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An approach toward 1,4,7 trimethyl tetracyclo [5.3.2.0(4,9).0(8,10)] dodeca-2,5,11-triene "truncatriene"

Karimi, Sasan, Ph.D.

City University of New York, 1991

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AN APPROACH TOWARD

1,4,7 TRIMETHYL TETRACYCLO

[5.3.2.0(4,9).0(8,10)] DODECA-2,5,11-TRIENE

"TRUNCATRIENE"

by

SASAN KARIMI

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

1991

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

7-26-91
Date

Chair of Examining Committee

7/30/91
Date

Executive Officer

Supervisory Committee

The City University of New York

Abstract

AN APPROACH TOWARD 1,4,7 TRIMETHYL TETRACYCLO [5.3.2.0(4,9).0(8,10)] DODECA-2,5,11-TRIENE "TRUNCATRIENE"

by

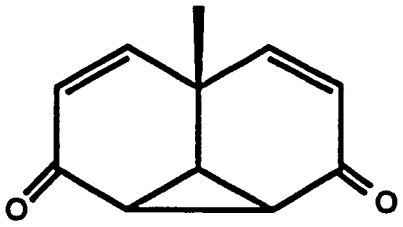
Sasan Karimi

Advisor: Professor Klaus Grohmann

Homoaromaticity is viewed by Winstein as a cyclic "aromatic" polyene where the conjugation is broken at one or more sites by methano or ethano bridges.

Among the neutral hydrocarbons yet known (e.g. 1,4,7-*cis-cis-cis* cyclononatriene, triquinacene, and C_{16}-hexaquinacene), triquinacene shows a small (4.5 Kcal/mol) stabilization energy on the basis of heats of hydrogenation measurements. We are interested in the synthesis of the hydrocarbon 16, since its spherical geometry and rigidity may lead to an alignment of the pπ orbital overlap in order to provide homoaromatic stabilization.

This thesis focuses on the synthesis of the key intermediate 12, an intramolecular alkylation (54 to 57 and 92 to 93) to construct a tricyclic carbon skeleton, and formation of the tetracyclo-[4.4.0.$0^{1,6}$.$0^{2,4}$]-decane-5-one framework (54 to 58 and 55 to 72) *via* possible Favorskii or S_N2' rearrangements.



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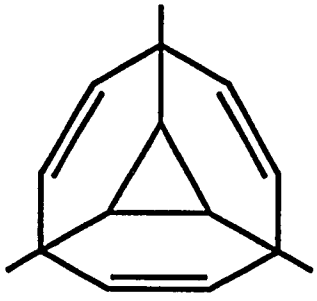


16

ACKNOWLEDGEMENTS

I wish to express my deepest gratitude to my adviser Professor Klaus Grohmann, for giving me the opportunity to be a member of his group, and for teaching me how to appreciate the art of organic chemistry. His continuous support and intellectual discussions made the years of my graduate career pleasant and fruitful.

I am grateful to Professors W. F. Berkowitz, R. W. Franck, and J. M. Schulman who served in my committee and read this thesis at various stages of its preparation. It is a pleasure to acknowledge their helpful comments.

Special thanks go to Mr. Louis Todaro at Hoffmann-La Roche for his invaluable contribution for the X-rays on the chemistry of the bromo-decalone systems. I extend my thanks to Dr. M. Blumenstein for his expert help in recording the nmr spectra, and to Paula Longo who proofread this work.

Finally, I would like to dedicate this thesis to my family who supported me in every way throughout the years of my studies.

TABLE OF CONTENTS

Pages corresponding to spectral data available for compounds listed in section IV

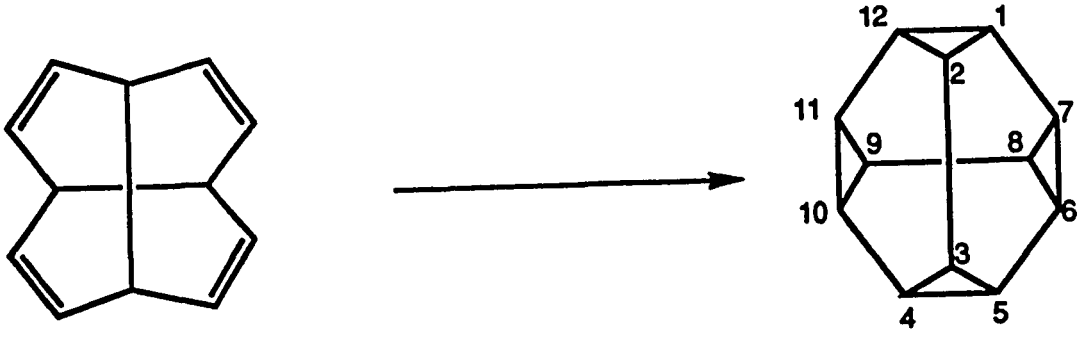
LIST OF SCHEMES

LIST OF FIGURES AND TABLES

I.1 *INTRODUCTION*

The chemistry of strained $(CH)_n$ hydrocarbons has been extensively investigated in the last two decades. Consequently, many of the possible $(CH)_6$, $(CH)_8$, and $(CH)_{10}$ structures have been synthesized and their surprising thermal and photochemical rearrangements have also been examined.[1] There are 506 possible members of the $(CH)_{12}$ system[2] some of which have become the subject of interest.[3-8] Among those, heptacyclo [5.5.0.0^{2,12}.0^{3,5}.0^{4,10}.0^{6,8}.0^{9,11}] dodecane 2, commonly called "Truncated Tetrahedrane" has attracted some synthetic attention[9-18] in the last two decades. Nevertheless, its synthesis has not yet been achieved.

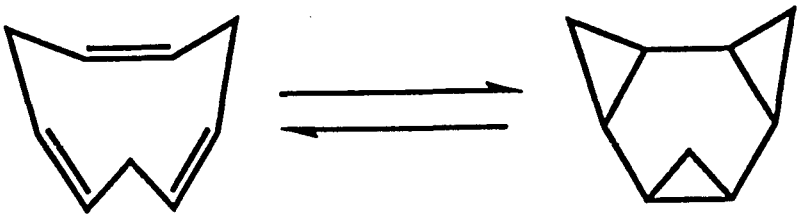
Woodward and Hoffmann suggested[19] that the tetraene 1 may be a potential photochemical precursor for 2 through a photochemically allowed [2+2+2+2] cycloaddition in an all-antara fashion.



1 2

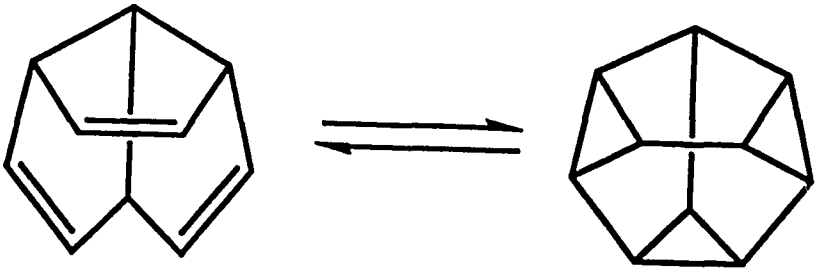
In 1970, Gleiter and coworkers, demonstrated[20] the significance of homoconjugation within the concept of homoaromaticity[21] for *cis,cis,cis*-1,4,7-cyclononatriene 3. The trishomobenzene 4, a tautomer of 3, has not yet been synthesized.

Prinzbach and coworkers have estimated[22] that the symmetry-allowed isomerization of 3 to 4 occurs with an activation energy of 28.2 Kcal/mol.

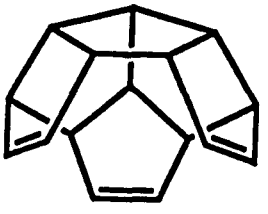


3 4

However, some neutral six-electron trishomoaromatic analogs of benzene have been synthesized; namely 1,4,7-cyclononatriene[23] 3, triquinacene[24] 5, diademane[25] 6, and C_{16}-hexaquinacene[26] 7.



5 6



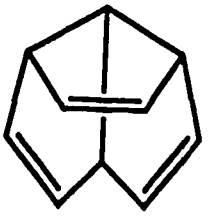
7

Based on ^1H NMR, heats of hydrogenation,[27] X-ray crystallographic studies,[28] and theoretical findings,[29] it was concluded that the triene 3 is not homoaromatic. For example, in the crystal structure analysis of 3, the non-bonded carbon atoms are 2.46 Å apart and have a bond angle of 54.18°. The orbital overlap for 3 proved to be very low (s=0.066).[30] In the case of triquinacene 5, both bond distances and bond angles are increased in magnitude to 2.533 Å and 59.18°, but the orbital overlap is still very low (s=0.054). From the crystal structure of 7, there appears to be a great increase in the bond distances but a decrease of bond angle, 33.99°. At this angle, there seems to be a $\pi-\pi$ repulsion within the cavity of this molecule, hence forcing the cyclopentene rings pucker outward. Therefore, this type of closed shell repulsion reduces the magnitude of orbital interpenetration in 7 to only 0.054 which is identical to the value found for 5. In diademane 6, this type of interaction does not exist.[31]

I.2 *Homoaromaticity of Triquinacene*

Paquette and coworkers[32] discuss the homoaromaticity of triquinacene based on the thermochemical definition rather than the structural or spectroscopic features. By this definition, (like in benzene, where its heat of hydrogenation is less than 3 times that of cyclohexene) triquinacene has a heat of hydrogenation (-78.0 Kcal/mol) that is less than 3 times that of the reference monoolefin, tetrahydrotriquinacene (-27.5 Kcal/mol) by 4.5 Kcal/mol. They then conclude that triquinacene enjoys a small degree of homoaromaticity. At this time, Schulman and coworkers reported[33,34] the geometry-optimized *ab initio* calculation for the above mentioned compounds. According to Schulman, the heats of hydrogenation for going from triquinacene to dihydro, tetrahydro, and hexahydro triquinacene are all equal. Dewar, challenged[35] the concept of homoaromaticity of triquinacene and argued that compound 5 is a neutral hydrocarbon and aromaticity in it would involve a cyclic conjugation in a ring containing three weak homoconjugative interactions. Dewar and coworkers carried out AM_1, *ab initio*, and MM_2 calculations for

triquinacene 5, dihydro 8, tetrahydro 9, and hexahydro triquinacene 10, and stated that triquinacene shows no significant homoaromatic stabilization. Dewar and coworkers concluded, therefore, that based on calculations and a particular model, triquinacene 5 is not an aromatic species and the effect of homoconjugation on its energy is very small. Dewar also argued that homoconjugative interaction may not necessarily lead to significant stabilization in a neutral cyclic conjugated hydrocarbon with an even numbered ring and three "long" (2.51 Å) C-C bonds.



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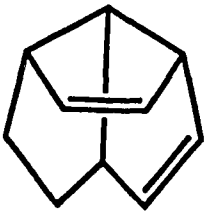

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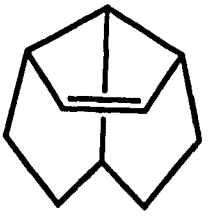

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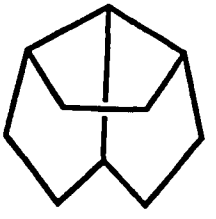
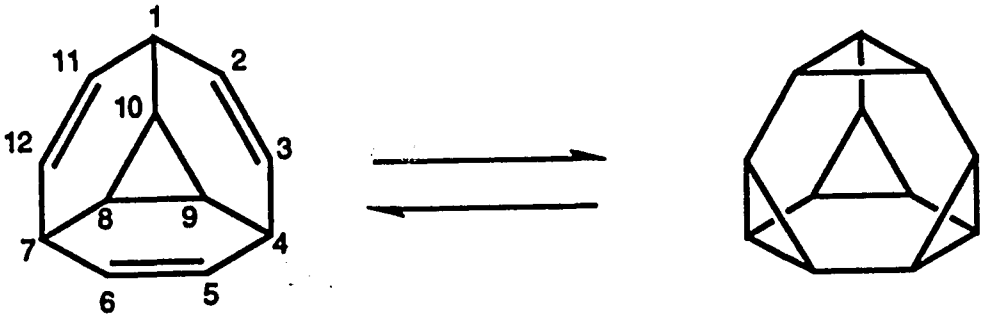


10

Tetracyclo [5.3.2.$0^{4,9}$.$0^{8,10}$] dodeca-2,5,11-triene 11 seems to be a good candidate to test the homoaromaticity of neutral molecules. The cyclopropane ring in 11 will force the three cyclohexene rings down, making the C_2-C_{11}, C_6-C_{12}, and C_3-C_5 distances shorter, thereby creating a better pπ orbital interaction. This type of interaction is absent in both diademane and triquinacene. Furthermore, the geometry of 11 is favorable for the degenerate thermal [2s+2s+2s] interconversion to 2.

Benson and coworkers[36] calculated a ΔG difference between 11 and 2 from the group energy to be ~15 Kcal/mole in favor of 11.

Schulman and Disch[37] used *ab initio* SCF calculation to examine the energy of $(CH)_{12}$ hydrocarbon 2, whose geometry approximates a truncated tetrahedrane. It was calculated that the triene 11 is more stable than 2 by ~16 Kcal/mol and that the tetraene 1 is less stable than 2 by ~24 Kcal/mol. They also tried to find the transition state for the interconversion of 11 $\rightarrow$ 2 by using 4-31G (SCF) energies for geometries that are linearly interpolated between 11 and 2. From the 4-31 G calculations, the energy of activation for 2 was estimated to be 24 Kcal/mol when scaled by the 4-31 G (SCF) energy of activation found for the tropilidine-norcaradiene rearangement. While this value is less than the value found for the energy of activation for the decomposition of diadamantane and homodiadamantane (31.6 and 28.3 Kcal/mol, respectively), it is almost equal to the calculated value for trishomobenzene (24-26 Kcal/mol). In view of the strain energy associated with 2, if formed, 2 may open to 11 spontaneously.



11 2

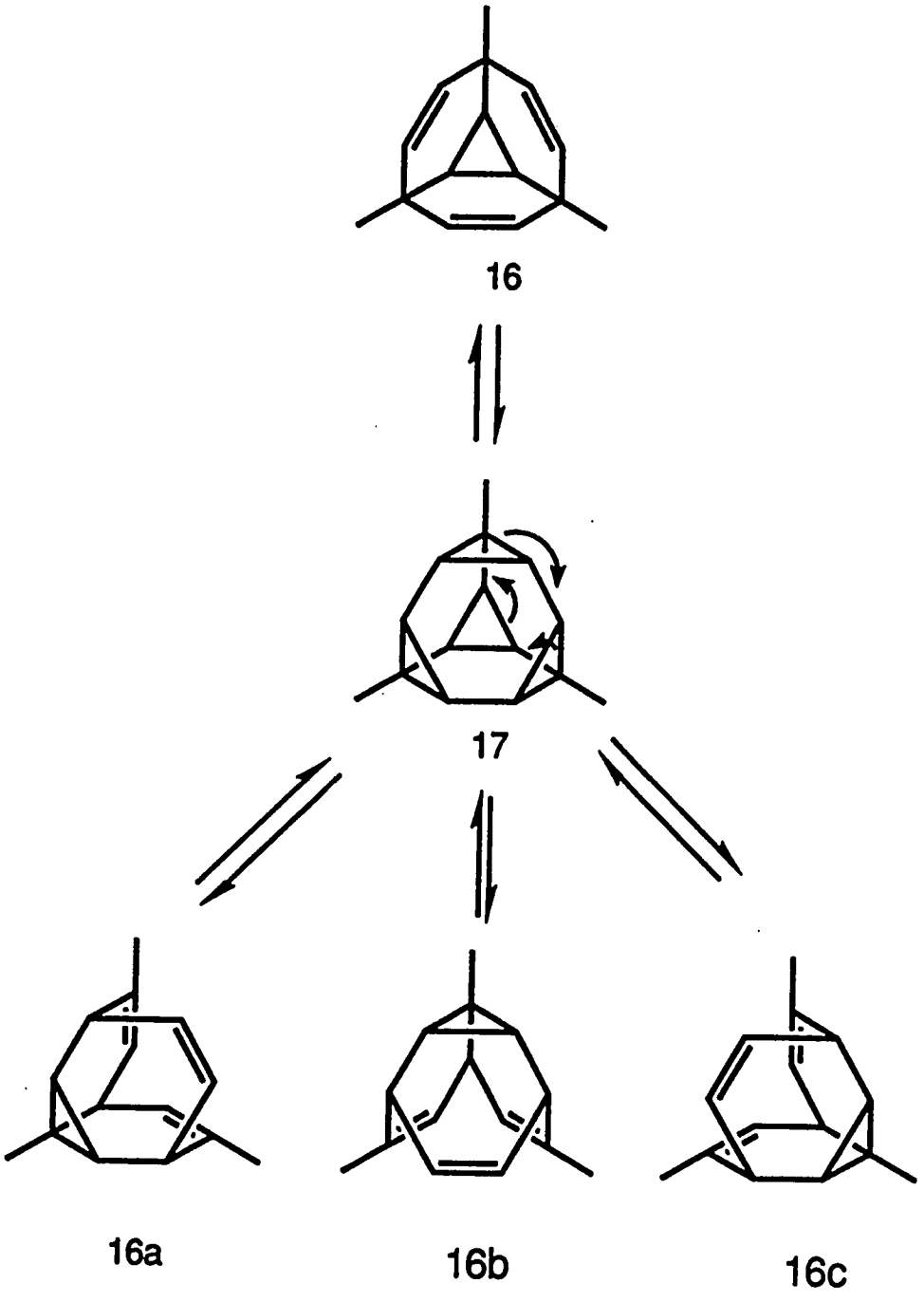
Diademane 6 is structurally similar to 2. In diademane the three cyclopropanes attached to trishomobenzene are connected to a methine carbon, whereas in truncane 2, the cyclopropanes are capped by the fourth cyclopropane ring. From the calculated activation energy[38] for diademane 6 reverting to triquinacene 5, we may be able to estimate the energy of activation of the process of 11→ 2. When warmed diademane smoothly rearranges to triquinacene with a half-life of ~60 min, at 90°C, identified by means of its ^{1}H-NMR, with an activation energy of 31 Kcal/mole. This [$\sigma 2_s + \sigma 2_s + \sigma 2_s$] cycloreversion process is an allowed process and is facilitated by the considerable ring strain.

