- group are diastereotopic and couple with each other (geminal and vicinal coupling) to produce a complex splitting patterns. Indeed, the ^1H NMR (C_6D_6) spectrum at room temperature shows four multiplets centered at 3.54, 3.77, 3.94 and 4.12 ppm. Also, the spectrum shows two pairs of doublets corresponding to the

methylene bridges centered at 4.28 (J = 15.0 Hz), 4.34 (J = 13.5 Hz), 4.98 (J = 13.8 Hz) and 5.06 (J = 14.7 Hz). Furthermore, in the ^{13}C NMR ($CDCl_3$) spectrum, besides the two carbon signals at 23.4 and 28.9 ppm corresponding to the two different types of methylene bridges, there are 20 carbon signals corresponding to aromatic carbons. These spectra and reasoning by analogy with the arguments presented above suggest that the product is the 1,3-disubstituted alkyl derivative. Examination of Table 4.2 indicates that of the two possible 1,3-substituted conformations that are consistent with the observed ^1H NMR spectrum, one is 1,3-alternate and the other is 1,2-alternate. It is more likely the molecule adopts a 1,3-alternate conformation since the methyl group is not shielded by the opposing naphthalene rings, hence precluding the 1,2-alternate conformation. Based on a COSY experiment and the coupling constants, the doublets at 4.28 and 5.06 ppm are coupled to each other, as are the other doublets.

4.6. Experimental.

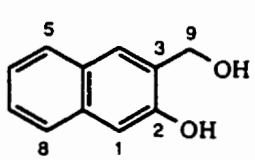
Methyl 3-hydroxy-2-naphthoate (58).



58

To a solution of 3-hydroxy-2-naphthoic acid (**9**) (3.8 g, 0.02 mol) in 20 mL of methanol was added concentrated sulfuric acid (0.82 ml) at room temperature. The temperature was raised to reflux for 8 h. The reaction mixture was cooled to rt to form a yellow solid which was filtered, washed with 10% aqueous $NaHCO_3$ and dried to give 3.93 g (97%) of **58**, m.p. 69-70 °C; ^1H NMR (C_6D_6) δ = 3.31 (s, 3H, CH_3), 7.02 (t, J = 7.8 Hz, 1H, H-6 or H-7), 7.15 (br, 1H, H-7 or H-6), 7.35 (d, J = 8.7 Hz, 1H, H-5 or H-8), 7.41 (s, 1H, H-4), 7.50 (d, J = 8.7 Hz, 1H, H-8 or H-5), 8.31 (s, 1H, H-1), 10.93 (s, 1H, OH).

3-(hydroxymethyl)-2-naphthol (56).

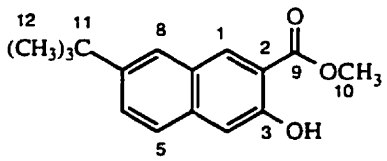


56

A solution of methyl 3-hydroxy-2-naphthoate (**58**) (1.88 g, 9.31 mmol) in anhydrous

THF (30 mL) was added at rt to a suspension of LAH (0.71 g, 19 mmol) in dry THF (50 mL) over 30 min, and the mixture stirred at rt for 3 h. The reaction was quenched by pouring the suspension into cold, wet diethyl ether, then the mixture was treated with aqueous 10% HCl at 0 °C. The ether layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated to give a pale yellow solid, 1.52 g (94%) which could be crystallized for analysis from ethanol-water, m.p. 186-188 °C (lit. m.p. 185 °C)[62]; ^{1}H NMR (acetone-d_6) δ = 4.50 (t, J = 5.7 Hz, 1H, CH_2**OH**), 4.88 (d, J = 5.7 Hz, 2H, H-9), 7.18 (s, 1H. H-1), 7.25 (m, 1H, H-6 or H-7), 7.33 (m, 1H, H-7 or H-6), 7.65 (d, J = 8.1 Hz, 1H. H-5 or H-8), 7.77 (d, J = 8.1 Hz, 1H, H-5 or H-8), 7.83 (s, 1H, H-4), 8.79 (s, 1H, OH); ^{13}C NMR (acetone-d_6) δ = 61.7 (C-9), 109.7, 123.9, 126.5, 126.7, 126.9, 128.4, 129.5, 131.7, 135.1, 154.6 (C-2); MS *m/z* (%) 174 (M^+, 28), 156 (39), 129 (12), 128 (100), 127 (15), 115 (13), 64 (13), 63 (9), 51 (9).

Methyl 7-*tert*-butyl-3-hydroxy-2-naphthoate (60).

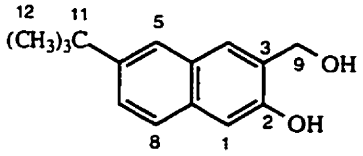


60

To a solution of methyl 3-hydroxy-2-naphthoate (**58**) (307 mg, 1.52 mmol) in 1,1,2,2-tetrachloroethane (5 mL) at 0 °C, under Ar was added *tert*-butyl chloride (0.66 mL,

6.1 mmol) followed by the addition of $AlCl_3$ (410 mg, 3.04 mmol) in portions over 15 min. The reaction solution was stirred at rt for 24 h. Work-up was effected by the addition of cold water at 0 °C and then extraction with 50 mL of $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent removed by vacuum distillation. The crude product was purified by PLC using ethyl acetate-petroleum ether (10:90) to give **60** as a light yellow solid (0.28 g, 73%), m.p. 102-103 °C; ^{1}H NMR ($CDCl_3$) δ = 1.39 (s, 9H, H-12), 4.02 (s, 3H, H-10), 7.27 (s, H-4), 7.62 (m, 2H, H-7, H-8), 7.71 (s, 1H, H-5), 8.46 (s, 1H, H-8), 8.46 (s, 1H, H-1), 10.93 (s, 1H, OH); ^{13}C NMR (C_6D_6) δ = 31.5 (C-12), 35.0 (C-11), 52.2 (C-10), 112.3, 114.9, 124.6, 127.0, 127.3, 128.9, 133.0, 137.3, 146.8, 157.5 (C-2), 170.9 (C-9); MS *m/z* (%) 259 (M^++1, 12), 258 (M^+, 67), 243 (49), 227 (23), 226 (100), 212 (15), 211 (93), 183 (16), 155 (11), 139 (11), 115 (13), 92 (12), 83 (10), 78 (32), 76 (10), 71 (11), 69 (15), 57 (21), 55 (15); HRMS H^+ 258.1253 calcd for $C_{16}H_{18}O_3$ 258.1256.

6-*tert*-Butyl-3-(hydroxymethyl)-2-naphthol (61).



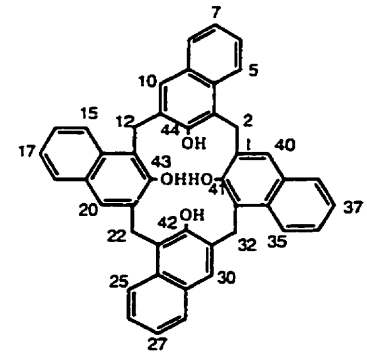
61

A solution of methyl 7-*tert*-butyl-3-hydroxy-2-naphthoate (**60**) (1.1 g, 3.9 mmol) in anhydrous THF (15 mL) was added at rt to a suspension of LAH (0.29 g, 7.8 mmol) in anhydrous THF (20 mL) over 40 min, and the reaction mixture stirred at rt for 2 h. The

reaction was quenched by pouring the suspension into cold, wet diethyl ether followed by addition of aqueous 10% HCl at 0 °C. After the separation of the organic layer, the aqueous layer was extracted with 30 mL of diethyl ether. The combined ether layers were dried over anhydrous $MgSO_4$, filtered and evaporated to give **61** as a light yellow solid (0.81 g, 90%), m.p. 174-176 °C; ^{1}H NMR (acetone-d_6) δ = 1.38 (s, 9H, *tert*-Bu), 4.87 (d, J = 5.4 Hz, 2H, H-9), 7.13 (s, 1H, H-1), 7.50 (d, J = 8.7 Hz, 1H, H-7), 7.61 (d, J = 8.7 Hz, 1H, H-8), 7.73 (s, 1H, H-5), 7.79 (s, 1H, H-4), 8.68 (s, 1H, OH); ^{13}C NMR (acetone-d_6) δ = 30.4, 62.2, 109.8, 109.9, 123.9, 125.8, 127.0, 127.5, 129.8, 131.8, 131.4, 133.7, 146.8, 154.7; MS *m/z* (%) 231 (M^++1, 8), 230 (48), 213 (20), 212 (100), 198 (10), 197 (59), 184 (41), 169 (32), 152 (10), 141 (10), 128 (13), 115 (12), 77 (10), 71 (29), 57 (15), 43 (59), 41 (14); NOE (%) **OH/** H-4 (2), H-1 (6.0); **H-4/** H-5 (7), H-9 (2); **H-5/** H-4 (4), H-12 (0.6); **H-8/** H-7 (11), H-1 (4.0); **H-7/** H-8 (0.3), H-12 (0.3); **H-1/** H-8 (7), OH (2); HRMS H^+ 230.1308 calcd for $C_{15}H_{18}O_2$ 230.13.07

Calix[4]naphthalene (57).

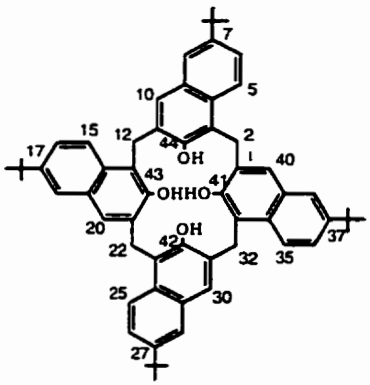
To a solution of 3-(hydroxymethyl)-2-naphthol (**56**) (0.87 g, 5.1 mmol) in dioxane (70 mL) was added $TiCl_4$ (0.61 mL, 5.5 mmol) dropwise at 60 °C under N_2. The mixture was refluxed for 36 h. Work-up of the reaction mixture was effected by first evaporating the dioxane under vacuum. The crude product was dissolved in 30 mL of $CHCl_3$, and the resulting suspension was subjected to flash chromatography using CH_2Cl_2-petroleum ether (1:1) to give **57** as a light brown solid (0.104 g, 13%), m.p. >300 °C dec. (lit. m.p. 384-386



57

°C)[62]; I.R. (Nujol, cm^{-1}): 3406 (br, OH), 1256, 1182, 1091, 1048, 844, 747; ^1H NMR ($CDCl_3$) δ = 4.58 (s, 8H, H-2, H-12, H-22, H-32), 7.23 (dd, J = 7.8, 0.9 Hz, 4H, H-6, H-16, H-26, H-36), 7.51 (m, 4H, H-7, H-17, H-27, H-37), 7.61 (d, J = 7.8 Hz, 4H, H-8, H-18, H-28, H-38), 7.86 (s, 4H, H-10, H-20, H-30, H-40), 8.38 (d, J = 8.7 Hz, 4H, H-5, H-15, H-25, H-35), 10.96 (s, 4H, OH); ^{13}C NMR (DMSO-d_6) δ = 25.6 (C-2, C-12, C-22, C-32), 119.4, 122.8 (C-6, C-16, C-26, C-36 or C-7, C-17, C-27, C-37), 123.0 (C-5, C-15, C-25, C-35), 125.9 (C-7, C-17, C-27, C-37 or C-6, C-16, C-26, C-36), 128.1 (C-8, C-18, C-28, C-38), 128.4 (C-10, C-20, C-30, C-40), 128.6, 129.3, 131.4, 149.7 (C-41, C-42, C-43, C-44); MS *m/z* (%) 626 (M^++2, 12), 625 (M^++1, 47), 624 (M^+, 100), 607 (9), 606 (15), 588 (7), 467 (10), 450 (8), 449 (11), 325 (8), 324 (8), 311 (21), 297 (7), 296 (8), 295 (23), 294 (11), 281 (15), 169 (38), 157 (58), 141 (19).

***tert*-Butylcalix[4]naphthalene (62).**



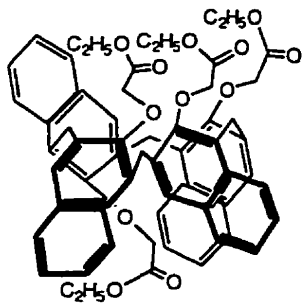
62

To a solution of 6-*tert*-butyl-3-(hydroxymethyl)-2-naphthol **61** (0.41 g, 1.8 mmol) in dioxane (60 mL) was added $TiCl_4$ (0.21 mL, 1.8 mmol) dropwise at 60 °C under N_2. The mixture was refluxed for 24-30 h. Work-up of the reaction was effected by evaporating the solvent under vacuum and then dissolving the crude product in 50 mL of $CHCl_3$. Insoluble material was removed by filtration. The solution was concentrated to about 10 mL and subjected to flash chromatography using CH_2Cl_2-petroleum ether (1:1) to give **62** as a light brown solid (102 mg, 31%), m.p. 246-249 °C dec.; I.R. (Nujol, cm^{-1}): 3284 (br, OH), 1305, 1232, 1162, 1097, 899; ^1H NMR ($CDCl_3$) δ = 1.32 (s, 36H, *tert*-Bu), 4.52 (s, 8H, H-2, H-12, H-22, H-32), 7.51 (d, J = 1.8 Hz, 4H, H-8, H-18, H-28, H-38), 7.58 (dd, J = 9.0, 1.8 Hz, 4H, H-6, H-16, H-26, H-36), 7.76 (s, 4H, H-10, H-20, H-30, H-40), 8.28 (d, J = 9.0 Hz, 4H, H-5, H-15, H-25, H-35), 10.62 (s, 4H, OH); ^{13}C NMR ($CDCl_3$) δ = 26.0 (C-2, C-12, C-22,

C-32), 31.2 ($C(\mathbf{C}H_3)_3$), 34.4 ($\mathbf{C}(CH_3)_3$), 119.3, 122.6 (C-5, C-15, C-25, C-35), 123.7 (C-8, C-18, C-28, C-38), 125.0 (C-6, C-16, C-26, C-36), 128.2, 129.2, 129.7, 129.9 (C-10, C-20, C-30, C-40), 145.8, 147.6; +FAB-MS *m/z* (%) 848 (M^+, 17), 847 (6), 829 (11), 813 (5), 811 (11), 630 (4), 619 (5), 618 (5), 617 (8), 545 (3), 437 (16), 425 (7), 423 (11), 407 (18), 406 (9), 393 (13), 391 (12), 389 (7), 377 (11), 367 (10), 351 (11), 289 (12), 265 (12), 253 (10), 252 (11), 239 (16), 237 (9), 227 (16), 226 (20), 225 (73), 223 (10), 215 (10), 214 (14), 213 (71), 211 (15), 209 (14).

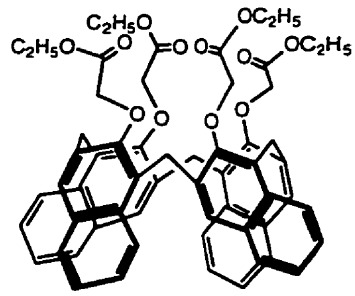
Tetrakis((ethoxycarbonyl)methoxy)calix[4]naphthalenes (70a) and (70b).

To a suspension of calix[4]naphthalene **57** (88 mg, 0.14 mmol) in anhydrous THF (16 mL) was added NaH (113 mg, 2.82 mmol). The reaction mixture was stirred at room temperature for 30 min and then an excess of ethyl bromoacetate (0.17 mL, 1.4 mmol) was added. The mixture was refluxed for 3 h. The work-up was effected by evaporating the solvent to dryness. The crude product was then neutralized by adding 5 mL of water followed by 5 mL of aqueous 10% HCl. The mixture was extracted with 30 ml of $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to give the crude product, which was purified by PLC using $CHCl_3$ to give, in order of increasing polarity: **tetrakis((ethoxycarbonyl)methoxy)calix[4]naphthalene (70a)**, as a colorless solid (28 mg, 21%), m.p. 70-72 °C; I.R. ($CHCl_3$, cm^{-1}): 1757 (br), 1735 (br), 1622, 1596, 1501, 1438, 1374, 1283 (br), 1236, 1179, 1107, 1063, 1032, 946, 881, 850; ^1H NMR ($CDCl_3$) δ = 1.04, 1.15, 1.22, 1.36 (t each, 3H, CH_3), 3.28 and 3.44 (2d, J = 16.8 and 17.4



70a

Hz, 2H), 4.03 (m,15H), 4.44 and 4.57 (2d, J = 15.3 and 15.6 Hz, 4H), 4.76 (d, J = 13.5 Hz, 1H), 4.88 and 4.92 (2d, J = 5.1 and 6.0 Hz, 2H), 6.07 (s, 1H), 6.56 (d, J = 8.4 Hz, 1H), 7.00 (m, 4H), 7.22 (d, J = 7.2 Hz, 1H), 7.42 (m, 4H), 7.55 (d, J = 7.5 Hz, 1H), 7.56 (s, 1H), 7.87 (m, 3H), 8.12 (m, 2H), 8.24 (s, 1H), 8.42 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 14.1, 14.3, 24.1, 28.9, 29.5, 31.2, 59.6, 60.8, 61.0, 61.1, 67.6, 70.6, 71.0, 72.2, 76.6, 120.0, 123.0, 123.1, 123.4, 123.5, 123.7, 124.0, 124.1, 124.5, 124.7, 125.4, 125.7, 126.7, 127.4, 127.5, 128.1, 128.3, 128.5, 128.6, 129.3, 130.2, 130.4, 130.5, 130.7, 130.8, 130.9, 131.7, 132.0, 132.4, 132.5, 133.5, 134.0, 135.5, 153.6, 154.1, 154.3, 155.2, 168.8, 169.1, 169.2, 169.9; +FAB-MS *m/z* (%) 986 (M^++H_2O, 20), 968 (M^+, 1), 967 (5), 966 (16), 965 (35), 964 (42), 891 (11), 789 (5), 626 (4), 614 (9); and **tetrakis((ethoxycarbonyl)methoxy)calix[4]-naphthalene (70b)** as a colorless solid (12 mg, 9%), m.p. 95-97 °C; I.R. ($CHCl_3$, cm^{-1}): 3054, 2980, 2929, 1757, 1613, 1502, 1434,1376, 1283, 1201, 1179, 1106, 1063, 742; ^{1}H NMR ($CDCl_3$) δ = 1.28 (t, J = 6.9 Hz, 12H, $4CH_3$), 4.12 (d, J = 14.7 Hz, 4H, Ar**C**$\mathbf{H_2}$Ar, equatorial), 4.21 (q, J = 6.9 Hz, 8H, 4COO**C**$\mathbf{H_2}$), 4.64 (d, J = 16.5 Hz, 4H, O**C**$\mathbf{H_2}$CO), 5.11

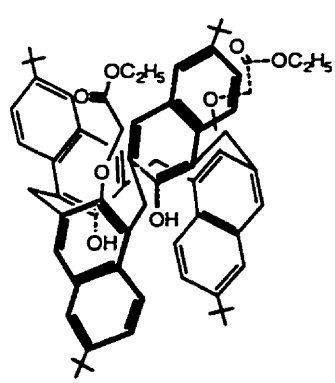


70b

(d, J = 15.9 Hz, 4H, OC**H**$_2$CO), 5.31 (d, J = 14.7 Hz, 4H, ArC**H**$_2$Ar, axial), 7.13 and 7.82 (br, 2OH, aromatic); ^{1}H NMR (DMSO-d_6 at 140 °C) δ = 1.25 (t, J = 6.9 Hz, 12H, OCH$_2$C**H**$_3$), 4.17 (d, J = 14.1 Hz, 4H, ArC**H**$_2$Ar, equatorial), 4.20 (q, J = 6.9 Hz, 8H, 4COOC**H**$_2$), 4.70 (d, J = 15.3 Hz, 4H, OC**H**$_2$CO), 5.03 (d, J = 15.6 Hz, 4H, OC**H**$_2$CO), 5.15 (d, J = 14.1 Hz, 4H, ArC**H**$_2$Ar, axial), 6.84 (s, 4H), 7.06 (m, 8H), 7.17 (m, 4H), 7.91 (d, J = 8.7 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ = 14.2 (**C**H$_3$), 60.6 (Ar-**C**H$_2$-Ar and COO**C**H$_2$), 71.6 (O**C**H$_2$CO$_2$), 123.3, 123.5, 124.7, 128.1, 128.7, 130.3, 131.6, 134.3, 154.4, 170.1 (O**C**O$_2$); +FAB-MS *m/z* (%) 988 (M$^+$+2+H$_2$O, 69), 987 (M$^+$+1+H$_2$O, 100), 986 (M$^+$+H$_2$O, 7), 965 (8), 964 (9), 902 (8), 901 (16), 900 (17).

Ester Derivatives of *tert*-butylcalix[4]naphthalene 62. To a stirred solution of **62** (130 mg, 0.153 mmol) in anhydrous THF (10 mL) was added NaH (61 mg, 1.5 mmol) in one portion at rt under N_2. The reaction mixture was left to stir at room temperature for 15 min. Excess ethyl bromoacetate (0.17 mL, 1.5 mmol) was added, and then the mixture was refluxed for 6 h. Work-up of the reaction mixture was effected by evaporating the solvent

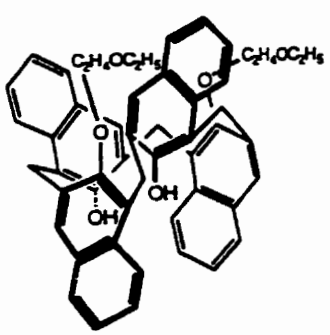
and dissolving the residue in 20 mL of $CHCl_3$. The organic solution was washed twice with 20 mL of aqueous 10% HCl. The combined organic layers were dried, filtered and evaporated in the usual manner. The crude product was purified by PLC using $CHCl_3$-petroleum ether (90:10) to give, in order of increased polarity: **mono((ethoxycarbonyl)-methoxy)*tert*-butylcalix[4]naphthalene (62a)** as a pale yellow solid (9.0 mg, 6%), m.p. 220-225 °C; ^{1}H NMR ($CDCl_3$) δ = 1.19 (s , 9H , *tert*-Bu), 1.22 (s, 9H, *tert*-Bu), 1.40 (s, 9H, *tert*-Bu), 1.41(s, 9H, *tert*-Bu), 1.40 (br, 3H, CH_3), 4.26 (dd, J = 14.3, 6.9 Hz, 1H), 4.74 (d, J = 15.3 Hz, 1H, OCH_2CO), 4.78 (d, J = 20.1 Hz, 2H), 4.98 (d, J = 15.3 Hz, 1H, OCH_2CO), 7.31 (d, J = 8.7 Hz, 2H), 7.45 (m, 2H), 7.60 (m, 6H), 7.83 (d, J = 4.2, 2H), 8.24 (m, 4H), 9.10 (s, 1H, OH), 9.34 (s, 1H, OH), 9.51 (s, 1H, OH); **bis((ethoxycarbonyl)-methoxy)*tert*-butylcalix[4]naphthalene (62b)** as a pale yellow solid (27 mg, 19%), m.p. 213-216 °C;



62b

^{1}H NMR (C_6D_6) δ = 0.86 (s , 18H, *tert*-Bu), 1.00 (t, *J* = 7.5 Hz, 6H, OCH_2CH_3), 1.41 (s, 18H, *tert*-Bu), 3.92-4.07 (m, 4H, OCH_2CH_3), 4.27 (d, *J* = 15.3 Hz, 2H, $ArCH_2Ar$), 4.37 (d, *J* = 14.7 Hz, 2H, OCH_2CO), 4.43 (d, *J* = 13.8, 2H, $ArCH_2Ar$), 4.75 (d, *J* = 15.3 Hz, 2H, $ArCH_2Ar$), 4.94 (d, *J* = 13.2 Hz, 2H, $ArCH_2Ar$), 5.27 (d, *J* = 15.3 Hz, 2H, OCH_2CO), 6.64 (d, *J* = 1.5 Hz, 2H), 6.89 (dd, *J* = 9.0, 1.5 Hz, 2H), 7.45 (s, 2H), 7.68 (dd, *J* = 9.0, 1.5 Hz, 2H), 7.89 (d, *J* = 1.8 Hz, 2H), 7.95 (s, 2H), 8.04 (d, *J* = 8.7 Hz, 2H), 8.42 (d, *J* = 9.0 Hz, 2H), 8.46 (s, 2H, OH); ^{13}C NMR ($CDCl_3$) δ = 14.2 (CH_3), 23.9 ($ArCH_2Ar$), 29.5 ($ArCH_2Ar$), 31.0 ($C(CH_3)_3$), 31.4 ($C(CH_3)_3$), 34.4 ($C(CH_3)_3$), 34.5 ($C(CH_3)_3$), 61.5 (OCH_2CH_3), 72.7 (OCH_2CO_2), 121.3, 122.6, 123.3, 123.6, 124.1, 124.5, 124.9, 127.6, 128.2, 128.7, 129.5, 129.6, 130.6, 131.6, 133.3, 144.5, 146.7, 150.9, 151.9, 168.6 (OCO_2); +FAB-MS *m/z* (%) 1043 (M^++Na, 3), 1020 (M^+, 2), 1018 (2), 1017 (7), 1016 (15), 1015 (20), 1014 (6), 983 (3), 982 (3), 966 (4), 943 (4).

Bis(2-ethoxyethoxy)calix[4]naphthalene (57a).



57a

To a stirred solution of **57** (50 mg, 0.08 mmol) in anhydrous DMF (5 mL) was added NaH (32 mg, 0.80 mmol) in one portion at rt under N_2. The reaction mixture was stirred at rt for 15 min. Excess ethyl bromoacetate (0.11 mL, 0.81 mmol) was added, and then the temperature was raised to 80 °C for 10 h. The work-up of the reaction mixture was effected by evaporating the solvent, and the residue was diluted by adding 20 mL of CH_2Cl_2. The organic layer was washed twice with 20 mL aqueous 10% HCl. The organic layer was dried, filtered and the solvent was evaporated in the usual manner. The crude product was purified by PLC using CH_2Cl_2 to give **57a** as a colourless solid (20 mg, 33%), m.p. > 300 °C dec. ; I.R. (Nujol, cm^{-1}): 3395, 1239, 1185, 1102, 1053, 956; ^1H NMR (C_6D_6) δ = 1.19 (t, J = 6.9 Hz, 3H, $OCH_2\mathbf{CH_3}$), 3.49 (q , J = 6.9 Hz, 4 H, $O\mathbf{CH_2}CH_3$), 3.54 (m, 2H, OCH_2CH_2O), 3.77 (m, 2H, OCH_2CH_2O), 3.94 (m, 2H, OCH_2CH_2O), 4.12 (m, 2H, OCH_2CH_2O), 4.28 (d, J = 15.0 Hz, 2H, $ArCH_2Ar$), 4.34 (d, J = 13.5 Hz, 2H, $ArCH_2Ar$), 5.00 (d, J = 13.8 Hz, 2H, $ArCH_2Ar$), 5.06 (d, J = 14.7 Hz, 2H, $ArCH_2Ar$); ^1H NMR ($CDCl_3$) δ = 1.30 (t, J = 6.9 Hz, 6H, $OCH_2\mathbf{CH_3}$), 3.79 (m, 4H, $O\mathbf{CH_2}CH_3$), 4.00 (m, 2H), 4.10 (m, 2H), 4.22 (m, 2H), 4.40 (m, 6H), 4.78 (s, 1H, $ArCH_2Ar$), 4.83 (br, 2H, $ArCH_2Ar$), 4.88 (s, 1H, $ArCH_2Ar$), 7.05 (m, 2H), 7.29 (m, 6H), 7.44 (s, 2H), 7.53 (m, 2H), 7.80 (d, J = 8.1 Hz, 2H), 7.87 (s, 2H), 8.17 (d, J = 8.7 Hz, 2H), 8.36 (d, J = 8.7 Hz, 2H), 8.41 (s, 2H, OH); ^{13}C NMR ($CDCl_3$) δ = 15.2 ($OCH_2\mathbf{CH_3}$), 23.4 ($Ar\mathbf{CH_2}Ar$), 28.9 ($Ar\mathbf{CH_2}Ar$), 67.0, 69.1, 75.7, 107.0, 121.0, 121.9, 122.6, 123.6, 124.1, 124.7, 125.0, 125.7, 127.4, 128.2, 128.3, 128.6, 129.3, 131.5, 131.6, 132.4, 133.9, 151.0, 152.4; +FAB-MS *m/z* (%) 768 (M^+, 1), 767 (1).

Chapter 5

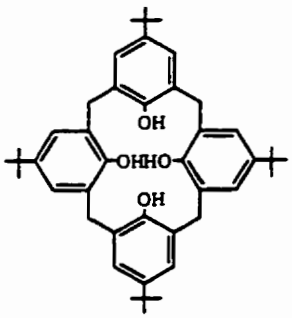
Bis(spirodienone) Derivatives of Calix[4]naphthalenes

5.1. Bis(spirodienone) Derivatives of Calixarenes

As discussed in Chapter 1, upper rim and lower rim functionalizations both have been used for modification of calixarenes. Additionally, there is a third strategy for modification of calixarenes by total or partial replacement of the hydroxyl groups by hydrogens[72] or amino[73] or SH groups.[74] In a different modification, the phenol rings of calixarene derivatives have been oxidized to quinones.[75] Related to this strategy, a novel recent approach for the modification of calixarenes, in which the hydroxyl groups of *p-tert*-butylcalix[4]arenes are oxidized into carbonyl and five-membered cyclic ether functionalities, was reported.[76] This was done by treatment of *p-tert*-butylcalix[4]arene with 2 equivalents of phenyltrimethylammonium tribromide (PTMATB) in a two-phase basic system (CH_2Cl_2, 28% aqueous NaOH) at reflux temperature. This resulted in the formation of three main products (A, A', B) from six possible isomers, as shown in Scheme 5.1. These molecules contain two stereogenic centers and are named " bis(spirodienones)."

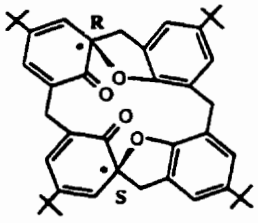
In contrast with the colorless starting material *p-tert*-butylcalix[4]arene, the three products are yellow, in agreement with the presence of dienone moieties in each product. No ring bromination was observed since positions ortho and para to the hydroxyl groups are blocked by the methylene and *tert*-butyl groups, respectively. In the absence of base no

Scheme 5.1.

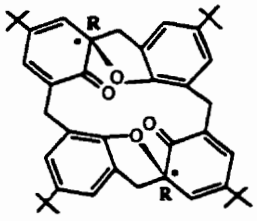


PTMATB. 28% NaOH.

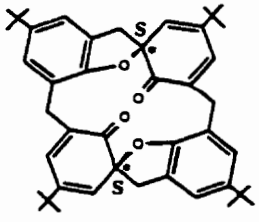
CH_2Cl_2, reflux



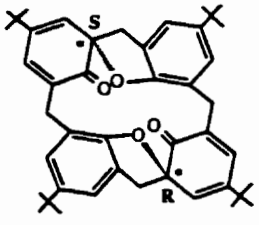
B (C_S, SR)



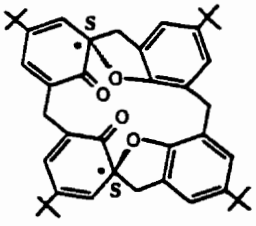
A' (C_2, RR)



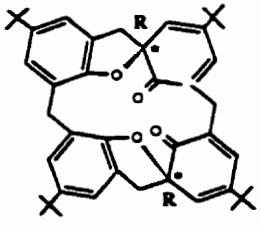
A' (C_2, SS)



A (C_1, SR)



C_2 (SS)



C_2 (RR)

reaction was observed. The formation of the products was explained by first assuming deprotonation of the hydroxyl groups to produce phenolate ions which can undergo bromination to yield an *o*-bromocyclohexadienone derivative. The second step is the replacement of the bromine atoms by the phenoxy groups of a neighboring ring resulting in a five-membered-ring ether.[76] Each of the spirodienones A, A', and B display two *tert*-butyl signals in their ^{1}H NMR spectra. The ^{1}H NMR spectrum of the methylene region of B displays six doublets in a 1:1:1:1:2:2, ratio which is consistent with a molecule of C_s symmetry, as shown in Figure 5.1. Compounds A and A' display, in their ^{1}H NMR spectra, similar patterns for the methylene region, i.e. , four doublets in a ratio 1:1:1:1 (Figure 5.1). Since the ^{1}H NMR spectrum of A is similar to that of A' in the number of signals and the splitting patterns, it was difficult to assign structures for these two products. Therefore, the structures of A and A' were determined by x-ray analyses. The importance of these compounds is the fact that they can be used to partially replace the hydroxyl groups of calixarenes by hydrogen, halogen, amino and sulfonato groups,[77 a, b] which can affect the rigidity, conformation and complexation properties of the resulting calixarenes. Also, since these spirodienones are chiral, it is possible to convert calixarenes into chiral derivatives.

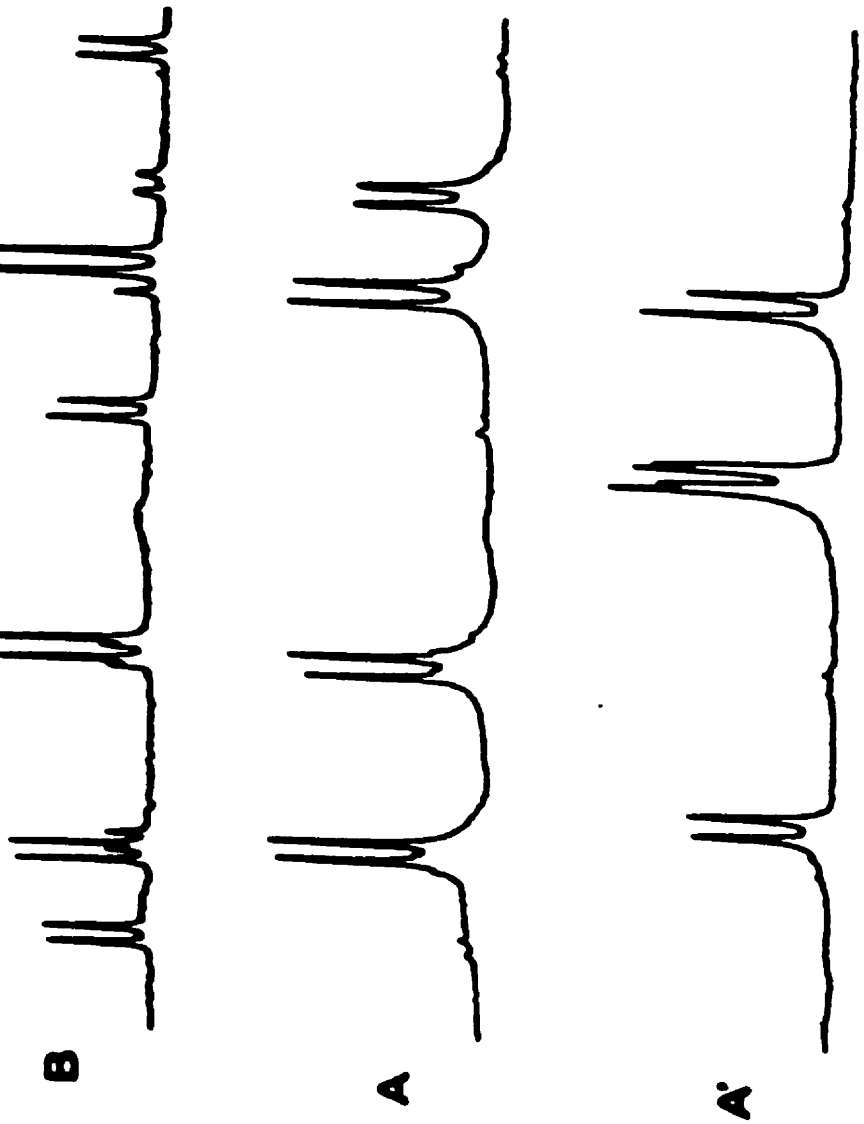


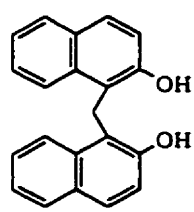
Fig. 5.1. ^{1}H NMR Spectra of the Methylene Region of Bis(spirodienones) A, A' and B.

5.2. Spirodienones Derived from Calix[4]naphthalenes

5.2.a. Oxidation of calix[4]naphthalene (57)

When the naphthalene-ring containing compound bis (2-hydroxy-1-naphthyl)-methane (**71**) was oxidized using either NaOCl/base or Br_2/AcOH/NaOAc, a single product was obtained to which a spirodienone structure **72** was assigned, as shown in Scheme 5.2.[78] In our hands, spirodienone **72** was also produced as a single product in 83% yield from **71** using a two-phase basic system (CH_2Cl_2, 28% NaOH) in the presence of PTMATB. Naphthol dimers bis(1-hydroxy-2-naphthyl)methane (**15**) and its derivatives, **73a** and **73b** were evaluated. Our attempts to oxidize **15** using one equivalent of PTMATB, as was used with the other dimers **73a** and **73b**, failed, even after refluxing for up to 48 h. When three equivalents of PTMATB were used, spirodienone **74a** was formed in 40% yield at room temperature in just one hour. When two equivalents of PTATB were used, **74a** was produced , but in lower yield (20%). These observations suggest that one equivalent of PTMATB was consumed in brominating the *para*-position of the naphthalene ring rather than the *ortho* position to form the *o*-bromo-cyclohexadienone intermediate. This latter intermediate would be required to form the tetrahydrofuran ring by intramolecular nucleophilic substitution of the bromine atom by the phenoxy group of the neighboring ring. Indeed, the spectral data indicate the presence of a bromine atom in the product formed when one equivalent of PTMATB was used. Therefore, when the para positions

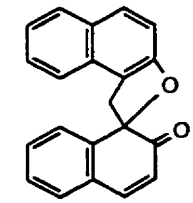
Scheme 5.2



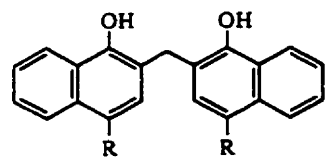
71

NaOCl, base or
Br_2, AcOH, NaOAc or

PTMATB, 28% NaOH,
CH_2Cl_2.



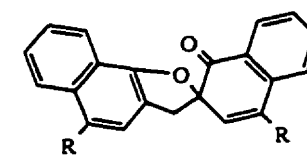
72



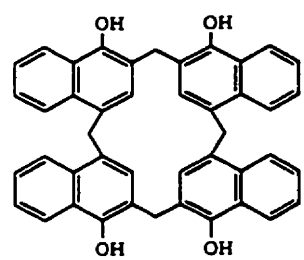
15 R = H
73a R = Br
73b R = Cl

PTMATB

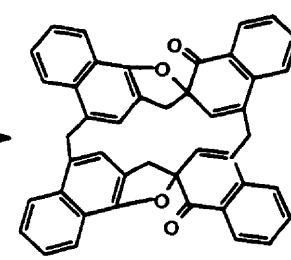
28% NaOH, CH_2Cl_2



74a R = Br
74b R = Cl

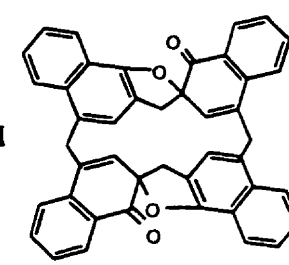


13

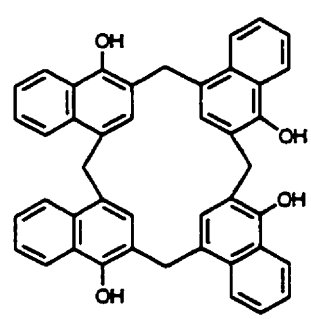


75

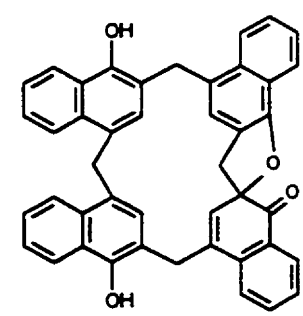
or / and



76



11

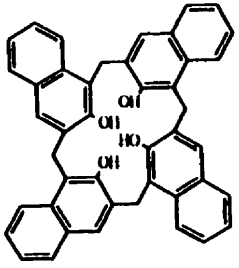


77

of **15** blocked by bromine or chlorine atoms (**73a** and **73b**), formation of the corresponding spirodienones with one equivalent of PTMATB at room temperature in 1-2 h was observed. On the other hand, when the above oxidation conditions were employed with **11** and **13**, which are calix[4]naphthalenes derived from 1-naphthol, no formation of bis(spirodienones) **75-77** was observed. The reactions yielded only intractable resinous products. In order to account for the failure of **11** and **13** to produce the corresponding spirodienones, inspection of Dreiding models suggested that the C-O bond would be difficult to form since the oxygen atom of the OH group is too remote from the carbon that would become the stereocenter.

However, when calix[4]naphthalene **57**, which more closely resembles calix[4]arenes by the fact that the hydroxyl groups are located on the lower rim, was subjected to the same oxidation conditions, a single product was obtained in 30% yield, as shown in Scheme 5.3. This product was yellow, consistent with the presence of dienone moieties. I.R. spectroscopy revealed that the product contains a carbonyl group but no hydroxyl group. In addition to the carbonyl signal at 195.4 ppm, in its ^{13}C NMR ($CDCl_3$) spectrum, there are 18 signals in the 112-154 ppm region corresponding to aromatic carbons. The signal at 83.1 ppm can be attributed to C-3 (C-23), i.e., the sp^3 carbon which is attached to the ether oxygen. The two aliphatic carbon signals at 29.2 and 41.7 ppm correspond to C-2 (C-22) and C-12 (C-32), respectively. In its ^1H NMR spectrum ($CDCl_3$, Figure 5.2) shows two aromatic singlets at 7.01 and 7.57 ppm (integrated for two protons

Scheme 5.3.

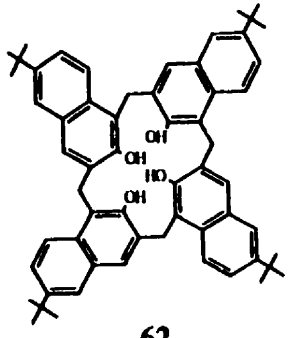


57

PTMATB, 28% NaOH

CH_2Cl_2, reflux, 2h,
30%

78 (C_2) **OR** **79 (C_i)**



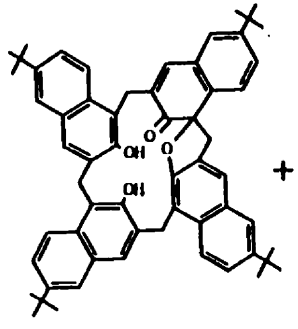
62

PTMATB, 28% NaOH

CH_2Cl_2, reflux, 2h,

81 (C_i) 20% + **80 (C_2)** 30%

1 equiv. of PTMATB,
sat. $NaHCO_3$, CH_2Cl_2, °C.



81a (36%)

+ **81 (C_i)** 18% + **80 (C_2)** 26%

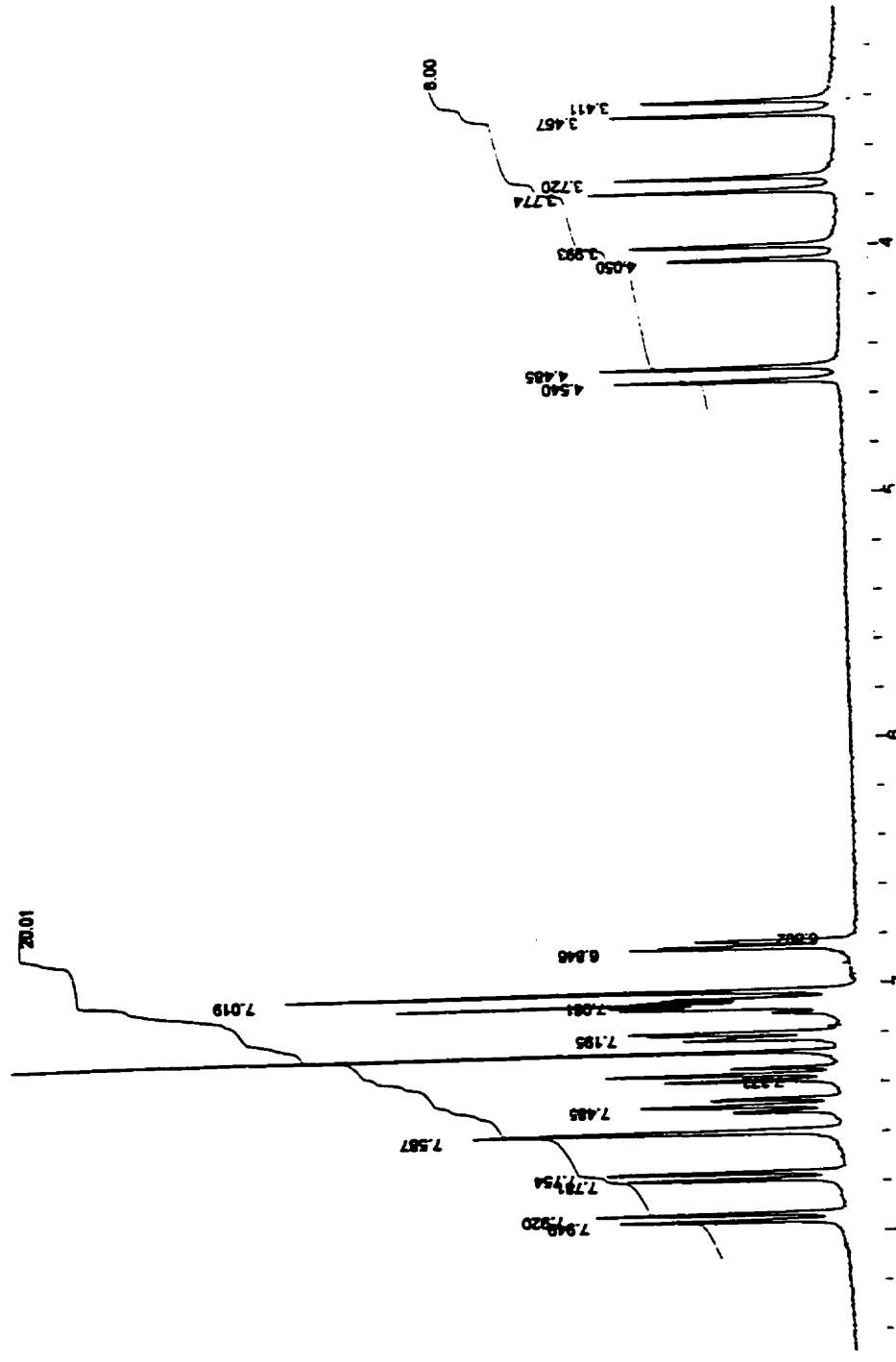


Fig. 5.2. ^{1}H NMR Spectrum of Bis(spirodienone) 78 in $CDCl_3$.

each) corresponding to two cyclohexadienone protons (H-10 and H-30), and two aromatic protons (H-20 and H-40), respectively. There are also four doublets between 3.40-4.53 ppm due to the methylene protons. The spectra are consistent only with a structure having either C_2 or C_i symmetry, i.e., a structure with alternating cyclohexadienone and aromatic rings depicted as **78** or **79**, respectively (Figure 5.6). In order to establish the solid-state conformation and to assign unequivocally the correct symmetry (**78** or **79**) to the product, single crystals suitable for x-ray analysis were obtained from $CHCl_3$. X-ray diffraction analysis (Figures 5.3 and 5.6) showed that the correct structure for this product which has C_2 symmetry, corresponds to **78**. The structure of **78** shown in Figure 5.6 is the (*3S, 23S*) enantiomer. This conformation also exists in solution as a racemic mixture. The agreement between the solid and solution state structure was confirmed by NOED experiments, since irradiation of the aromatic doublets centered at $\delta = 7.91$ (H-15, H-35) simultaneously enhances the two methylene doublets at 3.73 (H_e-12, H_e-32) and 4.50 (H_a-12, H_a-32) (Figure 5.6). This NOE could not occur unless in solution the molecule adopts the same conformational structure which was observed in the solid state. Based on the coupling constant values and NOED experiments, the two doublets centered at 3.42/4.01 ppm are coupled to each other, and the doublets at 3.73/4.50 ppm are coupled to each other. Inspection of models reveals that the equatorial protons H-12 (H-32) are closer to the cyclohexadienone protons H-10 (H-30) than the axial ones. The doublet at 3.73 ppm was assigned to the equatorial protons H-12 and H-32 since NOE enhancement occured for

cyclohexadienone protons H-10 (H-30) at 7.01 ppm when this doublet was irradiated.

5.2.b. Oxidation of *tert*-Butylcalix[4]naphthalene (62)

Tert-butylcalix[4]naphthalene (**62**) was also oxidized to spirodienone derivatives using similar reaction conditions. In this oxidation, two products were obtained in 20% yield for the less polar product **81** and in 30% yield for the remaining product **80**, as shown in Scheme 5.3. In contrast with **62**, which is light brown, these two products are yellow, which is consistent with the presence of dienone moieties in each. As judged by I.R. spectroscopy, the two species contain carbonyl groups ($\nu_{c=o}$ stretching (Nujol), **81**: 1712 cm^{-1}; **80**: 1680 cm^{-1}) and no hydroxyl groups. The ^{13}C NMR ($CDCl_3$) spectra of dienones **81** and **80** display carbonyl signals at 194.4 and 195.5 ppm, respectively, 18 signals in the 111-154 ppm region corresponding to the aromatic carbons, signals at 85.1 and 82.9 ppm, respectively, which are assigned to the spiro carbons C-3, C-23, and six aliphatic signals in the region 20.0-34.0 ppm. In their ^1H NMR ($CDCl_3$) spectra, compounds **81** and **80** display similar patterns for the methylene region, i.e., four doublets in a ratio 1:1:1:1 and two *tert*-butyl signals, as shown in Figures 5.4 and 5.5, respectively. Compound **80** displays two *tert*-butyl signals, at 1.22 and 1.42 ppm, four doublets at 3.41 (J =16.5 Hz), 3.68 (J = 16.2 Hz), 3.98 (J = 16.5 Hz) and 4.49 ppm (J = 16.2 Hz). By COSY, the doublets at 3.41 and 3.98 ppm are coupled, and the doublets at 3.68 and 4.49 ppm are coupled. Compound **81** displays two *tert*-butyl signals at 1.21 and 1.47 ppm, four doublets at 3.71 (J = 17.1, Hz),

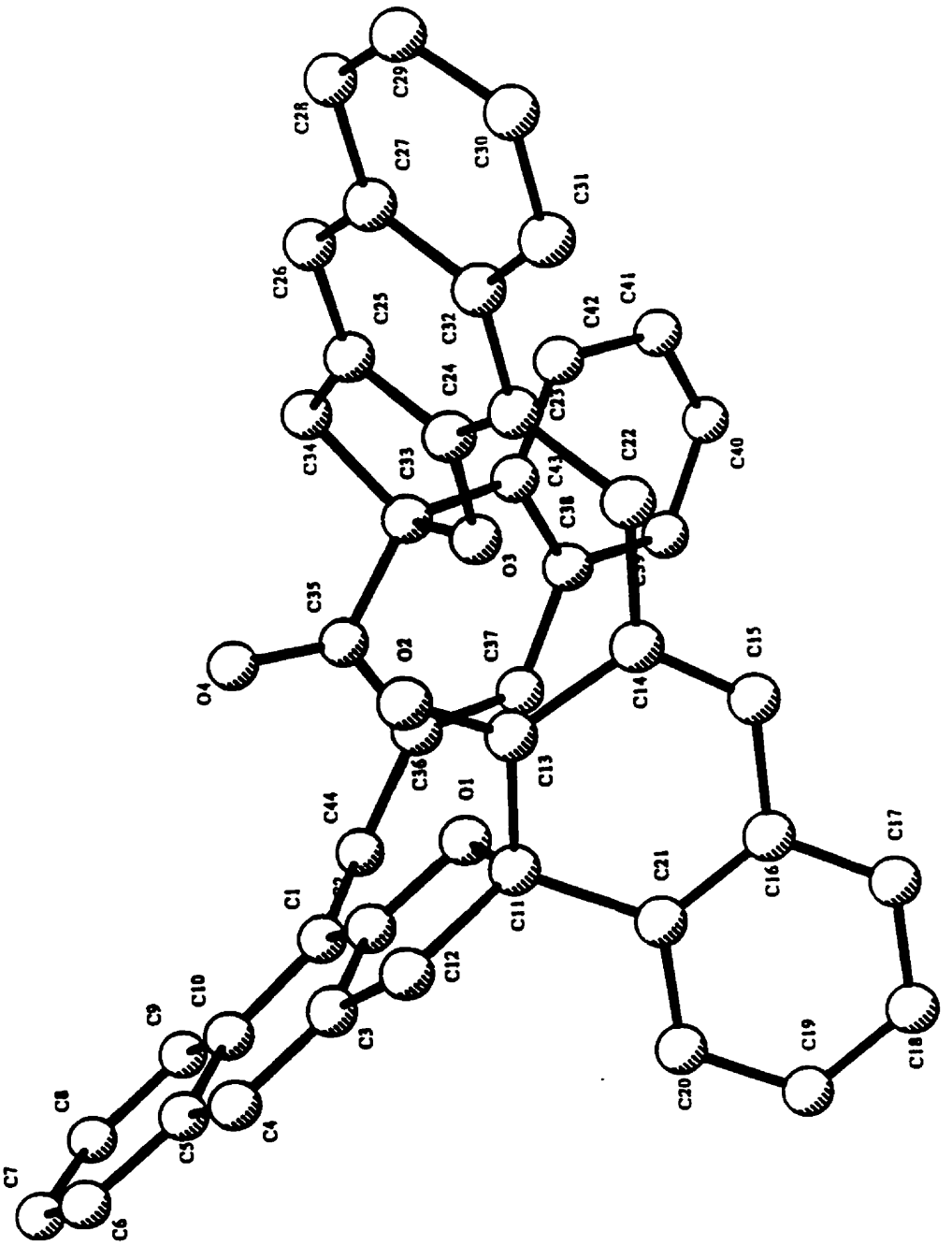


Fig. 5.3. X-ray Crystal Structure of Bis(spirodienone) 78.

3.73 (J = 15.6 Hz), 4.04 (J = 15.6 Hz) and 4.38 ppm (J = 16.8 Hz). These spectra are consistent only with structures **80** and **81** with C_2 or C_i symmetry.

It is interesting to note that the geminal coupling constants for the methylene protons in both bis(spirodienones) **78** and **80** are almost equal (16.5 Hz). This suggests that bis(spirodienone) **80** could be in a conformational structure that is similar to that of bis(spirodienone) **78**, as shown in Figure 5.6. To confirm this, an NOED experiment on **80** revealed that irradiation of the aromatic doublet centered at 7.87 ppm enhances simultaneously the coupled doublets at 3.68 and 4.49 ppm by 2% and 4%, respectively. These methylene and aromatic doublets must correspond to H-12 (H-32) and H-15 (H-35), respectively. Indeed, inspection of molecular models reveals that among several possible conformations, the conformation of bis(spirodienone) **78** (having the two carbonyl groups pointing inward in order to relieve the steric interaction between the two *tert*-butyl groups) is the only conformation in which the aromatic protons H-15 and H-35 are in close proximity to the methylene protons on C-12 and C-32, with the C_{15}-H_{15} and C_{35}-H_{35} bonds approximately bisecting the H_{12a}-C_{12}-H_{12e} and H_{32a}-C_{32}-H_{32e} bond angles, respectively. The other methylene protons on C-2 and C-22, which are part of the five-membered rings, have their corresponding $H_{2\alpha}$-C_2-$H_{2\beta}$ and $H_{22\alpha}$-C_{22}-$H_{22\beta}$ bond angles bisected by the C_{40}-H_{40} and C_{20}-H_{20} bonds, respectively. The remainder of the NOE data are in accordance with this conclusion. Thus, irradiation of the aromatic singlet at 7.09 ppm resulted in enhancement of one methylene doublet of H-12 (H-32) at 3.68 ppm indicating that these protons are in

close proximity to one another. Therefore, the doublet at 3.68 ppm is assigned to the equatorial protons H-12 (H-32) and the aromatic singlet at 7.09 ppm to the cyclohexadienone protons H-10 (H-30).

The ^{1}H NMR ($CDCl_3$) spectrum of compound **81** displays two *tert*-butyl signals at 1.21 and 1.47 ppm, four doublets centered at 3.71 (J =17.1 Hz), 3.73 (J = 15.6 Hz), 3.75 (J = 15.6 Hz) and 4.38 ppm (J = 16.8 Hz). A COSY experiment shows that the doublets centered at 3.71 and 4.38 ppm are coupled to each other whereas the doublets centered at 3.73 and 4.04 ppm are coupled to each other. On the basis of the large coupling constant of the methylene pair at 3.71 and 4.38 ppm, we assigned these signals to the methylene protons which are part of the five-membered rings, as was also observed in the bis(spirodienone) derived from calix[4]arenes.[76] In order to assign the conformational structure for compound **81**, a NOED experiment revealed that saturation of the aromatic doublet (H-15, H-35) centered at 8.03 ppm simultaneously enhances the methylene doublet at 3.73 ppm (H_e-12, H_e-32) and the aromatic singlet signal at 6.83 ppm (H-10, H-30) and *vice-versa*. Also, saturation of the aromatic doublet at 7.26 ppm (H-5, H-25) enhances only the methylene doublet at 3.71 ppm (H_β-2, H_α-22). Inspection of molecular models suggests that, among several conformational possibilities, the one in which each pair of carbonyl and ether oxygens are pointing in different directions (C_i symmetry, Figure 5.6) is the only conformation which is consistent with the NOE observations made above. Indeed, this NOE prediction was confirmed later by the single-crystal x-ray analysis shown in Figure

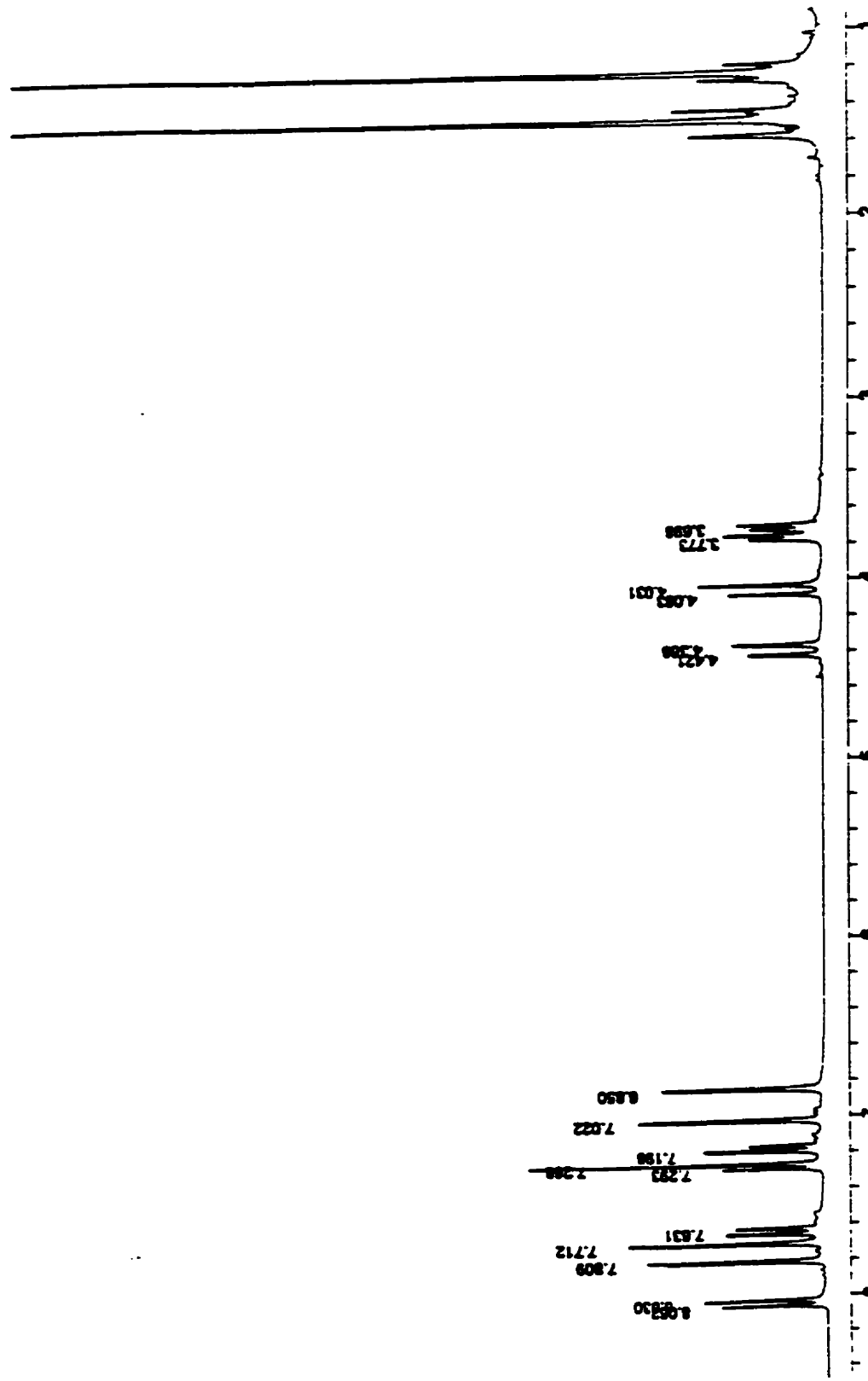


Fig. 5.4. ^{1}H NMR Spectrum of *tert*-butyl- Bis(spirodienone) 81 in $CDCl_3$.

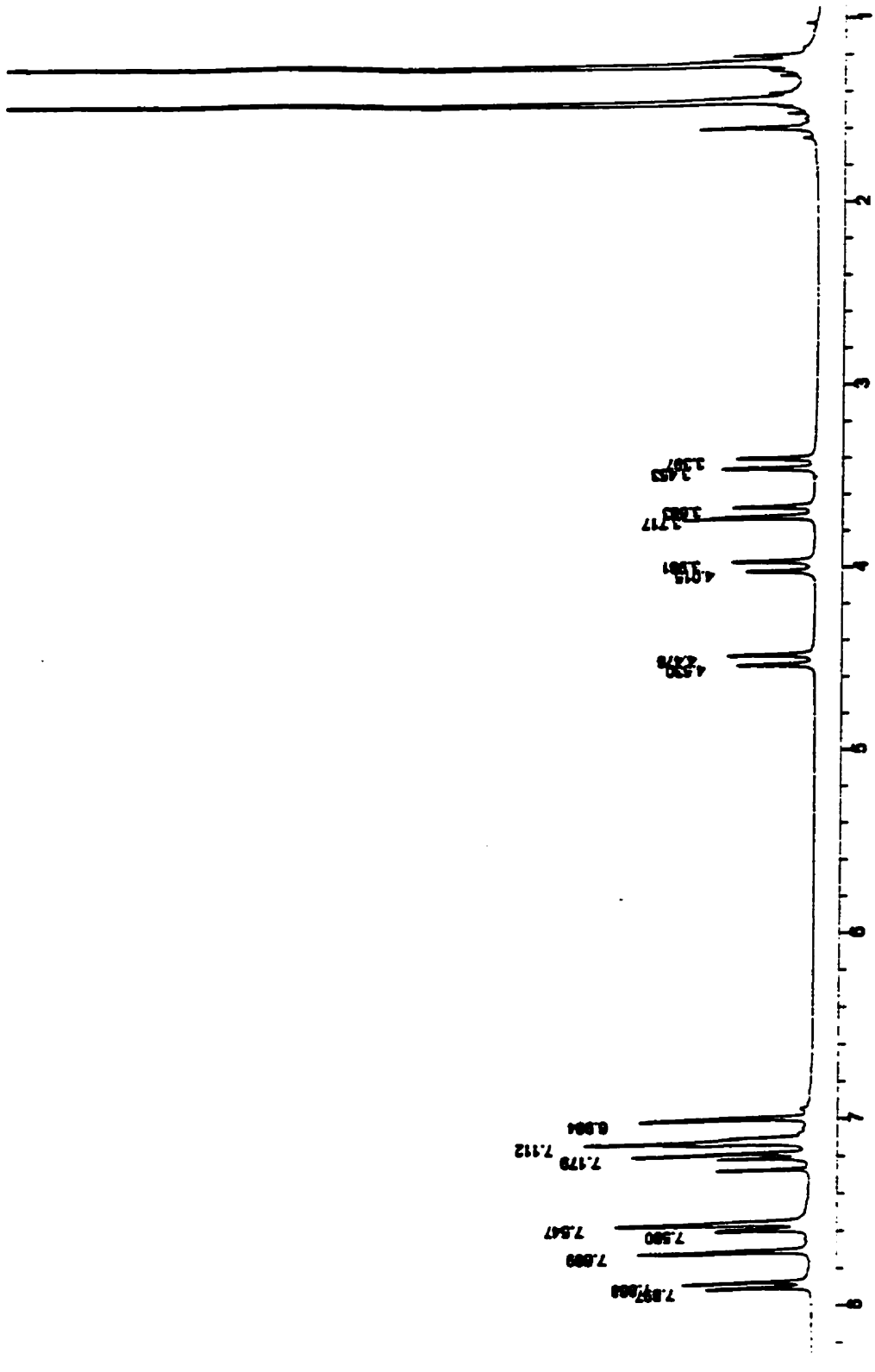


Fig. 5.5. ^{1}H NMR Spectrum of *tert*-butyl- Bis(spirodienone) 80 in $CDCl_3$.

5.6a. The structure of **81** depicted is that of the (*3R, 22S*) enantiomer.

5.3. Partial Oxidation of *tert*-Butylcalix[4]naphthalene (62).

Oxidation of calix[4]naphthalenes **57** and **62** under relatively harsh conditions (28% aqueous NaOH, reflux 2 h) results in the formation of bis(spirodienone) products in which all of the hydroxyl groups were converted to carbonyl and ether oxygen functionalities. On the other hand, when calix[4]naphthalene **62** was oxidized under milder conditions (weak base; aqueous saturated $NaHCO_3$ at 0 °C) formation of mono(spirodienone) **81a** as major product (36%) in addition to bis(spirodienones) **81** and **80** in 18% and 26% yields, respectively (Scheme 5.3) occurs. The ^1H NMR ($CDCl_3$) spectrum of spirodienone **81a** displays four signals for the *tert*-butyl groups (1.33, 1.39, 1.42 and 1.43 ppm) and eight doublets for the methylene protons (3.54, 4.00, 4.06, 4.12, 4.36, 4.37, 4.54 and 4.61 ppm). I.R. spectroscopy shows that the product contains a carbonyl group (1,677 cm^{-1}) and a hydroxyl group (3 368 cm^{-1}). The ^{13}C NMR ($CDCl_3$) spectrum shows signals at 85.1 and 194.3 ppm, corresponding to the spiro and carbonyl carbons, respectively.

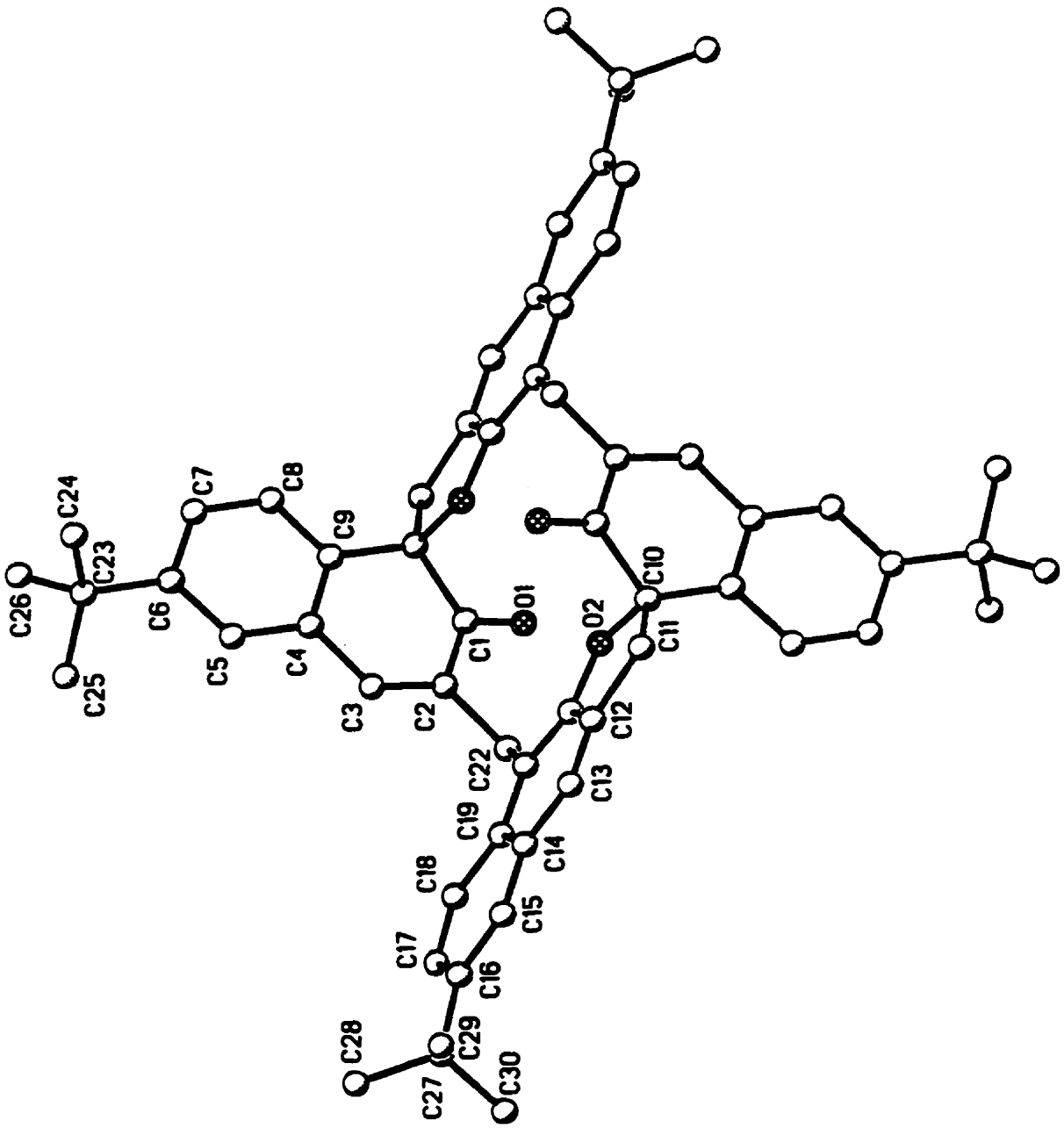
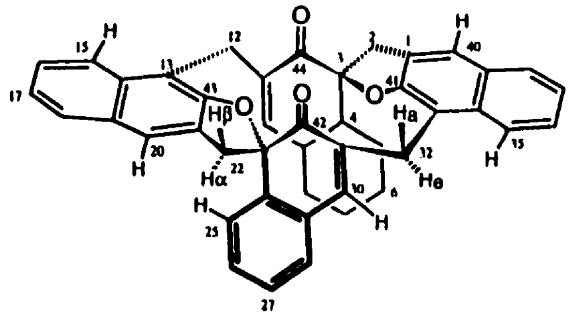
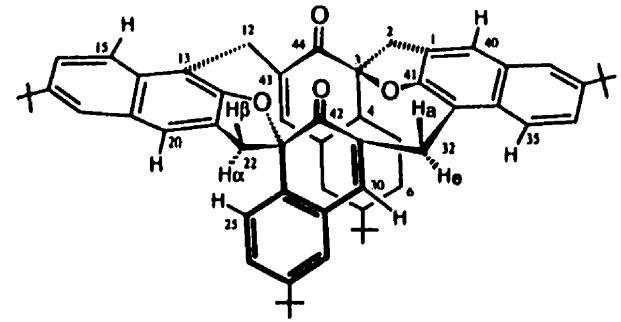


Fig. 5.6a. X-Ray Crystal Structure of Bis(spirodienone) 81.

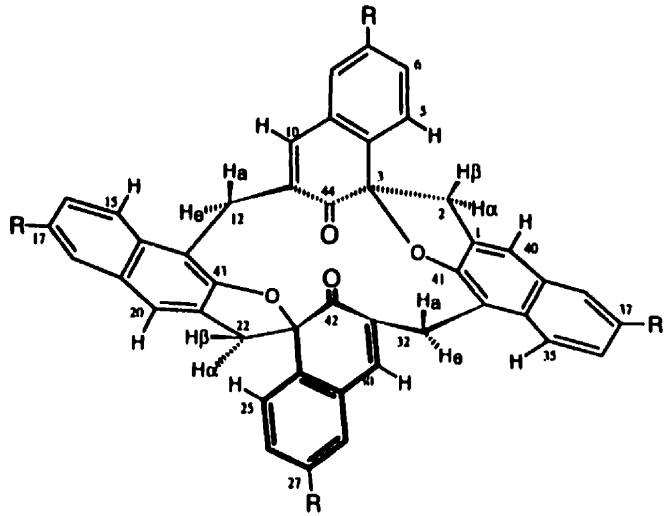
Fig. 5.6. Conformational Structures of Spirodienones



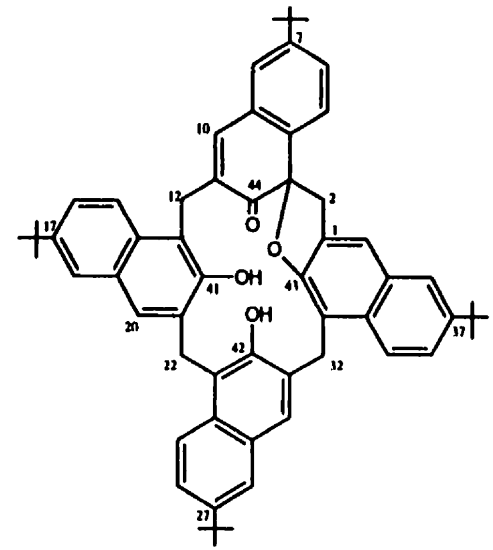
78 (C_2)



80 (C_2)



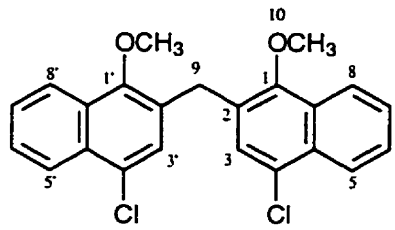
79 R = H (C_i)
81 R = *tert*-Bu (C_i)



81a

5.4. Experimental.

Bis(4-chloro-1-methoxy-2-naphthyl)methane (73).

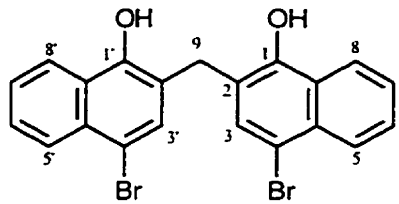


73

Compound **73** was prepared following the procedure used to produce **29** to give a colorless solid in 34% yield, m.p. 122.5-124 °C; ^{1}H NMR ($CDCl_3$) δ = 3.95 (s, 6H, H-10, H-10'), 4.35 (s, 2H, H-9), 7.31 (s, 2H, H-3, H-3'), 7.53 (m, 4H, H-6, H-6', H-7, H-7'), 8.15 (m, 2H, H-5, H-5'), 8.22 (m, 2H, H-8, H-8'); ^{13}C NMR ($CDCl_3$) δ = 28.8 (C-9), 62.3 (C-10, C-10'), 122.5, 124.9, 126.8, 127.4, 128.1, 128.9, 129.1, 130.9, 152.8 (C-1, C-1'); MS *m/s* (%) 401 (M^+ ^{37}Cl ^{37}Cl, 3), 399 (M^+ ^{37}Cl ^{35}Cl, 24), 397 (M^+, ^{35}Cl, ^{35}Cl, 24), 396 (100), 361 (20), 351 (22), 349 (33), 345 (13); HRMS M^+ 396.0688, calc. For $C_{23}H_{18}Cl_2O_2$ 396.0684.

Bis(4-bromo-1-hydroxy-2-naphthyl)methane (73a).

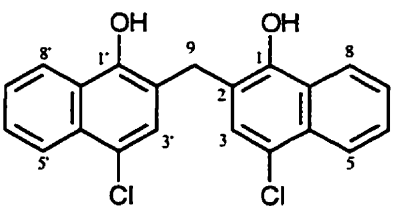
To a solution of bis(4-bromo-1-methoxy-2-naphthyl)methane (**29**) (0.75 g, 1.6 mmol) in 25 mL of anhydrous CH_2Cl_2 maintained at -78 °C and under N_2 was added BBr_3 (0.58 mL, 6.2 mmol) dropwise with stirring. The reaction was stirred at -78 °C for 5 h; at -20 °C for 1 h, at 0 °C for 1 h and finally at room temperature for 2 h. Aqueous saturated $NaHCO_3$ was added dropwise until the mixture became basic. A precipitate formed, which



73a

was filtered and washed several times with aqueous saturated $NaHCO_3$ and then with water to give **73a** as a brown solid, 0.54 g (77%), m.p. 205-208 °C dec.; ^1H NMR (acetone-d_6) δ = 4.40 (s, 2H, H-9), 7.56 (m, 4H, H-6, H-6', H-7, H-7'), 7.79 (s, 2H, H-3, H-3'), 8.08 (m, 2H, H-5, H-5'), 8.36 (m, 2H, H-8, H-8'), 9.05 (s, 2H, OH); ^{13}C NMR (acetone-d_6) δ = 30.8 (C-9), 79.3, 113.5, 123.3, 123.6, 127.2, 127.6, 128.2, 132.5, 132.9; MS *m/s* (%) 441 (1.4), 439 (4), 362 (1), 361 (6), 359 (6), 281 (5), 236 (17), 234 (16), 224 (32), 222 (36), 144 (23), 128 (11), 127 (23), 126 (12), 115 (100); HRMS M^+ 457.9345, calcd for $C_{21}H_{14}{}^{81}Br^{79}BrO_2$ 457.9361.

Bis(4-chloro-1-hydroxy-2-naphthyl)methane (73b).

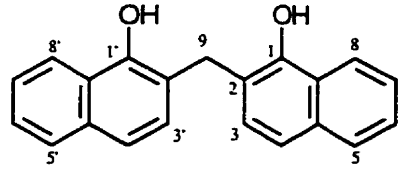


73b

To a solution of bis(4-chloro-1-methoxy-2-naphthyl)methane (**73**) (244 mg, 0.621

mmol) in 55 mL of anhydrous benzene was added BBr_3 (0.58 mL, 6.2 mmol) dropwise, with stirring under N_2 at rt. The reaction was stirred at rt for 24 h. The reaction was quenched by adding 5 mL of H_2O, followed by 20 mL aqueous of saturated $NaHCO_3$. The mixture was extracted with four portions of $CHCl_3$ (100 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated on rotary evaporator to give **73b** as a colorless solid (150 mg, 66%), m.p. 207-209 °C dec.; ^{1}H NMR (acetone-d_6) δ = 2.80 (br, OH), 4.39 (s, 2H, H-9), 7.59 (s, 2H, H-3, H-3'), 7.61 (m, 4H, H-6, H-6', H-7, H-7'), 8.13 (m, 2H, H-5, H-5'), 8.36 (m, 2H, H-8, H-8'); ^{13}C NMR (acetone-d_6) δ = 30.7 (C-9), 122.9, 123.2, 124.8, 127.1, 127.9, 129.3; MS *m/s* (%) 372 (M^+, ^{37}Cl ^{35}Cl, 1), 369 (M^+, ^{35}Cl ^{35}Cl, 2), 368 (8), 351 (4), 331 (2), 268 (3), 250 (3), 239 (6), 180 (32), 179 (11), 178 (100), 162 (4), 144 (10), 127 (9), 115 (17); HRMS H^+ 368.0368, calcd for $C_{21}H_{14}Cl_2O_2$ 368.0371.

Bis(1-hydroxy-2-naphthyl)methane (15).

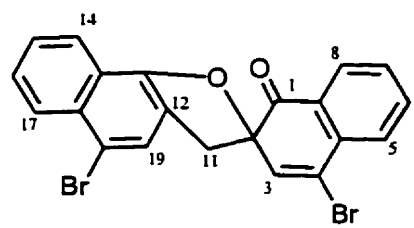


15

Compound **15** was prepared from **30**, following the procedure used to prepare **73b**, to give a light brown solid in 82% yield, m.p. 168-170 °C; ^{1}H NMR ($CDCl_3$) δ = 4.28 (s,2H, H-9), 6.73 (s, 2H, 2OH), 7.45 (m, 4H, H-6, H-6', H-7, H-7'), 7.76 (d, *J* = 8.1 Hz, 2H, H-5,

H-5'), 8.02 (d, J = 8.1 Hz, 2H, H-8, H-8'); ^{13}C NMR ($CDCl_3$) δ = 31.4 (C-9), 120.4, 120.6, 121.2, 125.6, 125.7, 127.9, 128.3, 147.7 (C1, C-1'); MS *m/s* (%) 301 (M^++1,1), 300 (M^+, 8), 296 (4), 282 (27), 281 (60), 157 (9), 156 (34), 145 (12), 144 (100), 141 (11), 128 (29), 127 (10), 126 (11), 116 (12), 115 (29).

Oxidation of bis(4-bromo-1-hydroxy-2-naphthyl)methane (73a). General procedure:

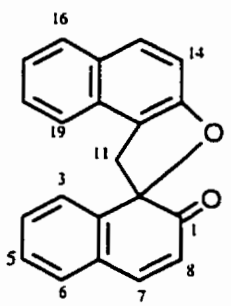


74a

To a solution of **73a** (175 mg, 0.391 mmol) in CH_2Cl_2 (10 mL) was added a solution of phenyltrimethylammonium tribromide (PTMATB) (15 mg, 0.39 mmol) in 2 mL of CH_2Cl_2 at rt. An aqueous 28% solution of NaOH (6.5 g) was added dropwise at rt. The reaction was left stirring at rt for 1 h. The reaction mixture was diluted with 20 mL of CH_2Cl_2. The organic layer was separated and washed with 20 mL of brine followed by 20 mL of water. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent removed on a rotary evaporator. The crude product was purified by PLC using CH_2Cl_2-petroleum ether (1:1) to give **74a** as yellow crystals (62 mg, 36%), m.p. 185-188 °C dec. ; I.R. ($CHCl_3$, cm^{-1}): 1693, 1589, 1451, 1388, 1358, 1297, 1271, 1190, 1090, 758; ^{1}H NMR ($CDCl_3$) δ = 3.45 (d, J = 15.6 Hz, 1H, H-11), 3.80 (d, J = 15.6 Hz, 1H, H-11), 6.88 (s, 1H),

7.53 (m, 3H), 7.60 (s, 1H), 7.76 (m, 2H), 7.96 (d, J = 8.1 Hz, 1H), 8.07 (d, J = 7.8 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 40.8 (C-11), 87.6 (C-2), 113.8, 118.4, 121.4, 122.1, 122.4, 126.1, 126.4, 127.3, 127.5, 128.0, 128.3, 128.6, 123.0, 132.0, 134.4, 135.3, 135.5, 194.4 (C-1); MS *m/s* (%) 458 (M^+ ^{81}Br ^{81}Br, 7), 456 (M^+ ^{81}Br ^{79}Br, 14), 454 (M^+ ^{79}Br ^{79}Br, 8), 442 (12), 441 (49), 440 (25), 439 (100), 438 (13), 437 (52), 377 (17), 375 (17), 296 (11), 222 (5), 188 (9), 187 (12), 148 (12), 139 (13), 134 (36), 126 (8), 120 (45), 118 (12), 113 (7), 107 (13), 101 (10); HRMS M^+ 453.9182 calcd for $C_{21}H_{12}{}^{79}Br_2O_2$ 453.9204.

Oxidation of bis(2-hydroxy-1-naphthyl)methane (71).

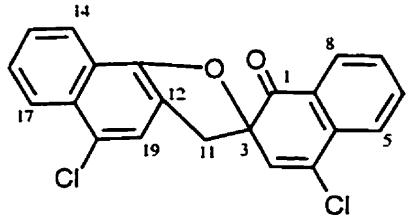


72

Compound **71** was oxidized as above to give **72** as an orange crystals (83%), m.p. 168-170 °C; I.R. (Nujol, cm^{-1}): 1683, 1631, 1239, 1205, 1023, 808; ^{1}H NMR ($CDCl_3$) δ = 3.49 (d, J = 15.6 Hz, 1H, H-11), 4.03 (d, J = 15.6 Hz, H-11), 6.22 (d, J = 10.2 Hz, 1H), 7.22 (m, 5H), 7.42 (m, 4H), 7.78 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 42.8 (C-11), 89.3 (C-2), 111.8, 115.1, 122.4, 123.2, 123.6, 125.5, 126.9, 128.7,

128.8, 129.5, 129.7, 129.8, 130.6, 130.8, 143.4, 144.9, 145.4, 157.7, 197.9 (C-1); MS *m/z* (%) 298 (M^+, 6), 282 (25), 281 (100), 267 (7), 239 (13), 139 (5), 134 (6), 119 (16).

Oxidation of bis(4-chloro-1-hydroxy-2-naphthyl)methane (73b).



74b

Compound **73b** was oxidized as above to give **74b** as yellow crystals (39%), m.p. 175-177 °C dec.; I.R. ($CHCl_3$, cm^{-1}): 1693, 1593, 1511, 1452, 1391, 1362, 1271, 1191, 1091, 759; ^1H NMR ($CDCl_3$) δ = 3.43 (d, J = 15.5 Hz, 1H, H-11), 3.79 (d, J = 15.6 Hz, 1H, H-11), 6.61 (s, 1H), 7.40 (s, 1H), 7.53 (m, 3H), 7.77 (m, 2H), 7.95 (d, J = 8.1, 1H), 8.09 (d, J = 8.7 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 41.1 (C-11), 86.8 (C-2), 117.9, 121.1, 122.1, 122.6, 124.0, 124.8, 125.9, 126.4, 127.1, 128.1, 128.2, 130.0, 130.1, 130.8, 131.5, 134.7, 135.4, 153.1, 194.3 (C-1); MS *m/s* (%) 368 (9) 367 (M^+ ^{35}Cl ^{35}Cl, 4), 366 (M^+, 16), 353 (13), 352 (16), 351 (68), 350 (24), 349 (100), 331 (16), 239 (22), 237 (9), 202 (10), 166 (9), 134 (11), 120 (26), 113 (5).

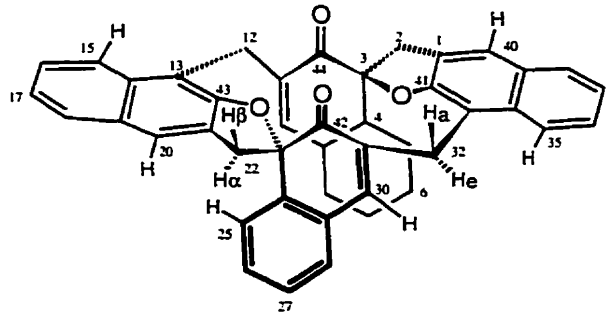
Oxidation of bis(1-hydroxy-2-naphthyl)methane (15).

a. Using one equivalent of PTMATB at reflux temperature for 48 h produced a light brown solid, m.p. 161-163 °C; ^1H NMR (acetone-d_6) δ = 4.37 (s, 2H), 7.41-7.51 (m, 4H), 7.58 (m,

2H), 7.74 (s, 1H), 7.82 (m, 1H), 8.06 (m, 1H), 8.31 (m, 2H); ^{13}C NMR (acetone-d_6) δ = 113.1, 121.6, 122.2, 122.3, 123.3, 123.8, 126.0, 126.2, 126.4, 126.5, 126.9, 127.4, 127.7, 128.0, 128.7, 129.5, 132.3, 132.9, 134.8; MS *m/z* (%) 380 (1), 378 (2), 300 (2), 281 (4), 225 (5), 224 (21), 223 (7), 222 (22); HRMS H^+ 378.0276, calcd for $C_{21}H_{13}{}^{81}BrO_2$ 378.0078.

b. Using three equivalents of PTMATB at room temperature for 1.5 h produced after purification by PLC using $CHCl_3$-petroleum ether (50:50), yellow crystals whose m.p. and spectroscopic properties were identical with those of **74a**.