I.3 *PURPOSE AND STRATEGY*

The purposes of this thesis are: (a) to develop a synthetic methodology leading to the triene 16, and (b) to study and explore the ΔH and energy of activation for 16→ 17, and the strain energies as well.

Like in compound 11, molecular models of 16 show that the improved spherical geometry in this triene should lead to a better alignment of the pπ orbital overlap as compared to compounds 3, 5, and 7.

We chose to synthesize the title trimethyl substituted truncatriene 16 because its degenerate thermal [2s+2s+2s] interconversion to 17 and its subsequent [σ2s+σ2s+σ2s] cycloreversion places the three methyl groups on different kinds of carbon atoms. This creates a significant structural difference between 16 and 16a, 16b, or 16c. In 16, one expects to see from the ^{1}H and ^{13}C NMR, only one signal for the three methyl groups since they are equivalent. In structures 16a, 16b, or 16c which are identical, the magnetically non-equivalent methyl groups should display a set of two signals in both ^{1}H or ^{13}C NMR spectra. In 16a, one expects to see that the two methyl groups on the olefinic carbons C_2 and C_6 appear slightly downfield than the methyl group on the cyclopropyl C_9.



16

17

16a

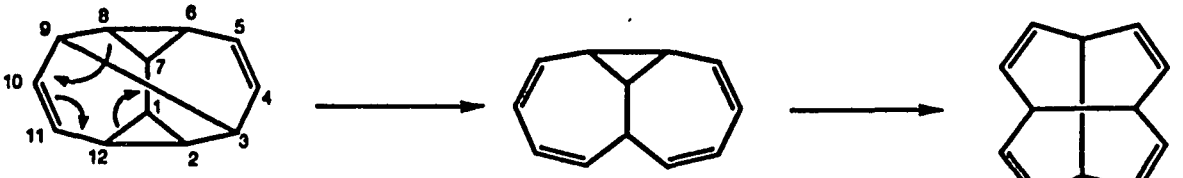
16b

16c

I.4 *PREVIOUS RESULTS*

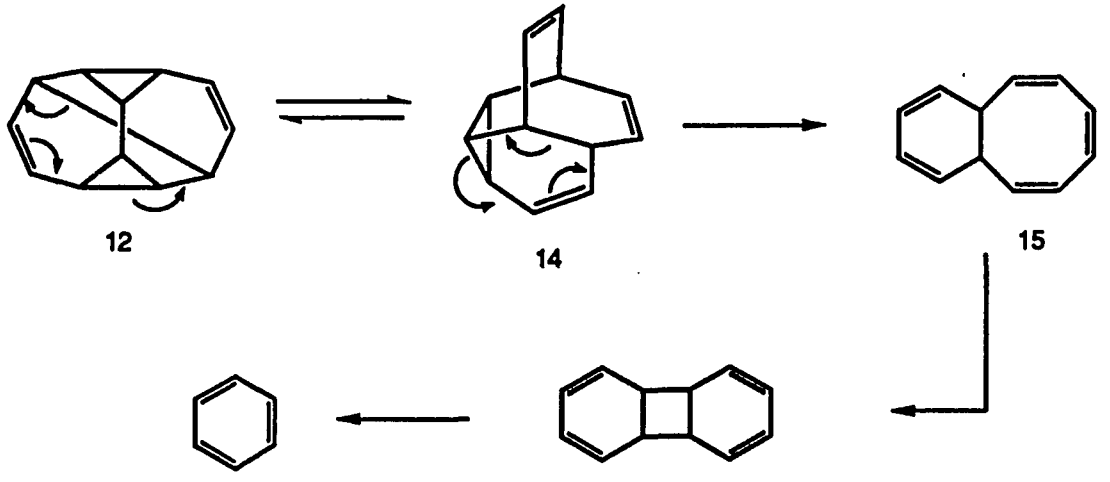
Vedejs approach towards the tetraene 1

Pentacyclo [5.5.0.0^{2,12}.0^{6,8}.0^{3,9}] dodeca-4,10-diene 12 was prepared by Vedejs,[10] in the hope that it would be converted to 13 by a retro-Diels-Alder cleavage. Subsequent Cope rearrangement of the divinyl cyclopropane 13 should have given rise to the tetraene 1 directly.



12 13 1

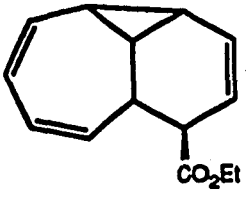
When 12 was subjected to vapor phase pyrolysis in a quartz reactor, there was no detectable amount of 13 present. In fact, 12 on heating above 160°C, rearranged exclusively to benzene.



12 14 15

The mechanism of this rearrangement may involve a 6-π electron transformation of 12 to 14, followed by a retro-Diels-Alder reaction of 14 to 15. Similar retro-Diels-Alder reactions of this type have been observed[39] for cleavage of tetracyclo [4.4.0.0^{2,10}.0^{5,7}] deca-3,8 diene. This mechanistic hypothesis was further elaborated when 14 was synthesized via a different pathway. It was found that 14 on thermolysis above 160°C did in fact fragment to benzene. More interestingly, between temperatures 120° and 150°C, 14 rearranges to 12. This shows that interconversion of 14 occurs to the more stable isomer 12 at high temperature. Although this experiment provides evidence that the rearrangement of 12 to benzene involves 14 as an intermediate, it does not rule out 13 as a possible reactive intermediate which may equilibrate with either 12 or 14 during the thermolytic rearrangement.

Vedejs[11] later synthesized a variety of stable divinyl cyclopropanes and planned to convert these intermediates into the corresponding Cope rearranged products.



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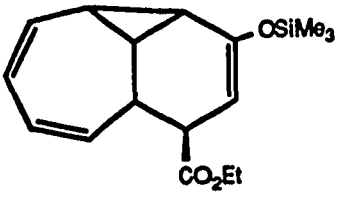

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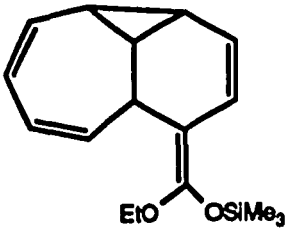

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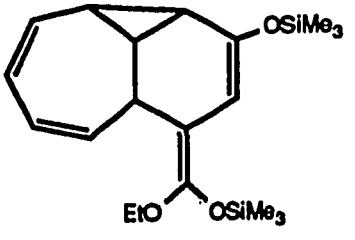
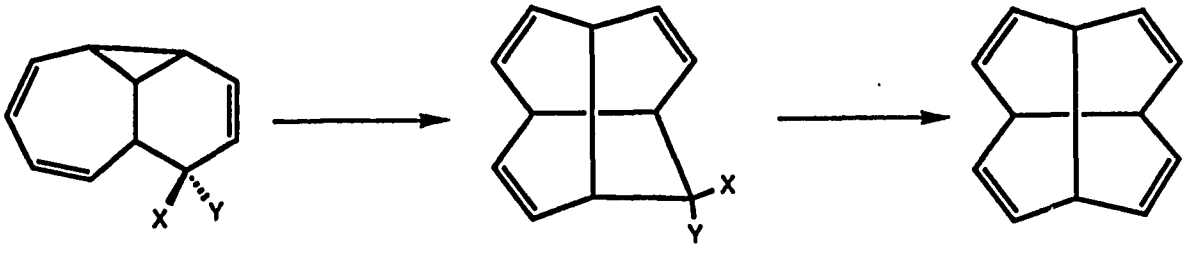


21

It was hoped that compound 18 under Cope rearrangement would give rise to 22a. Hydroxylation of the ester enolate 22a should produce 22b. Reduction and tosylation of 22b to 22c followed by a pinacol type ring expansion should afford the desired skeleton of 1 directly.



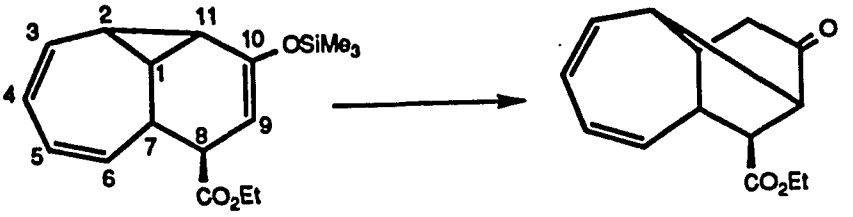
18
X = CO_2Et
Y = H

22a, X = CO_2Et
Y = H
22b, X = CO_2Et
Y = OH
22c, X = CH_2OTs
Y = OH

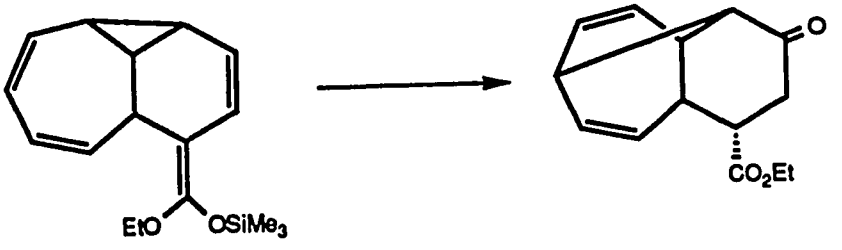
1

Vedejs and coworkers encountered difficulties at the very first step. It was observed that the divinyl cyclopropane 18 on thermolysis, underwent a bond cleavage at C_2-C_{11} followed by bond making between C_2 and C_9 to afford 23. The reason for a lack of Cope for either structure 18 or 19 is as follows: compounds 18 and 19 contain a double bond and an sp^3 hybridized carbon in the six membered-ring. Cope rearrangement in these structures, as observed by molecular models, requires flattening of the six-membered ring for a six-center Cope transition state. This increases the activation energy for the Cope rearrangement, hence the reaction chooses the homolytic cleavage path as described earlier. Vinyl cyclopropanes 20 and 21 on the other hand, contain a double bond and an sp^2 hybridized carbon in the six-membered ring. Thermolysis of 20, results in bond cleavage at

C_2-C_{11} followed by bond forming between C_4 and C_{11} to give 24. consequently, rearrangement of these vinyl cyclopropanes is not a successful strategy for the synthesis of the desired rearranged isomer 22.



18 23

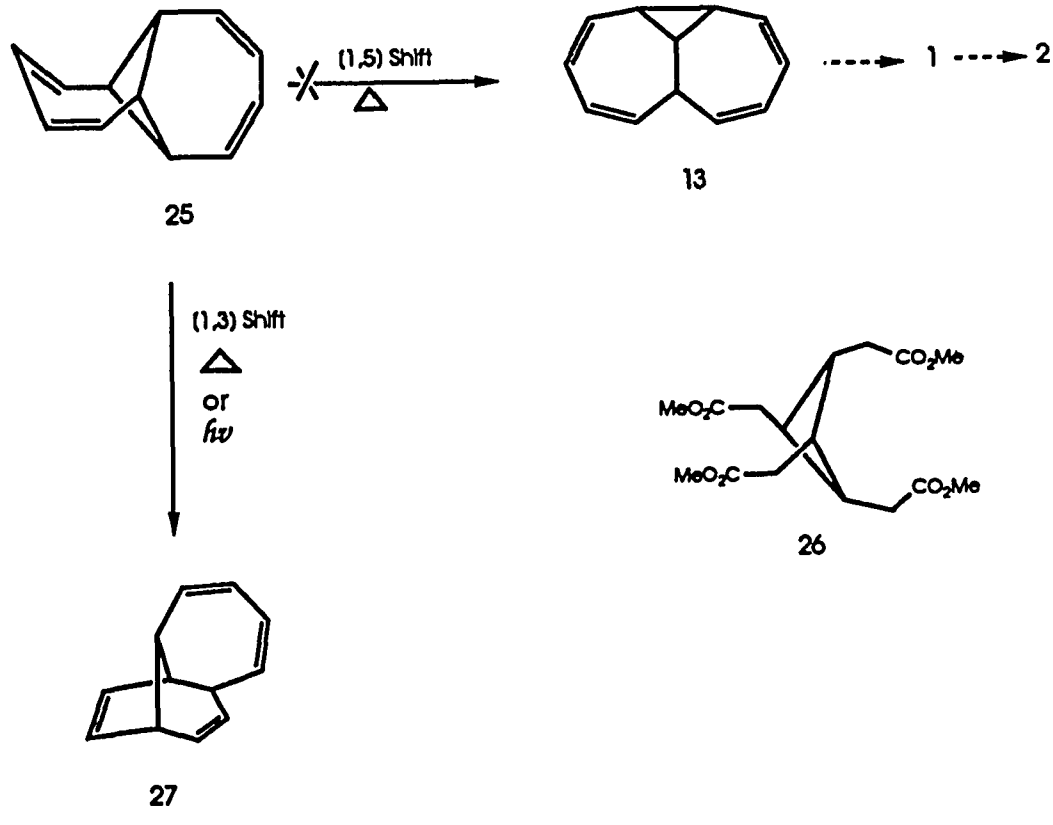


20 24

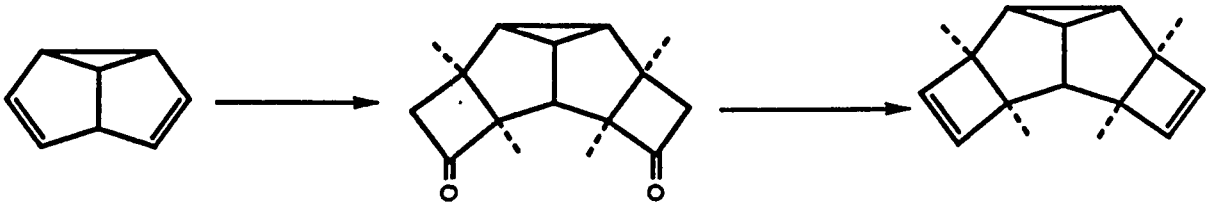
Brousseau's approach towards the truncane 2

Rearrangement of tricyclo [5.5.0.$0^{2,8}$] dodecatetraene 25 was envisioned as another approach[15] to the synthesis of truncated tetrahedrane *via* the divinyl cyclopropane intermediate 13.

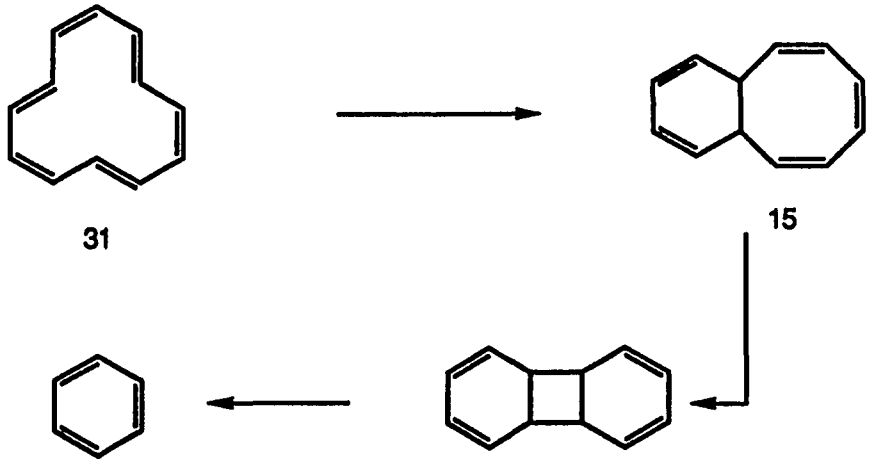
Attempted synthesis of 25 by Dieckmann or acryloin condensation of the tetraester 26 was unsuccessful. However, the hydrocarbon 25 was later synthesized,[40] and it was shown that heating a $CDCl_3$ solution of 25 to 80°C induces clean rearrangement to 27. The same isomerization was observed when compound 25 was subjected to irradiation with a TLC UV lamp (λ 254 nm). It was then concluded by Paquette that,[40] "compound 25 finds [1,3] sigmatropic migration to be most accessible from its ground and exited states."



In an effort to make 13, compound 30 was prepared[15] in hope that it would isomerize to 13 by conrotatory ring openings of the cyclobutene rings. The reaction of the semibullvalene 28 with dichloro-ketene gave a crude material whose ir, nmr, and mass spectrum were in agreement with the desired bis-adduct. This adduct, without purification, was dechlorinated to give 29 as the only product. The diketone 29 was reduced, the resulting di-alcohol was mesylated, and elimination gave 30 in 50-65 % yield based on the mesylated compound. Vacuum pyrolysis of 30 gave benzene, perhaps through the intermediacy of annulene 31. There seem to be precedent[41] for $(CH)_{12}$ hydrocarbon behaving in similar fashion. As demonstrated by Schroeder,[41] 12-annulene 31 thermally rearranges to benzene *via* the valence bond tautomer 15.