Oxidation of calix[4]naphthalene (57). General procedure:



78 (C_2)

To a solution of calix[4]naphthalene **57** (40 mg, 0.06 mmol) in CH_2Cl_2 (7 mL) was added PTMATB (48 mg, 0.12 mmol) in one portion, followed by aqueous 28% NaOH (0.26 g) at rt under N_2. The reaction was refluxed for 2 h then the reaction mixture was cooled to rt and diluted with 15 mL of $CHCl_3$ and 10 mL of water. The organic layer was separated and washed with 10 mL of brine followed by 10 mL water. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified

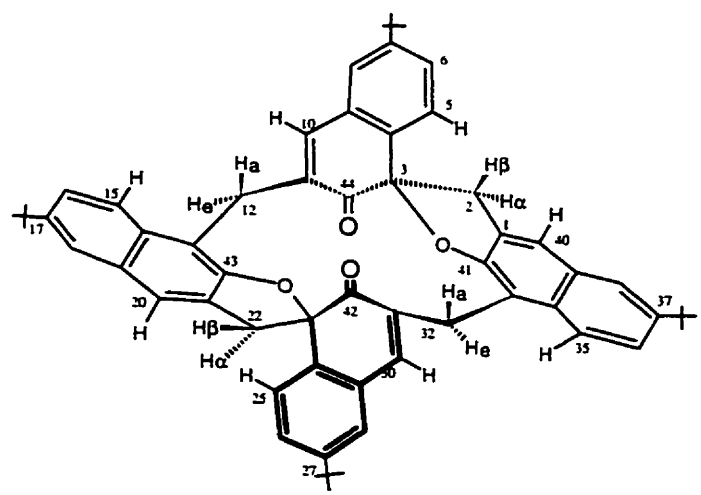
by PLC using $CHCl_3$ to give **78** as yellow crystals (13 mg, 30%), m.p. 248-250 °C dec. ; I.R. ($CHCl_3$, cm^{-1}): 3070, 3025, 2926, 1678, 1636, 1435, 1384, 1261, 1149, 1097, 976, 750; ^1H NMR ($CDCl_3$) δ = 3.42 (d, J = 16.5 Hz, 2H, H_α-2, H_α-22), 3.73 (d, J = 16.5 Hz, 2H, H_e-12, H_e-32), 4.01 (d, J = 16.5 Hz, 2H, H_β-2, H_β-22), 4.50 (d, J = 16.2 Hz, 2H, H_a-12, H_a-32), 6.81 (m, 2H, H-8, H-28), 7.01 (s, 2H, H-10, H-30), 7.05 (m, 4H, H-6, H-7, H-26, H-27), 7.19 (dd, J = 2.4, 6.5 Hz, 2H, H-5, H-25), 7.35 (t, J = 7.2 Hz, 2H, H-17, H-37), 7.48 (t, J = 7.2 Hz, 2H, H-16, H-36), 7.57 (s, 2H, H-20, H-40), 7.75 (d, J = 8.1 Hz, 2H, H-18, H-38), 7.91 (d, J = 8.40 Hz, 2H, H-15, H-35); NOE (%) **H_α-2 (H_α-22)**/ H_β-2 (H_β-22)(4.9), H-5 (H-25)(3.3); **H_e-12 (H_e-32)**/ H_a-12 (H_a-32)(6), H-10 (H-30), H-15 (H-35)(2.8); **H_β-2 (H_β-22)**/ H_α-2 (H_α-22)(6.1); **H_a-12 (H_a-32)**/ H_e-12 (H_e-32)(5.9), H-15 (H-35)(2.9); **H-8 (H-28)**/ H-10 (H-30), H-7 (H-27, H-6, H-26); **H-7 (H-27, H-6, H-26)**/ H-5 (H-25)(7), H-8 (H-28)(6.2); **H-5 (H-25)**/ H-6 (H-26); **H-17 (H-37)**/ H-16 (H-36)(5.5), H-18 (H-38)(8.1); **H-16 (H-36)**/ H-17 (H-37)(6.7), H-15 (H-35)(6.2); **H-20 (H-40)**/ H-18 (H-38)(14.4); **H-18 (H-38)**/H-20 (H-40)(10.2), H-17 (H-37)(8.8); **H-15 (H-35)**/ H-16 (H-36)(9), H_a-12 (H_a-32)(3.6), H_e-12 (H_e-32)(2.9); ^{13}C NMR ($CDCl_3$) δ = 29.2 (C-12, C-32), 41.7 (C-2, C-22), 83.1 (C-3, C-23), 112.0 , 121.8 (C-20, C-40),122.4 (C-15, C-35), 123.2 (C-17, C-37), 125.8 (C-16, C-36), 126.9 (C-5, C-25), 128.0 (C-8, C-28), 128.3 (C-18, C-38), 128.6 and 128.7 (C-7, C-27, C-6, C-26), 129.7, 130.0, 130.8, 133.2, 134.3, 140.0 (C-10, C-30), 141.4, 154.3 (C-41, C-43), 195.4 (C-42, C-44); MS *m/s* (%) 620 (M^+, 51), 619 (100), 602 (25), 601 (35), 592 (10), 587 (11), 574 (17), 377 (8), 376 (10), 335 (12), 311 (19), 310 (25), 309 (13), 297

(11), 296 (14), 295 (29), 294 (20), 293 (15), 282 (17), 281 (39), 280 (11), 279 (10).

Oxidation of *tert*-butylcalix[4]naphthalene (62).

Compound **62** was oxidized as above, but the crude product was purified by PLC using CH_2Cl_2-petroleum ether (50:50) to give two yellow products. Compound **81** was the less polar of the two:

1. Spirodienone 81.

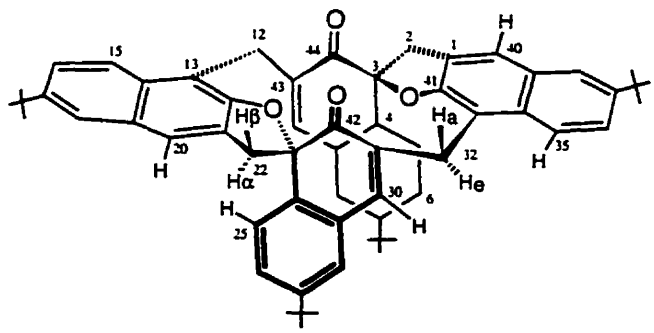


81 (C_i)

Spirodienone **81** was isolated as dark yellow crystals (19 mg, 20%), m.p. > 300 °C dec. ; I.R. ($CHCl_3$, cm^{-1}): 2962, 2869, 1680, 1603, 1451, 1410, 1363, 1096, 991; ^1H NMR ($CDCl_3$) δ = 1.21 (s, 18H, 2 *tert*-Bu), 1.47 (s, 18H, 2 *tert*-Bu), 3.71 (d, J = 17.1 Hz, 2H, H_β-2, H_α-22), 3.73 (d, J = 15.6 Hz, 2H, H_e-12, H_e-32), 4.04 (d, J = 15.6 Hz, 2H, H_a-12, H_a-32),

4.38 (d, J = 16.8 Hz, 2H, H_{α}-2, H_{β}-22), 6.83 (d, J = 1.8 Hz, 2H, H-10, H-30), 7.00 (d, J = 1.8 Hz, 2H, H-8, H-28), 7.16 (dd, J = 8.1, 1.8 Hz, 2H, H-6, H-26), 7.26 (d, J = 8.1 Hz, 2H, H-5, H-25), 7.62 (dd, J = 9.0, 1.8 Hz, 2H, H-16, H-36), 7.69 (s, 2H, H-20, H-40), 7.79 (d, J = 1.8 Hz, 2H, H-18, H-38), 8.03 (d, J = 9.0 Hz, 2H, H-15, H-25); ^{13}C NMR ($CDCl_3$) δ = 21.9 (C-2, C-12, C-22, C-32), 31.0 [$C(CH_3)_3$], 31.4 [$C(CH_3)_3$], 34.6 [$C(CH_3)_3$], 34.9 [$C(CH_3)_3$], 85.1 (C-3, C-23), 114.9, 121.7 (C-20, C-40), 123.0 (C-15, C-35), 123.8 (C-18, C-38), 124.8 (C-16, C-36), 126.0 (C-6, C-26),126.7 (C-8, C-28), 127.0 (C-5, C-25), 129.7, 130.0, 131.0, 131.7, 135.5, 135.7, 141.7 (C-10, C-30), 145.4, 152.7, 153.6, 194.4 (C-42, C-44); FAB MS *m/z* (%) 867 (M^++Na^+, 45), 844 (M+, 57), 843 (30), 842 (11), 841 (13), 811 (31), 799 (12), 783 (10), 771 (16), 631 (11), 617 (16), 615 (14), 603 (12), 589 (10), 587 (10), 575 (10), 573 (11), 423 (21), 407 (34), 377 (35), 265 (41), 213 (100);

2. Spirodienone 80



80 (C_2)

Spirodienone **80** was isolated as light yellow crystals (29 mg, 30%), m.p. 270-272

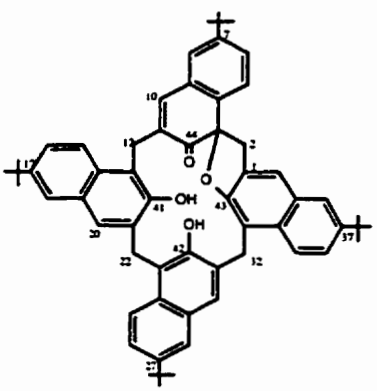
°C; I.R. ($CHCl_3$, cm^{-1}): 2952, 2904, 2869, 1680, 1504, 1447, 1426, 1363, 1269, 1099, 979; ^1H NMR ($CDCl_3$) δ = 1.22 (s, 18H, 2 *tert*-Bu at C-7, 27), 1,42 (s, 18H, 2 *tert*-Bu at C-17, C-37), 3.41 (d, J = 16.5 Hz, 2H, H_α-2, H_α-22), 3.68 (d, J = 16.2 Hz, 2H, H_e-12, H_e-32), 3.98 (d, J = 16.5 Hz, 2H, H_β-2, H_β-22), 4.49 (d, J = 16.2 Hz, 2H, H_a-12, H_a-32), 6.98 (d, J = 1.8 Hz, 2H, H-8, H-28), 7.09 (s, 2H, H-10, H-30), 7.10 (dd, J = 8.1, 1.8 Hz, 2H, H-6, H-26), 7.17 (d, J = 8.1 Hz, 2H, H-5, H-25), 7.53 (s, 2H, H-20, H-40), 7.57 (d, J = 1.8 Hz, 2H, H-16, H-36), 7.69 (d, J = 1.8 Hz, 2H, H-18, H-38), 7.87 (d, J = 9.0 Hz, 2H, H-15, H-35); NOE (%) **H-8 (H-28)/** H-10 (H-30)(5.4); **H-10 (H-30)/** H-8 (H-28)(13.3), H_e-12 (H_e-32)(3.6); **H-5 (H-25)/** H-6 (H-26)(2.7), H_α-2 (H_α-22)(2.6); **H-16 (H-36)/** H-18 (H-38)(7.8), H-15 (H-25)(3.2); **H-18 (H-38)/** H-20 (H-40)(7.1); **H-15 (H-35)/** H-16 (H-36)(3.3), H_a-12 (H_a-32)(3.4), H_e-12 (H_e-32)(1.8); ^{13}C NMR ($CDCl_3$) δ = 30.3 (C-12, C-32), 31.1 (C(CH3)3 at C-7 and C-27), 31.4 (C(CH3)3 at C-17 and C-37), 31.5, 34.5, 41.9 (C-2, C-22), 82.9 (C-3, C-23), 111.2, 121.5 (C-20, C-40), 122.1 (C-15, C-35), 123.5 (C-18, C-38), 124.3 (C-16, C-36), 124.8 (C-8, C-28), 125.7 (C-10, C-30 or C-6, C-26), 127.1 (C-5, C-25), 129.6, 129.9, 130.8, 131.2, 134.3, 138.7, 140.3 (C-10, C-30 or C-6, C-26), 145.5, 151.6, 154.1, 195.5 (C-42, C-44). FAB MS *m/s* (%) 882 (M^++K^+, 18), 868 (100), 867 (M^++Na^+, 15).

Partial oxidation of calix[4]naphthalene (62). To a solution of calix[4]naphthalene **62** (55 mg, 0.45 mmol) in CH_2Cl_2 (5 ml) was added PTMATB (24 mg, 0.45 mmol) at 0 °C followed by the addition of 5 mL of aqueous saturated $NaHCO_3$ at 0 °C. The reaction was left to stir at 0 °C for 4 h. The reaction mixture was worked-up by diluting it with 10 mL of

chloroform and 10 mL of water. The organic layer was separated and washed first twice with 20 mL of brine and then with 10 mL of water. The crude product was purified by PLC using benzene-hexane (50:50) to give according to their increasing polarity the following three products:

1. Spirodienone 81, 10 mg (18%) whose melting point and spectroscopic properties are identical with those of **81** isolated above;

2. Spirodienone 81a as an orange solid (36%); m.p. 278-280 °C; I.R. ($CHCl_3$, cm^{-1}): 3368



81a

(br, OH), 2870, 1677 (CO), 1607, 1506, 1450, 1364, 1231, 1097, 998, 923, 818; ^1H NMR ($CDCl_3$) δ = 1.33 (s, 9H, *tert*-Bu), 1.39 (s, 9H, *tert*-Bu), 1.42 (s, 9H, *tert*-Bu), 1.43 (s, 9H, *tert*-Bu); 3.54 (d, J = 17.7 Hz, 1H), 4.00 (d, J = 15.9 Hz, 1H), 4.06 (d, J = 15.9 Hz, 1H), 4.12 (d, J = 18.0 Hz, 1H), 4.36 (d, J = 15.6 Hz, 1H), 4.37 (d, J = 14.7 Hz, 1H), 4.54 (d, J = 14.7 Hz, 1H), 4.61 (d, J = 14.7 Hz, 1H), 7.31 (s, 1H), 7.44 (s, 1H), 7.50 (s, 1H), 7.52 (s,

1H), 7.55 (m, 2H), 7.61 (s, 1H), 7.65 (m, 2H), 7.73 (d, J = 6.0 Hz, 2H), 8.10 (d, J = 9.0 Hz, 1H), 8.28 (br, OH), 8.32 (d, J = 9.3 Hz, 1H), 8.37 (d, J = 9.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 24.91, 25.5, 28.6, 31.1, 31.3, 34.4, 34.5, 34.8, 39.4, 85.1, 114.4, 119.7, 121.6, 121.8, 122.3, 122.4, 122.8, 123.4, 123.9, 124.3, 124.9, 125.0, 126.6, 126.7, 127.5, 127.8, 128.2, 128.3, 129.5, 129.9, 130.2, 130.8, 135.1, 136.7, 143.6, 144.9, 145.2, 145.7, 146.1, 148.9, 150.1, 152.4, 153.3, 194.3; +FAB MS *m/z* (%) 846 (M^+, 10), 830 (12), 829 (21), 828 (16), 813 (14), 812 (23), 811 (34), 614 (11), 423 (13), 407 (24), 406 (14), 405 (12);

3. **Spirodienone 80**, 14 mg (26%) whose melting point and spectroscopic properties are identical with those of **80**, isolated above.

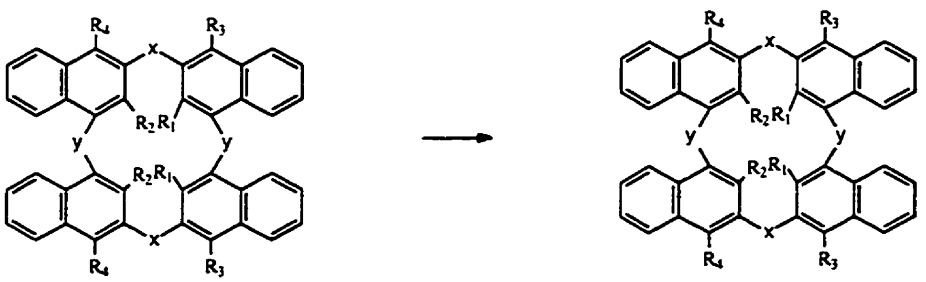
Chapter 6

Synthesis of Dihomo- and Tetrahomocalix[4]naphthalenes

6.1. Introduction.

Calix[4]arenes, 1-naphthol-derived calix[4]naphthalenes (**10-13**) and calix[4]naphthalenes derived from 3-hydroxy-2-naphthoic acid (**57** and **62**) can be considered to be compounds possessing [1.1.1.1]metacyclophane structures. The substitution by ethylene bridges of either two or all of the methylene bridges of calix[4]naphthalenes derived from 3-hydroxy-2-naphthoic acid or 1-naphthol, produces new classes of calix[4]naphthalenes known as dihomo- (**82a-84a**) or tetrahomocalix[4]naphthalenes **85a**, as shown in Figure 6.1.

Figure 6.1.



82. $R_1 = R_2 = H$, $R_3 = R_4 = OCH_3$, $X = CH_2SCH_2$, $Y = CH_2$.
83. $R_2 = R_3 = H$, $R_1 = R_4 = OCH_3$, $X = CH_2SCH_2$, $Y = CH_2$.
84. $R_3 = R_4 = H$, $R_1 = R_2 = OCH_3$, $X = CH_2SCH_2$, $Y = CH_2$.
85. $R_3 = R_4 = H$, $R_1 = R_2 = OCH_3$, $X = CH_2CH_2$, $Y = CH_2SCH_2$

82a. $R_1 = R_2 = H$, $R_3 = R_4 = OCH_3$, $X = CH_2CH_2$, $Y = CH_2$.
83a. $R_2 = R_3 = H$, $R_1 = R_4 = OCH_3$, $X = CH_2CH_2$, $Y = CH_2$.
84a. $R_3 = R_4 = H$, $R_1 = R_2 = OCH_3$, $X = CH_2CH_2$, $Y = CH_2$.
85a. $R_3 = R_4 = H$, $R_1 = R_2 = OCH_3$, $X = Y = CH_2CH_2$

These homologues (dihomo- and tetrahomocalix[4]naphthalenes) are examples of [1.2.1.2](1,3)- and [2.2.2.2](1,3)naphthalenophanes, respectively. This substitution increases the size of the annulus of the macrocyclic compounds: the resulting increased

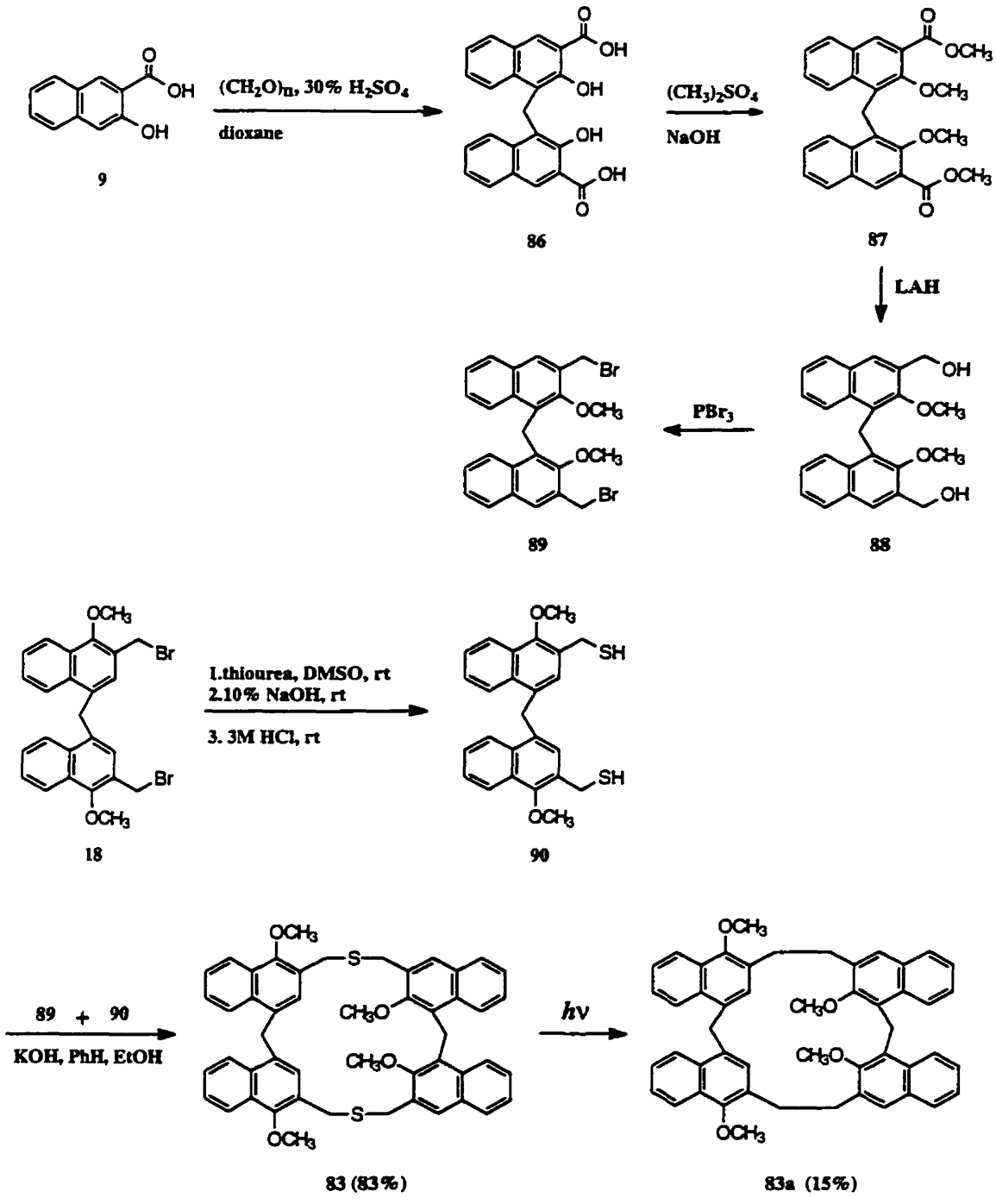
conformational mobility is reflected in their temperature-dependent (VT) ^{1}H NMR spectra. The procedures employed to synthesize **82a-85a** were methods commonly employed in cyclophane chemistry. The precursor dithia compounds **82-85** were synthesized by base-mediated nucleophilic coupling of the appropriate bis(mercaptomethyl) with bis(bromomethyl) compounds under high dilution conditions, as shown in Schemes 6.1, 6.2, and 6.4.

Calix[4]naphthalenes **83a-85a** were obtained by a final photolytic sulfur extrusion step in trimethyl or triethylphosphite. Such reactions have also been used by others to synthesize cyclophanes.[79, 80] Among many sulfur extrusion approaches available,[81] the direct photochemical reaction is the most attractive one since it has the fewest number of steps and occurs at room temperature under neutral conditions.[80, 82]

6.2. Synthesis of Dihomocalix[4]naphthalenes.

Scheme 6.1 outlines the procedures used to synthesize **83**. Condensation of 3-hydroxy-2-naphthoic acid (**9**) with paraformaldehyde in dioxane and 30% aqueous H_2SO_4 as catalyst, gave dimer **86** in high yield. Using a two-phase basic system (CH_2Cl_2, 10% aqueous NaOH) in the presence of dimethylsulphate and a phase-transfer catalyst (Adojen^R) converted **86** to the biester **87**. Bis(bromomethyl) **89** was formed from the corresponding bis(hydroxymethyl) **88**, which in turn was obtained by $LiAlH_4$ reduction of the bisester **87**. Bis(bromomethyl) **18** was converted into the corresponding bis(mercaptomethyl) **90** under very mild conditions in high yield. The precursor

Scheme 6.1.



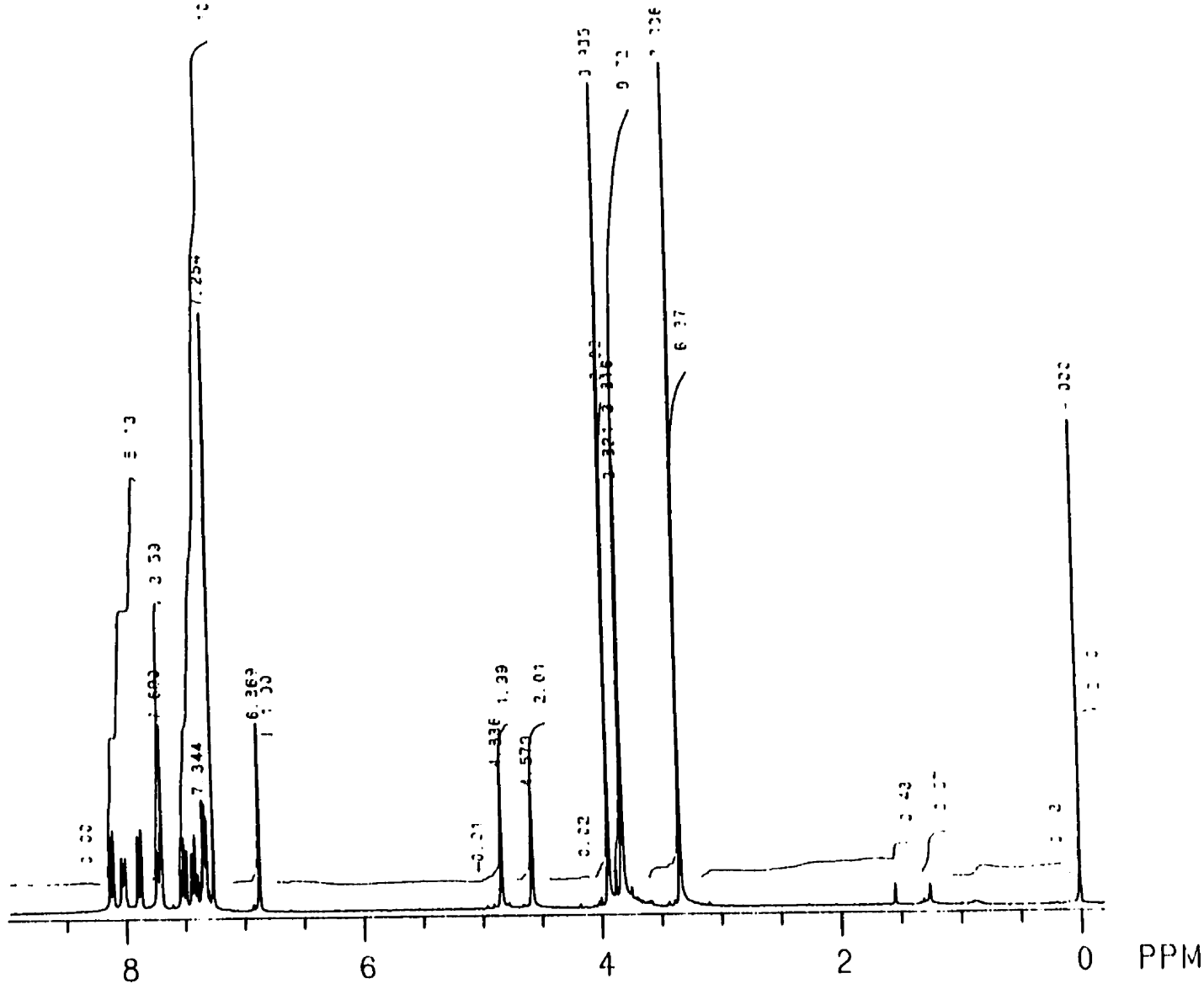
9 86 87 89 88 18 90

83 (83%) 83a (15%)

dithiacalix[4]naphthalene **83** was synthesized by base-mediated coupling of the corresponding bis(mercaptomethyl) **90** with bis(bromomethyl) **89** in 85% yield. Photochemical irradiation of **83** in triethylphosphite afforded **83a** in 15% yield.

The ambient temperature ^{1}H NMR spectrum (Figure 6.2) of the dithia compound **83** indicates conformational mobility since all signals including all the methylene protons which appear as singlets are sharp and well defined. The molecule has C_{2v} symmetry as evidenced by, among other features, the two singlets due to two sets of equivalent methoxyl groups at 3.94 ppm (C-6 and C-21) and 3.34 ppm (at C-45 and C-46), and two sets of methylene protons at 4.84 and 4.58 ppm. Examination of molecular models indicates that of two possible C_{2v}-symmetry conformations one is crown-like and the other is 1,2-alternate-like. Since one set of the methoxyl signals appears at high field (3.34 ppm) this suggests that they are shielded by the opposite rings, thus precluding a crown-like conformation in solution. Further evidence for the assignment of the higher field signals to the intra-annular methoxyl groups derives from the following complexation experiment conducted with **83**. When a THF solution of **83** was treated with a silver nitrate solution,[83] a crystalline product, **83b** was obtained. Its ^{1}H NMR spectrum (Figure 6.3) reveals that complexation has occurred since the higher field methoxyls appear as a very broad signal centered at 3.39 ppm, whereas the lower field methoxyl signal at 4.03 ppm is much sharper. Of the two methylene signals, it is the higher field one at 4.64 ppm which has broadened. These findings are in agreement with a complex formed between the silver ion and one half of the molecule, possibly with the methoxyls at C-45 and C-46

Fig. 6.2. ^{1}H NMR Spectrum of Dithiadihomocalix[4]naphthalene 83 in $CDCl_3$.



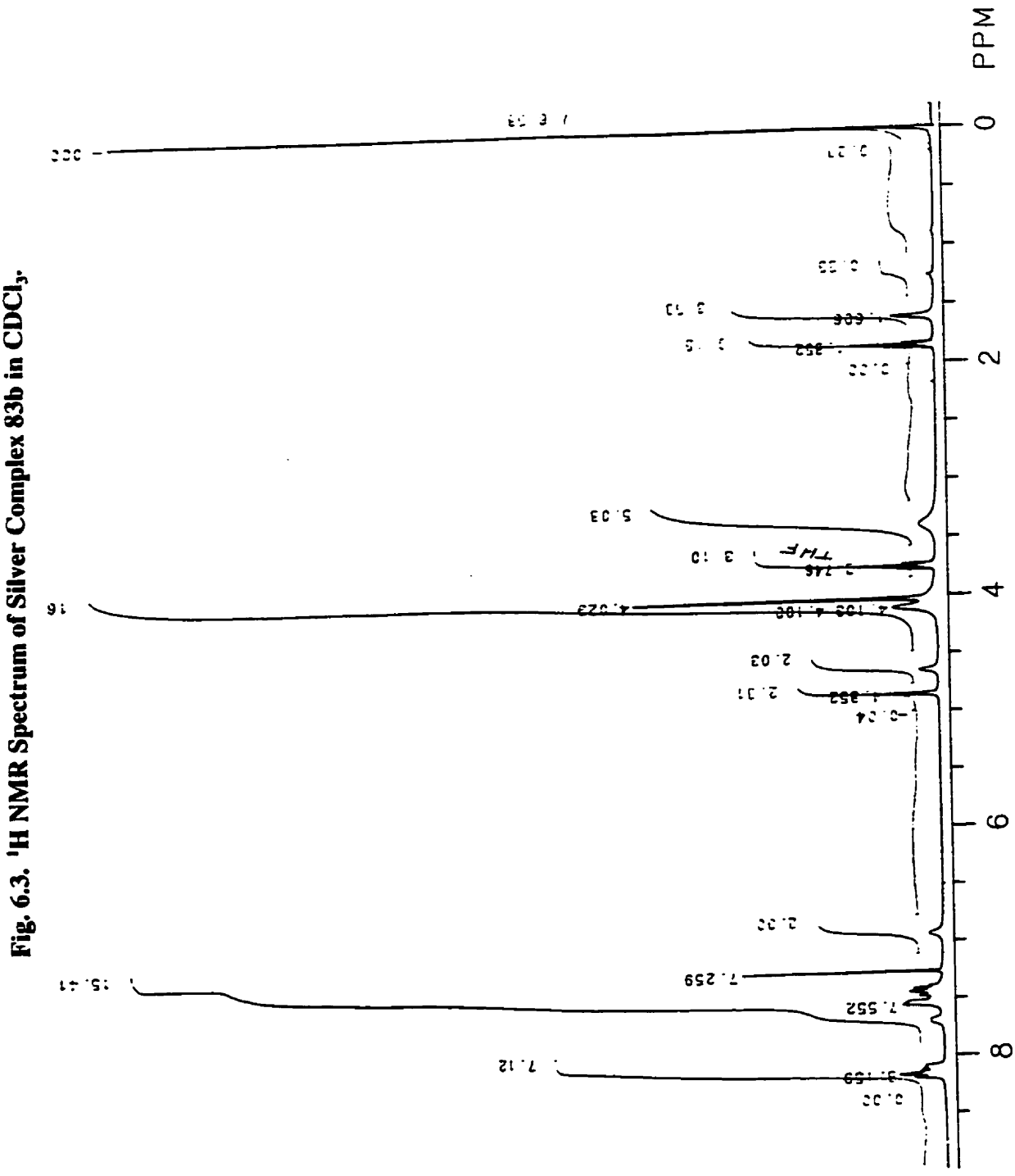
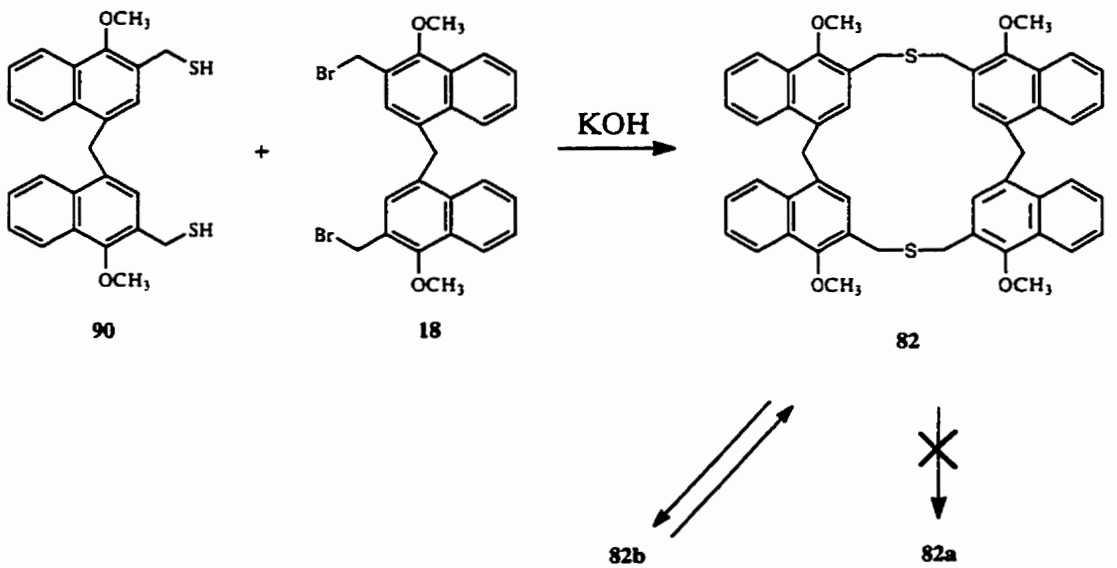


Fig. 6.3. ^{1}H NMR Spectrum of Silver Complex 83b in $CDCl_3$.

or the sulfur atoms. The signals at 1.35 and 3.75 ppm indicate the presence of THF which could be present as an inclusion molecule. The ambient temperature ^{1}H NMR spectrum (Figure 6.4) of dihomocalixnaphthalene **83a** also indicates conformational mobility since the ethylene and methylene protons appear as broad signals at 3.04 and 2.85 ppm, respectively.

The precursor dithiacalix[4]naphthalene **82,** which was also synthesized in 81% yield by reacting bis(mercaptomethyl) **90** with bis(bromomethyl) **18** (Scheme 6.2), is soluble in warm DMSO, but insoluble in most of the common organic solvents that were tried.

Scheme 6.2.



Attempts to produce **82a** by a photolytic sulfur extrusion approach failed. A silver

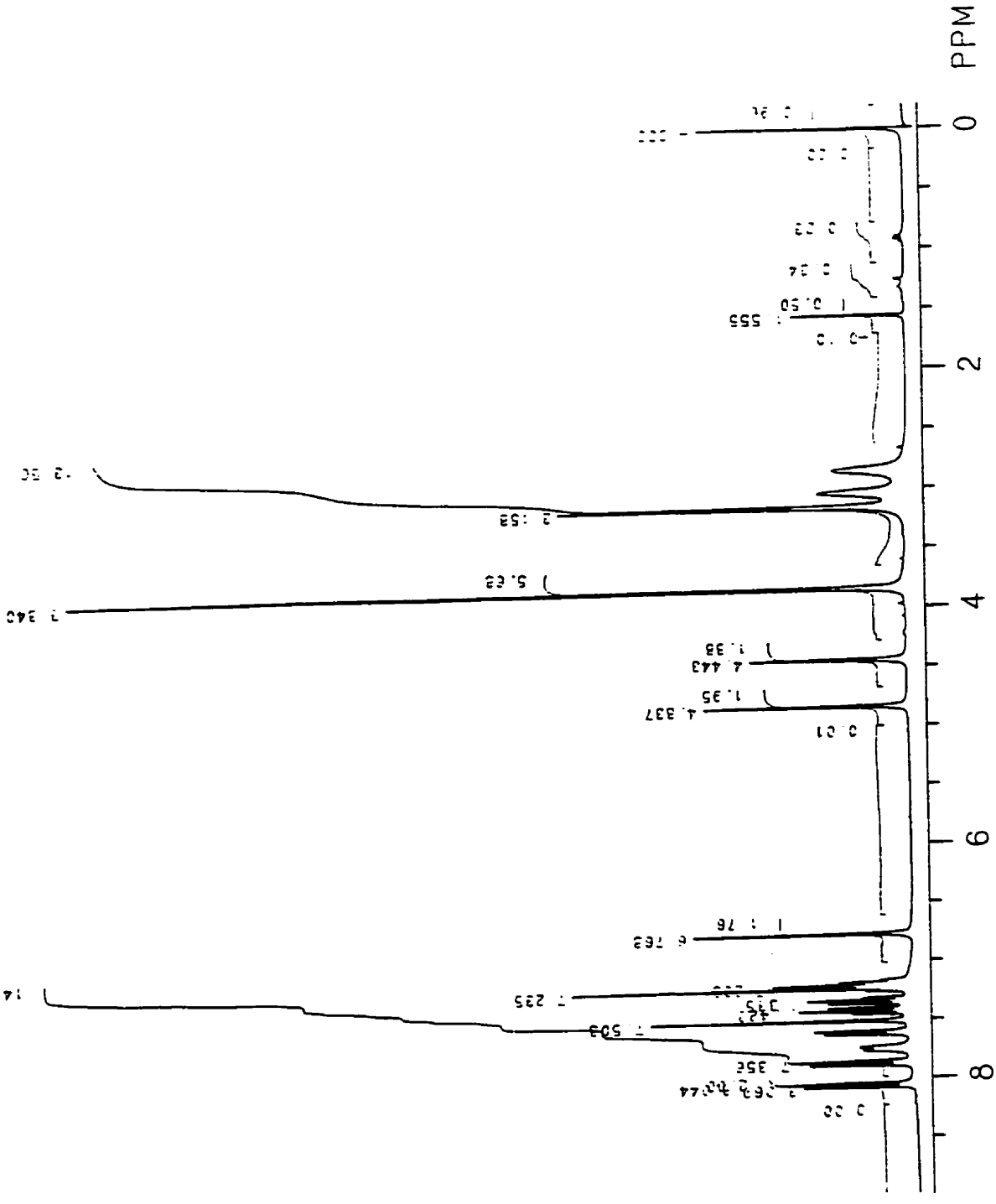


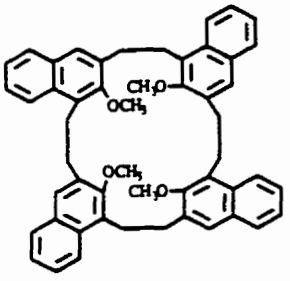
Fig. 6.4. ^{1}H NMR Spectrum of Dihomocalix[4]naphthalene 83a in $CDCl_3$.

ion complex **82b** can also be produced from **82**. Interestingly, **82b** is much more soluble than its precursor, but when a suspension of **82b** was irradiated in triethyl- phosphite, the only change was reversion back to **82**. Oxidation of **82** to its corresponding sulfone followed by pyrolysis has been investigated but with no success.

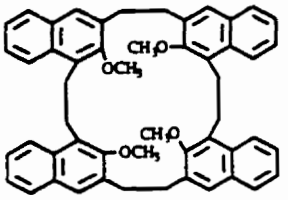
6.3. Synthesis of Tetrahomocalix[4]naphthalene (85a).

6.3.a. One-pot procedure: In order to enlarge the annulus of calix[4]naphthalenes derived from 3-hydroxy-2-naphthoic acid, we were interested in synthesizing tetrahomocalix[4]naphthalene **85a** and its structural isomers (**91a-93a**, Figure 6.5).

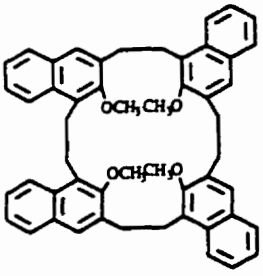
Figure 6.5.



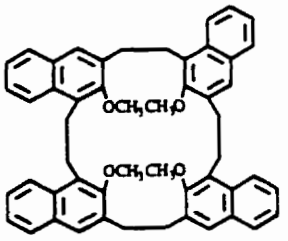
91a



85a



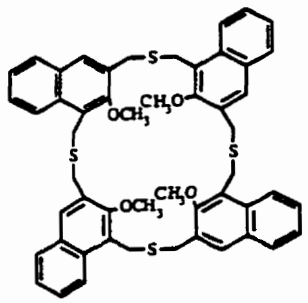
92a



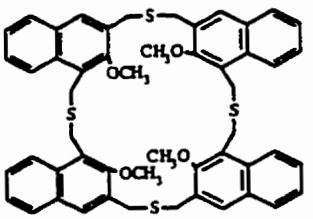
93a

The synthetic approach employed was the base-mediated coupling of 1,3-bis(bromomethyl)-2-methoxynaphthalene (**97**) with its corresponding bis(mercapto-methyl) derivative **98** (Scheme 6.3) to produce several isomers of tetrathia[3.3.3.3](1,3)-naphthalenophanes (**91-94**, Figure 6.6). These are potential precursors to tetrahomo-calix[4]naphthalenes (**85a**, **91a-93a**) after sulfur extrusion. Attempts to produce these tetrathia-precursors gave after TLC separation, four isomeric 11,22-dimethoxy-2,13-dithia[3.3](1,3)naphthalenophanes (**99-102**, Figure 6.7). However, when each of the compounds (**99-102**) was photolyzed in triethyl- or trimethylphosphite, two isomeric tetrahydrodibenzopyrenes were obtained instead of the expected corresponding [2.2](1,3)-naphthalenophanes. These findings will be the subject of Chapter 7.

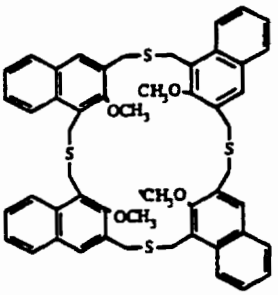
Figure 6.6.



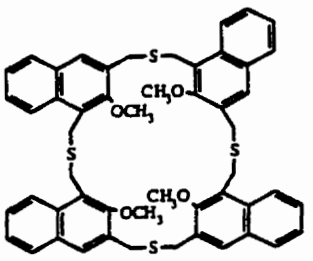
91



94

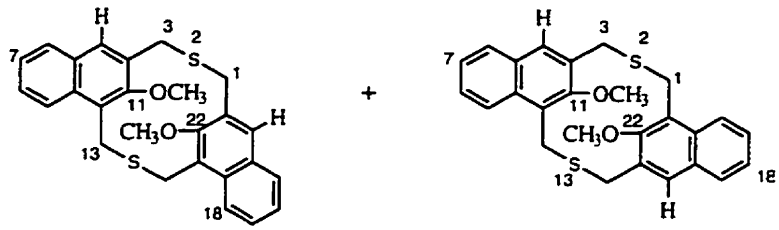


92



93

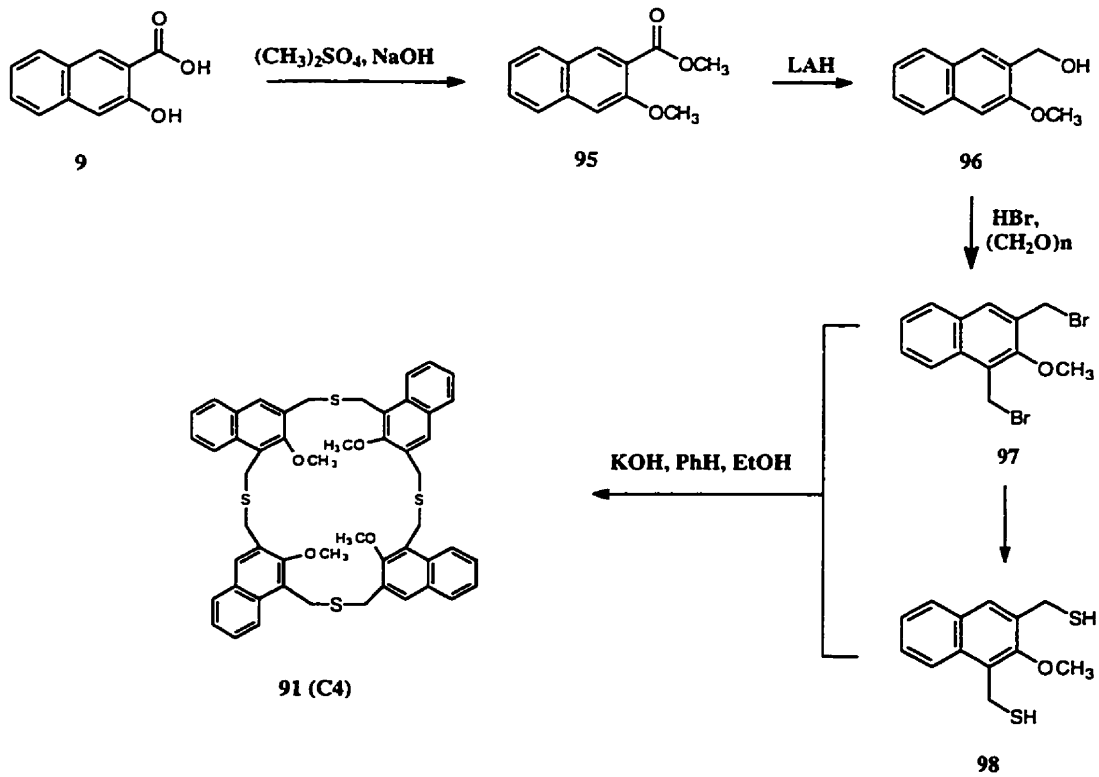
Figure 6.7.



99 *cisoid-anti*
100 *cisoid-syn*

101 *transoid-anti*
102 *transoid-syn*

Scheme 6.3.



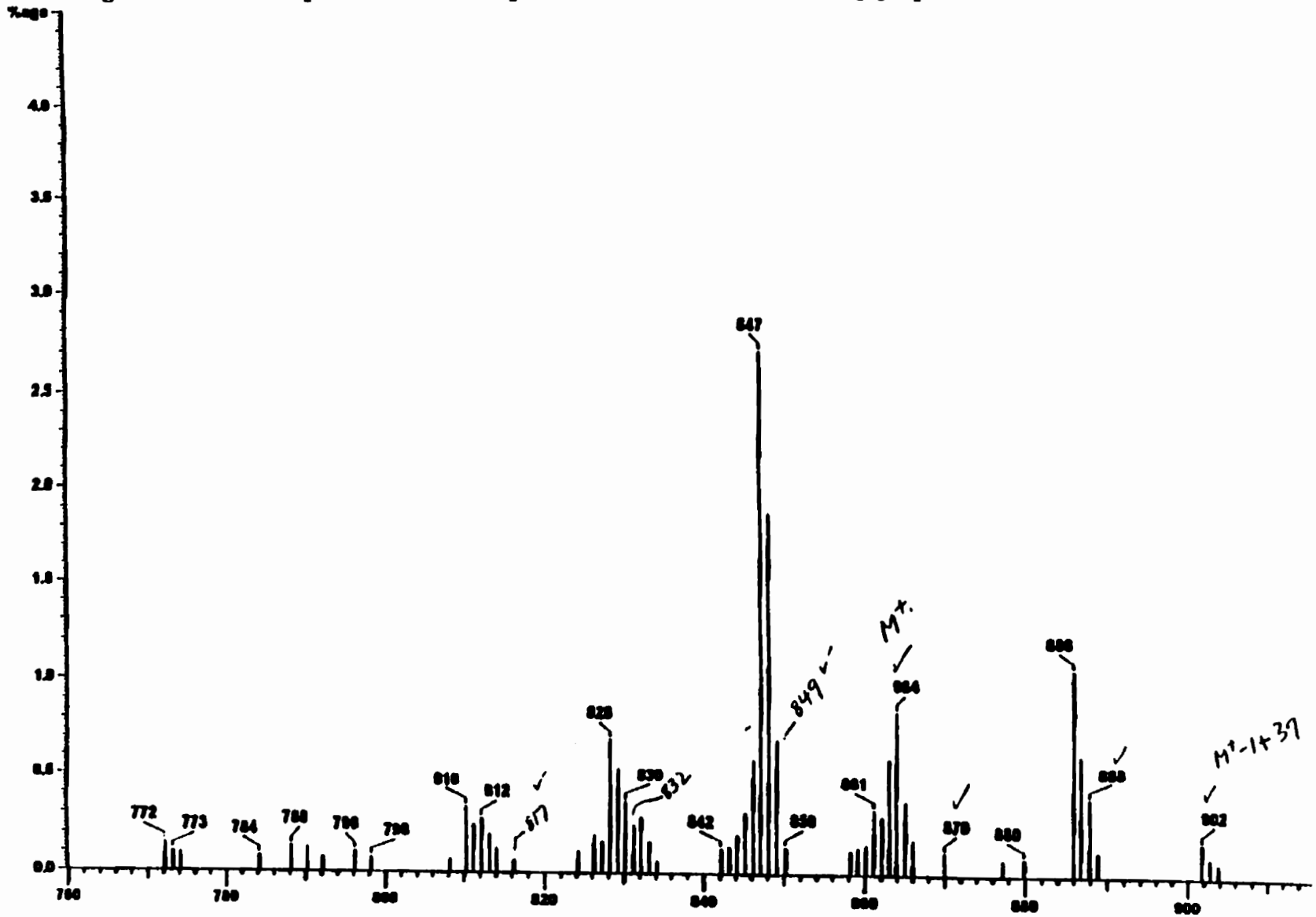
9 **95** **96** **97** **98** **91 (C4)**

In addition to the four dithia[3.3](1,3)naphthalenophanes isolated by PLC, a fifth fraction which was the most polar one was also isolated in 17% yield. Its spectral properties were distinctly different from those of any of compounds **99-102**. This fraction which was homogeneous to TLC, appears to be an inseparable mixture of possibly all four isomeric tetrathia[3.3.3.3](1,3)naphthalenophanes **91-94**. To confirm this, a +FAB-MS spectrum (Figure 6.8) shows two peaks at *m/e* = 864 and 902, which correspond to the molecular mass of the tetrathia isomers and (molecular mass-1)+K^+, respectively. The presence of the K^+ ion could be evidence of it being present as an inclusion ion. The ^1H NMR ($CDCl_3$) spectrum of this fifth fraction (Figure 6.9) shows additional, well-defined signals in the methylene and methoxyl group region, which are not present for any of the tetrathiacalix[4]naphthalenes **91-94**. To test whether these signals are a result of rigid or locked conformation of possibly one of the tetrathianaphthalenophanes, the solvent was changed to toluene and the temperature was raised gradually to 100 °C, as shown in Figure 6.10. These spectra clearly show that there is no collapse in any of these signals upon heating and that therefore they are due to components of the mixture.

6.3.b. Convergent Procedure.

Since we were unable to isolate and identify any of the tetrathiacalix[4]-naphthalenes **91-94**, which are potential precursors for tetrahomocalix[4]naphthalenes from the one pot procedure, a convergent procedure was used to synthesize one of the tetrahomocalix[4]naphthalenes, **85a**, as shown in Scheme 6.4. Starting from 3-hydroxy-2-naphthoic acid **9**, sequential methylation, reduction and bromination gave 3-

Fig. 6.8. +FAB MS Spectrum of The Expected Tetrathiatetrahomocalix[4]naphthalenes 91-94 Mixture.



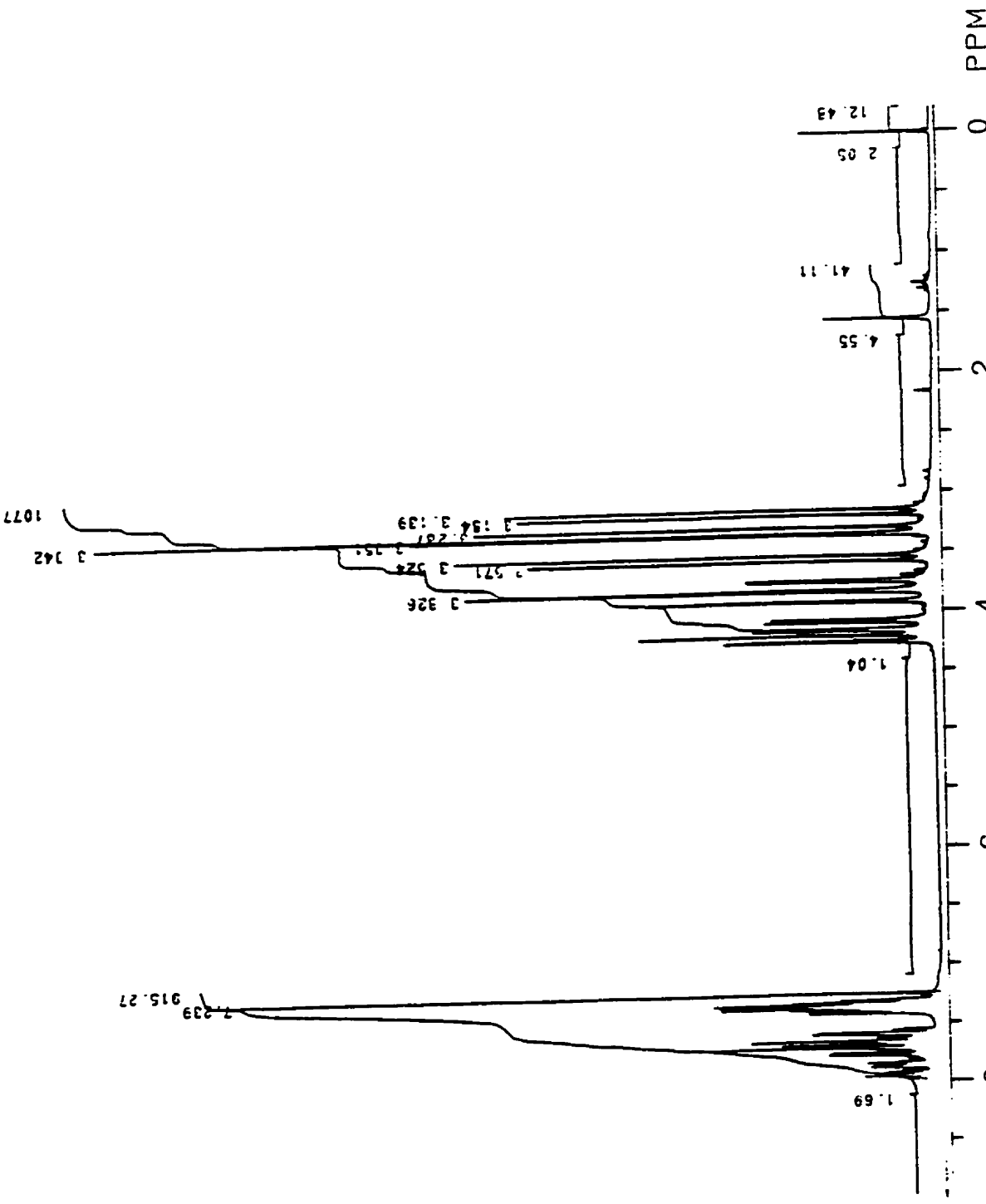
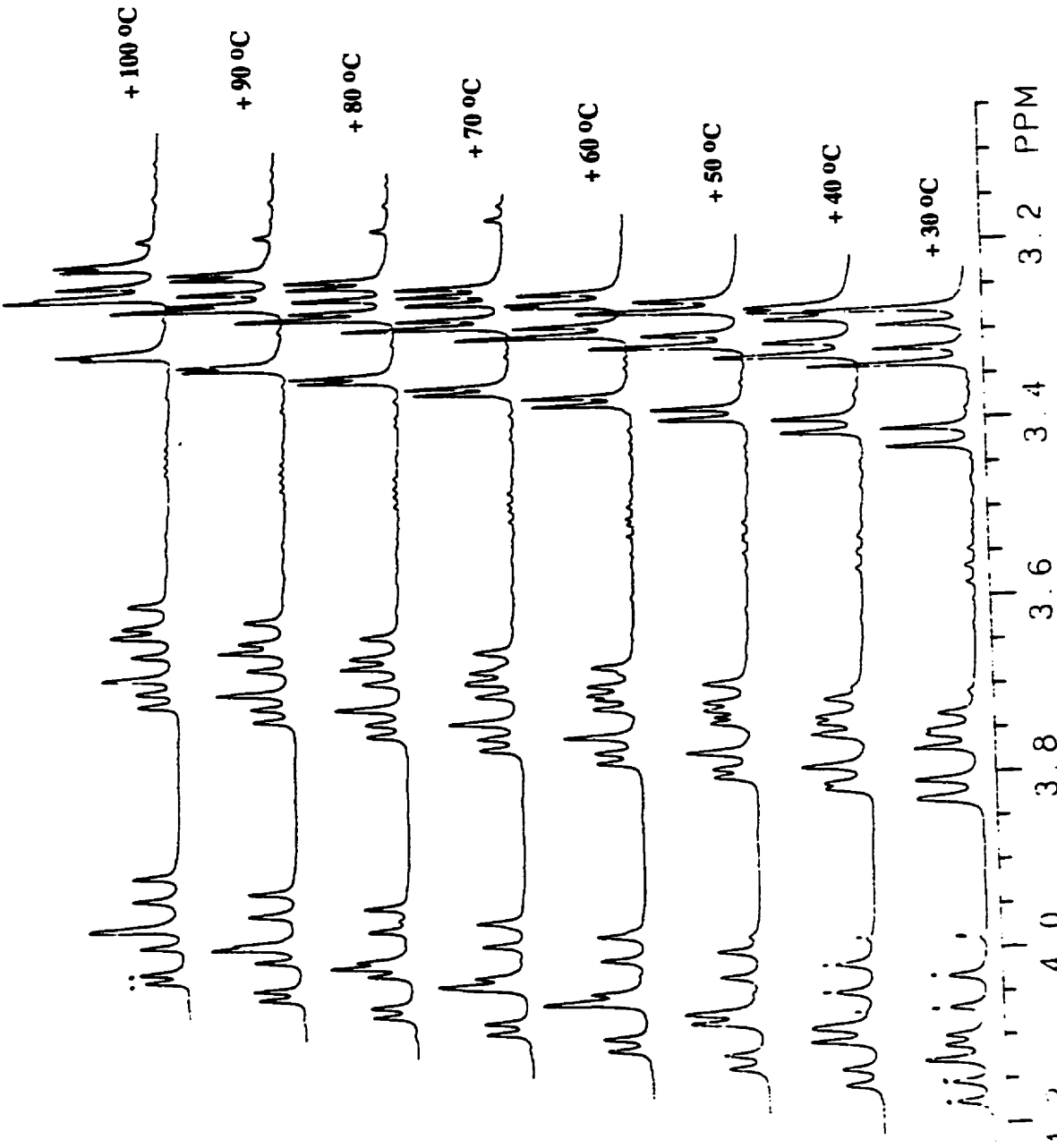


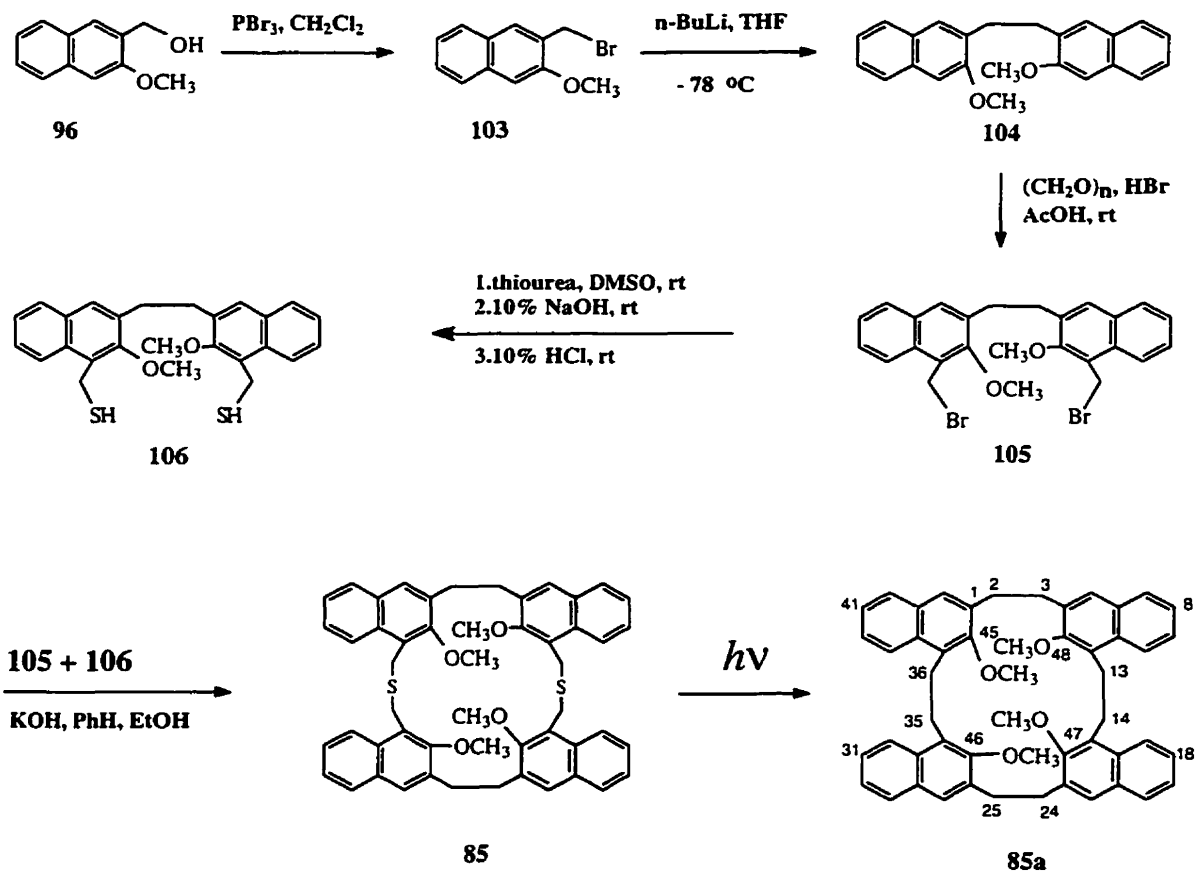
Fig. 6.9. ^{1}H NMR Spectrum of The Expected Tetrathiatetrahomocalix[4]naphthalenes 91-94 in $CDCl_3$.

Fig. 6.10. VT ^{1}H NMR Spectra of 91-94 mixture in Toluene-d_8.



bromomethyl-2-methoxynaphthalene **103** in 80% yield. Wurtz coupling of **103** using *n*-BuLi at - 78 °C gave bis(2-methoxy-3-naphthyl)ethane **104** in 92% yield. Bromomethylation of **104** using $(CH_2O)_n$ and HBr in acetic acid gave bis[1-(bromomethyl)-2-methoxy-3-naphthyl]ethane **105** in 84%. Reaction of **105** with thiourea formed the bis(isothiouronium) salt, which was subsequently hydrolyzed to form bis[1-(mercaptomethyl)-2-methoxy-3-naphthyl]ethane **106** in 70% yield. Base-mediated

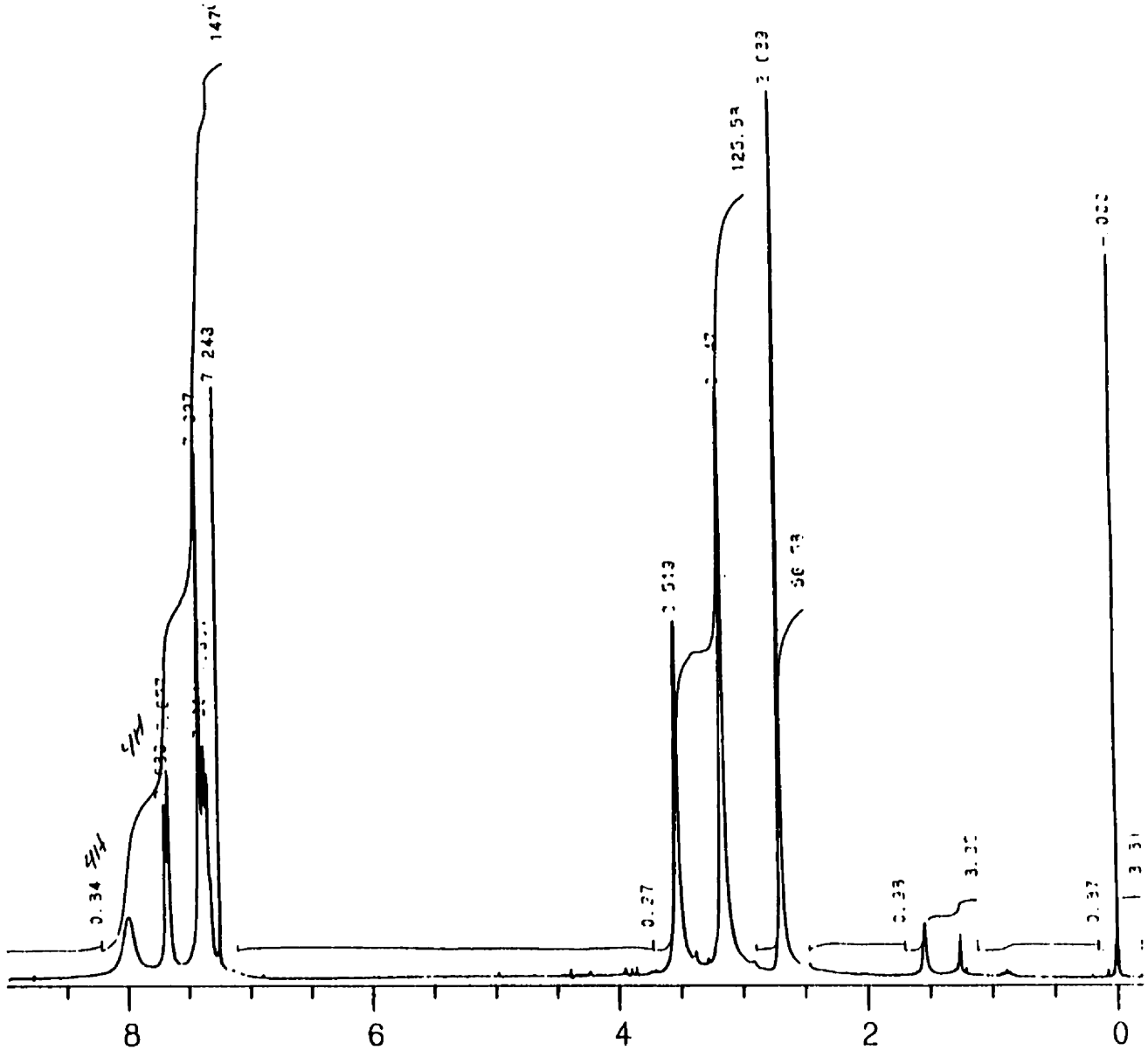
Scheme 6.4.



nucleophilic coupling of **105** with **106** under high dilution conditions afforded dithiatetrahomocalix[4]naphthalene **85** in 56% yield. Photochemical irradiation of **85** in triethylphosphite gave **85a** in 26% yield.

Based on NOED experiments on compound **85a**, the signal at 2.69 ppm was assigned to the ethano-bridges at C-2, C-3/C-24, C-25 while the signal at 3.52 ppm was assigned to the other ethano-bridges C-13, C-14/C-35, C-36. An unusual feature of the ^{1}H NMR spectrum (Figure 6.11) of **85a** is that the chemical shift of the signal due to ethano-bridges is situated at relatively high field 2.69 ppm. This clearly indicates that these ethano-bridges are shielded by the two opposite naphthalene rings. Examination of molecular models suggests that the molecule is rapidly interconverting between two 1,2-alternate types of orientation of the naphthalene rings. The ambient temperature ^{1}H NMR spectrum (Figure 6.11) indicates that it is conformationally flexible since all signals including those due to the ethano bridges which appear as singlets are sharp and well-defined. Using variable-temperature (VT) ^{1}H NMR, it can be seen (Figure 6.12) that the signal due to the ethano bridges at 3.52 ppm becomes broader at 0 °C and splits into two broad signals at -15 °C. Therefore, -10 °C was assigned as an approximate coalescence temperature for **85a**. The conformational mobility of the molecule is frozen completely at - 40 °C as revealed by the appearence of an AB system due to one of the ethano bridges. The signal due to the other ethano bridge which appears at 2.69 ppm by contrast, does not broaden significantly or even split on cooling down to a temperature of - 60 °C.

Fig. 6.11. ^{1}H NMR Spectrum of Tetrahomocalix[4]naphthalene 85a in $CDCl_3$.



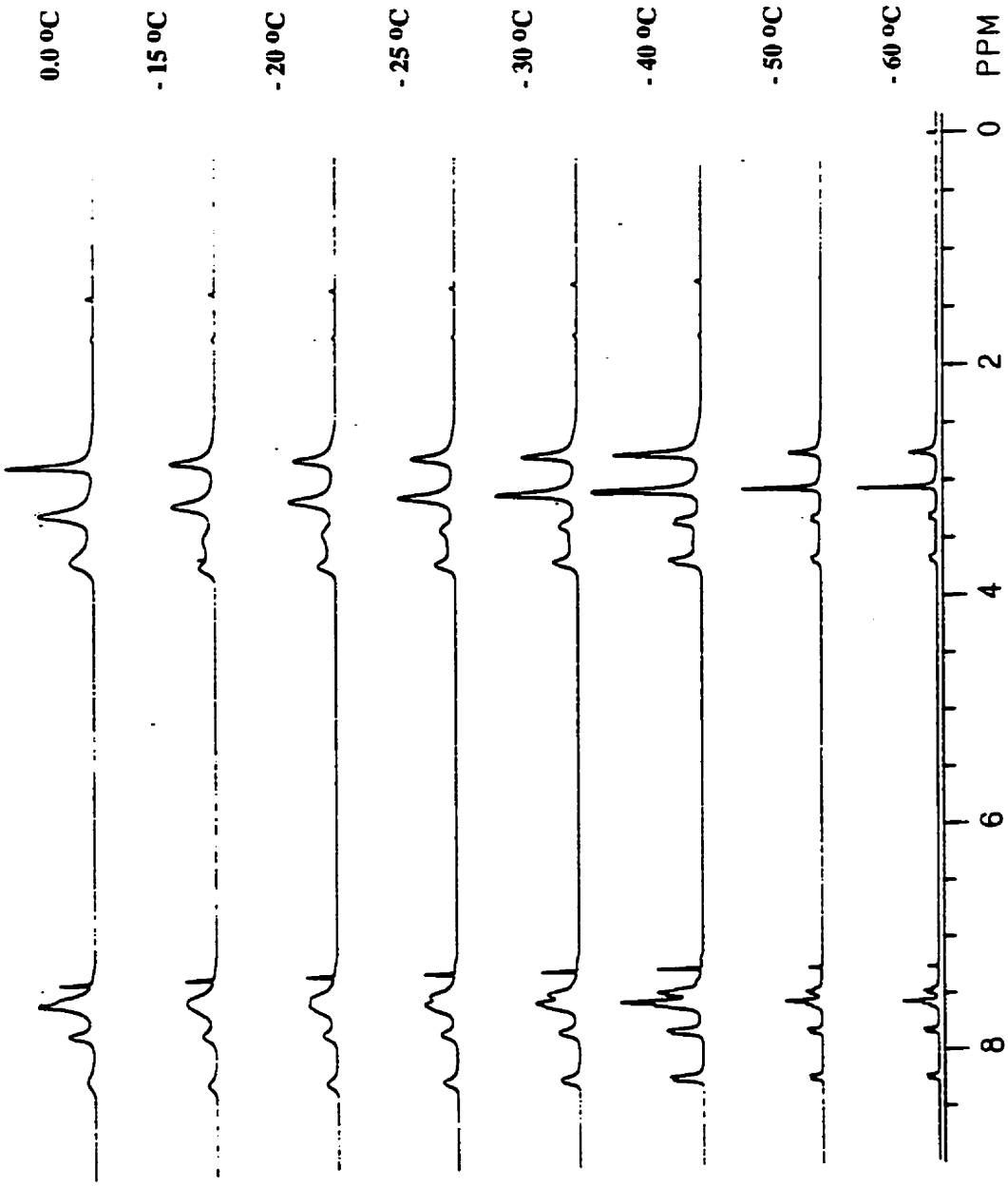
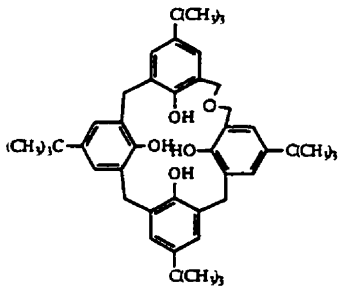


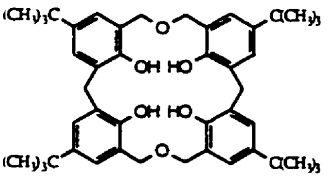
Fig. 6.12. VT ^{1}H NMR Spectra of Tetrahomocalix[4]naphthalene 85a in $CDCl_3$.

6.4. Synthesis of Dihomooxacalix[4]naphthalenes.

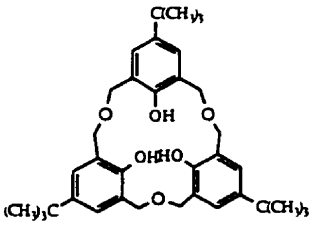
Figure 6.13.



X



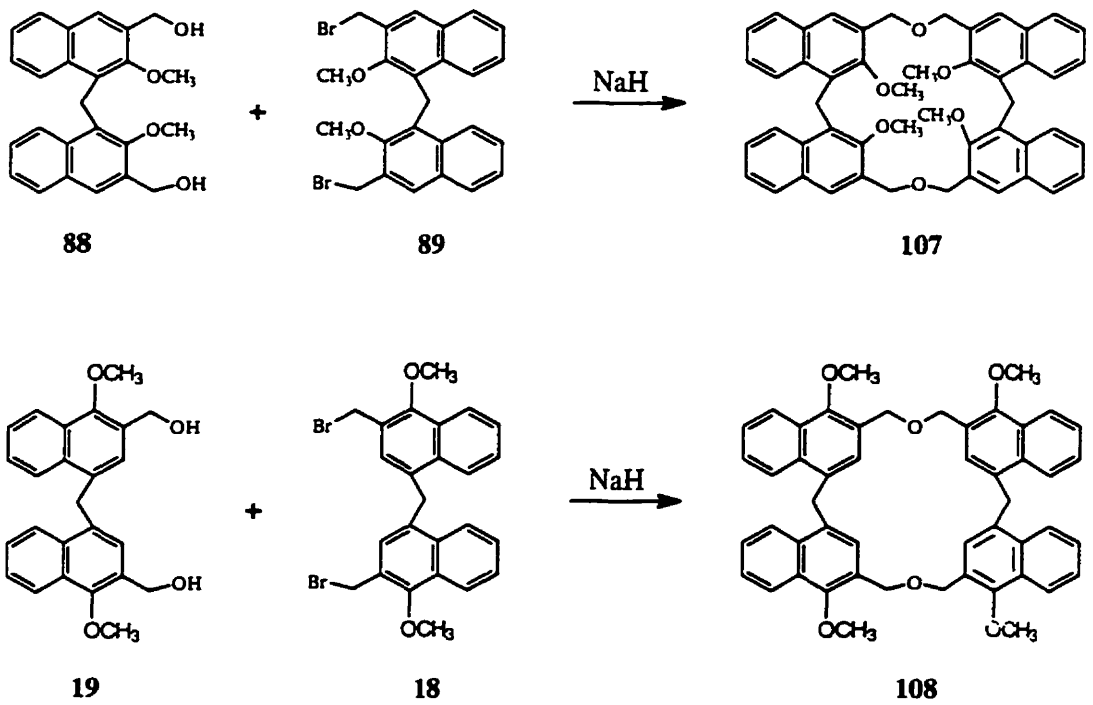
Y



Z

In 1983, Dhawan and Gutsche found that refluxing suitable bis(hydroxymethyl) precursors in xylene afforded oxacalixarenes **X-Z**.[84] It was believed that the formation of these products occurs by an intra- and intermolecular dehydration process. The importance of these compounds, particularly **Z**, is that the ether ring oxygens may act cooperatively with phenolic oxygen upon binding of metal ions.[85a-c] Therefore, to enhance the complexation properties of calixnaphthalenes, ether linkages at the bridges of calixnaphthalenes derived from 3-hydroxy-2-naphthoic acid and 1-naphthol were introduced. A convergent approach to synthesize ether-ring containing calix[4]naphthalene compounds **107** and **108** (Scheme 6.5) was employed.

Scheme 6.5.



The precursors **19**, **18**, **88** and **89** were synthesized previously as shown in Schemes 2.6 and 6.1. Once again, the ambient temperature ^{1}H NMR spectra of **107** and **108** indicate that they are conformationally flexible since all methylene signals appear as singlets. Using variable-temperature (VT) ^{1}H NMR, it can be seen that the signals due to compound **108** do not broaden or split even on cooling to a temperature of - 60 °C indicating that it is still conformationally flexible at that temperature (Figure 6.14). The VT ^{1}H NMR spectrum for compound **107**, by contrast, shows that the signal due to the

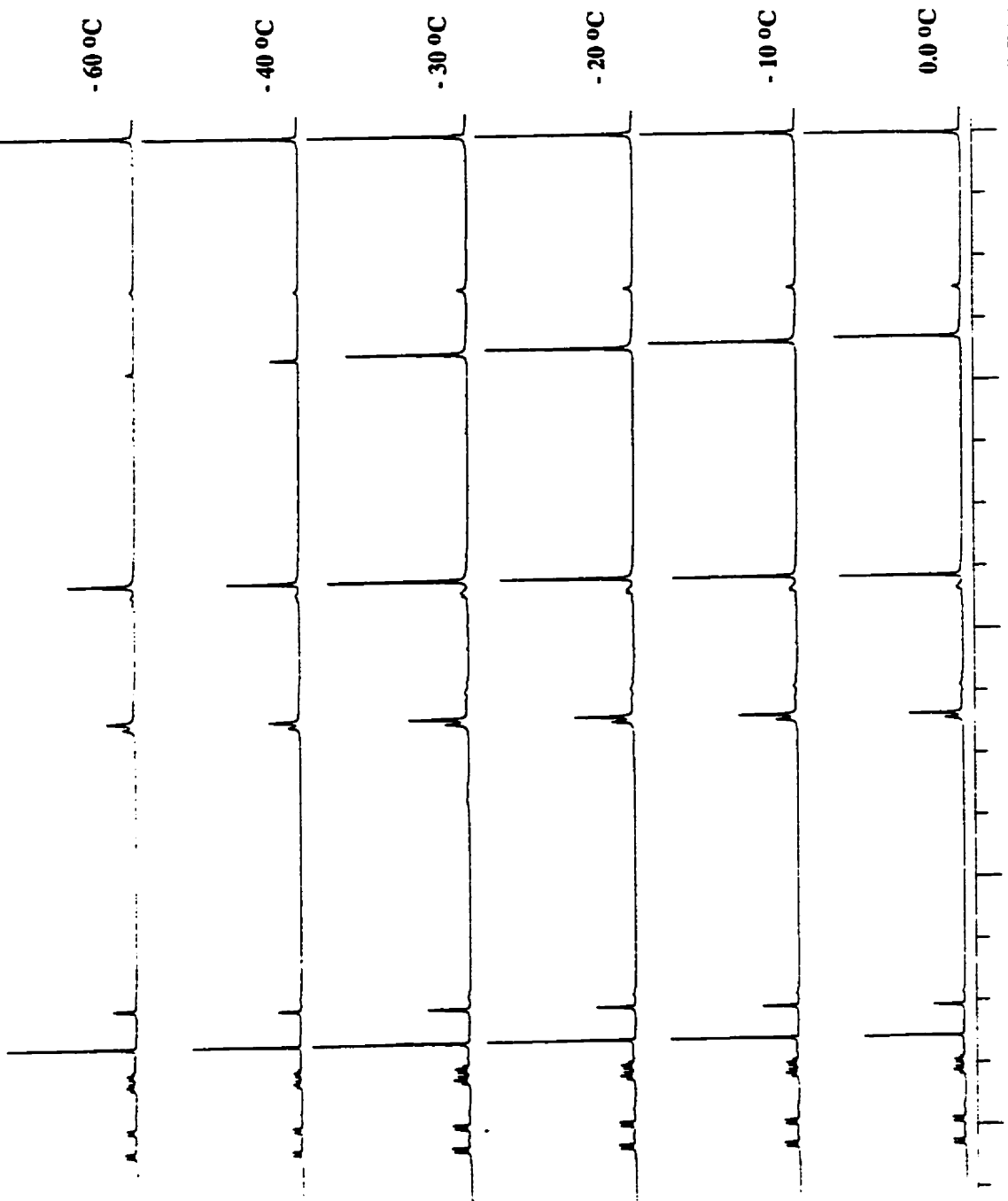


Fig. 6.14. VT ^{1}H NMR Spectra of Dihomooxocalix[4]naphthalene 108 in $CDCl_3$.

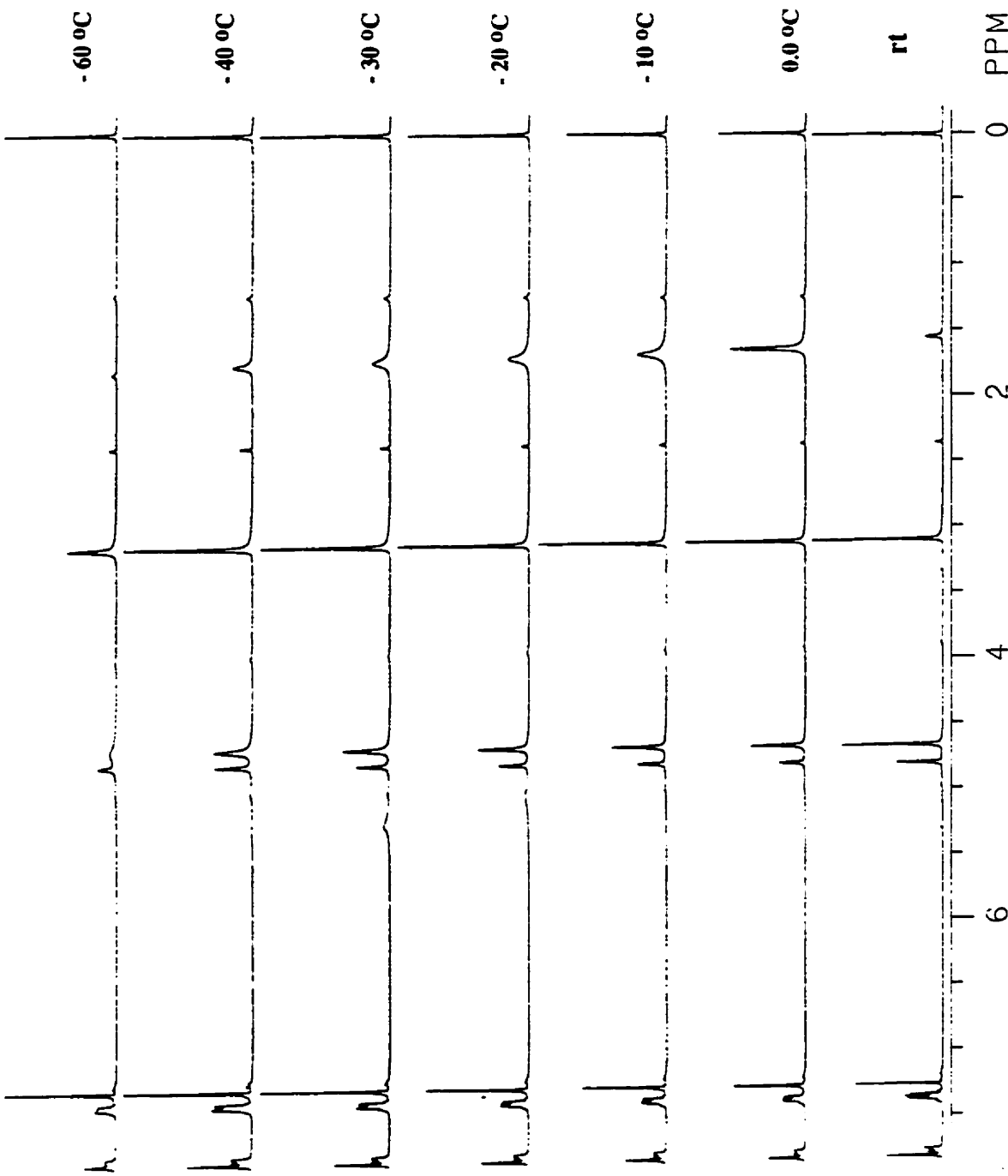
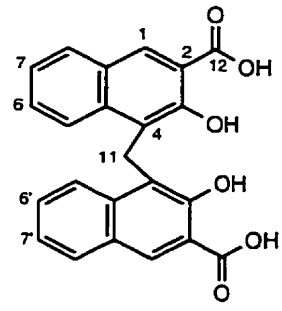


Fig. 6.15. VT ^{1}H NMR Spectra of Dihomooxocalix[4]naphthalene 107 in $CDCl_3$.

ether bridges which appears at 4.67 ppm becomes very broad at - 60 °C (Figure 6.15). This indicates that the conformational mobility of this compound is more restricted than the conformational mobility of compound **108** since the methoxyl groups are located intra-annularly.

6.5. Experimental.

4,4'-Methylenebis(3-hydroxy-2-naphthoic acid) (86).

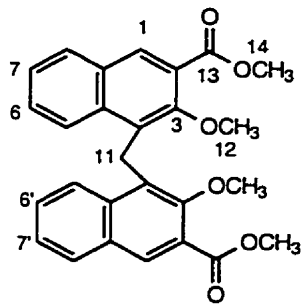


86

To a solution of 3-hydroxy-2-naphthoic acid (**9**) (1.9 g, 10 mmol) and paraformaldehyde (0.345 g, 12 mmol) in 20 mL of dioxane was added 4 mL of 30% aqueous H_2SO_4 at room temperature. The temperature was raised to 80-90 °C for 3 h. A yellow precipitate formed. After the reaction mixture was cooled to room temperature, the yellow precipitate was filtered and washed with excess water followed by ethanol and finally with petroleum ether to give a 100% yield of 4,4'-methylenebis(3-hydroxy-2-naphthoic acid) (**86**) as a yellow solid, m.p. > 300 °C dec. (lit. m.p, Aldrich, 220-223 °C); ^{1}H NMR (DMSO-d_6) δ = 3.5 (br, OH), 4.80 (s, 2H, H-11), 7.26 (t, J = 7.5 Hz, 2H, H-6, H-6'), 7.39 (t, J = 7.8 Hz, 2H, H-7, H-7'), 7.90 (d, J = 8.1 Hz, 2H, H-5, H-5' or H-8, H-8'),

8.12 (d, J = 8.7 Hz, 2H, H-8, H-8' or H-5, H-5'), 8.50 (s, 2H, H-1, H-1'), 12.08 (br. OH); ^{13}C NMR (DMSO-d_6) δ = 19.9 (C-11), 114.0, 120.6, 123.3, 123.4, 126.8, 128.9, 130.2, 131.6, 136.2, 153.4 (C-3, C-3'), 172.0 (C-12, C-12'); MS *m/s* (%) 388 (M^+, 9), 370 (3), 324 (8), 200 (15), 188 (51), 171 (14), 170 (100).

4,4'-Methylenebis(methyl-3-methoxy-2-naphthoate) (87).

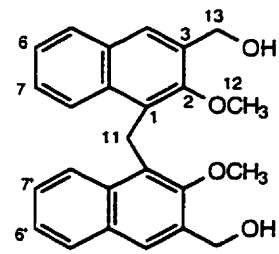


87

To a suspension of **86** (12 g, 31 mmol) in CH_2Cl_2 (150 mL) were added water (100 mL), phase-transfer catalyst (Adogen^R, 2.0 mL) and dimethylsulphate (23.5 mL). To the stirred mixture at room temperature was added 100 mL of aqueous 10% NaOH dropwise over a period of 20 min. The mixture was stirred at room temperature for an additional 5 h. After separation of the two layers, the aqueous layer was extracted with 50 mL of CH_2Cl_2. The solvent was removed on a rotary evaporator. The crude product was treated with 30 mL of diethyl ether. A precipitate formed, which was filtered and washed with 10 mL of cooled diethyl ether to give **87** as a colorless solid (12.3 g, 90%); m.p. 130-131 °C (lit.[86] m.p. 133 °C); ^{1}H NMR ($CDCl_3$) δ = 3.81 (s, 6H, H-12, H-12'), 4.01 (s, 6H, H-14, H-14'), 5.02 (s, 2H, H-11), 7.30-7.48 (m, 4H, H-6, H-7, H-6', H-7'), 7.76 (d, J = 7.8 Hz, 2H,

H-8, H-8'), 8.17 (d, J = 8.4 Hz, 2H, H-5, H-5'), 8.26 (s, 2H, H-1, H-1'); ^{13}C NMR ($CDCl_3$) δ = 22.6 (C-11), 52.3 (C-14, C-14'), 62.7 (C-12, C-12'), 123.8 (C-4, C-4'), 124.7 (C-8, C-8'), 125.2 (C-7, C-7'), 128.3 (C-6, C-6'), 129.3 (C-5, C-5'), 129.8 (C-2, C-2'), 130.1 (C-9, C-9'), 132.3 (C-1, C-1'), 135.2 (C-10, C-10'), 153.6 (C-3, C-3'), 166.9 (C-13, C-13'); MS *m/z* (%) 445 (M^++1, 20), 444 (M^+, 70), 413 (34), 412 (67), 398 (32), 397 (100), 354 (14); HRMS M^+ 444.1578, calcd for $C_{27}H_{24}O_6$ 444.1573.

Bis(3-hydroxymethyl-2-methoxy-1-naphthyl)methane (88).

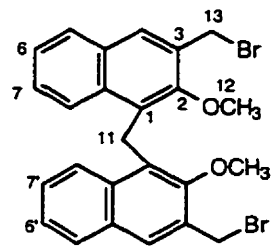


88

To a suspension of LAH (260 mg, 6.84 mmol) in dry THF (10 mL) under N_2 at rt was added dropwise a solution of **87** (1.52 g, 3.42 mmol) in dry THF (15 mL) over 20 min. The reaction mixture was stirred at rt for 3 h, and the reaction mixture, was worked-up by adding the mixture to wet diethyl ether at 0 °C, followed by the addition of aqueous 10% HCl. The organic layer was separated, and the aqueous layer was extracted twice with 50-ml portions of diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent evaporated on a rotary evaporator to give **88** as a cream-colored solid (1.2 g, 90%). The sample was crystallized from ethanol-water for analysis, m.p. 73-75 °C; ^{1}H NMR ($CDCl_3$) δ = 2.51 (br, 2H, OH), 3.81 (s, 6H, H-12, H-

12'), 4.89 (s, 4H, H-13, H-13'), 4.91 (s, 2H, H-11), 7.25 (m, 4H, H-6, H-6', H-7, H-7'), 7.64 (m, 2H, H-5, H-5'), 7.67 (s, 2H, H-4, H-4'), 8.10 (m, 2H, H-8, H-8'); ^{13}C NMR ($CDCl_3$) δ = 22.5 (C-11), 61.3 (C-12, C-12'), 62.1 (C-13, C-13'), 124.3 (C-8, C-8'), 124.6 (C-6, C-6'), 125.8 (C-7, C-7'), 127.0 (C-4, C-4'), 128 1 (C-5, C-5'), 128.5 (C-1, C-1'), 130.9 (C-3, C-3'), 132.9 (C-10, C-10'), 133.1 (C-9, C-9'), 153.7 (C-2, C-2'); MS *m/z* (%) 389 (M^++1, 25), 388 (M^+, 100), 353 (14), 352 (46), 351 (18), 335 (7), 325 (24), 324 (21), 310 (14), 309 (52), 295 (17); HRMS M^+ 388.1667, calcd for $C_{25}H_{24}O_4$ 388.1673.

Bis(3-bromomethyl-2-methoxy-1-naphthyl)methane (89).

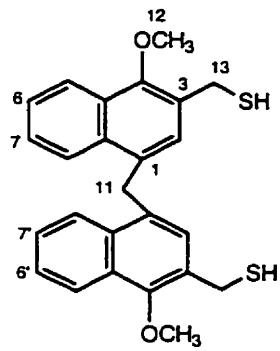


89

To a solution of **88** (2.89 g, 7.45 mmol) in CH_2Cl_2 (170 mL) was added PBr_3 (2.31 mL, 5.78 mmol) dropwise at rt under N_2. The solution was stirred at room temperature for 5 h. Work-up of the reaction was effected by adding cold water. The organic layer was separated and washed with water. After the organic layer was dried over anhydrous $MgSO_4$ and filtered, the solvent was evaporated on a rotary evaporator. The crude product was washed with diethyl ether to give **89** as a colorless solid (2.56 g, 67%), m.p. 182-184 °C; ^{1}H NMR ($CDCl_3$) δ = 4.06 (s, 6H, H-12, H-12'), 4.81 (s, 4H, H-13, H-13'),

4.95 (s, 2H, H-11), 7.27 (m, 4H, H-6, H-6', H-7, H-7'), 7.64 (m, 2H, H-5, H-5'), 7.75 (s, 2H, H-4, H-4'), 8.10 (m, 2H, H-8, H-8'); ^{13}C NMR ($CDCl_3$) δ = 23.0 (C-11), 29.5 (C-13, C-13'), 62.9 (C-12, C-12'), 124.7 (C-8, C-8'), 125.0 (C-6, C-6'), 126.7 (C-7, C-7'), 128.2 (C-5, C-5'), 129.2 (C-1, C-1'), 130.4 (C-4, C-4'), 130.5 (C-3, C-3'), 130.9 (C-10, C-10'), 133.7 (C-9, C-9'), 153.6 (C-2, C-2'); MS *m/z* (%) 516 (M^+ ^{81}Br ^{81}Br, 25), 514 (M^+ ^{81}Br ^{79} Br, 47), 512 (M^+ ^{79}Br ^{79}Br, 24), 435 (12), 433 (12), 308 (15), 265 (56); HRMS M^+ 511.9994, calcd for $C_{25}H_{22}Br_2O_2$ 511.9986.

Bis(3-mercaptomethyl-4-methoxy-1-naphthyl)methane (90).

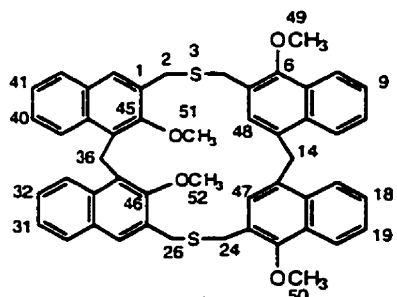


90

To a solution of **18** (540 mg, 1.06 mmol) in DMSO (25 mL) was added thiourea (200 mg, 2.65 mmol) under N_2, and the solution was stirred at rt for 5 h. The reaction was quenched by pouring the solution into a cold aqueous 10% solution of NaOH (25 mL), and the resulting solution was left to stir at rt for 2 h. The mixture was neutralized at 0 °C by adding aqueous 10% HCl. The precipitate was filtered, washed repeatedly with water, and air-dried to give **90** (391 mg, 88%), m.p. 75-77 °C; ^{1}H NMR ($CDCl_3$) δ = 1.76 (t, J = 7.5 Hz, 2H, SH), 3.82 (d, J = 7.5 Hz, 4H, H-13, H-13'), 4.02 (s, 6H, H-12, H-12'), 4.75 (s,

2H, H-11), 7.02 (s,2H, H-2, H-2'), 7.51 (m, 4H, H-6, H-7, H-6', H-7'), 7.98 (d, J = 8.1 Hz, 2H, H-8, H-8'), 8.17 (d, J = 8.1 Hz, 2H, H-5, H-5'); ^{13}C NMR ($CDCl_3$) δ = 23.1 (C-11), 35.1 (C-13, C-13'), 62.7 (C-12, C-12'), 122.9, 124.4, 126.0, 126.2, 128.3, 128.5, 129.1, 132.5, 132.8, 152.0 (C-4, C-4'); MS *m/z* (%) 420 (M^+, 66), 387 (45), 183 (100); HRMS M^+ 420.1240, calcd for $C_{25}H_{24}O_2S_2$ 420.1216.

Dithiadihomocalix[4]naphthalene (83).

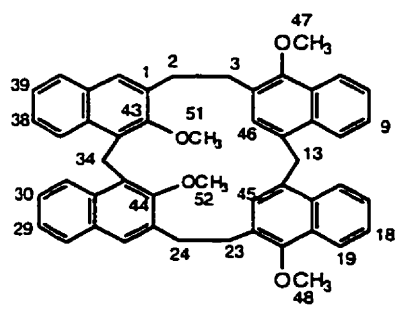


83

A solution consisting of **89** (1.96 g, 3.83 mmol) and **90** (1.61 g, 3.83 mmol) was prepared in benzene (200 mL). This solution was added dropwise, over a 15 h period, into a solution of ethanolic KOH (2.51 g, in 500 mL of 95% ethanol) under N_2. The mixture was stirred vigorously during the addition, and it was stirred for an additional 24 h after the addition was completed. A colorless precipitate formed, which was filtered by suction filtration, washed with water, and air-dried. The product was flash chromatographed (CH_2Cl_2 /petroleum ether 80:20) to give **83** (350 mg). The filtrate was concentrated to 50 mL, and the colorless crystals which separated were filtered and washed with aqueous 10% HCl, cold water, ethanol and finally with petroleum ether to

give **83** (2.15 g) whose melting point was identical with that of the first crop obtained from the first filtration. The total yield of **83** was 2.50 g (85%), m.p. 173-175 °C; ^{1}H NMR ($CDCl_3$) δ = 3.34 (s, 6H, H-51, H-52), 3.81 (s, 4H, H-2, H-26 or H-4, H-24), 3.82 (s,4H, H-2, H-26 or H-4, H-24), 3.94 (s, 6H, H-49, H-50), 4.58 (s, 2H, H-36), 4.84 (s, 2H, H-14), 6.87 (s, 2H, H-47, H-48), 7.34 (m, 4H), 7.41 (m, 2H), 7.51 (m, 2H), 7.69 (s, 2H, H-30, H-44), 7.72 (m, 2H), 7.88 (d, J = 8.1 Hz, 2H), 8.01 (m, 2H), 8.12 (d, J= 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ = 23.9, 30.8, 32.0, 34.9, 61.6, 62.7, 122.9, 123.7, 124.3, 124.5, 125.8, 126.0, 126.1, 128.2, 128.4, 128.6, 128.8, 129.9, 130.8, 131.2, 132.2, 132.7, 153.1, 155.25; MS *m/z* (%) 707 (3), 692 (2), 601 (5), 587 (3), 570 (3), 555 (8), 537 (4), 524 (6), 387 (48); HRMS M^+ 772.2658, calcd for $C_{50}H_{44}O_4S_2$ 772.2681.

Dihomocalix[4]naphthalene (83a).



83a

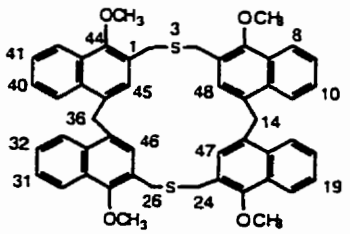
A solution of **83** (96 mg, 0.13 mmol) in triethylphosphite (5.0 mL) under Ar in a quartz tube was irradiated at 254 nm with stirring for 22 h. The solvent was removed by vacuum distillation, and the residue was dissolved in $CHCl_3$ and purified by PLC using $CHCl_3$-petroleum ether (50:50) to give **83a** (13 mg, 15%), m.p. 153-155 °C; ^{1}H NMR

($CDCl_3$) δ = 2.85 (br s, 4H), 3.04 (br s, 4H), 3.16 (br s, 6H, H-49, H-50), 3.84 (s, 6H, H-47, H-48), 4.43 (s, 2H, H-34), 4.84 (s, 2H, H-13), 6.77 (s, 2H, H-45, H-46), 7.21 (m, 4H), 7.38 (m, 4H), 7.51 (s, 2H, H-28, H-40), 7.61 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 7.5 Hz, 2H), 7.87 (d, J = 8.1 Hz, 2H), 8.05 (dd, J = 8.4, 0.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ = 23.9, 30.5, 31.1, 34.7, 60.7, 61.1, 61.9, 122.5, 123.4, 124.0, 124.1, 124.9, 125.2, 126.9, 128.0, 128.3, 128.3, 129.8, 130.6, 130.8, 131.9, 132.0, 134.9, 152.4, 155.8; MS *m/s* (%) 709 (21), 707 (100), 676 (5), 354 (17); HRMS M^+ 708.3230, calcd for $C_{50}H_{44}O_4$ 708.3240.

Silver ion complex (83b). A solution of **83** (110 mg, 0.151 mmol) in 2.5 mL of THF was added dropwise to a solution of $AgNO_3$ (25 mg, 0.15 mmol)) in THF (5.0 mL). The mixture was protected from light and stirred at rt for 24 h under Ar. The grey precipitate was filtered and vacuum-dried to afford **83b** (52 mg), m.p. 135-138 °C dec. ; ^1H NMR ($CDCl_3$) δ = 1.61 (s, H_2O), 1.85 (m, THF), 3.40 (br, 6H), 3.75 (m, THF), 4.03 (s, 8H), 4.10 (br s, 6H), 4.64 (br, 2H), 4.85 (s, 2H), 6.93 (br, 2H), 7.41 (m, 6H), 7.54 (m, 4H), 7.69 (m, 2H), 8.13 (m, 6H); +FAB MS (matrix: 3-nitrobenzyl alcohol) *m/z* (%) 880 (M^+).

Dithiadihomocalix[4]naphthalene (82).

A solution consisting of **18** (0.34 g, 0.67 mmol) and **90** (0.28 g, 0.67 mmol) was prepared in benzene (40 mL). This solution was added dropwise, over a 10 h period, into a solution of ethanolic KOH (0.23 g, in 110 mL 95% ethanol) under N_2. The mixture was stirred vigorously during the addition, and it was stirred for an additional 18 h after the addition was completed. A colorless precipitate formed, which was filtered by suction filtration, washed successively with aqueous 10% HCl, water, ethanol and finally air-dried

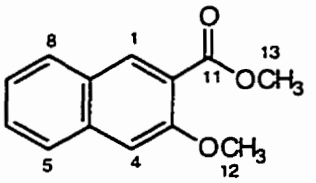


82

to give 0.42 g of **82** (81%), m.p. 285-290 °C; ^{1}H NMR ($CDCl_3$) δ = 3.76 (s, 8H, H-2, H-4, H-24, H-26), 3.85 (s, 12H, 4OCH_3), 4.61 (br, 4H, H-14, H-36), 6.70 (s, 4H, H-45, H-46, H-47, H-48), 7.46 (m, 8H, H-9, H-10, H-19, H-31, H-32, H-40, H-41), 7.94 (m, 4H, H-8, H-20, H-30, H-42), 8.10 (m, 4H, H-11, H-17, H-33, H-39); ^{13}C NMR ($CDCl_3$) δ = 31.3 (C-14, C-36), 34.5 (C-2, C-4, C-24, C-26), 63.0 (OCH_3), 122.8, 124.2, 124.4, 125.7, 126.1, 128.2, 128.3, 129.5, 131.8, 132.8; MS *m/z* (%) 772 (M^+, 5), 731 (6), 679 (6), 601 (16), 529 (10), 387 (20), 386 (22); HRMS M^+ 772.2695, calcd for $C_{50}H_{44}O_4S_2$ 772.2681.

Silver ion complex (82b). To a solution of **82** (121 mg, 0.157 mmol) in 6.0 mL of THF was added $AgNO_3$ (26 mg, 0.16 mmol) in THF (5.0 mL). The mixture was protected from light and stirred at rt for 24 h under Ar. The grey precipitate was filtered and vacuum-dried to afford **82b** (98 mg), m.p. 220-224 °C dec. ; ^{1}H NMR ($CDCl_3$) δ = 1.58 (s, H_2O), 1.85 (m, THF), 3.75 (m, THF), 3.98 (s, 12H), 4.25 (s, 8H), 4.72 (s, 4H), 7.15 (s, 4H), 7.56 (m, 4H), 8.13 (m, 4H); +FAB MS (matrix: 3-nitrobenzyl alcohol) *m/z* (%) 880 (M^+).

Methyl 3-methoxy-2-naphthoate (95).

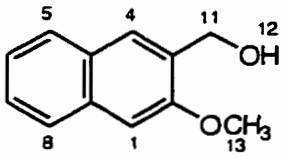


95

To a suspension of **9** (14 g, 72 mmol) in CH_2Cl_2 (360 mL) were added water (215 mL), phase-transfer catalyst (Adogen^R, 5 mL) and dimethylsulphate (52 mL). To the vigorously stirred mixture at room temperature was added aqueous 10% NaOH (180 mL) dropwise over a period of 30 min. The mixture was stirred at rt for an additional 2 h. After the separation of the two layers, the aqueous layer was extracted with 100 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent evaporated on a rotary evaporater. The crude product was purified by vacuum distillation to produce a golden oily compound **95** (11.3 g, 52.3 mmol, 73%). ^{1}H NMR ($CDCl_3$) δ = 3.96 (s, 3H, H-12), 4.00 (s, 3H, H-13), 7.21 (s, 1H, H-4), 7.52 (m, 2H, H-6, H-7), 7.74 (d, J = 8.4 Hz, 1H, H-5 or H-8), 7.82 (d, J = 7.8 Hz, 1H, H-5 or H-8), 8.31 (s, 1H, H-1); ^{13}C NMR ($CDCl_3$) δ = 52.0 (OCH_3), 55.7 ($COCH_3$), 106.5, 121.5, 124.2, 126.2, 128.2, 128.4, 132.9, 155.5 (C-2), 166.5 ($COCH_3$); MS *m/z* (%) 216 (M^+, 100), 185 (83), 183 (31), 155 (23), 142 (18), 128 (13), 127 (53), 115 (12), 114 (25).

3-Hydroxymethyl-2-methoxynaphthalene (96).

To a suspension of LAH (2.83 g, 74.5 mmol) in dry THF (100 mL) under N_2 at 0 °C was added dropwise a solution of **95** (11.3 g, 52.3 mmol) in dry THF (60 mL) over 30

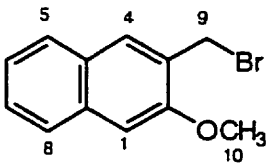


96

min. The reaction was stirred at room temperature for an additional 2 h. The reaction mixture was worked-up by adding the mixture to wet diethyl ether at 0 °C followed by aqueous 10% HCl. The organic layer was separated, and the aqueous layer was extracted twice with 100-ml portions of diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent evaporated on a rotary evaporator. The crude product was purified by flash chromatography using ethyl acetate-hexane ether (30:70) to give colorless solid **96** (8.30 g, 84%); m.p. 68-69 °C (lit. m.p. 71-72 °C)[87]; IR (Nujol, cm^{-1}) 3602, (br, OH), 1650 (s), 1640, 1550, 1500 (s); ^1H NMR ($CDCl_3$) δ = 2.39 (t, J = 6.0 Hz, 1H, H-12), 3.98 (s, 3H, H-13), 4.83 (d, J = 6.0 Hz, 2H, H-11), 7.13 (s, 1H, H-1), 7.35 (m, 1H, H-6 or H-7), 7.44 (m, 1H, H-7 or H-6), 7.75 (m, 3H, H-4, H-5, H-8); ^{13}C NMR ($CDCl_3$) δ = 55.4 (C-13), 62.5 (C-11), 105.2, 123.9, 126.3, 126.4, 127,5, 127.6, 128.6, 130.5, 134.1, 155.9; MS *m/z* (%) 188 (M^+, 100), 172 (10), 159 (52), 155 (13), 144 (22), 128 (23), 127 (36), 115 (30).

3-Bromomethyl-2-methoxynaphthalene (103).

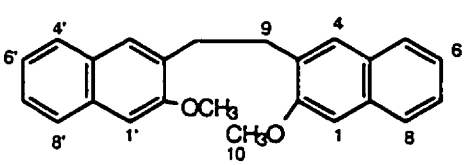
To a solution of **96** (8.31 g, 0.044 mmol) in CH_2Cl_2 (400 mL) was added PBr_3 (6.7 mL, 17 mmol) dropwise at rt under N_2 over a period 30 min. The solution was stirred for an additional 3 h. Work-up of the reaction was effected by adding 10 mL of cold water in



103

small portions. The organic layer was separated and washed twice with 60 mL of water. After the organic layer was dried over anhydrous $MgSO_4$ and filtered, the solvent was removed on a rotary evaporator. The crude product was purified by flash chromatography using CH_2Cl_2-petroleum ether (30:70) to give **103** as a colorless solid (9.50 g, 86%); m.p. 142-144 °C; ^1H NMR ($CDCl_3$) δ = 4.01 (s, 3H, H-10), 4.71 (s, 2H, H-9), 7.13 (s, 1H, H-1), 7.34 (m, 1H, H-6 or H-7), 7.44 (m, 1H, H-7 or H-6), 7.73 (t, 2H, H-8 and H-5), 7.81 (s, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ = 29.3 (C-9), 55.6 (C-10), 105.8, 124.0, 126.5, 126.9, 127.7, 130.3; MS *m/z* (%) 252 (M^+ ^{81}Br, 17), 250 (M^+ ^{79}Br, 17), 172 (14), 171 (100), 142 (10), 141 (83), 129 (5), 128 (34), 127 (10), 115 (15), 86 (15).

1,2-Bis(2-methoxy-3-naphthyl)ethane (104).

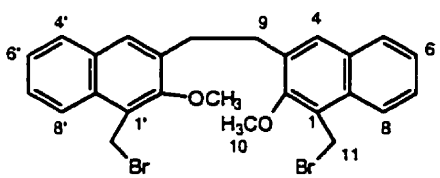


104

To a solution of **103** (0.94 g, 3.7 mmol) in dry THF was added *n*-BuLi (1.50 mL, 1.9 mmol) under Ar at - 78 °C. The reaction was stirred at - 78 °C for an additional 2 h. The reaction was quenched by adding 50 mL of $CHCl_3$ followed by 20 mL of water. The

organic layer was separated, dried over anhydrous $MgSO_4$, filtered and then evaporated to give **104** as a colorless solid (0.59 g, 92%), m.p. 184-185.5 °C; ^{1}H NMR ($CDCl_3$) δ = 3.13 (s, 4H, H-9, H-9'), 3.93 (s, 6H, H-10, H-10'), 7.14 (s, 2H, H-1, H-1'), 7.34 (m, 4H, H-6, H-6', H-7, H-7'), 7.59 (s, 2H, H-4, H-4'), 7.70 (t, H-5, H-5', H-8, H-8'); ^{13}C NMR ($CDCl_3$) δ = 30.9 (C-9, C-9'), 55.3 (C-10, C-10'), 104.7, 123.4, 125.4, 126.3, 127.1, 128.1, 128.8, 132.5, 133.4, 144.9, 156.6 (C-2, C-2'); MS *m/z* (%) 342 (M^+, 31), 172 (15), 171 (100), 143 (13), 142 (9), 141 (65), 128 (22), 115 (23).

1,2-Bis(1-bromomethyl-2-methoxy-3-naphthyl)ethane (105).

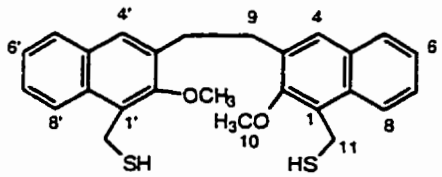


105

To a solution of **104** (0.33 g, 0.96 mmol), paraformaldehyde (0.116 g, 3.84 mmol) in acetic acid (6 mL) was added a solution of 15% HBr in acetic acid (6 mL) dropwise under N_2 at rt. The reaction mixture was stirred at rt for an additional 48 h. A precipitate formed, which was filtered and washed several times with petroleum ether to give **105** as a colorless solid (0.43 g, 84%); m.p. 177-179 °C; ^{1}H NMR ($CDCl_3$) δ = 3.18 (s, 4H, H-9, H-9'), 4.04 (s, 6H, H-10, H-10'), 5.12 (s, 4H, H-11, H-11'), 7.45 (m, 2H, H-6, H-6' or H-7, H-7'), 7.58 (m, 2H, H-7, H-7' or H-6, H-6'), 7.75 (s, 2H, H-4, H-4'), 7.78 (dd, J = 8.1, 0.6 Hz, 2H, H-8, H-8' or H-5, H-5'), 8.08 (d, J = 8.4 Hz, 2H, H-5, H-5' or H-8, H-8'); ^{13}C

NMR ($CDCl_3$) δ = 25.3 (C-9, C-9'), 31.7 (C-11, C-11'), 61.6 (C-10, C-10'), 123.4, 124.7, 125.4, 126.3, 128.1, 130.4, 131.2, 131.2, 134.6, 155.7 (C-2, C-2'); MS *m/z* (%) 530 (M^+ ^{81}Br ^{79}Br, 5), 528 (M^+ ^{79}Br ^{79}Br, 9), 450 (29), 449 (100), 447 (93), 370 (10), 369 (25), 354 (10), 353 (32).

1,2-Bis(1-mercaptomethyl-2-methoxy-3-naphthyl)ethane (106).

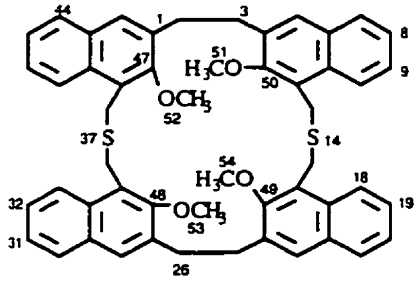


106

To a solution of **105** (1.61 g, 3.06 mmol) in DMSO (80 mL) was added thiourea (0.59 g, 7.7 mmol) under N_2. The solution was stirred at rt for 5 h. The reaction was quenched by pouring the solution into cold aqueous 10% NaOH (15 mL), and the resulting solution was stirred at room temperature for 2 h. The mixture was neutralized at 0 °C by the addition of aqueous 10% HCl. The precipitate was filtered, washed repeatedly with water and air-dried. The crude product was purified by flash chromatography using CH_2Cl_2-petroleum ether (70:30) to give **106** as a colorless solid (0.922 g, 70%); m.p. 141-143 °C; ^1H NMR ($CDCl_3$) δ = 2.00 (t, *J* = 6.9 Hz, 2H, SH), 3.2 (s, 4H, H-9, H-9'), 3.99 (s, 6H, H-10, H-10'), 4.29 (d, *J* = 7.2 Hz, 4H, H-11, H-11'), 7.43 (m, 2H, H-6, H-6' or H-7, H-7'), 7.53 (m, 2H, H-7, H-7' or H-6, H-6'), 7.69 (s, 2H, H-4, H-4'), 7.78 (d, *J* = 7.8 Hz, 2H, H-5, H-5' or H-7, H-7'), 8.00 (d, *J* = 8.1 Hz, 2H, H-7, H-7' or H-5, H-5'); ^{13}C NMR ($CDCl_3$) δ = 19.4 (C-9, C-9'), 31.8 (C-11, C-11'), 62.1 (C-10, C-10'), 123.3, 125.0, 126.0,

128.0, 128.3, 128.6, 130.7, 131.4, 134.9, 144.9, 154.4 (C-2, C-2'); MS *m/z* (%) 436 (M^++2, 7), 435 (M^++1, 17), 434 (M^+, 52), 403 (13), 402 (45), 401 (100), 400 (33), 370 (16), 369 (45), 355 (9), 354 (16), 353 (50), 337 (7), 224 (8), 215 (41), 210 (12), 209 (12), 201 (16), 200 (8), 197 (18), 185 (65), 184 (84), 183 (18).

Dithiatetrahomocalix[4]naphthalene (85).

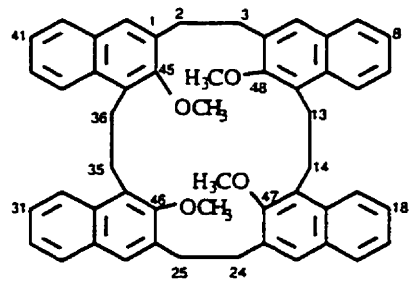


85

A solution of **105** (0.26 g, 0.49 mmol) and **106** (0.21 g, 0.49 mmol) was prepared in benzene (45 mL). This solution was added dropwise , over 5 h period into a solution of ethanolic KOH (0.321 g in 105 mL) under N_2. The mixture was stirred overnight. The solvent was evaporated on a rotary evaporator. The residue was dissolved in 50 mL of $CHCl_3$ and washed with aqueous 10% HCl. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by PLC using CH_2Cl_2-petroleum ether (60:40) to give **85** as a colorless solid (220 mg, 56%), m.p. 271-273 °C; ^{1}H NMR ($CDCl_3$) δ = 3.21 (s, 8H, H-2, H-3, H-25, H-26), 3.38 (s, 12H, OCH_3), 4.23 (s, 8H, H-13, H-15, H-36, H-38), 7.25 (m, 8H, H-8, H-9, H-19, H-20, H-31, H-32, H-42, H-43), 7.67 (br, 8H, H-7, H-10, H-18, H-21, H-30, H-33, H-41, H-44); ^{13}C NMR ($CDCl_3$) δ =

27.0 (C-2, C-3, C-25, C-26), 30.0 (C-13, C-15, C-36, C-38), 61.1 (C-51, C-52, C-53, C-54), 123.9, 124.7, 125.3, 127.7, 131.0, 131.6, 134.3, 155.1 (C-47, C-48, C-49, C-50); +FAB MS *m/z* (%) 799.4 (1), 398 (1), 378 (1), 306 (24), 289 (6), 288 (19), 272 (10).

Tetrahomocalix[4]naphthalene (85a).

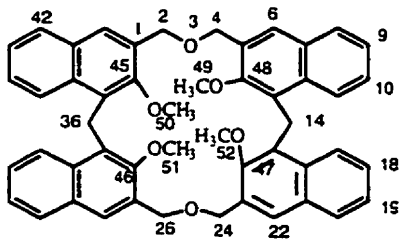


85a

A solution of **85** (80 mg, 0.11 mmol) in triethylphosphite (4 mL) under Ar in a quartz tube was irradiated at 254 nm with stirring for 3 days. The solvent was removed by vacuum distillation, and the residue was purified by PLC using CH_2Cl_2-petroleum ether (40:60) to give **85a** as a colorless solid (19 mg, 26%), m.p. 293-295 °C; ^{1}H NMR ($CDCl_3$) δ = 2.69 (s, 8H, H-2, H-3, H-24, H-25), 3.15 (s, 12H, OCH_3), 3.52 (s, 8H, H-13, H-14, H-35, H-36), 7.37 (br, 8H, H-8, H-9, H-18, H-19, H-30, H-31, H-40, H-41), 7.40 (s, 4H, H-5, H-22, H-27, H-44), 7.67 (d, J = 7.8 Hz, 4H, H-7, H-20, H-29, H-42), 8.0 (br, 4H, H-10, H-17, H-32, H-39); NOE (%) **H-10 (H-17, H-32, H-39)/** H-13 (H-14, H-35, H-36)(4.4); **H-7 (H-20, H-29, H-42)/** H-5 (H-22, H-27, H-42)(3.8); **H-5 (H-22, H-27, H-44)/**H-7 (H-20, H-29, H-42)(19), H-2 (H-3, H-24, H-25)(2.2); **H-13 (H-14, H-35, H-36)/** H-10 (H-17, H-32, H-39)(23.3); **H-2 (H-3, H-24, H-25)/** OCH_3 (1.8), H-5 (H-22, H-27, H-44)(6.1); ^{13}C NMR

($CDCl_3$) δ = 25.7 (C-13, C-14, C-35, C-36), 29.5 (C-2, C-3, C-24, C-25), 60.8 (OCH_3), 123.4 (C-10, C-17, C-32, C-39), 123.8 and 124.7 (C-8, C-9, C-18, C-19, C-30, C-31, C-40, C-41), 126.3 (C-5, C-22, C-27, C-44), 128.1 (C-7, C-20, C-29, C-42), 131.0, 132.3, 134.7, 155.4 (**C**-OCH_3); +FAB MS (matrix: 3-nitrobenzyl alcohol) *m/z* (%) 736 (M^+, 1), 734 (2), 617 (2), 474 (1), 422 (1), 399 (2), 328 (5), 307 (5), 306 (18), 294 (3), 288 (18).

Dihomooxacalix[4]naphthalene (107).

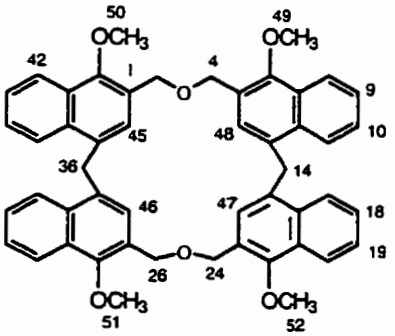


107

To a solution of NaH (96 mg, 2.3 mmol) in dry toluene (30 mL) was added a solution consisting of **88** (0.301 g, 0.776 mmol) and **89** (0.396 g, 0.776 mmol) in dry THF (15 mL) by syringe over a period of 3 h under Ar at reflux temperature. The reaction was stirred at reflux temperature overnight. The reaction mixture was cooled to room temperature and 20 mL of aqueous 10% HCl were added. The reaction mixture was extracted twice with 100 mL of $CHCl_3$. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was crystallized from $CHCl_3$ to give pale yellow crystals of **107** (0.195 g, 34%), m.p. > 300 °C dec.; ^1H NMR ($CDCl_3$) δ = 3.10 (s, 12H, OCH_3), 4.66 (s, 8H, H-2, H-4, H-24, H-26), 4.80 (s, 4H, H-14, H-36), 7.36 (m, 8H, H-9, H-10, H-18, H-19, H-31, H-32, H-40, H-41), 7.77 (m, 4H, H-8,

H-20, H-30, H-42), 7.81 (s, 4H, H-6, H-22, H-28, H-44), 8.07 (m, 4H, H-11, H-17, H-33, H-39); ^{13}C NMR ($CDCl_3$) δ = 23.7 (C-14, C-36), 61.8 (C-49, C-50, C-51, C-52), 67.3 (C-2, C-4, C-24, C-26), 123.8, 124.3, 126.1, 128.6, 129.3, 130.7, 131.0, 133.3, 155.6 (C-45, C-46, C-47, C-48).

Dihomooxacalix[4]naphthalene (108).



108

To a solution of NaH (100 mg, 2.34 mmol) in dry THF (35 mL) was added a solution consisting of **19** (0.31 g, 0.79 mmol) and **18** (0.398 g, 0.786 mmol) in dry THF (50 mL) by syringe over a period 5 h under Ar at rt. The reaction was stirred at reflux temperature for an additional 24 h. The reaction mixture was cooled to rt, and 20 mL of aqueous 10% HCl was added. A precipitate was formed, which was filtered and washed with CH_2Cl_2 to give **108** as a colorless solid (0.14 g, 23%), m.p. > 300 °C dec.; ^1H NMR ($CDCl_3$) δ = 3.57 (s, 12H, OCH_3), 4.67 (s, 8H, H-2, H-4, H-24, H-26), 4.70 (s, 4H, H-14, H-36), 7.03 (s, 4H, H-45, H-46, H-47, H-48), 7.49 (m, 8H, H-9, H-10, H-18, H-19, H-31, H-32, H-40, H-41), 7.95 (d, J = 8.1 Hz, 4H, H-8, H-20, H-30, H-42), 8.12 (d, J = 7.8 Hz, 4H, H-11, H-17, H-

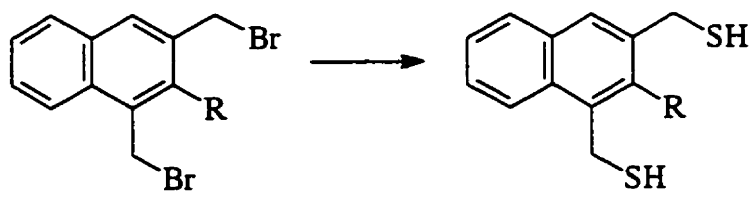
33, H-39); ^{13}C NMR ($CDCl_3$) δ = 35.0 (C-14, C-36), 62.7 (C-49, C-50, C-51, C-52), 68.0 (C-2, C-4, C-24, C-26), 122.8, 124.2, 125.6, 126.0, 126.1, 128.0, 128.5, 131.8, 133.0, 133.1, 153.1 (C-49, C-50, C-51, C-52).

Chapter 7

Synthesis of dibenzopyrenes and pyrenes

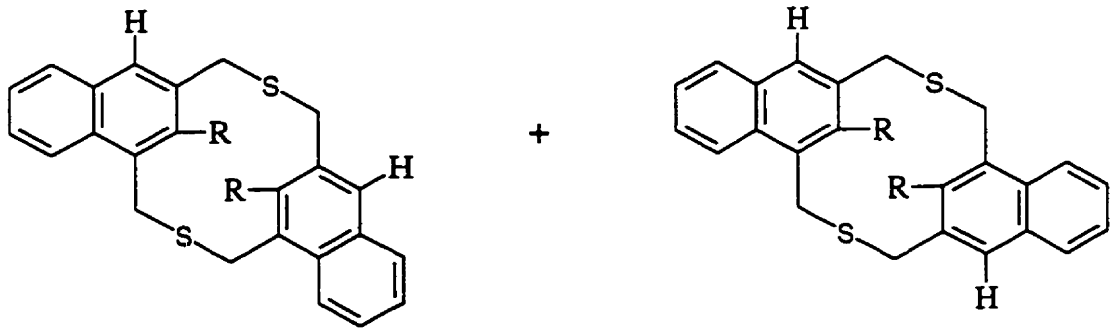
As previously mentioned in Chapter 6, we were interested in the synthesis of the tetrahomocalix[4]naphthalene **85a** and its structural isomers **91a-93a** (Figure 6.5). The synthetic approach which was employed was a base-mediated coupling of 1,3-bis(bromomethyl)-2-methoxynaphthalene (**97**) with its corresponding bis(mercaptomethyl) derivative **98** (Scheme 6.3). In principle, this reaction should produce several isomers of tetrathia[3.3.3.3](1,3)naphthalenophane, **91-94** (Figure 6.6). These are potential precursors to tetrahomocalix[4]naphthalenes **85a** and **91a-93a** after sulfur extrusion. Attempts to produce these tetrathia precursors resulted in formation of four isomeric 11,22-dimethoxy-2,13-dithia[3.3](1,3)naphthalenophanes, **99-102** in 18%, 19%, 10% and 34% yields, respectively after TLC separation of the crude product (Scheme 7.1). Isomer **101** was the least polar, followed by **99**, **102** and **100** in order of increasing polarity. These products are analogous to the corresponding 11,22-dimethyl- and 11,22-unsubstituted-2,13-dithia[3.3](1,3)naphthalenophanes (**103-106**) reported by Mitchell *et al.* [88] However, when each of the compounds **99-102** was photolyzed in triethylphosphite, 5,6,12,13-tetrahydrodibenzo[*b*,*def*]chrysene (**107**), or 6,7,13,14-tetrahydrobenzo[*rst*]pentaphene (**108**) were obtained (Scheme 7.2). Oxidation of these tetrahydro compounds was facile and produced dibenzopyrenes, **109** and **110**, respectively (Scheme 7.2). This type of sulfur extrusion with concomitant transannular cyclization appears to be general and could offer some advantages

Scheme 7.1.



97 R = OCH_3 **98** R = OCH_3

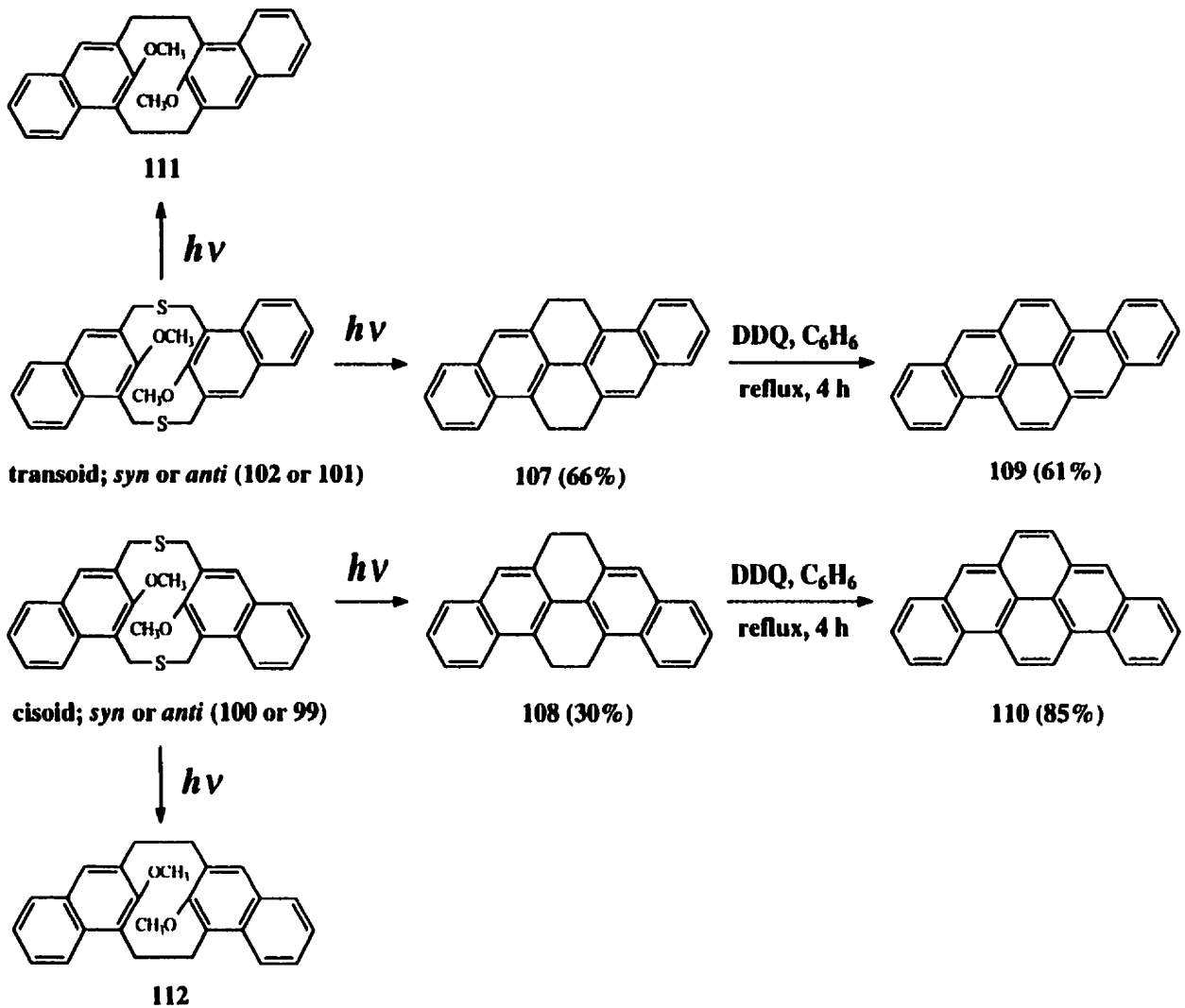
KOH, PhH, EtOH



99 *anti* R = OCH_3
100 *syn* R = OCH_3
103 *syn* R = H
104 *anti* & *syn* R = CH_3

101 *anti* R = OCH_3
102 *syn* R = OCH_3
105 *syn* R = H
106 *anti* & *syn* R = CH_3

Scheme 7.2.


OCH3
CH3O
111
hν
S
OCH3
CH3O
S
transoid; syn or anti (102 or 101)
hν
107 (66%)
DDQ, C6H6
reflux, 4 h
109 (61%)
cisoid; syn or anti (100 or 99)
hν
108 (30%)
DDQ, C6H6
reflux, 4 h
110 (85%)
hν
112

for the synthesis of dibenzopyrenes and pyrenes. The mechanism shown in Scheme 7.3 for one of the four isomers, i.e., **102** is proposed to account for the observed results.

The ^{1}H NMR spectrum of **101** has well-resolved signals with simple splitting patterns (as do, to varying degrees, the spectra of each of the other isomers **99**, **100** and **102**) that are consistent with a transoid-*anti* structure.[88] Support for the NMR assignments (of this, and the other isomers, Figure 7.1) is based upon 2-D and NOED experiments and by comparison with arguments presented by Mitchell *et al.*[88] for their closely related compounds **103-106**. The methoxyl groups of **101** at $\delta = 2.93$, are shielded by 0.64 ppm relative to those of its *syn* isomer **102** (Figures 7.2 and 7.5), respectively. The bridging methylene protons of **101** are diastereotopic and appear as two sets of AB quartets, one which is poorly resolved and is centred at $\delta = 3.26$. Since H-5 (H-16) is the only naphthalene-ring singlet, it was used as the reference signal together with NOE determinations to assign unequivocally the remaining naphthalene-ring protons H-6 to H-9 (H-16 to H-20) and also the remainder of the protons. The AB quartet at $\delta = 3.26$ is attributed to the H-3 (and H-14) protons since irradiation of this system produces a 5.6 % NOE enhancement of the H-5 (and H-16) singlet and also a 2.4 % NOE enhancement of the doublet at $\delta = 8.18$, which is due to H-20 (and H-9). Molecular models indicate that H-20 and H-9 can only be close to H-3x and H-14x, respectively, when the intraannular 12-membered dithia ring is in a conformation with S-2 pointing down and S-13 pointing up, as indicated in Figure 7.1. This is in agreement with the conformation proposed by Mitchell *et al.*[88] for the analogous compound *anti*-**106**. The other AB quartet has two clearly defined doublets; one centred at $\delta = 4.00$

Scheme 7.3.

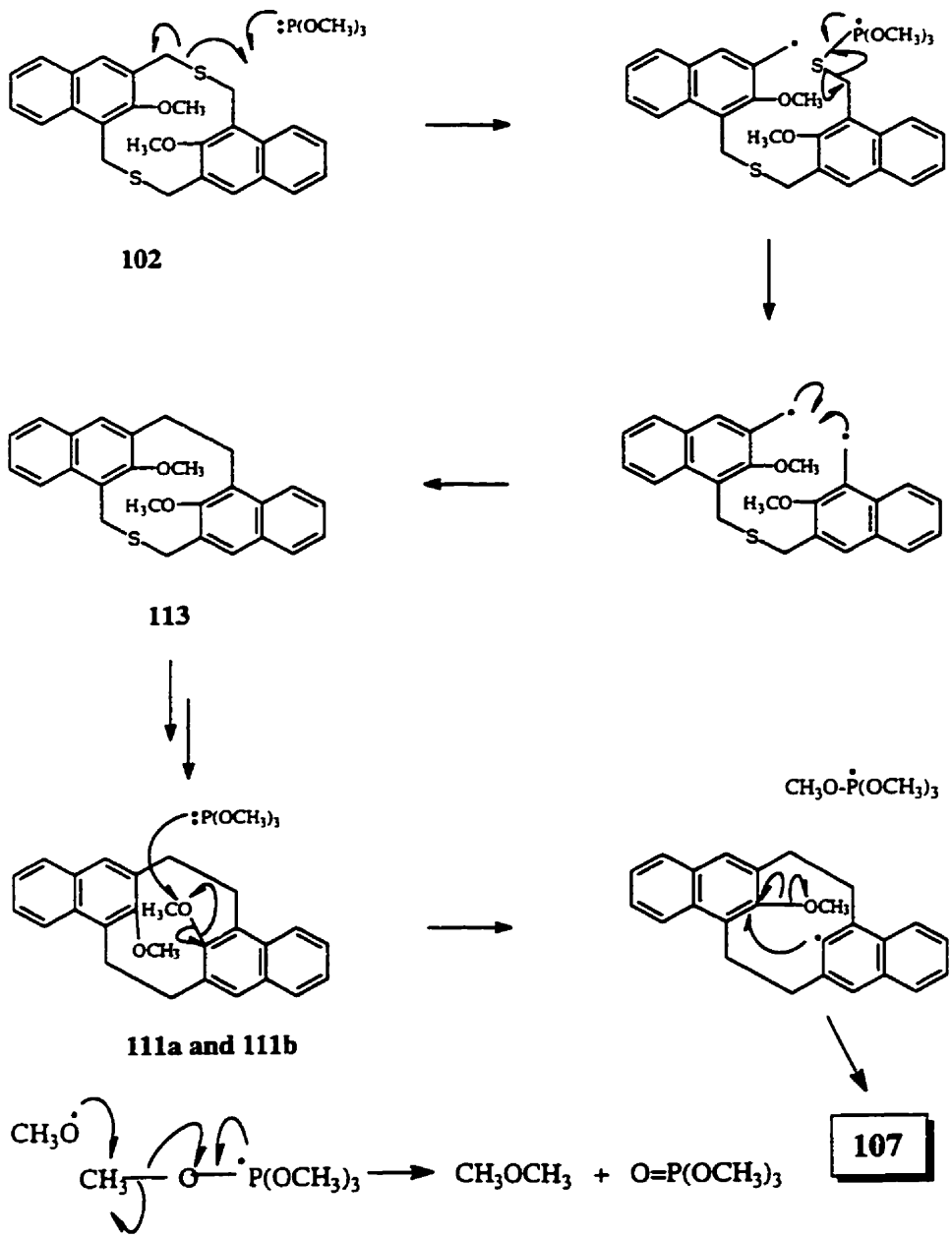
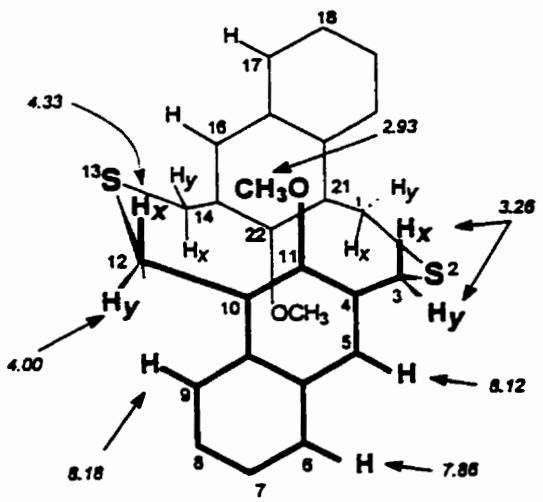
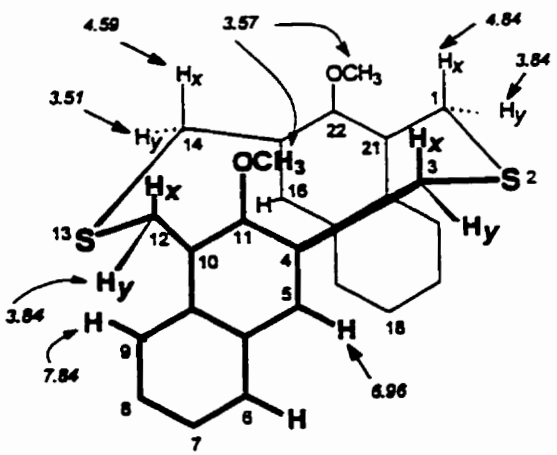

:P(OCH3)3
S
OCH3
H3CO
S
P(OCH3)3
S
OCH3
H3CO
S
102
OCH3
H3CO
S
OCH3
H3CO
S
113
:P(OCH3)3
H3CO
OCH3
CH3O-P(OCH3)3
OCH3
111a and 111b
CH3O
CH3
O
P(OCH3)3
CH3OCH3 + O=P(OCH3)3
107

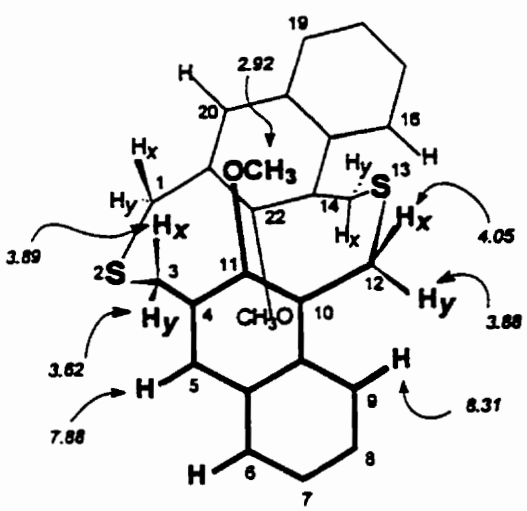
Figure 7.1. Selected ^1H δ Values and Preferred Conformations of Compounds 99-102



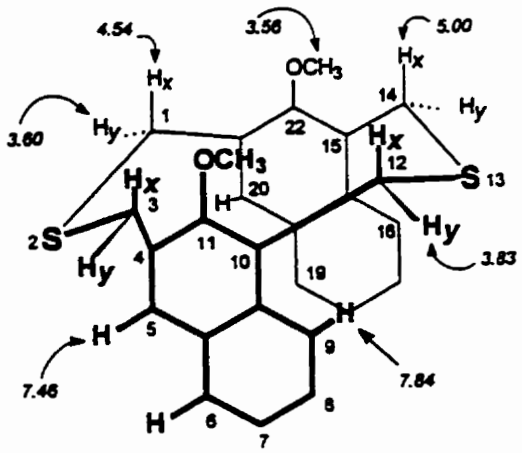
101 ***transoid-anti***



102 ***transoid-syn***



99 ***cisoid-anti***



100 ***cisoid-syn***

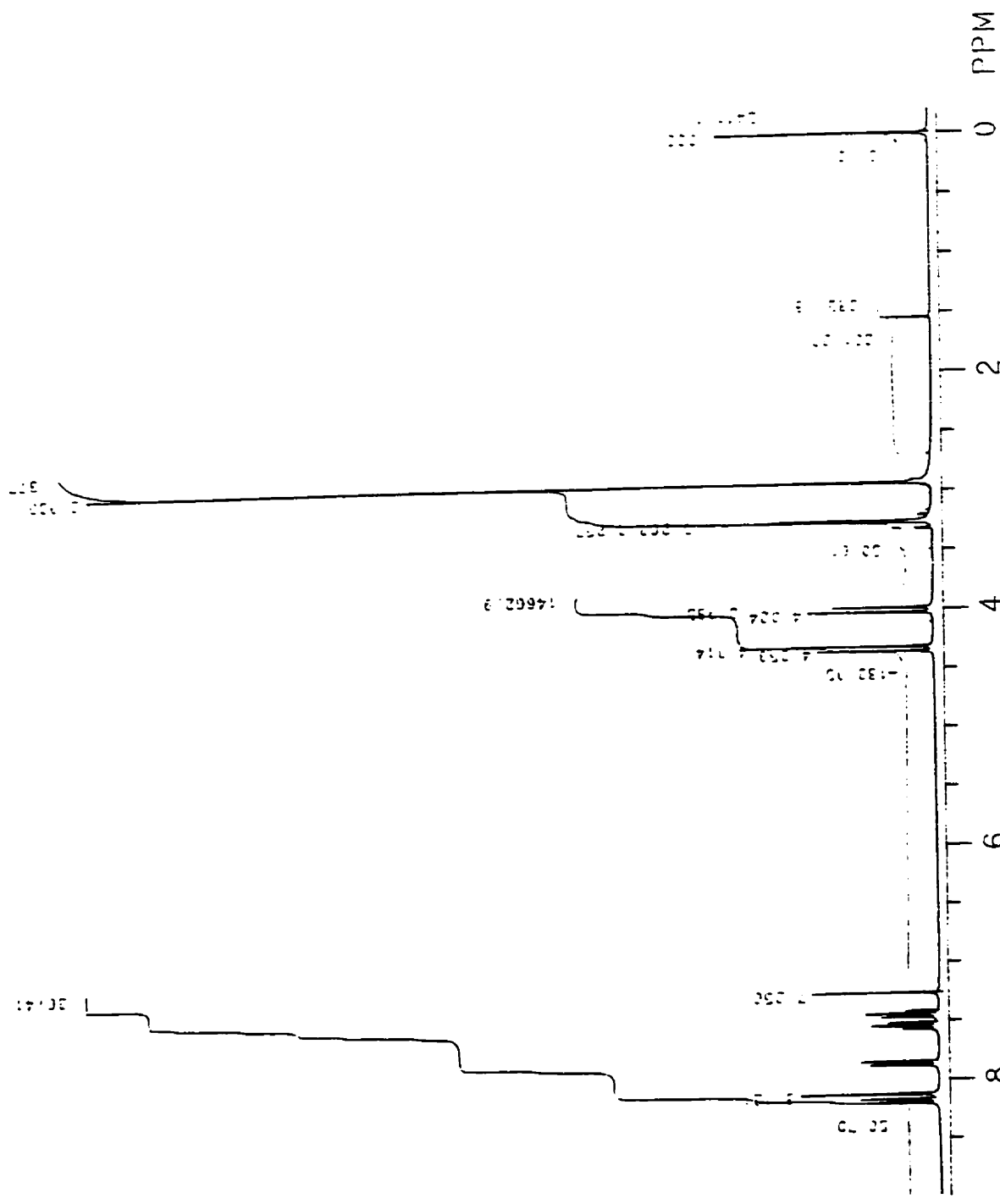


Fig. 7.2. ^{1}H NMR Spectrum of 101 in $CDCl_3$

(J = 11.7 Hz; H-1y and H-12y; *pseudo*-equatorial*), which is enhanced by 6.2 % when H-9 is irradiated and the other at δ = 4.33 (J = 11.7 Hz; H-1x and H-12x; *pseudo*-axial), which is not. A single crystal x-ray diffraction analysis on **101** (Figure 7.3) confirms the structural assignments and indicates that the preferred conformation in the solid state is the same as which appears to be the case in solution. Molecular modeling calculations using geometry optimizations were performed at the AM1 semiempirical level[89] using SPARTAN[90] are also consistent with the conformational assignment depicted in Figure 7.1.

Unequivocal chemical proof of the transoid structure of **101** (and of **102**, and also of the cisoid structures of isomers **99** and **100** -see below) was obtained unexpectedly from its photolysis in triethylphosphite,[82] which produced instead of the anticipated naphthalenophane **111**, a product whose NMR spectra showed it to be highly symmetrical and lacking the methoxyl groups. Mass spectral data indicated, and single crystal x-ray crystallography (Figure 7.4) confirmed it to be 5,6,12,13-tetrahydrodibenzo[*b*,*def*]chrysene (**107**). DDQ oxidation easily converted **107** to dibenzo[*b*,*def*]chrysene (**109**).[91]

The methoxyl groups in the ^{1}H NMR spectrum (Figure 7.5) of the *syn* isomer **102** are at δ = 3.57, which is more typical for an unshielded 2-naphthyl methoxyl group (δ = 3.92 in 2-methoxynaphthalene and δ = 3.86 in bis(2-methoxy-1-naphthyl)methane). The bridging methylene protons are diastereotopic and appear as two sets of AB quartets, each having

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* "*Pseudo*-axial" protons refer to bridging methylene group protons which are in, or are directed towards the planes of the naphthalene rings; "*pseudo*-equatorial" protons refer to bridging methylene group protons which are out of , or are directed out of the planes of the rings.

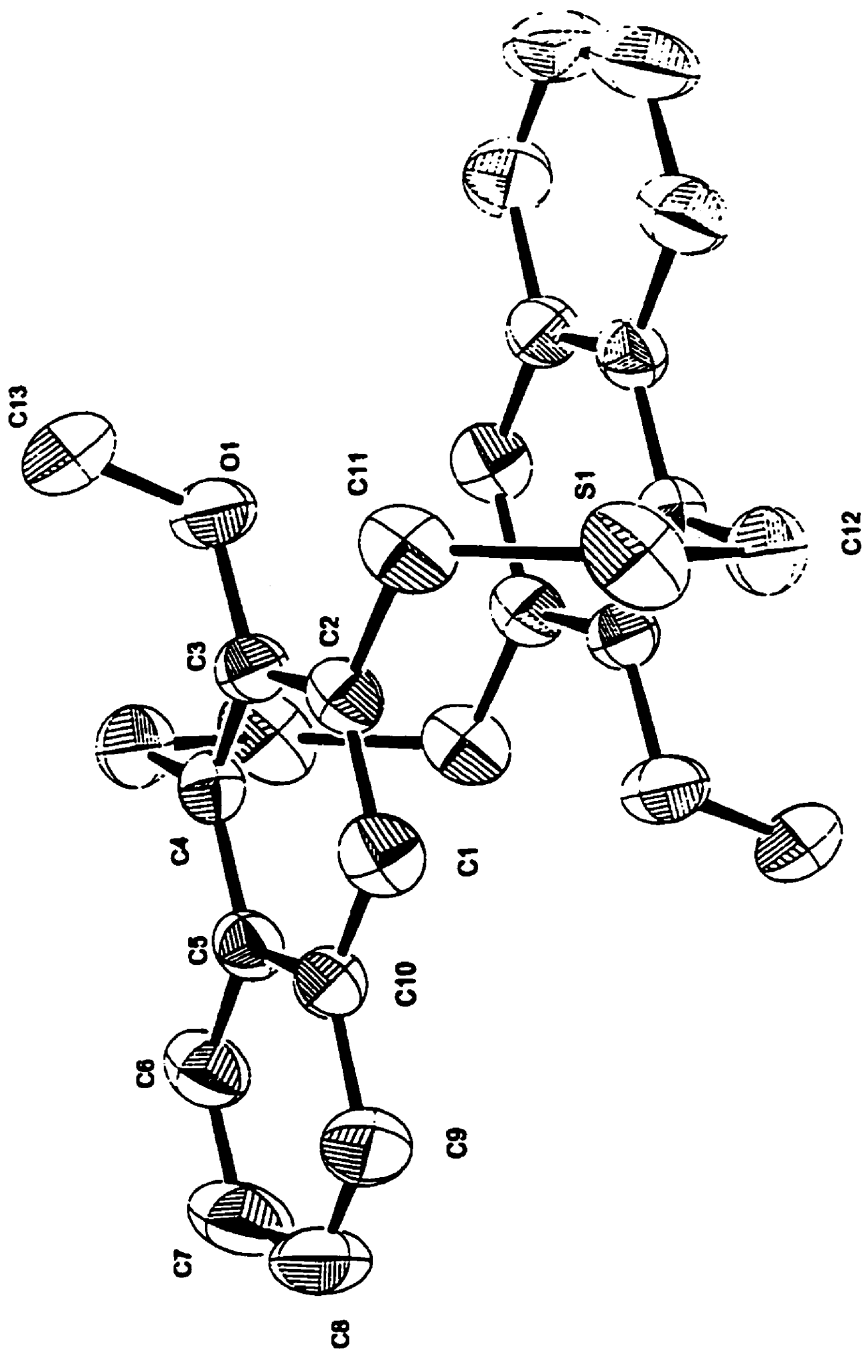


Figure 7.3. X-Ray Crystal Structure of 101

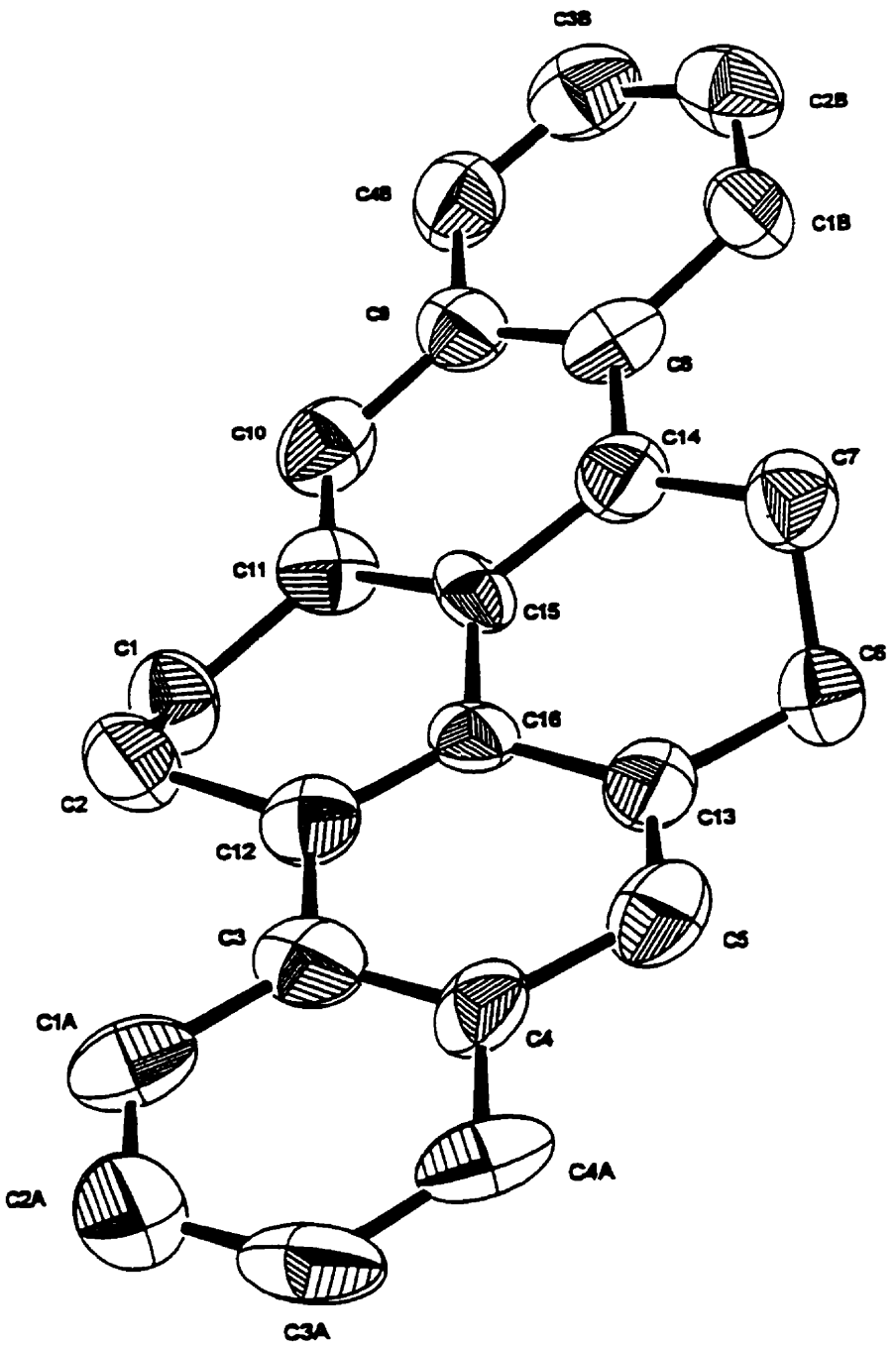


Figure 7.4. X-Ray Crystal Structure of 107

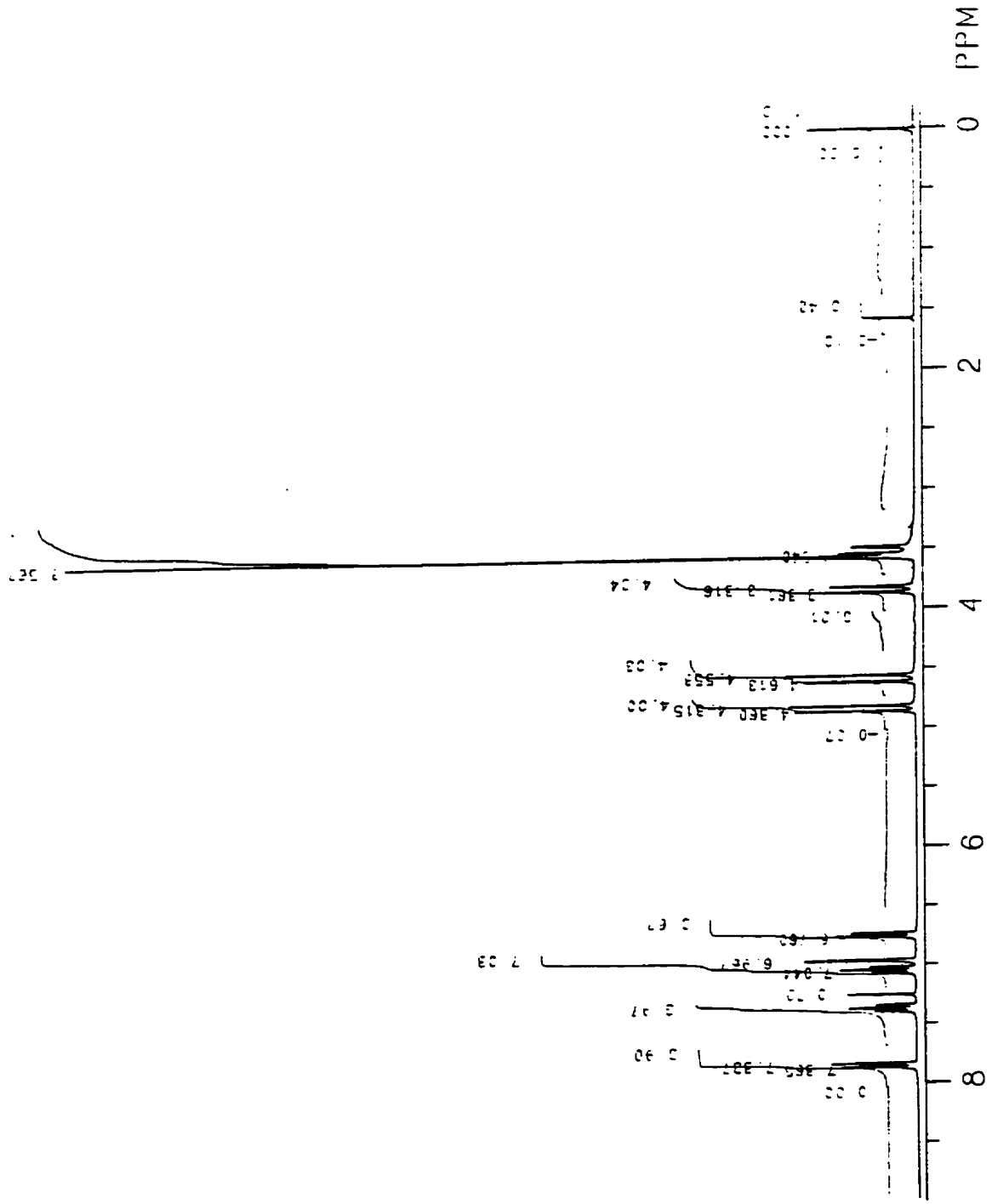


Fig. 7.5. ^{1}H NMR Spectrum of 102 in $CDCl_3$

a pair of clearly defined doublets. One AB quartet has a doublet centred at δ = 4.84 (*J*= 13.5 Hz) assigned to H-1x and H-12x, which is coupled to the doublet centred at δ = 3.84, assigned to hydrogens H-1y and H-12y. The other AB quartet, assigned to the H-3x (and H-14x) protons, has a doublet centred at δ = 4.59 (*J* = 16.4 Hz), which is coupled to the doublet at δ = 3.51 (H-3y; H-14y). The transoid hydrogens H-5 and H-16 are eclipsed by the opposing naphthalene rings and appear as a singlet at δ = 6.96, which is shielded by 1.16 ppm compared to the corresponding signal in **101**. The conformational assignment shown is further supported by NOE determinations and molecular modeling calculations. For example, there is an enhancement of H-1x (H-12x) on saturation of H-3x (H-14x), and *vice-versa*. Photolysis of **102** under the conditions employed for **101** also produced **107**.

The ^{1}H NMR spectrum of **99** (Figure 7.6) is consistent with its cisoid-*anti* structure. The methoxyl groups of **99** are at δ = 2.92, indicating shielding by 0.64 ppm relative to those of its cisoid-*syn* isomer **100**. The bridging methylene protons appear as two overlapping sets of AB quartets, whose respective pairs of coupled doublets are centred at δ = 4.05 (*J* = 13.8 Hz; H-12x, H-14x) and δ = 3.88 (H-12y, H-14y); and at δ = 3.89 (*J* = 13.8 Hz, H-1x, H-3x) and δ = 3.62 (H-1y, H-3y). The singlet at δ = 7.88, due to the cisoid hydrogens H-5 and H-20, is deshielded relative to the corresponding signal (at δ = 7.46) for **100**. NOED experiments with **99** reveal that irradiation of *either* H-3x (H-1x) *or* H-3y (H-1y) enhances H-5 (H-20) by 1.4% and 1.9%, respectively. However, irradiation of *only* H-12y (H-14y) enhances H-9 (H-16) by 7.7%. Irradiation of H-12x (H-14x) does not enhance H-9 (H-16). To account for these NMR observations, the preferred conformation appears to be one in

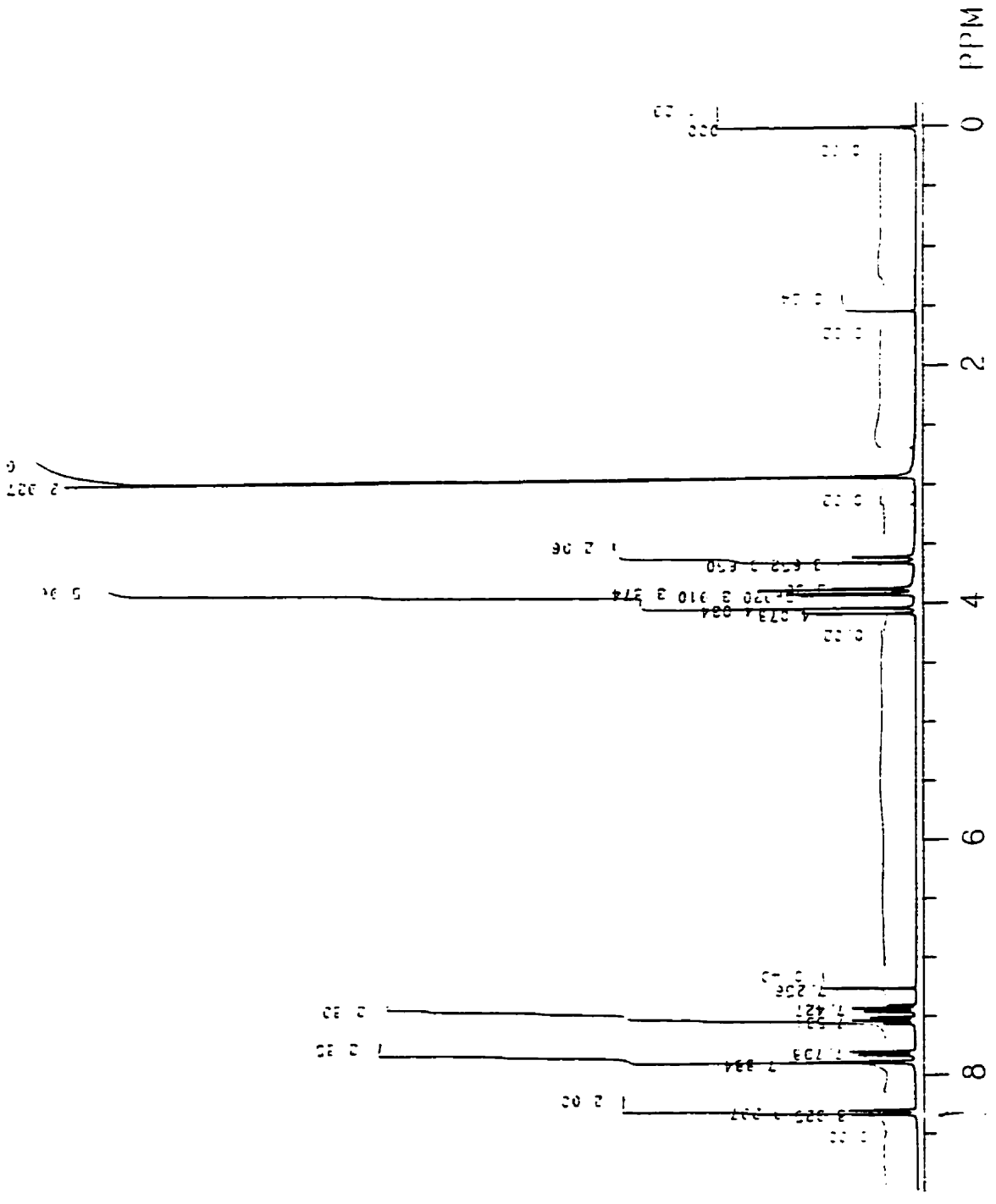


Fig. 7.6. ^{1}H NMR Spectrum of 99 in $CDCl_3$

which there is, on average, a skewing of the C-1--S-2--C-3 bridge, which would place the S-2--C-3--C-4 bonds in a nearly coplanar arrangement with the C-4--C-11 naphthalene ring (in dynamic equilibrium with the conformation which places S-2--C-1--C-21 bonds in a nearly coplanar arrangement with the C-21--C-22 naphthalene ring) . Since only H-9 (H-16) is enhanced when H-12y (H-14y) is irradiated, the other (C-12--S-13--C-14) bridge cannot be similarly skewed. This is also in general agreement with the interpretations made without any such NOE data by Mitchell *et al.* for the ^{1}H- NMR spectra of their analogous *anti*-**104.**

The line shapes and chemical shifts for the bridging methylene protons in the cisoid-*syn* compound **100** (Figure 7.7) are similar to those observed in the transoid-*syn* isomer **102.** In **100**, one AB quartet has a doublet centred at $\delta = 5.00$ (J= 14.7 Hz) assigned to H-12x (and H-14x), which is coupled to the doublet centred at $\delta = 3.83$ (H-12y, H-14y). The other AB quartet due to the protons on C-1 (and C-3) has a doublet centred at $\delta = 4.54$ (J= 15.0 Hz) assigned to H-1x (and H-3x), and its coupled doublet at $\delta = 3.60$ assigned to H-1y (and H-3y). Mitchell *et al.* assigned a preferred conformation to the analogous compound *syn*-**104** for which they postulated that, in order to minimize the *peri* interactions between the methylene bridge protons and the protons on the A-rings (H-5 and H-20 in **100**), the C-1--S-2--C-3 bridge should be pointing up and the C-12--S-13--C-14 bridge pointing down in a *boat-chair* type of conformation. NOE determinations did not permit distinguishing unequivocally between such a *boat-chair* type of conformation and one in which both bridges are pointing down in a *chair-chair* type of conformation. Molecular modeling[89, 90] calculations however clearly indicate that the latter is energetically favoured (by 6.35

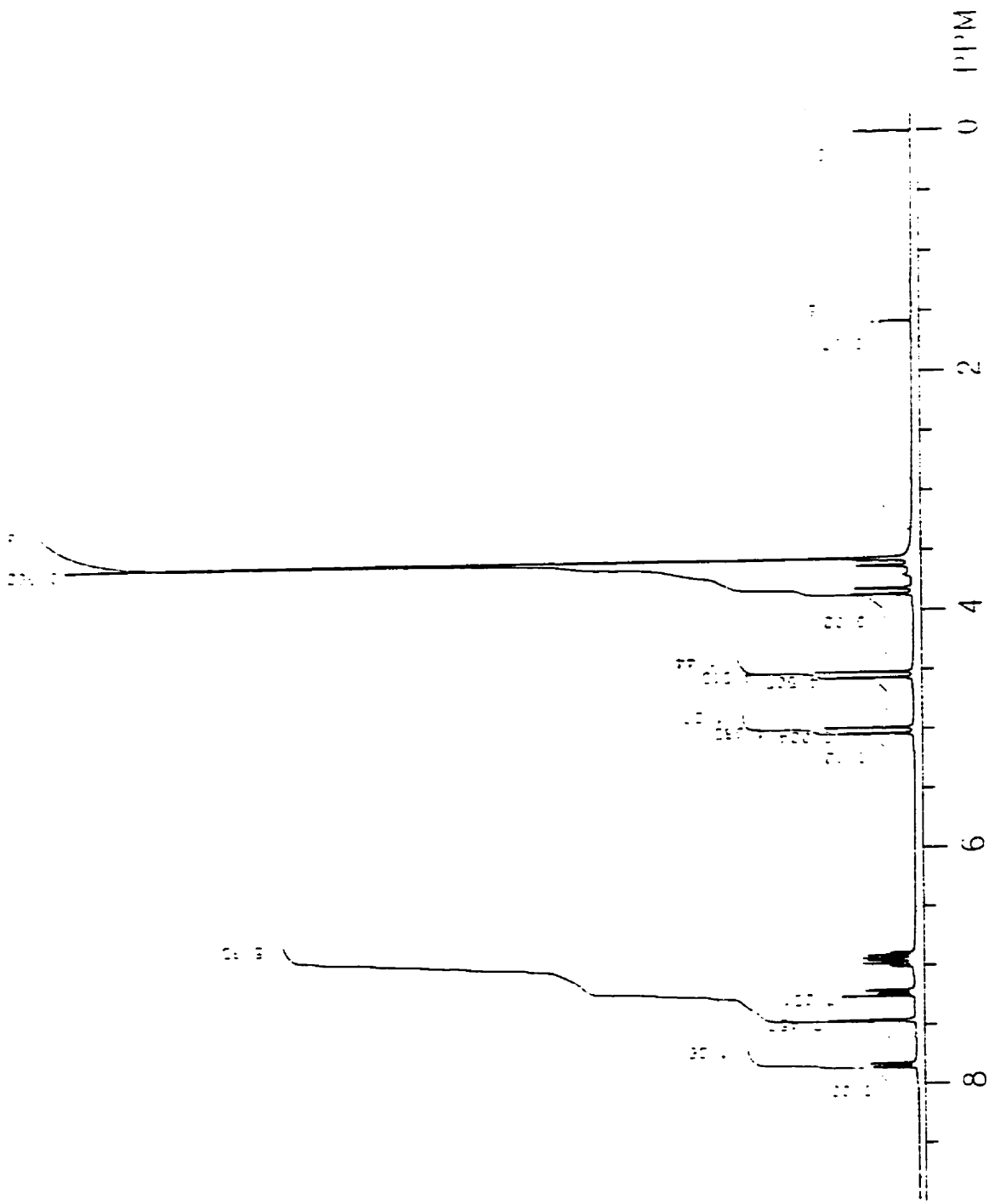


Fig. 7.7. ^{1}H NMR Spectrum of 100 in $CDCl_3$

kcal/mol). Also, the optimized geometries of the two conformations reveal that the distance between H-3y and H-5 (the *peri* interaction referred to above) is only 2.40 Å in the *boat-chair*, but 2.71 Å in the *chair-chair* conformation.

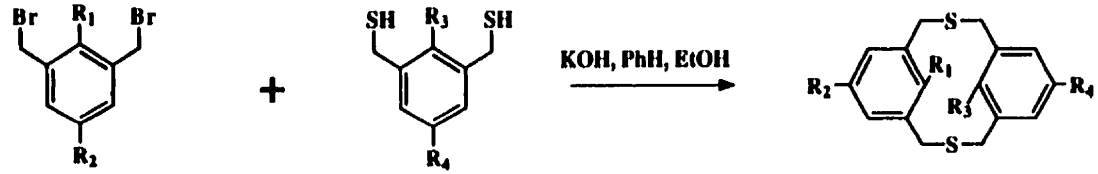
Photolysis of either **99** or **100**, under the same conditions employed for **101** and **102**, produced only 1,2,6,7-tetrahydro-3.4,9.10-dibenzopyrene (**108**). DDQ oxidation of **108** afforded 3.4,9.10-dibenzopyrene (**110**). Both of the isomeric benzopyrenes **109** and **110** had identical physical properties with those previously reported.[91]

We are unaware of any other reports of similar one-pot sulphur extrusion/ transannular cyclizations from 2,13-dithia[3.3]naphthalenophanes, or 2,11-dithia-[3.3]cyclophanes leading to either tetrahydrodibenzopyrenes or tetrahydropyrenes, respectively. Boekelheide *et al.* [82] first reported the photochemical transformation in trimethylphosphite, of 6-methyl- and 9-methyl-2,11-dithia[3.3]cyclophane to the corresponding [2.2]metacyclophanes but did not report the formation of any of the corresponding pyrenes. Earlier, Mitchell and Boekelheide[92,79] had reported the transformation of 9,18-dimethyl-2,11-dithia[3.3]metacyclophanes into the corresponding 15,16-dimethyldihydropyrene, but the sequence involved several steps including a Stevens rearrangement and elimination step. On the other hand, there are many examples that have been reported in which halogen-induced[93,94,95] and photolytically-induced[96] transannular cyclization of various [2.2]metacyclophanes produce the corresponding tetrahydropyrenes. However, all of these instances involve prior formation of the cyclophanes from the precursor dithiaphanes, a process which usually requires two separate steps involving

oxidation of the disulphides to the bissulphones, followed by a vacuum pyrolysis.

In order to ascertain whether the photolysis products of compounds **99-102** were general, the reactions leading to the dithia[3.3]metacyclophane precursors, **120-124**, of the tetrahydropyrenes **127-130**, respectively were examined, as summarized in Scheme 7.4. Boekelheide *et al.* [82] had not observed any cyclization during the photolytic sulfur elimination reaction of dithiacyclophane **125** in which only hydrogen atoms are present at both the 9- and 18-positions, or when **126** in which a methyl group and a hydrogen atom are present at the 9- and 18-positions, respectively. The reactions of dithia[3.3]metacyclophanes **120-124**, in which at least one methoxyl group was present at these intraannular positions, were therefore examined. Intermediate compounds **114-119** were all synthesized and coupled by standard procedures to give the corresponding dithiacyclophanes **120-124** in good yields. Photolytic sulfur elimination/intraannular cyclization occurred in all cases, except with **124**, to produce the tetrahydropyrenes **127-129**. At least one intraannular methoxyl group therefore appears to be necessary to allow for the *in situ* transannular cyclization step. The presence of an electron-withdrawing group at the 6- or 15-positions, e.g. bromine in the case of **124**, however, appears to inhibit the sulphur elimination/intrannular cyclization. It can be noted that Yamato and coworkers[95] have reported the cyclization of various substituted 8-methoxy[2.2]-metacyclophanes themselves to the corresponding tetrahydropyrenes using benzyltrimethyl ammonium tribromide (BTMA Br_3). However, in agreement with results reported in this work for **124**, they too were unable to effect cyclization when a bromine

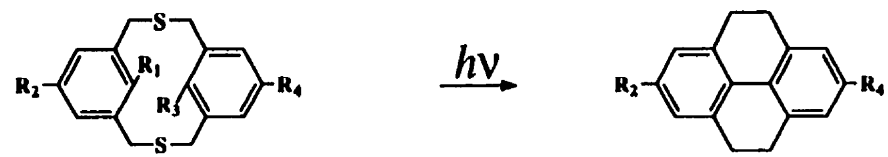
Scheme 7.4.