28 29 30

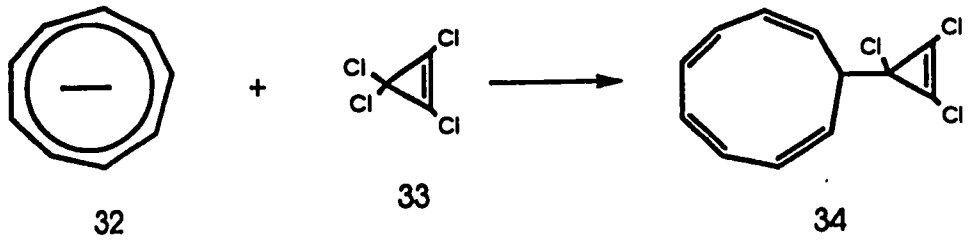


31 15

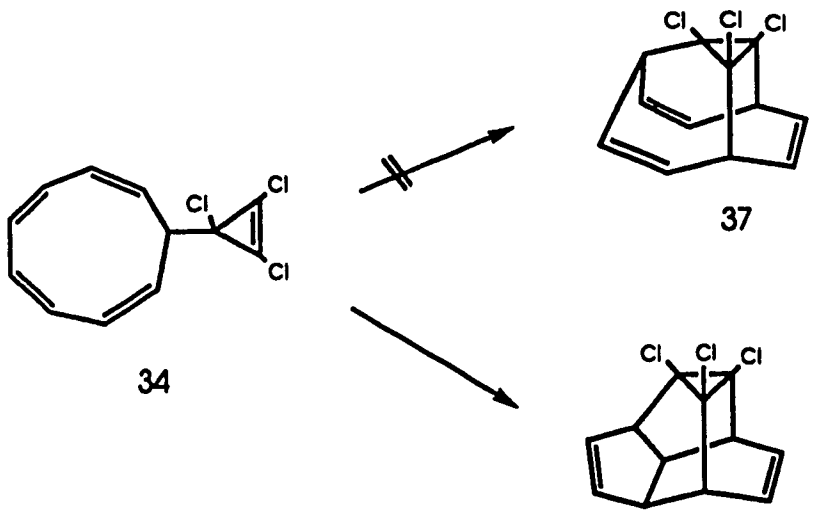
Mock's approach to the triene 11

In an attempt to synthesize 11, Mock and coworkers[42] devised the synthesis of precursor 37 and its conversion to the triene 11 *via* dehalogenation method.

The attempted synthesis of 37 involved a reaction between lithium-cyclononatetraenide and tetrachlorocyclopropene. The product of this reaction, after chromatography, multiple sublimations, and recrystallizations gave a crystalline material, mp 152-154°C. Mass spectrum of this compound gave, a molecular ion of 258 confirming 3 chlorines, and a composition of $C_{12}H_9Cl_3$ based on the elemental analysis. Finally the structure of this compound was confirmed by X-ray crystallography to be 36.

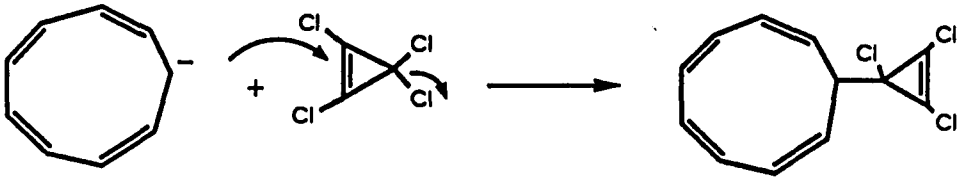


32 33 34

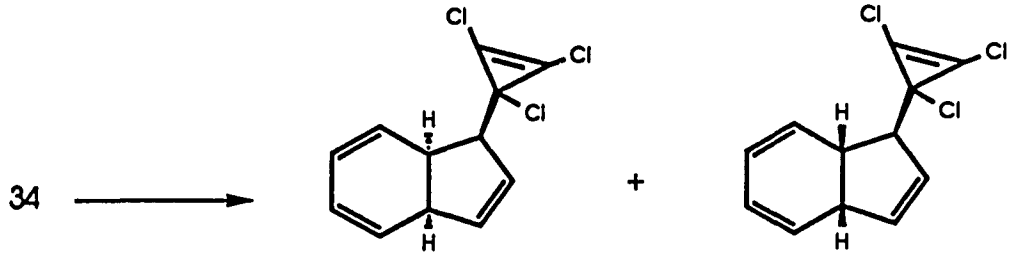


34 37 36

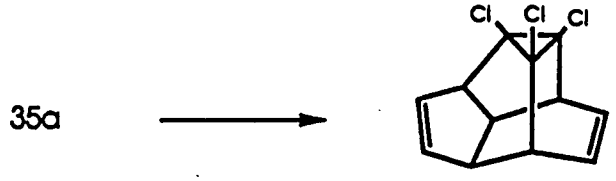
Mechanistically, the formation of 36 is initially formulated by an S_N2' displacement to produce 34. Intermediate 34 undergoes a disrotatory ring closure to afford 35a and 35b as a mixture of diastereomers. The epimer 35a is expected to be the minor product based on the evidence provided in the literature.[43] It is believed that the cycloadduct 36 is derived from the minor product 35a. Moreover, it is stated that "the low yield observed (for compound 36) is thus partially rationalized in as much as the balance of material presumably was converted to a polymeric substance which was indeed the major product."



34



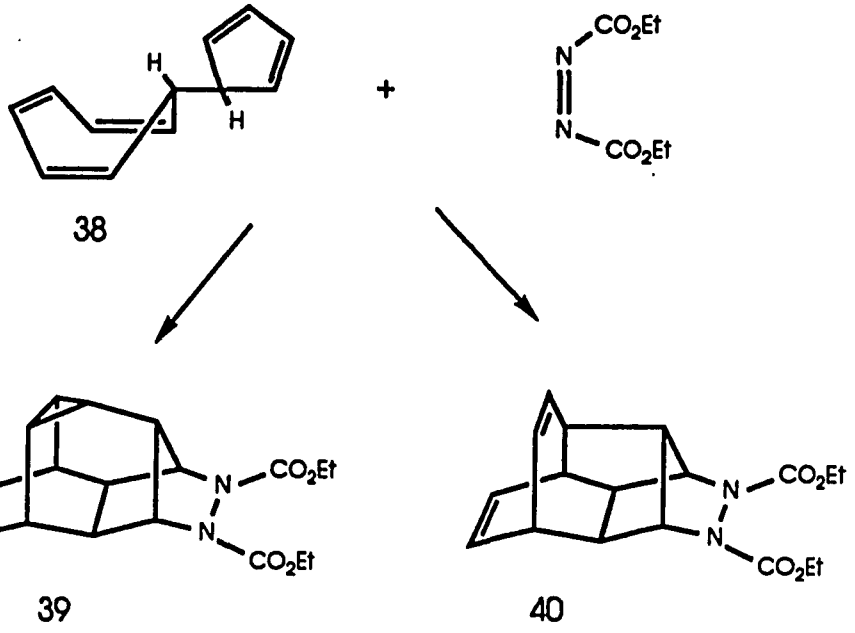
35a 35b



36

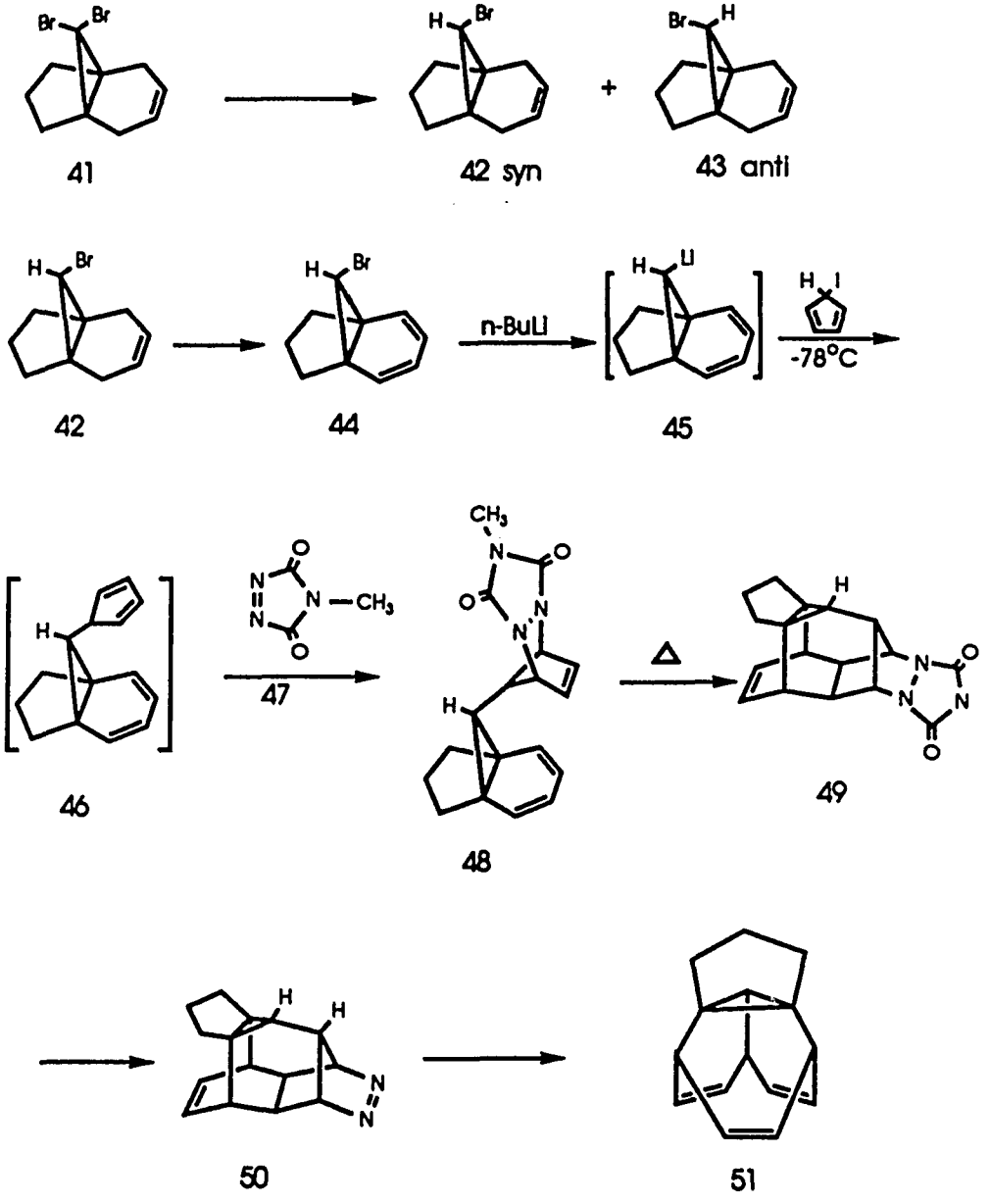
Paquette's approach to 51

In view of the well known domino Diels-Alder reactions reported by Paquette, Park[16] tried the Diels-Alder reaction of 38 and diethylazodicarboxylate. This reaction afforded 40 and none of 39, because the cycloheptatriene ring acted as a diene or a 4π cycloaddition component.

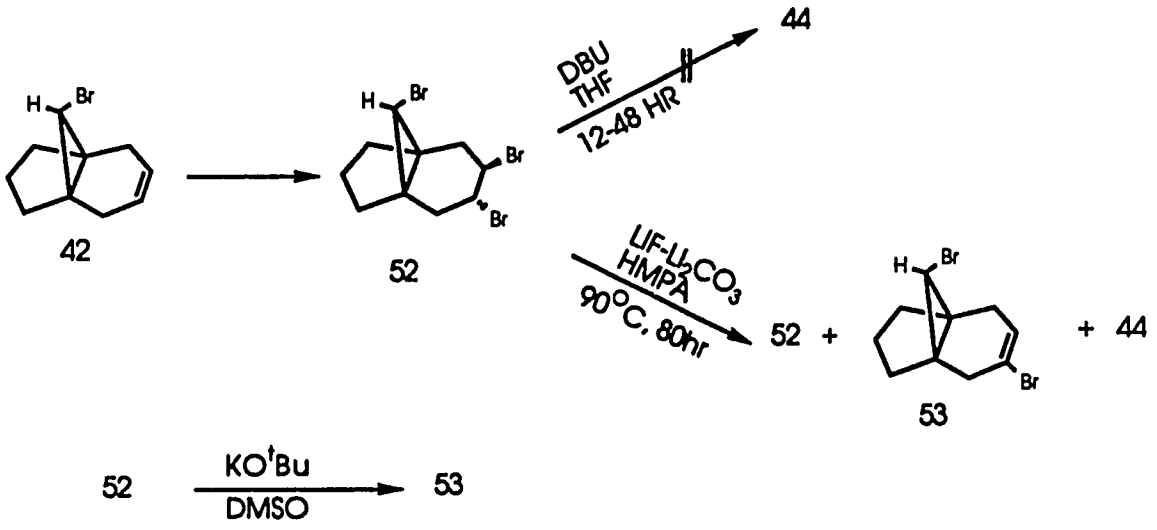


It was therefore decided to shift the cycloheptatriene-norcaradiene valence isomerization to the norcaradiene tautomer. Vogel and coworkers,[44] investigated the effect of 1,6 polymethylene bridges on cycloheptatriene-norcaradiene valence tautomerism. They reported when n=3, there is sufficient strain on the cycloheptatriene form to enforce complete "freezing in" of the norcaradiene tautomer.

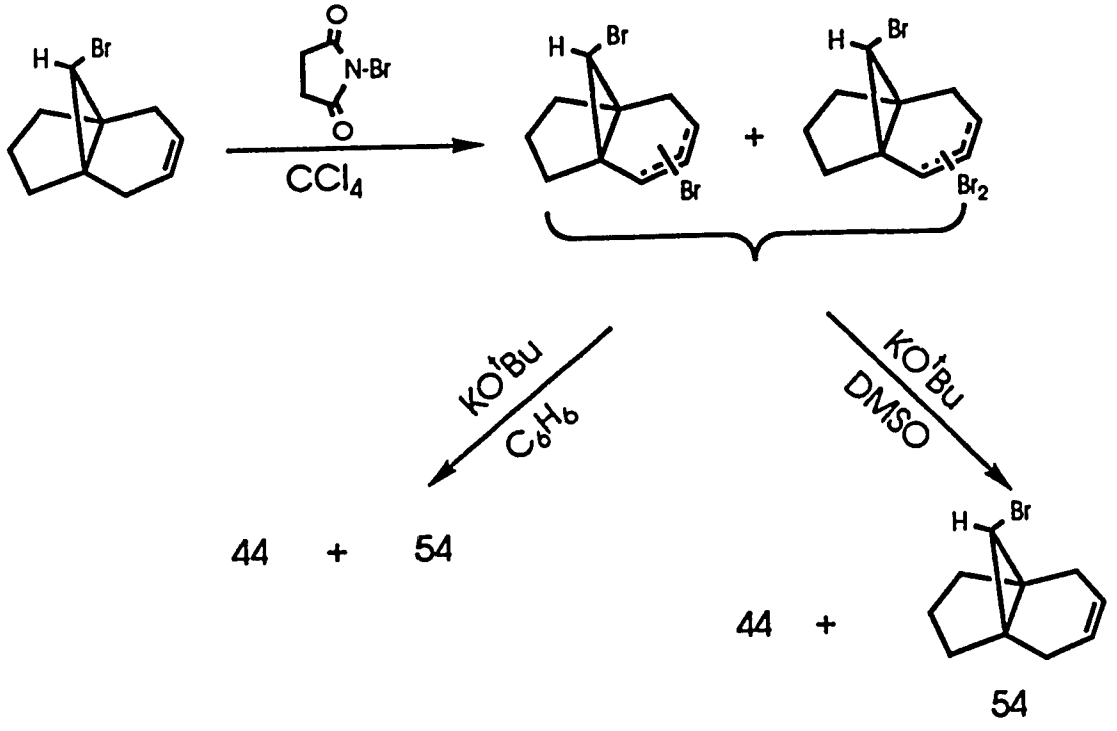
Based on these observations Paquette and coworkers designed the following Scheme for the synthesis of heptacyclo-[5.5.0.0^{2,12}.0^{3,5}.0^{4,10}.0^{6,8}.0^{9,11}] dodecane 51, using the syn-10-bromo-tricyclo[4.3.1.0^{1,6}]dec-3-ene 42 as the starting material in the Diels-Alder reaction sequence.