114 $R_1 = OCH_3$; $R_2 = t$-Bu
115 $R_1 = OCH_3$; $R_2 = H$
115 $R_1 = OCH_3$; $R_2 = H$
116 $R_1 = H$; $R_2 = H$
117 $R_1 = H$; $R_2 = Br$

118 $R_3 = OCH_3$; $R_4 = t$-Bu
118 $R_3 = OCH_3$; $R_4 = t$-Bu
119 $R_3 = OCH_3$; $R_4 = H$
118 $R_3 = OCH_3$; $R_4 = t$-Bu
118 $R_3 = OCH_3$; $R_4 = t$-Bu

120 $R_1 = R_3 = OCH_3$; $R_2 = R_4 = t$-Bu
121a *anti*-$R_1 = R_3 = OCH_3$; $R_2 = H$; $R4 = t$-Bu
121b *syn*-$R_1 = R_3 = OCH_3$; $R_2 = H$; $R4 = t$-Bu
122a *anti*-$R_1 = R_3 = OCH_3$; $R_2 = R_4 = H$
122b *syn*-$R_1 = R_3 = OCH_3$; $R_2 = R_4 = H$
123 $R_1 = R_2 = H$; $R_3 = OCH_3$; $R_4 = t$-Bu
124 $R_1 = H$; $R_2 = Br$; $R_3 = OCH_3$; $R_4 = t$-Bu
125 $R_1 = R_3 = H$; $R_2 = R_4 = CH_3$
126 $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$



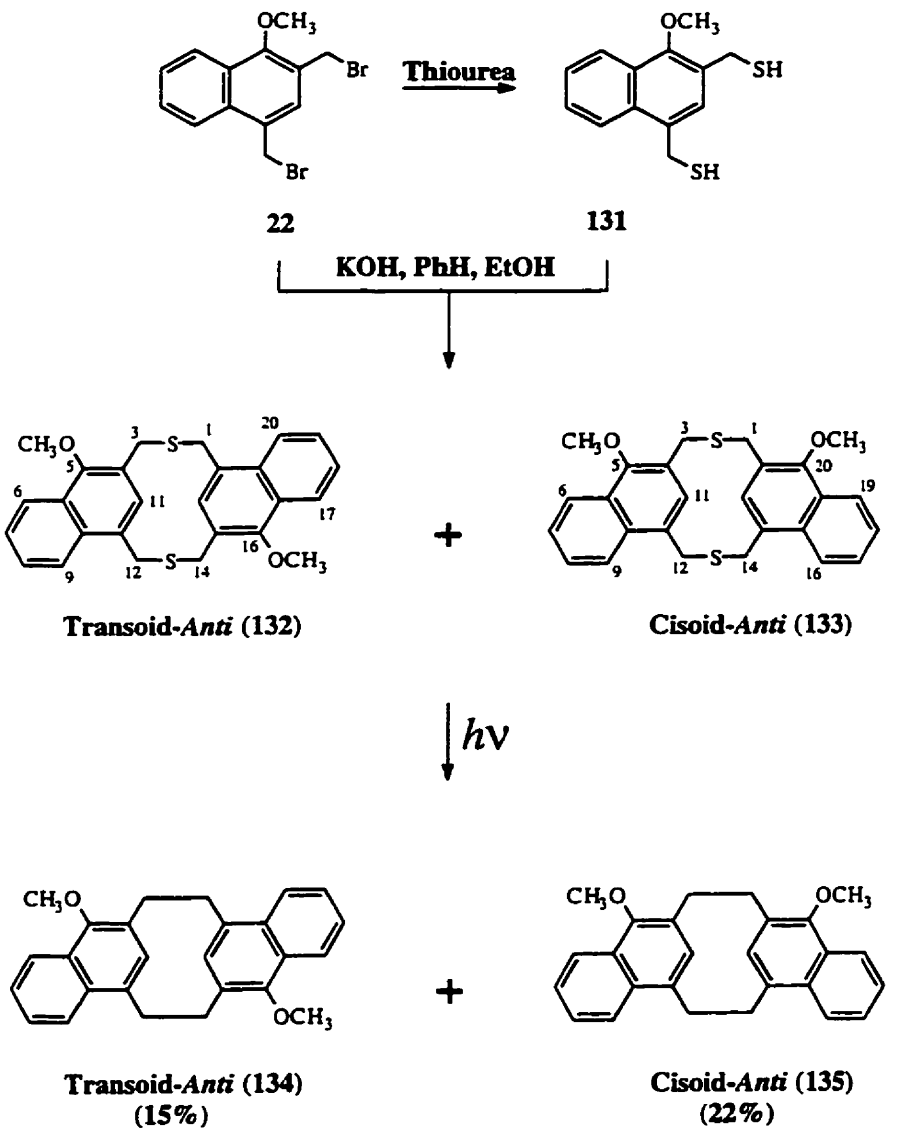
120-123

127 $R_2 = R_4 = t$-Bu
128 $R_2 = H$; $R_4 = t$-Bu
129 $R_2 = R_4 = H$
130 $R_2 = Br$; $R_4 = t$-Bu

atom or other electron-withdrawing groups were present in the *para*-positions (R_2 or R_4, in Scheme 7.4). DDQ oxidation easily converted **127-129** into the corresponding pyrenes.

To further support these findings, dithia[3.3](1,3)naphthalenophanes **132** and **133** with methoxyl groups at the 5- and 16- positions, and the 5- and 20-positions, respectively, were synthesized and subjected to the same photolytic conditions. Synthesis of **132** and **133** was achieved by the base-mediated coupling of **22** and **131** (Scheme 7.5). It was possible by repeated PLC separation to obtain small amounts of the less polar transoid-*anti*-dithianaphthalenophane **132** in a pure enough form to enable it to be unambiguously characterized. Cisoid-*anti*- **133**, however, was always contaminated with small amounts of **132**. That **132** and **133** are conformationally more mobile than **99-102** is evident by the fact that the bridging methylene protons appear as sharp singlets in their respective ambient temperature ^{1}H NMR spectra. Photolysis of PLC purified fractions, which contained a mixture of **132** and **133**, afforded two easily separable products whose spectral properties are consistent with the novel transoid-*anti* and cisoid-*anti*-[2.2](1,3)naphthalenophane structures **134** and **135**, respectively. These are the first [2.2](1,3)naphthalenophanes to be reported. In light of the previous discussions, **132** is most likely the precursor of **134**, and **133** the precursor of **135**. That both compounds are *anti* is evident by the fact that the intraannular protons appear upfield at $\delta = 4.51$ in both cases. Although the chemical shifts for the ethano bridge protons in both compounds are almost the same, their line shapes are dramatically different. In **135**, they appear as two distinct AX systems, centred at $\delta = 3.97$ and 2.01 ($J =$

Scheme 7.5.

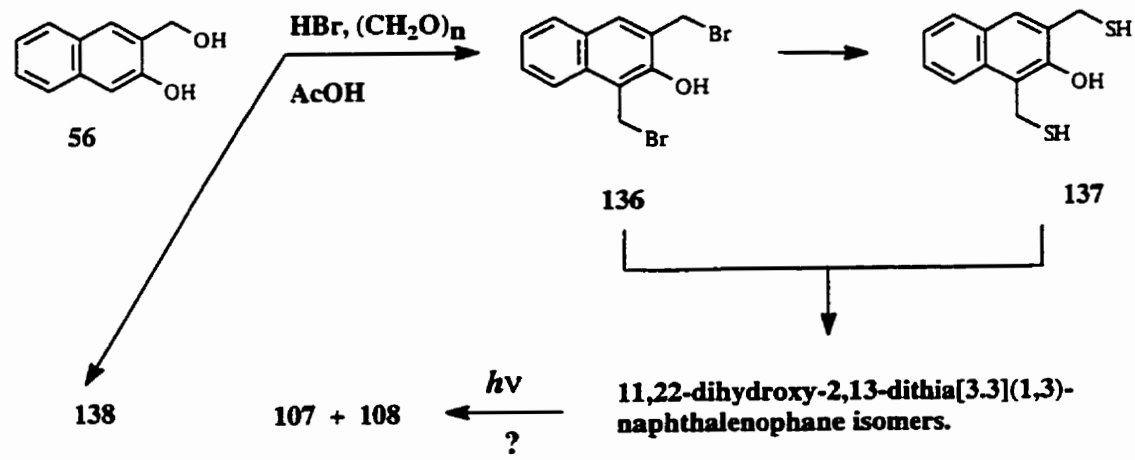

OCH3
Br
Br
Thiourea
OCH3
SH
SH
22
131
KOH, PhH, EtOH
CH3O
OCH3
hν
Transoid-Anti (132)
Cisoid-Anti (133)
Transoid-Anti (134)
(15%)
Cisoid-Anti (135)
(22%)

10.1 Hz), and at δ = 3.72 and 2.16 (J = 9.0 Hz) whereas in **134** they appear as two multiplets, one set of signals consisting of a doublet of triplets centred at δ = 3.95, which is coupled to a triplet of doublets centred at δ = 2.24; and the second set consisting of a doublet of triplets centred at δ = 3.72, which is coupled to a triplet of doublets centred at δ = 2.00. No transannular cyclized products were detected from the photolyses.

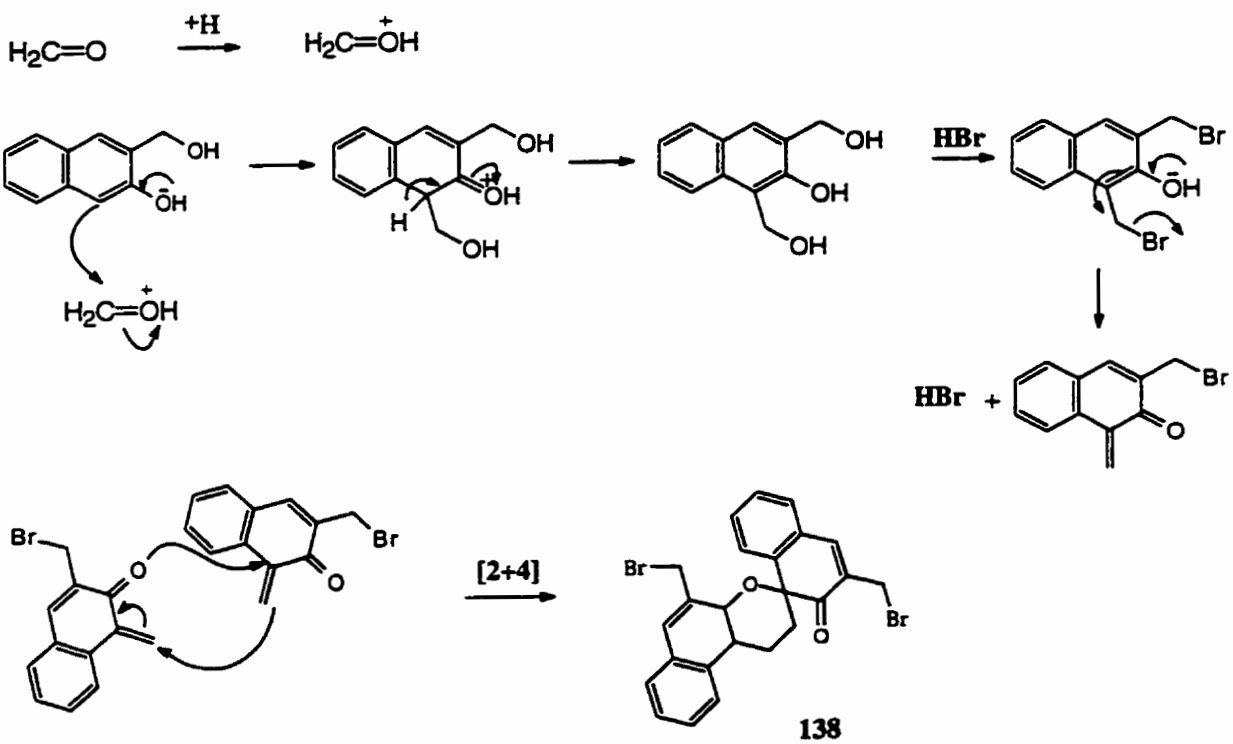
The mechanism depicted in Scheme 7.3 is consistent with the results found for a typical example in which photolytic sulfur elimination/intrannular cyclization reaction did occur. Thus, when the photolysis of **102** was interrupted after 7 h, three new products in addition to **107** were isolated and characterized. These were, in order of increasing polarity, **107**, and the three intermediate compounds *anti*-dimethoxy[2.2](1,3)naphthalenophane, **111a**, mono-thia compound **113** and the syn-dimethoxy [2.2](1,3)naphthalenophane, **111b** which convert to **107** upon further photolysis.

As can be seen from Scheme 7.3, the formation of tetrahydropyrenes and tetrahydrodibenzopyrenes occurred via photolytic sulfur extrusion and intramolecular cross-coupling of the dithia[3.3]metacyclophanes and dithia[3.3](1,3)naphthalenophanes, respectively. To shed light on whether or not this process is due to both electronic and steric effects of the methoxyl groups or due to an electronic effect only, we tried to prepare various 11,22-dihydroxy-2,13-dithia[3.3](1,3)naphthalenophane isomers which, could then be subjected to the photolytic sulfur extrusion reaction. The same conditions that were used previously to prepare **97** were chosen to transform 3-(hydroxymethyl)-2-naphthol (**56**) into bis[1,3-(hydroxymethyl)]-2-naphthol (**136**) as shown in Scheme 7.6. However, treatment of

Scheme 7.6.



Scheme 7.7.



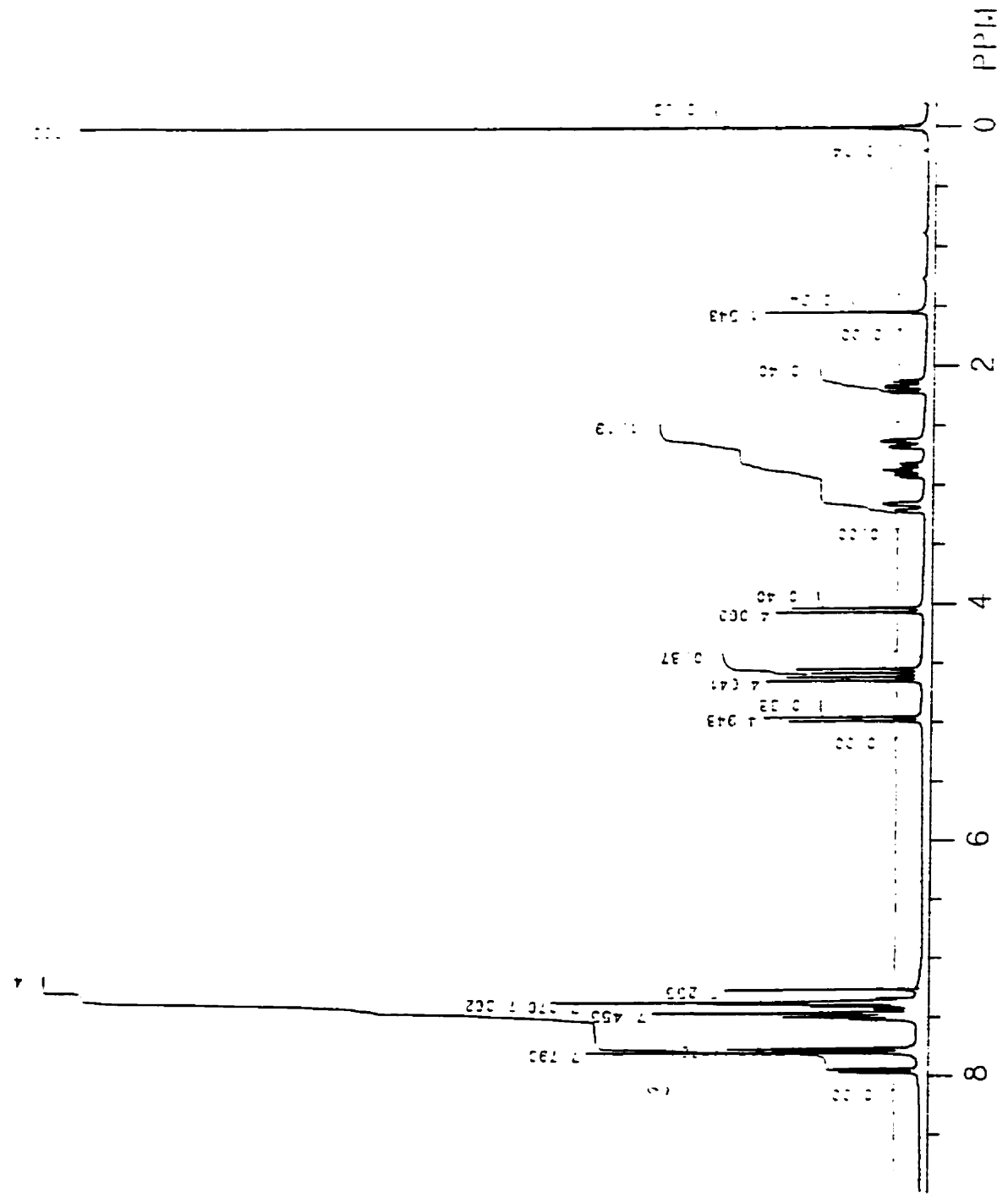


Fig. 7.8. ^{1}H NMR Spectrum of 138 in $CDCl_3$

56 with a 15% acetic acid solution of HBr and paraformaldehyde in acetic acid as solvent produced, after column chromatographic purification, a yellow crystalline solid in 20% yield.

The spectral properties of this product were distinctly different from those expected of **136**. The ^{1}H NMR ($CDCl_3$) spectrum (Figure 7.8) shows complex patterns of signals centered at δ = 2.18, 2.62, 2.87 and 3.17 ppm. Also, the ^{13}C NMR ($CDCl_3$) spectrum revealed four signals at 18.4, 27.7, 30.1 and 33.1 ppm, instead of two signals, which would have been expected for compound **136**. Furthermore, the I.R. spectrum indicated the presence of a carbonyl group having a stretching frequency at 1693 cm^{-1}, but no hydroxyl group. The MS spectrum revealed signals at *m/z* = 496, 498 and 500, which are consistent with the presence of two bromine atoms. On the basis of these data and in light of previous work, a Diels-Alder adduct formed by an intermolecular hetero-Diels-Alder reaction of **56** can be predicted. Indeed, this prediction was confirmed later by x-ray diffraction analysis, which gave the structure **138** as shown in Figure 7.9. A proposed mechanism for the formation of **138** is shown in Scheme 7.7.

In conclusion, we have observed that the photolysis in trimethyl- or triethylphosphite solution of various substituted dithiacyclophanes which possess either one, or two intraannular methoxyl groups can produce, in a single step, the corresponding tetrahydropyrenes. Similarly, the photolysis of similar intraannularly-substituted methoxy dithia[3.3](1,3)naphthalenophanes produced in a single step, the corresponding tetrahydrodibenzopyrenes. Photolysis of 5,16-dimethoxy and 5,20-dimethoxy-2,13-dithia[3.3](1,3)naphthalenophanes, **132** and **133**, afforded the anticipated 4,14-dimethoxy-

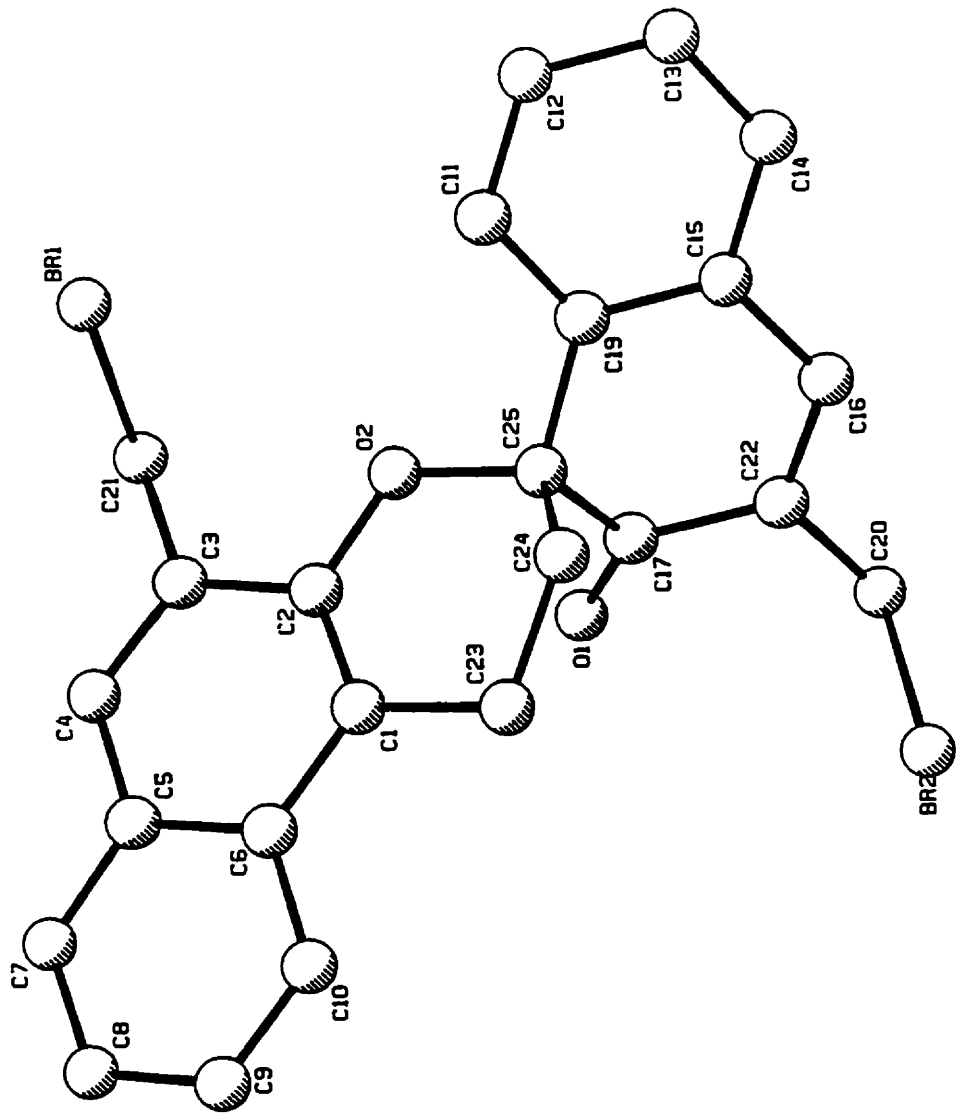


Figure 7.9. X-Ray Crystal Structure of 138

and 4,18-dimethoxy[2.2]naphalenophanes **134** and **135**, respectively.

Experimental

1,3-Bis(bromomethyl)-2-methoxynaphthalene (97). To a solution of 2-hydroxymethyl-3-methoxynaphthalene (14.1 g, 11.7 mmol) and paraformaldehyde (4.54 g, 150 mmol) in 200 mL of glacial acetic acid was added a 10% solution (200 mL) of HBr in glacial acetic acid. After stirring for 36 h at rt, a precipitate formed, which was filtered and washed several times with petroleum ether to afford 7.44 g of a colorless powder. The filtrate was diluted with CH_2Cl_2 (200 mL) and washed several times with water and finally with aqueous saturated $NaHCO_3$ solution until the washes were neutral. The organic layer was dried over $MgSO_4$ and the solvent evaporated on a rotary evaporator. The residue was washed with several portions of diethyl ether to give another 5.18 g of the crude product. The combined product (12.6 g, 49%), m.p. 114-116 °C, was used directly in subsequent steps, without further purification; ^{1}H NMR ($CDCl_3$) δ = 4.14 (s, 3H), 4.72 (s, 2H), 5.05 (s, 2H), 7.49 (m, 1H), 7.63 (m, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.94 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 24.7, 28.2, 62.4, 123.5, 125.3, 125.8, 127.6, 127.7, 128.6, 130.9, 132.4, 132.7, 154.7; MS *m/z* (%): 344 (16), 342 (9), 266 (14), 265 (100), 264 (15), 263 (97), 235 (13), 233 (15), 183 (13), 169 (18), 156 (24), 155 (90), 154 (20), 153 (20), 152 (13), 141 (32); HRMS M^+ = 341.9250, calcd for $C_{13}H_{12}Br_2O$ 341.9255.

1,3-Bis(mercaptomethyl)-2-methoxynaphthalene (98). A solution of **97** (0.41 g, 1.2 mmol) and thiourea (0.22 g, 2.9 mmol) in 25 mL of DMSO was stirred at rt under Ar for 5 h. The mixture was poured into 50 mL of aqueous 10% NaOH, which was cooled in an

ice-bath. The reaction mixture was stirred for an additional 2 h at rt under Ar, then cooled in an ice-bath and aqueous 4 N HCl added until the solution become acidic. The reaction mixture was extracted twice with 30-mL portions of CH_2Cl_2. The combined organic layer was washed with two 20-mL portions of H_2O and then with three 20-mL portions of aqueous saturated NaCl. After drying over anhydrous $MgSO_4$, filtering and evaporating the solvent, the crude product was flash chromatographed using CH_2Cl_2-petroleum ether (50:50) to give 0.21 g (0.84 mmol, 70%) of **98** as an oil; ^{1}H NMR ($CDCl_3$) δ = 1.97 (t, J = 7.8 Hz, 1H), 1.99 (t, J = 6.9 Hz, 1H), 3.89 (d, J = 7.8 Hz, 2H), 3.99 (s, 3H), 4.22 (d, J = 6.9 Hz, 2H), 7.46 (m, 2H), 7.73 (s, 1H), 7.76 (d, J = 7.8Hz 1H), 7.96 (d, J = 8.4 Hz 1H); ^{13}C NMR ($CDCl_3$) δ = 19.2, 24.1, 62.6, 123.3, 125.6, 126.6, 128.4, 128.5, 128.8, 131.3, 134.2; MS *m/z* (%) 250 (M^+, 75), 218 (16), 217 (100), 172 (19), 171 (99), 143 (17.5), 141 (23); HRMS: M^+ 250.0467, calcd for $C_{13}H_{14}OS_2$ 250.0485.

Base-mediated coupling of 97 with 98. To a solution of ethanolic KOH (481 mg in 170 mL of 95% ethanol) was added a solution of **97** (397 mg, 1.16 mmol) and **98** (290 mg, 1.16 mmol) in 70 ml of benzene, dropwise over 24 h under Ar at rt. The reaction was stirred for an additional 24 h after which the reaction solvent was evaporated on a rotary evaporator. The residue was dissolved in CH_2Cl_2 (50 mL), and the organic solution was washed with portions of aqueous 10% HCl until the aqueous layers become acidic. The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated on a rotary evaporator. A portion of the crude product (250 mg) was chromatographed by PLC using CH_2Cl_2-petroleum ether (60:40) to give five fractions in the following order of

increasing polarity:

transoid-*anti*-11,22-dimethoxy-2,13-dithia-[3.3](1,3)naphthalenophane (101) was obtained as a colorless crystalline compound (from $CHCl_3$, chlorobenzene, or toluene) (25 mg), m.p. 268-270 °C; ^{1}H-NMR ($CDCl_3$) δ = 2.93 (s, 6H), 3.26 (m, 4H), 4.0 (d, *J* = 11.7 Hz, 2H), 4.33 (d, *J* =11.7 Hz, 2H), 7.44 (m, 2H), 7.54 (m, 2H), 7.86 (d, *J* = 7.8 Hz, 2H), 8.12 (s, 2H), 8.18 (d, *J* = 8.4 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ = 22.9 (C-1, C-12), 25.9 (C-3, C-14), 61.1 (OCH_3), 119.8, 123.1 (C-9, C-20), 124.4 (C-7, C-20), 126.1 (C-8, C-19), 128.3 (C-6, C-17), 131.1, 131.3, 131.5 (C-5, C-16), 132.5, 156.7 (C-11, C-22); MS *m/z* (%): 432 (M^+, 6), 368 (11), 218 (10), 217 (17), 216 (14), 215 (12), 186 (45), 185 (100), 183 (14), 171 (19), 155 (54); HRMS M^+ 432.1193, calcd for $C_{26}H_{24}O_2S_2$ 432.1216; **cisoid-*anti*-11,22-dimethoxy-2,13-dithia[3.3](1,3)naphthalenophane (99)** was obtained as a colorless powder (37 mg), m.p. 123-125°C; ^{1}H NMR ($CDCl_3$) δ = 2.93 (s, 6H), 3.62 (d, *J* = 13.8 Hz, 2H), 3.88 (d, *J* = 13.8 Hz, 2H), 3.89 (d, *J* = 13.8 Hz, 2H), 4.05 (d, *J* = 13.8 Hz, 2H), 7.43 (m, 2H), 7.53 (m, 2H), 7.81 (d, *J* = 7.8 Hz, 2H), 7.88 (s, 2H), 8.31 (d, *J* = 8.4 Hz, 2H) ; ^{13}C NMR ($CDCl_3$) δ = 24.1 (C-12, C-14) , 26.7 (C-1, C-3), 61.2 (OCH_3), 122.0, 123.9 (C-9, C-16), 124.3 (C-7, C-18), 125.6 (C-8, C-17), 128.0 (C-6, C-19), 129.0, 131.6 (C-5, C-20), 133.0, 156.4 (C-11, C-22); MS *m/z* (%): 432 (M^+, 100), 247 (29), 217 (18), 216 (61), 215 (58), 214 (39), 201 (17), 186 (28), 185 (47), 184 (17), 183 (17), 171 (20), 167 (22), 155 (37); HRMS M^+ 432.1213, calcd for $C_{26}H_{24}O_2S_2$ 432.1216; **transoid-*syn*-11,22-dimethoxy-2,13-dithia[3.3](1,3)naphthalenophane (102)** was obtained as a colorless crystalline powder, (52 mg), m.p. 208 - 209°C; ^{1}H

NMR ($CDCl_3$) δ = 3.51 (d, *J* = 16.4 Hz, 2H), 3.57 (s, 6H), 3.84 (d, *J* = 13.5 Hz, 2H), 4.59 (d, *J* = 16.4 Hz, 2H), 4.84 (d, *J* = 13.5 Hz, 2H), 6.75 (d, *J* = 7.8 Hz, 2H), 6.96 (s, 2H), 7.04 (m, 2H), 7.37 (m, 2H), 7.85 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ = 27.6 (C-1, C-12) , 28.9 (C-3, C-14), 62.0 (OCH_3), 122.0, 123.3 (C-9, C-20), 124.1 (C-7, C-18), 124.90, 127.9 (C-6, C-17), 128.8 (C-5, C-16), 130.4, 130.5, 130.9, 155.3 (C-11, C-22); MS *m/z* (%): 432 (M^+, 46), 247 (11), 217 (10), 215 (20), 186 (10), 185 (36), 184 (22), 183 (16), 169 (20), 155 (14); +FAB MS (matrix: 3-nitrobenzyl alcohol) *m/z* (%): 433 (M^++1, 19), 432 (M^+, 41), 431 (6), 307 (10), 289 (10), 217 (14), 215 (44), 185 (61), 171 (26), 169 (30), 155 (43), 154 (100); HRMS M^+ 432.1231, calcd for $C_{26}H_{24}O_2S_2$ 432.1216; **cisoid-*syn*-11,22-dimethoxy-2,13-dithia[3.3](1,3)naphthalenophane (100)** was obtained as a colorless crystalline powder (48 mg), m.p. 238 - 240°C; ^1H NMR ($CDCl_3$) δ = 3.56 (s, 6H), 3.60 (d, *J* = 15.0 Hz, 2H), 3.83 (d, *J* = 14.7 Hz, 2H), 4.54 (d, *J* = 15.0 Hz, 2H), 5.00 (d, *J* = 14.7 Hz, 2H), 6.94 (m, 4H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.46 (s, 2H), 7.84 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ = 27.4 (C-12, C-14), 30.4 (C-1, C-3), 62.4 (OCH_3), 122.5, 124.0 (C-9, C-16), 124.25 and 124.34 (C-8, C-17 and C-7, C-18), 127.1 (C-6, C-19), 130.3 (C-5, C-20), 130.5, 130.7, 130.8, 155.1 (C-11, C-22); MS *m/z* (%): 432 (M^+, 88), 247 (44), 217 (28), 216 (58), 215 (100), 202 (10), 201 (32), 200 (18), 199 (5), 187 (13), 186 (52), 185 (10), 184 (87), 173 (10), 172 (18), 171 (35), 170 (15), 169 (35); HRMS M^+ 432.1185, calcd for $C_{26}H_{24}O_2S_2$ 432.1216.

A fifth fraction, which was the most polar one, was also isolated as an amorphous solid (42 mg), which decomposed at 138-140°C. NMR spectral properties indicated this

product to be a mixture, which could not be resolved by TLC. +FAB MS revealed the presence of several *pseudo*molecular ions suggestive of tetrameric species such as **91** and/or its isomers **92-94**.

5,6,12,13-Tetrahydrodibenzo[*b*,*def*]chrysene (107) from 102: ***(a) Irradiation for 24 h.*** A solution of **102** (141 mg, 0.326 mmol) in 10 mL of trimethylphosphite under Ar in a quartz tube was irradiated at 254 nm with stirring for 24 h. The triethylphosphite was removed by vacuum distillation, and the yellow residue was dried under vacuum. Chromatography by PLC using CH_2Cl_2-hexane (40:60) gave **107** (33 mg, 33%) as yellow crystals, m.p. 250-252°C; ^{1}H NMR ($CDCl_3$) δ = 3.18 and 3.21 (dd, J = 9.0, 7.5 Hz, 4H), 3.32 and 3.35 (dd, J = 9.3, 7.8 Hz, 4H), 7.46 (m, 4H), 7.62 (s, 2H), 7.80 (m, 2H), 8.11 (m, 2H). ^{13}C NMR ($CDCl_3$) δ = 23.8, 29.3, 123.5, 124.1, 125.3, 125.6, 128.0, 129.2, 130.9, 131.7, 133.1, 134.2; MS *m/z* (%): 306 (M^+, 100), 305 (33), 303 (15), 302 (18), 289 (12), 153 (13), 151 (17), 145 (22); HRMS M^+ 306.1413, calcd for $C_{24}H_{18}$ 306.1409; ***(b) Irradiation for 7 h:*** When a solution of **102** (100 mg, 0.231 mmol) in 6.0 mL of trimethylphosphite under Ar in a quartz tube was irradiated at 254 nm with stirring for 7 h and worked-up as before, chromatography by PLC using CH_2Cl_2-hexane (40:60) afforded in the following order of increasing polarity: **107** (6 mg, 9%); **transoid-*anti*-10,20-dimethoxy-[2.2](1,3)naphthalenophane (111a)**, (13 mg, 15%) as a colorless solid, m.p. >300 °C; ^{1}H NMR ($CDCl_3$) δ = 2.67 (s, 6H), 2.75 (m, 2H), 2.82 (m, 2H), 2.98 (m, 2H), 3.58 (m, 2H), 7.38 (m, 2H), 7.45 (m, 2H), 7.69 (s, 2H), 7.81 (dd, J = 8.1; 1.2 Hz, 2H), 8.10 (dd, J = 8.1, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ = 26.9, 31.4, 57.4,

117.6, 119.6, 120.6, 121.6, 124.7, 125.3, 129.6, 130.7, 131.4, 154.1; MS *m/z* (%): 368 (M^+, 59), 337 (23), 306 (100), 305 (20), 293 (3), 289 (4), 279 (4), 265 (4), 183 (13), 169 (7), 155 (12); HRMS M^+ 368.1703, calcd for $C_{26}H_{24}O_2$ 368.1776;

transoid-*anti*-11,21-dimethoxy-2-thia-[3.2](1,3)naphthalenophane (113) as a colorless solid (6 mg, 6%), m.p. 188-190 °C; ^{1}H NMR ($CDCl_3$) δ = 2.64 (s, 3H), 2.94 (s, 3H), 2.94 (m, 3H), 3.54 (m, 2H), 3.63 (d, *J* = 13.2 Hz, 1H), 3.76 (d, *J* = 12.9 Hz, 1H), 4.22 (d, *J*=13.2 Hz, 1H), 7.44 (m, 4H), 7.72 (s, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.94 (s, 1H), 8.05 (d, *J* = 8.7 Hz, 1H), 8.17 (d,*J* = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 23.3, 26.7, 28.1, 31.9, 60.3, 60.8, 120.9, 122.4, 123.7, 123.8, 124.0, 125.1, 125.2, 125.7, 128.0, 128.3, 128.9, 129.5, 130.2, 131.5, 132.0, 132.5, 133.4, 134.2, 156.8, 156.9; MS *m/z* (%): 400 (M^+, 94), 216 (13), 215 (89), 201 (7), 200 (6), 198 (7), 197 (8), 185 (100), 183 (24), 170 (14), 168 (57); HRMS M^+ 400.1493, calcd for $C_{26}H_{24}O_2S$, 400.1497;

transoid-*syn*-10,20-dimethoxy-[2.2](1,3)naphthalenophane (111b), as a colorless solid, (7 mg, 8%), m.p. 195-197 °C; ^{1}H NMR ($CDCl_3$) δ = 2.74 (m, 2H), 3.4 (m, 4H), 3.65 (s, 6H), 3.89 (m, 2H), 5.91 (s, 2H), 6.88 (d, *J* = 8.1 Hz, 2H), 6.99 (m, 2H), 7.25 (m, 2H), 7.63 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ = 23.9, 33.3, 62.2, 122.7, 123.1, 124.4, 124.8, 127.3, 127.4, 130.3, 131.8, 133.6, 158.5; MS *m/z* (%): 368 (M^+, 40), 337 (22), 306 (100), 305 (18), 293 (4), 289 (4), 279 (4), 265 (4), 183 (14), 169 (8), 155 (11); HRMS M^+ 368.1746, calcd for $C_{26}H_{24}O_2$ 368.1776.

5,6,12,13-Tetrahydrodibenzo[*b,def*]chrysene (107) from 101. Irradiation of **101** under identical conditions as were used with **102** afforded a product whose spectral and physical

properties were identical with those of **107**.

Dibenzo[*b,def*]chrysrene (109) from 107. A solution of **107** (20 mg, 0.065 mmol) and DDQ (41 mg, 0.16 mmol) in 8 mL of benzene was refluxed for 4 h. The solution was cooled to rt and then filtered through a short Florisil column eluted with benzene. Evaporation of the solvent afforded **109** (12 mg, 61%) which was crystallized from benzene to give pale orange crystals, mp 310-312 °C (lit. m.p. 308 °C).[91]

6,7,13,14-Tetrahydrobenzo[*rst*]pentaphene (108) from 99. A solution of **99** (84 mg, 0.19 mmol) in 6 mL of trimethylphosphite was irradiated for 24 h at 254 nm as described for **102**. After removal of the trimethylphosphite by vacuum distillation, the crude product was dried under vacuum and then chromatographed by PLC using CH_2Cl_2-hexane (20:80) to give **108** as a pale yellow solid (18 mg, 30%), m.p. 175-177°C; ^{1}H NMR ($CDCl_3$) δ = 3.10 (s, 4H), 3.40 (s, 4H), 7.45 (m, 4H), 7.59 (s, 2H), 7.77 (m, 2H), 8.14 and 8.11 (dd, J = 8.7, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ = 23.3, 29.9, 121.7, 122.9, 123.6, 124.4, 125.3, 125.5, 125.8, 126.5, 127.9, 128.0, 129.3, 130.5, 131.0, 133.2, 134.7; MS *m/z* (%): 306 (M^+, 100), 305 (37), 304 (18), 304 (18), 303 (20), 302 (24), 290 (11), 289 (15), 153 (25), 150 (24), 145 (23), 138 (15); HRMS M^+ 306.1411, calcd for $C_{24}H_{18}$ 306.1409.

Benzo[*rst*]pentaphene (110) from 108. A solution of **108** (22 mg, 0.072 mmol) and DDQ (41 mg, 0.16 mmol) in 8 mL of benzene was refluxed for 4 h. The solution was cooled to rt, filtered through a short Florisil column eluted with benzene. Evaporation of the solvent afforded **110,** 17 mg (85%) which was crystallized from benzene to give

yellow leafy crystals, mp 281-282°C (lit. m.p. 280°C).[91]

2,6-Bis(bromomethyl)-4-*tert*-butylanisole (114). To a solution of 4.95 g (0.033 mol) of *p-tert*-butylanisole, and 3.96 g (0.132 mol) of paraformaldehyde in 25 mL of acetic acid, was added 25 mL of a solution of 15% hydrogen bromide in acetic acid dropwise over 10 min at rt under N_2. The reaction temperature was raised to 90-95°C and after 2 days, the reaction mixture was cooled to rt, and then diluted with 50 mL of $CHCl_3$. The solution was washed several times with water and then with saturated aqueous $NaHCO_3$. The organic layer was separated and dried over anhydrous $MgSO_4$, filtered and the solvent evaporated. The oily product was purified by column chromatography on SiO_2 using $CHCl_3$-petroleum ether (20:80) to give 4.66 g (40%) of a colorless solid, m.p. 95-96 °C; ^{1}H NMR ($CDCl_3$) δ = 1.31 (s, 9H), 4.01 (s, 3H), 4.56 (s, 4H) and 7.36 (s, 2H); ^{13}C NMR δ = 28.1, 31.3, 34.4, 62.1, 129.3, 131.0, 147.9, 154.3; MS *m/z* (%): 352 (M^+ ^{81}Br ^{81}Br, 10), 350 (M^+ ^{81}Br ^{79}Br, 18), 348 (M^+ ^{79}Br ^{79}Br, 10), 337 (6), 335 (12), 333 (6), 272 (14), 271 (100), 269 (99), 241 (16).

2,6-Bis(bromomethyl)anisole (115). To a solution of 1.17 g (8.57 mmol) of 2,6-dimethylanisole in refluxing CCl_4 (100 mL) under N_2, was added *N*-bromosuccinimide 3.66 g (20.6 mmol) and 0.275 g of benzoyl peroxide[97] in portions, over 1 hour. The reaction mixture was refluxed with stirring for an additional 24 h. The solution was cooled to rt and filtered. The filtrate was washed with aqueous saturated $NaHSO_3$. After drying and filtering, the solvent was evaporated on a rotary evaporator, and the residue was chromatographed on SiO_2 using $CHCl_3$-petroleum ether (20:80) to give **115** as a

colorless solid, (0.98 g, 40%), m.p. 83-85 °C (lit. m.p. 75°C)[98] ; ^{1}H NMR ($CDCl_3$) δ = 4.05 (s, 3H), 4.57 (s, 4H), 7.12 (q, 1H), and 7.38 (d, 2H); ^{13}C NMR ($CDCl_3$) δ = 27.5, 62.3, 125.1, 131.9, 132.2 and 156.6; MS *m/z* (%): 296 (M^+ ^{81}Br ^{81}Br, 6), 294 (M^+ ^{81}Br ^{79}Br, 12), 292 (M^+ ^{79}Br ^{79}Br, 6), 215 (81), 213 (84), 185 (21) 183 (20), 119 (10), 106 (27), 105 (100), 104 (22), 103 (16), 79 (6), 77 (12), 65 (26), 63 (12), 51 (14), 39 (19).

1-Bromo-3,5-bis(bromomethyl)benzene (117). The procedure described above for **115** was employed to prepare **117** from 1-bromo-3,5-dimethylbenzene (2.58 g,13.9 mmol). The crude product was chromatographed on SiO_2 using CH_2Cl_2-petroleum ether (10:90) and crystallized from hexane to give **117**, (1.37 g, 29%); mp 97.5-99.0°C (lit. m.p. 95-98°C).[99]

5-*tert*-butyl-1,3-Bis(mercaptomethyl)-2-methoxybenzene (118). To a solution of **114** (1.25 g, 3.60 mmol) in 50 mL of DMSO, was added thiourea (0.66 g, 8.6 mmol), with stirring under N_2. After 5 h at rt the reaction was quenched by pouring the mixture into a cold aqueous 10% solution of NaOH (50 mL). The mixture was stirred at rt for 2 h, after which it was cooled to 0 °C and neutralized by addition of aqueous 3M HCl. The ensuing precipitate was filtered, washed with water, and air-dried. The colorless solid was purified by flash chromatography on SiO_2 using $CHCl_3$-petroleum ether (70:30) to give **118** as a colorless solid, (0.82 g, 89%), m.p. 80-81°C (lit. m.p. 81-82 °C)[99]; ^{1}H NMR ($CDCl_3$) δ = 1.31 (s, 9H), 1.90 (t, J = 7.5 Hz, 2H), 3.77 (d, J = 7.5 Hz, 4H), 3.88 (s, 3H), 7.23 (s, 2H); ^{13}C NMR ($CDCl_3$) δ = 23.5, 31.4, 34.5, 62.2, 126.2, 133.8, 147.6, 153.1; MS *m/z* (%): 258 (7), 257 (12), 256 (M^+, 72), 243 (5), 242 (7), 241 (47), 223 (48), 178 (13), 177 (100),

165 (17), 161 (11).

2,6-Bis(mercaptomethyl)anisole (119). The procedure described above for **118** was employed to prepare **119** from **115**. Flash chromatography on SiO_2 using $CHCl_3$-petroleum ether (60:40) gave **119** as a colorless solid (0.24 g, 65%), mp 28-29 °C; ^1H NMR ($CDCl_3$) δ = 1.89 (t, *J* = 7.8 Hz, 2H), 3.78 (d, *J* = 7.8 Hz, 4H), 3.90 (s, 3H), 7.24 (m, 3H); ^{13}C NMR ($CDCl_3$) δ = 23.2, 62.3, 124.9, 129.2, 134.8, 155.4.

Preparation of dithia[3.3]metacyclophanes: 6,15-di-*tert*-butyl-9,18-dimethoxy-2,11-dithia[3.3]metacyclophane (120). Typical procedure. A solution of **118** (0.54 g, 2.1 mmol) and **114** (0.72 g, 2.1 mmol) in 55 mL of benzene was added dropwise over 10 h with stirring, to a solution of 0.35 g of KOH in 250 mL of ethanol under N_2. After the addition was complete the reaction was stirred for additional 6 h. The mixture was then concentrated on a rotary evaporator, and the residue was dissolved in 50 mL of $CHCl_3$. The organic layer was washed with two 25-ml portions of aqueous 10% HCl, dried over $MgSO_4$ and filtered. The solvent was evaporated on a rotary evaporator, and the residue was flash chromotographed on SiO_2 using $CHCl_3$-petroleum ether (80:20) to give **120** as a colorless solid (0.38 g, 38%), m.p. 253 -255 °C (lit. m.p.257-258 °C)[97] ; ^1H NMR ($CDCl_3$) δ = 1.36 (s, 18H), 3.21 (s, 6H), 3.39 (d, *J* = 13.5 Hz, 4H), 3.79 (d, *J* = 13.5 Hz, 4H), 7.29 (s, 4H); ^{13}C NMR ($CDCl_3$) δ = 27.0, 31.4, 34.3, 60.7, 127.6, 127.7, 145.9, 156.4; MS *m/z* (%): 444 (M^+, 61), 4.29 (4), 387 (3), 267 (3), 253 (33), 223 (29), 222 (12), 221 (38), 220 (13), 192 (33), 191 (71), 189 (16), 177 (18), 176 (13), 175 (87), 165 (18).

Compounds **121**, **122** and **123** were obtained in the same manner as described

above.

***Anti*-, and *syn*-6-*tert*-butyl-9,18-dimethoxy-2,11-dithia[3.3]metacyclophane (121a and 121b).** A solution of **115** (0.69 g) and **118** (0.60 g) in 50 mL of benzene was added to ethanolic KOH (0.32 g in 250 mL) over 16 h. Chromatographic separation on SiO_2 using $CHCl_3$-petroleum ether (70:30) gave two compounds in order of increasing polarity: **121a**, and **121b**. ***Anti*-6-*tert*-butyl-9,18-dimethoxy-2,11-dithia[3.3]metacyclophane (121a)** was a colorless solid (0.075 g), m.p. 163-165°C; ^{1}H NMR ($CDCl_3$) δ = 1.37 (s, 9H), 3.20 (s, 3H), 3.27 (s, 3H), 3.39 (d, *J* = 13.5 Hz, 2H), 3.42 (d, *J* = 13.5 Hz, 2H), 3.77 (d, *J* = 13.5 Hz, 2H), 3.80 (d, *J* = 13.5 Hz, 2H), 7.01 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.30 (s, 2H); ^{13}C NMR ($CDCl_3$) δ = 26.3, 27.5, 29.7, 31.4, 34.3, 60.9, 123.7, 127.3, 127.9, 129.0, 130.5, 145.9, 156.6, 158.4; MS *m/z* (%): 388 (M^+, 59), 373 (4), 331 (3), 253 (13), 223 (13), 221 (25), 220 (11), 207 (13), 192 (13), 191 (43), 175 (74); HRMS M^+ 388.1520, calcd for $C_{22}H_{28}O_2S_2$ 388.1529. ***Syn*-6-*tert*-butyl-9,18-dimethoxy-2,11-dithia[3.3]metacyclophane (121b)** was a colorless, glassy oil which solidified after refrigeration to give a colorless solid (0.35 g), m.p. 107-108 °C; ^{1}H NMR ($CDCl_3$) δ = 1.19 (s, 9H), 3.35 (d, *J* = 14.7 Hz, 2H), 3.51 (s, 3H), 3.52 (s, 3H), 4.41 (d, *J* = 14.7 Hz, 2H), 6.64 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 2H), 6.97 (s, 2H); ^{13}C NMR ($CDCl_3$) δ = 14.2, 30.1, 30.5, 31.2, 34.2, 62.2, 124.5, 126.5, 129.2, 129.5, 130.7, 145.6, 155.0, 157.0; MS *m/z* (%) 388 (M^+, 79), 373 (5), 331 (4), 253 (16), 223 (17), 221 (29), 220 (16), 207 (15), 197 (13), 192 (19), 191(60), 177 (13), 176(13), 175 (83); HRMS M^+ 388.1515, calcd for $C_{22}H_{28}O_2S_2$ 388.1529.

***Anti-*, and *syn*-9,18-dimethoxy-2,11-dithia[3.3]metacyclophane (122a, 122b).** A solution of **115** (0.33 g) and **119** (0.23 g) in 60 mL of benzene was added to ethanolic KOH (0.73 g in 150 mL) over 8 h, and the reaction was stirred overnight. PLC separation using $CHCl_3$ gave two compounds in order of increasing polarity: **122a** and **122b**. ***Anti*-9,18-dimethoxy-2,11-dithia[3.3]metacyclophane (122a)** was a colorless solid (36 mg, 10%), m.p. 248-250 °C; ^1H NMR ($CDCl_3$) δ = 3.26 (s, 6H), 3.43 (d, *J* = 13.5 Hz, 4H), 3.80 (d, *J* = 13.5 Hz, 4H), 7.04 (t, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.5 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ = 26.9, 61.2, 123.8, 128.8, 130.7, 158.7; MS *m/z* (%): 332 (M^+, 43), 197 (19), 167 (16), 165 (25), 151 (15), 136 (12), 135 (40), 134 (27), 121 (29), 119 (27) 105 (44); HRMS M^+ 332.0903, calcd for $C_{18}H_{20}O_2S_2$ 332.0905. ***Syn*-9,18-dimethoxy-2,11-dithia[3.3]metacyclophane (122b)** was a colorless solid (136 mg, 36%), m.p. 220-223 °C; ^1H NMR ($CDCl_3$) δ = 3.37 (d, *J* = 14.7 Hz, 4H), 3.52 (s, 6H), 4.42 (d, *J* = 14.7 Hz, 4H), 6.64 (t, *J* = 7.8 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ = 30.2, 62.2, 124.2, 129.6, 130.6, 157.0; MS *m/z* (%): 332 (M^+, 100), 298 (3), 198 (5), 197 (48), 167 (35), 166 (16), 165 (47), 164 (28), 151 (20), 136 (32), 135 (79), 134 (52), 133 (56), 121 (42), 119 (36). HRMS M^+ 332.0896, calcd for $C_{18}H_{20}O_2S_2$ 332.0905.

6-*tert*-Butyl-9-methoxy-2,11-dithia[3.3]metacyclophane (123). A solution of **116** (0.63 g, 2.5 mmol) and **118** (0.65 g, 2.5 mmol) in 50 mL of benzene was added to ethanolic KOH (300 mL) over 6 h. The reaction mixture was stirred for an additional 2 h before work-up. The crude product was flash chromatographed on SiO_2 using $CHCl_3$-petroleum ether (80:20) to give **123** as a colorless solid (0.66 g), which could be crystallized from

hexane-benzene (10:1) to give needles (0.45 g, 51%), m.p. 177-178 °C (lit. m.p. 182.5-183 °C)[100]; ^{1}H NMR (CDCl3) δ = 1.12 (s, 9H), 3.47 (d, *J* = 14.1 Hz, 2H), 3.67 (d, *J* = 14.7 Hz, 2H), 3.69 (s, 3H), 3.77 (d, *J* = 14.7 Hz, 2H), 4.23 (d, *J* = 14.4 Hz, 2H), 6.88 (m, 2H), 6.94 (s, 2H), 7.03 (br, 1H); ^{13}C NMR ($CDCl_3$) δ = 31.1, 31.3, 34.1, 37.9, 62.1, 126.4, 126.6, 128.6, 129.3, 130.1, 137.8, 146.4, 154.1.

15-Bromo-6-*tert*-butyl-9-methoxy-2,11-dithia[3.3]metacyclophane (124). A solution of **117** (1.44 g, 4.26 mmol) and **118** (1.09 g, 4.26 mmol) in 230 mL of benzene was added dropwise to an ethanolic KOH solution (570 mL) over 16 h. The crude product was chromatographed on SiO_2 using $CHCl_3$-petroleum ether (80:20) to give **124** as a colorless solid (0.61 g, 58%), which was crystallized from hexane/benzene (1:1), m.p. 212-214 °C (lit. m.p. 218-219 °C)[100].

2,7-Di-*tert*-butyl-4,5,9,10-tetrahydropyrene (127). Typical Procedure. A solution of **120** (97 mg, 0.22 mmol) in 4.5 mL of triethylphosphite in a quartz tube was irradiated at 254 nm with stirring under Ar for 18 h. The triethylphosphite was removed by vacuum distillation, the crude product dried under vacuum and then chromatographed by PLC using $CHCl_3$-petroleum ether (1:9) to give **127** as a colorless solid (39 mg, 56%), m.p. 232-233 °C (lit. m.p. 234-235 °C)[101]; ^{1}H NMR ($CDCl_3$) δ = 1.34 (s, 18H), 2.87 (s, 8H), 7.07 (s, 4H); ^{13}C NMR ($CDCl_3$) δ = 28.7, 31.5, 34.5, 122.8, 128.1, 134.6, 149.6; MS *m/z* (%): 318 (M^+, 79), 304 (26), 303 (100), 273 (8), 205 (8), 203 (8), 202 (7), 144 (28).

2-*tert*-Butyl-4,5,9,10-tetrahydropyrene (128). A solution of **121** (0.16 g, 0.44 mmol) in 4.5 mL of triethylphosphite was photolyzed as above for 18 h. After work-up, the crude

product was chromatographed by PLC using $CHCl_3$-petroleum ether (20:80) to give **128** as a colorless solid (26 mg, 22%), m.p. 94-95°C (lit. m.p. 108-109.5°C)[101]; ^{13}C NMR ($CDCl_3$) δ = 28.4, 28.6, 31.4, 34.6, 122.9, 125.6, 125.8, 126.6, 128.1, 130.6, 134.9, 135.1, 150.1.

Alternatively, **128** (25 mg, 34%) was also obtained from the photolysis of **123** (110 mg, 0.284 mmol) in 4.0 mL of triethylphosphite.

4,5,9,10-Tetrahydropyrene (129). A solution of **122** (0.15 g, 0.35 mmol) in 4.5 mL triethylphosphite was photolyzed as above for 18 h. After work-up, the crude product was purified by PLC using $CHCl_3$-petroleum ether (20:80) to give **129** as a colorless solid (15 mg, 33%), m.p. = 132-134 °C (lit. m.p. 136-138 °C)[101]; ^1H NMR ($CDCl_3$) δ = 2.88 (s, 8H) and 7.53 (m, 6H); ^{13}C NMR ($CDCl_3$) δ = 28.3, 125.9, 127.0, 130.6, 135.4; MS *m/z* (%): 206 (M^+, 100).

Photolysis of (124). A solution of **124** (0.15 g, 0.35 mmol) in 5.0 ml of triethylphosphite was photolyzed as above for 6 h. After work-up, the crude product was chromatographed by PLC using $CHCl_3$-petroleum ether (20:80) to give three fractions in increasing order of polarity in the following amounts: 2 mg, 6 mg and 20 mg. None of the spectral characteristics of these products was consistent with those anticipated for 2-bromo-7-*tert*-butyl-4,5,9,10-tetrahydropyrene. These products were not further characterized.

Oxidation of 127 with DDQ. Typical procedure. A solution of **127** (65 mg, 0.20 mmol) and 116 mg of DDQ in 25 mL of benzene was refluxed for 8 h. After cooling, the reaction mixture was filtered through a short Florisil column eluted with benzene. The

solvent was evaporated to dryness on a rotary evaporator to give 62 mg (97%) of **2,7-di-*tert*-butylpyrene**, which, after crystallization from hexane, afforded pale yellow crystals mp 204-206 °C (lit. m.p. 210-212 °C)[101]. In a similar manner, **2-*tert*-butylpyrene**[101] and **pyrene** were obtained from **128** and **129**, respectively.

2,4-Bis(mercaptomethyl)-1-methoxynaphthalene (131). To a solution of 0.85 g (2.5 mmol) of 2,4-bis(bromomethyl)-1-methoxynaphthalene (**22**) in 50 mL of DMSO was added 0.47 g (0.21 mmol) of thiourea, with stirring, under N_2. After 6 h at rt, the reaction was quenched by pouring the mixture into a cold aqueous 10% solution of NaOH (50 mL). The mixture was stirred at rt for 2 h, after which it was cooled to 0 °C and acidified by addition of aqueous 4M HCl. The reaction mixture was extracted twice with two 30-mL portions of CH_2Cl_2. The organic layers were combined and washed with two 20-mL portions of water. The organic layers were combined and dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated on a rotary evaporator. The crude product was flash chromatographed on SiO_2 using CH_2Cl_2-petroleum ether (40:60) to give 0.45 g (1.8 mmol, 73%) of **131** as an oil; ^{1}H NMR ($CDCl_3$) δ = 1.89 (t, J = 6.9 Hz, 1H), 1.92 (t, J = 7.5 Hz, 1H), 3.92 (d, J = 7.5 Hz, 2H), 3.99 (s, 3H), 4.15 (d, J = 6.9 Hz, 2H), 7.42 (s, 1H), 7.55 (m, 2H), 8.03 (m, 1H), 8.13 (m, 1H); ^{13}C NMR ($CDCl_3$) δ = 23.0, 26.4, 62.7, 123.1, 124.1, 126.2, 126.4, 127.7, 128.6, 129.0, 131.4, 133.5, 152.8; MS *m/z* (%): 251 (M^++1, 5), 250 (M^+, 35), 218 (15), 217 (100), 184 (10), 183 (32), 171 (10), 154 (10), 141 (18), 115 (15); HRMS: M^+ 250.0486, calcd for $C_{13}H_{14}OS_2$ 250.0485.

Base-mediated coupling of 22 with 131. To a solution of ethanolic KOH (398 mg in 250

mL of 95% ethanol) was added a solution of **22** (610 mg, 1.78 mmol) and **131** (445 mg, 1.78 mmol) in 110 mL of benzene, dropwise over 12h under Ar at rt. The reaction was stirred for an additional 24 h, after which the reaction solvent was evaporated on a rotary evaporator. The residue was dissolved in 50 mL of CH_2Cl_2, and the organic solution was washed with two 25-mL portions of aqueous 10% HCl. The organic layers were combined and dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated on a rotary evaporator. The crude product was flash chromatographed on SiO_2 using CH_2Cl_2-petroleum ether (40:60) to give 0.711g (1.65 mmol, 91%) of a mixture of isomers **132** and **133**. A small amount of **5,16-dimethoxy-2,13-dithia[3.3](1,3)-naphthalenophane (132)** was obtained in a pure enough state from repeated PLC separation using (CH_2Cl_2-petroleum ether 40:60) to be characterized, m.p. 191-193°C; ^{1}H NMR ($CDCl_3$) δ = 3.82 (s, 6H), 4.02 (s, 4H), 4.18 (s, 4H), 7.21 (s, 2H), 7.26 (m, 4H), 7.80 (m, 2H), 7.99 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 31.6, 35.9, 62.2, 122.1, 124.3, 124.5, 125.2, 125.4, 127.7, 131.0, 131.2, 152.8; MS *m/z* (%): 433 (M^++1, 16), 432 (M^+, 48), 247 (11), 216 (11), 215 (35), 201 (10), 186 (17), 185 (100), 183 (14), 172 (7), 171 (23), 170 (25), 154 (11), 153 (13), 141 (25), 139 (11), 129 (11), 128 (11).

The mixture consisting of **132** and **133** could not be further separated using either flash chromatography or PLC and was used as a mixture directly in the subsequent photolytic step.

Transoid-*anti*-4,14-dimethoxy-[2.2](1,3)naphthalenophane (134) and Cisoid-*anti*-4,18-dimethoxy-[2.2](1,3)naphthalenophane (135). A solution of the mixture of **137**

and **138** (150 mg, 0.35 mmol) obtained as described above, in 3.5 mL of trimethylphosphite in a quartz tube was irradiated at 254 nm with stirring and under Ar for 24 h. The trimethylphosphite was removed by vacuum distillation, the yellow residue dried under vacuum and then chromatographed by PLC (CH_2Cl_2-hexane 45:55) to give two fractions, in order of increasing polarity: **134** and **135**. **Transoid-*anti*-4,14-dimethoxy[2.2](1,3)naphthalenophane (134)** was obtained as a colorless solid (21 mg, 15%), m.p. 230-233 °C; ^{1}H NMR ($CDCl_3$) δ = 2.00 (m, 2H), 2.24 (m, 2H), 3.72 (m, 2H), 3.95 (m, 2H), 4.10 (s, 6H), 4.51 (s, 2H), 7.52-7.55 (m, 4H), 8.15 (m, 4H), 8.23 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 33.1, 35.2, 63.0, 123.0, 123.7, 125.2, 125.4, 128.7, 129.5, 131.9, 136.3, 152.5; MS *m/z* (%): 369 (M^++1, 21), 368 (M^+, 53), 367 (26), 354 (16), 353 (12), 352 (55), 339 (16), 336 (28), 335 (18), 321 (12), 307 (7), 184 (20), 183 (100), 169 (17), 155 (28), 141 (58), 115 (57); HRMS M^+ 368.1777, calcd for $C_{26}H_{24}O_2$ 368.1775. **Cisoid-*anti*-4,18-dimethoxy[2.2](1,3)naphthalenophane (135)** was obtained as a colorless solid, which was further purified by PLC using ethyl acetate-petroleum ether (1:9) to give 28 mg (22%) of **135**, m.p. 189-191 °C; ^{1}H NMR ($CDCl_3$) δ = 2.01 (d, *J* = 10.0 Hz, 2H), 2.16 (d, *J* = 9.0 Hz, 2H), 3.72 (d, *J* = 9.0 Hz, 2H), 3.97 (d, *J* = 10.0 Hz, 2H), 4.08 (s, 6H), 4.45 (s, 2H), 7.52-7.55 (m, 4H), 8.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 33.6, 34.7, 63.0, 123.0, 123.5, 125.3, 125.4, 127.4, 128.7, 130.7, 132.0, 136.2, 152.3; MS *m/z* (%): 368 (M^+, 86), 353 (56), 340 (17), 339 (17), 338 (24), 337 (17), 337 (63), 322 (8), 321 (9), 306 (12), 184 (44), 183 (99), 169 (26), 155 (22), 154 (52), 153 (34), 152 (34), 144 (10), 141 (62); HRMS M^+ 368.1765, calcd for $C_{26}H_{24}O_2$ 368.1775.

Bromomethylation and intermolecular Diels-Alder reaction of 3-(hydroxymethyl)-2-naphthol. To a solution of **56** (1.17 g, 6.72 mmol) and paraformaldehyde (0.41 g, 13 mmol) in acetic acid (20 mL) was added a solution of 15% HBr in acetic acid (20 mL) dropwise at rt under Ar. The reaction mixture was stirred at rt for 24 h. The reaction mixture was worked-up by adding 70 mL of CH_2Cl_2, and the mixture was washed several times with H_2O and finally with 50 mL of saturated aqueous $NaHCO_3$. The organic layer was separated and dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated on a rotary evaporator. The crude product was purified by column chromatography using CH_2Cl_2-petroleum ether (50:50) to give **138** as a yellow crystalline solid (0.60 g, 20% yield). A sample was crystallized from $CHCl_3$, m.p.175-180 dec.; I.R. ($CHCl_3$, cm^{-1}): 1693, 1626, 1507, 1449, 1401, 1246, 1210; ^1H NMR ($CDCl_3$) δ = 2.18 (m, 1H), 2.62 (m, 1H), 2.87 (m, 1H), 3.17 (m, 1H), 4.04 (d, J = 9.9 Hz, 1H), 4.56 (d, J = 9.9 Hz, 1H), 4.62 (d, J = 9.6 Hz, 1H), 4.96 (d, J = 9.6 Hz, 1H), 7.39 (m, 3H), 7.46 (s, 1H), 7.49 (m, 2H), 7.76 (s, 2H), 7.95 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 18.4, 27.7, 30.1, 33.1, 83.0, 113.1, 121.9, 123.8, 126.3, 126.6, 126.9, 128.3, 128.4, 128.5, 128.6, 128.9, 129.7, 131.0, 131.6, 132.8, 141.7, 142.3, 145.2, 198.1; MS *m/z* (%) 500 (M^+ ^{81}Br ^{81}Br, 1), 498 (M^+ ^{81}Br ^{79}Br, 3), 496 (M^+ ^{79}Br ^{79}Br, 1), 336 (1), 250 (18), 249 (38), 248 (3), 170 (9), 169 (63), 142 (5), 141 (32), 139 (12), 115 (17), 78 (100).

References

1. R. M. Izatt, J. J. Christensen. *Progress in Macrocyclic Chemistry*, Vol.3, pp 241, John Wiley and Sons, Toronto, **1987**.
2. C. J. Pedersen. *J. Am. Chem. Soc.* 89, 7017, **1967**.
3. D. J. Cram and J. M. Cram. *Container Molecules and their Guests*, the Royal Society of Chemistry, **1994**.
4. F. Diederich. *Cyclophanes*, The Royal Society of Chemistry, **1991**.
5. Reference 1, Vol. 2, Vol. 3, **1987**.
6. Reference 5, Vol. 2, pp. 2-3.
7. C. D. Gutsche. *Calixarenes, Monographs in supermolecular chemistry*, Vol. 1, J. F. Stoddart, Ed. The Royal Society of Chemistry, Cambridge, **1989**.
8. J. Vicens and V. Böhmer. *Calixarenes: A Versatile Class of Macrocyclic Compounds*, ed., Kluwer Academic Press, Dordrecht **1991**.
9. A. Zinke and E. Ziegler. *Ber.*, B74, 1729, **1941**.
10. C. D. Gutsche and R. Muthukrishnan. *J. Org. Chem.* 43, 4905, **1974**.
11. C. D. Gutsche, M. Iqbal and D. Stewart. *J. Org. Chem.* 51, 742, **1986**.
12. B. T. Hayes and R. F. Hunter. *Chem. Ind.* 193, **1954**.
13. V. Böhmer, P. Chim and H. Kammerer. *Makromol. Chem.* 180, 2503, **1979**.
14. V. Böhmer, F. Marschollek and L. Zetta. *J. Org. Chem.* 52, 3200, **1987**.
15. V. Böhmer, L. Merkel and U. Kunz. *J. Chem. Soc., Chem. Commun.* 896,

1987.

16. V. Böhmer, K. Jung, M. Schon and A. Wolff. *J. Org. Chem.* 57, 790, **1992**.

17. N. Ehlinger, S. Lecocq, R. Perrin and M. Perrin. *Supermol. Chem.* 2, 71, **1993**.

18. Y. Ueda, T. Fujiwara, K. I. Tomita, Z. Asfari and J. Vicens. *J. Incl. Phenom. Mol. Recogn.* 15, 341, **1993**.

19. C. D. Gutsche and L. J. Bauer. *Tetrahedron Lett.* 22, 4763, **1981**.

20. C. D. Gutsche and L. J. Bauer. *J. Am. Chem. Soc.* 107, 6052, **1985**.

21. a) A. Arduini, A. Pochini, S. Reverberi, R. Ungaro. *J. Chem. Soc., Chem. Commun.* 981, **1984**. b) M. A. Mckervey, E. M. Seward, G. Ferguson, B. Ruhl. *J. Org. Chem.* 51, 3581, **1986**. G. Ferguson, B. Kaitner, M. A. Mckervery, E. M. Seward. *J. Chem. Soc., Chem. Commun.* 584, **1987**. M. A. Mckervery,; *et al. J. Am. Chem. Soc.* 111, 8681, **1989**. c) S. K. Chang, S. K. Kwon, I. Cho. *Chem. Lett.* 947, **1987**.

22. C. D. Gutsche, B. Dhawan, J. A. Levine, K. H. No and L. J. Bauer. *Tetrahedron*, 39, 409, **1983**.

23. J. W. Cornforth, E. D. Morgan, K. T. Potts and R. J. W. Ress. *Tetrahedron* 29, 1659, **1973**.

24. C. D. Gutsche, P. F. Pagoria. *J. Org. Chem.* 50, 5795, **1985**.

25. A. Arduini, A. Pochini, A. R. Sicuri, A. Secchi, R. Ungaro. *Tetrahedron Lett.* 31, 4653, **1990**.

26. S. Shinkai, T. Tsubaki, T. Sone, O. Manabe. *Tetrahedron Lett.* 26, 3343, **1985**.

27. S. Shinkai, S. Mori, H. Koreishi, T. Tsubaki, O. Manabe. *J. Am. Chem. Soc.* 108, 2409, **1986**.

28. Y. Morzherin, D. M. Rudkevich, W. Veboom, D. N. Reinhoudt. *J. Org. Chem.* 58, 7602, **1993**.

29. C. D. Gutsche, L. G. Lin. *Tetrahedron*, 41, 1633, **1986**.

30. S. Shinkai, K. Araki, J. Shibata, D. Tsdugawea, O. Manabe. *Chem. Lett.* 931, **1989**.

31. A. Arduini, G. Manfredi, A. Pochini, A. R. Sicuri, R. Ungaro. *J. Chem. Soc.*, *Chem. Commun.* 936, **1991**.

32. C. D. Gutsche, J. A. Levine, P. J. Sujeeth. *J. Org. Chem.* 50, 5802, **1985**.

33. C. D. Gutsche, K. C. Nam. *J. Am. Chem. Soc.* 110, 6153, **1988**.

34. M. Almi, A. Arduini, A. Casnati, A. Pochini, R. Ungaro. *Tetrahedron* 45, 2177, **1989**.

35. M. A. Markowitz, V. Janout, D. G. Castner, S. L. Regen. *J. Am. Chem. Soc.* 111, 8192, **1989**.

36. A. Arduini, A. Pochini, S. Reverberi, R. Ungaro, G. D. Andreetti. *Tetrahedron* 42, 2089, **1986**.

37. S. K. Chang, I. Cho. *J. Chem. Soc. Perkin Trans.2*, 211, **1986**.

38. A. Barrett, M. A. Mckervey, J. F. Malone, A. Walker, C. D. Gutsche, D. R.

Stewart. *J. Chem. Soc. Perkin. Trans.2*, 1475, **1993**.

39. K. Iwamoto, S. Shinkai. *J. Org. Chem.* 57, 7066, **1992**.

40. E. M. Collins, M. A. Mckervey, S. J. Harris. *J. Chem. Soc. Perkin 1*, 372, **1989**.

41. C. D. Gutsche, L. J. Bauer. *J. Am. Chem. Soc.* 107, 6059, **1985**.

42. W. Verboom, S. Datta, Z. A. Asfari, S. Harkema, D. N. Reinhoudt. *J. Org. Chem.* 57, 5394, **1992**.

43. T. Arimura, H. Kawabata, T. Matsuda, H. Satoh, K. Fujio, O. Manabe, S. Shinkai. *J. Org. Chem.* 56, 301, **1991**.

44. A. Wolff, V. Böhmer, W. Vogt, F. Ugozzoli, G. D. Andreetti. *J. Org. Chem.* 55, 5665, **1990**.

45. A. Ikeda, S. Shinkai. *J. Am. Chem. Soc.* 116, 3102-3110, **1994**.

46. N. Donaldson. *The Chemistry and Technology of Naphthalene Compounds*, Edward Arnold Publishers Ltd., London, **1958**.

47. J. F. Walker. *Formaldehyde*, American Chemical Society Monograph Series, No. 159, Reinhd Publishers Ltd, New York, **1964**.

48. J. Breslaner and A. Pictet. *Ber. Dtsch. Chem. Ges.* 40, 3785, **1907**.

49. J. Abel. *Ber. Dtsch. Chem. Ges.* 25, 3477, **1892**.

50. P. E. Georghiou and Z. Li. *Tetrahedron Lett.* 34, 2887, **1993**.

51. T. Miyata, T. Hirashima. *Yuki Gosei Kagaku Koyokai Shi.* 34, 434, **1976**.

52. T. Miyata, T. Hirashima. *Yuki Gosei Kagaku Koyokai Shi.* 34, 435, **1976**.

53. K. C. Schriber, M. C. Kennedy. *J. Org. Chem.* 21, 1310, **1956**.

54. O. M. Falana, E. Al-Farhan, P. M. Keehn. R. Stevenson. *Tetrahedron Lett.* 35, 65, **1994**.

55. W. P. Neumann,H. Hillgartner. *Synthesis* 537, **1971**.

56. S. Perumal, G. Vasuki, D. A. Wilson, D. W. Boykin. *Magn. Reson. Chem.* 30, 320, **1992**.

57. N. P. Bnu-Hoi, H. Lebihan, F. Binon, P. Rayet. *J. Org. Chem.* 15, 1060 **1950**.

58. P. A. Brady, J. Carnduff, D. G. Leppard. *Tetrahedron Lett.* 4183, **1972**.

59. J. Garnduff, and D. G. Leppard. *J. Chem. Soc., Chem. Commun.* 829, **1967**.

60. R. T. Ferris, D. Hamer. *J. Chem. Soc.* 1409, **1960**.

61. T. Miyata, T. Hirashima. *Yuki Gosei Kagaku Koyokai Shi* 34, 433, **1976**.

62. G. D. Andreetti, V. Böhmer, J. G. Jordan, M. Tabatabai, F. Ugozzoli, W. Vogt, A. Wolff. *J. Org. Chem.* 58, 4023, **1993**.

63. S. Shinkai, T. Armura, H. Kawabata, H. Murakami, K. Araki, K. Iwamoto, T. Matsuda. *J. Chem. Soc., Chem. Commun.* 1734, **1990**.

64. S. Shinkai, T. Armura, H. Kawabata, H. Murakami, K. Araki, K. Iwamoto, T. Matsuda. *J. Chem. Soc. Perkin Trans.1* 2429, **1991**.

65. S. Pappalardo, S. Caccamese, L. Giunta. *Tetrahedron Lett.* 32, 7747, **1991**.

66. K. Iwamoto, A. Janagi, T. Arimura, T. Matsuda, S. Shinkai. *Chem. Lett.* 1901, **1990**.

67. Bing Xu, J. Patrick,and M. Swager. *Angew Chem. Int. Ed. Engl.* 35, 2094, **1996**.

68. C. D. Gutsche, B. Dhawan, K. H. No, R. Muthukrishan. *J. Am. Chem. Soc.* 103, 3782, **1981**.

69. R. M. Izatt, J. D. Lamb, R. T. Hawkins, P. R. Brown, S. R. Izatt, J. J. Christensen. *J. Am. Chem. Soc.* 105, 1782, **1983**.

70. M. A. Mckervey, E. M. Seward, G. Ferguson, B. Ruhl, S. J. Harris. *J. Chem. Soc., Chem. Commun.* 388, **1985**.

71. A. Arduini, A. Casnati, M. Fabbi, P. Minari, A. Pochini, A. R. Sicuri, R. Ungaro. *Supermol. Chem.* 1, 235, **1993**.

72. F. Grynszpan, Z. Goren, S. E. Biali. *J. Org. Chem.* 56, 532, **1991**.

73. F. Ohseto, H. Murakami, K. Araki, S. Shinkai. *Tetrahedron Lett.* 33, 1217, **1992**.

74. Y. Ting, W. Verboom, L. C. Groenen, J. D. Van Loon, D. N. Reinhoudt. *J. Chem. Soc., Chem. Commun.* 1432, **1990**.

75. J. D. Van Loon, A. Arduini, L. Coppi, W. Verboom, A. Pochini, R. Ungaro, S. Harkems, D. N. Reinhoudt. *J. Org. Chem.* 55, 5639, **1990**.

76. M. L. Ariel, G. Flavio, A. Oleg, C. Shmuel, E. B. Silvio. *J. Org. Chem.* 58, 393, **1993**.

77. a) M. G. Joel, A. Oleg, E. B. Silvio. *J. Org. Chem.* 61, 8419, **1996**.

b) A. Oleg, C. Shmuel, E. B. Silvio. *J. Am. Chem. Soc.* 117, 9645, **1995**.

78. R. Pummerer, E. Cherbuliez. *Chem. Ber.* 27, 2957, **1914**; E. A. Shearing, S. Smiles. *J. Chem. Soc.* 1931, **1973**.

79. R. H. Mitchell, V. Boekelheide. *J. Am. Chem. Soc.* 96, 1547, **1974**.

80. T. Yamoto, A. Miyazawa, M. Tashiro. *Chem. Ber.* 126, 2505, **1993**.

81. F. Vogtle. *Cyclophane* I, pp 95-97, Boschke, F. L. (ED) Springer-Verlag, Berlin, **1983**.

82. V. Boekelheide, I. D. Reingold, M. Tuttle. *J. Chem. Soc., Chem. Commun.* 406, **1973**.

83. W. Xu, R. J. Puddephatt, K. W. Muir, A. A. Torabi. *Organometallics* 13, 3054, **1994**.

84. B. Dhawan, C. D. Gutsche. *J. Org. Chem.* 448, 1536, **1983**.

85. a) K. Araki, N. Hashimoto, H. Otsuka, S. Shinkai. *J. Org. Chem.* 58, 5958, **1993**. b) P. D. Hampton, Z. Bencze, W. Tong, C. E. Daitch. *J. Org. Chem.* 59, 5958, **1994**. c) B. Masci. *Tetrahedron* 51, 5459, **1995**.

86. S. Failla, P. Finocchiaro, V. K. Belsky, V. E. Zavodnik, A. N. Sobolev. *J. Inclusion phenom. Mol. Recognit. Chem.* 15, **1993**.

87. N. M. Przhiyalgovskaya, G. T. Mondodoev *Zh. Obshch. Khim*, 34(5), 1570, **1964**.

88. R. H. Mitchell, R. V. Williams, T. W. Dingle. *J. Am. Chem. Soc.*, 104, 2560, **1982**; R. H. Mitchell. *Cyclophanes*, Vol. 1, Academic Press, New York, **1983**.

89. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart. *J. Am. Chem. Soc.*

107, 3902, **1985**.

90. "SPARTAN," Version 4.1, Wavefunction, Inc., Irvine, CA.

91. E. Clar. *Polycyclic Hydrocarbons*, Vol. 2, Academic Press, London, **1964**.

92. R. H. Mitchell, V. Boekelheide. *Tetrahedron Lett.* 1197, **1970**.

93. T. Sato, K. Nishiyama, A. Murai. *J. Chem. Soc., Chem. Commun.* 163, **1972**.

94. T. Sato, M. Wakabayashi, T. Okamura, T. Amada, K. Hata. *Bull. Chem. Soc. Jpn.* 40, 2363, **1967**.

95. T. Yamato, S. Ide, K. Tokuhisa, M. Tashiro, *J. Org. Chem.* 57, 271, **1992** and references cited therein.

96. T. Sato, M. Wakabayashi, S. Hayashi, K. Hata. *Bull. Chem. Soc. Jpn.* 42, 773, **1969**.

97. T. Yamato, M. Tashiro. *J. Org. Chem.* 46, 1543, **1981**

98. F. Vogtle, P. Neumann. *Tetrahedron*, 26, 5299, **1970**.

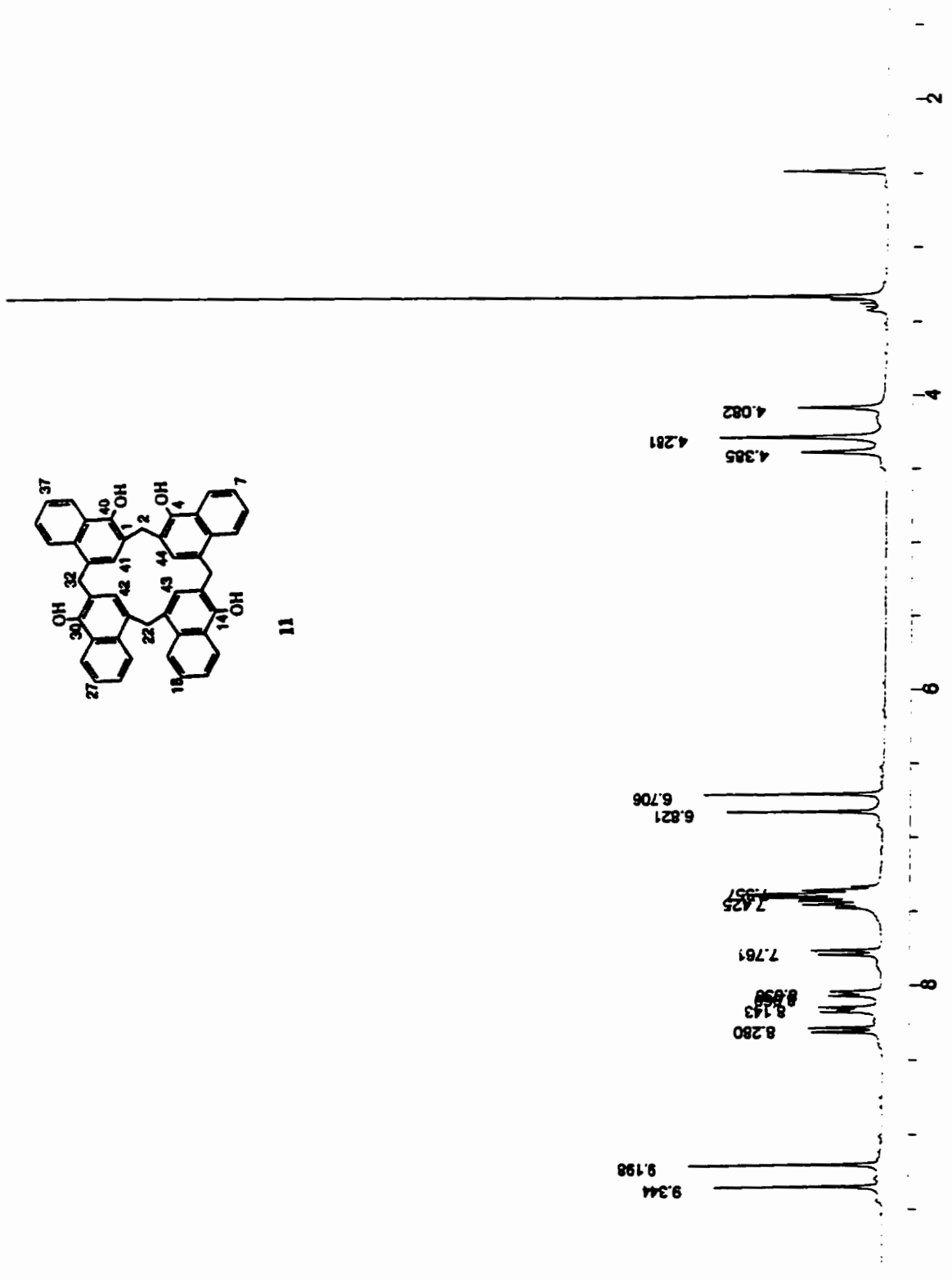
99. S. A. Sherrod, R. L. da Costa, R. A. Barnes, V. Boekelheide. *J. Am. Chem Soc.*, 96, 1565, **1974**.

100. T. Yamato, M. Tashiro. *Org. Prep. Proced. Int.*, 13, 1, **1981**.

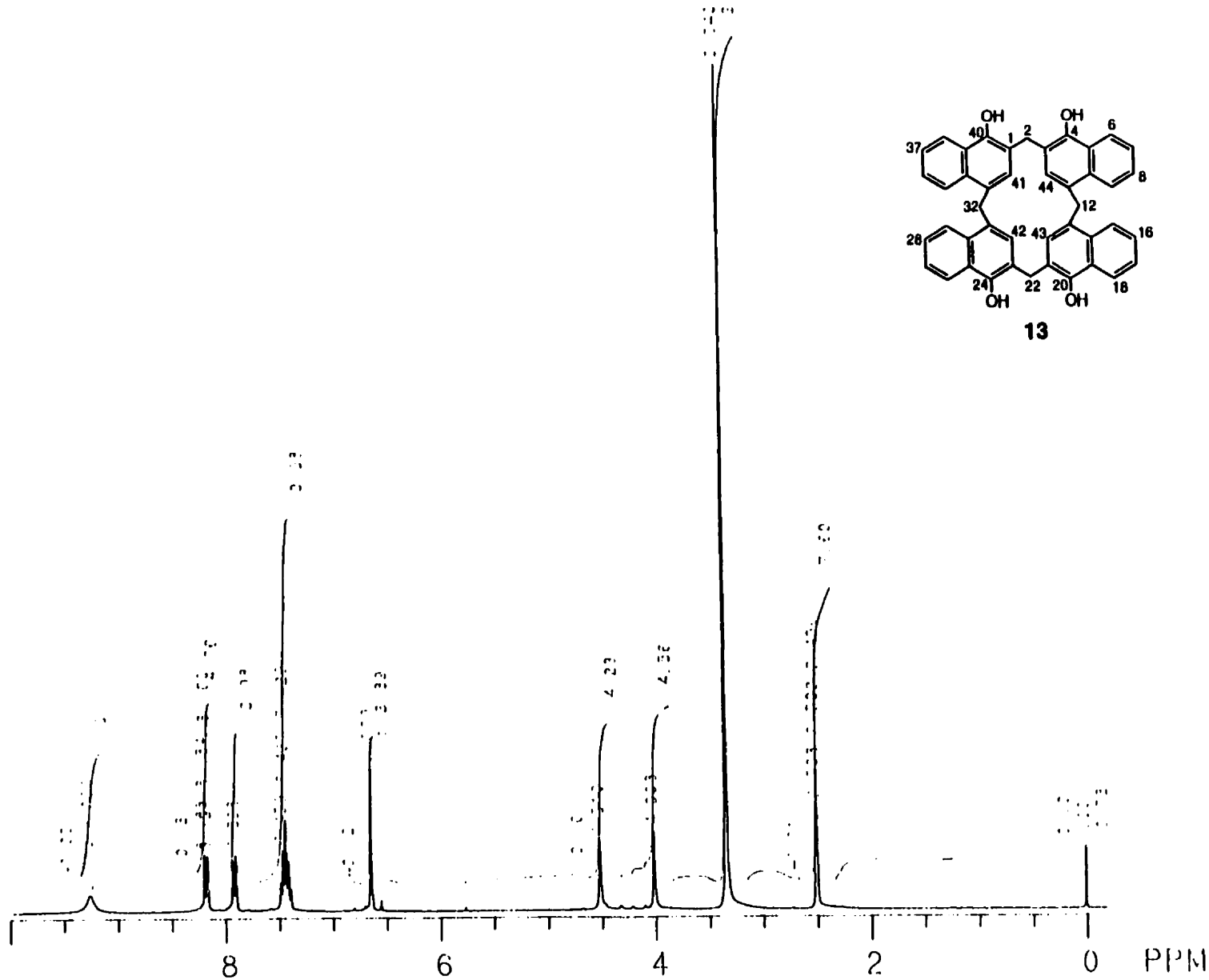
101. T. Yamato, M. Tashiro, K. Kobayashi, T. Arimura *J. Org. Chem.* 52, 3196, **1987**.