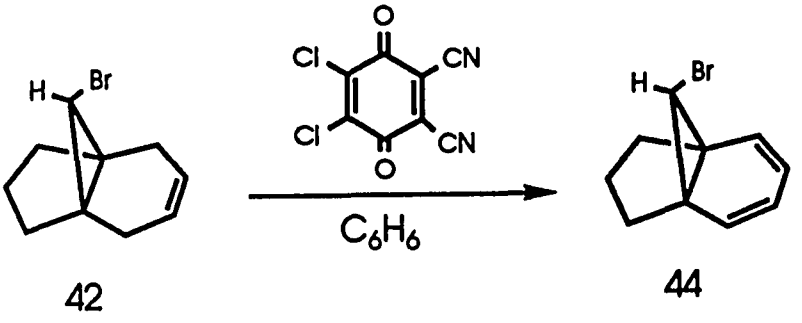
Compound 42 was made together with 43 from the reduction of 10,10-dibromotricyclo[4.3.1.$0^{1,6}$]dec-3-ene 41 by zinc dust in acetic acid.[45] These were separated chromatographically on neutral alumina. Compound 42 was subjected to bromination with one equivalent of bromine in methylene chloride at 0°C for half hour to give the tribromide 52. Attempted dehydrobromination of 52 in the presence of DBU did not occur, presumably due to the steric hindrance of the bromine atom on C_{10} and the methylene hydrogens on the trimethylene bridge. The next choice was LiF-Li_2CO_3 in HMPA mixed with small amounts of powdered glass.[46] After 80 hr at 90°C, only 10% of 44 was obtained along with unreacted starting material and dibromoene 53. When potassium t-butoxide was used as the base, the only product obtained was 53.



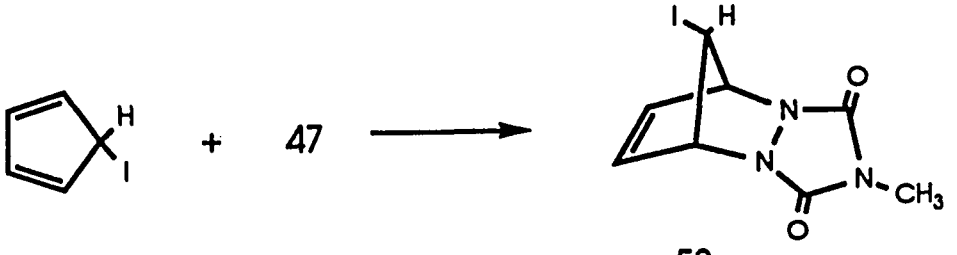
As a consequence of these findings, NBS was used in order to get allylic bromination (preferably, monobromination) of 42. The crude material was dehalogenated with potassium t-butoxide in DMSO to give less than 5% of the desired 44 along with decomposed material. In refluxing benzene the yield of 44 only increased to 10% , along with 12% of 53.



Due to the low yield of 44, an alternative method was undertaken. The reaction of 42 with DDQ[47] in refluxing benzene for 60-90 hrs resulted in 72-76% conversion to 44. To a solution of 44 in ether was added n-butyl lithium at 0°C. The resulting mixture was stirred for one hour to generate 45. The previously prepared 5-iodocylopentadiene[48] was added to the mixture of 44 and n-butyl lithium dropwise at -78°C. After 4 h, one equivalent of 47 was added and the mixture was allowed to warm up to room temperature over 1 h. Work-up and purification afforded the direct cycloaddition product 58. This meant that the lithiated intermediate 45 was not formed.



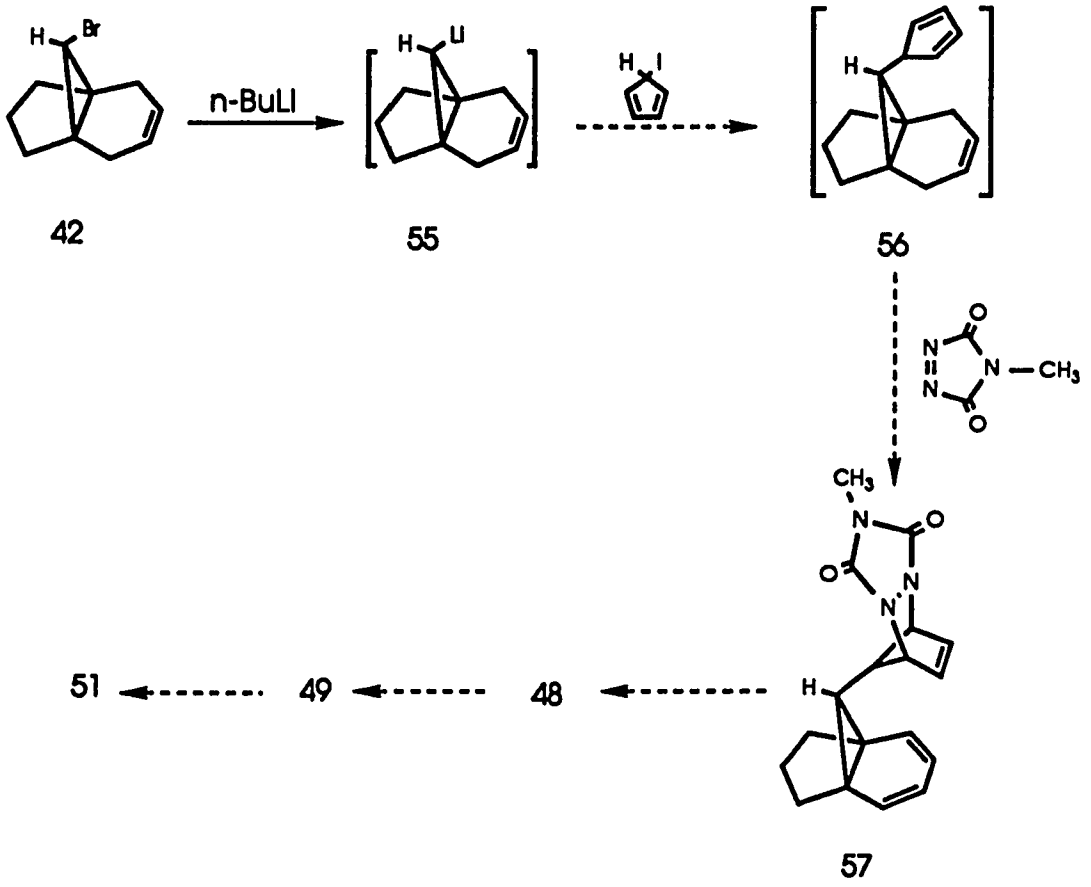
42 44



58

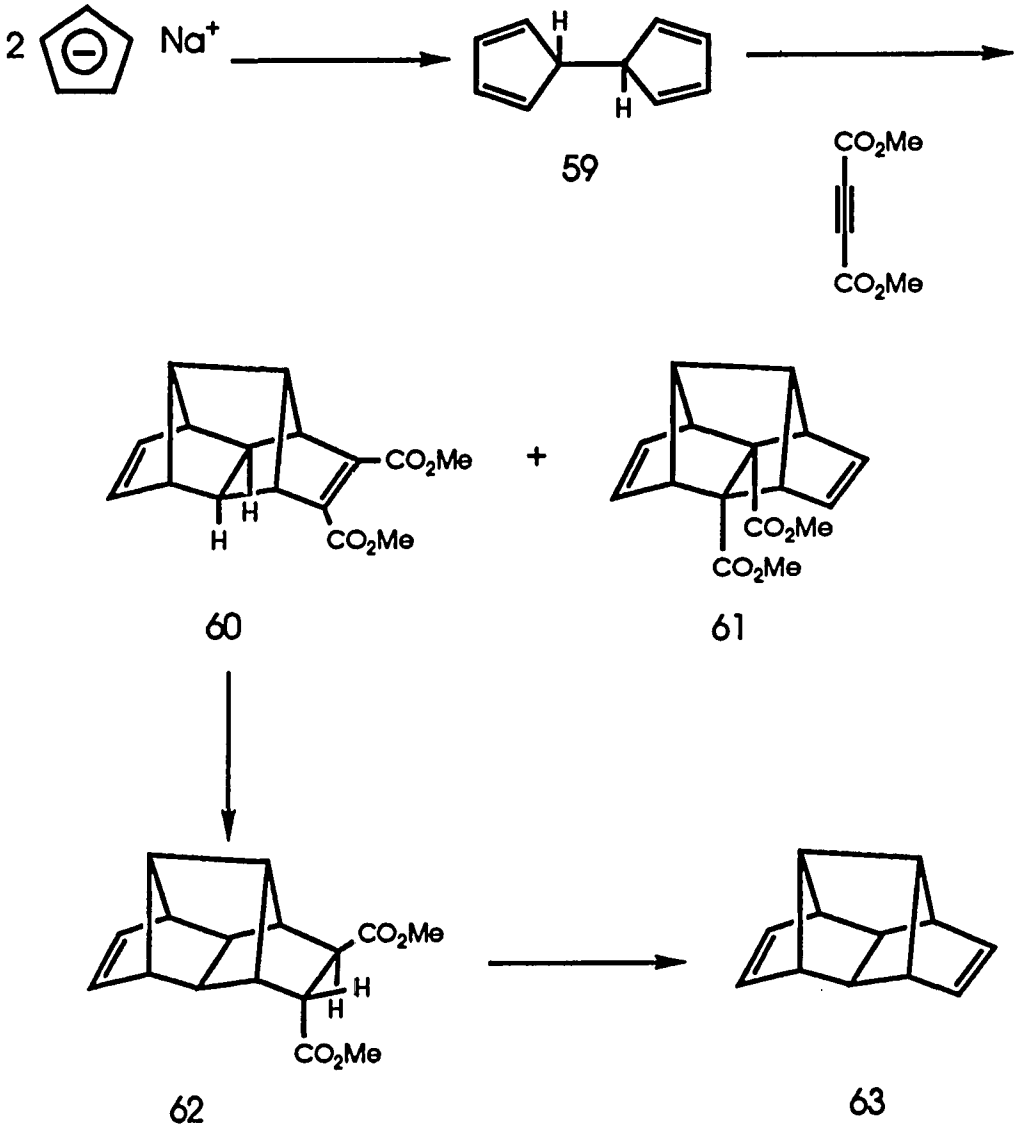
Due to the lack of experimental success, the synthetic plan was amended by doing lithiation-alkylation[45,49] on 42, instead of 44, and the conversion of cyclohexene to cyclohexadiene was delayed at a later stage. The lithiation reaction on 42 gave the same result. The direct cycloaddition product 58 of 5-iodocyclopentadiene and 47 was observed without any detection of 56.

Because of repeatedly unsuccessful results and the difficulty in the formation of 46 or 56, this synthetic route was abandoned.



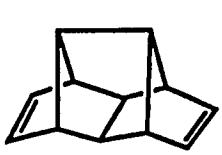
Park's approach to the tetraene 1

A synthetic approach to the tetraene 1, as reported in the Ph. D. thesis of Park[16], involves an oxidative cleavage of pentacyclo [4.4.2.$0^{2,7}$.0.^{3,12}.$0^{8,11}$] dodeca-4,9-diene 63 to the resulting 2,4,6,8-*endo,exo,endo,exo*-tetracarbomethoxytricyclo-[3.3.0.$0^{3,7}$] octane 65 in good yield.

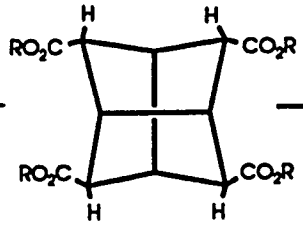


The carbocyclic framework of 62 was prepared by a domino Diels-Alder cycloaddition.[50] Sodium cyclopentadienide was oxidatively coupled by addition of iodine to afford 59 which was reacted *in-situ* with dimethyl acetylendicarboxylate. The two diesters formed in this reaction 60 and 61 were subjected to saponification, and 60 was separated as a water-soluble dicarboxylate. The other ester, due to steric hindrance, remained unchanged. Acidification of the basic extracts and reesterification afforded 60, which on reduction of its electron-poor double bond, followed by epimerization, gave 62. Saponification of 62, followed by heating at 180°C with two equivalents of Cu_2O and 2,2'-dipyridyl in quinoline solution[51,52] afforded the diene 63.

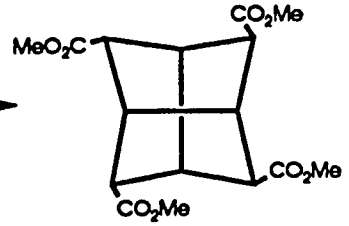
The suspension of diene 63 in water containing sodium hydroxide was reacted with three equivalents of potassium permanganate. Acidification with hydrochloric acid, followed by the removal of water by the freeze-dry technique, resulted in the formation of the tetracarboxylic acid 64a which on treatment with excess diazomethane in ether afforded 64b in 51% yield. The tetraester 64b was epimerized to the thermodynamically more stable all-trans isomer 65 before reduction. In view of the stereochemistry of the ester groups in 64b, reduction at this stage was avoided given the fact that the tetraol 69 might undergo a cyclic ether formation to 70. Many attempts were made towards the reduction of compound 65 with Red-Al, LAH, DIBAL-H. There were no signs of reduction. At this point it was decided to stop and devise an alternative procedure.



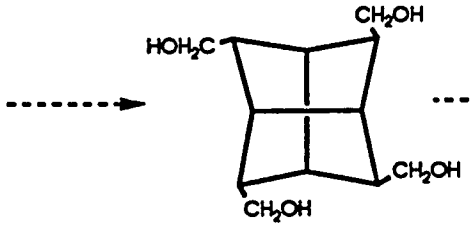
63



64 a, R=H
b, R=Me



65



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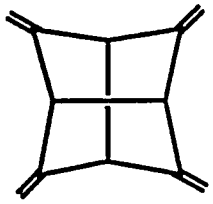

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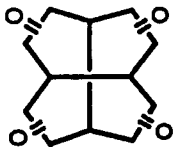

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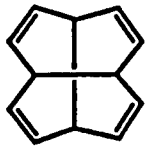

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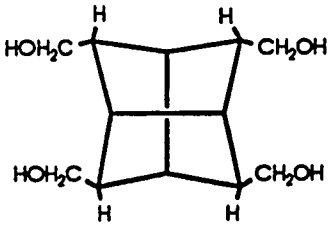

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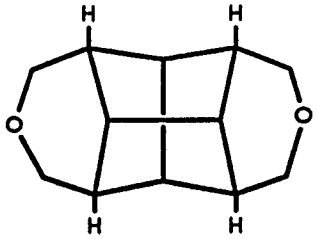
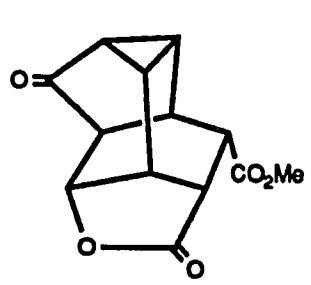


70

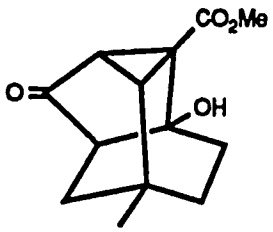
Watt's approach to the triene 11

It is interesting to note that C. I. Watt, in his Ph. D. thesis,[53] considered compound 74 which is closely related to our tetracyclic compounds (58 and 72 discussed in sections II and III), as immediate precursors to achieve their synthetic objective of the triene 11. It should be noted that compound 74, like compounds 58, and 72 from sections II and III, all containing a C_{10} skeleton, need an additional two carbons to complete the required skeleton for the triene 11. To achieve this, it was decided by Watt that the ketone 74 under ring expansion can give rise to a C_{11} skeleton, requiring the introduction of a one-carbon bridge between the C_5 and C_8 positions, with subsequent cleavage of C_7-C_8 bond.

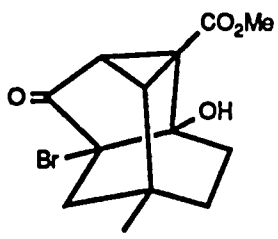
Their approach to triene 11 involved the reaction of maleic anhydride with 7-cyano-cycloheptatriene which proceeded smoothly to gives 7 : 3 ratio of 71 to 72. The minor product was the desired endo isomer based on the ^1H NMR of the olefinic protons which appears at 6.17 ppm for the minor product and 5.93 ppm for the major product. Adduct 71 was treated with methanolic sulfuric acid, and the diesters were later dissolved in anhydrous trifluoroacetic acid and heated briefly to give the ketolactone 74. Ketone 74 was subjected to ring expansion using the triethyloxonium fluoroborate catalyzed reaction with ethyl diazoacetate. The reaction proceeded to give a mixture of two β-ketoesters in which under hydrolysis and decarboxylation afforded 75 and 76 in good yields.