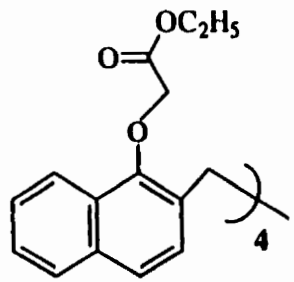
Appendix A

^{1}H NMR Spectra of Compounds
(in order of compound number)

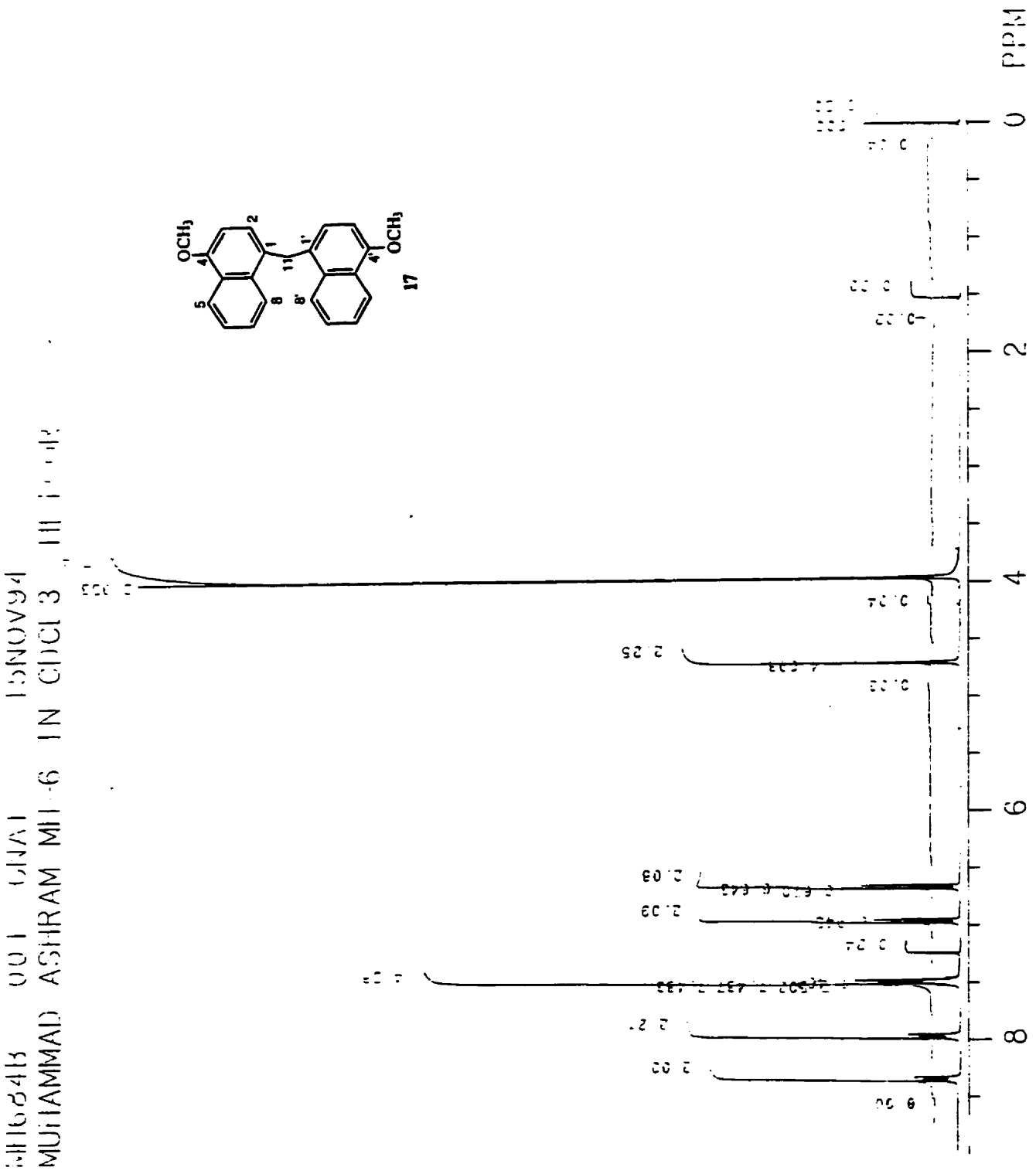

9.344
9.198
8.280
8.143
8.050
7.761
7.425
6.821
6.706
4.385
4.281
4.082
2
4
6
8
OH
OH
OH
OH
37
40
1
2
4
7
32
41
42
44
43
30
22
14
27
18

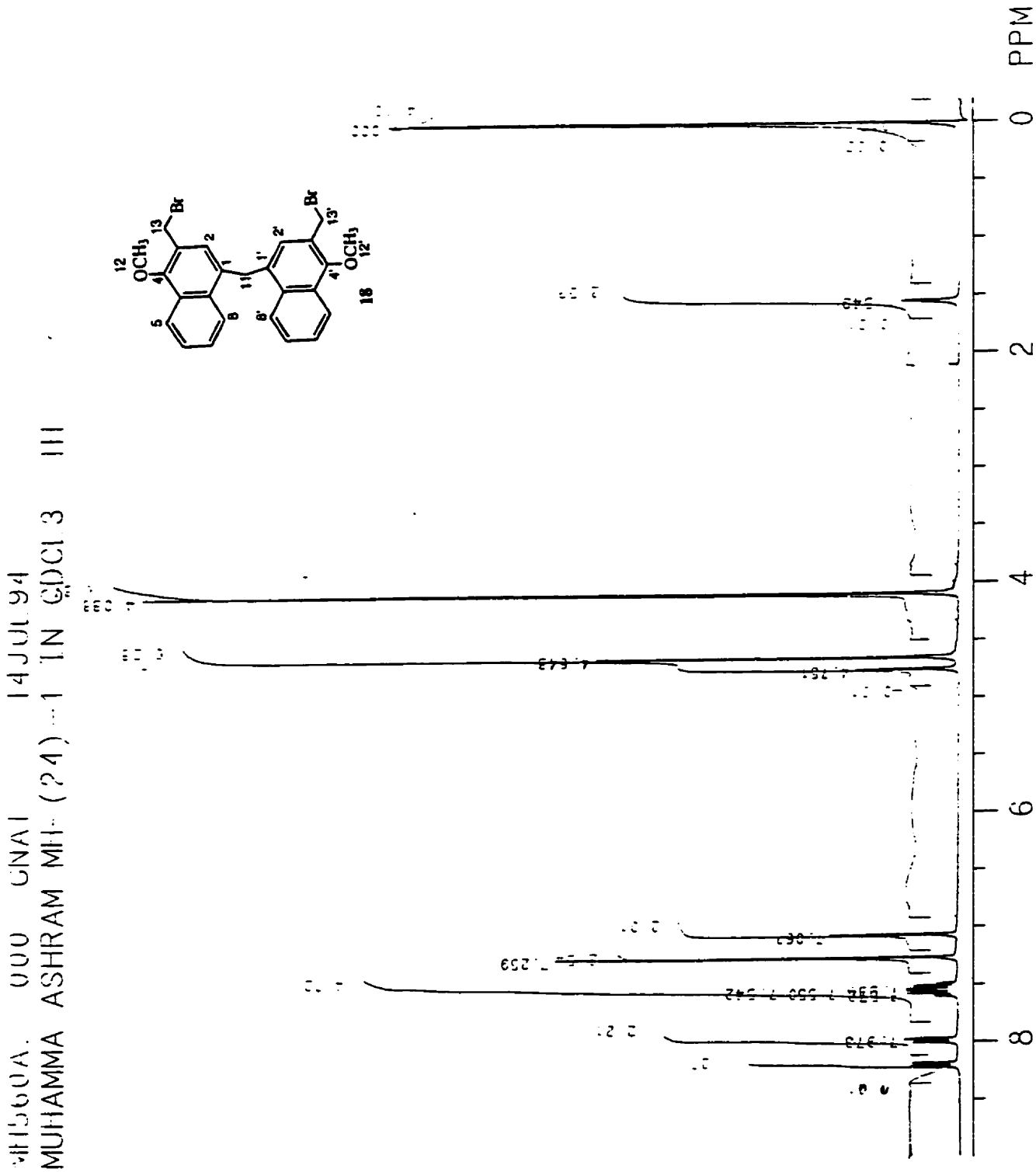
11


OH
OH
40
1
2
4
6
37
41
44
8
32
12
42
43
26
16
24
22
20
18
OH
OH
13
8
6
4
2
0
PPM



tetra-ester derivative of C-12


OCH3
OCH3
17
PPM
0
2
4
6
8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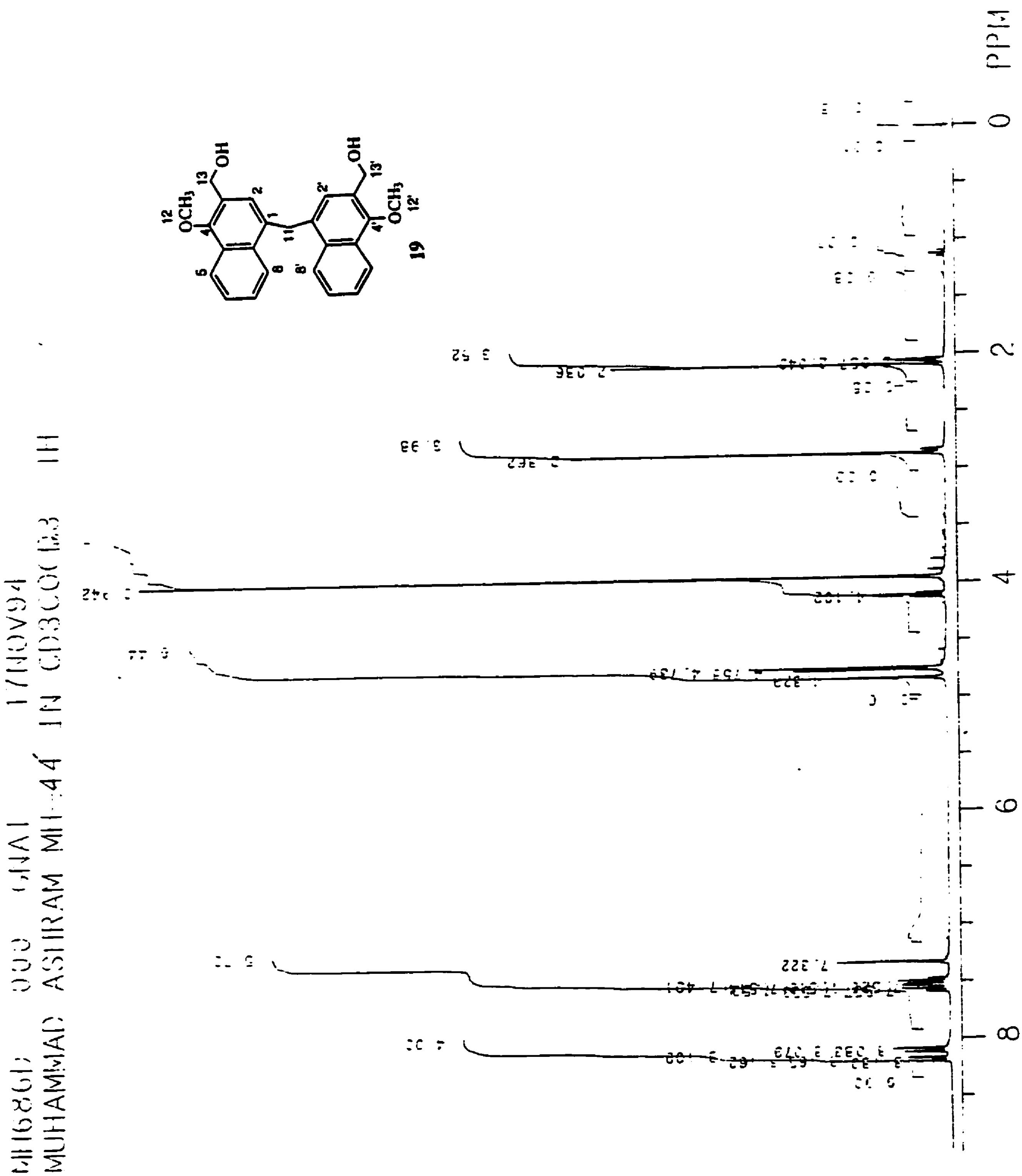
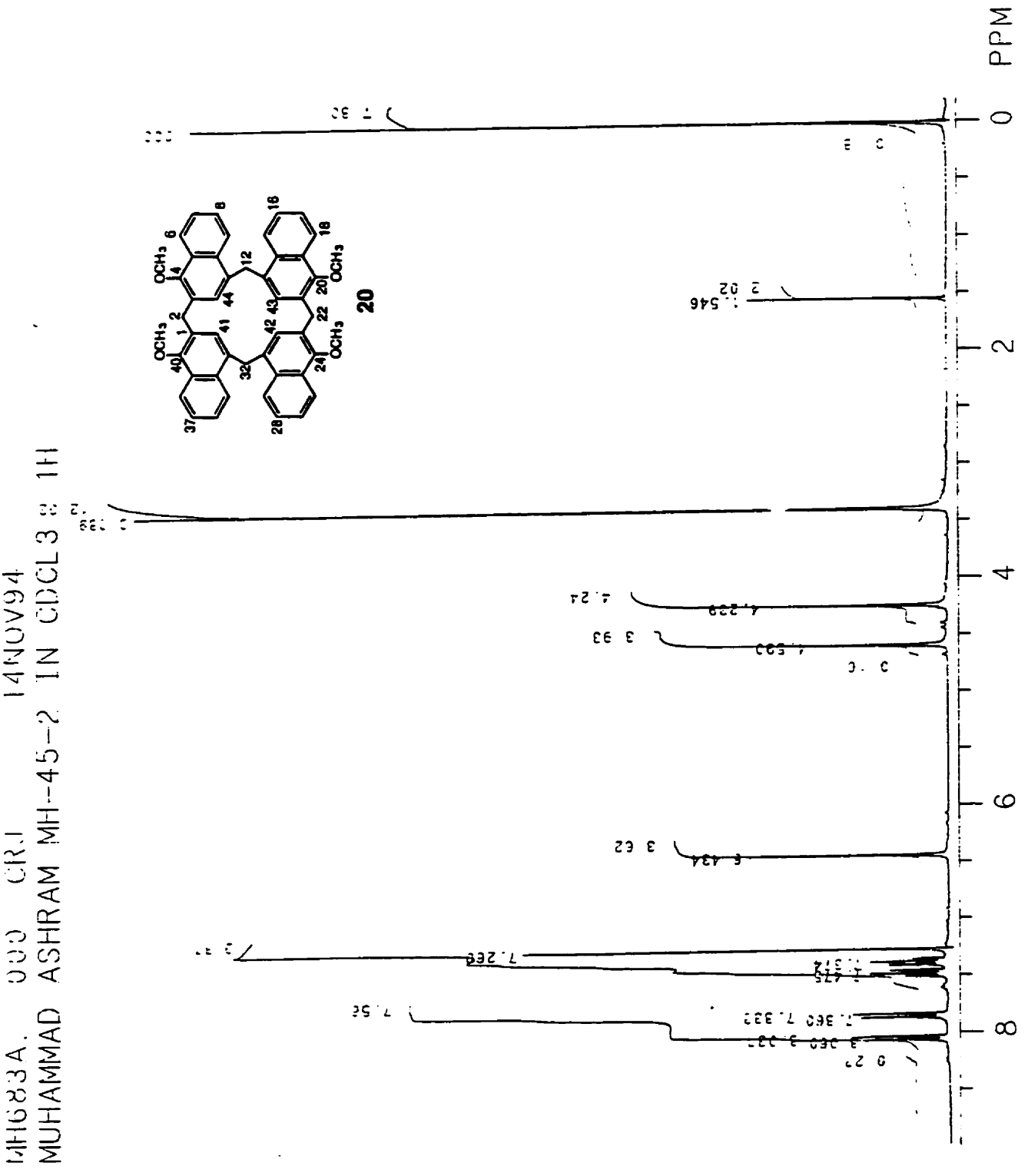
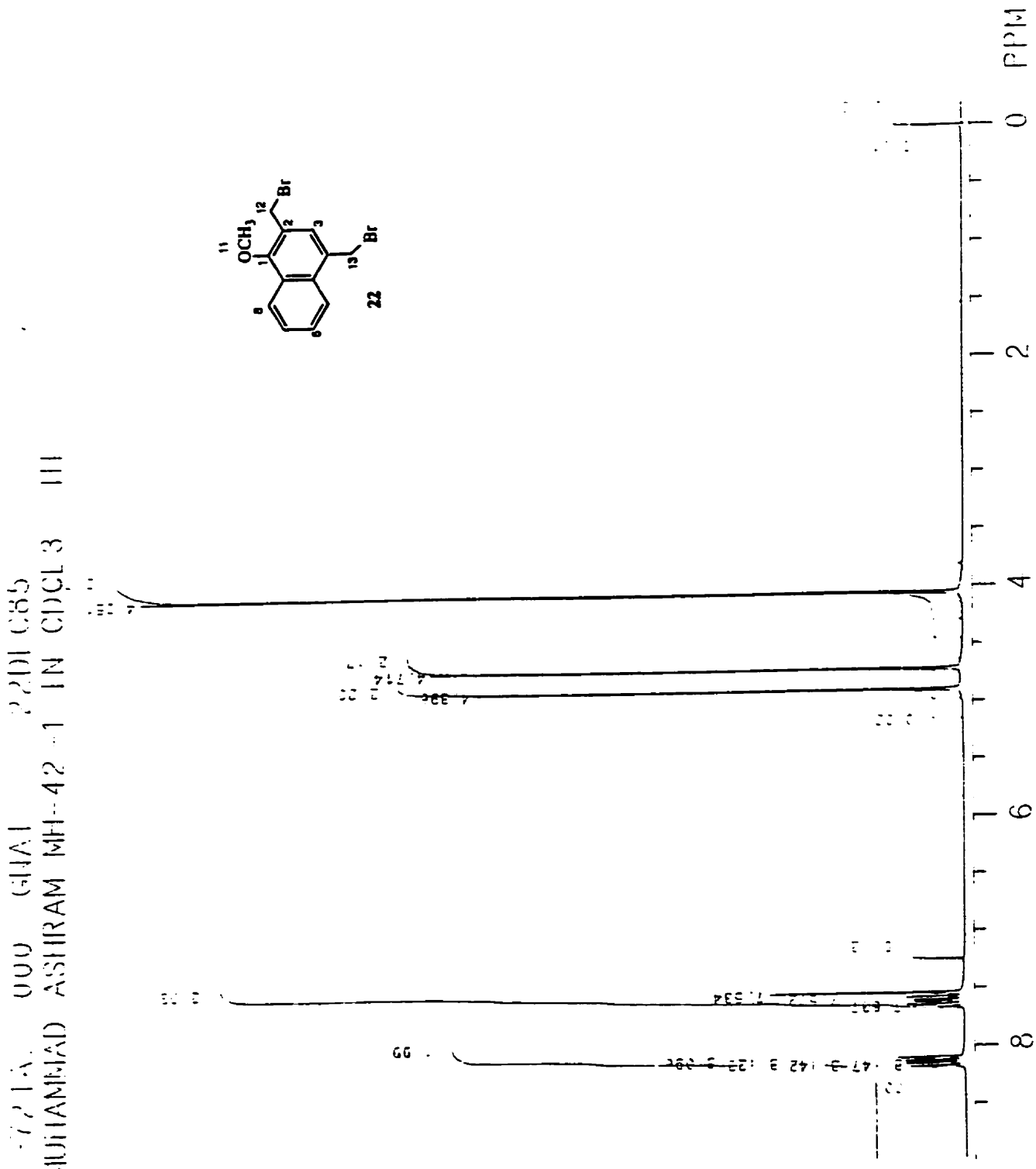
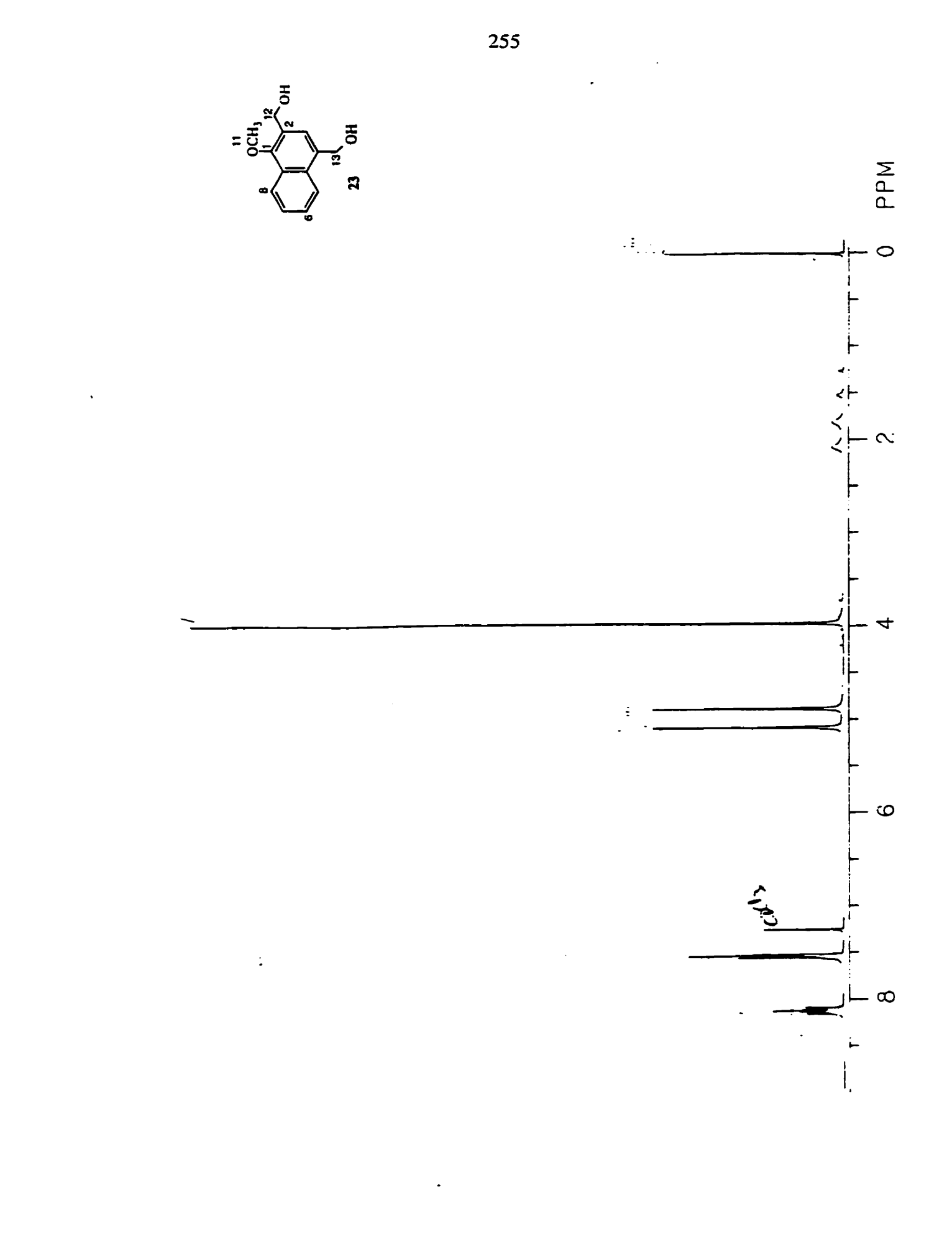
PPM
0
2
4
6
8
Br
OCH3
Br
OCH3


MH688GD 000 GNAT 17NOV94
MUHAMMAD ASHRAM MH-44 IN CD3COCD3 1H
OCH3
OH
OCH3
OH
19
PPM
0
2
4
6
8
7.322


MH6883A. 000 CRJ 14NOV94
MUHAMMAD ASHRAM MH-45-2 IN CDCL3 @ 1H
PPM
0
2
4
6
8
20


22
PPM
0
2
4
6
8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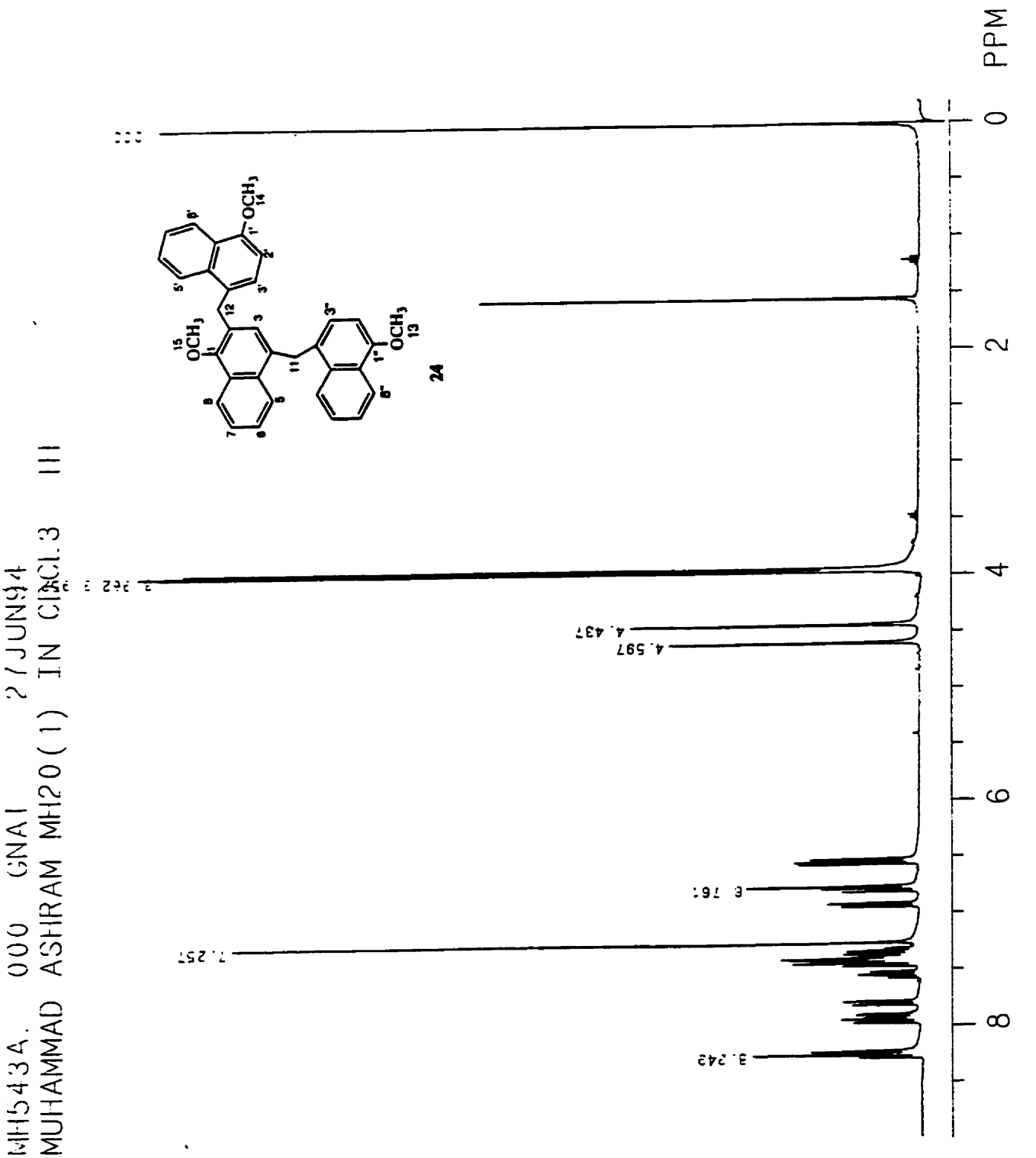
12
OH
2
13
OH
8
6
23
PPM
0
2
4
6
8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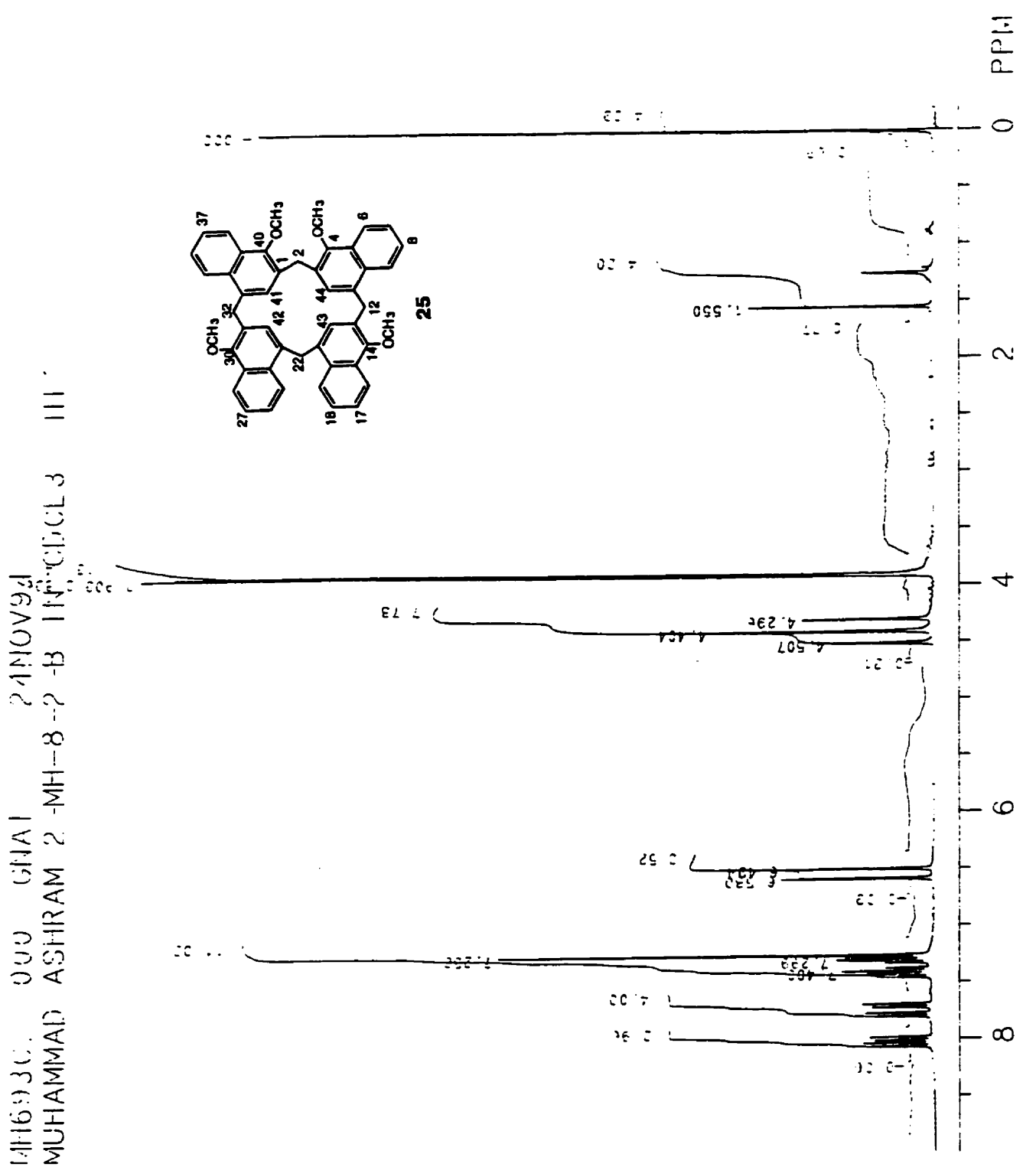
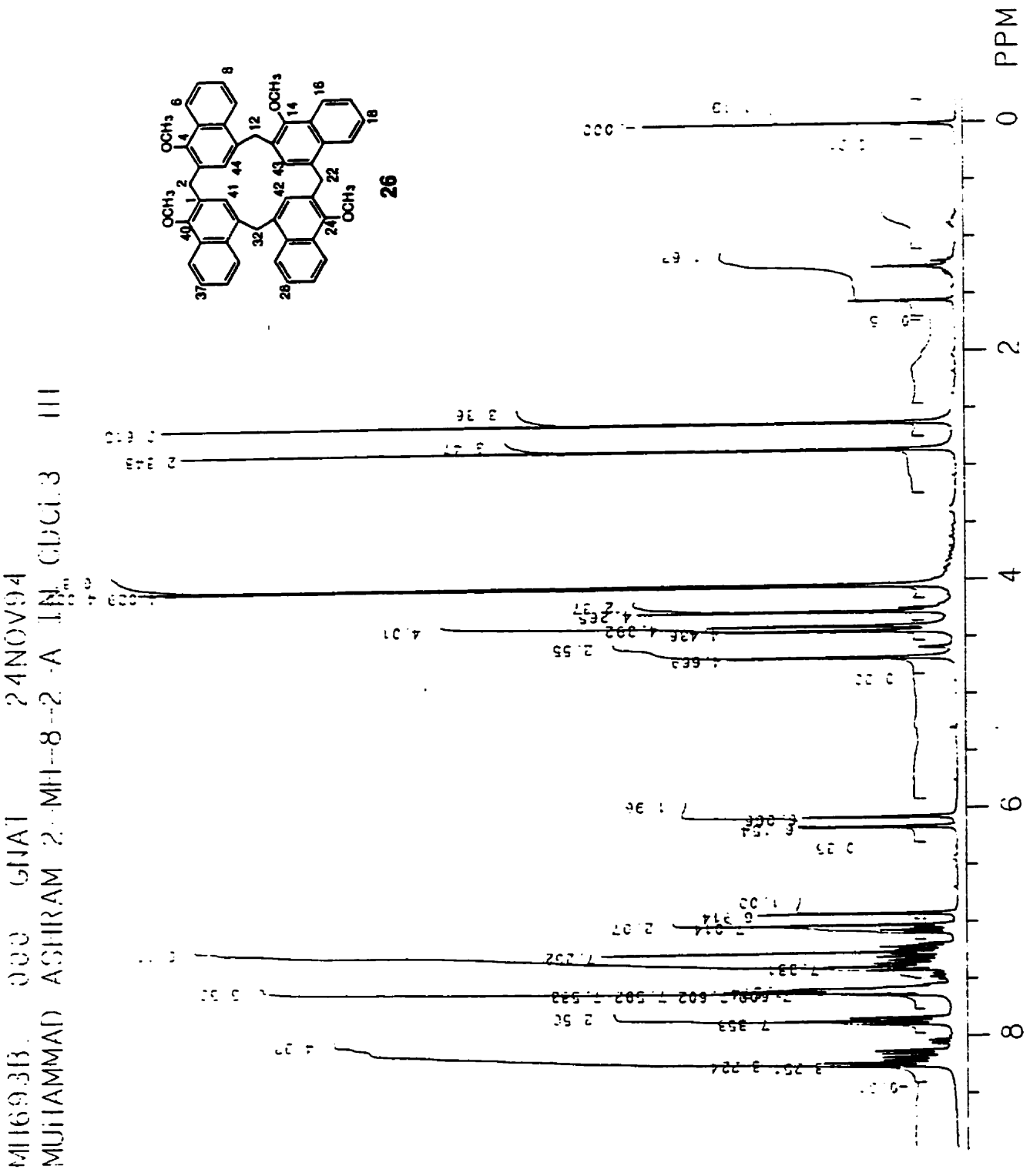
3.242
4.597
4.437
7.761
7.257
3.243
8
6
4
2
0
PPM
OCH3
15
OCH3
13
OCH3
14
24


MUHAMMAD ASHRAM 2 -MH-8--2 -B IN CDCL3
PPM
0
2
4
6
8
OCH3
OCH3
OCH3
OCH3
25


MU169-3B 000 GNAT 24NOV04
MUHAMMAD ASHRAM 2-MU-8-2-A IN CDCL3 III
PPM
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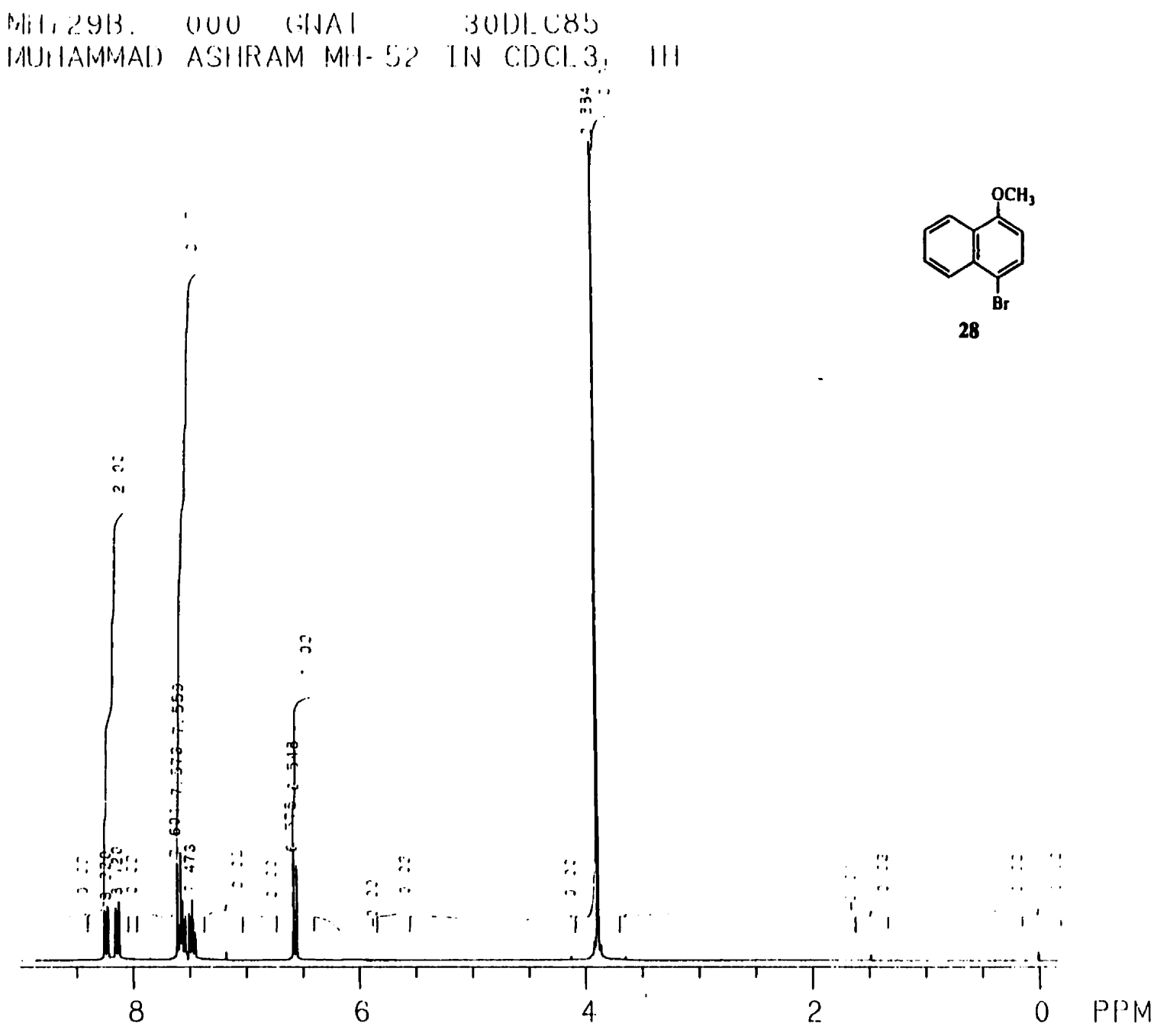
4
6
8
OCH3
OCH3
OCH3
OCH3
26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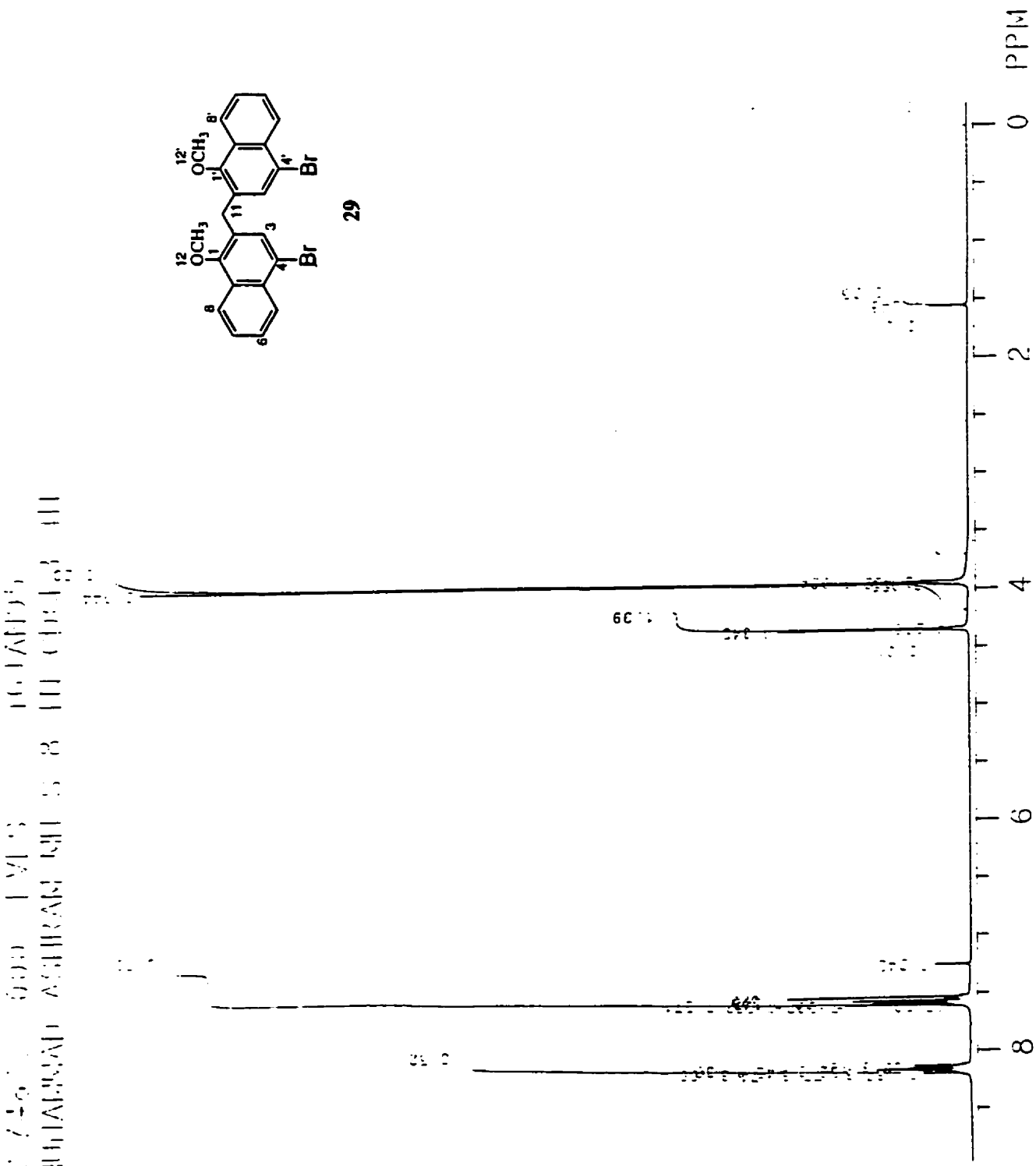
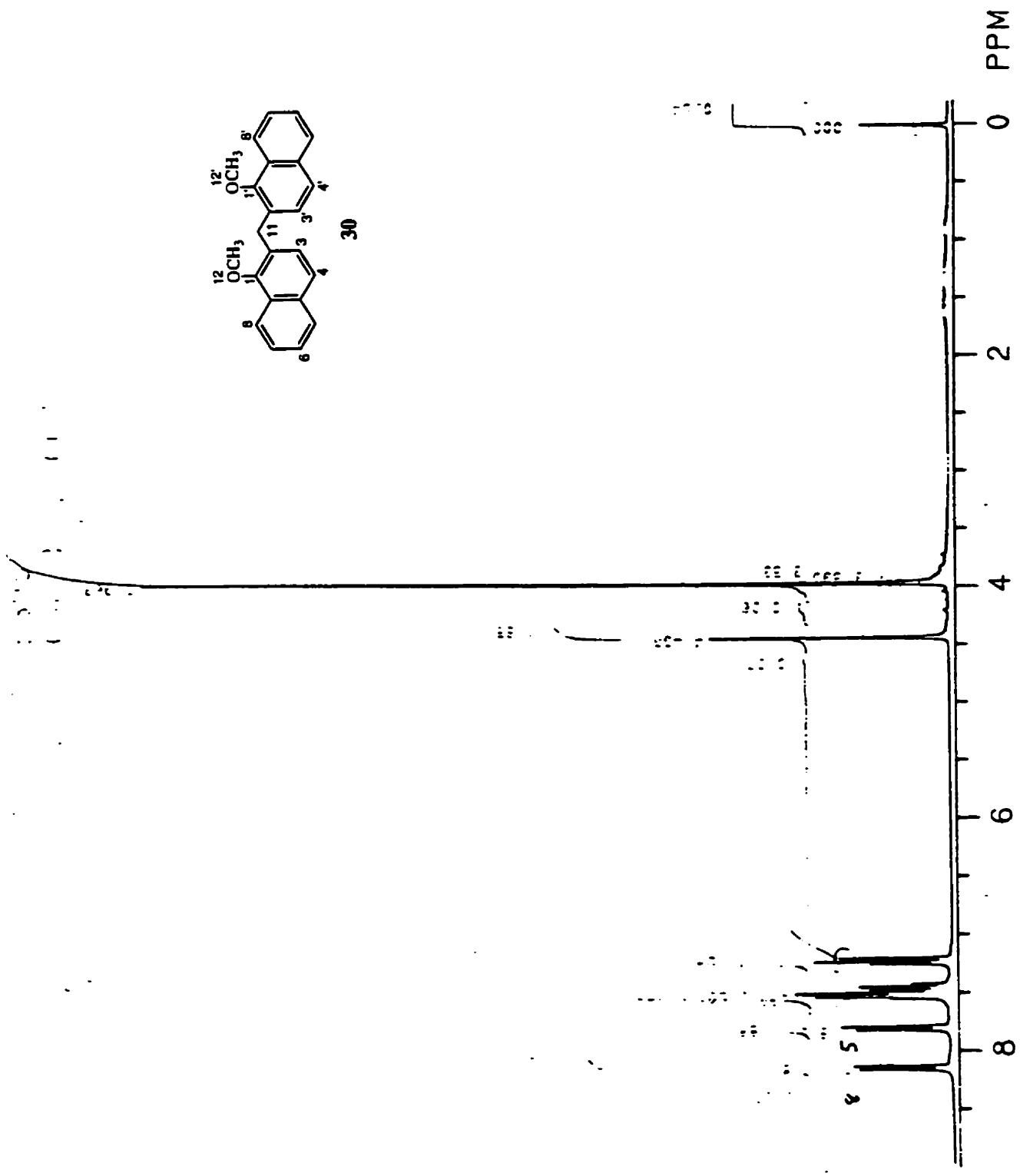
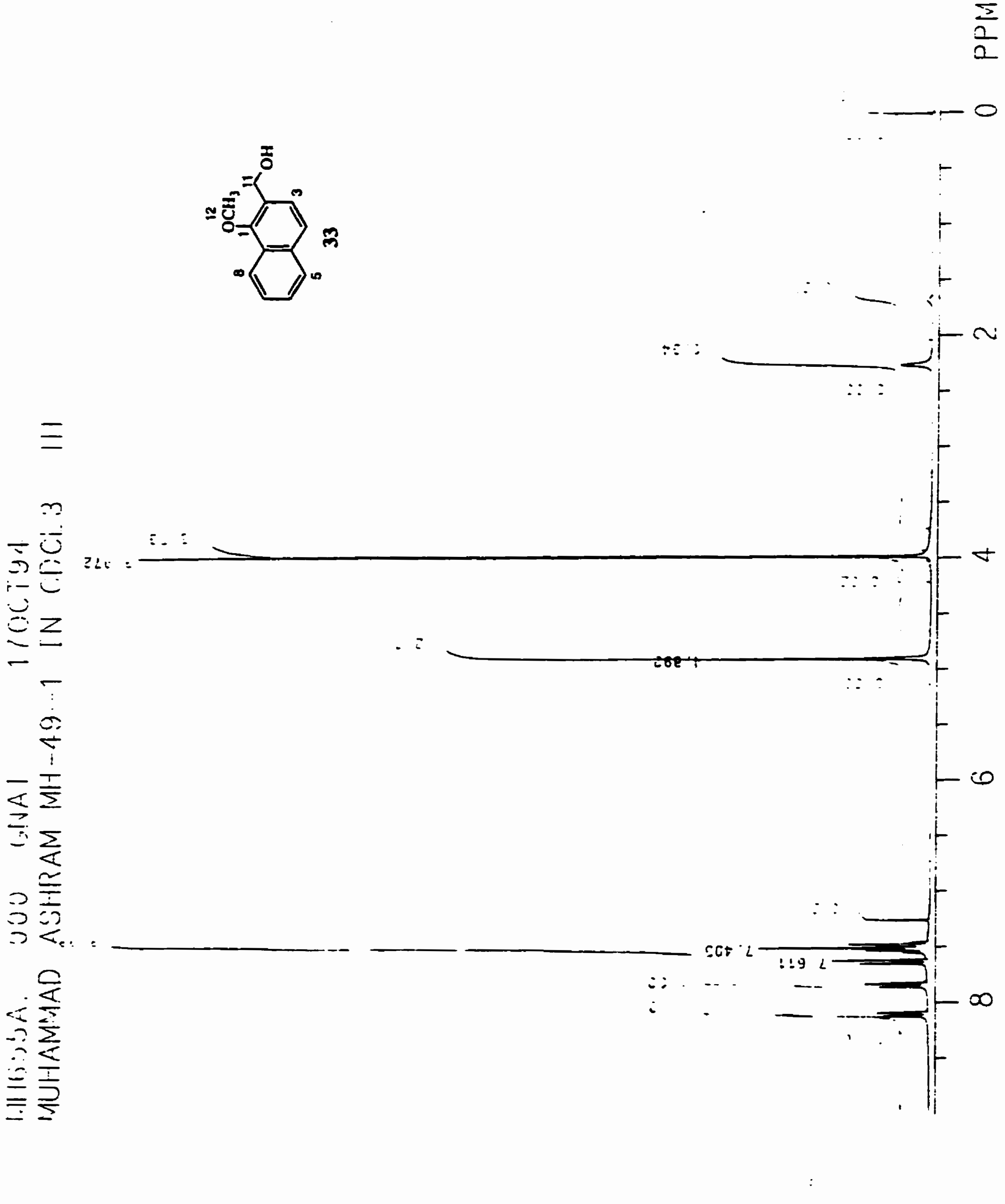
OCH3
Br
28
8
6
4
2
0
PPM


12'
OCH3
8'
1'
4'
Br
11'
11
12
OCH3
1
3
4
Br
8
6
29
PPM
0
2
4
6
8


PPM
0
2
4
6
8
OCH3
12'
11'
8'
4'
3'
11
3
4
OCH3
12
1
8
6
30


17OCT94
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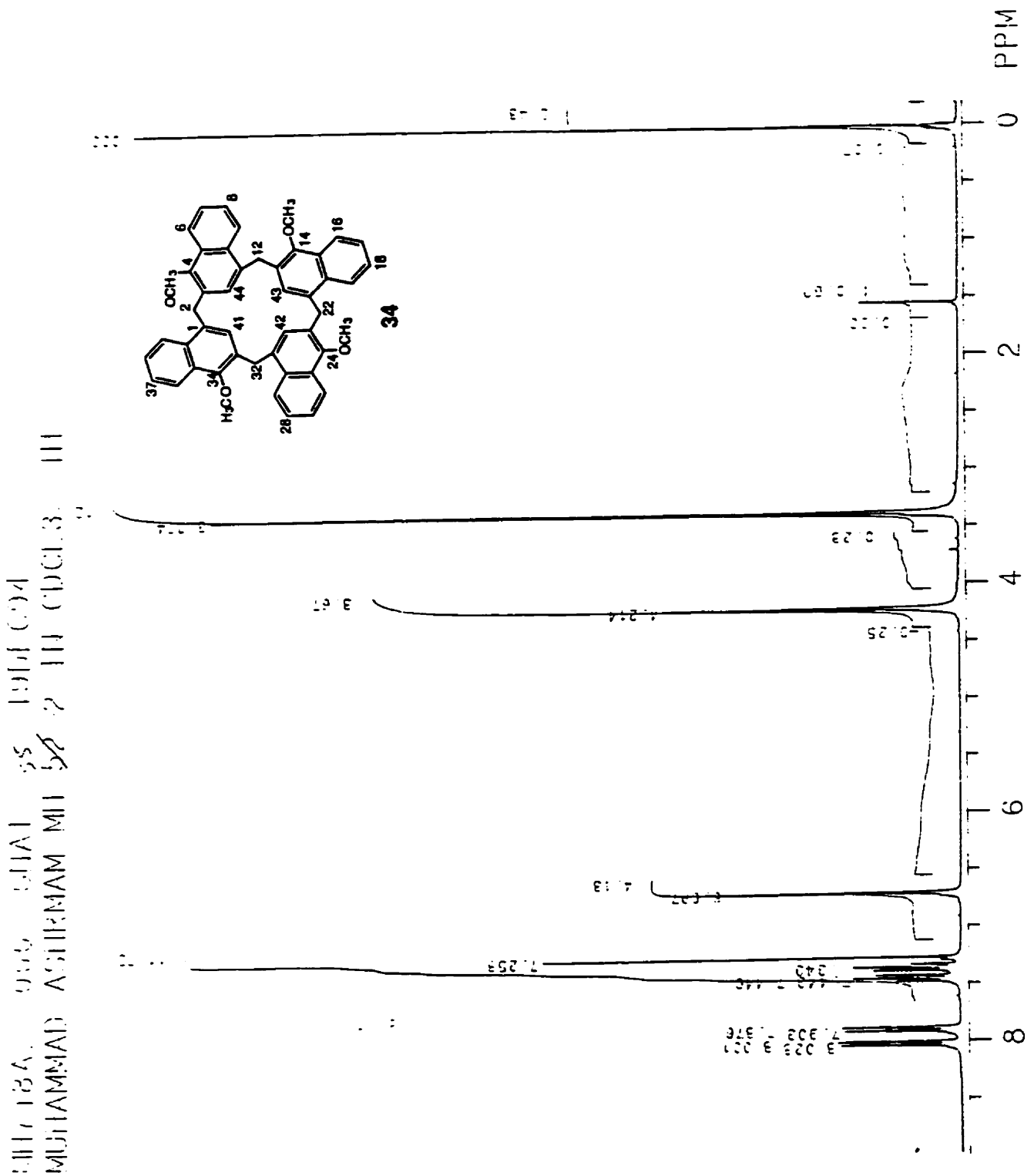
33
7.405
7.611
0
2
4
6
8
PPM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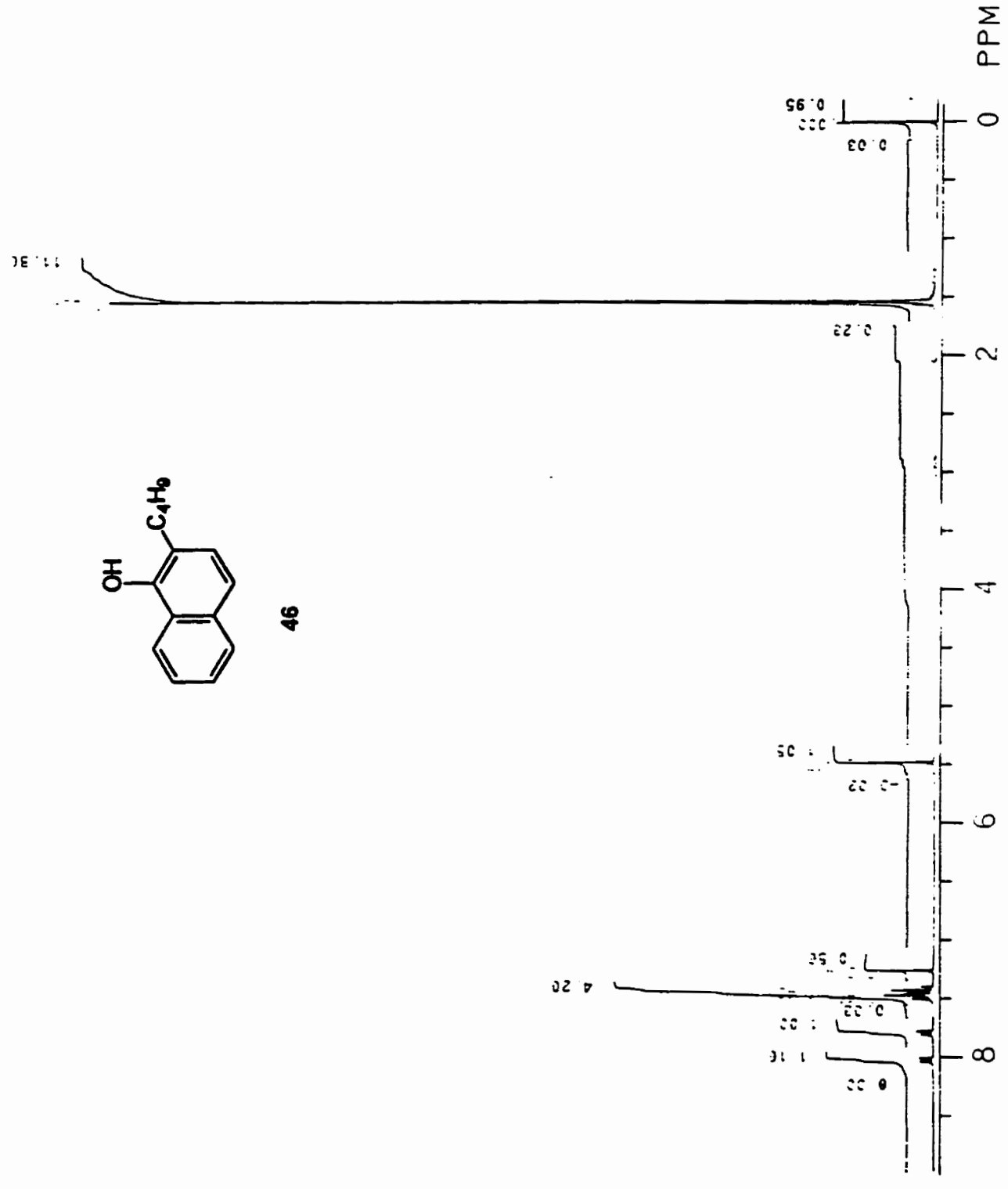
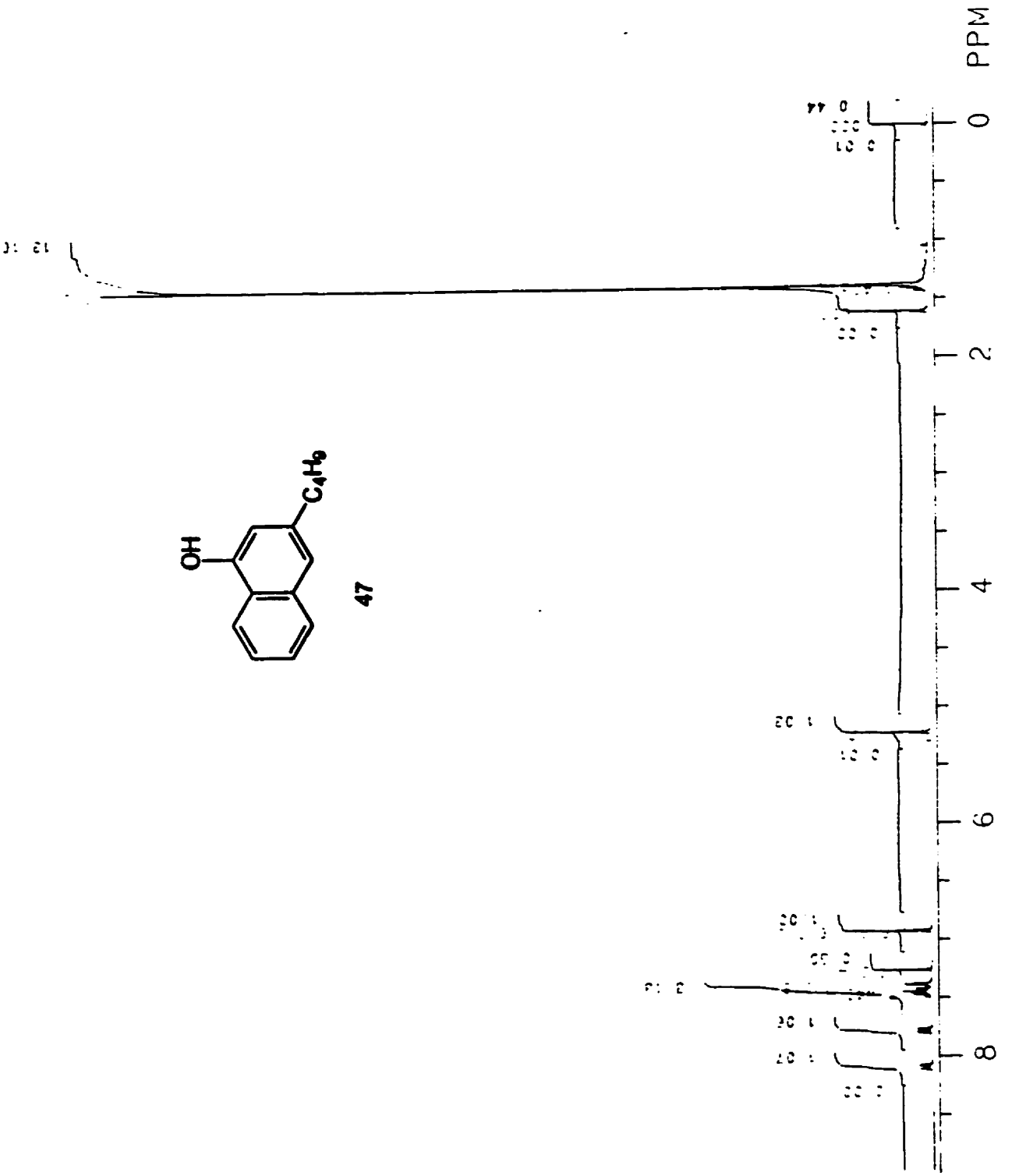
OCH3
H3CO
34
PPM
0
2
4
6
8

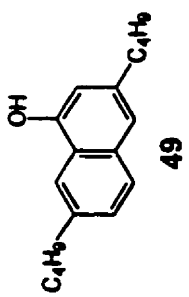


46



47

48



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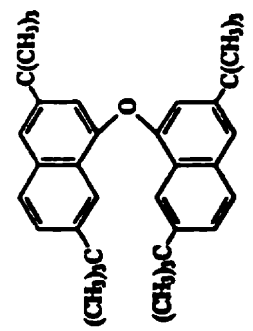
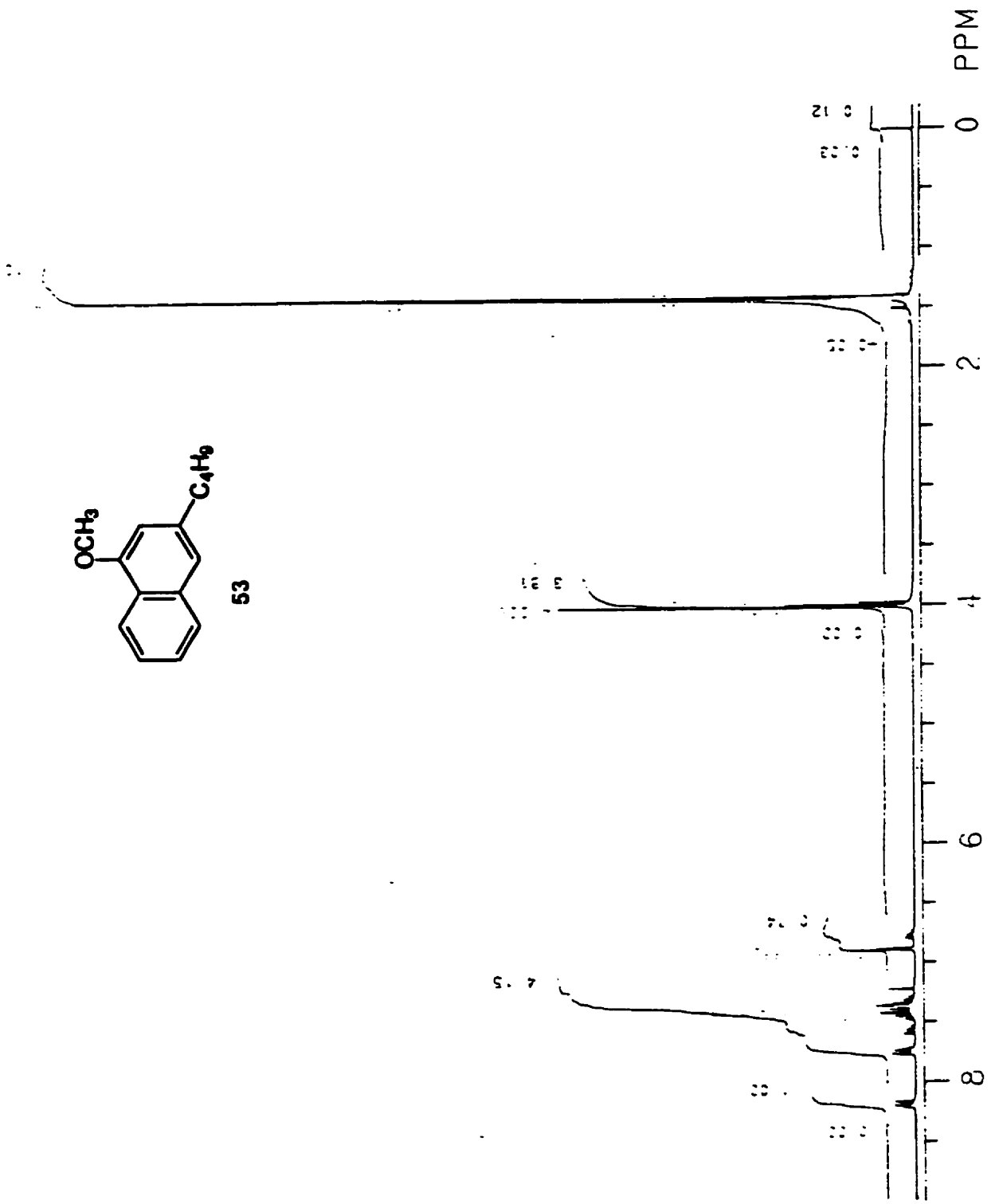
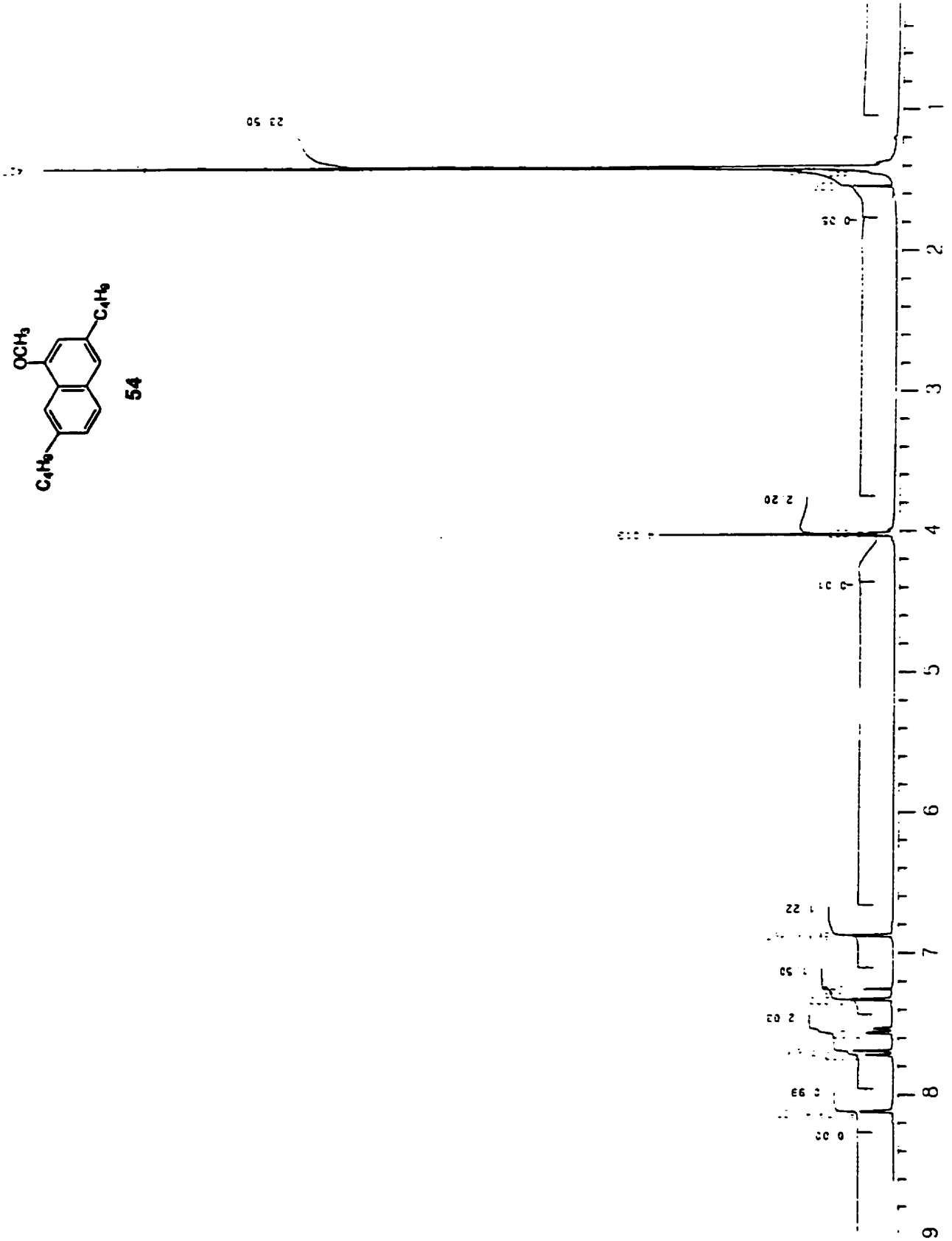
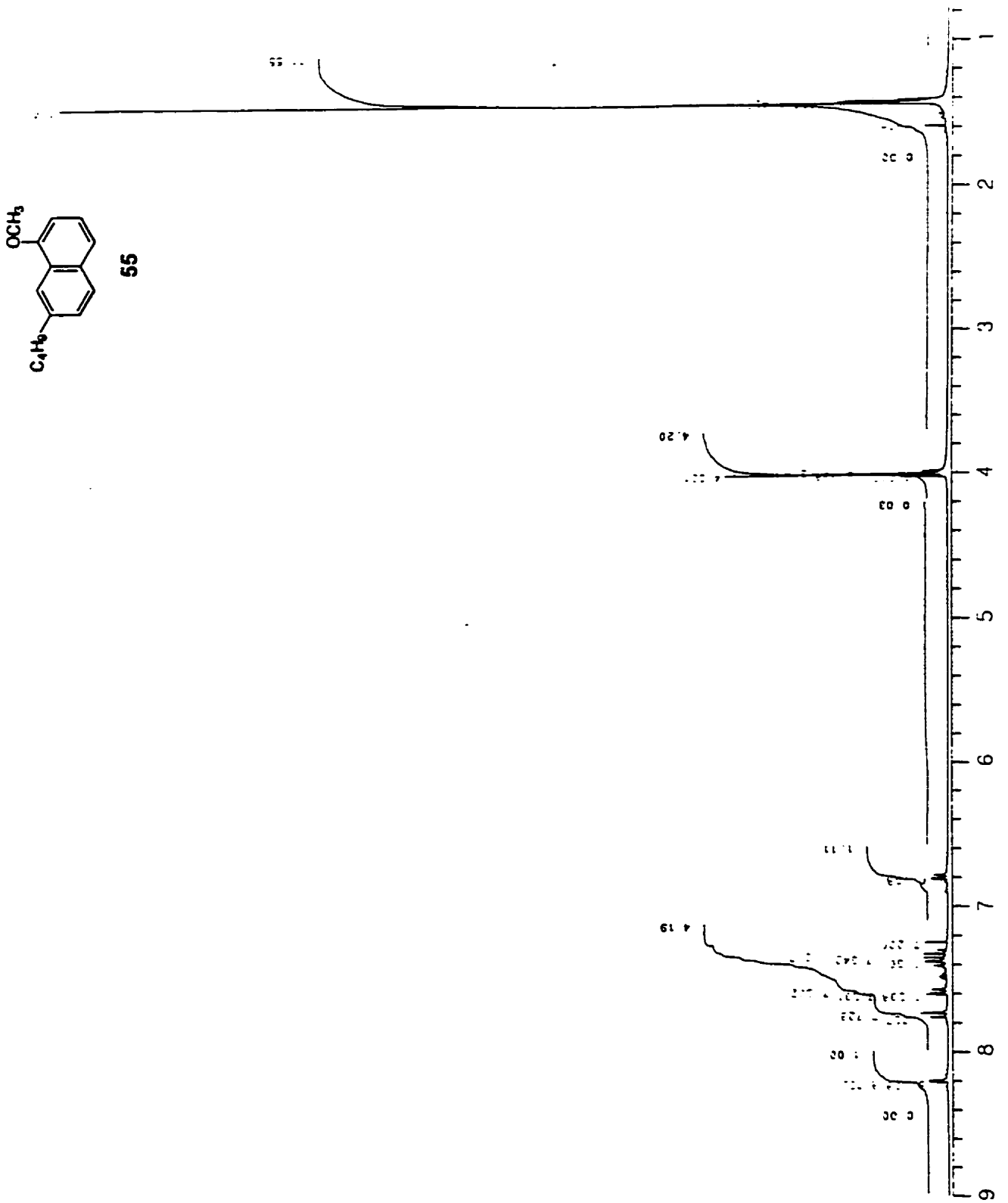