74

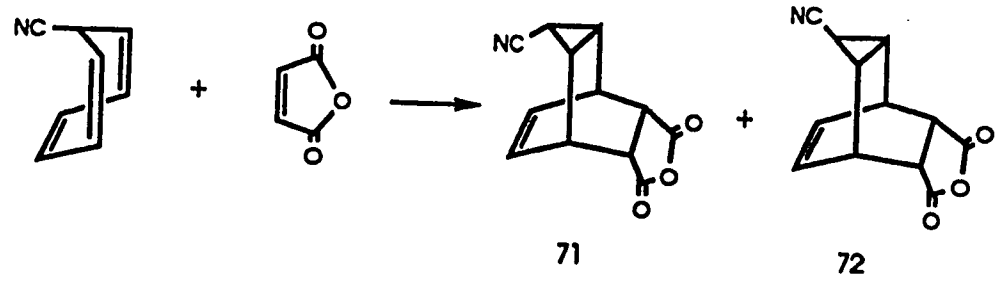


58

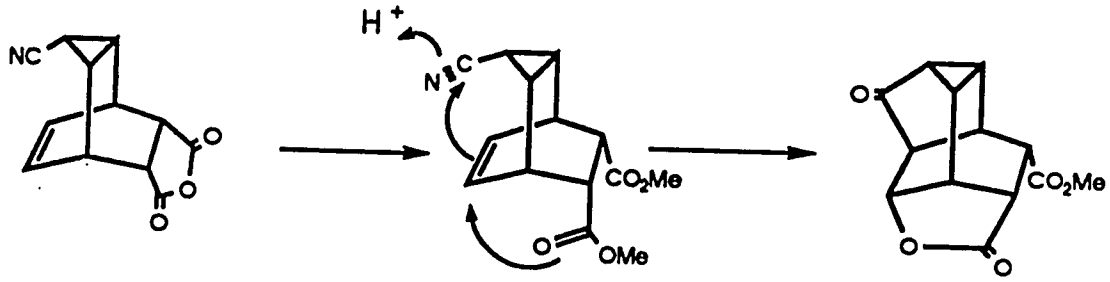


72

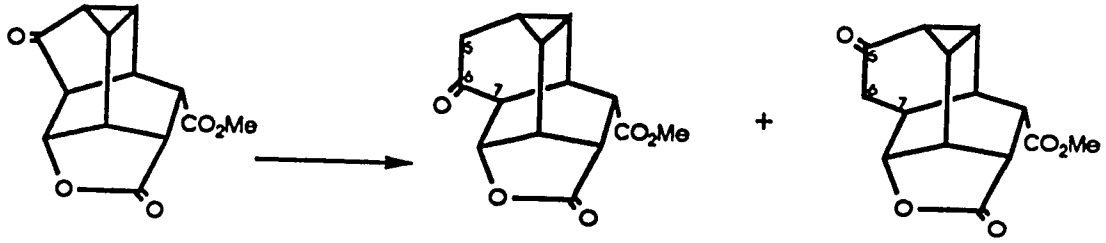
Tetracyclic compounds from sections II and III



71 72



73 74



74 75 76

Introduction of a carbon bridge between

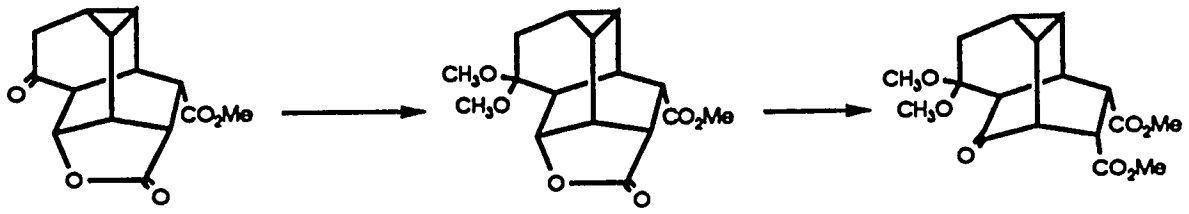
C_5-C_8

Bond breaking between

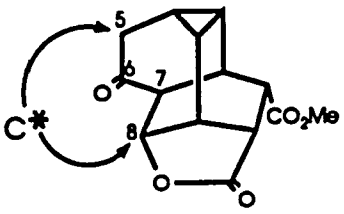
C_7 - C_8

gives rise to skeleton of 11

In 76, the most frustrating problem is the lack of any convenient point of attack for cleavage of the C_7-C_8 bond. One would have to functionalize either the six or seven positions. Electrophilic attack at C_6 would also involve the cylopropane ring. Ketolactone 75 on the other hand looks more amenable than 76 in the general approach forming the first bond, i.e., C* to C_5 or C* to C_8 followed by attack from the least hindered side to place C* in the correct position for cyclization. The first attempt at formation of the one-carbon bridge were predicted upon prior formation of the C*-C_8 bond. The ketone at the six position of 75 was ketalized to 77, both to protect it during the projected attack at the much more hindered eight position, and to prevent any possible premature retroaldol reaction under the basic condition necessary for oxidation of the γ lactone ring. The lactone and the ester group were saponified and the oxygen at C_8 was converted to a ketone by ruthenium tetraoxide. Acidification and reesterification with diazomethane gave 78. Attempted reaction with methylenetriphenyl phosphorane in DMSO gave only recovered starting material, perhaps due to steric crowdedness of the ketone at C_8.

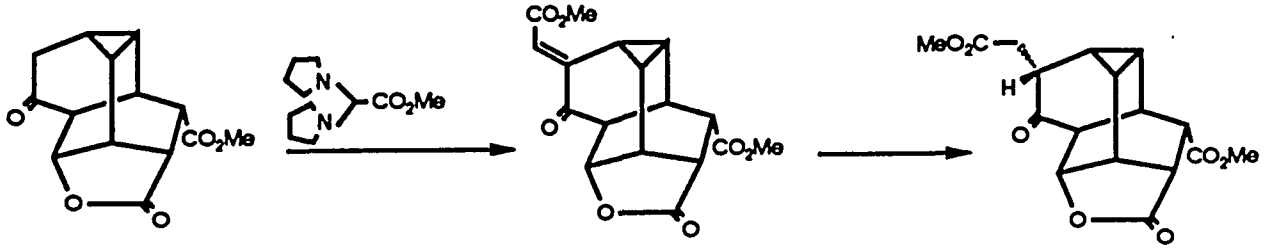


75 77 78



75

At this stage, approaches to involve forming the C*-C_5 bond were considered.[53] The first attempt involved introduction of a carbomethoxymethylene group at the five position. Attempts to reduce the double bond of 79 by catalytic hydrogenation led to reduction of the double bond and hydrogenolysis of the cyclopropane ring.

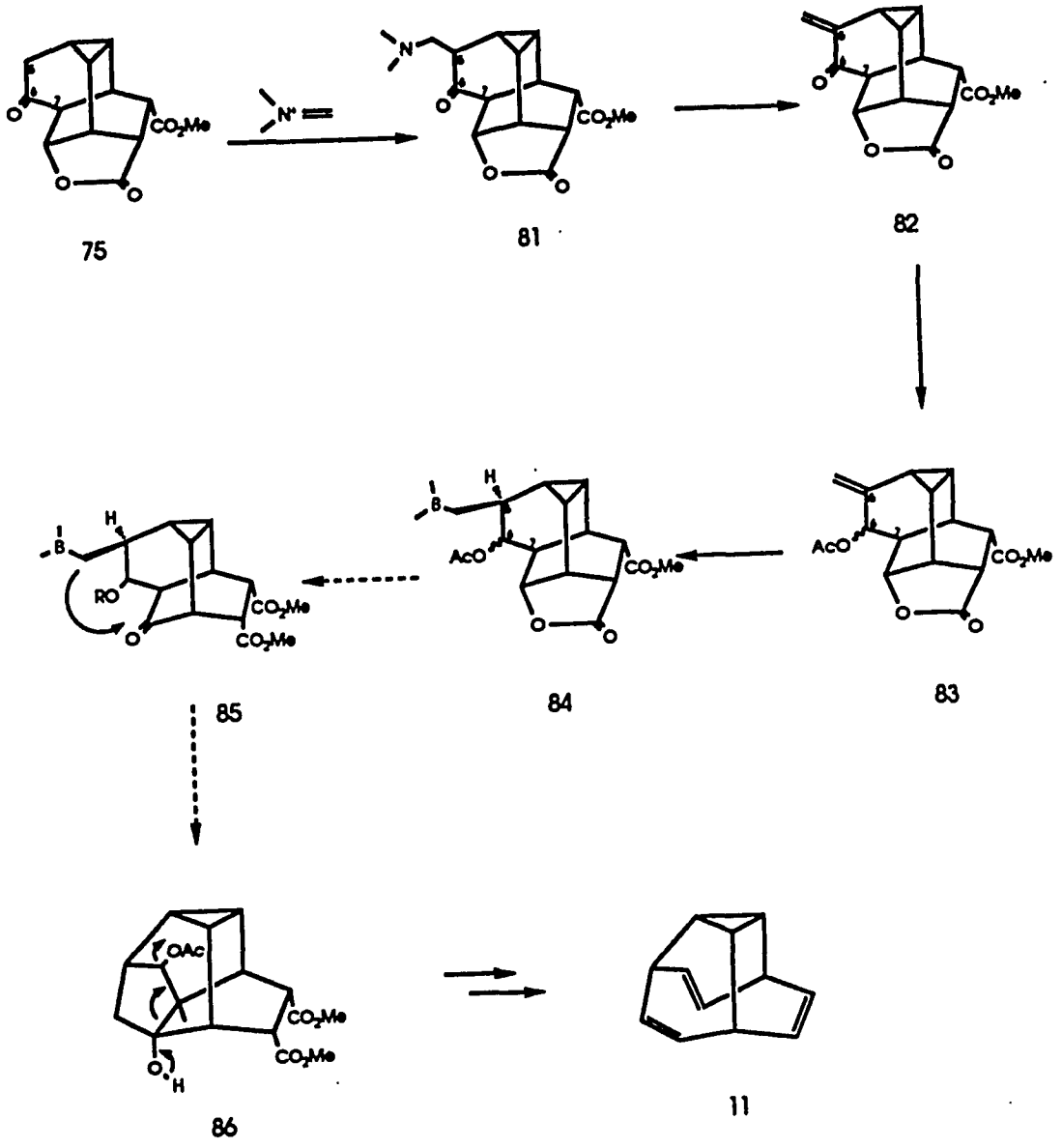


75 79 80

Introduction of the new carbon atom C* as a methylene group was now considered, in the hope that, after reduction of the ketone, a hydroboration reaction could be used to effect both reduction of methylene from the less hindered side, and cyclization in one step.

Treatment of 75 in chloroform with a trace of trifluoroacetic acid and the salt, dimethylmethyleneammonium chloride,[54] gave compound 81 in quantitative yield. This compound was immediately reacted with methyl iodide and eliminated to give the exomethylene compound 82 which was reduced with sodium borohydride, and then

acetylated to give 83. An attempt to effect hydroboration with 9-borabicyclononaene led to slow disappearance of starting material. At this stage, progress towards the target 11 was discontinued.

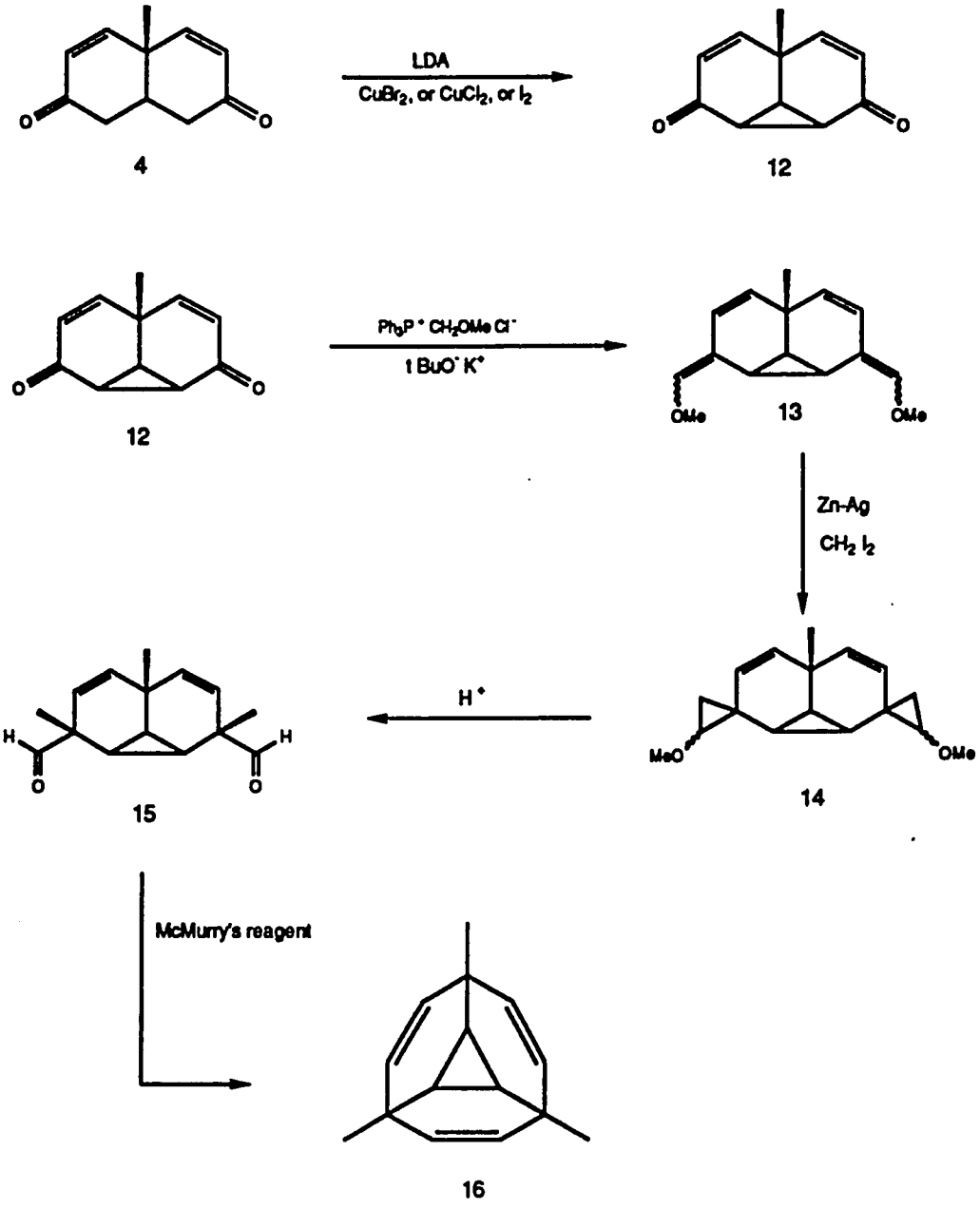


75 81 82 83 84 85 86 11

II.1 *SYNTHETIC APPROACH*

Our approach to the synthesis of the triene 16, is shown in Scheme 1. Compound 4 (Scheme 2), with a *cis*-fused stereochemistry, appears to be a suitable starting material in our synthetic strategy, because it appears suitable for the formation of a cyclopropane ring bond between C_1 and C_8 to produce compound 12.

Scheme 1

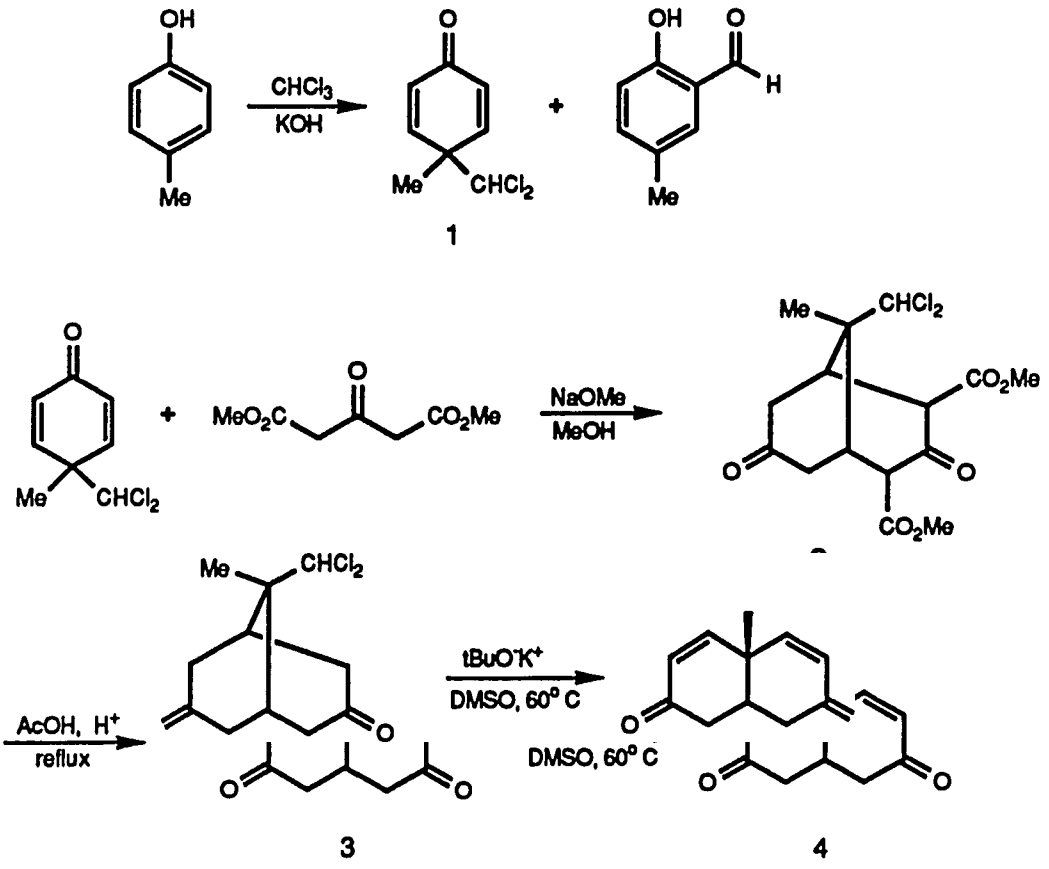


The first step involving oxidative coupling of the dianion of compound 4 *via* treatment with various oxidizing agents (e. g. $CuCl_2$, $CuBr_2$, I_2), could result in the formation of the tricyclic dienedione 12. The three-step scheme of conversion of ketones or aldehydes into enol ethers,[1] cyclopropanation of the olefinic intermediate with methylene iodide over Zn-Cu couple,[2] and aqueous acid cleavage of the resultant methoxy cyclopropane compounds,[3] has been shown to be the equivalent of α-alkylation of aldehydo or keto compounds. However, a comment should be made on some of the difficulties that we anticipate in Scheme 1. A Wittig olefin synthesis of 12 carries with it the possibility of involving the cyclopropane ring in the reaction. Moreover, the bis-Simmons-Smith reaction of vinyl enol-ether 13 requires the incoming carbene to attack from the convex side of the roof-like starting material, selectively at the exocyclic enol double bonds and leave the endocyclic double bonds intact. Having solved these problems, the desired product 15 places the two aldehyde groups in the proper orientation for coupling[4] to give the triene 16 directly.