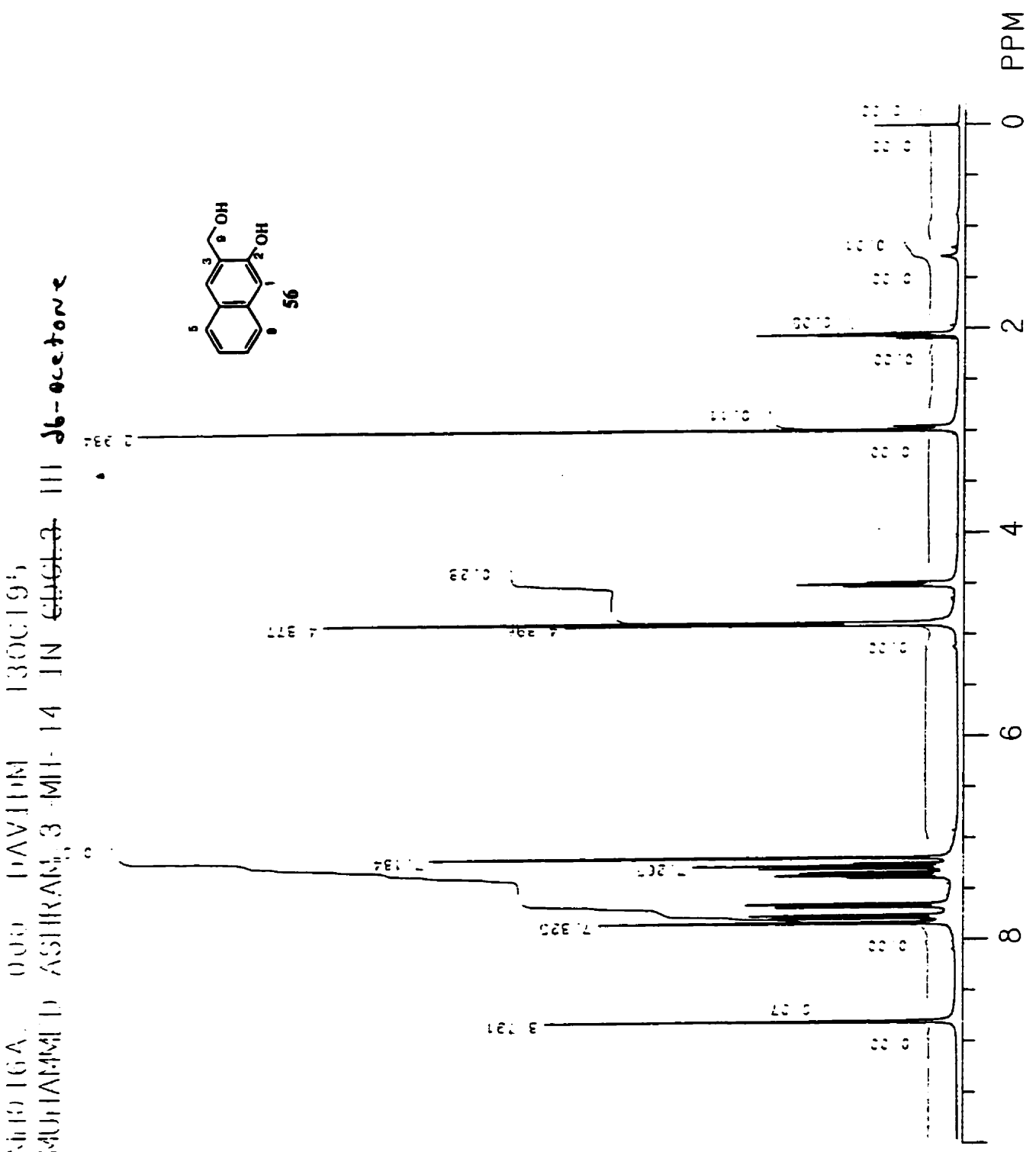
50

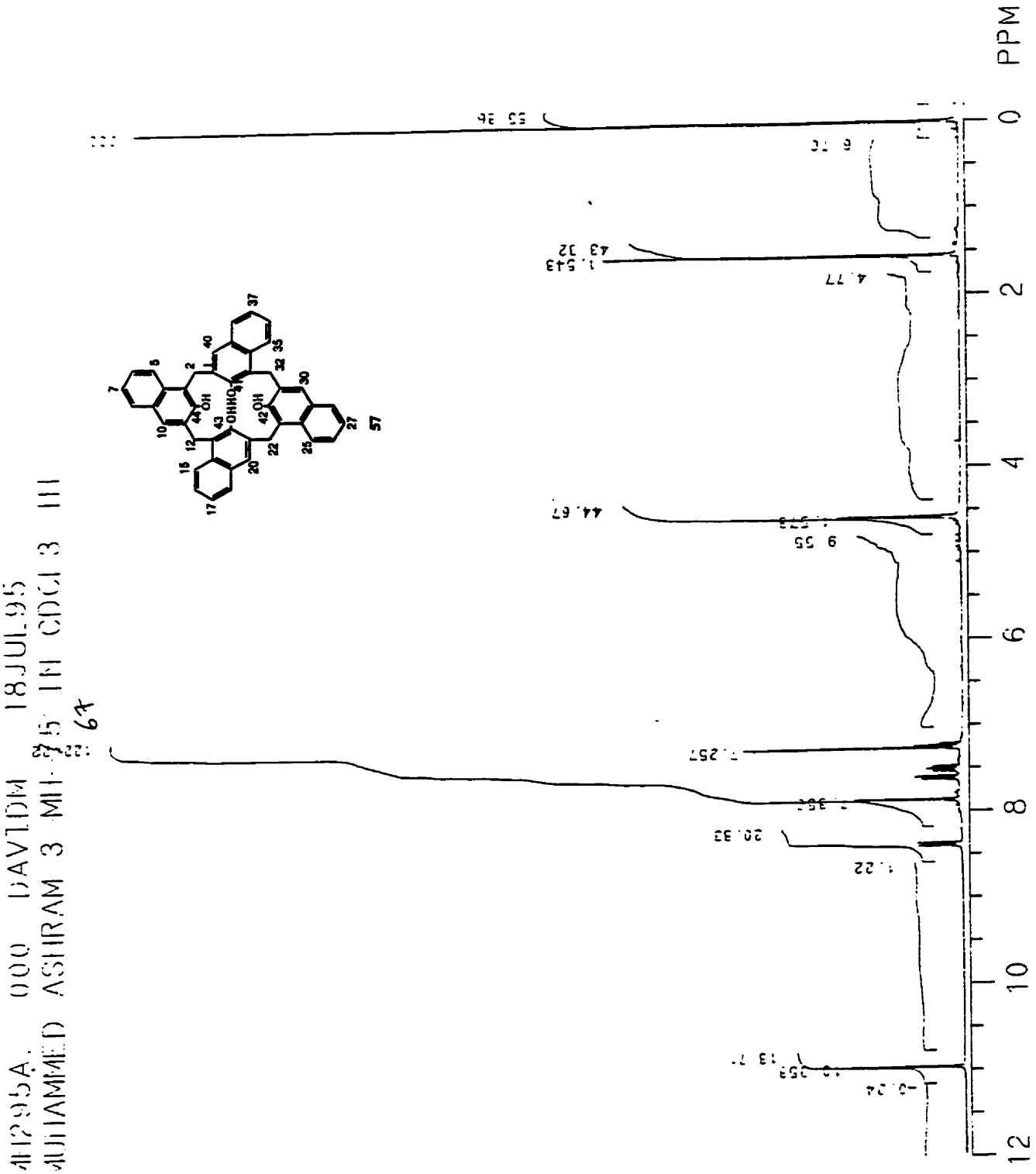


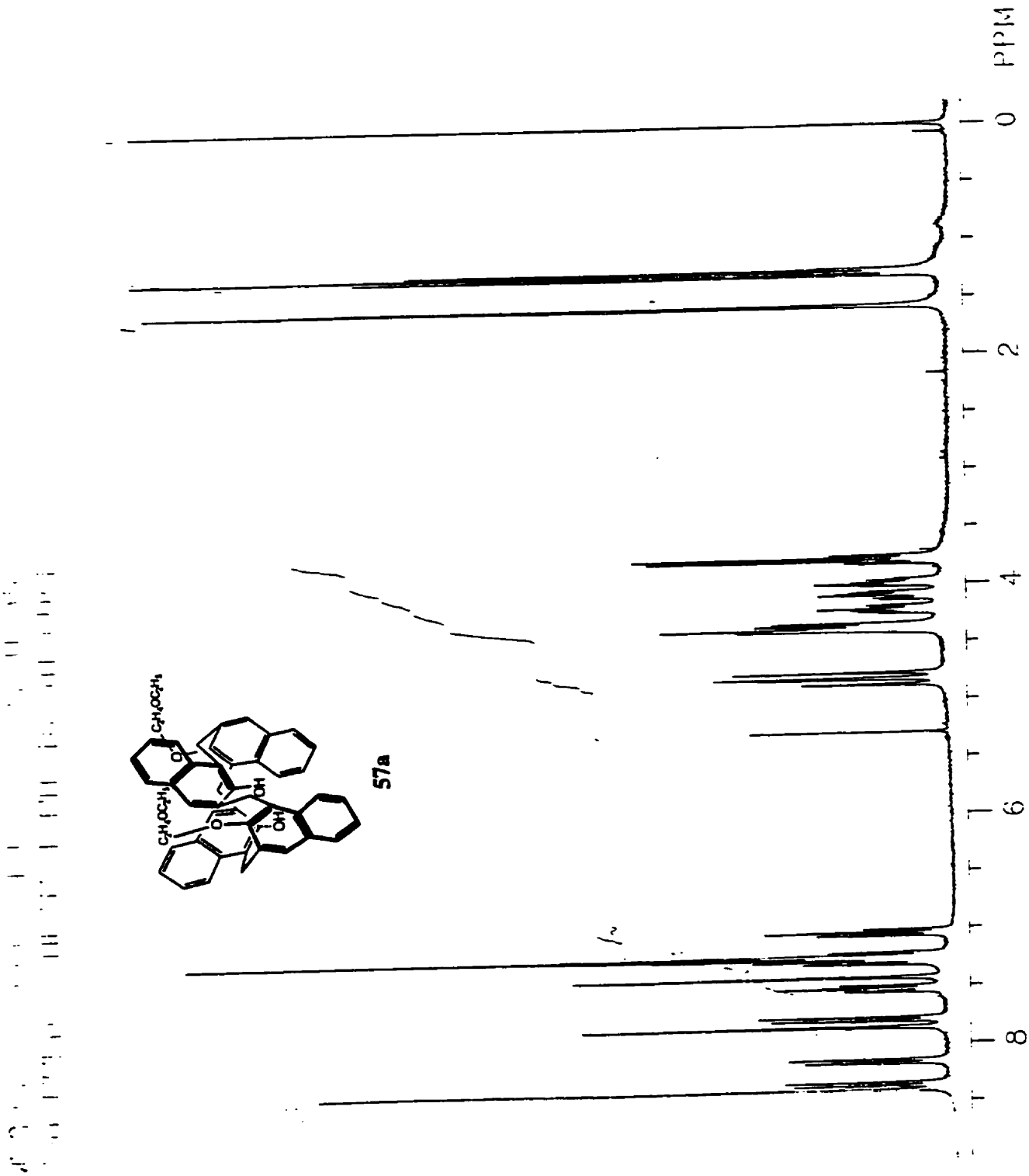
53

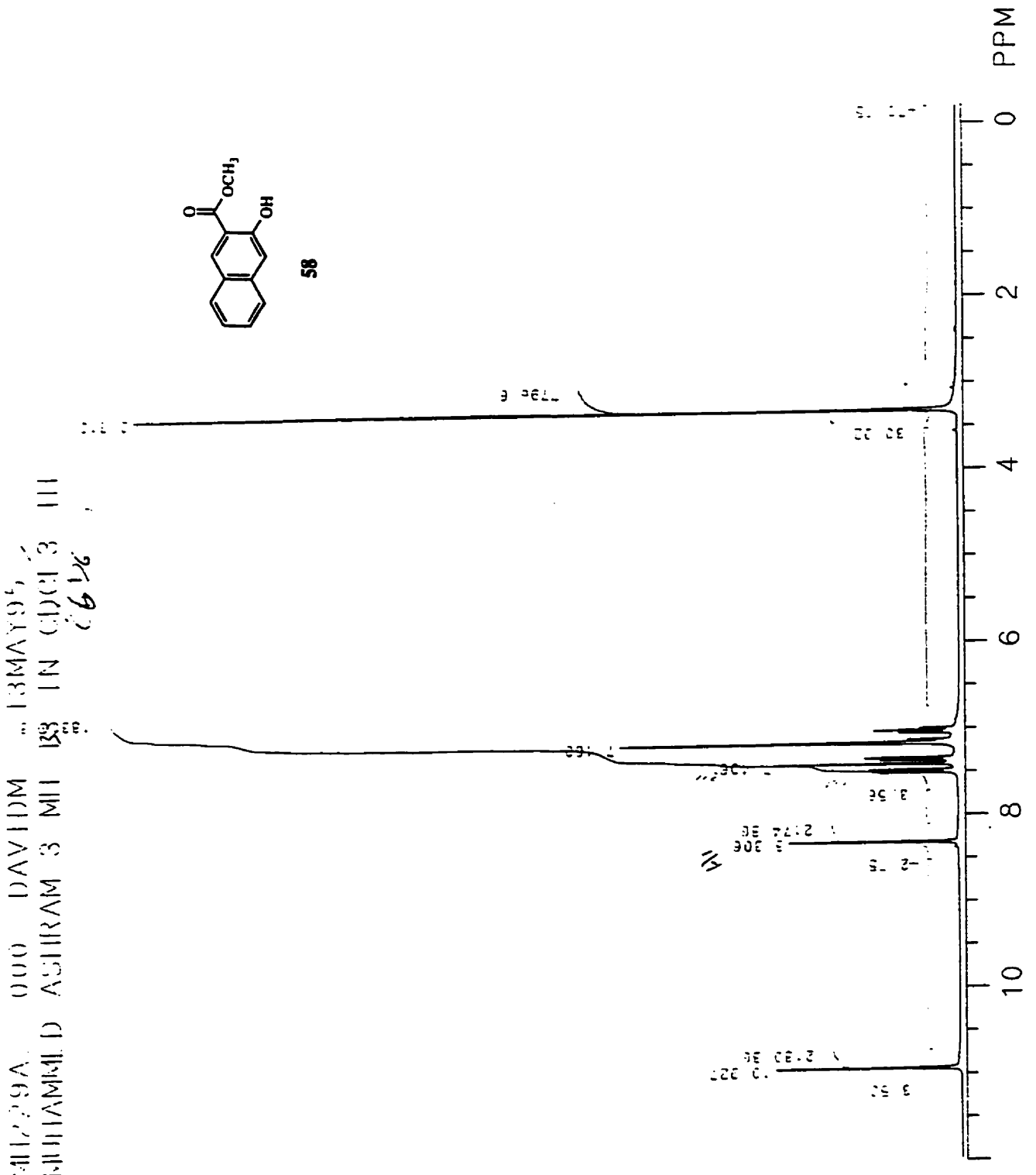

OCH3
C4H9
C4H9
54


OCH3
C4H9
55

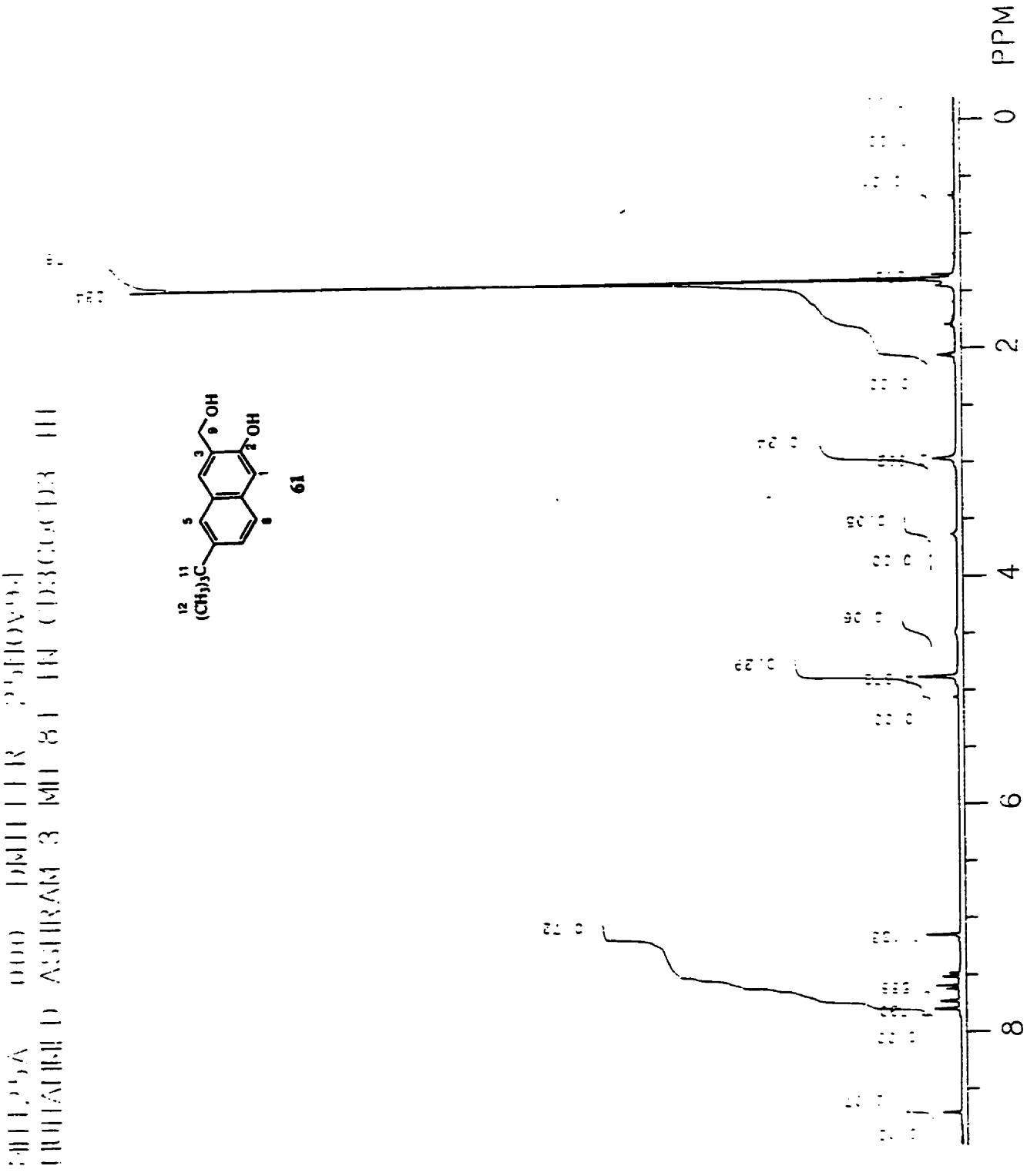

56
PPM
0
2
4
6
8

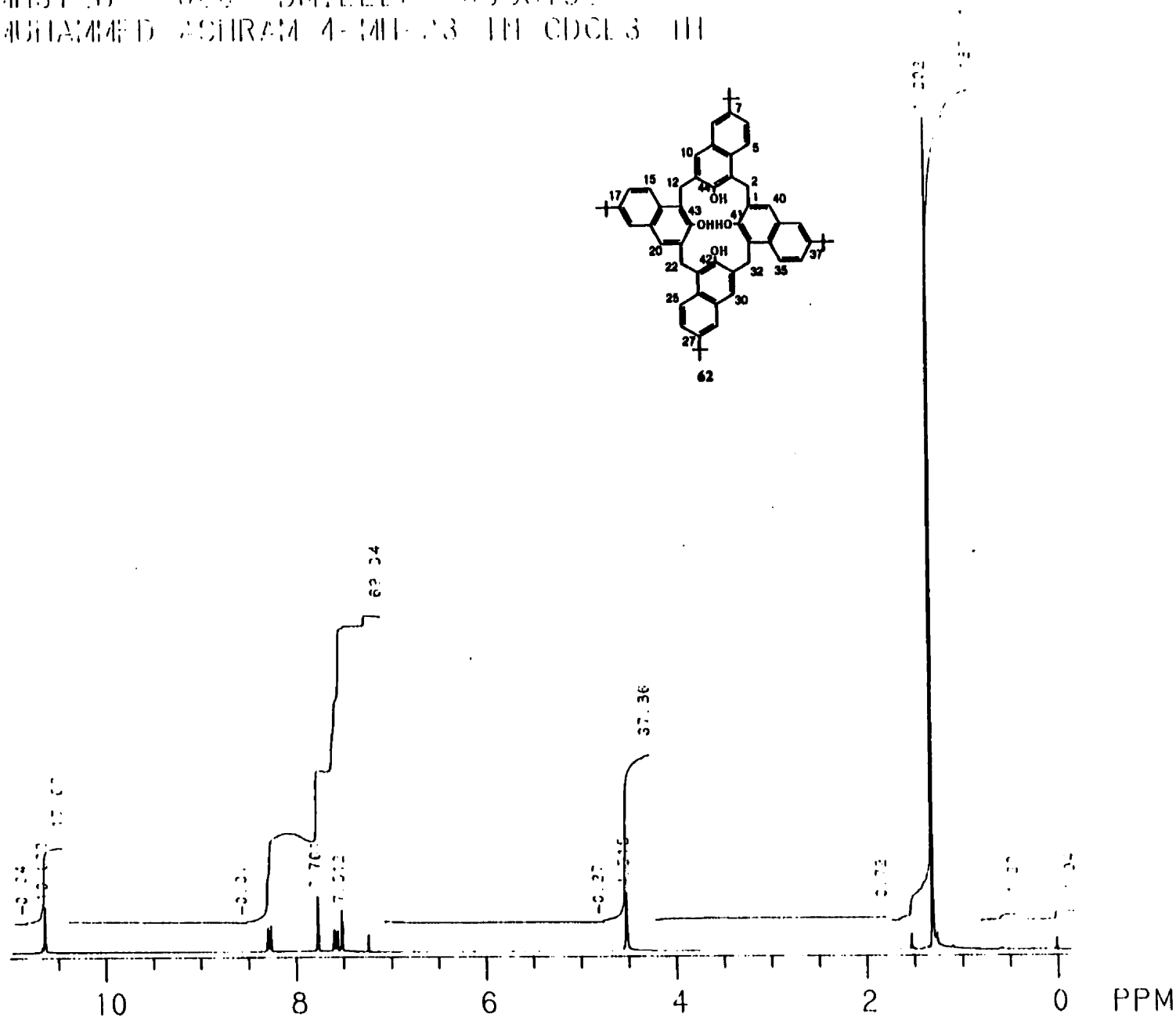

MR295A. 000 DAV1DM 18JUL95
MUHAMMED ASHRAM 3 MR-295 IN CDCL3 III
PPM
0
2
4
6
8
10
12
OH
OH
OHHO

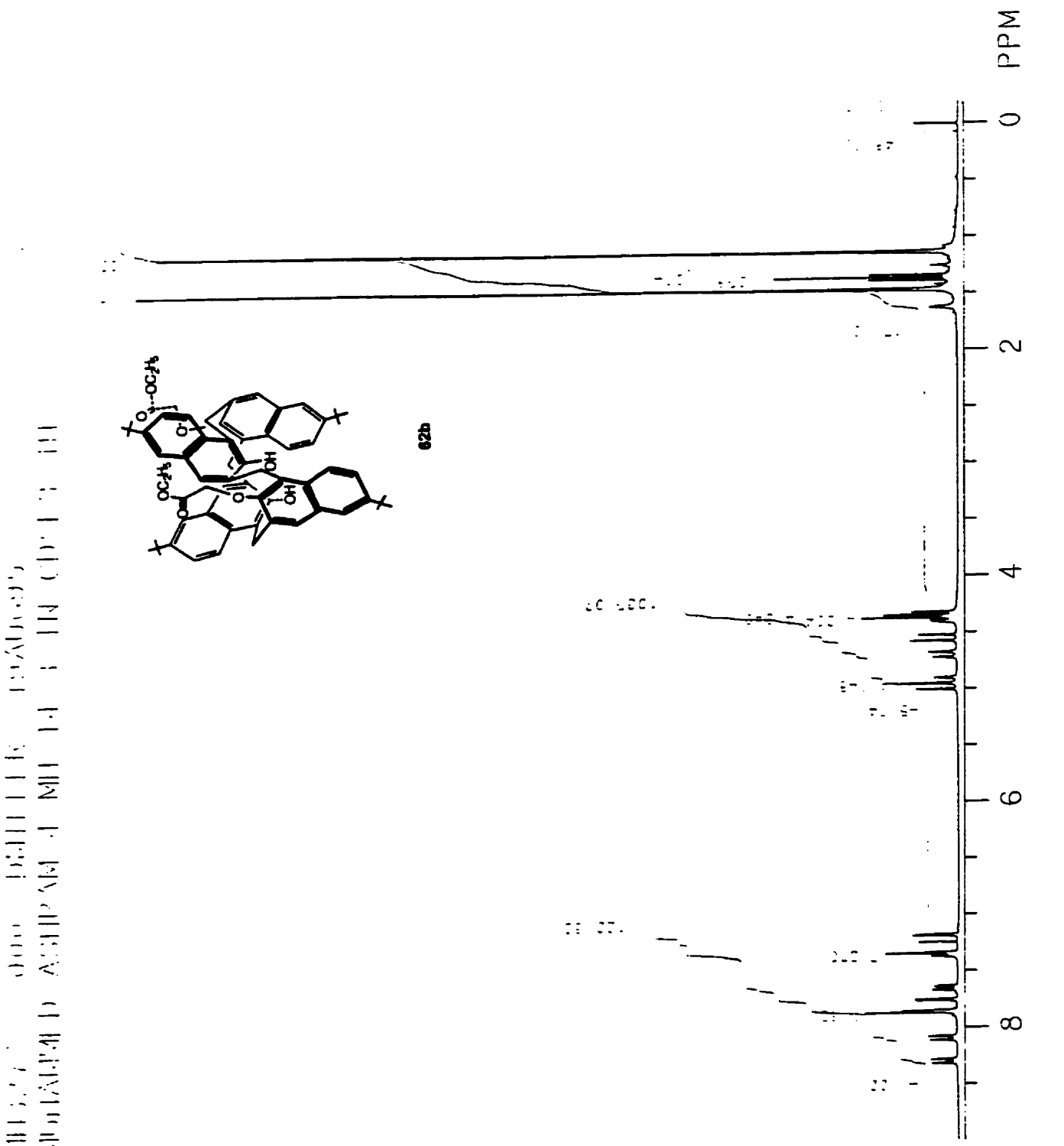

57a
OH
OH
O
O
C6H4OC6H5
C6H4OC6H5
8
6
4
2
0
PPM

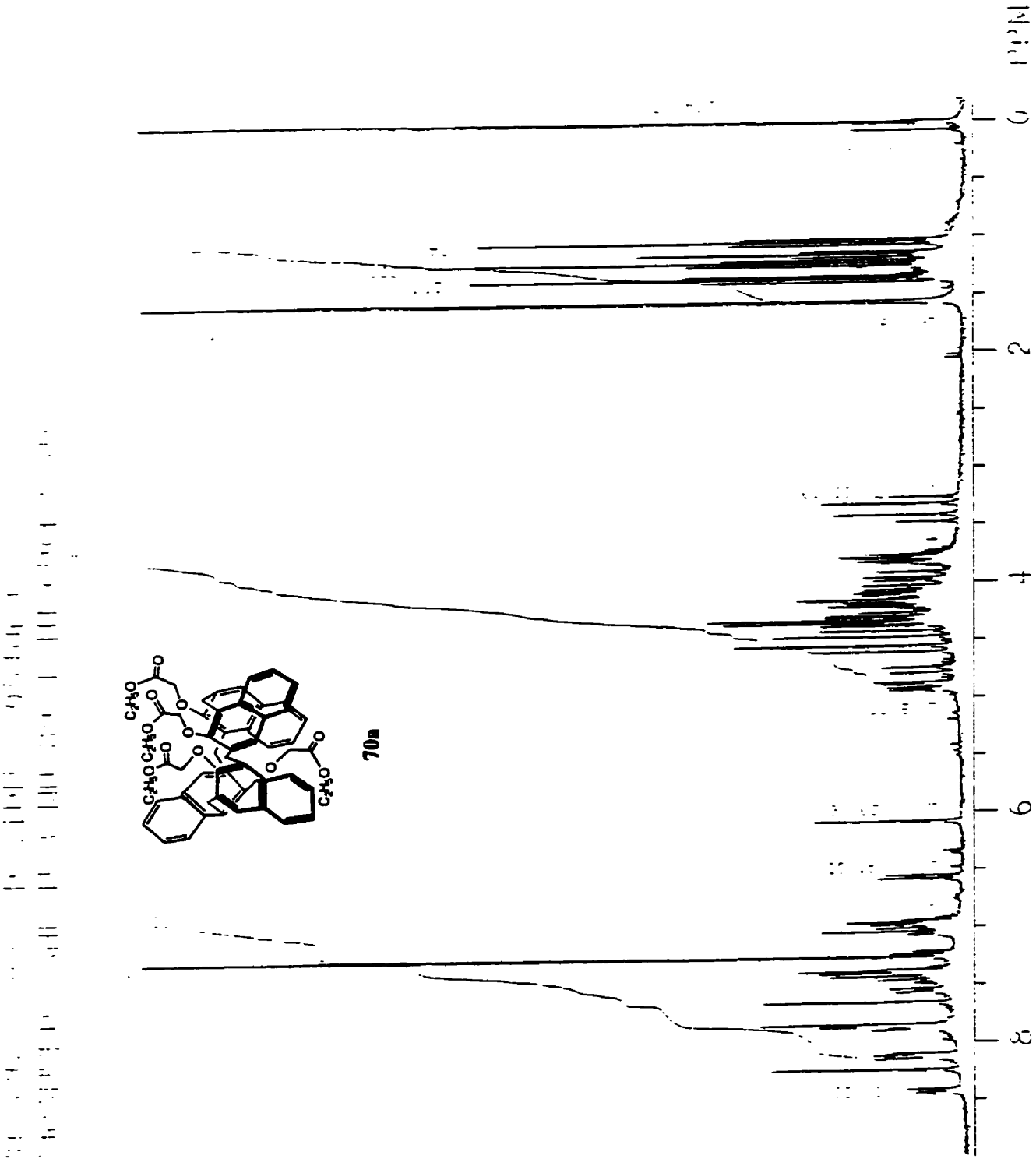

OCH3
OH
58
PPM
0
2
4
6
8
10

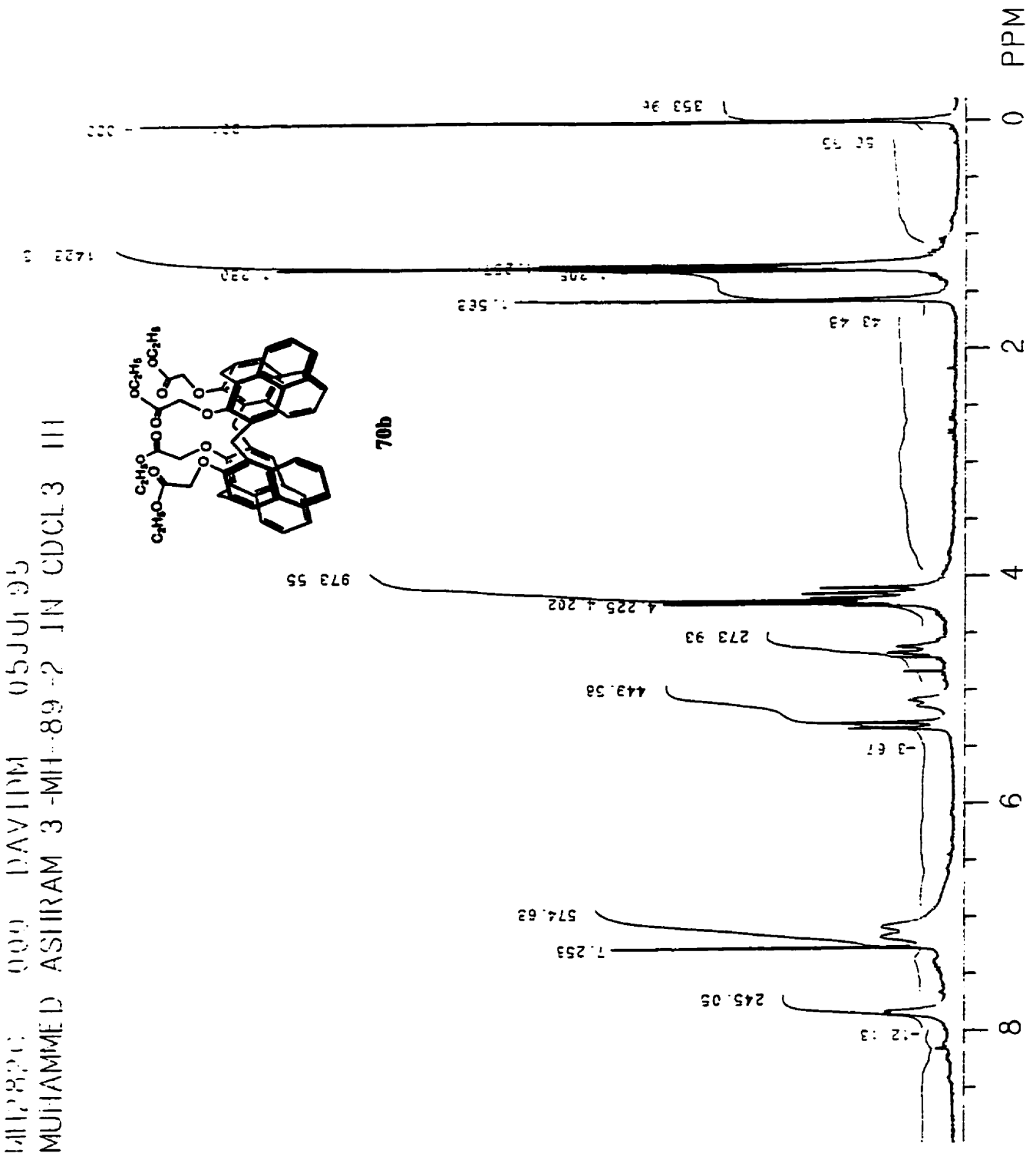
PPM
0
2
4
6
8
10
OCH3
10
OH
(CH3)3C
60

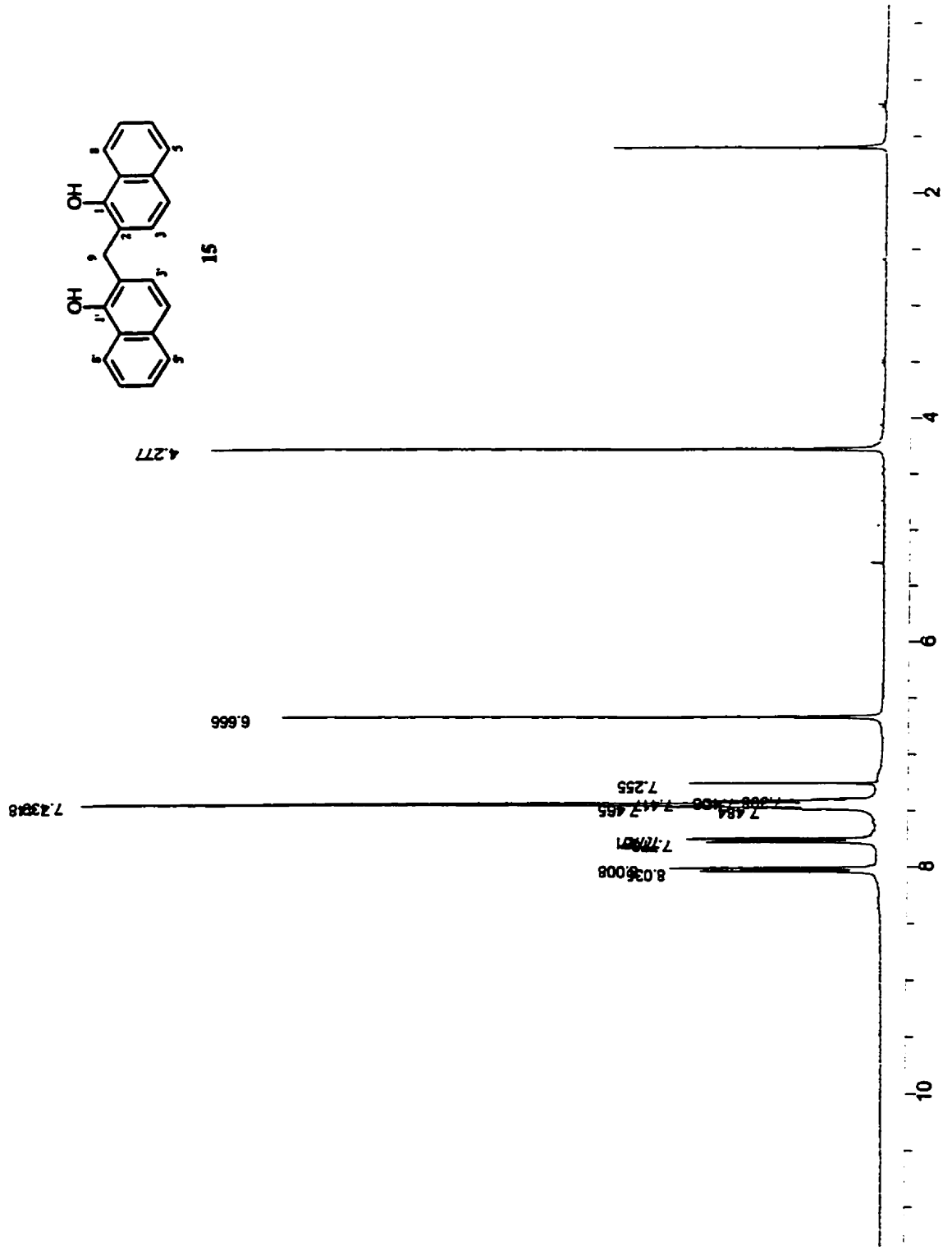

61
PPM
0
2
4
6
8

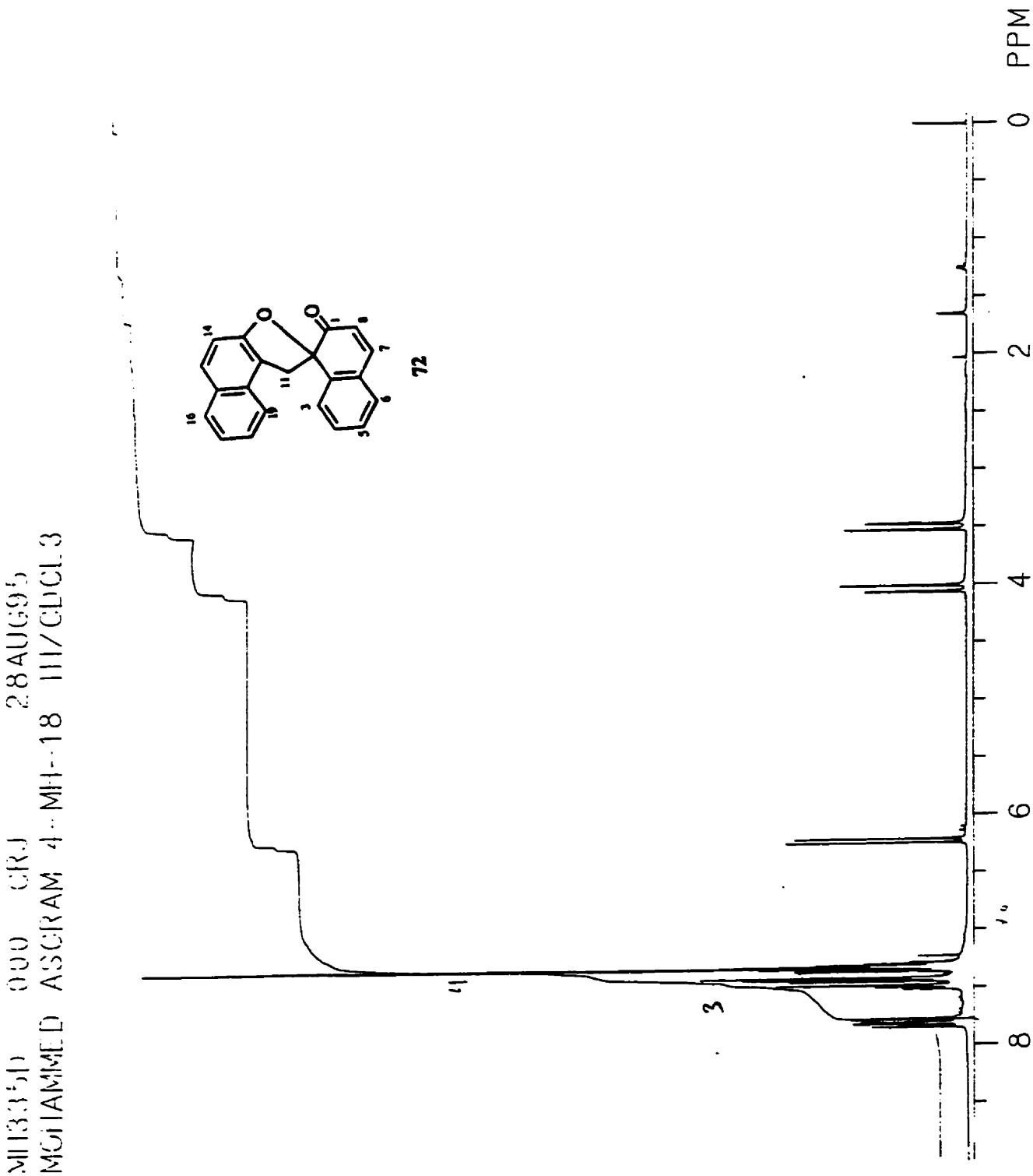

10
8
6
4
2
0
PPM

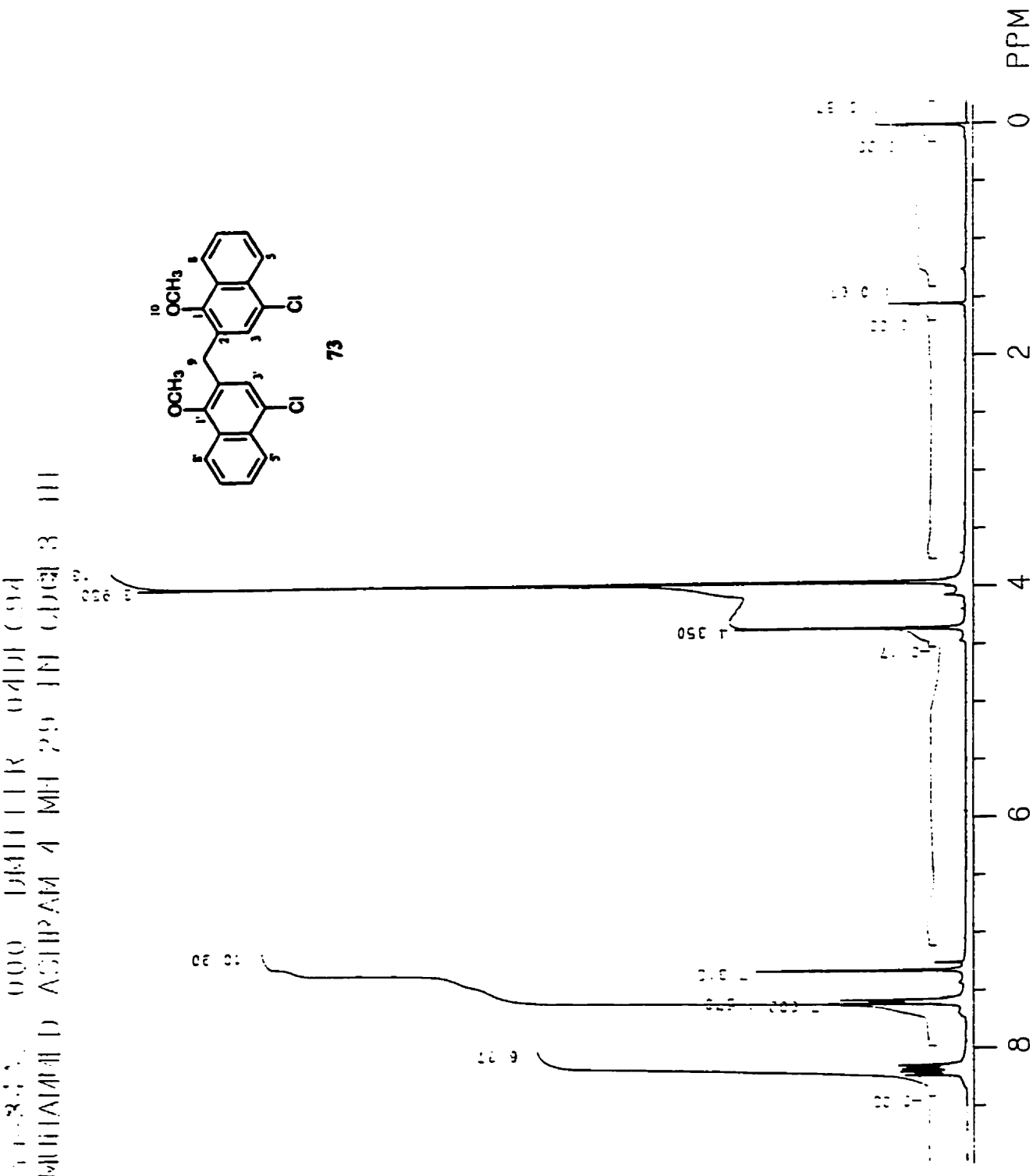

PPM
0
2
4
6
8
62b

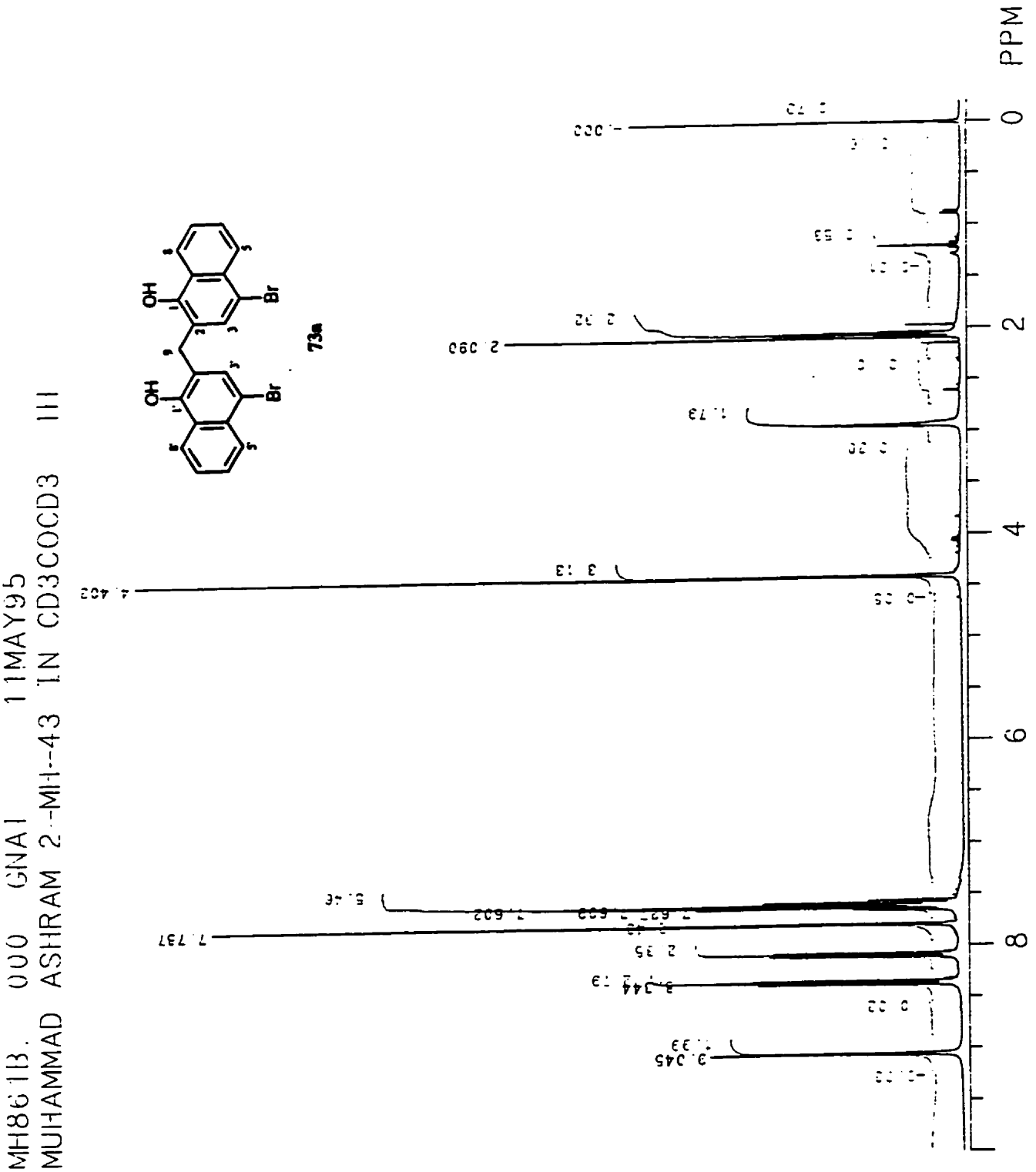

70a
PPM
8
6
4
2
0

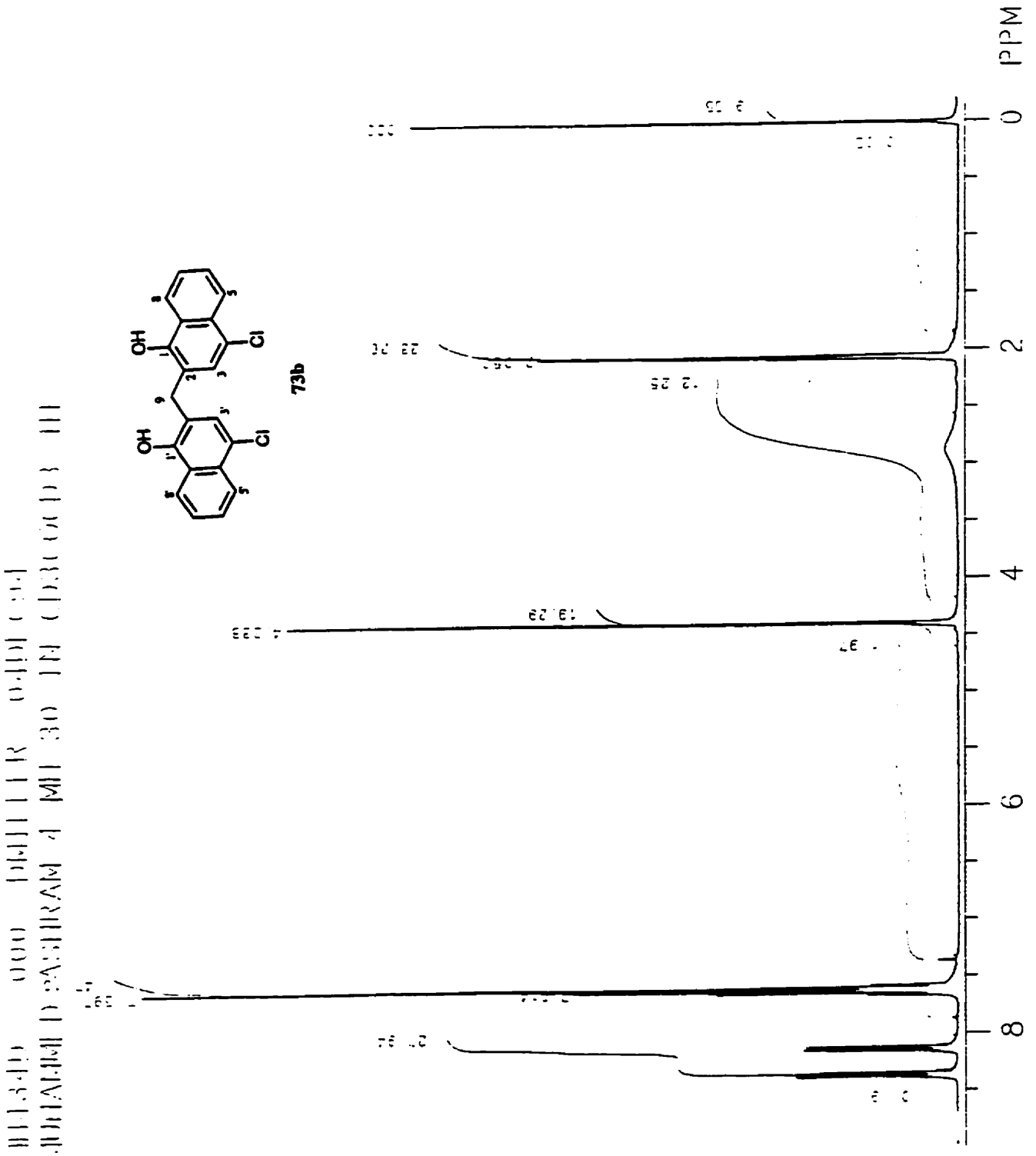

MUHAMMED ASHRAM 3-MH-89-2 IN CDCL3 III
70b
PPM
0
2
4
6
8
973.55
4.225
4.202
273.93
443.58
574.63
7.253
245.05
1.563
4.43
1.353

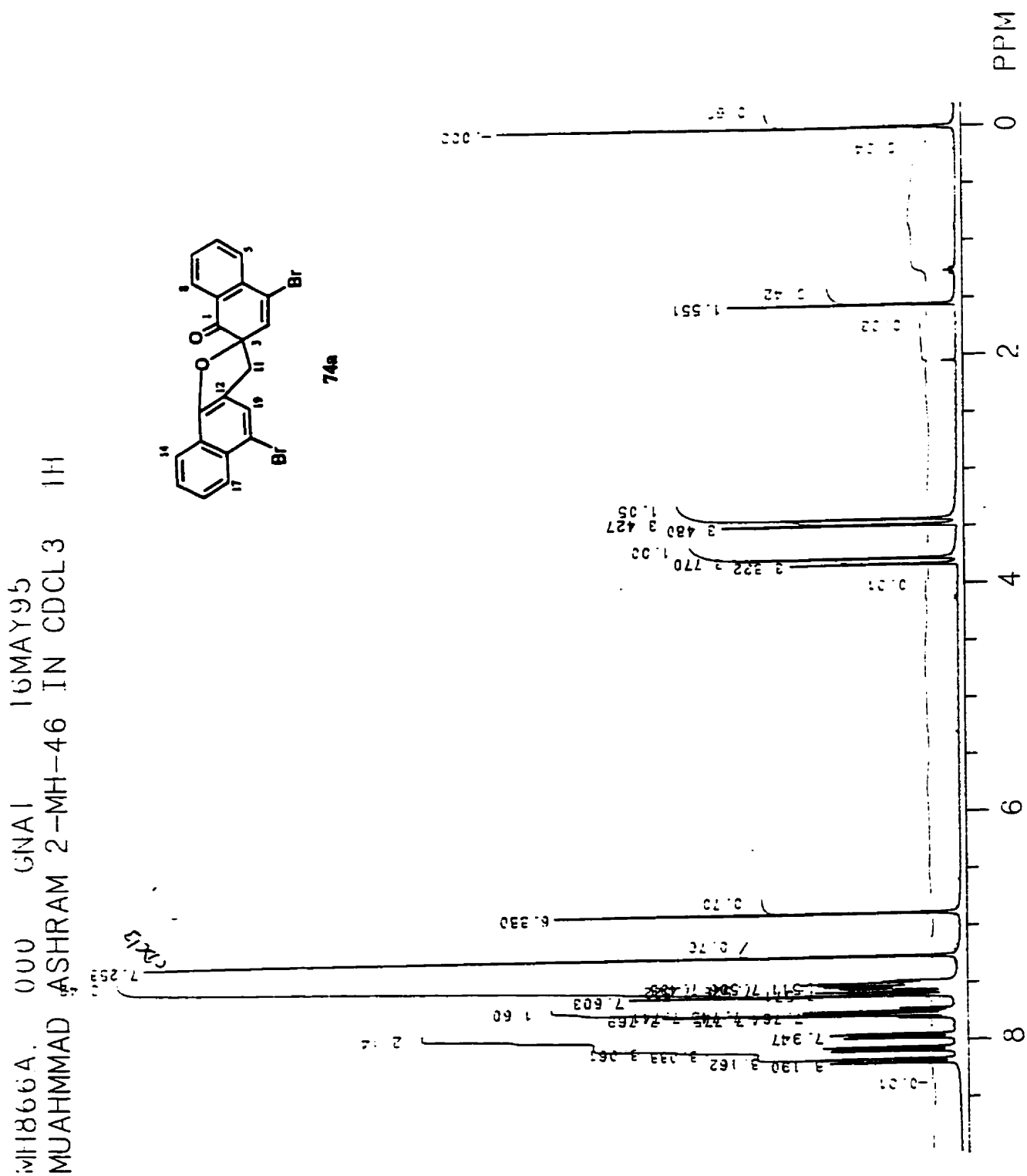

15
OH
OH
8.036
8.006
7.484
7.255
6.666
4.277
2
4
6
8
10

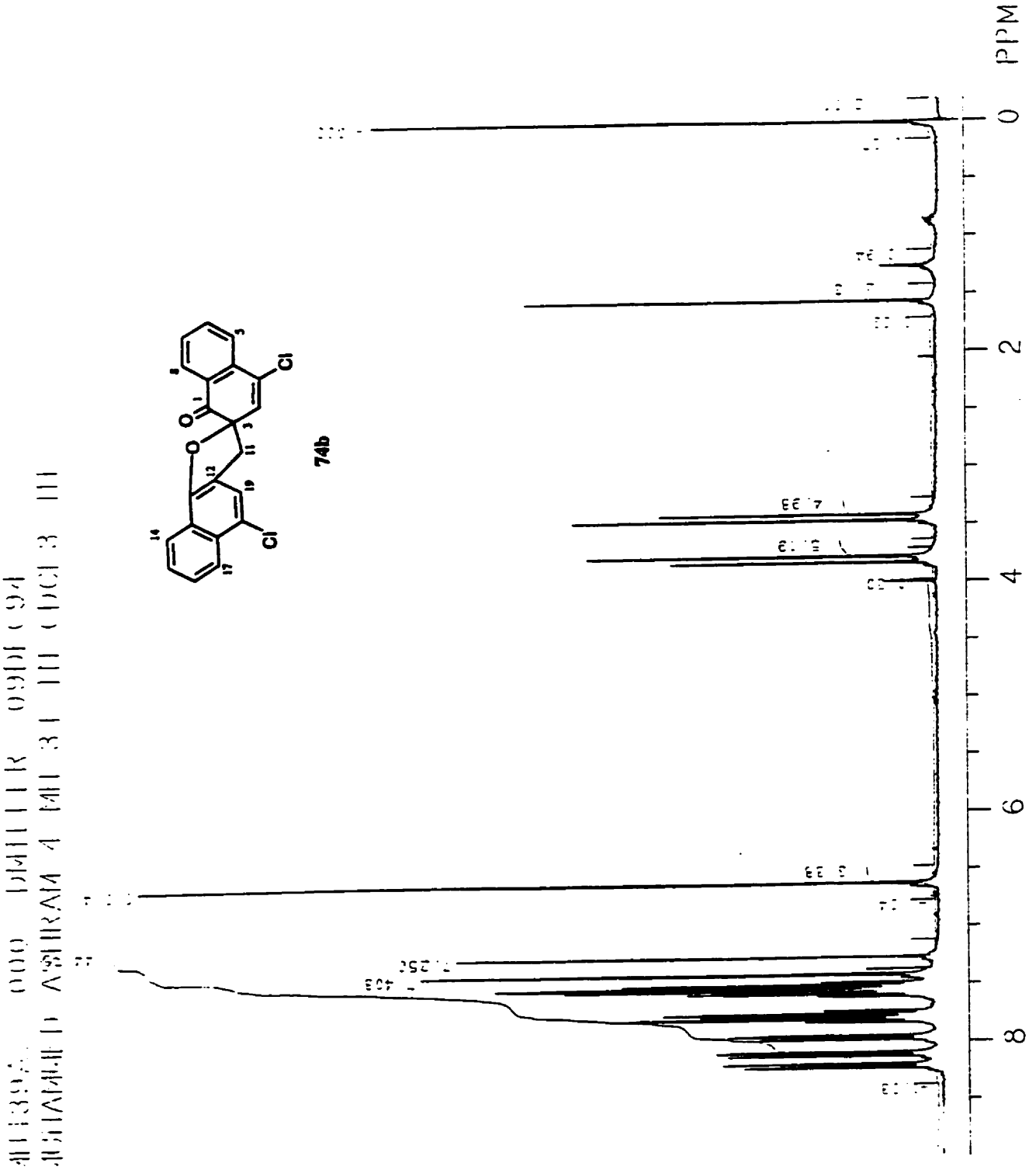

MH33510 000 CRJ 28AUG95
MOHAMMED ASCRAM 4--MH-18 111/CDCL3
72
11
3
8
6
4
2
0
PPM

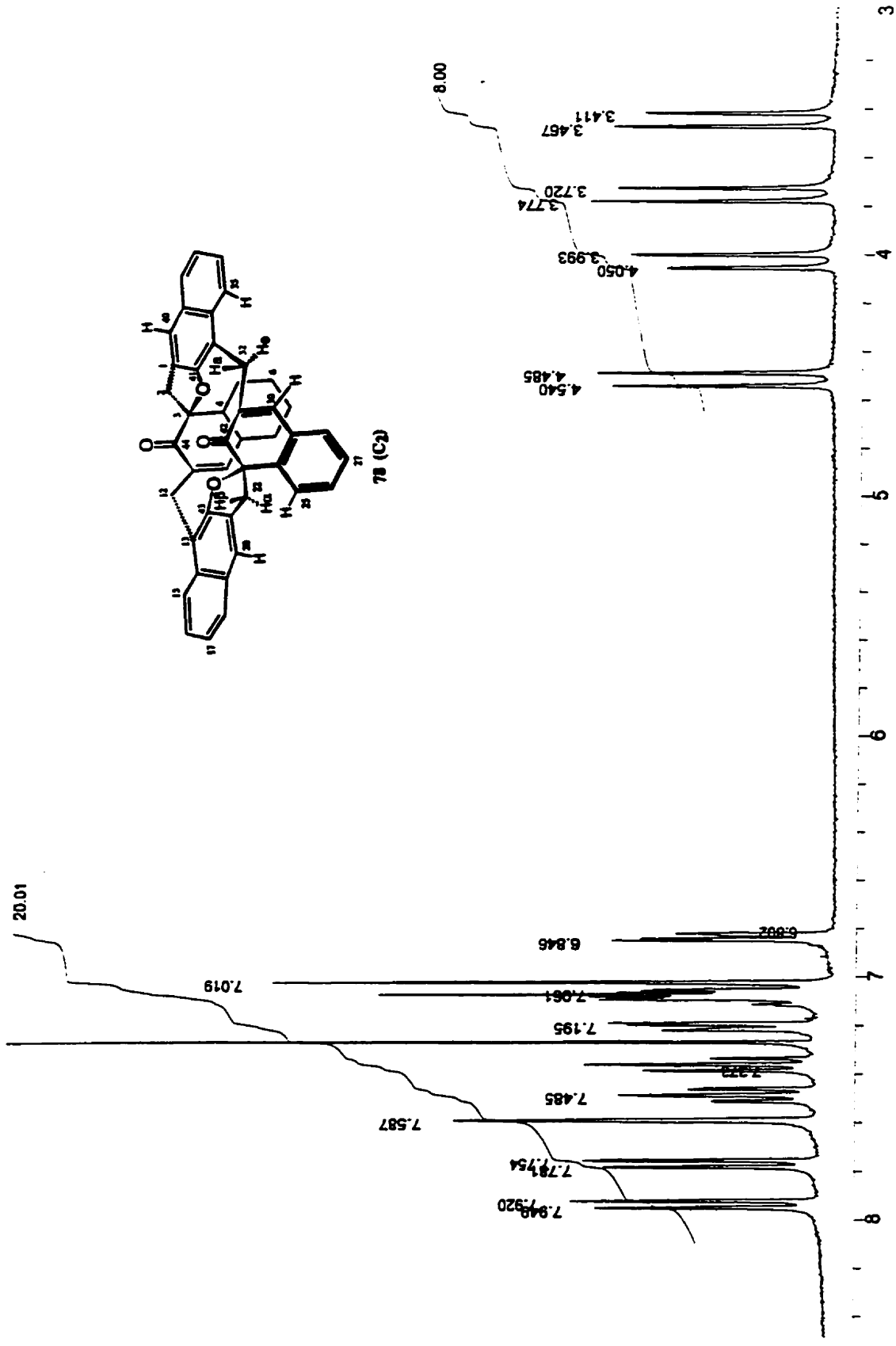

OCH3
Cl
OCH3
Cl
73
PPM
0
2
4
6
8

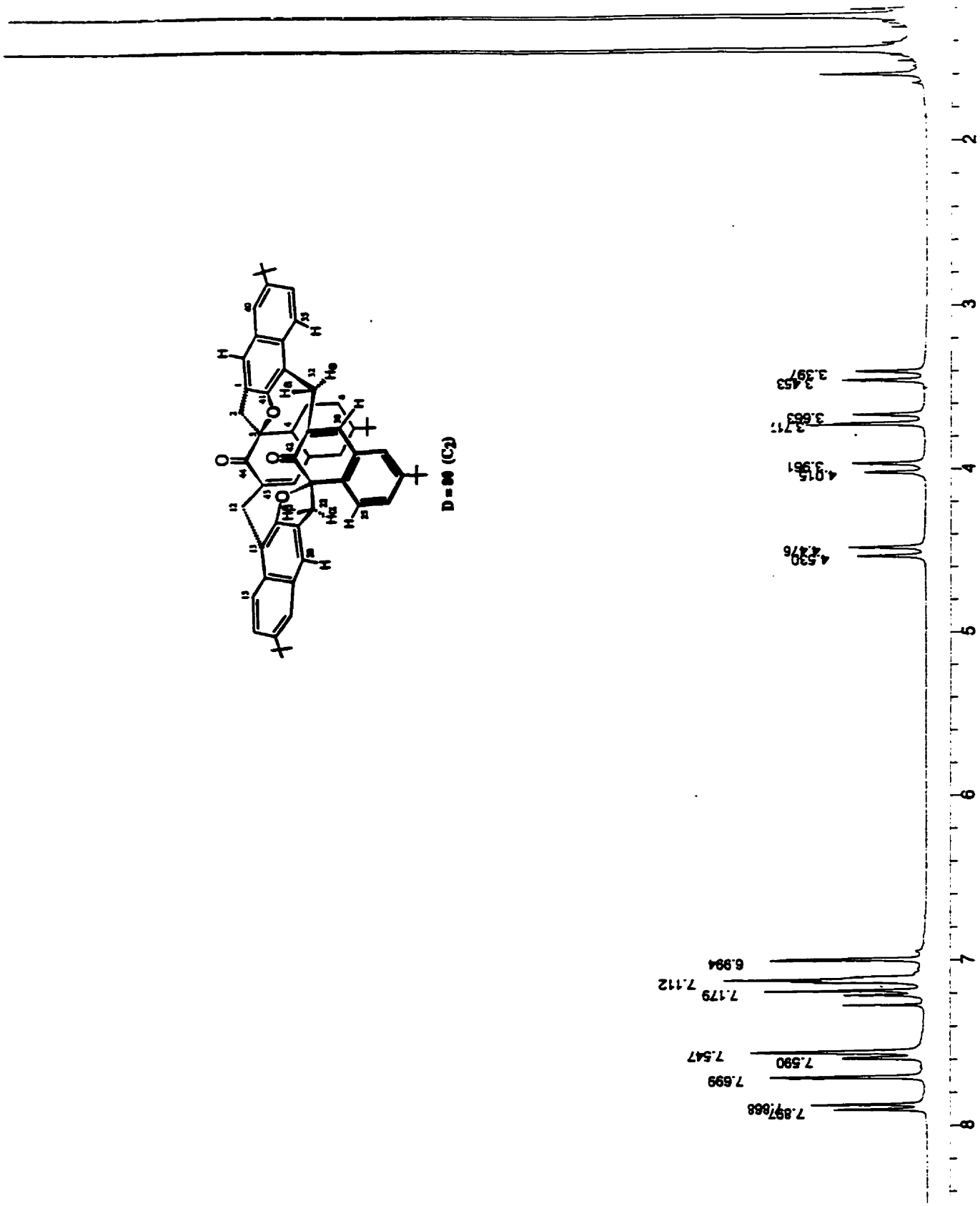

MH8613. 000 GNAI 11MAY95
MUHAMMAD ASHRAM 2-MH-43 IN CD3COCD3 111
OH
Br
OH
Br
73a
PPM
0
2
4
6
8
4.402
3.13
7.737
5.46
3.345
2.090
1.73

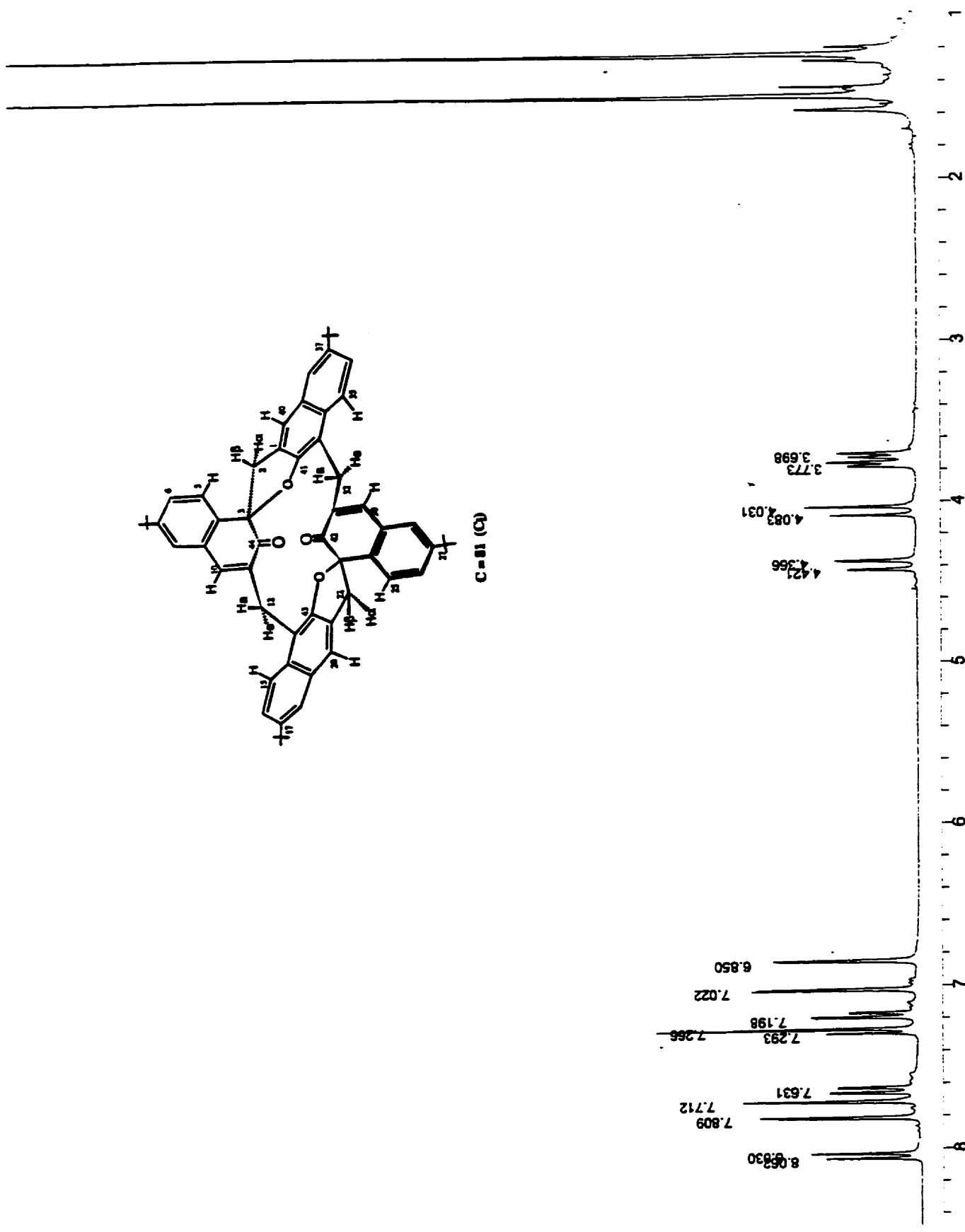

OH
Cl
OH
Cl
73b
PPM
0
2
4
6
8

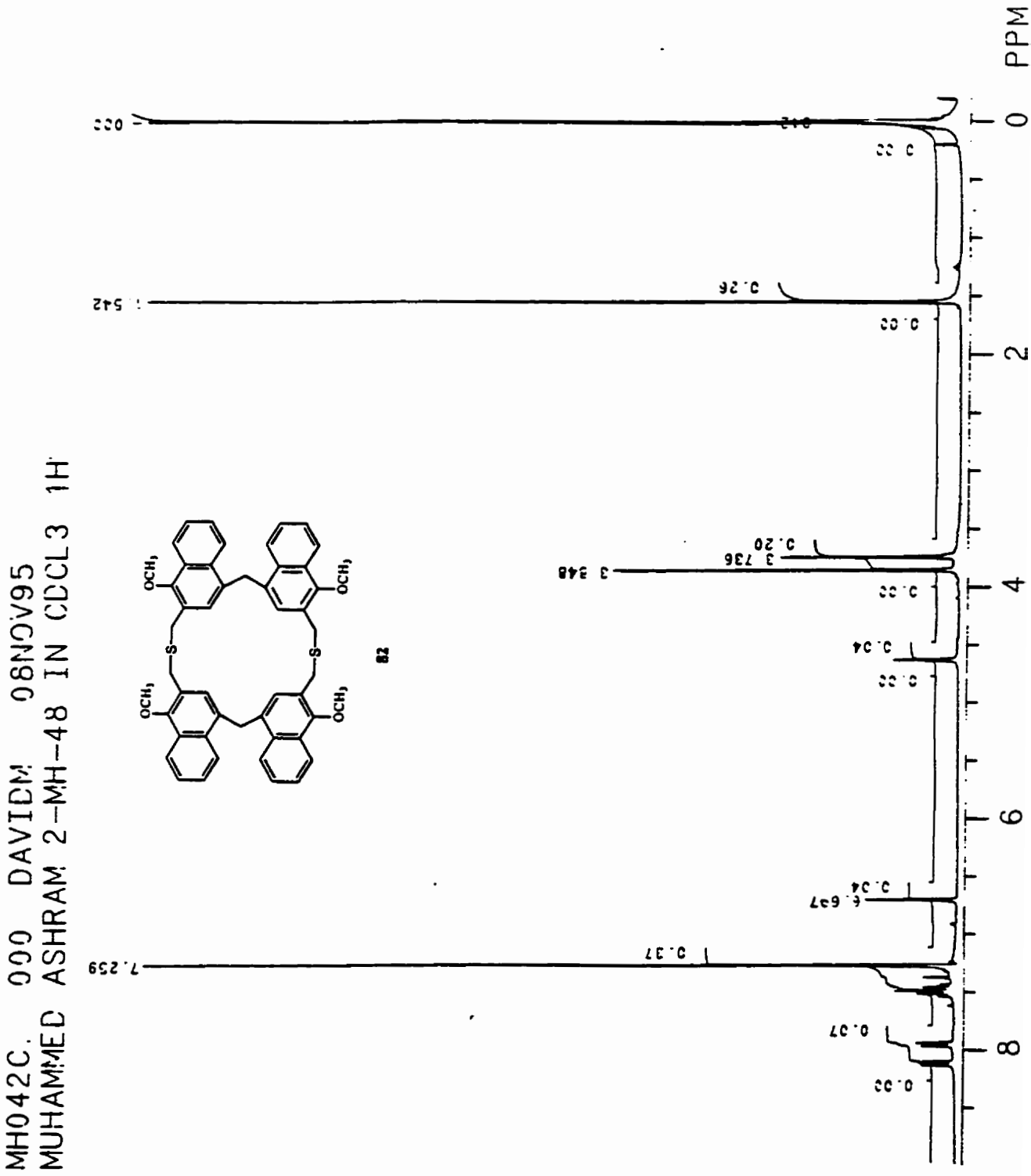

MH8664. 000 GNAI 16MAY95
MUAHMMAD ASHRAM 2-MH-46 IN CDCL3 1H
PPM
0
2
4
6
8
74a
Br
Br
O

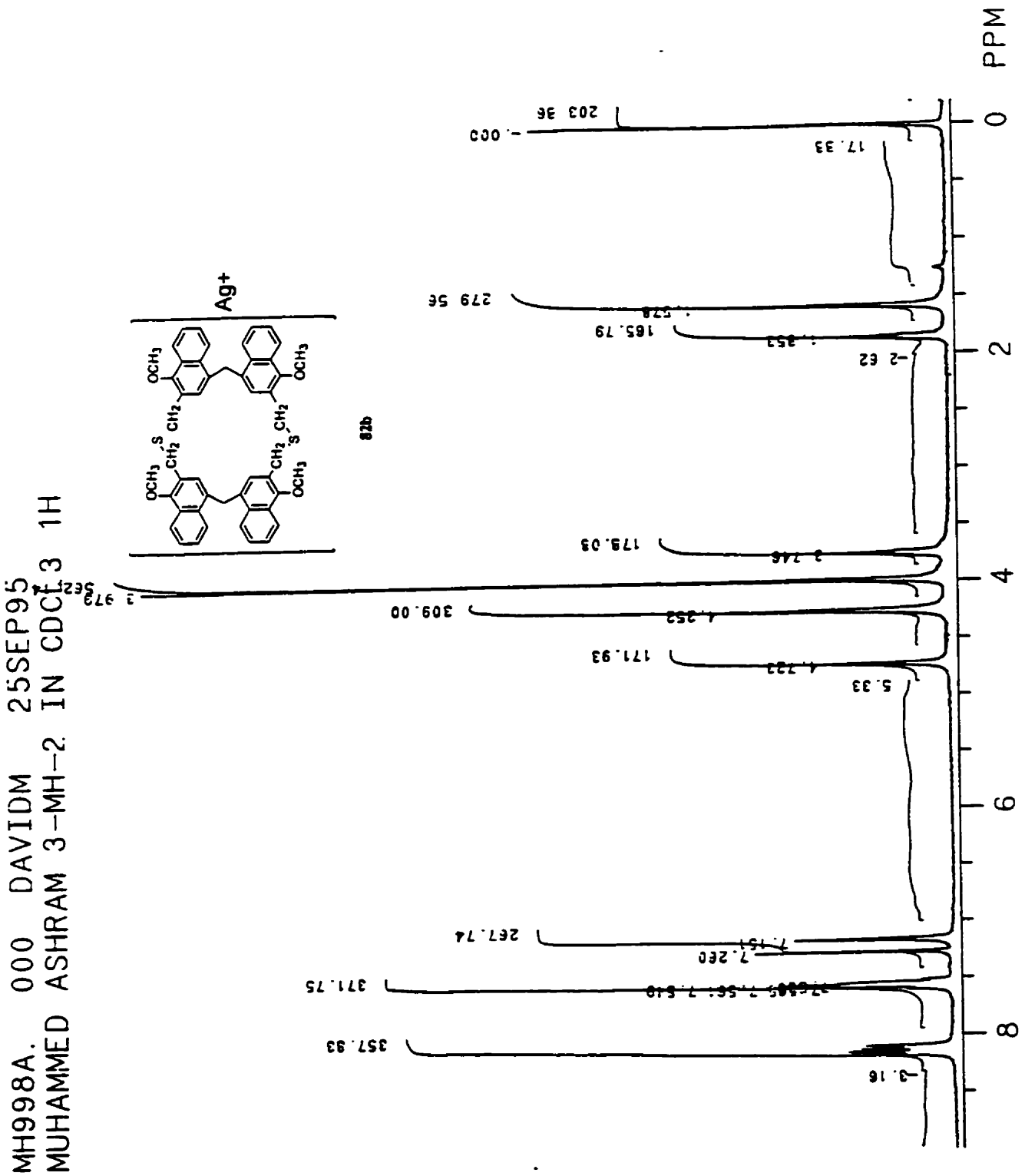

74b
Cl
Cl
O
PPM
0
2
4
6
8

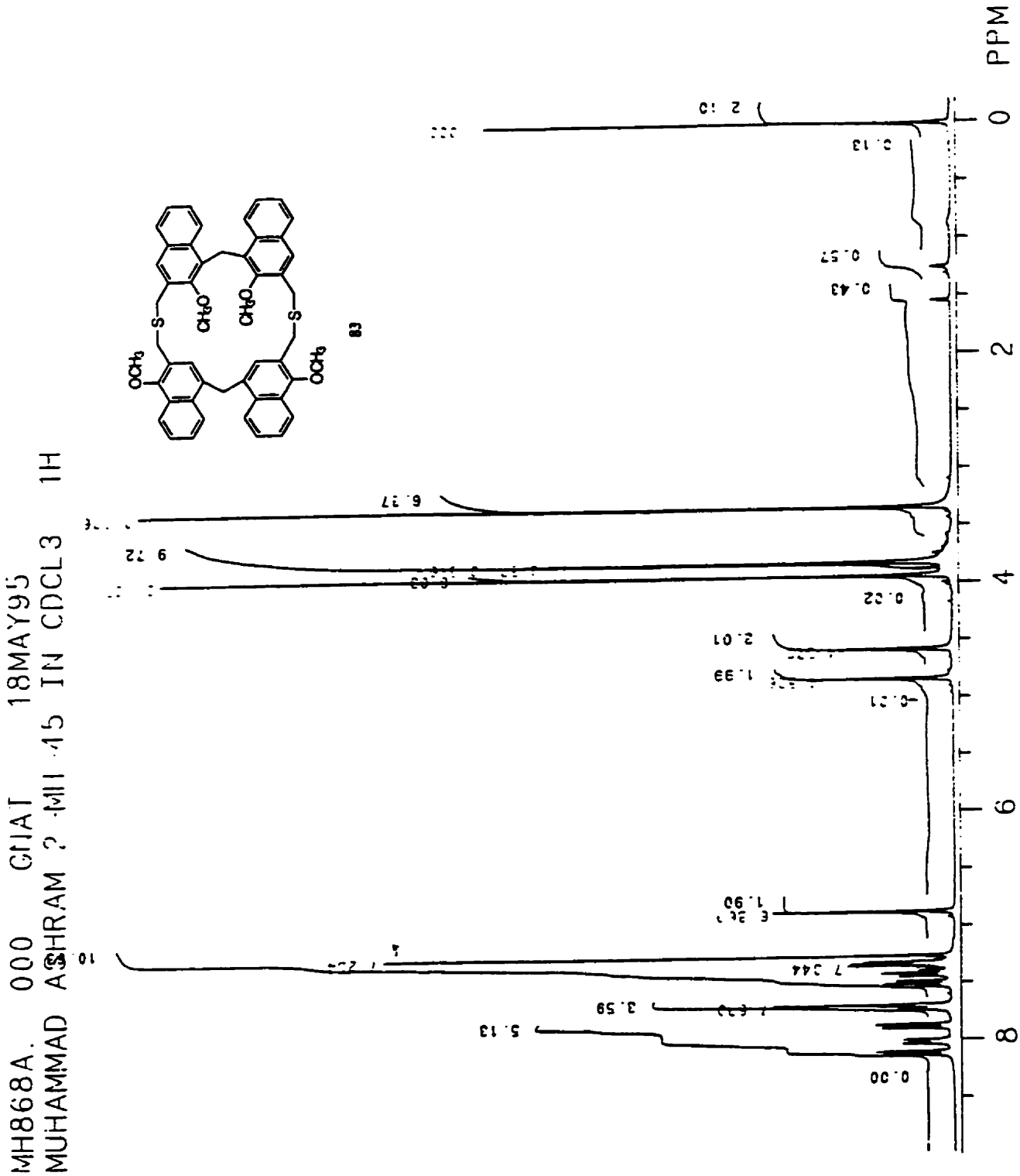

7B (C2)
20.01
8.00
7.949
7.920
7.794
7.754
7.587
7.485
7.373
7.195
7.061
7.019
6.846
6.802
4.540
4.485
4.050
3.993
3.774
3.720
3.467
3.411

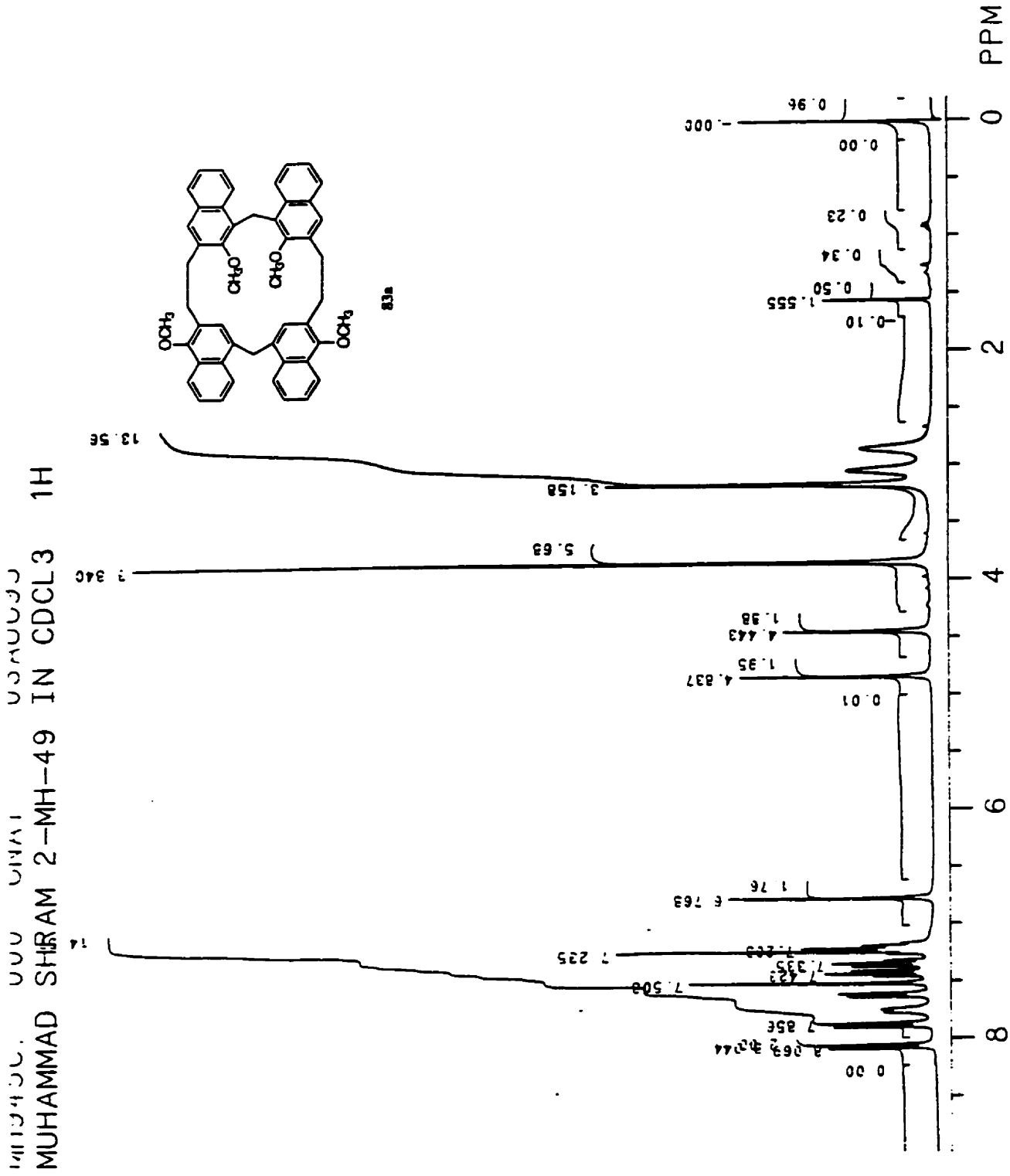

7.897
7.868
7.699
7.590
7.547
7.179
7.112
6.994
4.530
4.476
4.015
3.961
3.717
3.683
3.453
3.397
D = 98 (C2)

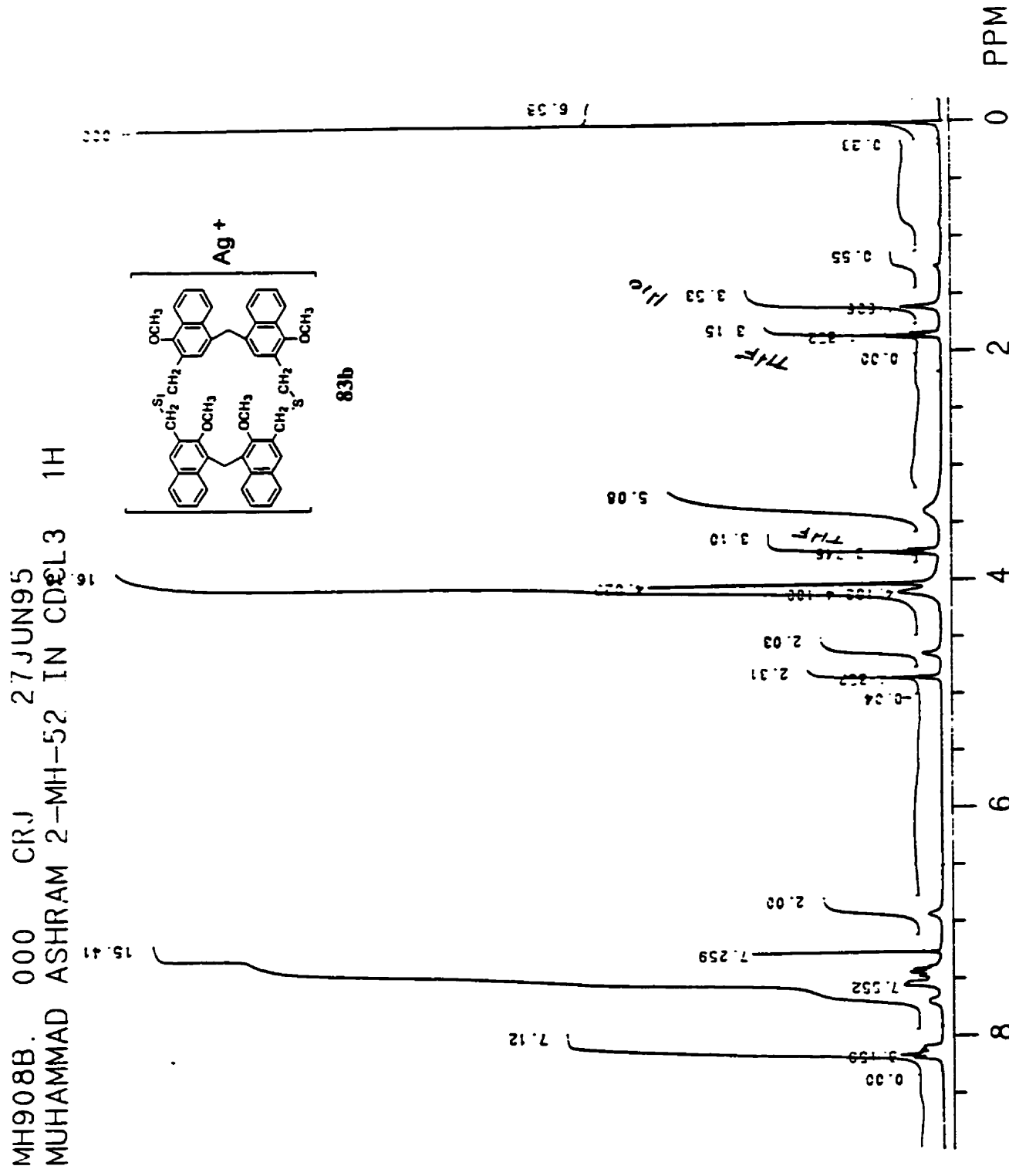

8.062
8.030
7.809
7.712
7.631
7.293
7.266
7.198
7.022
6.850
4.421
4.366
4.083
4.031
3.773
3.698
C-81 (C)

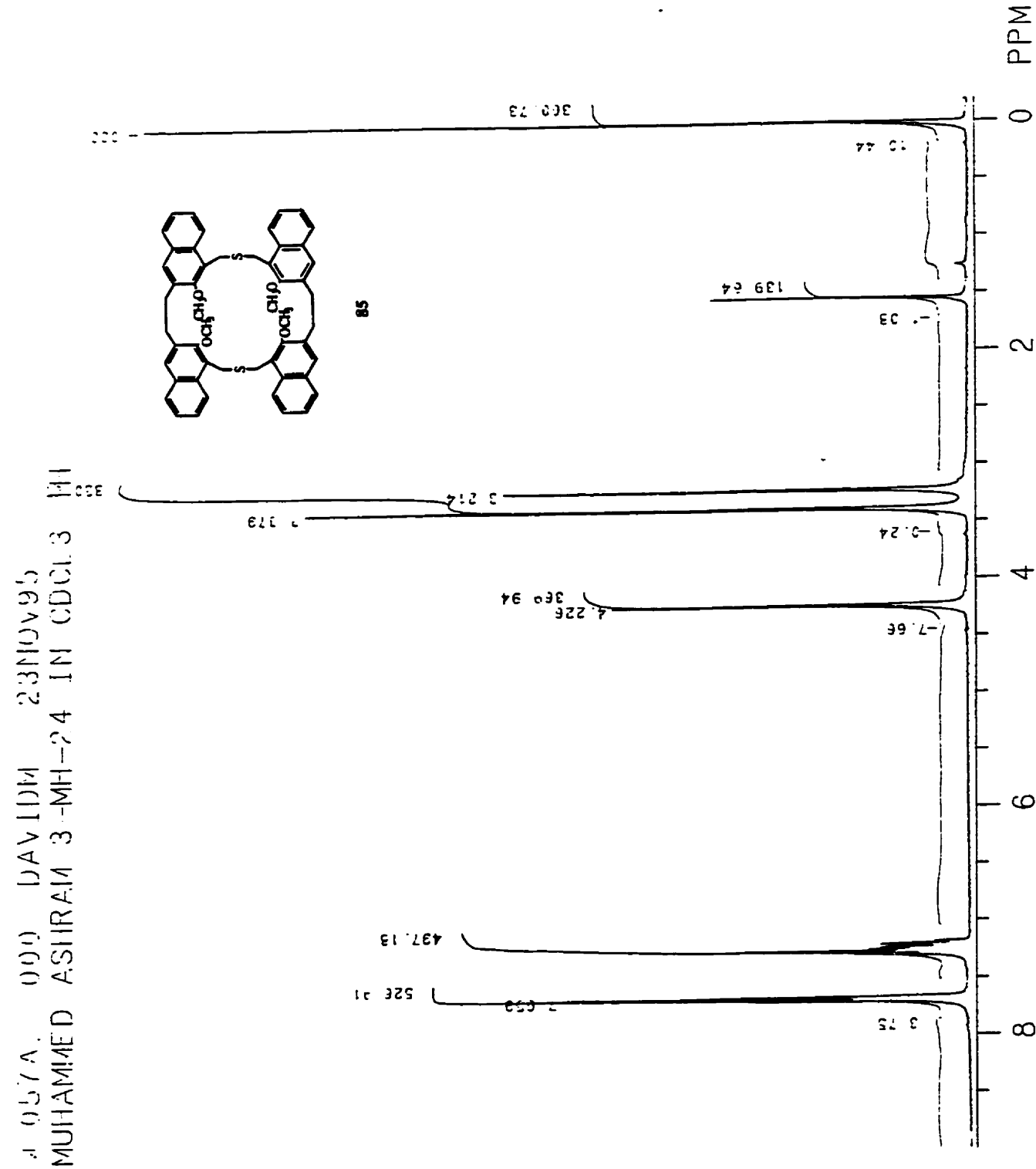

MH042C. 000 DAVIDM 08NOV95
MUHAMMED ASHRAM 2-MH-48 IN CDCL3 1H
PPM
0
2
4
6
8
7.259
5.42
3.736
3.348
6.637
0.37
0.26
0.20
0.04
0.07
OCH3
S
B2

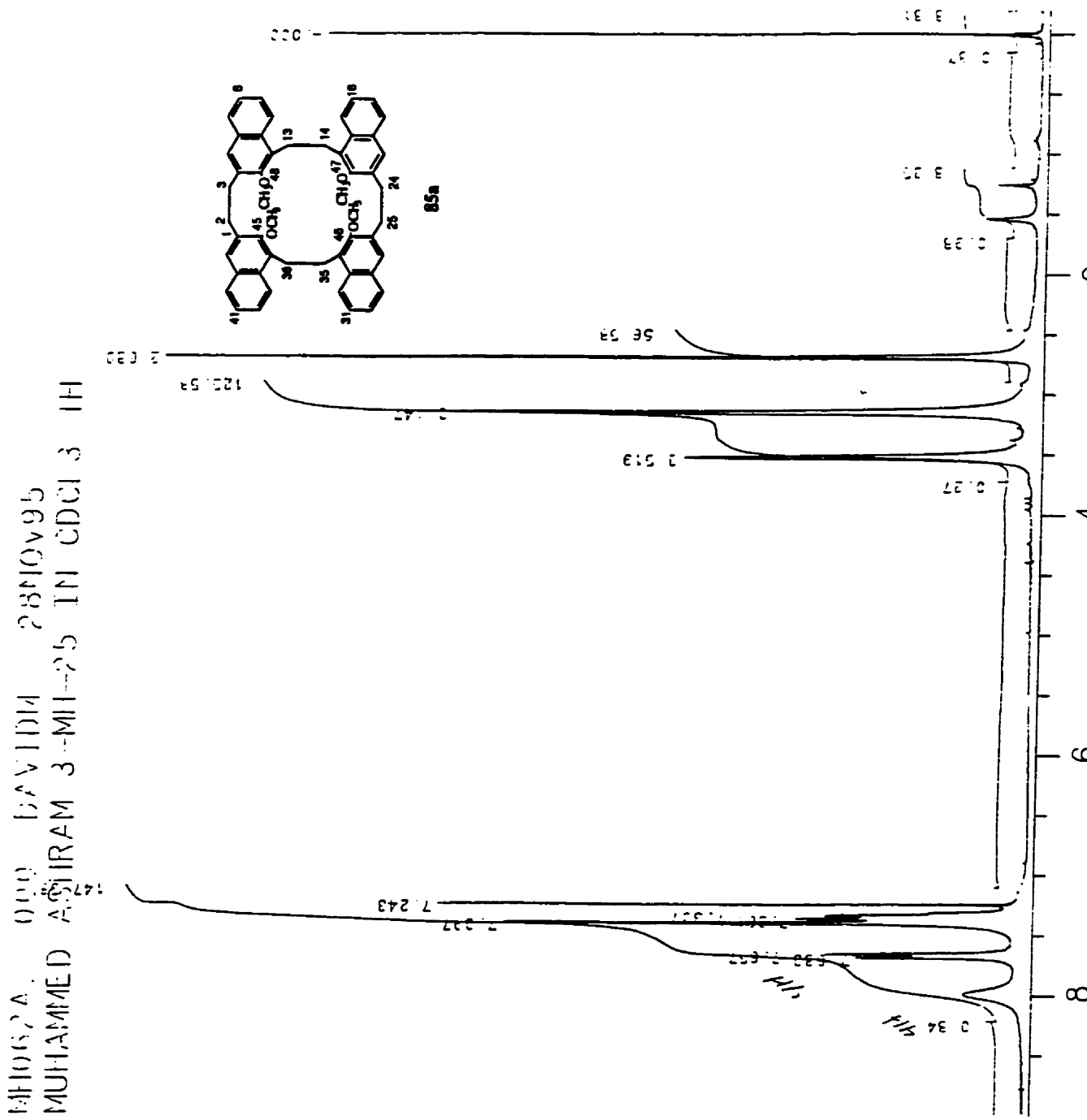

MH998A. 000 DAVIDM 25SEP95
MUHAMMED ASHRAM 3-MH-2 IN CDCL3 1H
PPM
0
2
4
6
8
Ag+
OCH3
CH2
S
82b
203.36
17.33
279.56
165.79
2.62
179.03
3.746
309.00
4.252
171.93
4.723
5.33
267.74
7.260
371.75
3.16
357.93