II.2 *RESULTS AND DISCUSSIONS*

The synthesis of the known dienedione 4 is shown in scheme 2. Dienone 1 was obtained[5] *via* a Reimer-Tiemann reaction of 4-methyl-cresol in the presence of chloroform and base in 25% yield. With a minor modification in Mayer's procedures,[6] the yields of compounds 2 and 3 were improved in our laboratory. For example, the yield of Michael condensation of 1 with 1,3 acetone dicarboxylate to afford the diester 2 was increased from 72 to 85% when we used a 5:1 ratio of diketone 1 to sodium methoxide. Similarly, hydrolysis and decarboxylation of 2 to the diketone 3 by the action of phosphoric acid (85%) in refluxing acetic acid improved the yield of diketone 3 to ~90% yield as opposed to the previously reported[6] yield of 63%. The dienedione 4 was synthesized according to Wenkert's method[7] through an exhaustive dehydrohalogenation of diketone 3 with potassium t-butoxide in dimethylsulfoxide.

Scheme 2



In order to optimize the yield for the precursor 4, we modified Wenkert's procedure[7] slightly to make it more convenient on a multigram scale. The results of these modifications are listed (Table I). Addition of 1.2 equivalents of solid potassium t-butoxide to a solution of compound 3 in DMSO (method A) afforded dienedione 4 (37% isolated yield), and a dimer 5 (20% isolated yield) whose structure was confirmed by X-ray crystallography.[8] When the addition order was reversed (method B), the product distribution was entirely in favor of compound 4 (45-50% isolated yield). Method (B) provided an optimum yield of 4 when only 1.8 equivalents of the base was used. Upon addition of 2 equivalents of the base, the yield of 4 decreased and afforded an unidentifiable product as revealed by ^{1}H NMR specrum. Formation of the dimer 5 (method A) indicates that the rate of the intermolecular attack on compound 3 is faster than the rearrangement to give the dienedione 4. This competition was eliminated when the addition order was reversed where the reaction produced 4 as the only isolable compound. To further improve the yield of compound 4, method (C) was considered where a solution of diketone 3 dissolved in DMSO was added dropwise to a solution of potassium t-butoxide in DMSO. Under these conditions, the yield of 4 declined drastically (see Table I), and afforded *p*-cresol and an unidentifiable compound as revealed by the ^{1}H NMR spectra.

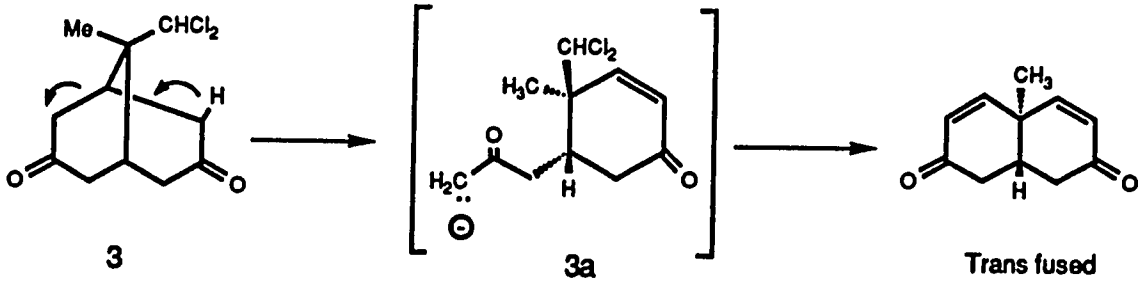
Table I

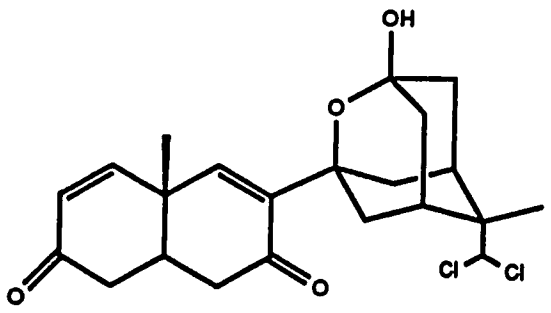
entry	method	t-BuOK (eq.)	rx time (h)	%dienedione 4	%dimer 5	%unreacted 3	%*p*-cresol	unidentifiable product
1	A	1.2	2	37	20	0	-	-
2	B	2	2	45	0	0	0	present
3	B	1.8	2	50	0	<5	0	-
4	C	2.3	3	20	0	0	10	present

Method A: solid potassium t-butoxide was added to a solution of 3 in DMSO
Method B: solid dione 3 was added to a solution of potassium t-butoxide in DMSO
Method C: a solution of dione 3 in DMSO was added dropwise to a solution of potassium t-butoxide in DMSO

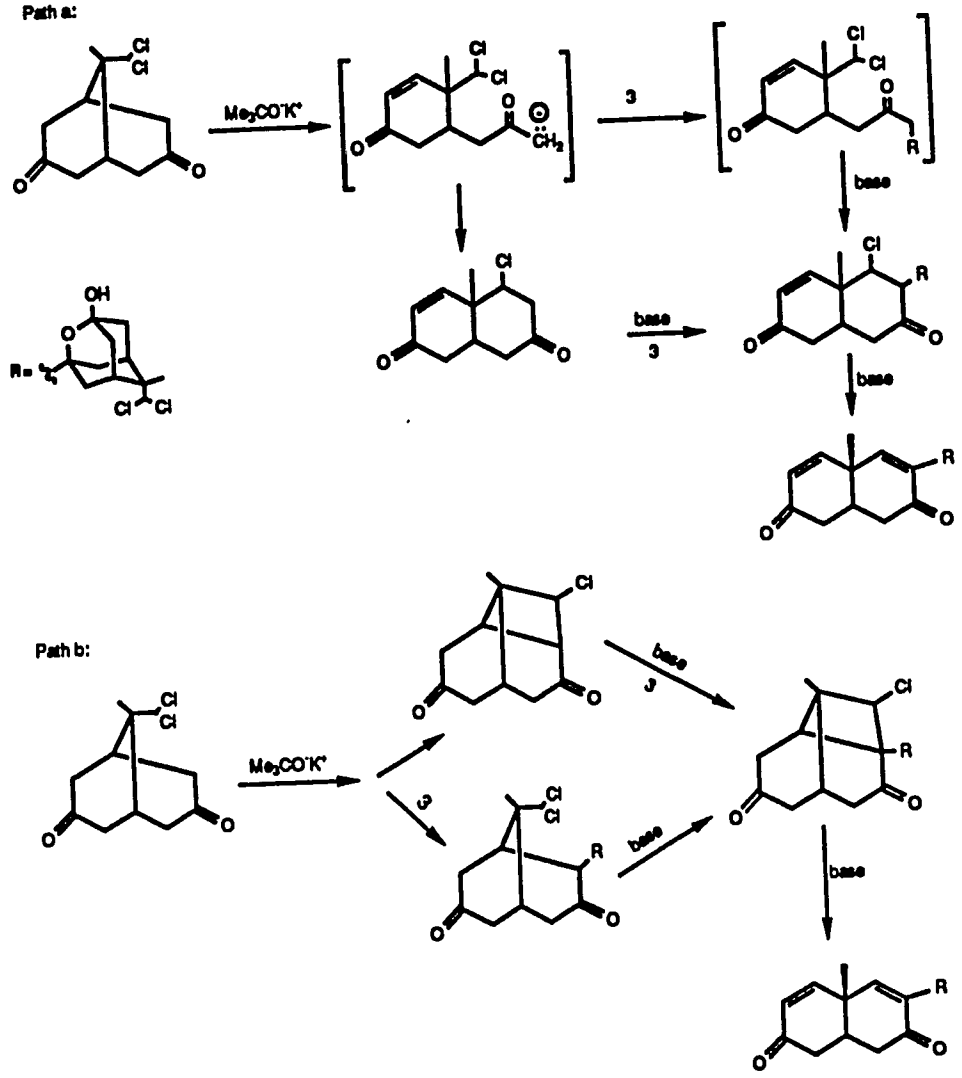
Mechanistically, for the transformation of 3 to 5, under the conditions specified, three possible pathways (a), (b) and (c) are conceivable (see page 35). Paths (a) and (b) can also be offered as mechanistic rational for dienedione 4.

It seems likely that 4 and 5 arise from pathway (b). This is due to the fact that the stereochemistry remains unchanged when an intramolecular chloride displacement occurs through which a cyclobutane intermediate is formed; hence, giving rise to only the *cis*-fused skeleton. It is also possible to envision the *cis*-fused stereochemistry of both compounds 4 and 5 *via* the opened intermediate involving path (a). However, the lack of *trans*-fused isomer implies that the prefered proton removal by the base must have occurred from the opposite side of the dichloromethyl group. Proton removal from the same side of the dichloromethyl group (shown below), followed by ring opening affords the intermediate 3a that can undergo a ring closure to afford the *trans*-fused isomer which we never observed. Further elaboration of the mechanism of this reaction is under investigation.





5


Path a:
Me2CO-K+
3
base
base
base
R=
Path b:
Me2CO-K+
base
base
base
Path c:
Me2CO-K+
3
base

II.3 *Synthesis of the tricyclic compound 12*

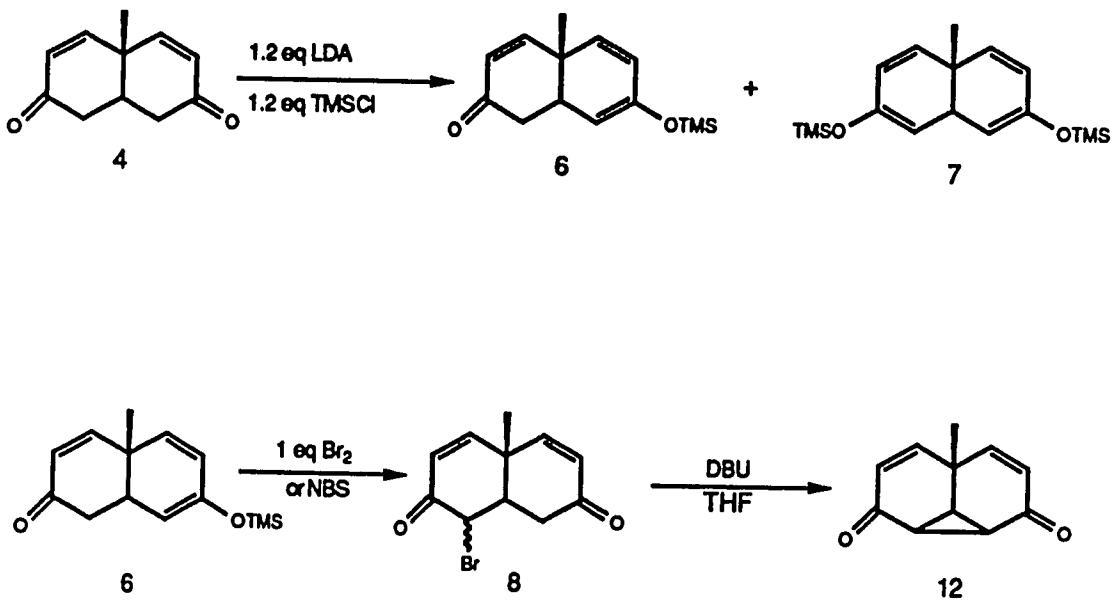
The original strategy involving oxidative coupling of the dianion of compound 4 *via* treatment with various oxidizing agents (e.g. $CuCl_2$, $CuBr_2$, I_2) was unsuccessful. Starting dienedione 4 was recovered quantitatively. However, the tricyclic dienedione 12 was synthesized *via* two different pathways as shown in Schemes 3 and 4.

Scheme 3 involves silylation of dienedione 4 by the use of 1.2 eq. of lithium diisopropylamide in tetrahydrofuran-hexane solution at -78°C, and 1.2 eq. of trimethylsilyl chloride.[9,10] In order to maximize the yield of 6, LDA was added slowly to the dienedione-THF solution. Following the work-up and ether extraction, the concentrated liquid was chromatographed on silica gel and eluted with 10% ethyl acetate in hexane. This allowed the separation of mono (silylenol) ether 6 (49%), bis (silylenol) ether 7 (35%) and the starting material 4 (13%). Under the conditions described in the experimental section, the formation of the bis (silylenol) ether was unavoidable.

Compound 6 was brominated at -78°C by rapid addition of 1.2 eq. of bromine as a solution in dry methylene chloride[11,12] or dry tetrahydrofuran. The mixture decolorized immediately and was left stirring for five minutes before it was quenched with cold saturated sodium bicarbonate. Extraction of this mixture with ether allowed the isolation of mono-bromo dienedione 8 in 66% yield. The structure of 8 was confirmed by its ^1H NMR spectrum. The nmr spectrum shows a doublet at 5.23 ppm for the downfield proton on the bromine-containing carbon. The two vinyl β protons appear as a doublet of doublets at 6.6 ppm, and the two α-protons show up as a multiplet at 6.16 ppm.

Treatment of 8 with excess 1,8 diazabicyclo [5.4.0] undec -7- ene[13] (DBU) in refluxing dry tetrahydrofuran for twenty hours caused the elimination of hydrogen bromide and gave the desired tricyclic dienedione 12 in 20% yield (Scheme 3). The structure of 12 was determined by both its ^1H as well as ^{13}C NMR spectra.

Scheme 3



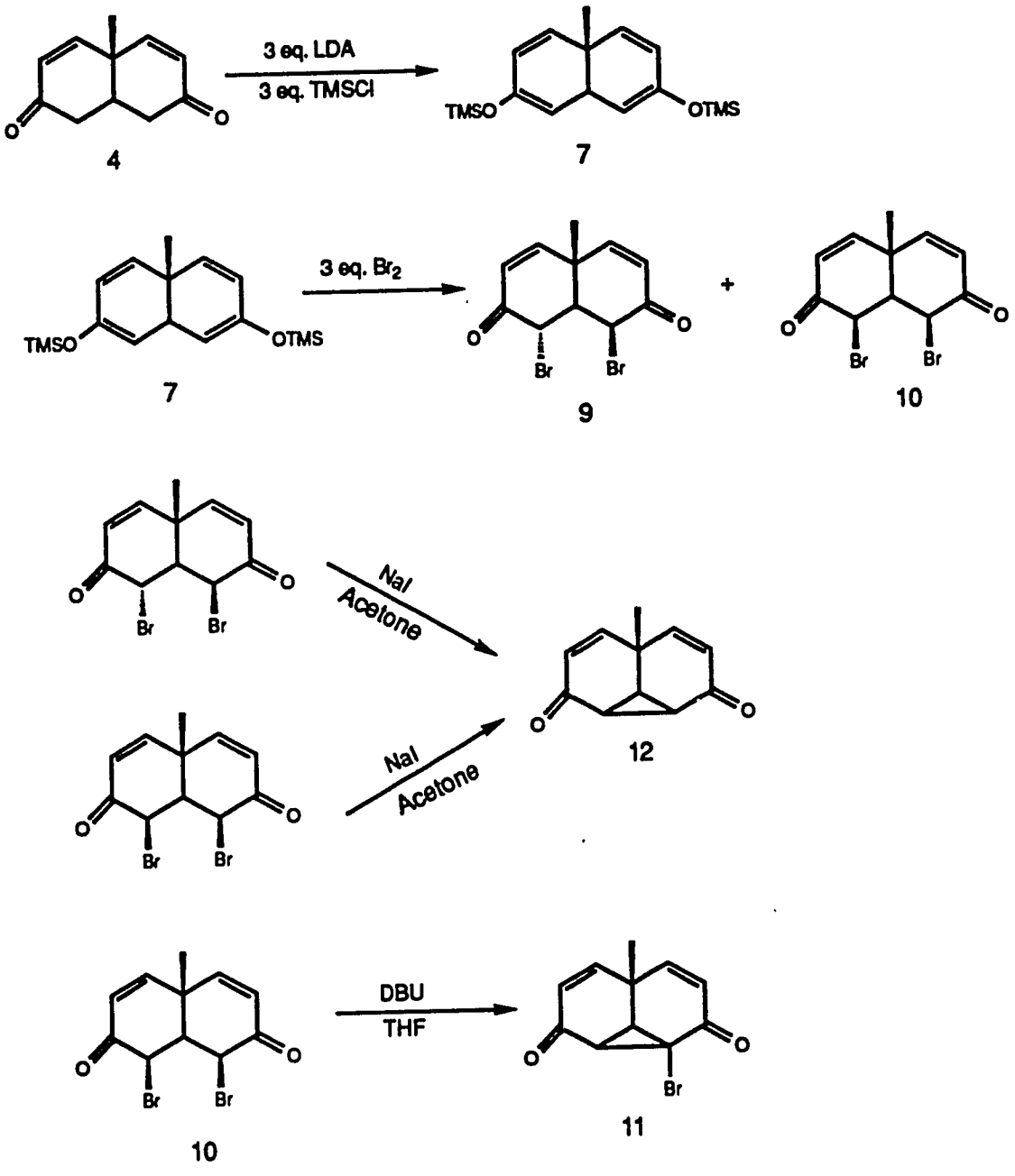
4 6 7

6 8 12

Scheme 4, shows the synthesis of the tricyclic dienedione 12 via the bis (silylenol) ether 7. We were able to increase the yield of 7 to 92% by treating 7 with 3 eq. of lithium diisopropylamide and 3 eq. of trimethylsilyl chloride. Further treatment of 7 with 3 eq. of bromine[11,12] allowed the isolation of two brominated compounds that were separated chromatographically to give 9 and 10 in 10 and 53% yields respectively. The stereochemistry of these regioisomers was assigned clearly by the use of the 300 MHz ^1H NMR spectra. The nmr coupling pattern for the magnetically non-equivalent vinylic protons in 9, has an AB system containing a set of two doublets of doublets. The protons on C_1 and C_8 bromine-containing carbons, show up as a singlet and a doublet respectively. The latter is a doublet at 4.43 ppm which is indicative of coupling to the ring junction proton. Dreiding models suggest that the singlet at 4.5 ppm has a dihedral angle of almost 90° with respect to the ring junction proton. All this information gives unambiguous evidence for the *trans* configuration of the two bromine atoms in compound 9 (one bromine up and one down). In 10 on the other hand, a set of doublets of doublets for the vinylic protons, and a doublet for two protons on the bromine substituted carbons, are characteristic of the *cis* configuration of the two bromine atoms (both bromines up). That the stereochemistry of both bromine atoms in 10 resulted from an attack of bromine on the convex face of compound 7 is not surprising, in view of the fact that the A and the B rings are *cis*-fused.