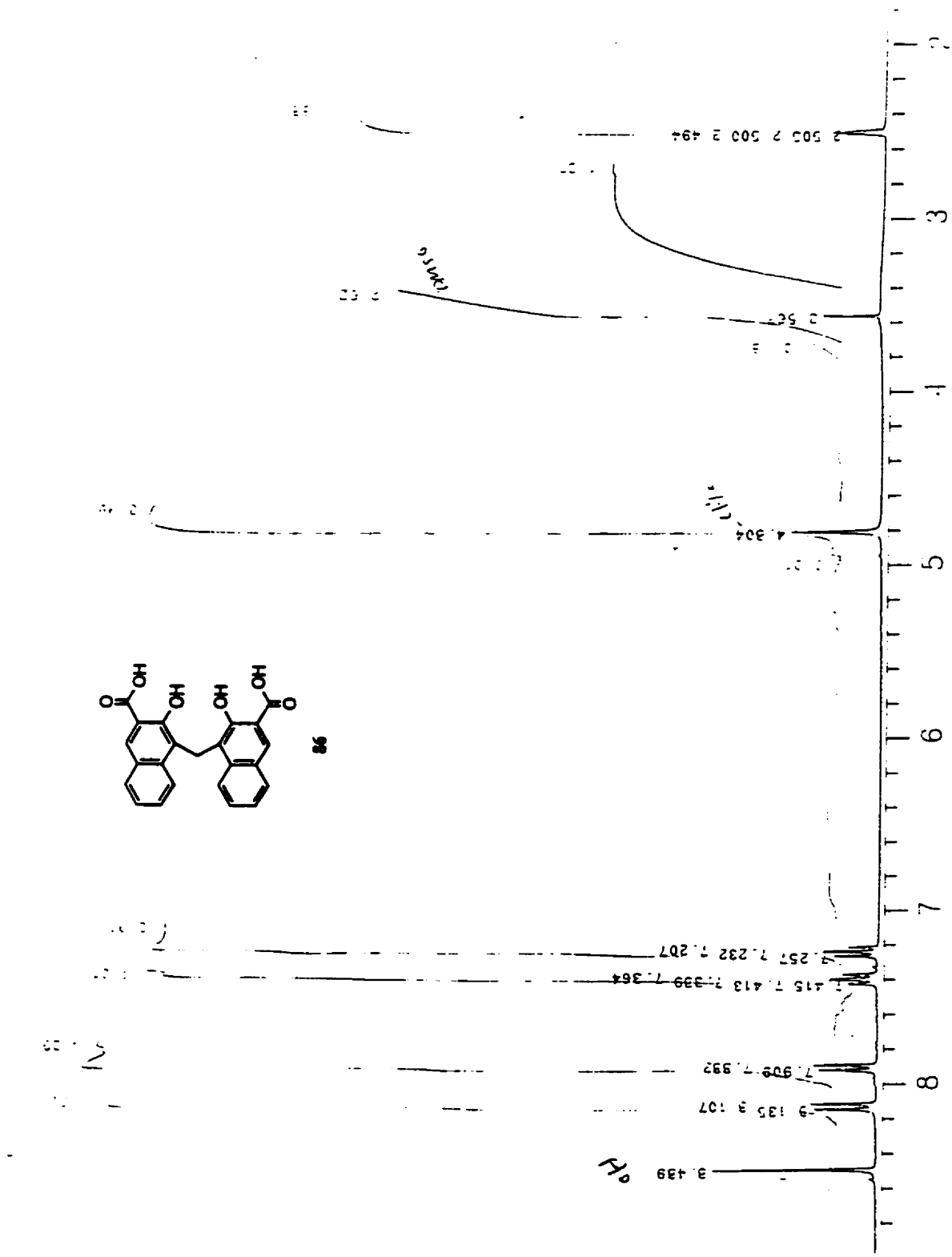

MH868A. 000 CHAT 18MAY95
MUHAMMAD ASHRAM 2 MI 15 IN CDCL3 1H
PPM
0
2
4
6
8
10
0.00
5.13
3.59
7.344
1.90
6.21
1.39
2.01
0.02
9.72
6.37
2.10
0.13
0.57
0.43
OCH3
CH2O
S

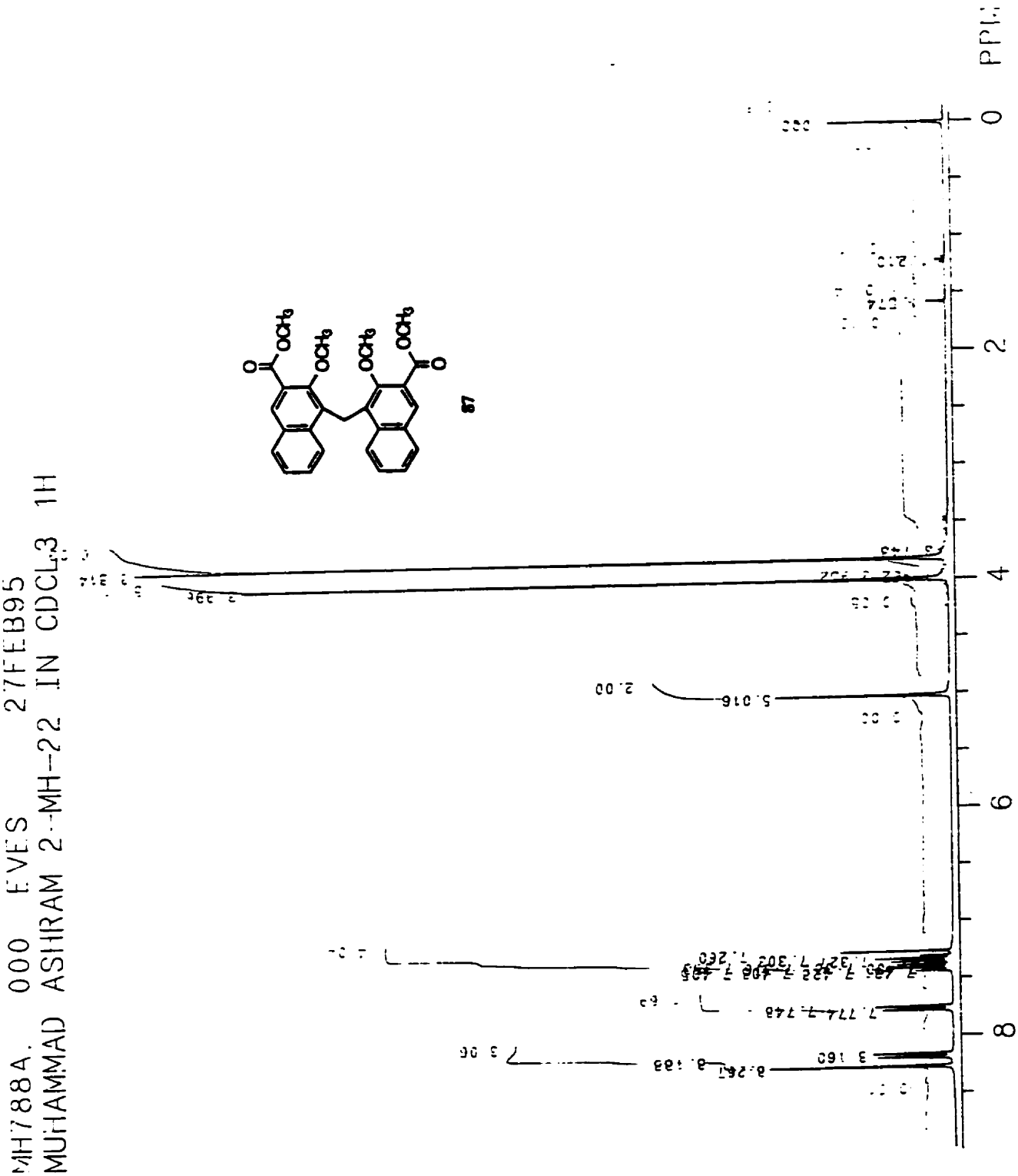

MUHAMMAD SHARAM 2-MH-49 IN CDCL3 1H
PPM
0
2
4
6
8
83a
OCH3
CH2O
CH2O
OCH3
13.56
3.158
5.63
3.34C
1.38
4.443
1.35
4.837
0.01
1.76
6.763
7.235
7.508
7.856
0.30
0.96
0.00
0.23
0.34
0.50
1.555
0.10

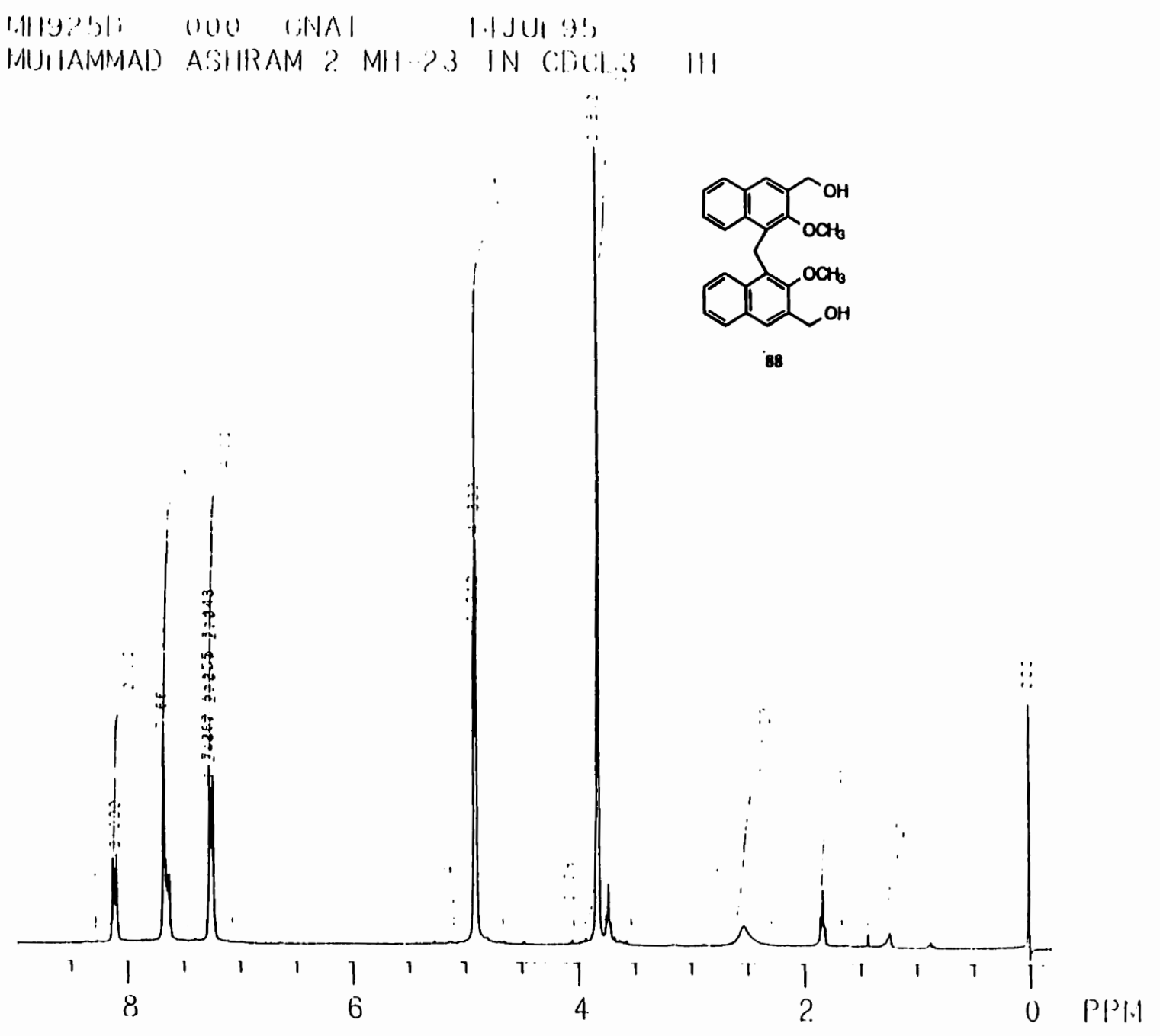

MH908B. 000 CRJ 27JUN95
MUHAMMAD ASHRAM 2-MH-52 IN CDCL3 1H
Ag+
OCH3
CH2
Si
S
83b
PPM
0
2
4
6
8
16.00
15.41
7.259
7.552
7.12
2.00
2.03
2.31
5.08
3.10
3.15
3.33
0.33
0.55
0.00

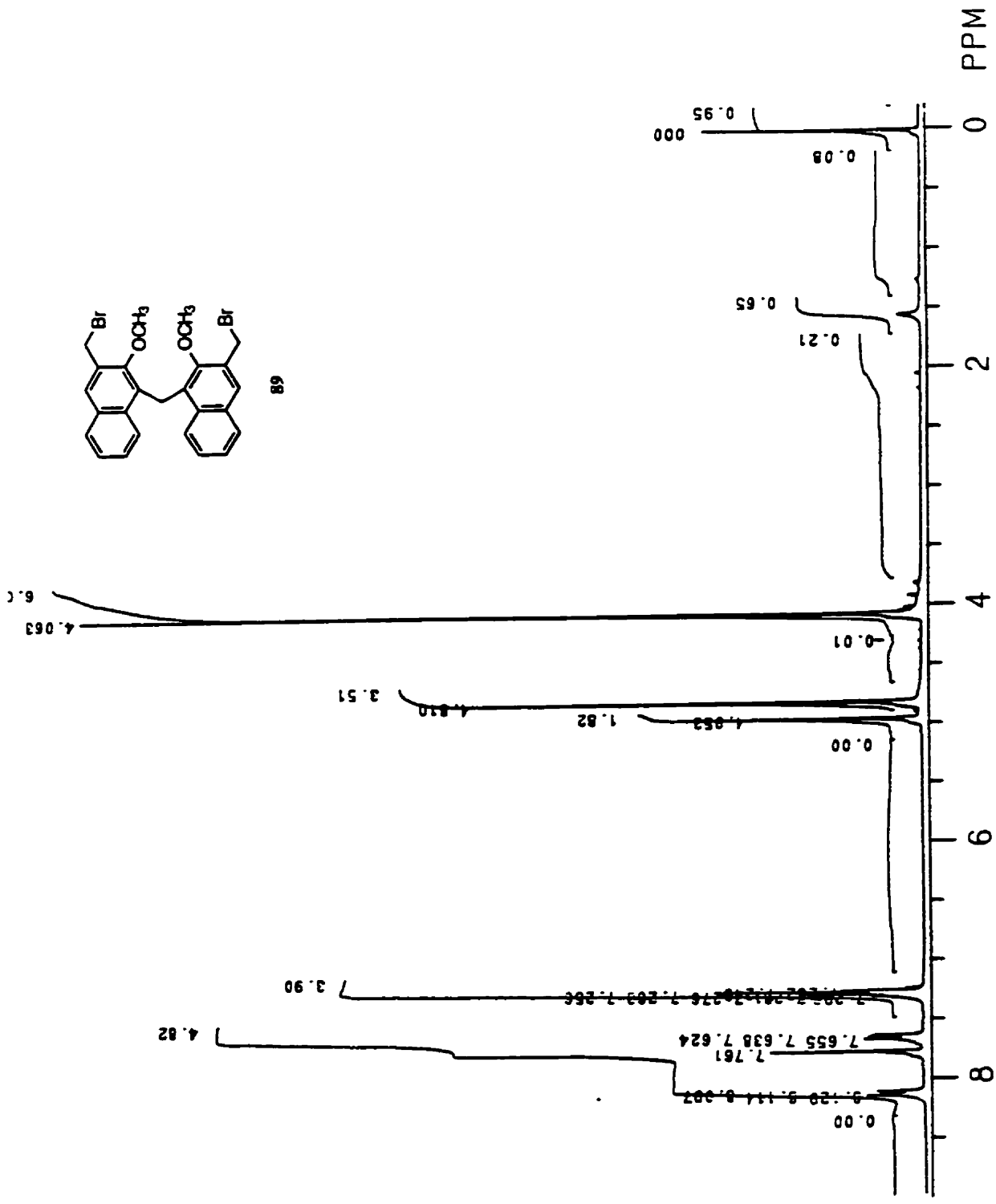

MUHAMMED ASHRAM 3-MH-24 IN CDCL3
PPM
0
2
4
6
8
85

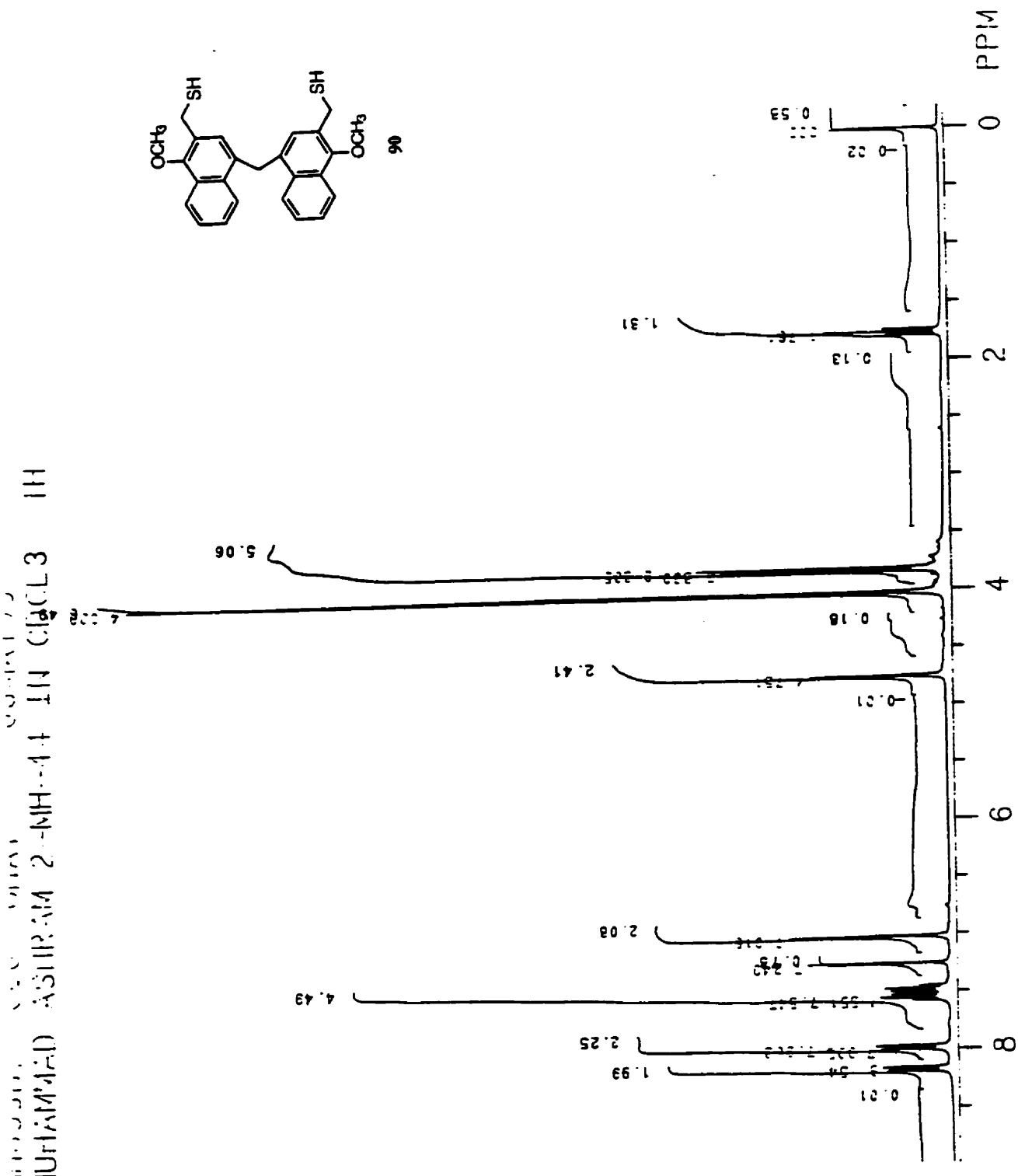

MUHAMMED ASGHIRAM 3-MII-25 IN CDCl 3 1H
85a

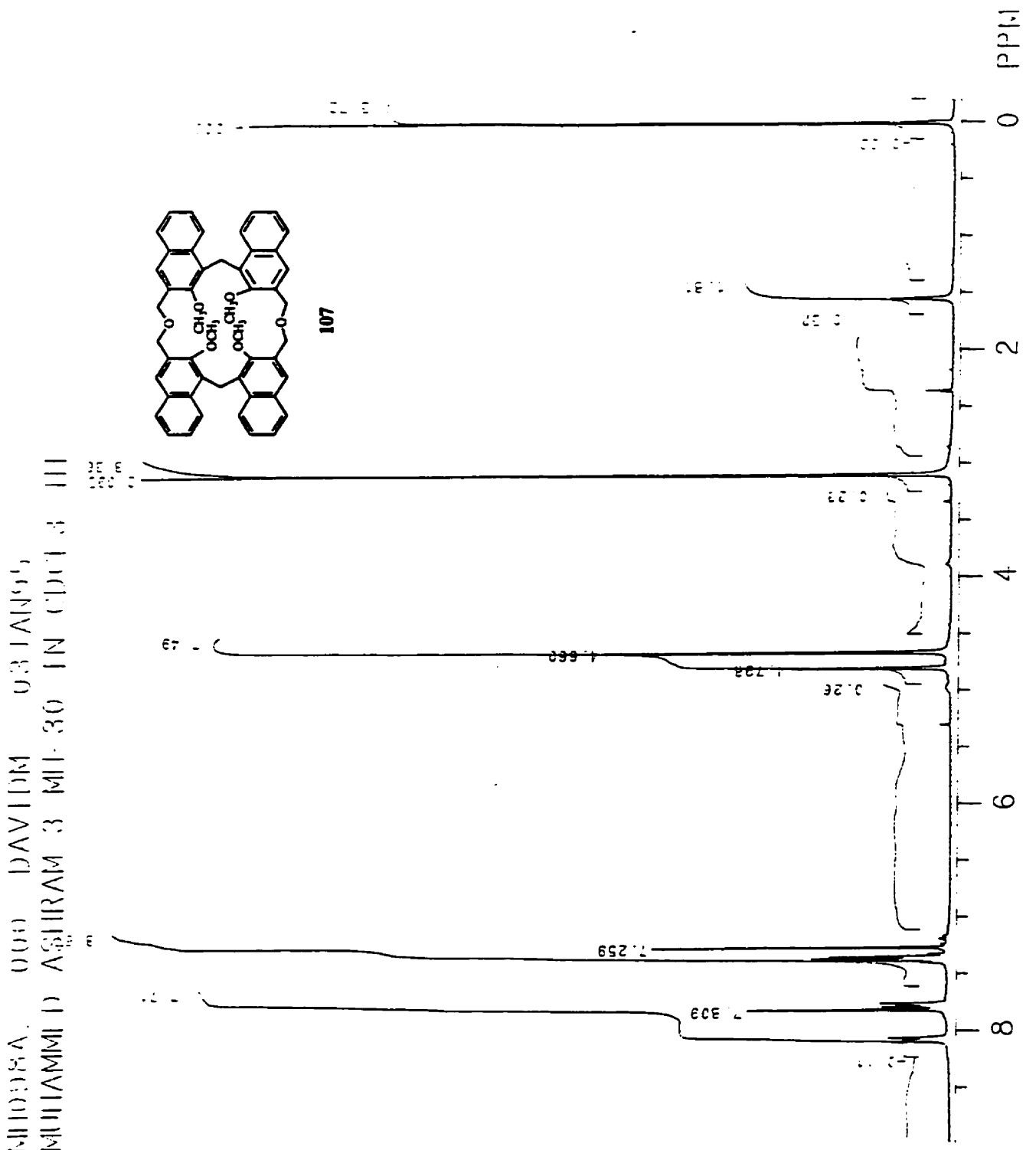


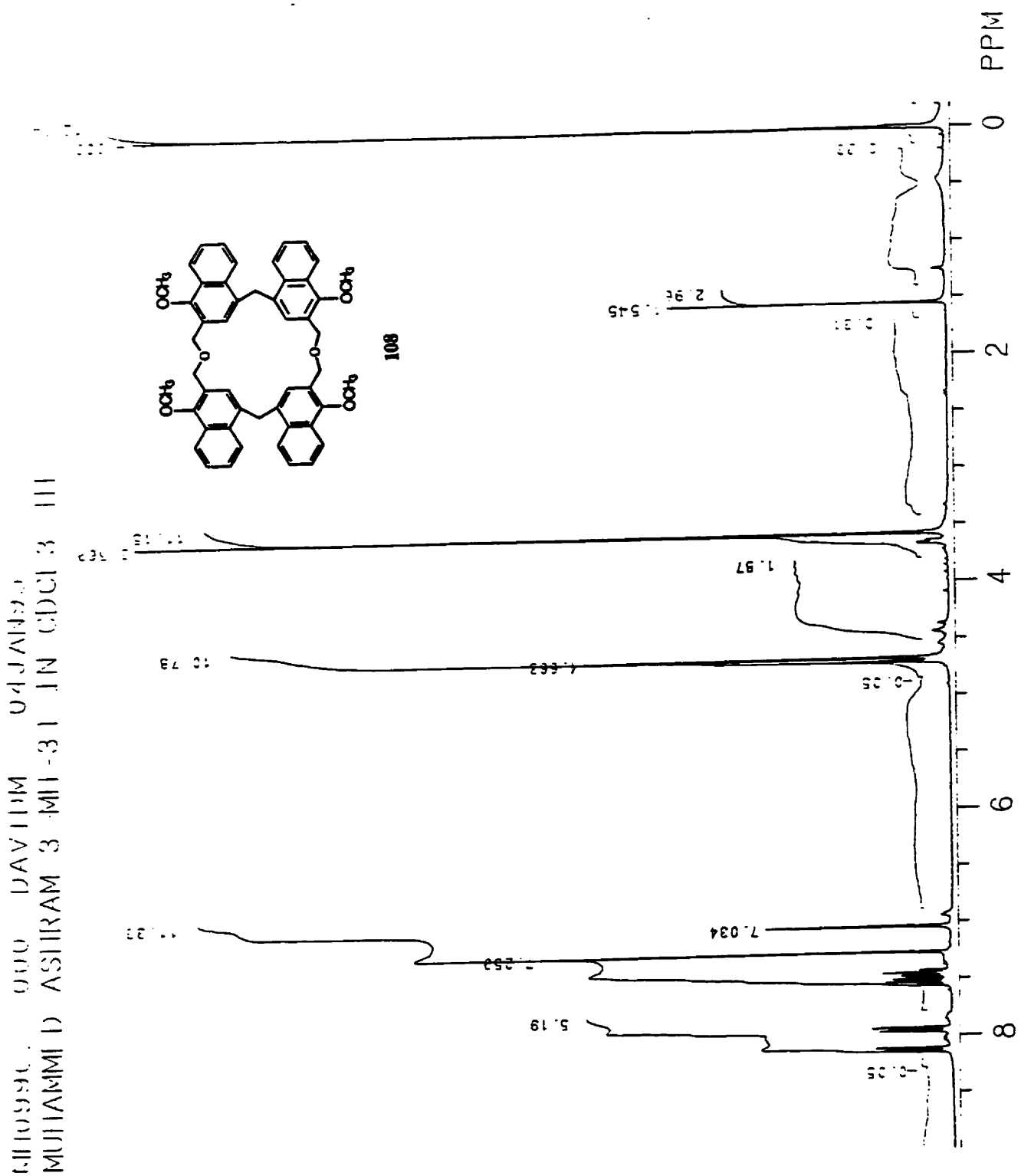

MH7888A. 000 EVES 27FEB95
MUHAMMAD ASHRAM 2-MH-22 IN CDCL3 1H
87
PPM

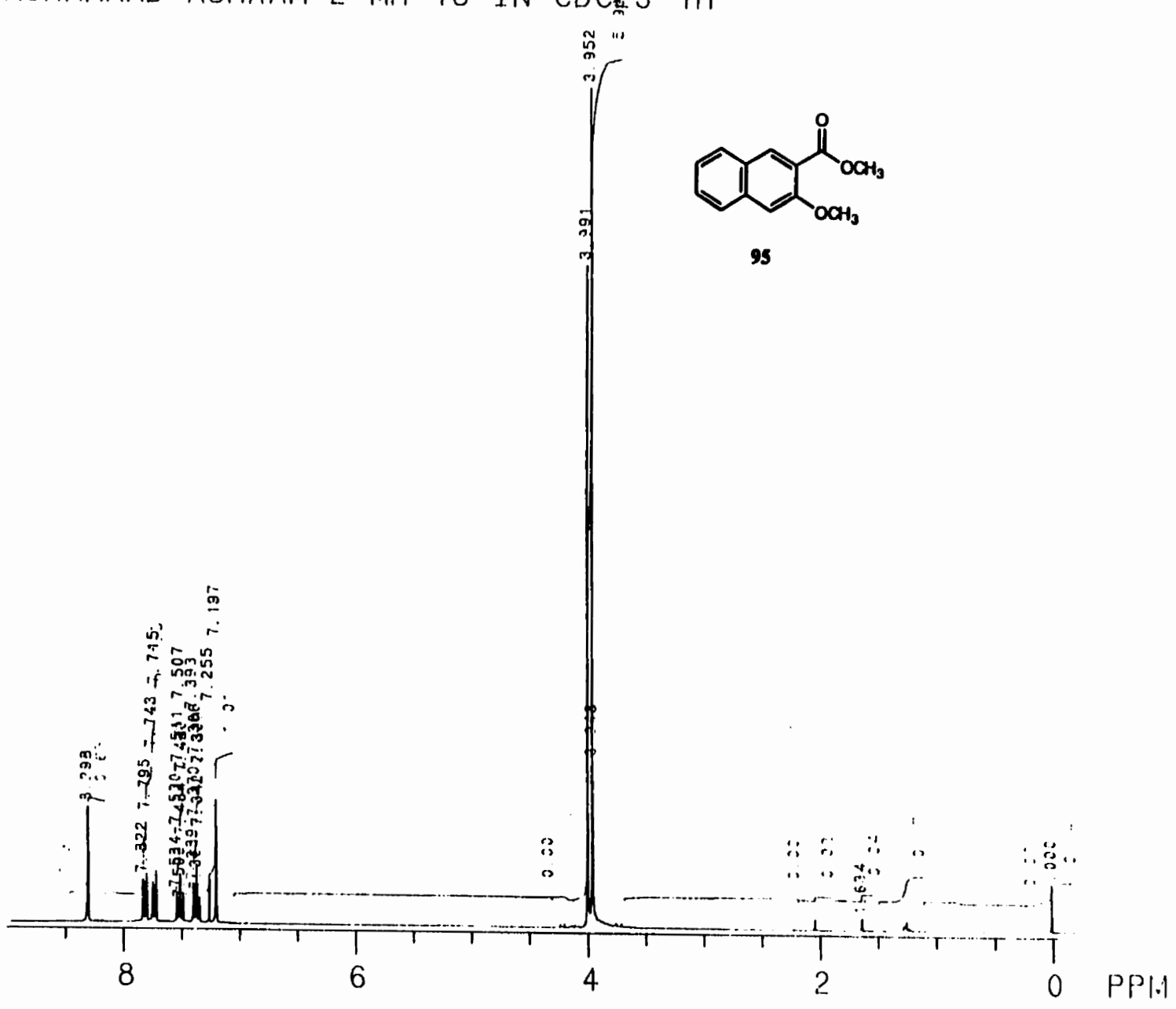

MH9251F 000 GNAT 14JUL95
MUHAMMAD ASHRAM 2 MH-23 IN CDCL3 1H
OH
OCH3
OCH3
OH
88
8
6
4
2
0
PPM

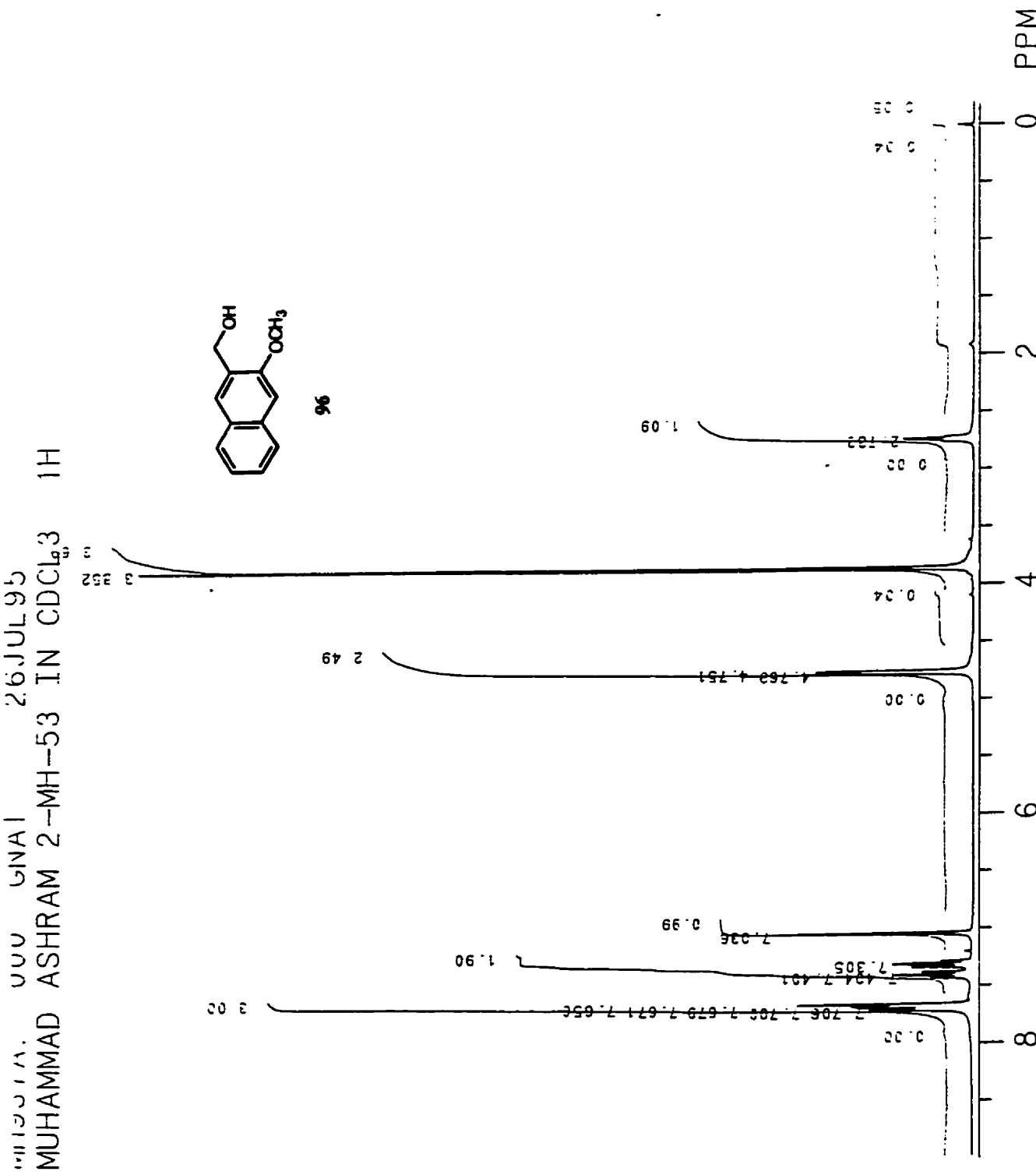

PPM
0
2
4
6
8
0.95
0.08
0.65
0.21
0.01
0.00
1.82
3.51
4.82
3.90
7.761
7.655 7.638 7.624
0.00
4.063
Br
OCH3
OCH3
Br
68

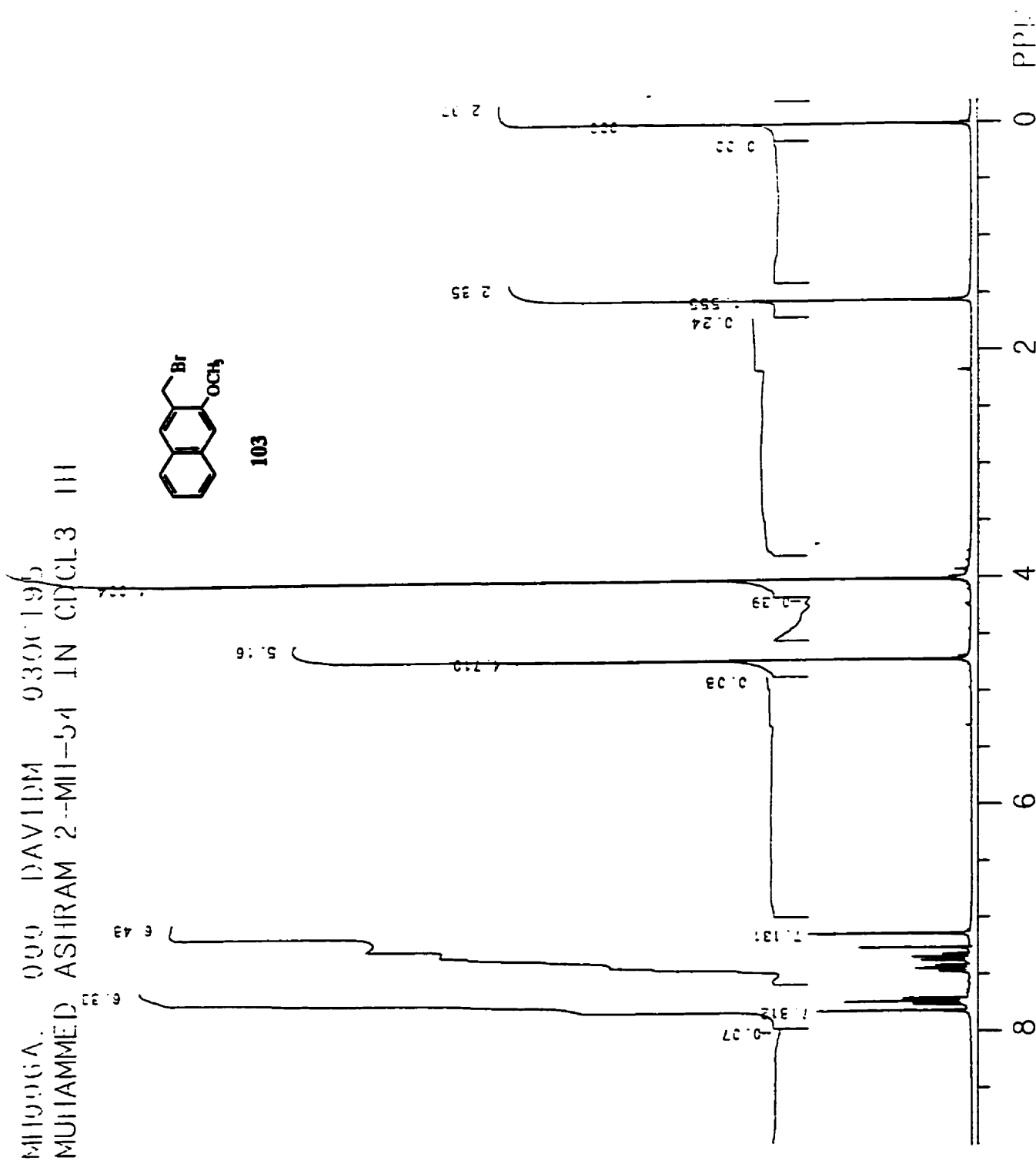

SH
SH
OCH3
OCH3
90
PPM
0
2
4
6
8
0.53
0.32
1.31
0.13
5.06
0.18
2.41
0.21
2.08
4.43
2.25
1.99
0.21

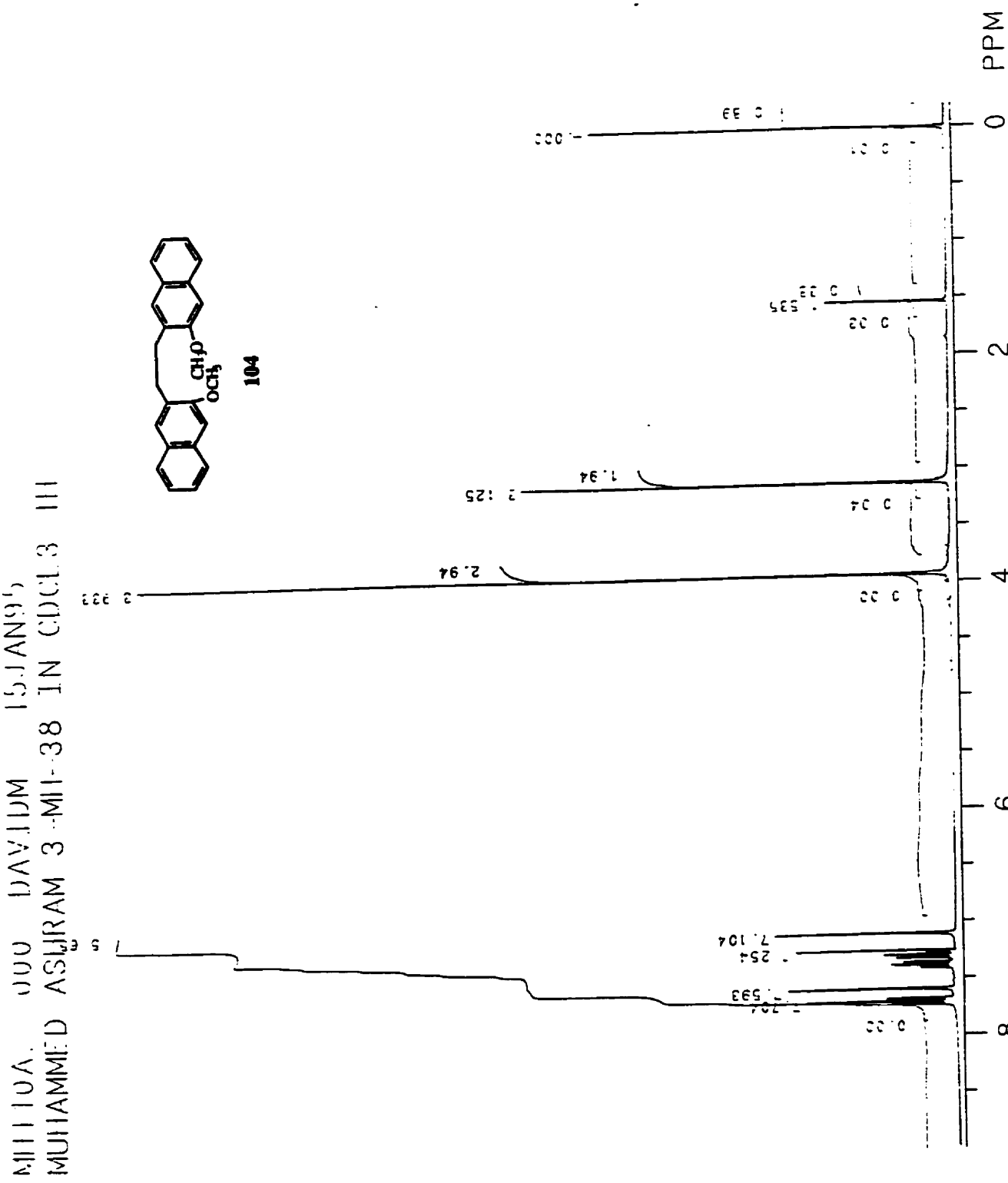

107
7.259
7.303
PPM

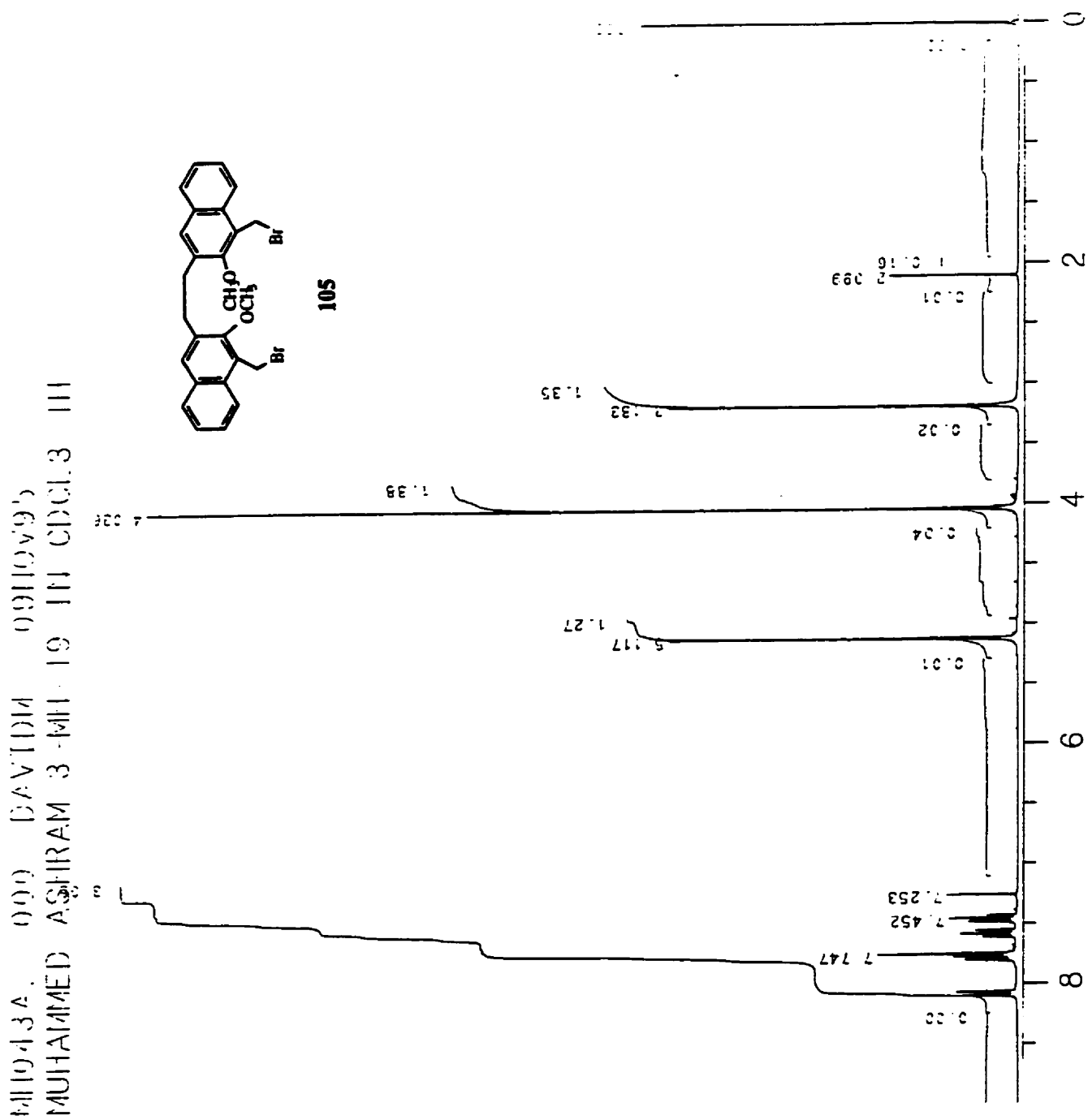

108
7.034
5.19
1.97
2.98
1.545
PPM

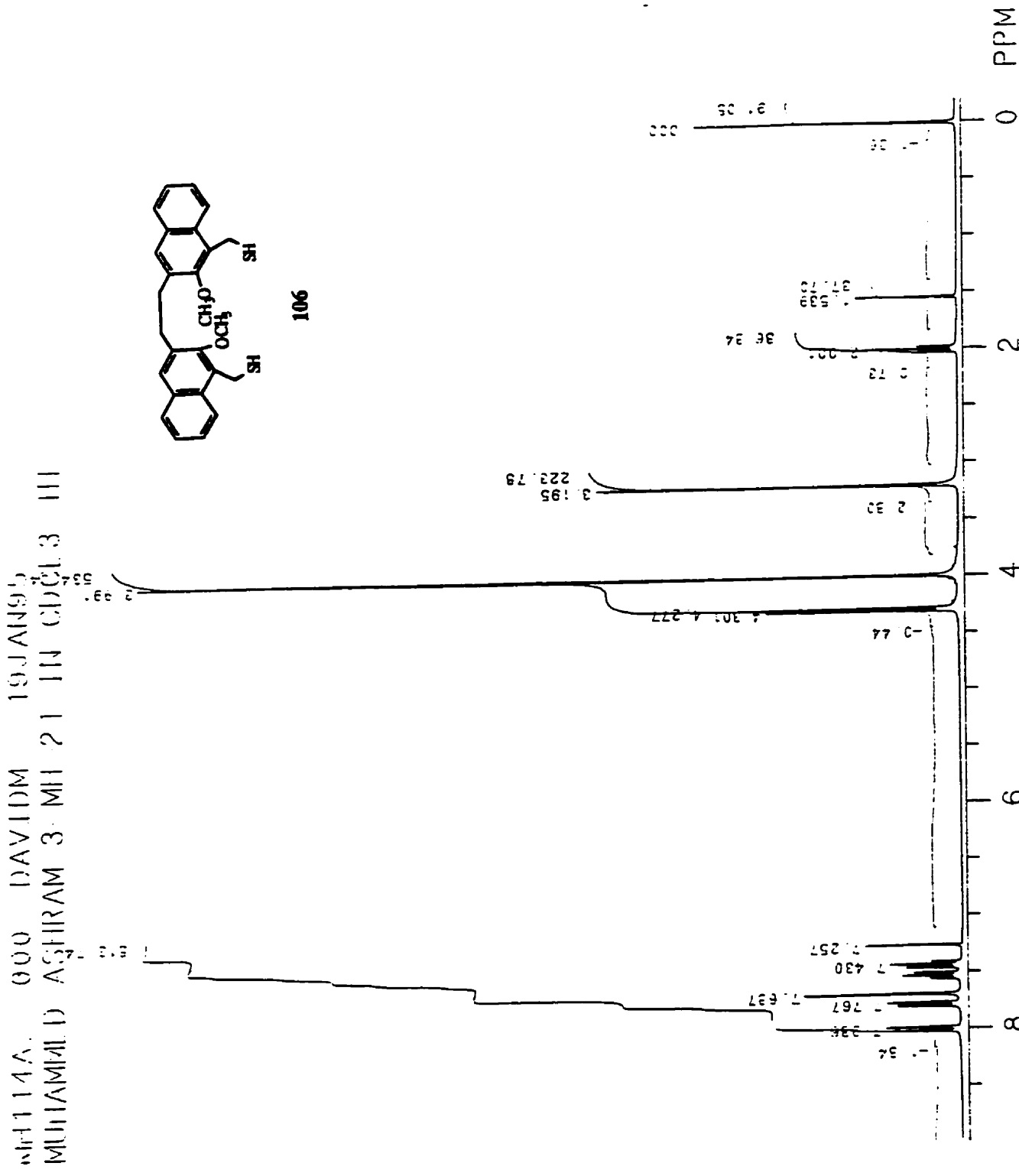

MH762A. 000 EVES 01FEB95
MUHAMMAD ASHRAM 2--MH--18 IN CDCL3 1H
3.952
3.391
7.393
7.255
7.197
95
8
6
4
2
0
PPM

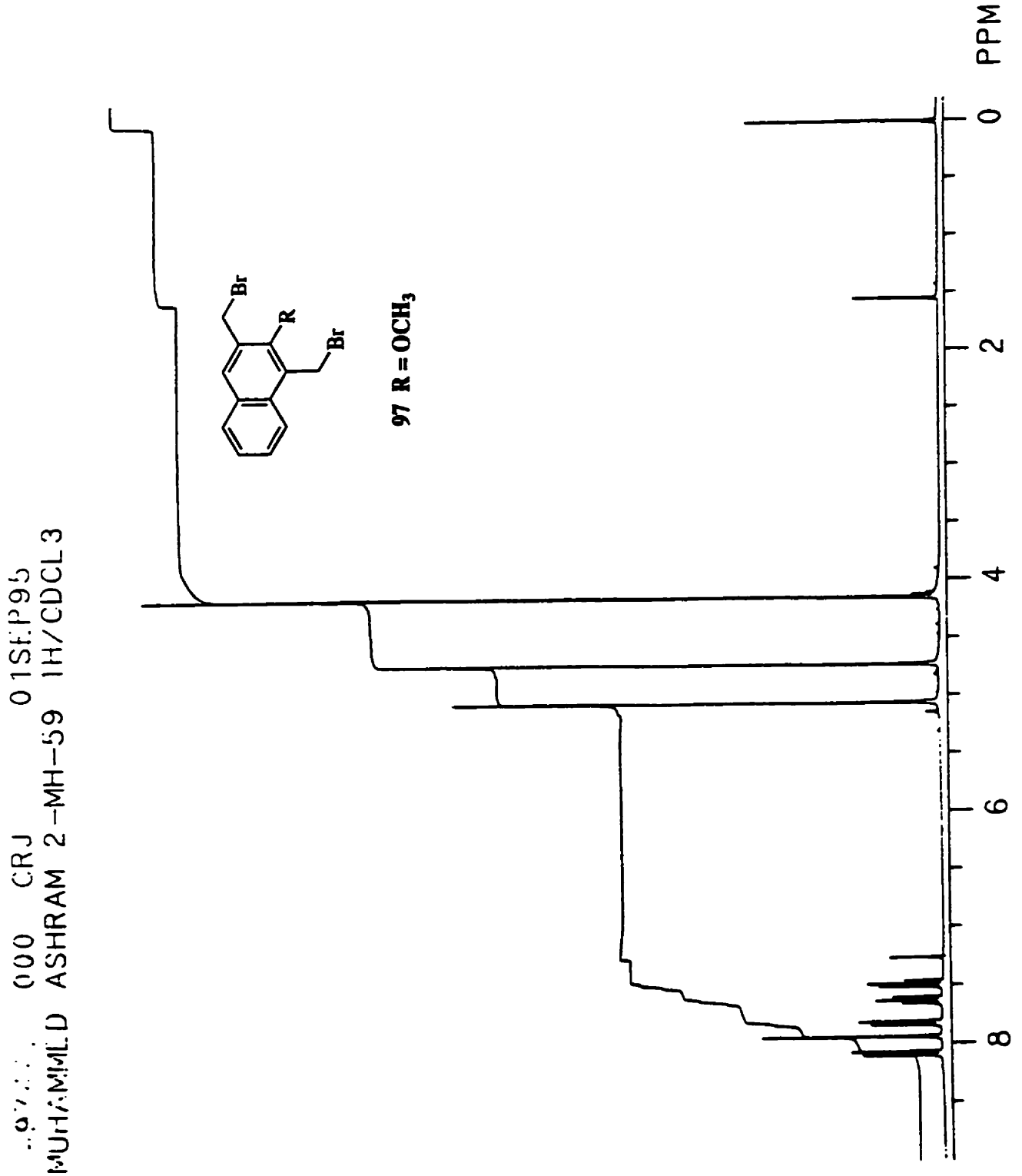

MUHAMMAD ASHRAM 2-MH-53 IN CDCL3 1H
96
PPM

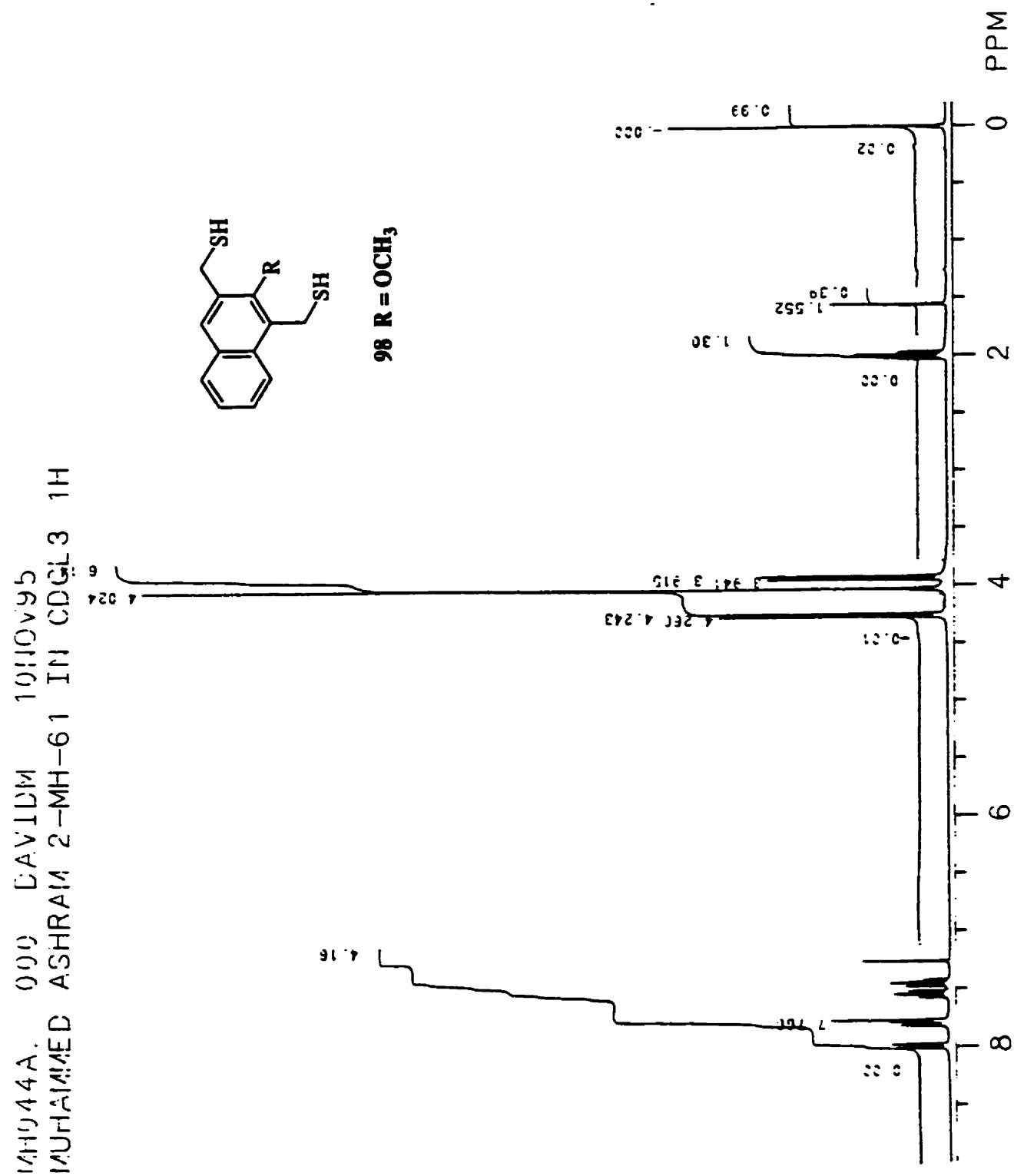

MUHAMMED ASHRAM 2-MII-54 IN CDCL3 III
Br
OCH3
103
PPM

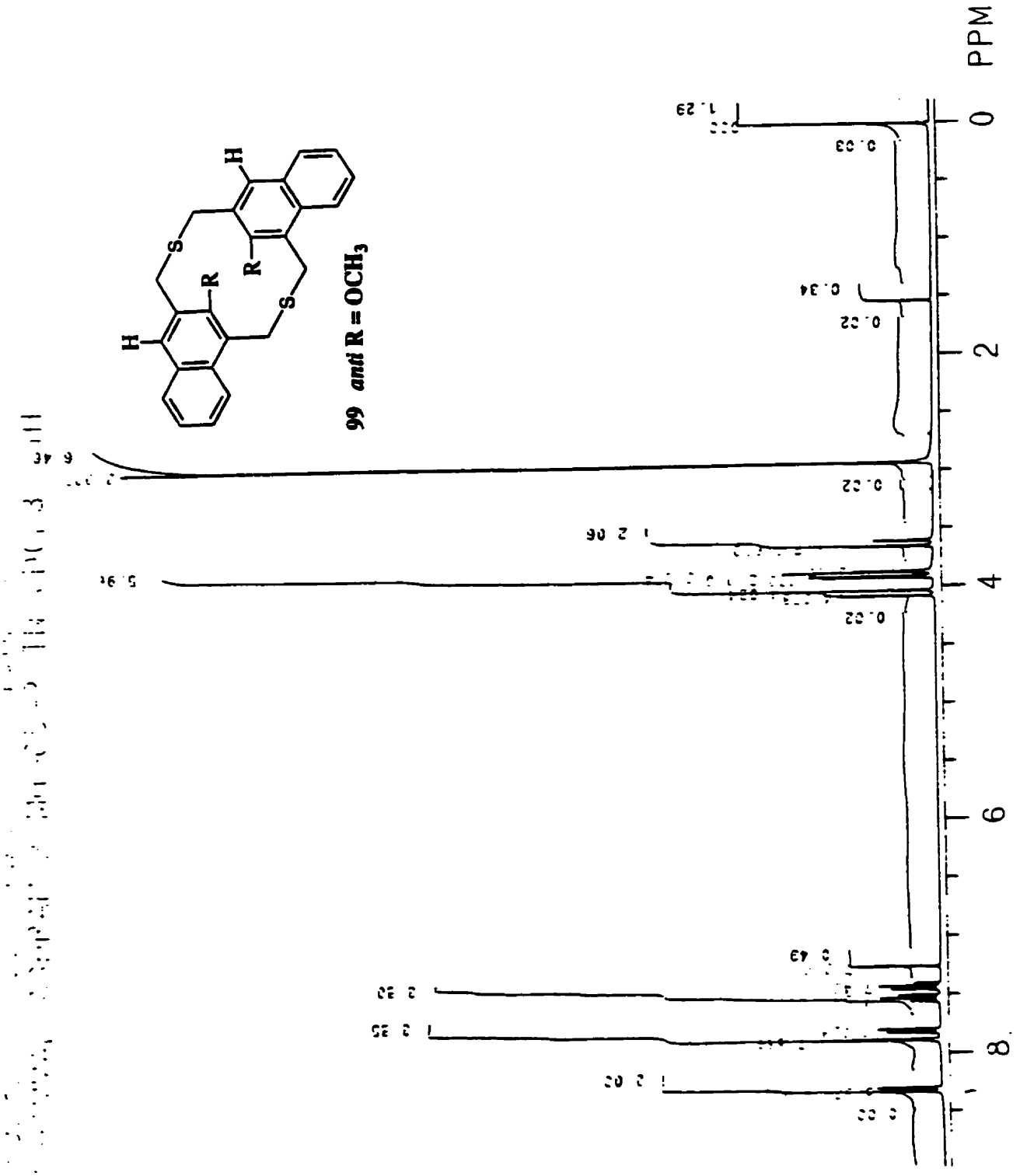

MUHAMMED ASLJRAM 3-MII-38 IN CDCL3 III
104
PPM

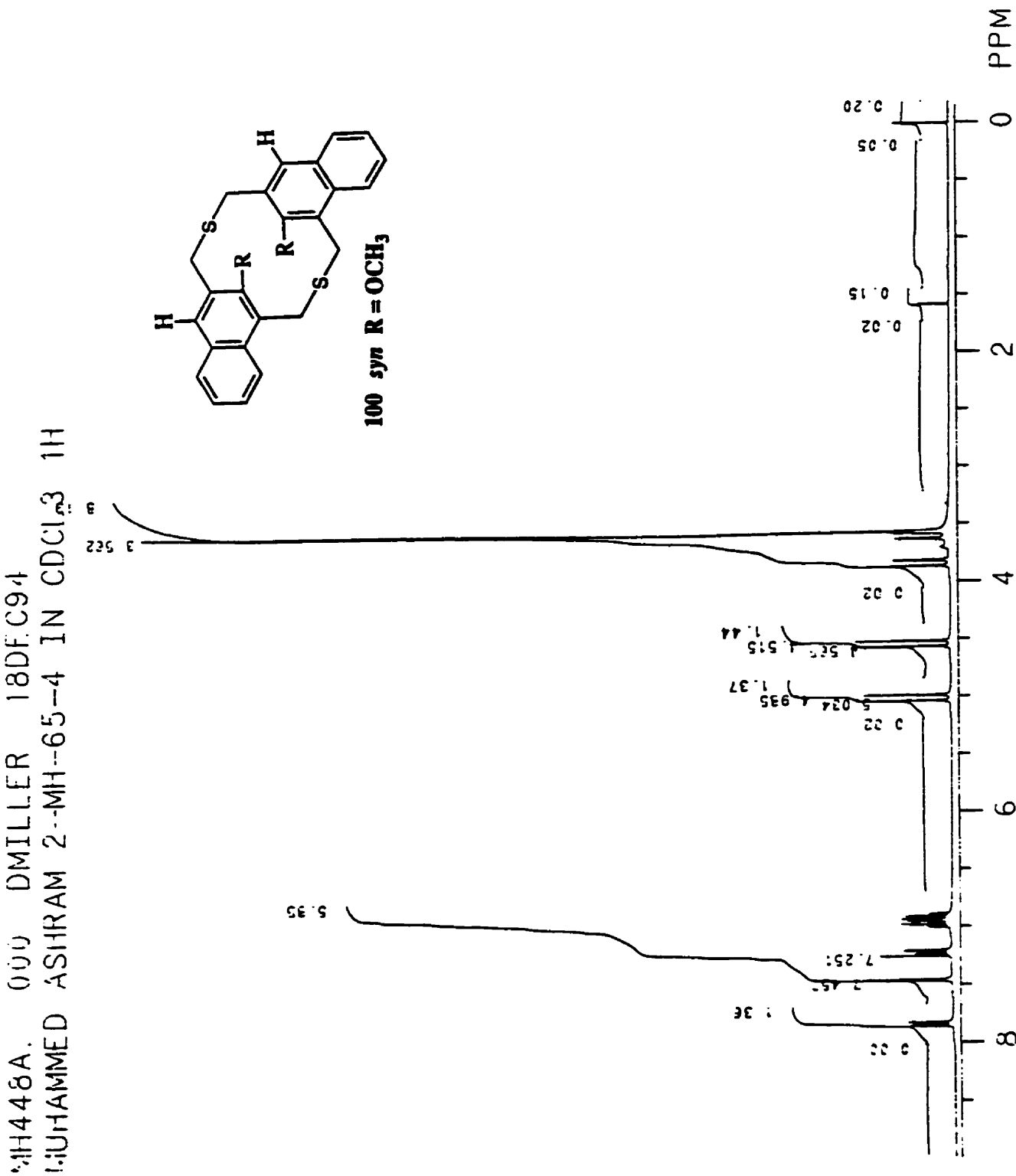

105

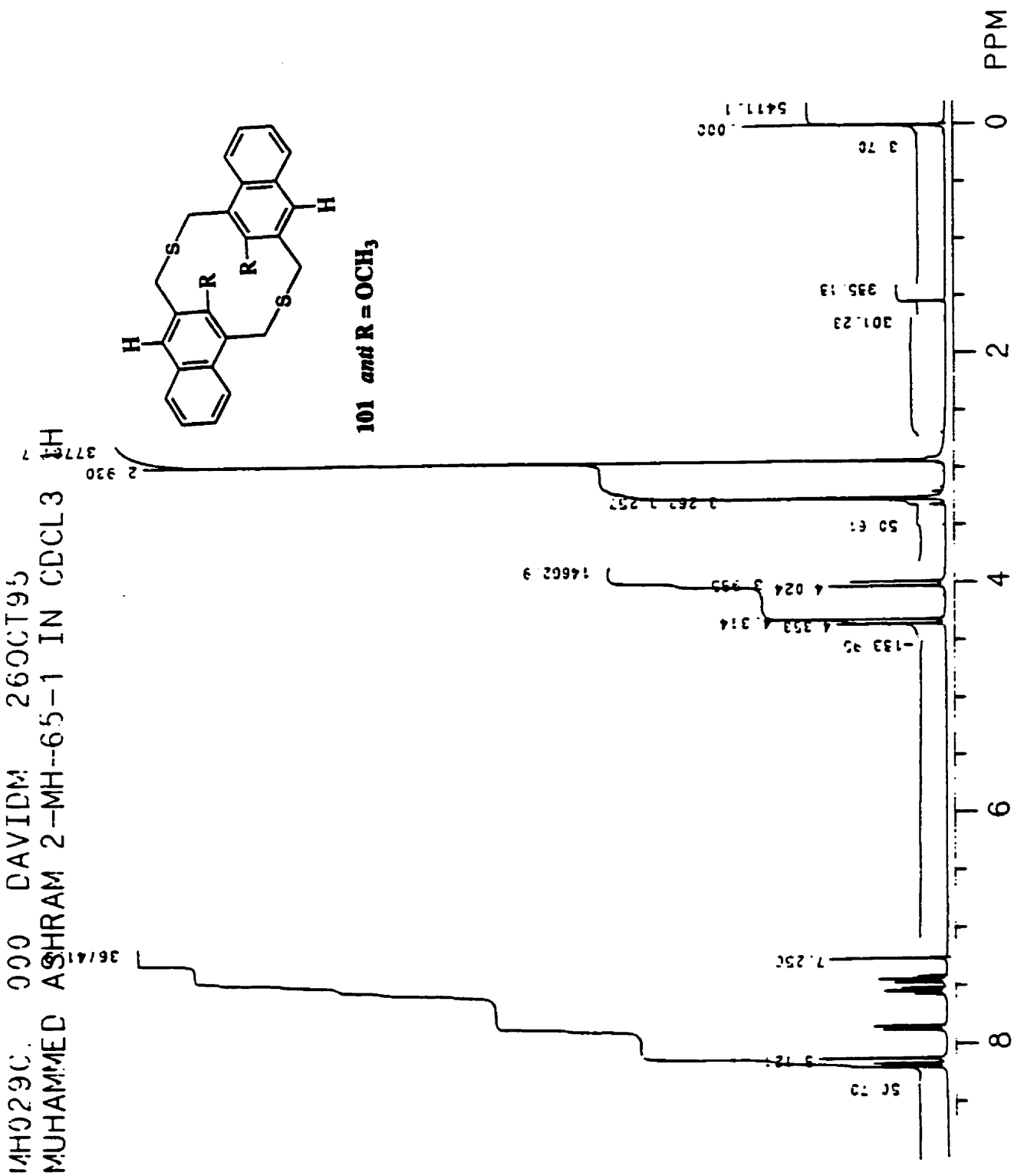

106
SH
SH
CH2O
OCH3
PPM
0
2
4
6
8

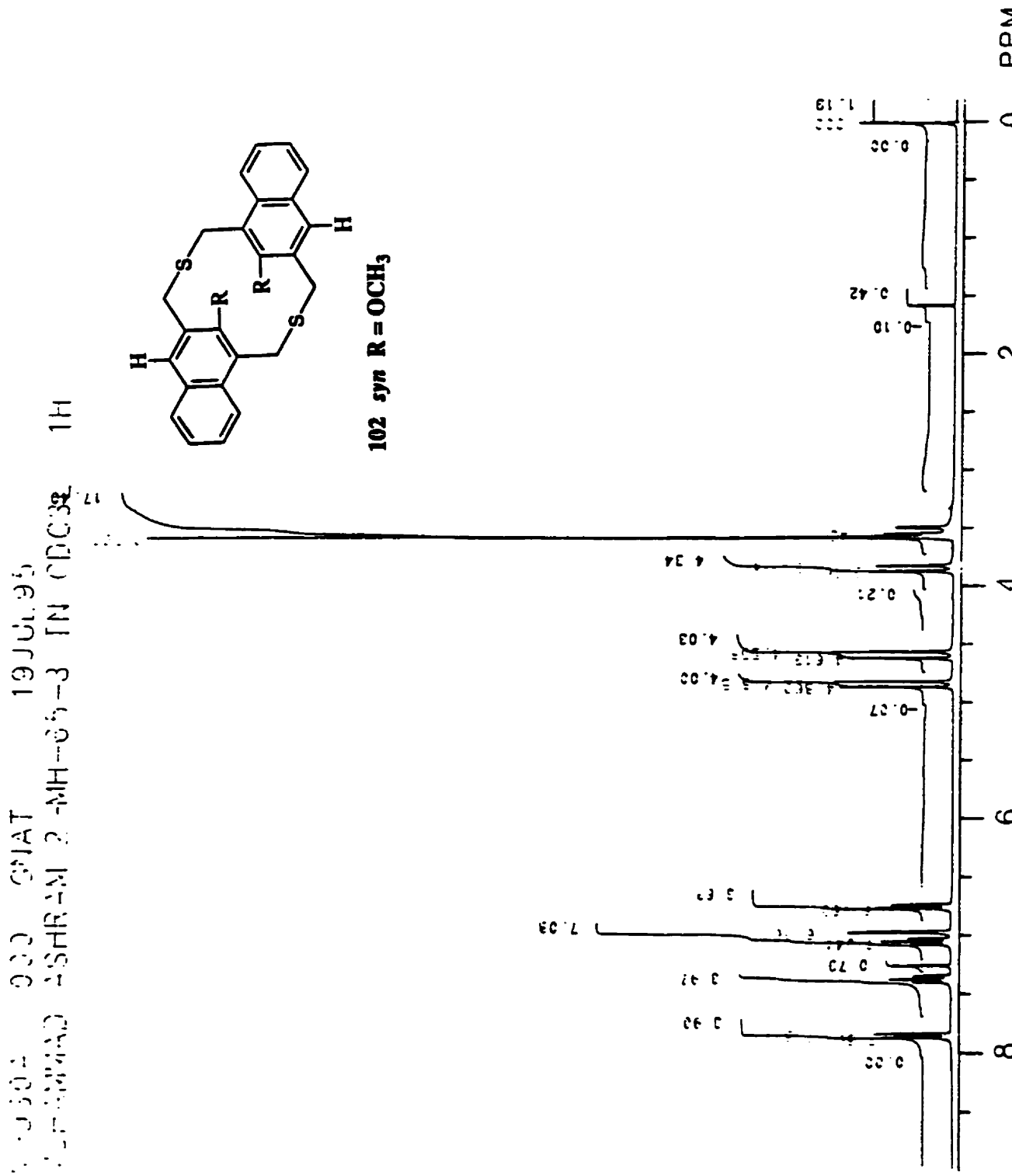

000 CRJ 01SEP95
MUHAMMILD ASHRAM 2-MH-59 1H/CDCL3
Br
R
Br
97 R = OCH3
0
2
4
6
8
PPM

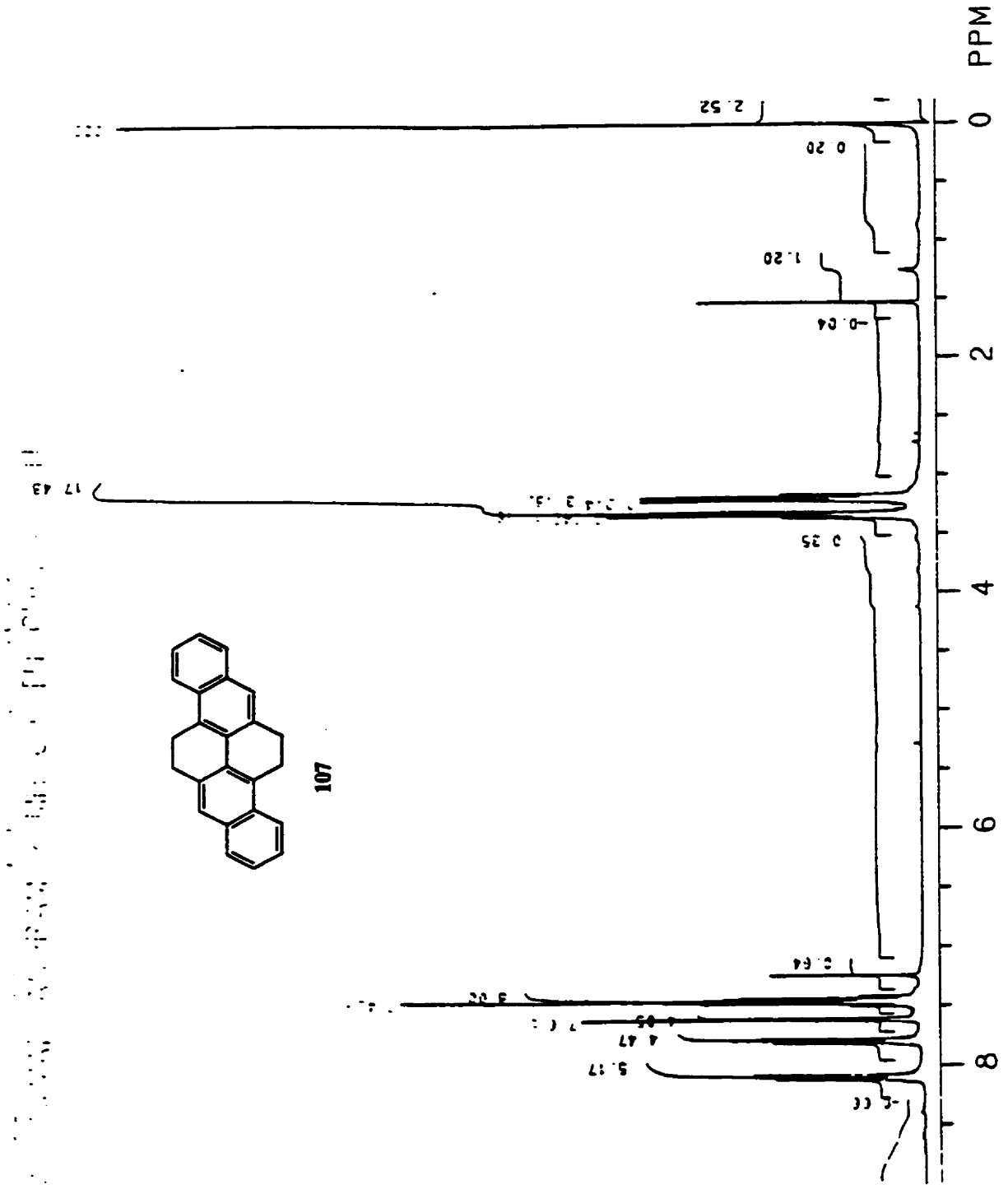

SH
R
SH
98 R = OCH3
PPM
0
2
4
6
8


H
S
R
R
S
H
99 anti R = OCH3
PPM
0
2
4
6
8

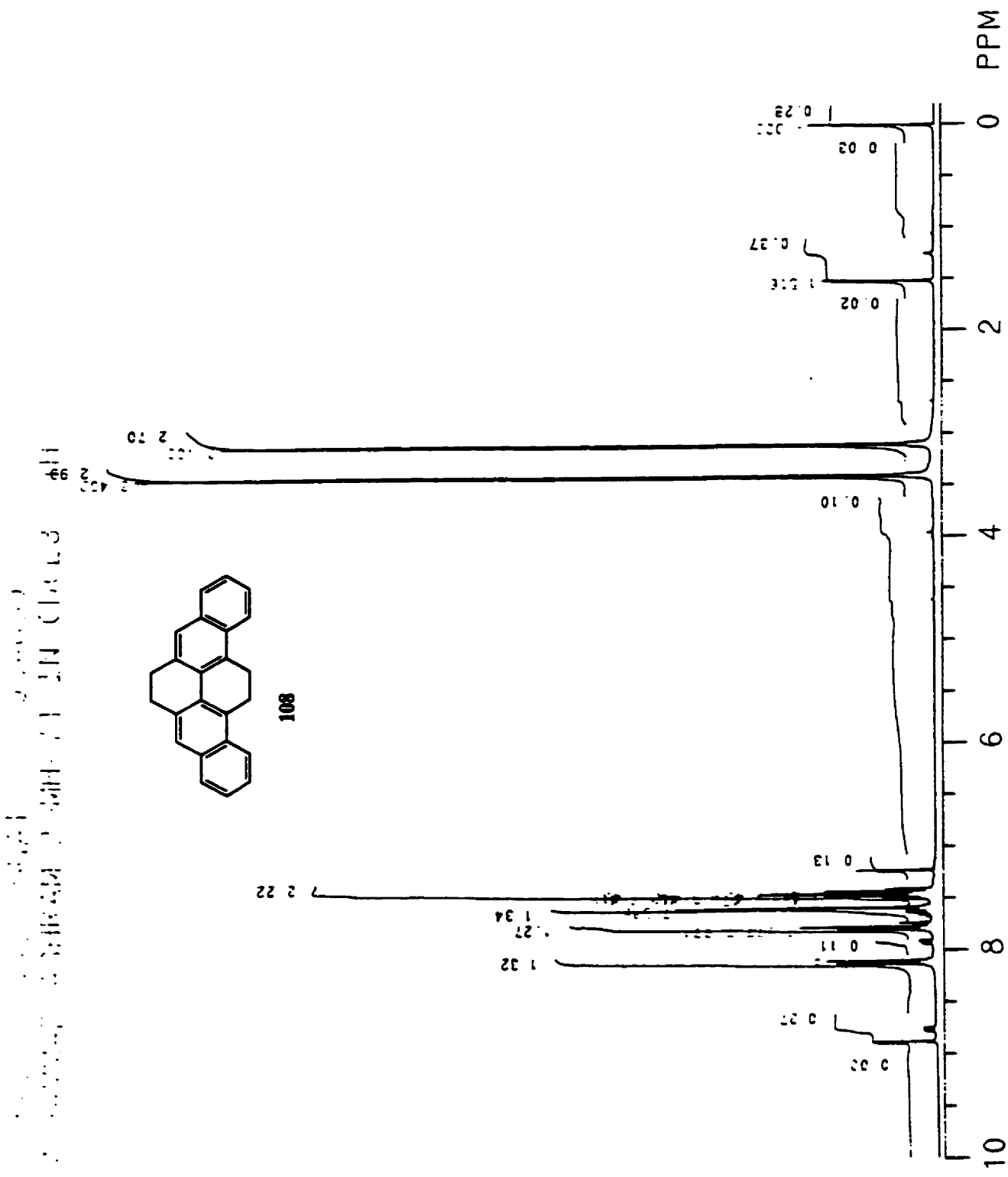

100 syn R = OCH3
PPM
0
2
4
6
8

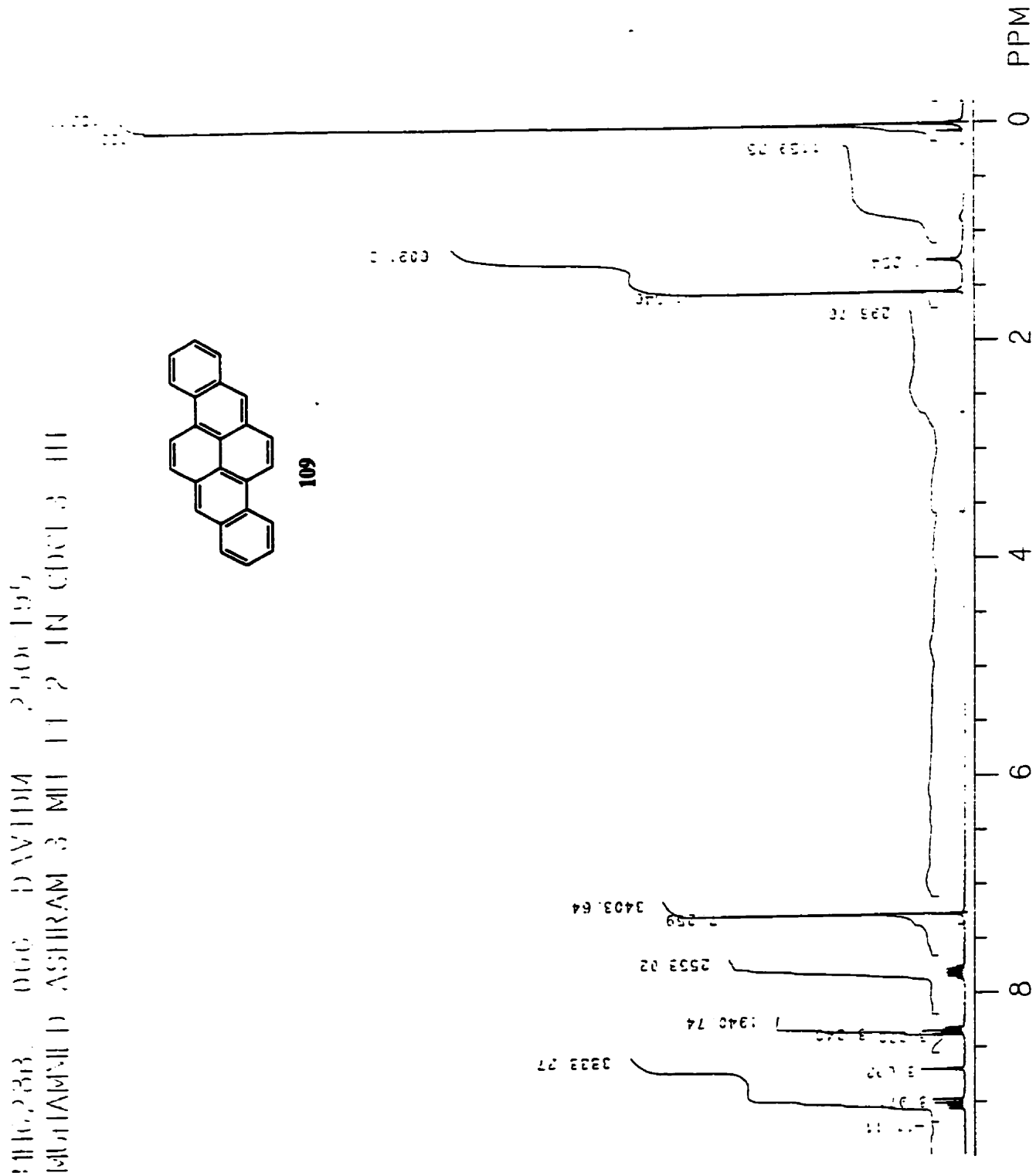

101 anti R = OCH3
MUHAMMED ASHRAM 2-MH--65-1 IN CDCL3 1H
PPM


S
R
R
S
H
H
102 syn R = OCH3
1H
19JUL95
ppm

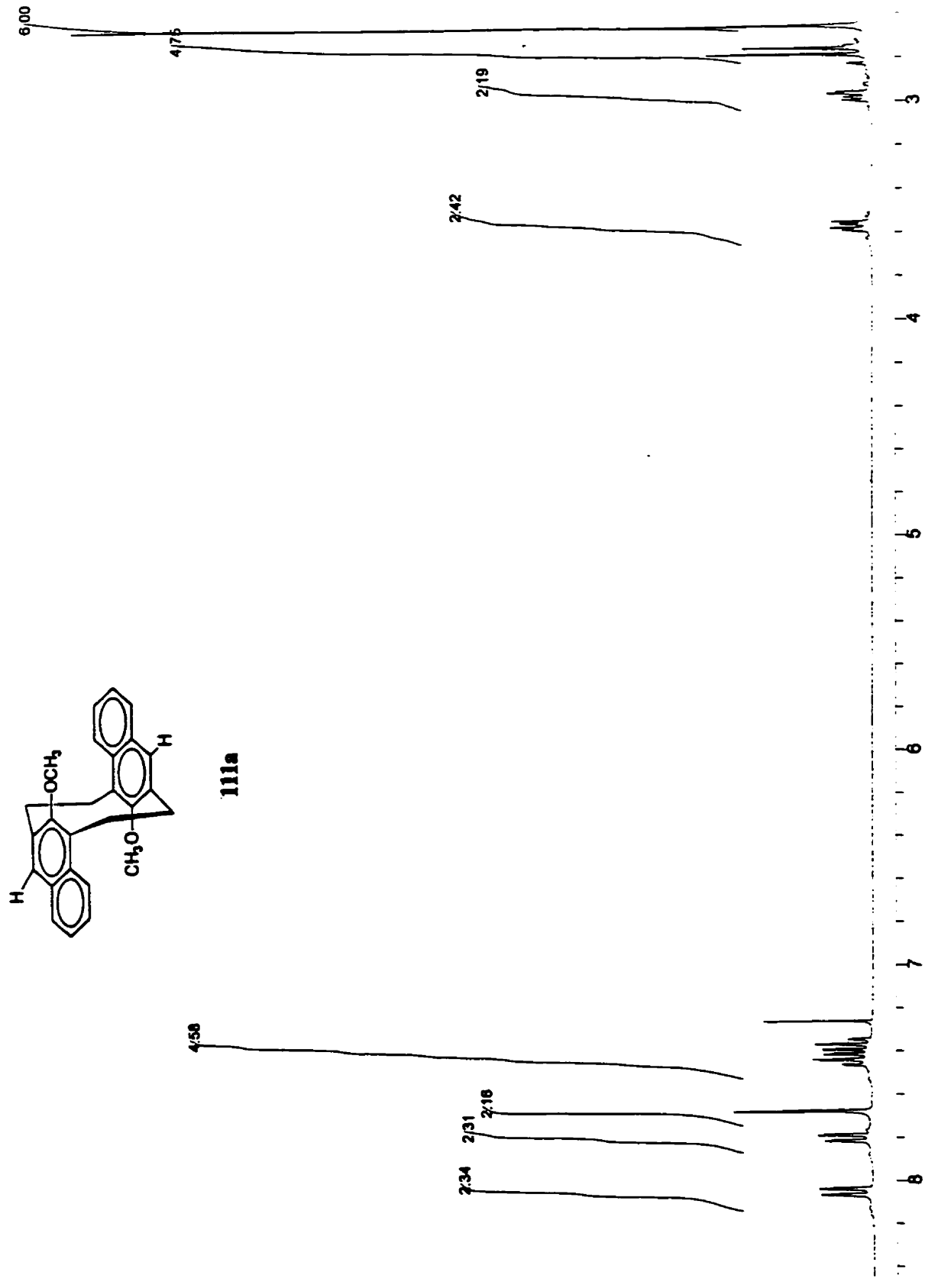


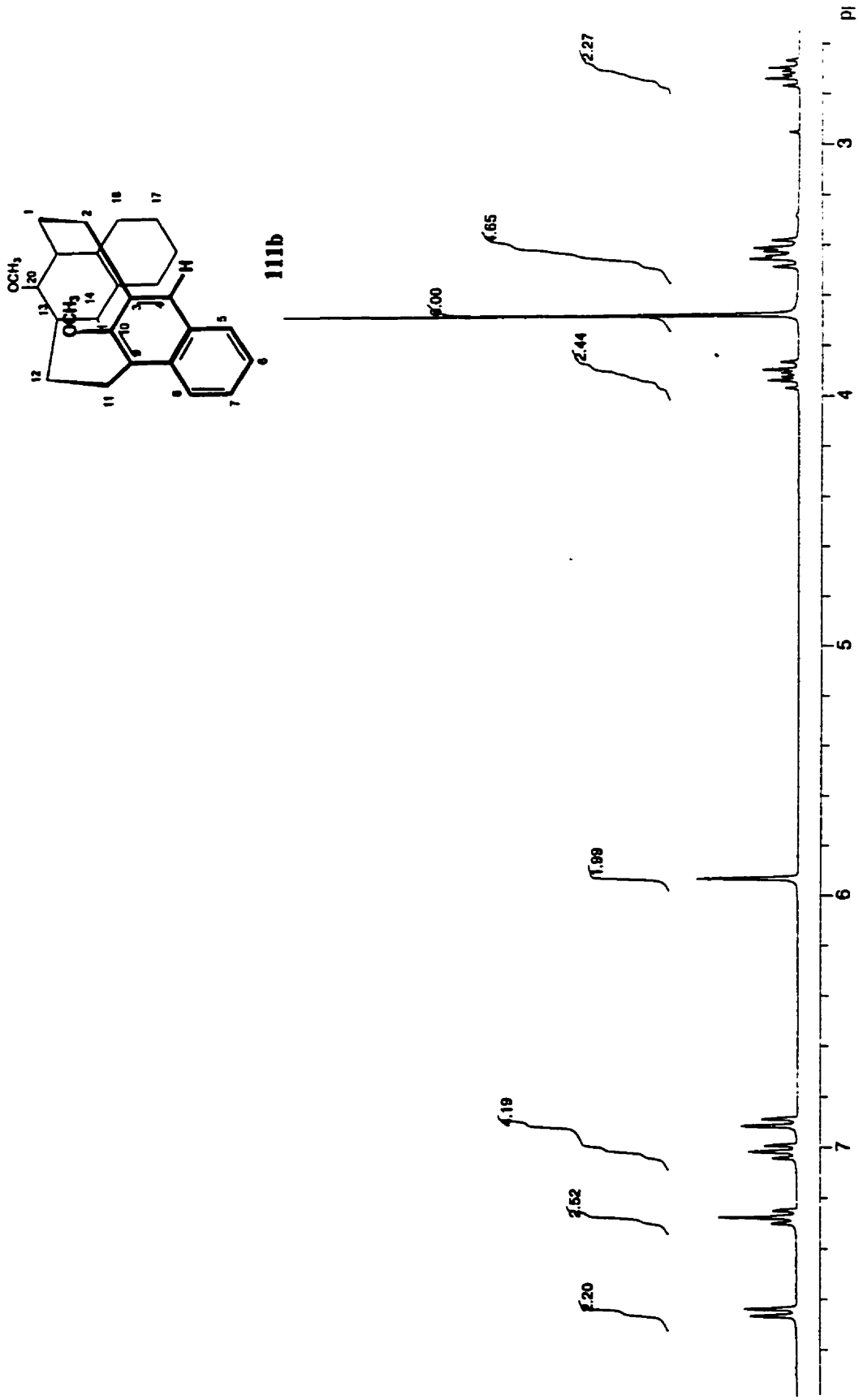
107

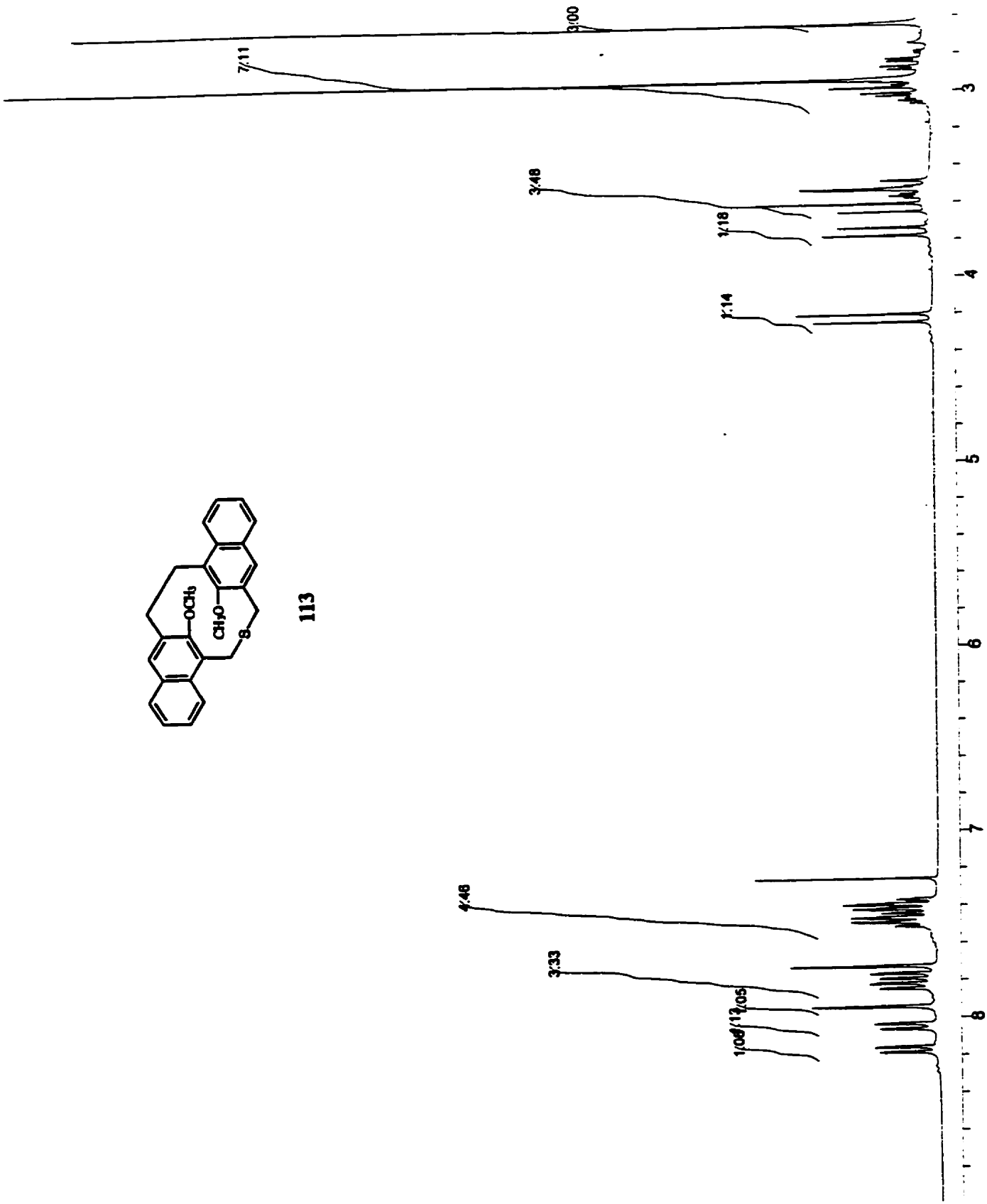

PPM
0
2
4
6
8
10
108


PPM
0
2
4
6
8
3403.64
2553.02
1940.74
3333.27
298.16
109

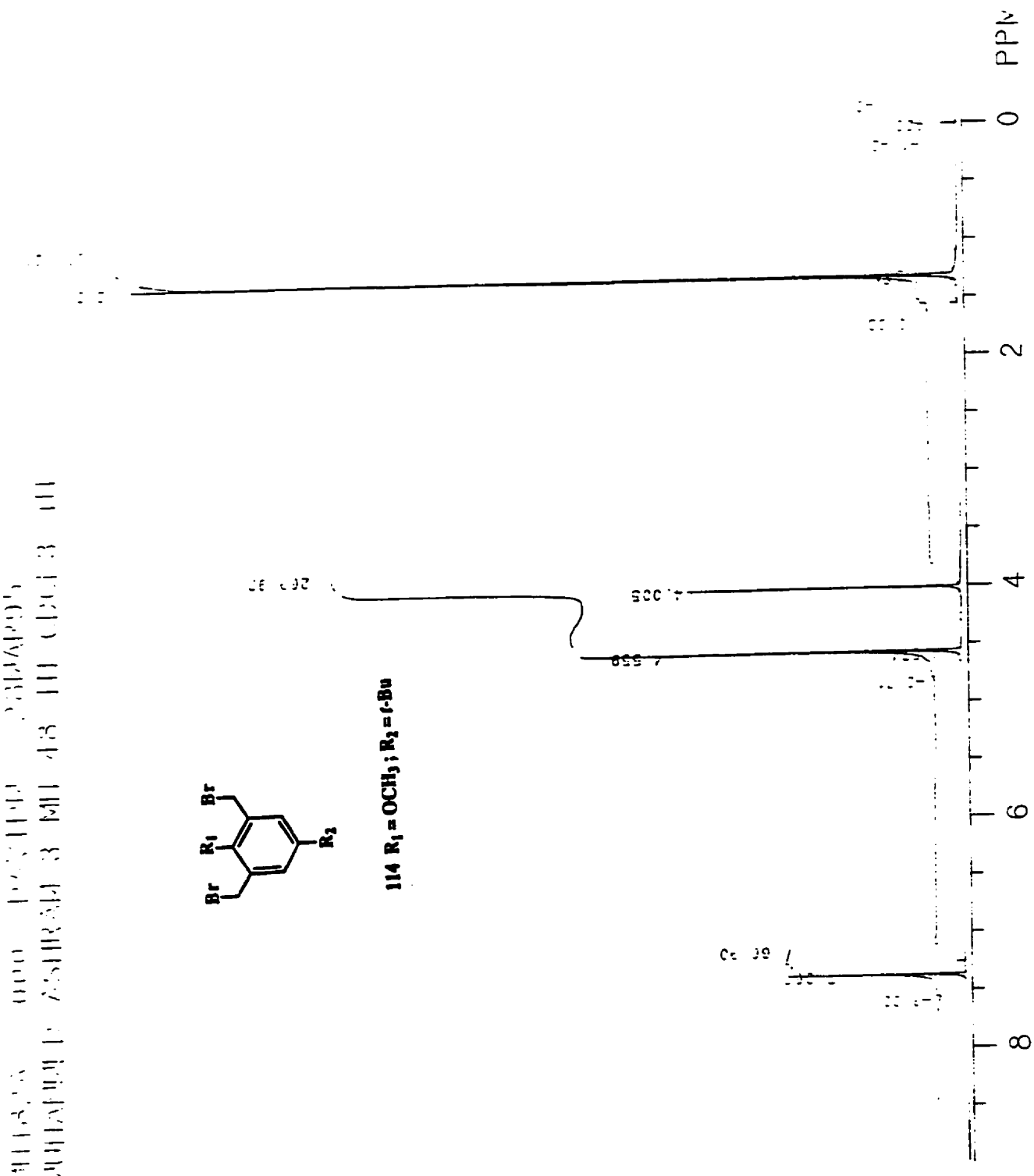
110


6.00
4.76
2.19
2.42
4.58
2.16
2.31
2.34
OCH3
CH3O
H
H
111a
3
4
5
6
7
8

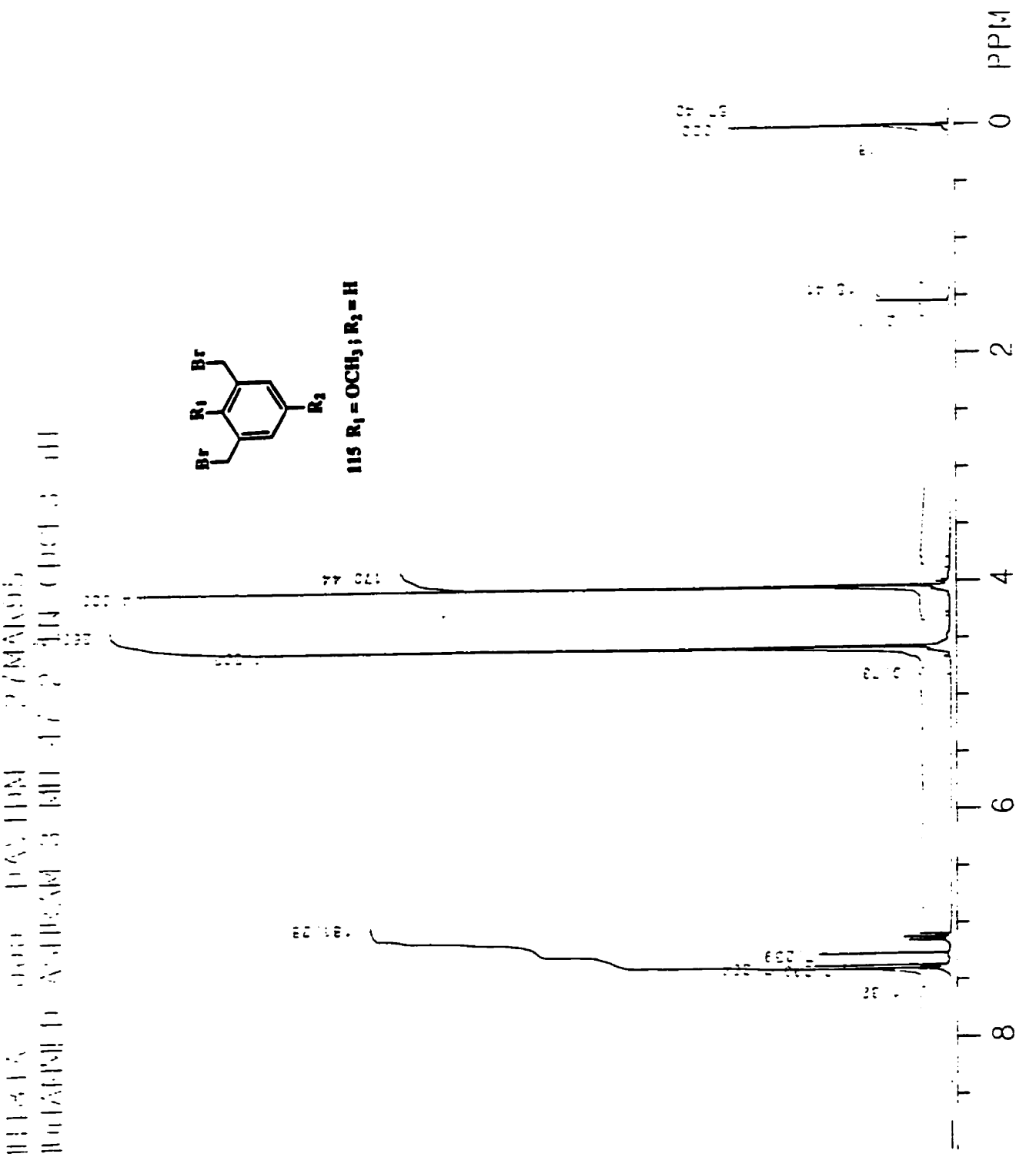

111b
OCH3
OCH3
H
1.20
4.19
2.52
1.99
6.00
4.65
2.44
2.27
ppm

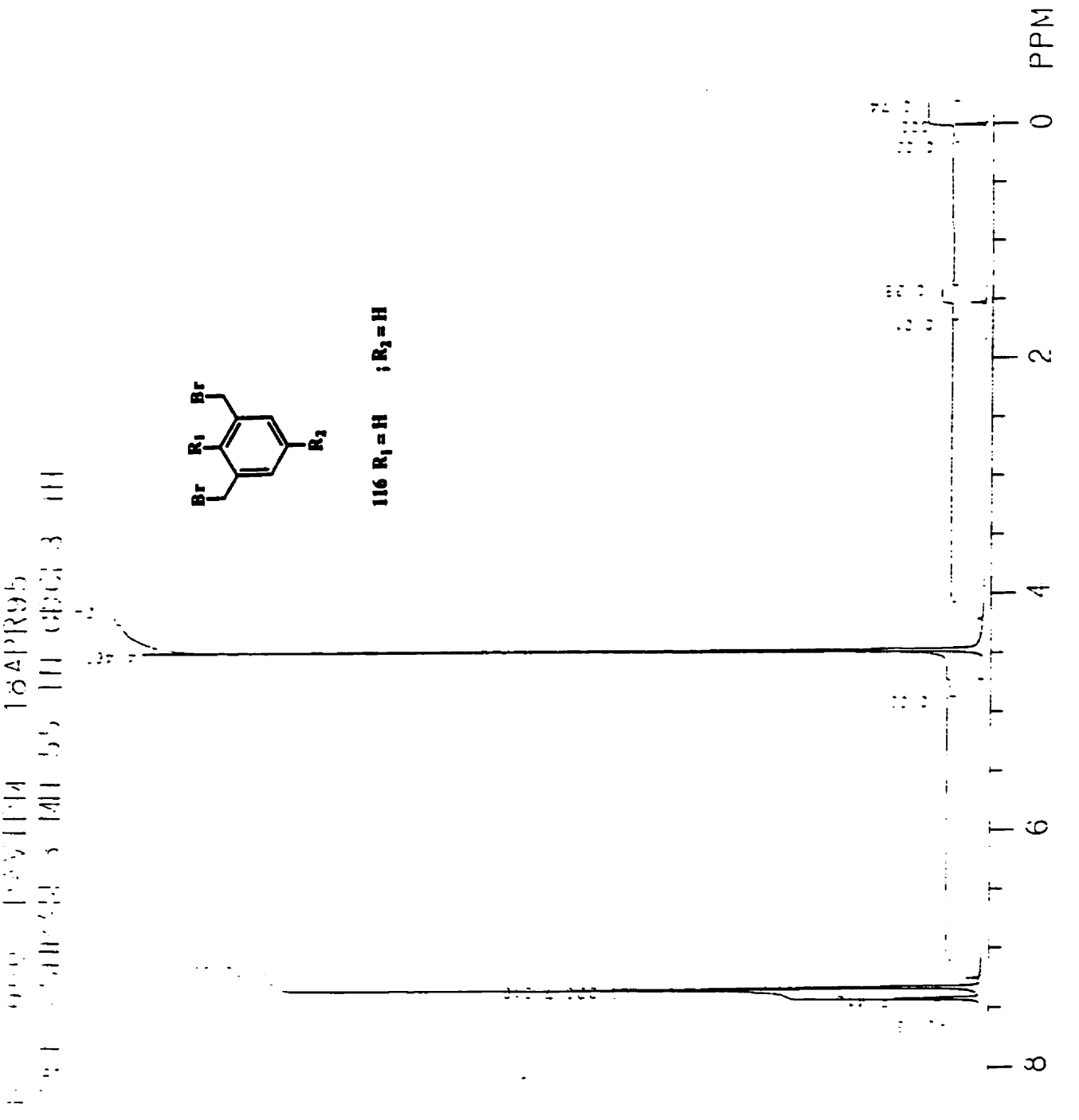


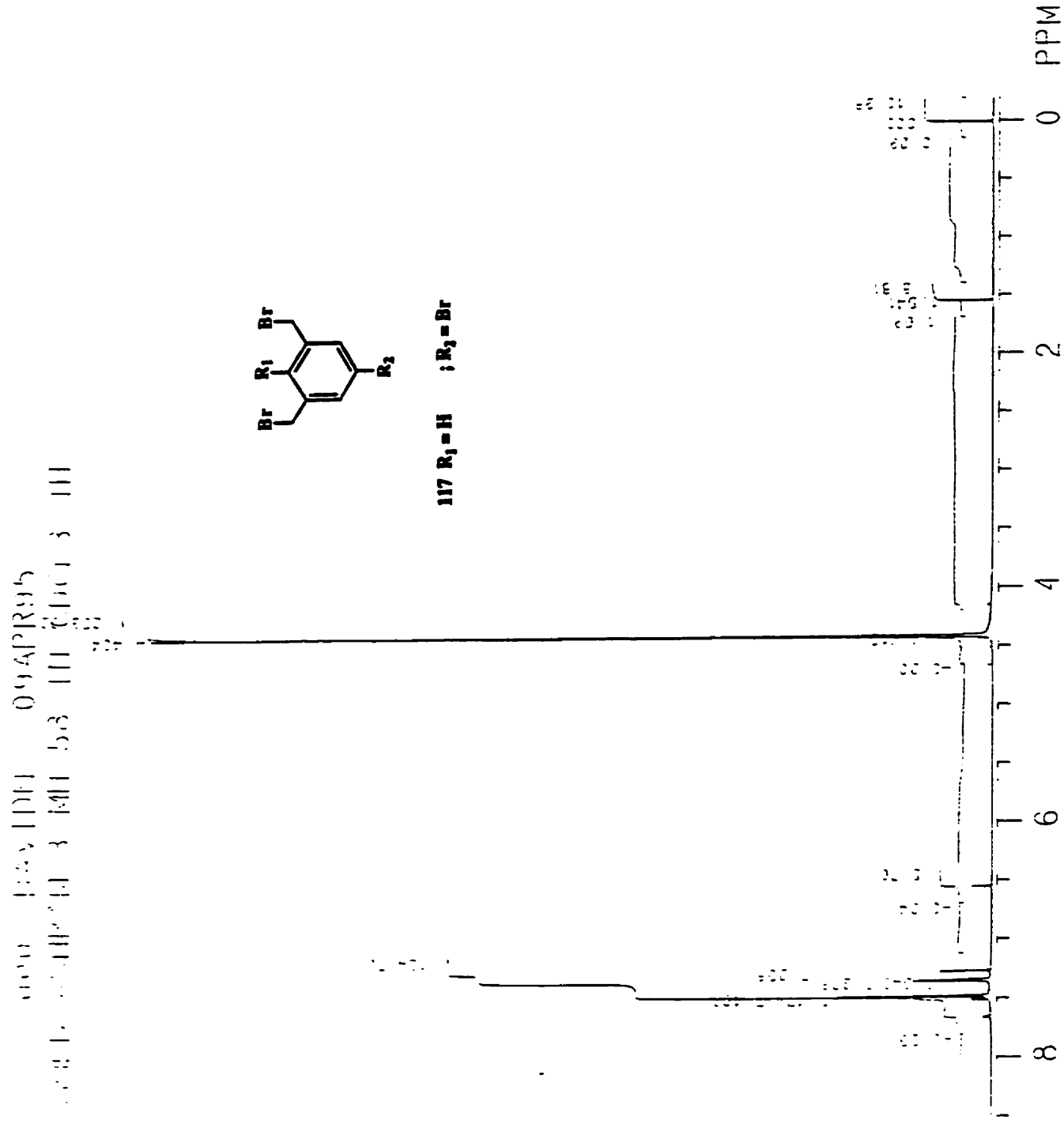
113

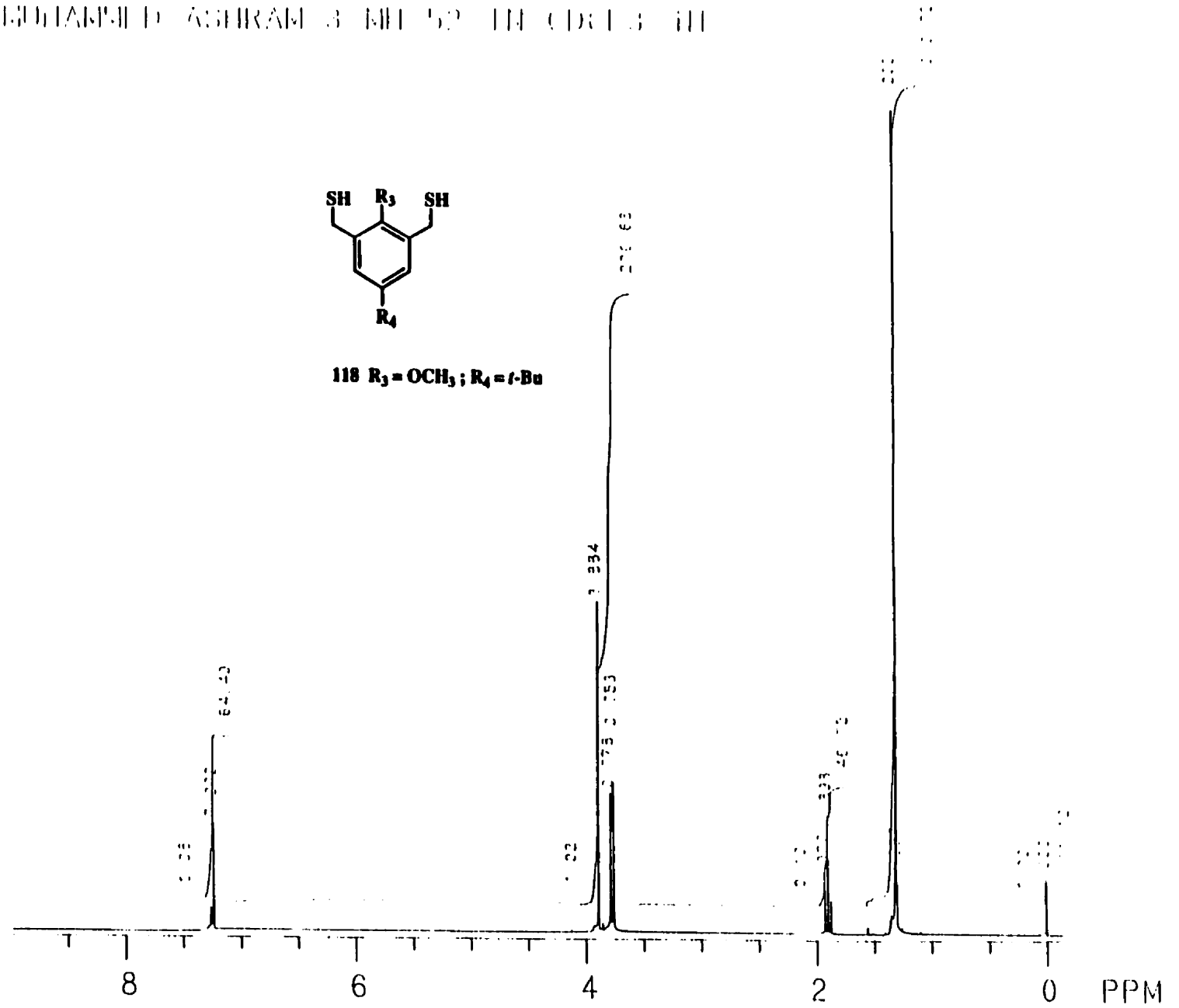


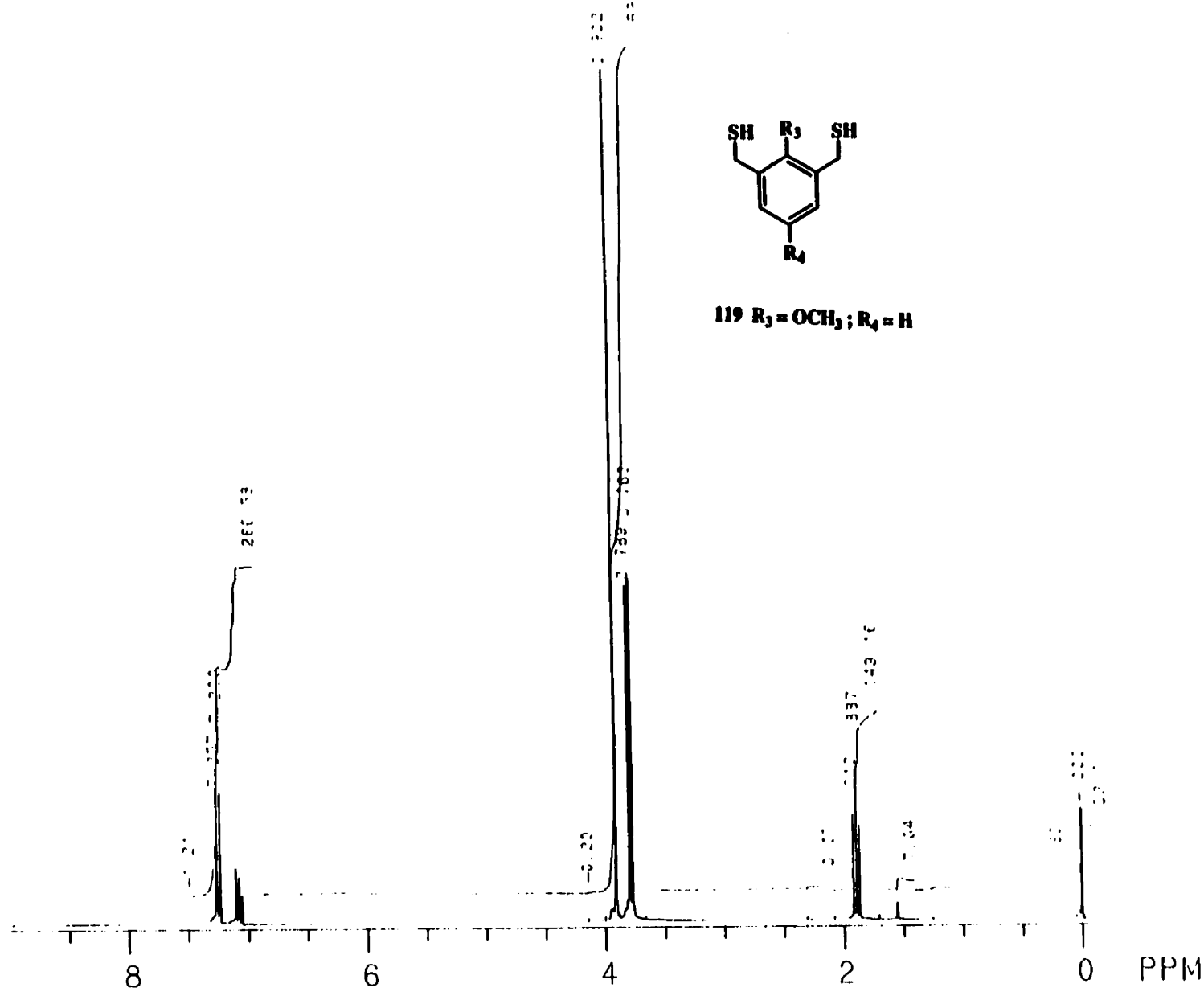
114 $R_1 = OCH_3$; $R_2 = t$-Bu

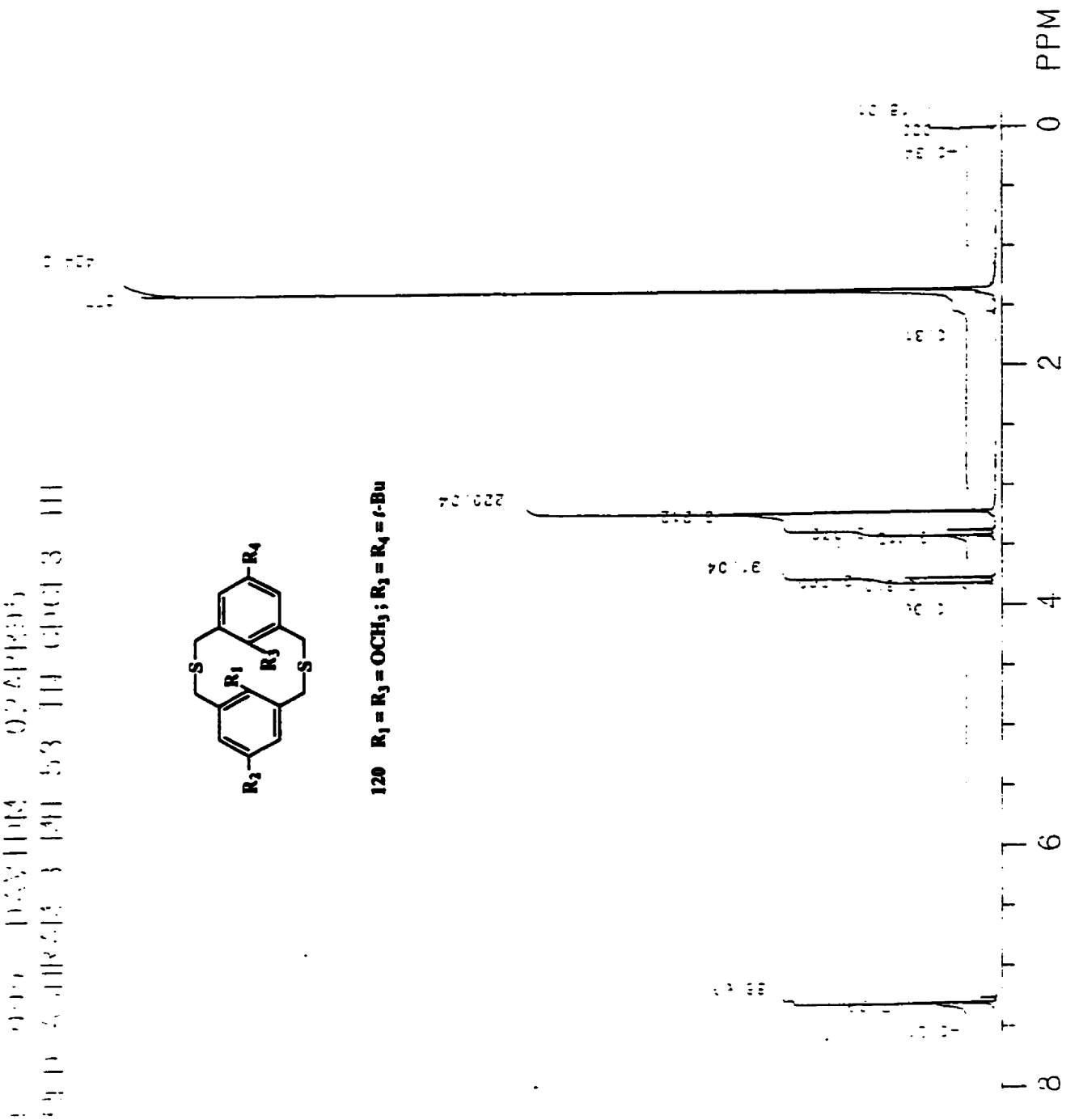

Br
R1
Br
R2
115 R1 = OCH3 ; R2 = H
PPM
0
2
4
6
8


Br
Br
R1
R2
116 R1=H ; R2=H
PPM
0
2
4
6
8

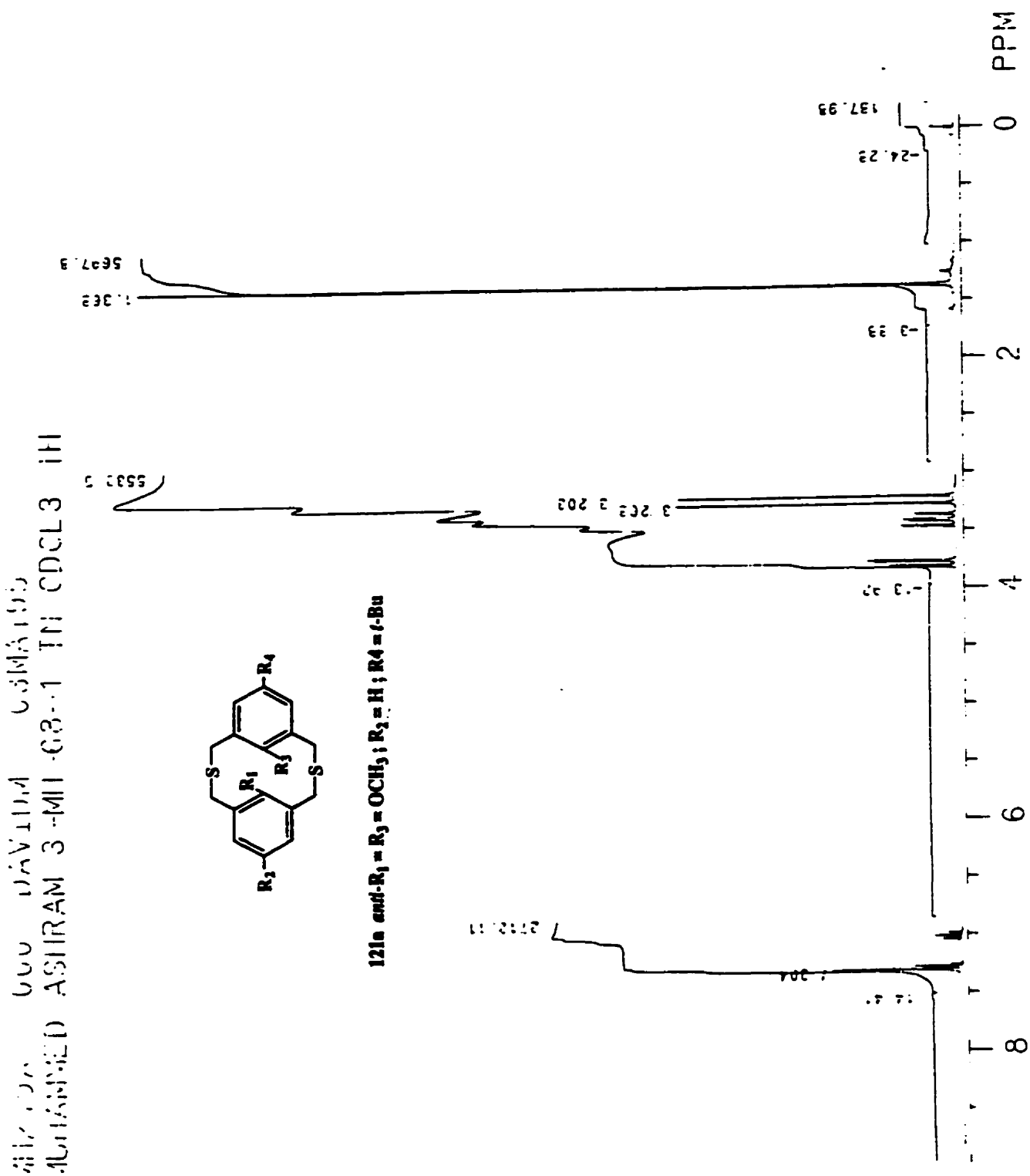

Br
Br
R1
R2
Br
117 R1 = H ; R2 = Br
PPM
0
2
4
6
8

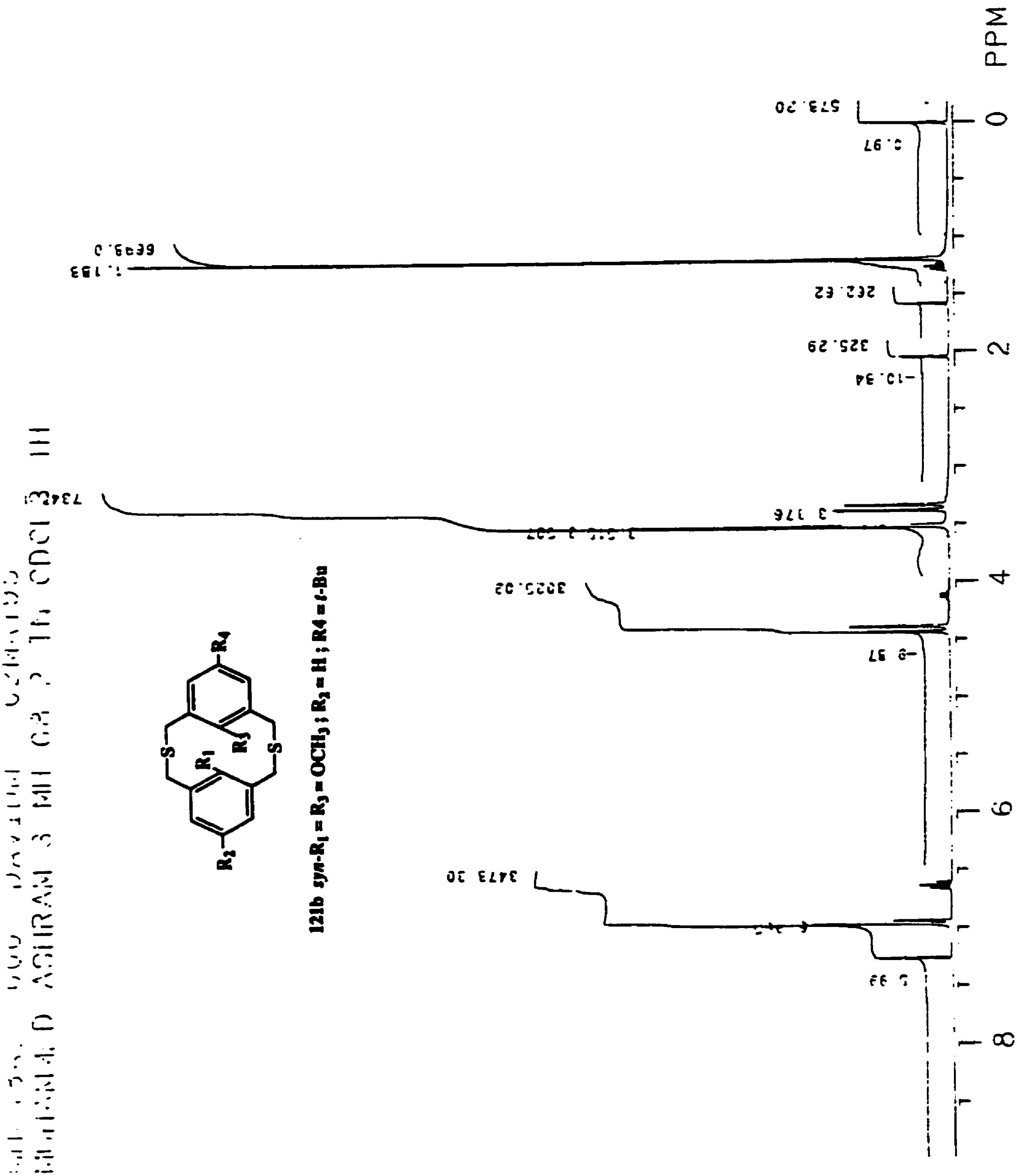

SH
R3
SH
R4
118 R3 = OCH3 ; R4 = t-Bu
8
6
4
2
0
PPM


SH
R3
SH
R4
119 R3 = OCH3 ; R4 = H
8
6
4
2
0
PPM

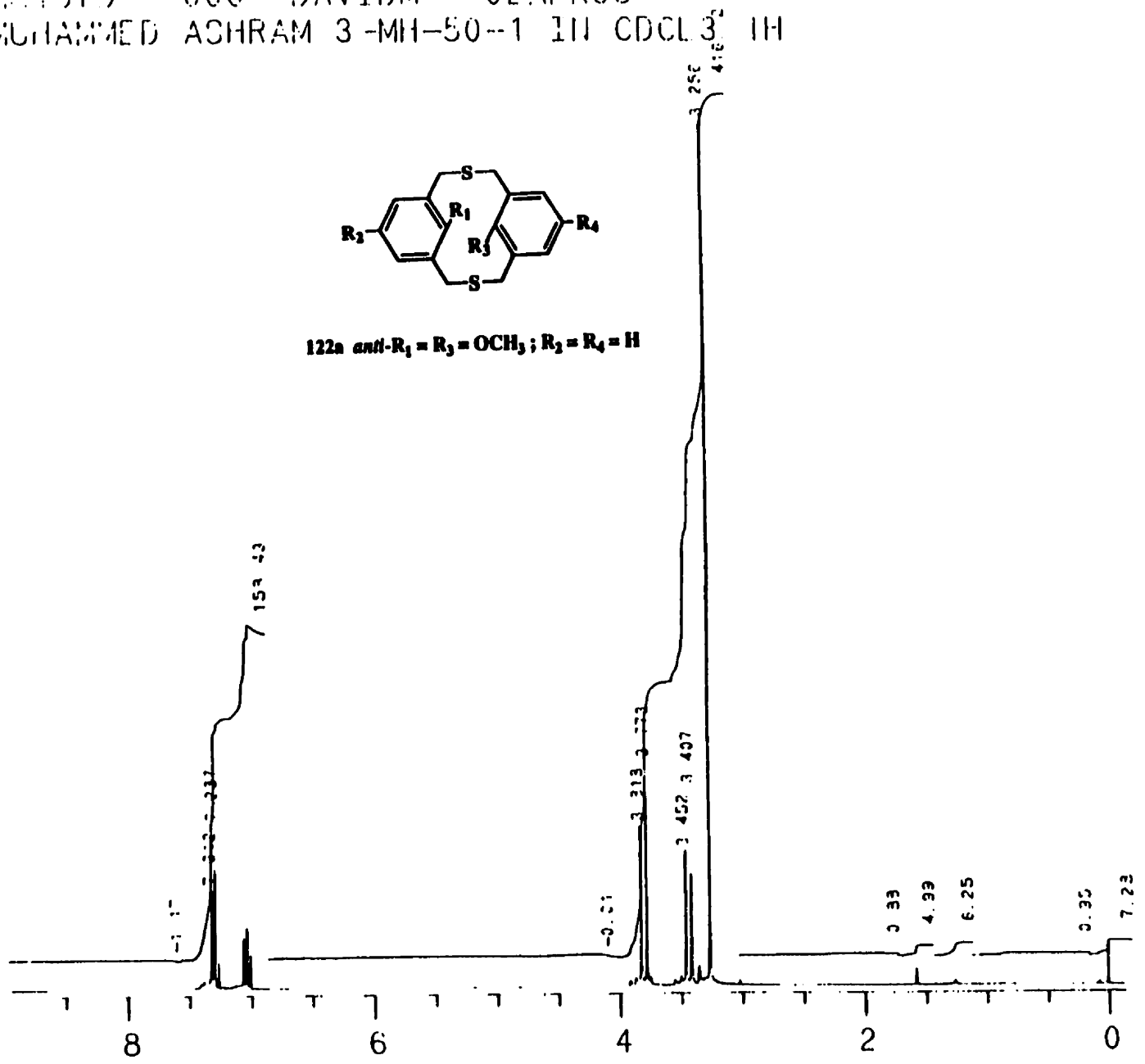


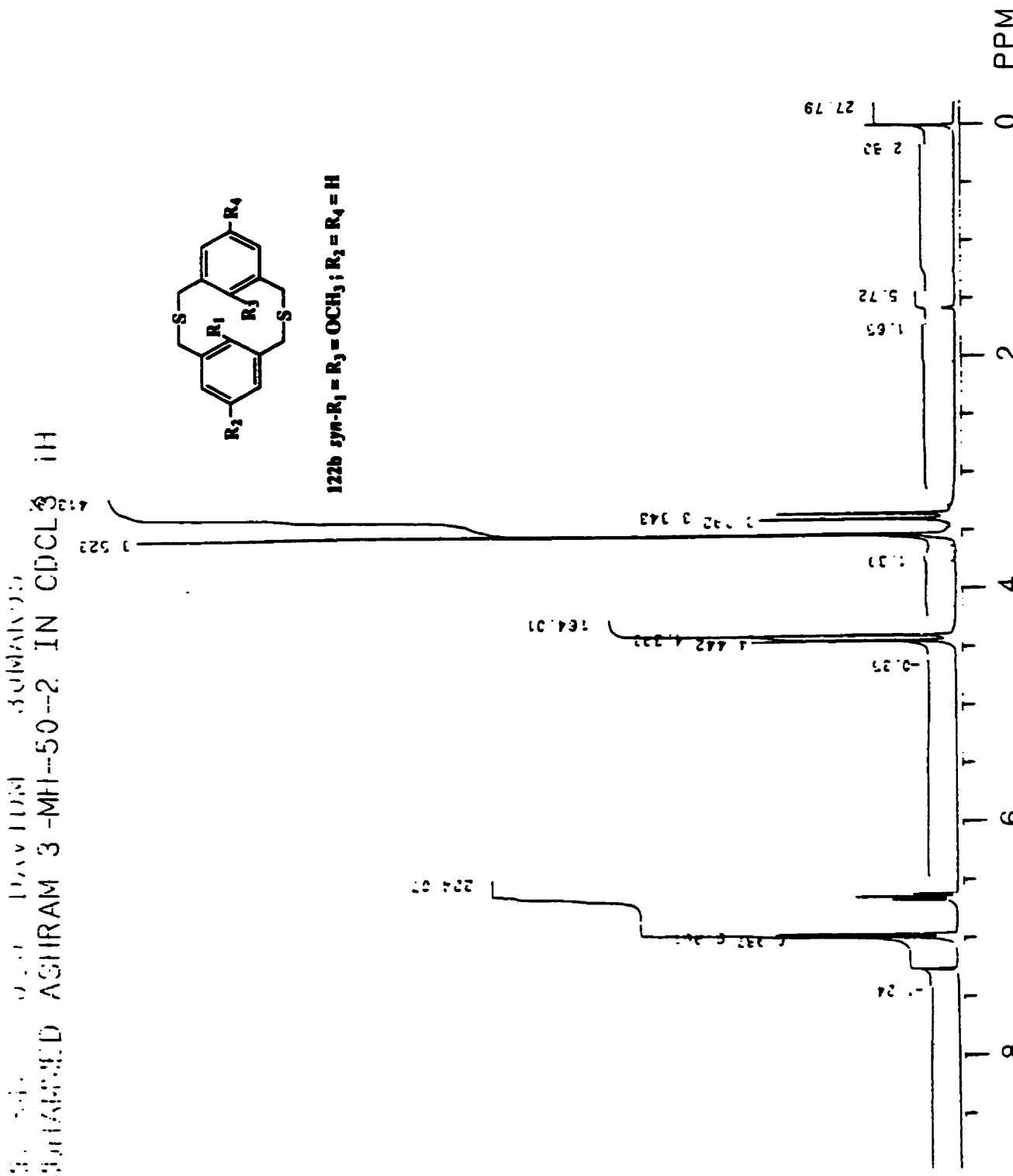
120 $R_1 = R_3 = OCH_3$; $R_2 = R_4 = t\text{-Bu}$

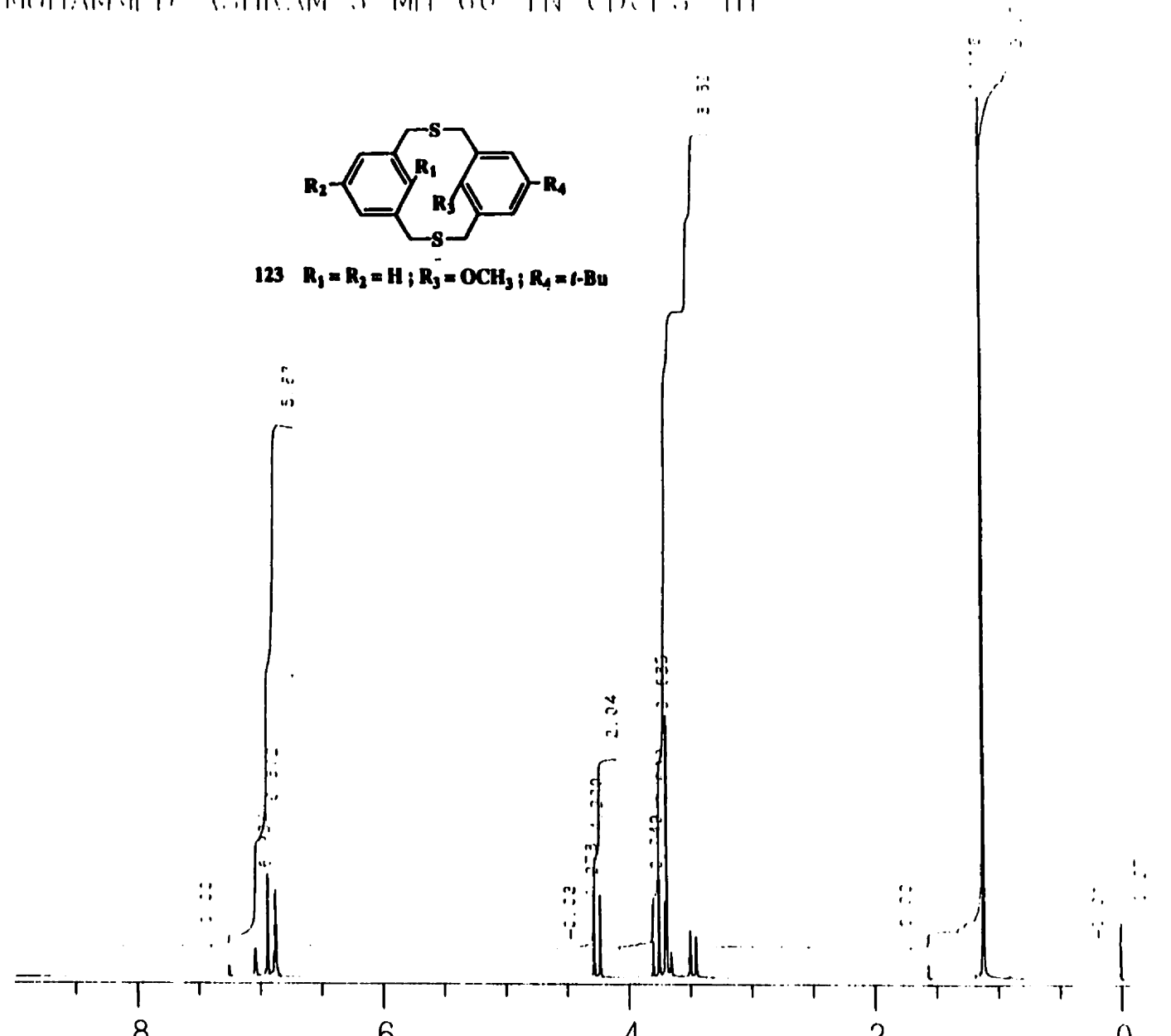

PPM
0
2
4
6
8
137.93
24.23
3.33
3.262
3.203
5533.5
5697.3
1.362
121a anti-R1 = R3 = OCH3 ; R2 = H ; R4 = t-Bu



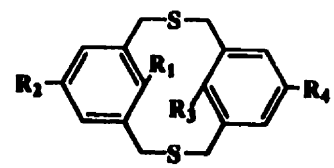
121b *syn*-$R_1 = R_3 = OCH_3$; $R_2 = H$; $R4 = t$-Bu


MOHAMMED ACHRAM 3-MH-50--1 1H CDCL3 1H
S
R1
R2
R3
R4
S
122a anti-R1 = R3 = OCH3 ; R2 = R4 = H
8
6
4
2
0
PPM

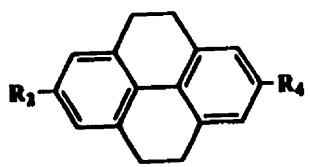

122b syn-R1 = R3 = OCH3 ; R2 = R4 = H
S
S
R1
R3
R4
R2
BRUKER AC 300 FT NMR SYSTEM
AGHIRAM 3-MH-50-2 IN CDCL3 1H
PPM
0
2
4
6
8
27.79
2.30
5.72
1.65
7.343
7.322
7.323
7.33
164.01
4.442
4.333
0.35
224.07
7.337
7.341
7.24


S
R1
R2
R4
R3
S
123 R1 = R2 = H ; R3 = OCH3 ; R4 = t-Bu
8
6
4
2
0
PPM

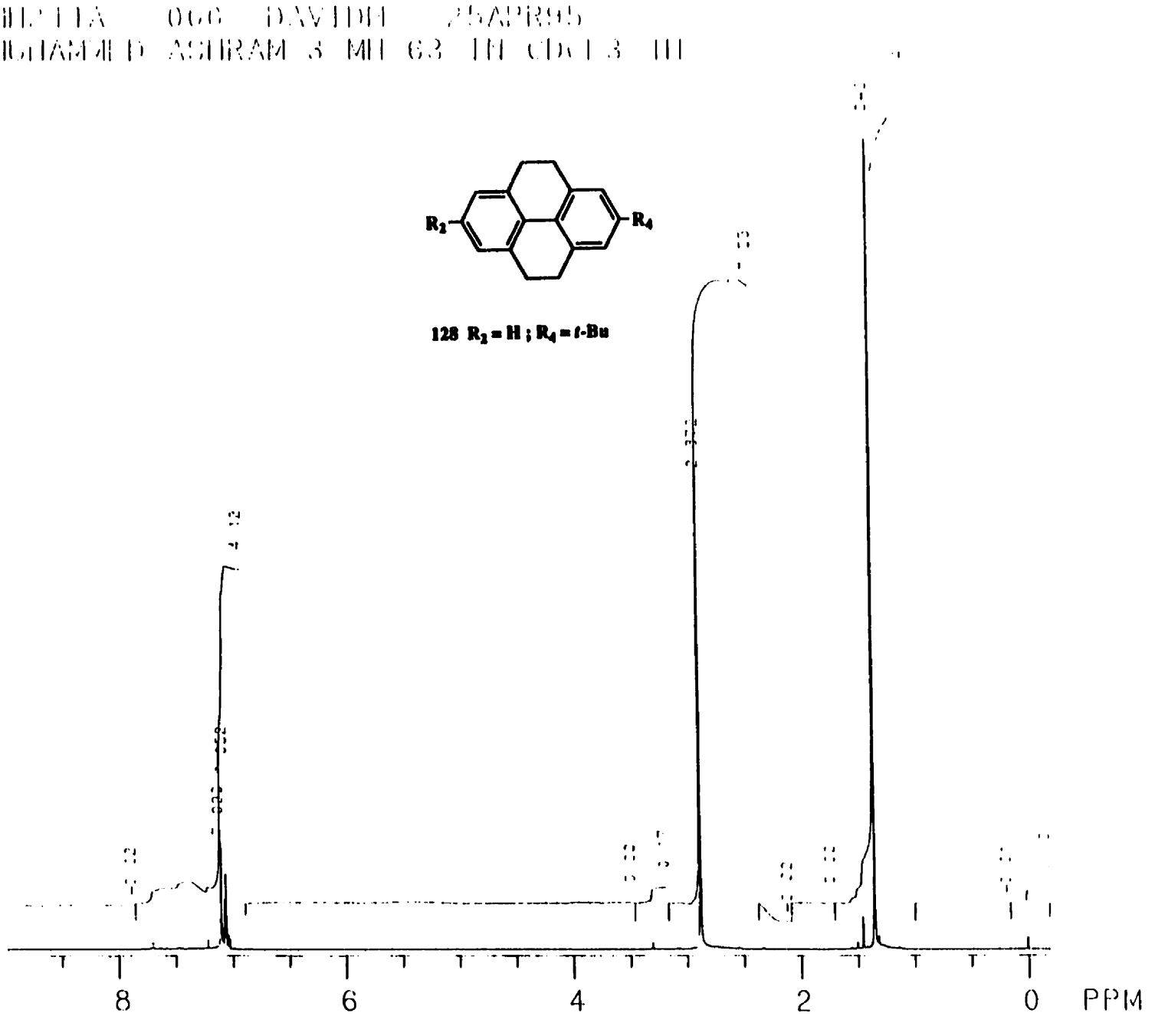
HELP-LA 000 DAVIDM 13APR95
MEASURED ASHRAM 3 MI 59 IN CDCl3 @ 111

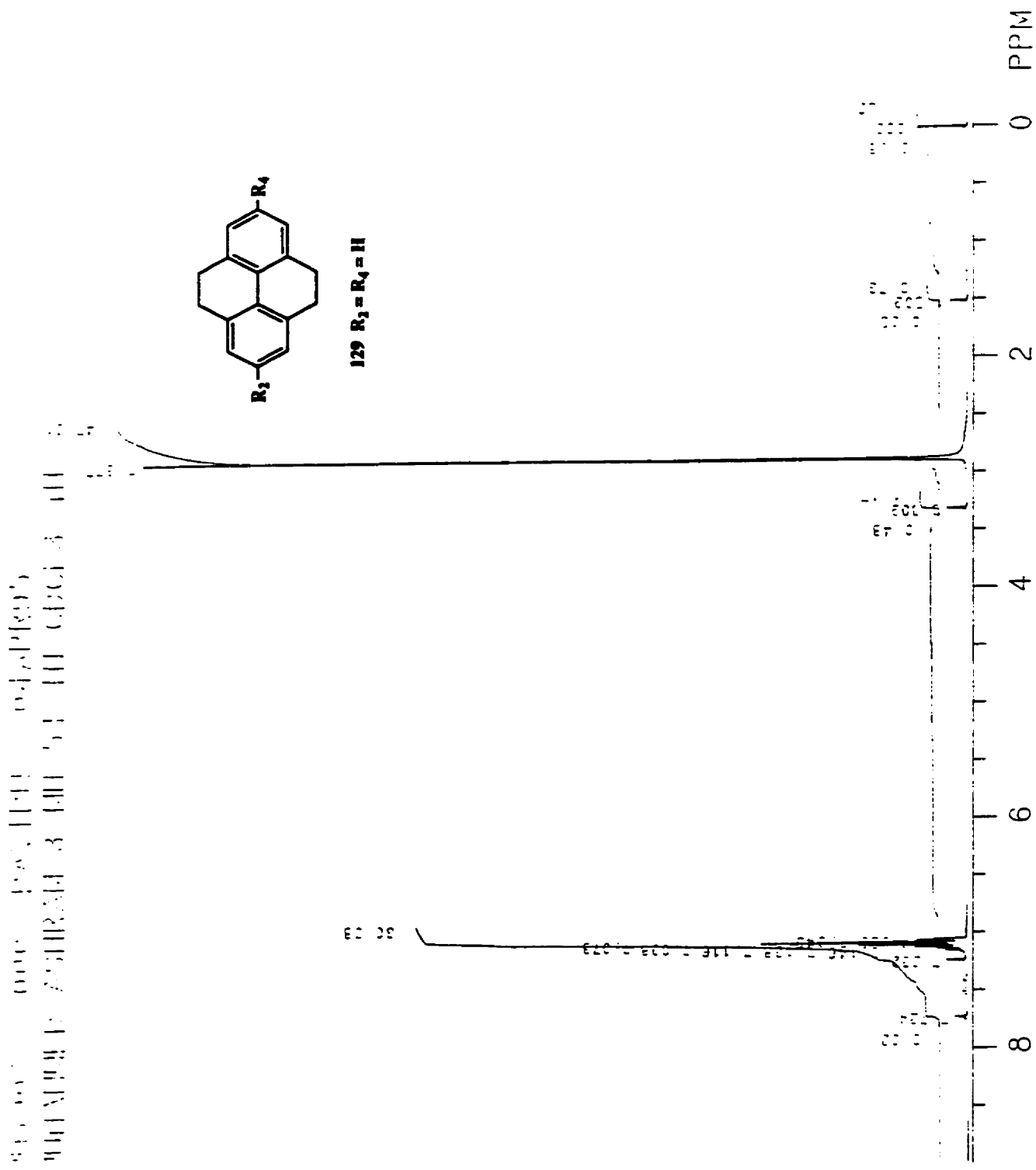


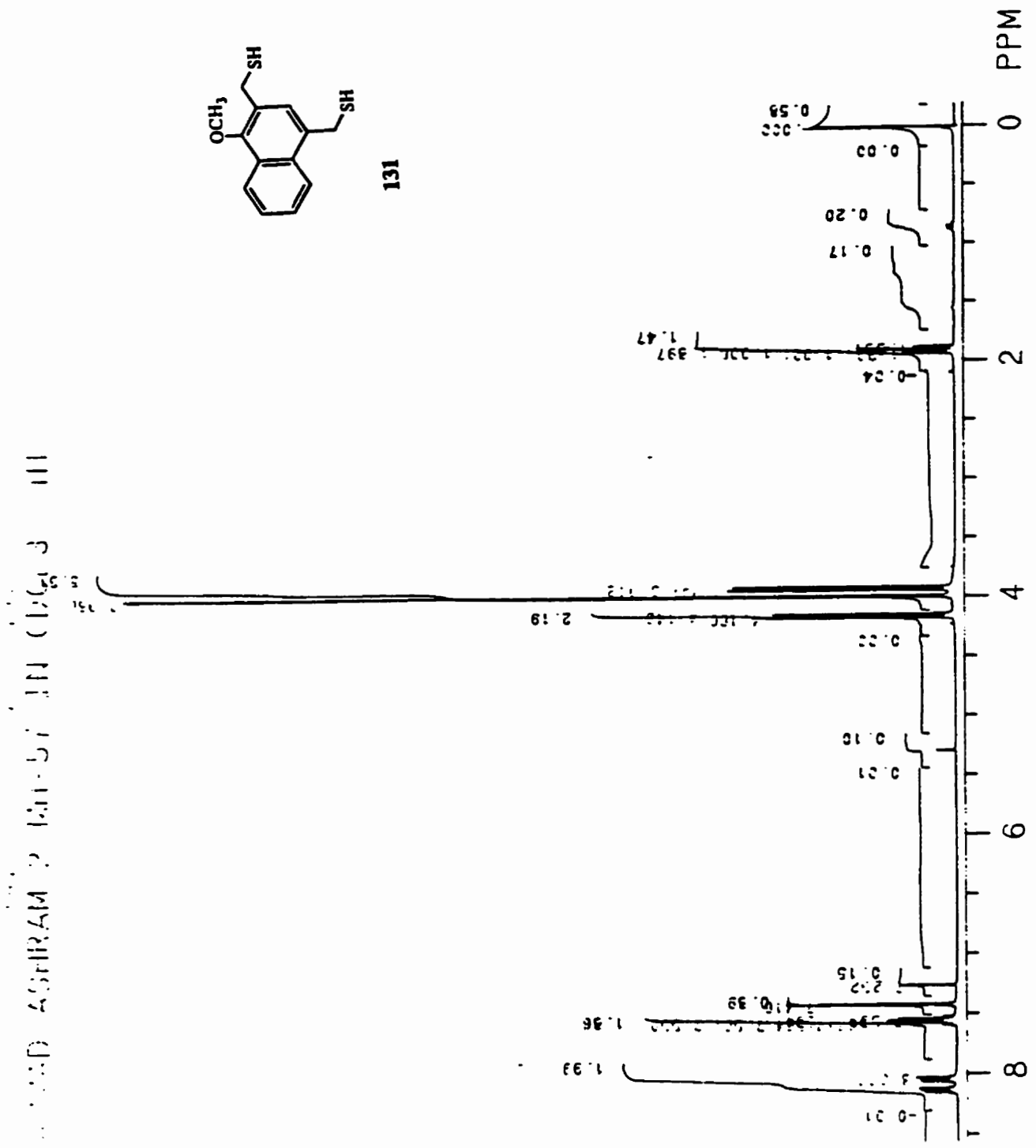
124 $R_1 = H$; $R_2 = Br$; $R_3 = OCH_3$; $R_4 = t\text{-}Bu$

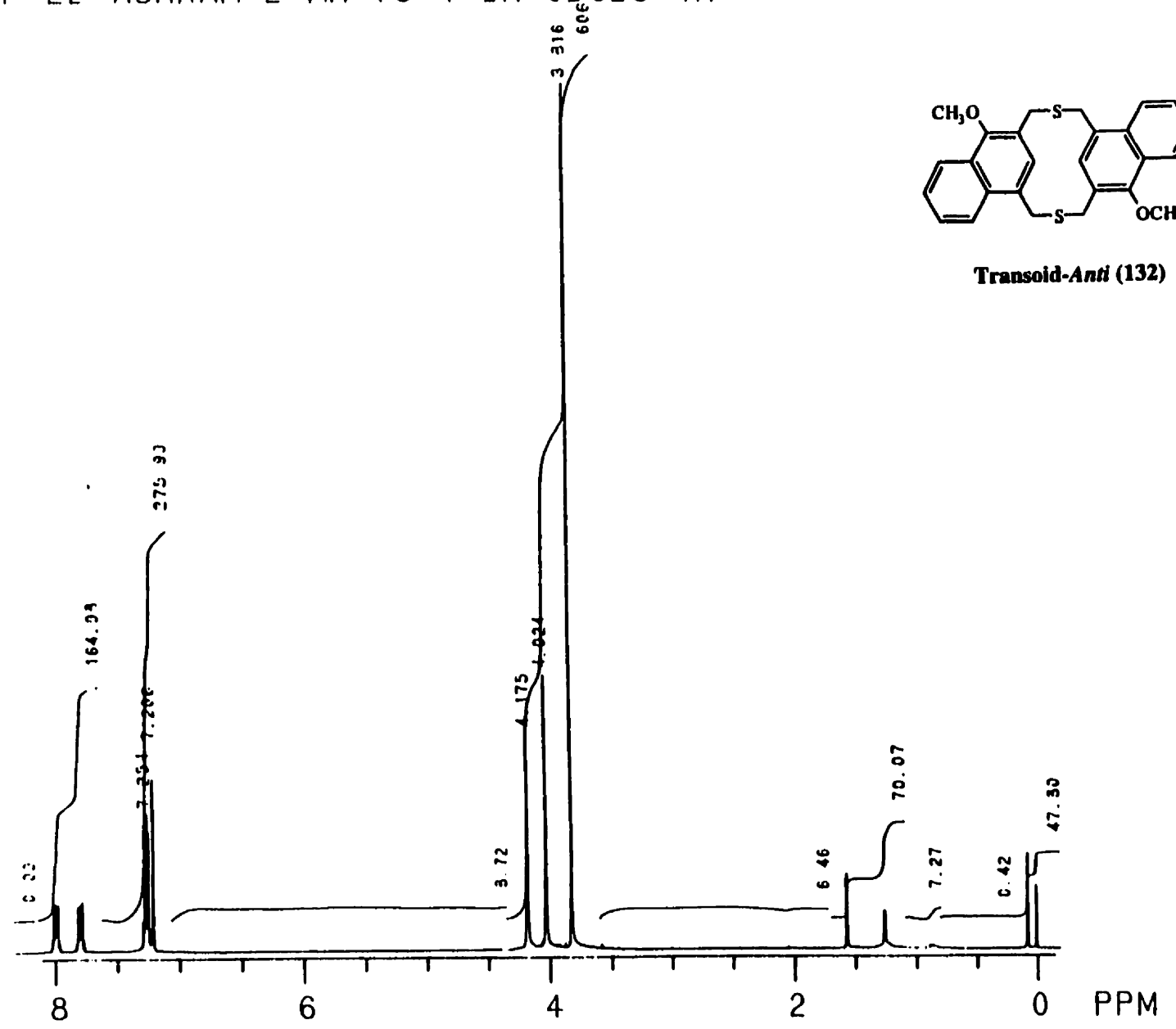


127 $R_1 = R_4 = t\text{-Bu}$

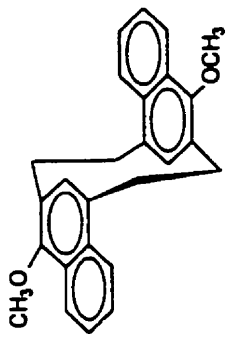

DELTA 006 DAVIDH 25APR95
DEGASSED ACIDRAM 3 MG 63 IN CDCL3 III
R2
R4
128 R2 = H ; R4 = t-Bu
8
6
4
2
0
PPM


R4
R3
129 R3=R4=H
PPM
0
2
4
6
8

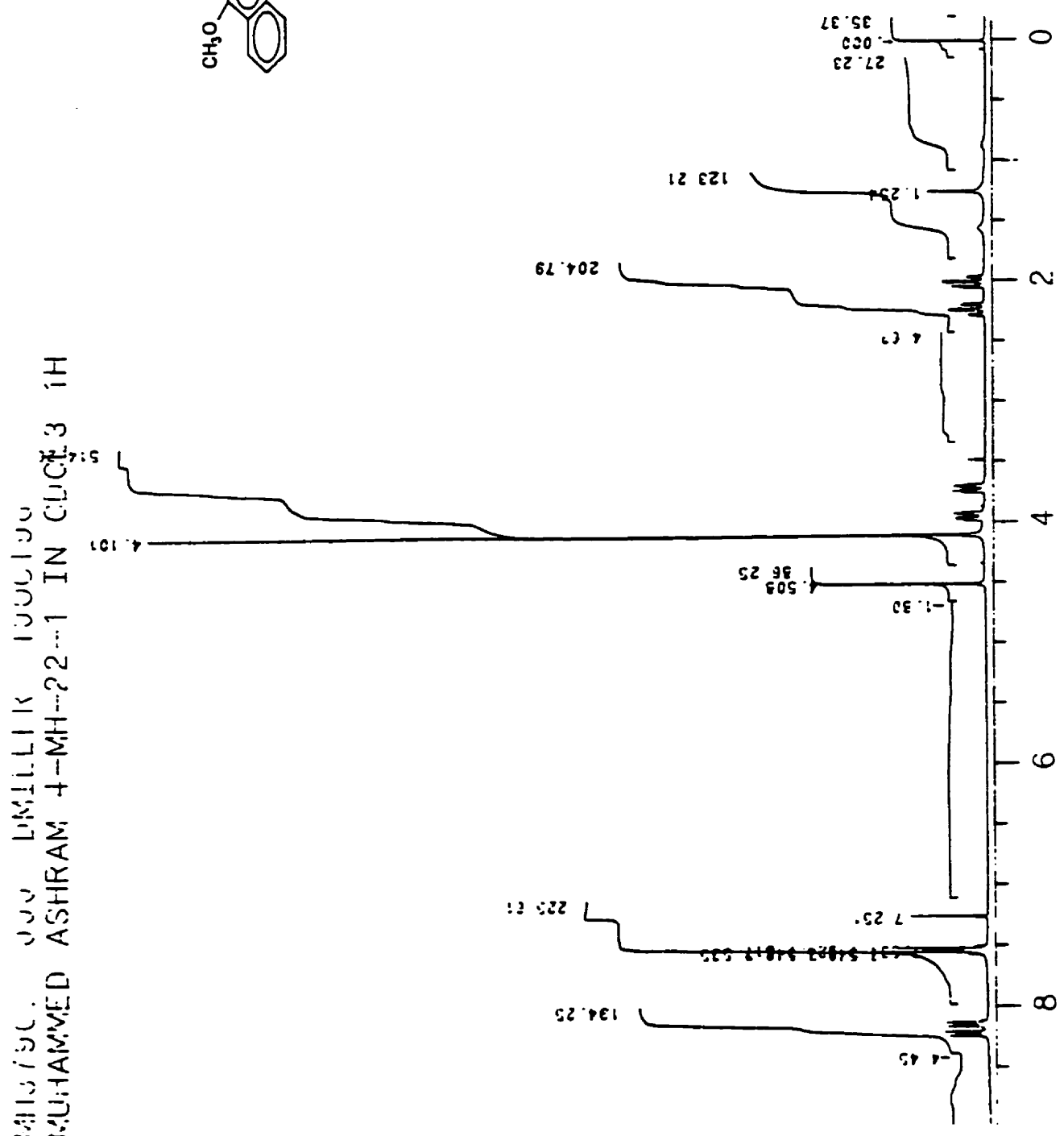

SH
SH
OCH3
131
PPM
0
2
4
6
8
1.47
2.19
1.96
1.93

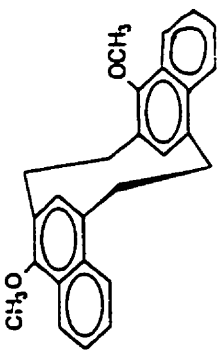


Transoid-*Anti* (132)

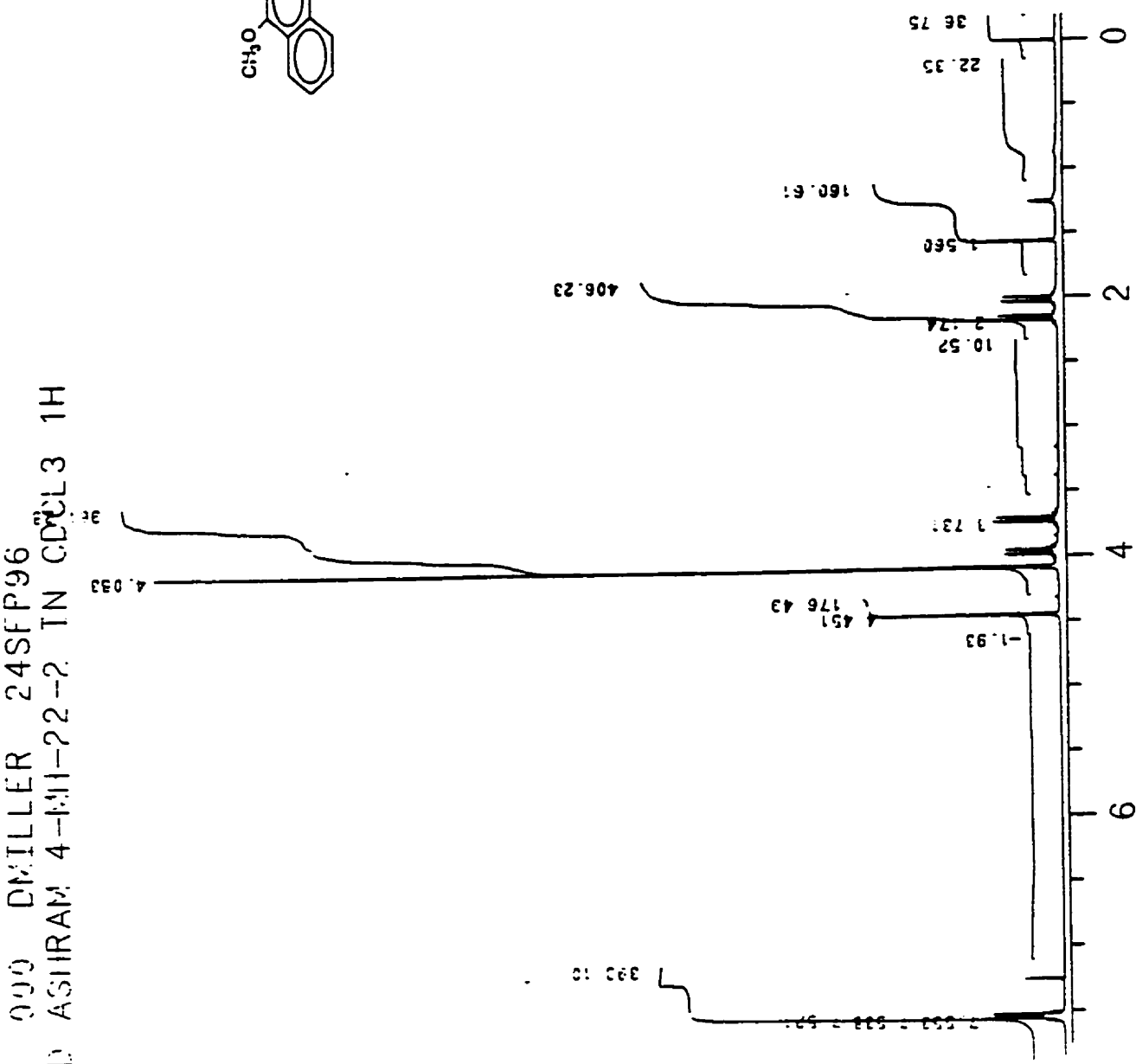


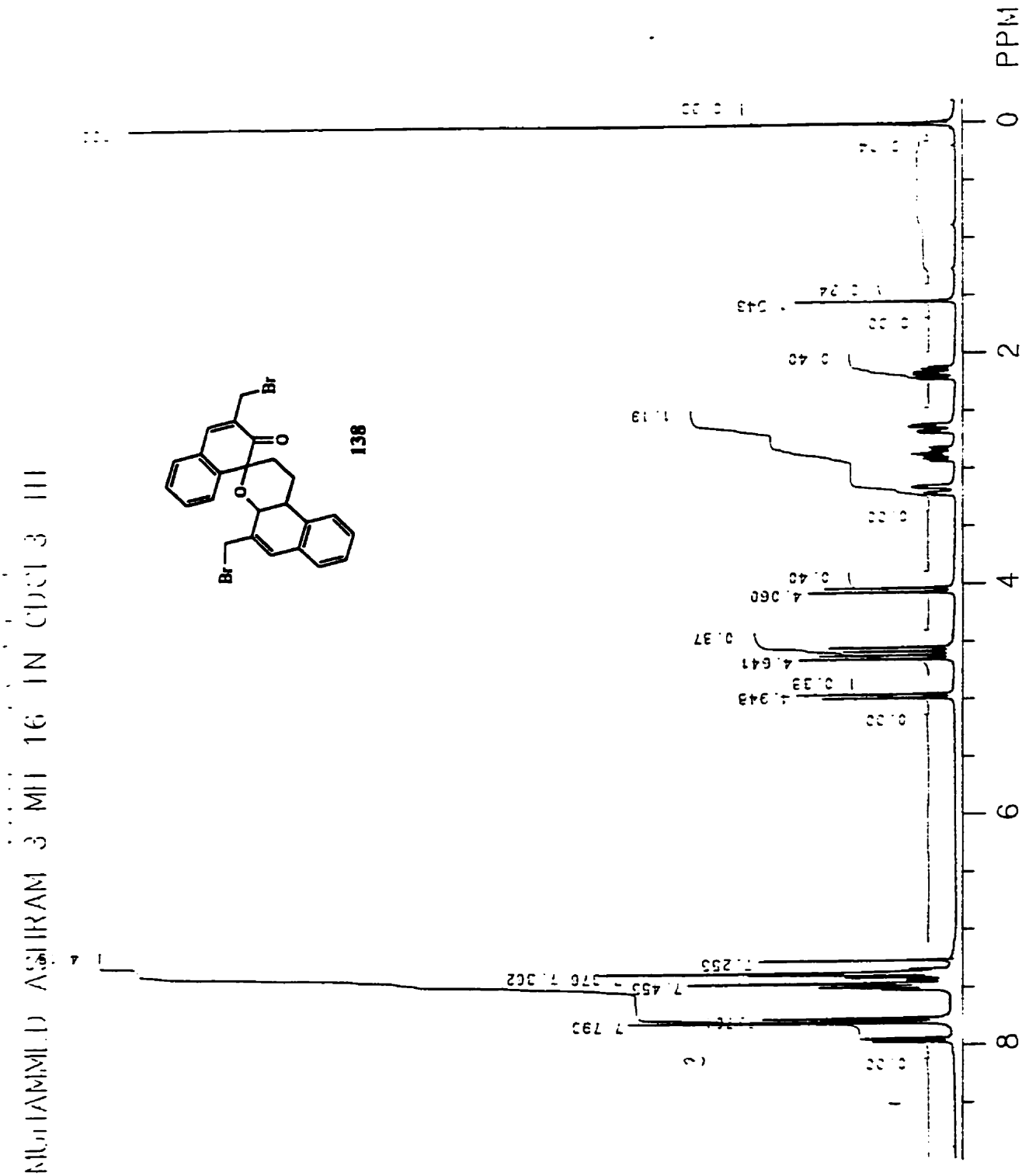
(134)




OCH3
CH3O

(135)


DMTLLER 24SEP96
ASHRAM 4-III-22-2 TN CDCL3 1H
PPM
0
2
4
6
36.75
22.35
160.61
1.560
406.23
2.74
10.52
1.731
4.033
4.451
4.176
1.93
3.93


Br
O
O
Br
138
PPM
0
2
4
6
8

Appendix B

X-Ray Data of compounds
(in order of compound number)

X-Ray Data For Calix[4]naphthalene (57). $C_{44}H_{32}O_4$, triclinic, space group P-1 (#2), a = 12.688(2) Å, b = 14.108(4) Å, c = 11.955(2) Å, α = 98.15(2)°, β = 105.56(2)°, γ = 100.80(2)°, Z = 2, D_{calc} = 1.278 g/cm^3. Intensity data were measured at 296 K on a Rigaku AFC6S diffractometer with graphite monochromated Cu-Kα (λ = 1.54178 Å) to $2\theta_{max}$ (deg) 120.2°; a final R = 0.064 for 4487 reflections with I>2.00σ(I); R_w = 0.063, gof = 4.78.

X-Ray Data For Bis(spirodienone) (78). $C_{44}H_{28}O_4$, monoclinic, space group $P2_1/n$ (#14), a = 13.744(3) Å, b = 11.839(5) Å, c = 18.438(4) Å, β = 94.12(2)°, Z = 4, D_{calc} = 1.378 g/cm^3. Intensity data were measured at 296 K on a Rigaku AFC6S diffractometer with graphite monochromated Cu-Kα (λ = 0.71069 Å) to $2\theta_{max}$ (deg) 50.1°; a final R = 0.101 for 2061 reflections with I>2.00σ(I); R_w = 0.088, gof = 3.38.

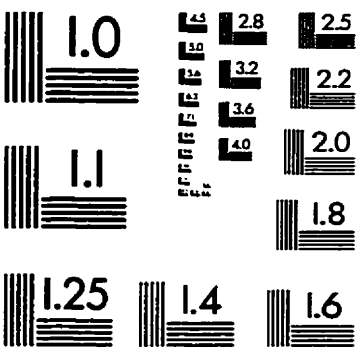
X-Ray Data For Bis(spirodienone) (81). $C_{60}H_{60}O_4.2CH_3CN.2CHCl_3$, triclinic, space group P-1 (#2), a = 12.455(4) Å, b = 13.527(3) Å, c = 9.6046(19) Å, α = 100.216(19)°, β = 102.082(2)°, γ = 85.77(3)°, Z = 1, D_{calc} = 1.244 g/cm^3. Intensity data were measured at 296 K on a Rigaku AFC6S diffractometer with graphite monochromated Cu-Kα (λ = 1.54178 Å) to $2\theta_{max}$ (deg) 60.08°; refinement on F^2, R_1 = 0.0983 for 3036 reflections with I>2.00σ(I); R_{2w} = 0.3418, gof = 1.328 for all reflections.

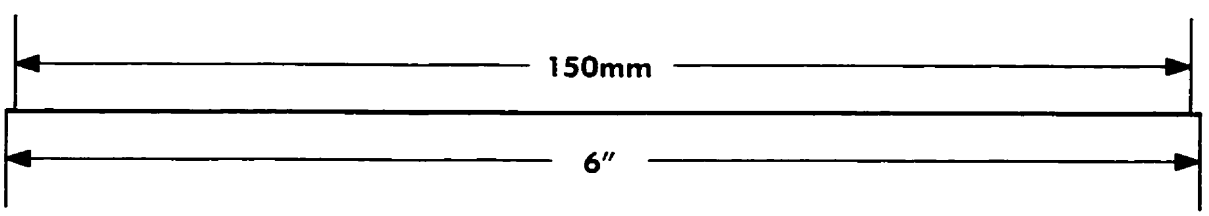
X-Ray Data For Transoid-anti-11,22-dimethoxy-2,13-dithia[3.3](1,3)naphthaleno-Phane (101). $C_{26}H_{24}O_2S_2$, triclinic, space group P1 (#2), a = 8.599(2) Å, b = 9.192(2) Å, c = 8.273(2) Å, α = 108.68(2)°, β = 112.54(2)°, γ = 103.00(2)°, Z = 1, D_{calc} = 1.368 g/cm^3,

crystal size = 0.400 x 0.350 x 0.250 mm. Intensity data were measured at 299 K on a Rigaku AFC6S diffractometer with graphite monochromated Mo-Kα (λ = 0.71069 Å) to $2\theta_{max}$ (deg) = 50,1°; 1853 unique reflections converged to a final R = 0.034 for 1587 reflections with I>2.00σ(I); R_w = 0.036, gof = 2.62.

X-Ray Data For 5,6,12,13-tetrahydrodibenzo[*b,def*]chrysene (107). $C_{24}H_{18}$, triclinic, space group $P2_1$ (#4), a = 11.229(5) Å, b = 15.31(1) Å, c = 14.338(4) Å, β = 105.08(3)°, Z = 6, D_{calc} = 1.283 g/cm^3, crystal size = 0.400 x 0.400 x 0.100 mm. Intensity data were measured at 299 K on a Rigaku AFC6S diffractometer with graphite monochromated Mo-Kα (λ = 0.71069 Å) to $2\theta_{max}$ (deg) = 50,1°; 4394 unique reflections converged to a final R = 0.046 for 2123 reflections with I>2.00σ(I); R_w = 0.030, gof = 1.18.

X-Ray Data For (138). $C_{24}H_{18}O_2Br_2$, monoclinic, space group $P2_1/n$ (#14), a = 9.529(4) Å, b = 17.524(8) Å, c = 12.147(5) Å, β = 98.82(4)°, Z = 4, D_{calc} = 1.651 g/cm^3, crystal size = 0.400 x 0.300 x 0.120 mm. Intensity data were measured at 299 K on a Rigaku AFC6S diffractometer with graphite monochromated Mo-Kα (λ = 0.71069 Å) to $2\theta_{max}$ (deg) = 50,1°; 3913 unique reflections converged to a final R = 0.047 for 1946 reflections with I>2.00σ(I); R_w = 0.032, gof = 1.65.





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