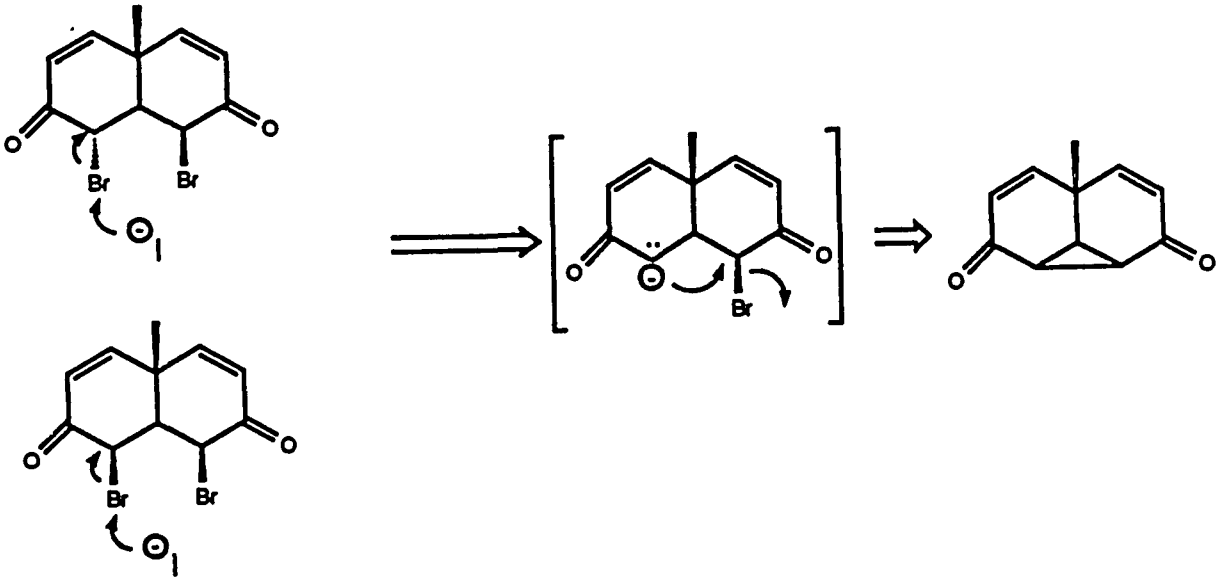
Various reactions were tried on both 9 and 10 adducts in order to get to 12. The reactions of Zn-Cu Couple[14,15] on both of these dibromides failed to produce the desired product. However, when 10 was treated with DBU, cyclization occurred to give the mono-bromo tricyclic dienedione 11 (Scheme 4) as suggested from its spectroscopic data. Attempted purification of 11 in order to reduce it with tri-n-butyl tin hydride, led to its decomposition. An alternative sequence, dehalogenation method using sodium iodide in acetone,[16] was used to convert compounds 9 and 10 to compound 12 in 68 and 44% yield, respectively (Scheme 4):

Scheme 4

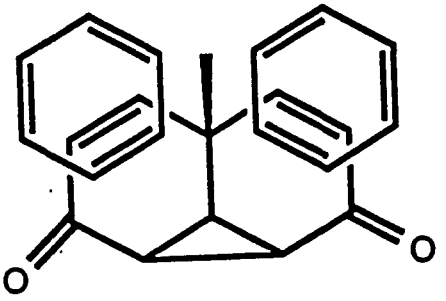

3 eq. LDA
3 eq. TMSCl
TMSO
OTMS
4
7
3 eq. Br_2
9
10
NaI
Acetone
12
DBU
THF
11

The conversion of 9 and 10 into 12 may be viewed as an S_N2 reaction of the iodide ion on the bromine (sometimes called the Finkelstein reaction) taking advantage of the fact that sodium iodide is soluble in acetone. The equilibria in these two reactions are shifted by the precipitation of sodium bromide. The progress of these reactions can be observed by the slow formation of brown color (perhaps due to the presence of IBr or I_2) from the nucleophilic addition of iodide to the bromine atoms in compound 9 and 10 (Scheme 5). After the loss of IBr, the concerted displacement of the bromine ion is followed by an intramolecular cyclization giving rise to 12.

Scheme 5



When the ^1H NMR spectrum of 12 is determined in $CDCl_3$ solution, it is found that the cyclopropyl protons all resonate at 2.24 ppm as a sharp singlet (Figure 1). Dilution of $CDCl_3$ solution of 12 with benzene causes the cyclopropyl protons to appear as a complex multiplet and shifts the remaining protons in the molecule slightly upfield. These results are indicative of complex formation between 12 and benzene. The positive end of the molecule in 12 associates with the electron system of the ring, and the negative end of the carbonyl is as far away from the ring as possible consistent with a planar complex as below:[17]



When the ^1H NMR spectrum of 12 was examined in C_6D_6, the splitting of the cyclopropyl protons became very distinct (Figure 2). The α-protons attached to C_1 and C_8 appeared as a doublet at 1.6 ppm split by the proton at the ring junction . The junction cyclopropyl proton on C_{8a} appears as a triplet at 1.05 ppm split by the neighboring α-protons. The four vinyl protons attached to C_3, C_4, C_5, and C_6 split one another into two sets of doublets, one centered at 5.62 ppm for the β-protons, and the other at 5.5 ppm assigned for the α-protons.

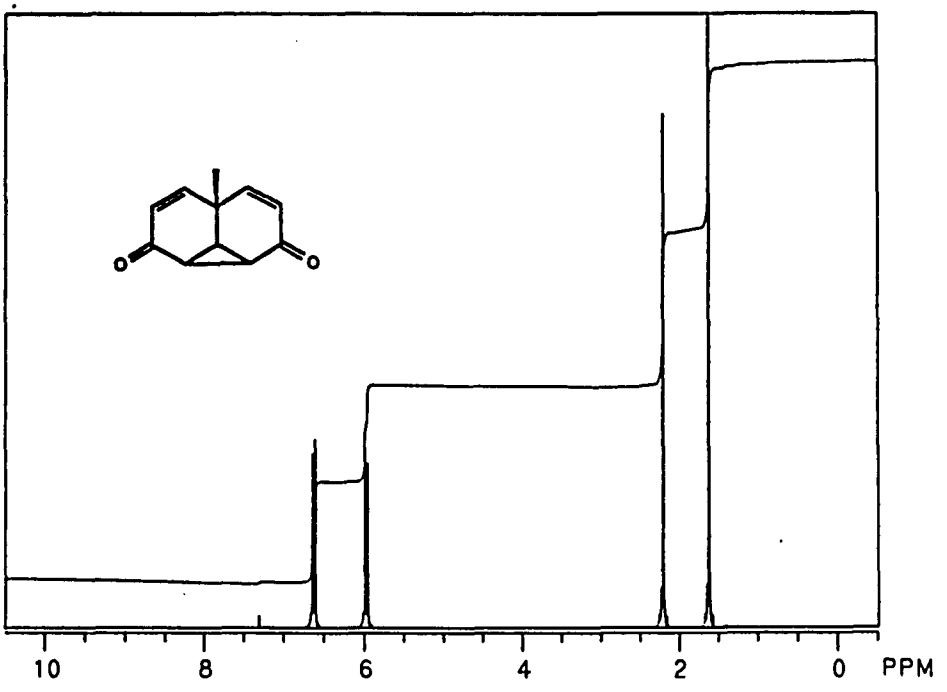


Figure **1.** Figure above shows the ^1H NMR spectrum of 12 in $CDCl_3$.

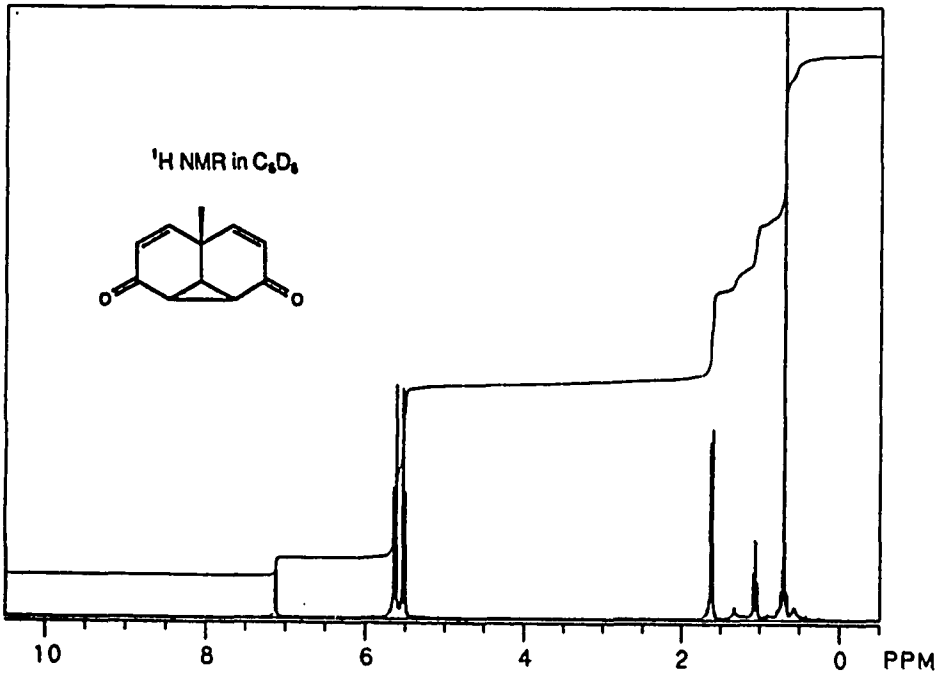
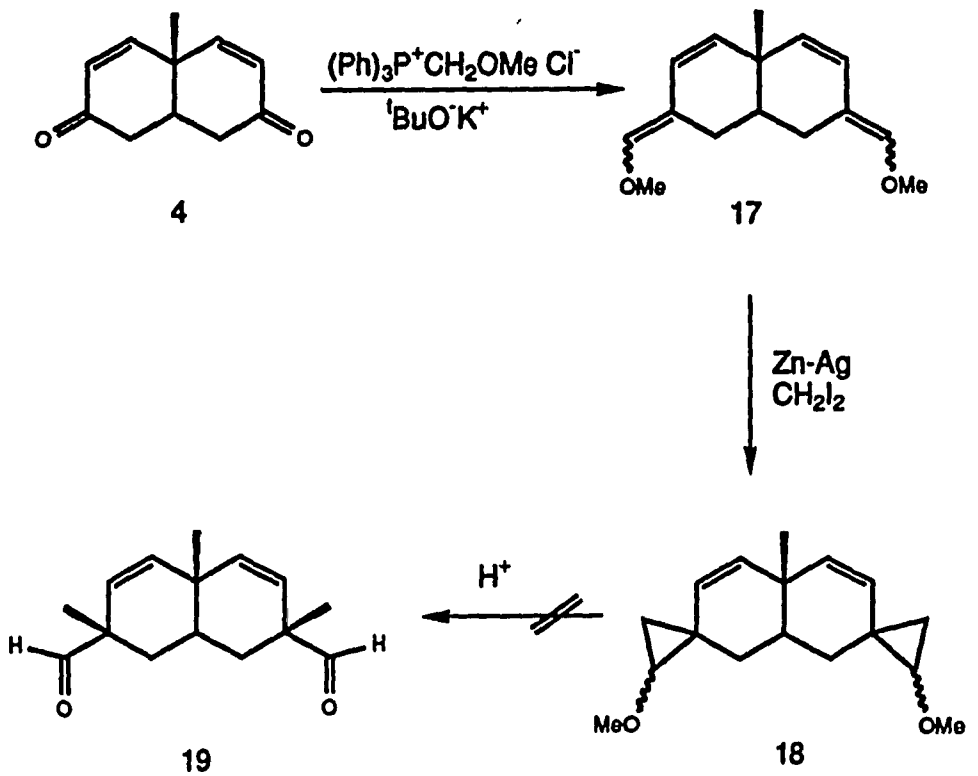


Figure **2.** Figure above shows the ^1H NMR spectrum of 12 in C_6D_6.

II.4 *Model studies of tricyclic compound 12*

The dienedione 4 was chosen as the closest model to the tricyclic dienedione 12 in developing the synthetic scheme 1 leading to the triene 16. Scheme 6 proposes a method of angular methylation of 4 by way of cyclopropanation of its enol ether and acid-catalyzed hydrolysis of the resulting cyclopropyl ether as reported by Wenkert[3]. The bis-Wittig reaction of 4 with methoxymethylene-triphenylphosphorane[1] (derived from the corresponding phosphonium chloride using potassium t-butoxide as base[18]) was accomplished in 81% yield and gave 17 in a mixture of three isomers, as indicated by proton NMR spectra. We achieved this olefination by using (methoxy (trimethyl silyl) methyl) lithium, a reagent developed by Magnus[19] generated by treatment of (methoxymethyl) trimethyl silane with *sec*-Butyl lithium. Treatment of the bis-enol ether 17 with the Simmons-Smith[2] reaction yielded a mixture of inseparable methoxy cyclopropanes. This mixture also contained some undesired Simmons-Smith adduct derived from attack on the endocyclic double bonds. This conclusion was reached by examining the ^{1}H NMR spectrum of the mixture. The integration of the methoxy groups compared to the olefinic hydrogens gave a ratio of ~5:1 respectively, as opposed to a 1.5:1 for a pure compound. Repurification of the mixture afforded compound 18, one of the pure isomers of the bis-methoxy cyclopropane derivatives with the correct integration ratio (see NMR). Acid hydrolysis of compound 18 was unsuccessful and it led to intractable materials. While the Simmons-Smith reaction with simple olefins leads to cyclopropanes in good yields, the reaction with conjugated olefins (e.g. enol ether 17) is often complicated[20] and the yields are generally low. We encountered the same difficulty even when we used the improved[21] version of the Simmons-Smith reaction namely using Zn-Ag couple in place of the Zn-Cu couple. Low yields were obtained again when we treated 17 with diethylzinc and methylene iodide. This method is known to be particularly suitable for the conversion of vinyl ethers into the corresponding cyclopropanes.[22]

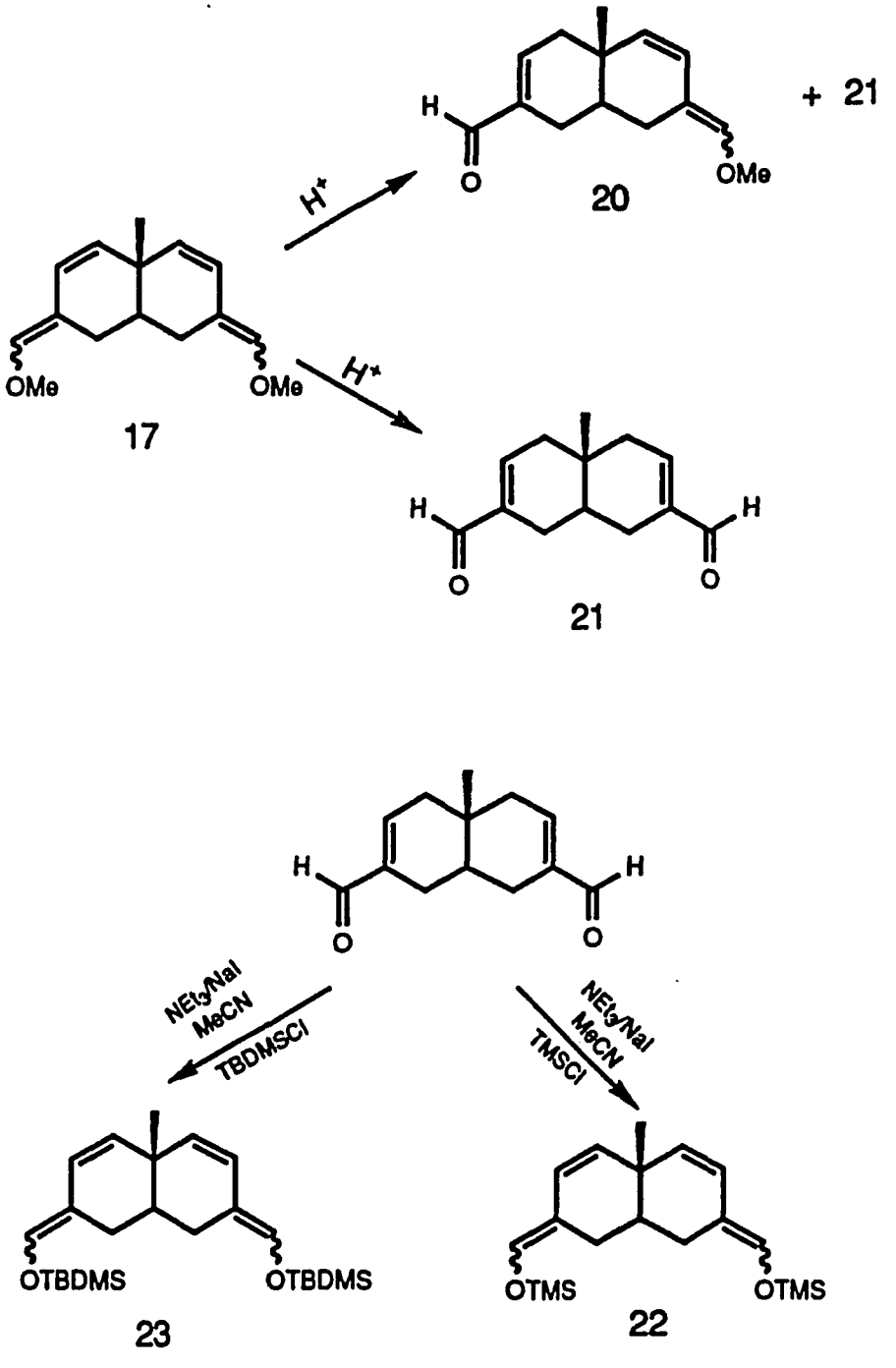
Scheme 6



4 17 18 19

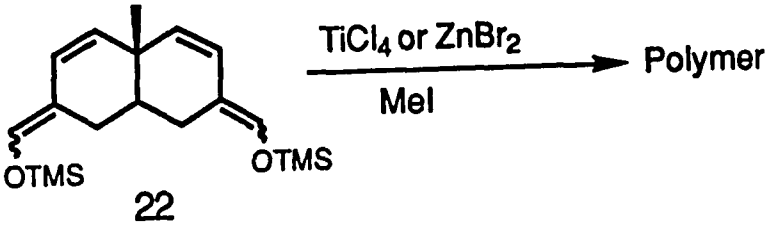
We then looked into the cyclopropanation of the silyl enol ether[23] of the aldehyde 21, as an alternative form of α-methylation, hoping to get some stereoselectivity in the cycloproponated product. For this reason, as shown in Scheme 7, we converted the vinyl enol ether 17 in the presence of 5N HCl in THF to the α–β unsaturated aldehyde 21 quantitatively. Following the acid hydrolysis of compound 17 with TLC indicates that 17 is first converted to 20 before it is completely transformed into 21. Compound 20 displays a larger R_f value than compound 21. The mono-enol ether 20 can be isolated together with compound 21 if the reaction is stopped before completion. Further treatment of 21 by the method of Duboudin and coworkers,[24,25] led to the preparation of the bis-silyl ether 22 in quantitative yield. Compound 22, although stable enough to be isolated, was a very moisture sensitive compound which did not survive purification on silica gel (even when triethylamine was applied), and hydrolyzed back to its starting dialdehyde 21. It was therefore decided to make the more stable silyl enol ether using t-butyldimethylsilyl chloride. The same procedure[25] was used in order to convert 21 to 23. Silyl enol ether 23 was stable enough to be chromatographed and was obtained in 93% yield. Subsequent treatment of 23 by the Simmons-Smith reaction did not show any stereoselectivity towards cyclopropanation of the enolic double bonds and gave rise to a mixture of inseparable bis Simmons-Smith adducts. Therefore, we encountered the same problem here as we did in the conversion of vinyl enol ether 17 to 18.

Scheme 7

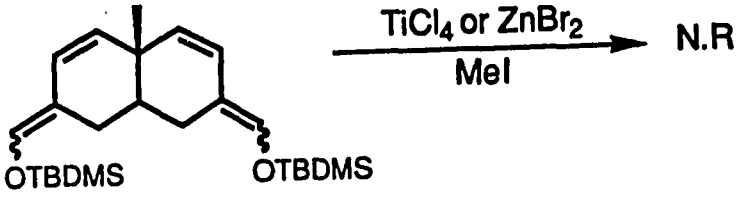

H
O
OMe
20
+ 21
H+
OMe
OMe
17
H+
H
H
O
O
21
H
H
O
O
NEt3/NaI
MeCN
TBDMSCl
NEt3/NaI
MeCN
TMSCl
OTBDMS
OTBDMS
23
OTMS
OTMS
22

In view of the ready availability of both enol ethers 22 and 23, we have examined the Friedel-Crafts alkylation of these enol ethers as a method of introducing a methyl group α-to the carbonyls[26] (Scheme 8). Using 22 as the substrate, its reaction with methyl iodide in the presence of titanium tetrachloride or anhydrous zinc dibromide as a catalyst led to polymeric compounds due to condensation. Compound 23, however, remained unchanged under these conditions.

Scheme 8



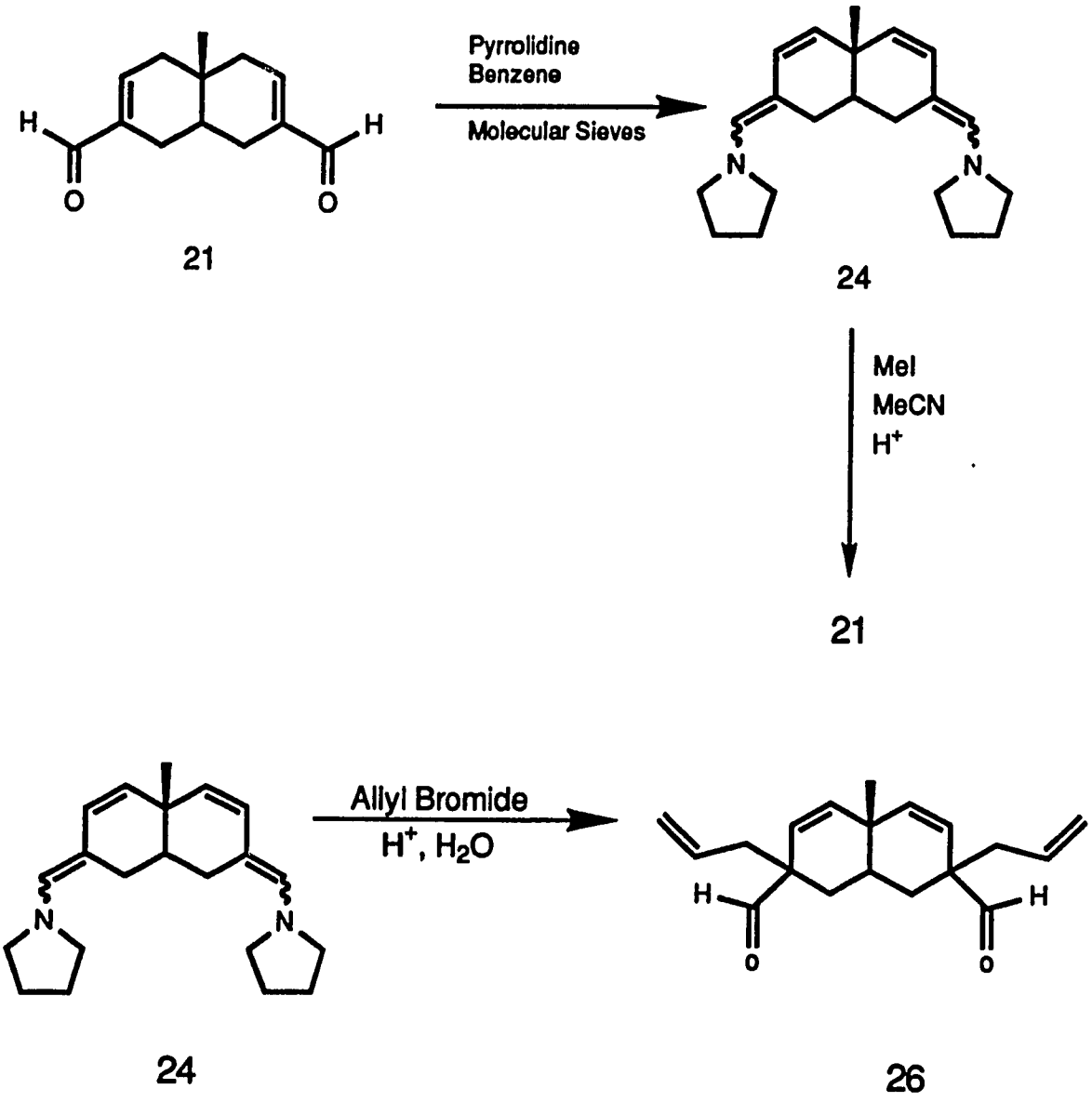
22



23

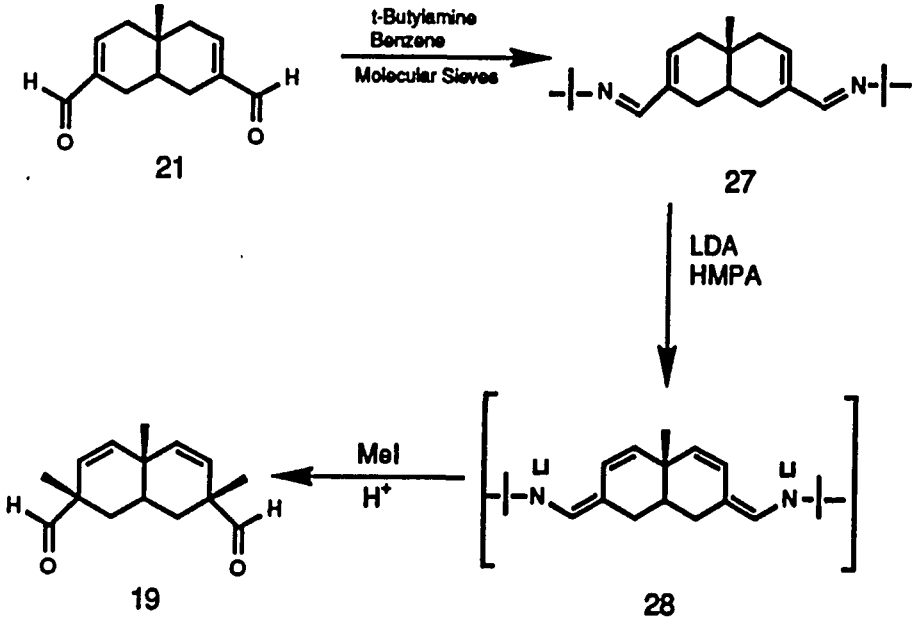
As an alternative, we considered alkylating the aldehyde 21 via formation of nitrogen derivatives such as enamines or metallated imines (imine anions). We used pyrrolidine in order to make the pyrrolidine enamine since they have been found most generally useful in alkylation with alkyl halides.[27] The enamine 24 was prepared by using 5 equivalents of pyrrolidine to 1 equivalent of aldehyde 21 in the presence of molecular sieves[28,29,30] as a dehydrating agent. Enamine 24 was subjected to methylation using methyl iodide (Scheme 9) followed by the hydrolysis of the product. The ^{1}H NMR analysis of this reaction product confirmed the regeneration of the aldehyde 21. This led us to believe that the enamine 24 gave only nitrogen alkylation rather than the desired carbon alkylation. It turns out that enamines derived from aldehydes, on treatment with simple unactivated primary alkyl halides give almost entirely N-alkylation.[31] However, as Stork has shown,[27] alkylation with particularly reactive halides (allyl, benzyl, propargyl halides) leads to C-alkylation through an initial quarternary ammonium salt which then undergoes Claisen rearrangement with usual structural inversion.[32] Treatment of our pyrrolidine enamine 24 with allyl bromide did in fact result, after hydrolysis, in α-alkylation giving 26 as a mixture of three aldehydes as indicated by its ^{1}H NMR spectrum (Scheme 9).

Scheme 9


H
H
O
O
21
Pyrrolidine
Benzene
Molecular Sieves
N
N
24
MeI
MeCN
H+
21
N
N
24
Allyl Bromide
H+, H2O
H
H
O
O
26

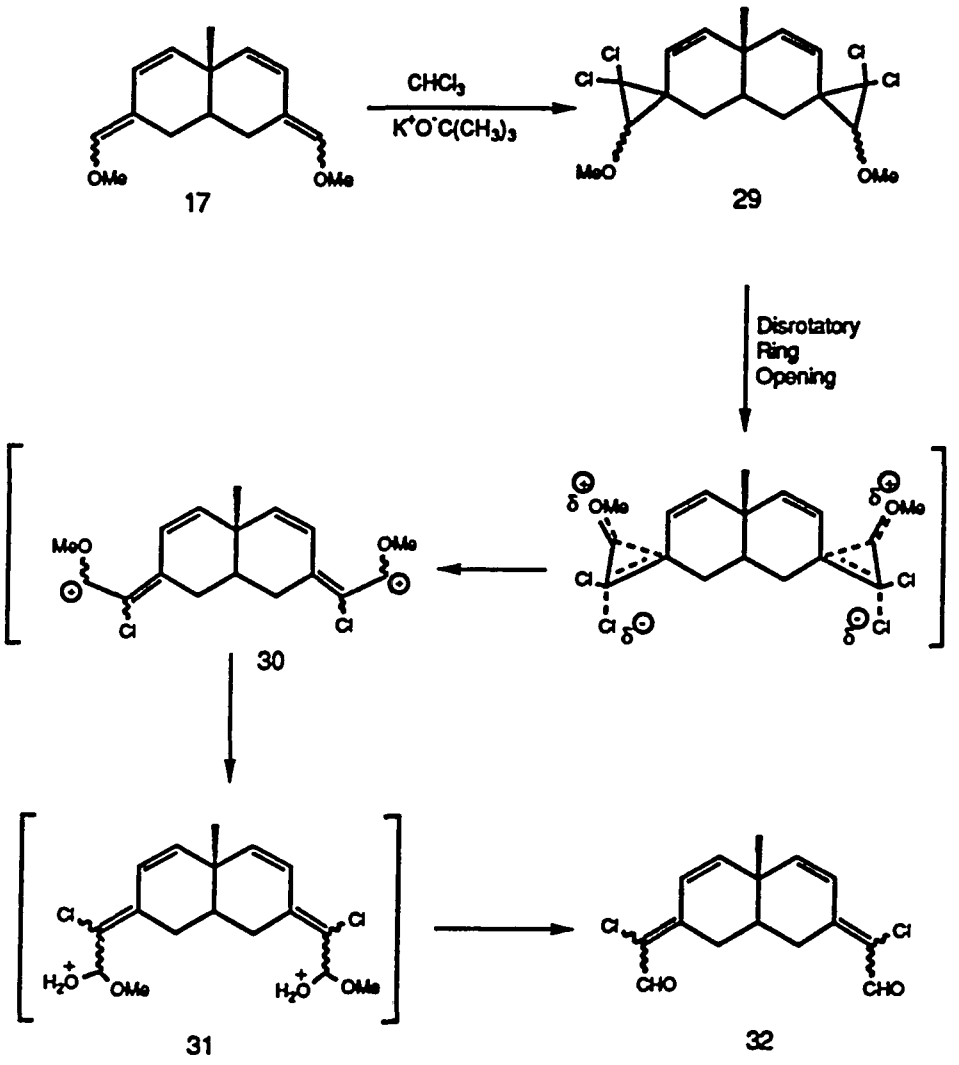
At this time we turned our attention to a method for the alkylation of aldehyde 21 based on the C-alkylation of the magnesium[33] or lithium[34] salts of N-substituted imines (Scheme 10). We treated aldehyde 21 with 4 eq. of t-butyl amine in the presence of molecular sieves as a dehydrating reagent and obtained the corresponding imine 27 in quantitative yield. When 27 was treated with 3 eq. of lithium diisopropylamide (containing 3eq. of HMPA) followed by addition of methyl iodide, it gave, after acid hydrolysis, less than 10% of what it appears to be an α-alkylated product and ~90% of recovered 21 as indicated by ^{1}H NMR spectrum. From the crude ^{1}H NMR spectrum, we observed a peak with the symmetry of an AB system in the olefinic region, and a singlet in the aldehydic region, which suggested that there might be only one isomer (19) as a result of this alkylation. In order to clarify this assumption, we are trying to maximize the yield for this reaction.

Scheme 10



As a final attempt in the methylation reaction series, we chose the Simmons-Smith reaction involving dichlorocarbene as a substitute for a simple carbene generated from methylene iodide. This idea came to mind in view of the fact that dichlorocarbene, by being more stable than the parent methylene carbene, should react more selectively with the electron rich enol double bonds and leave the cyclohexene double bonds intact. The reaction was tried by generating dichlorocarbene from the reaction of chloroform and potassium t-butoxide,[35] and 17 went along with our synthetic scheme. Our original joy at having formed 29 was mitigated when it quickly started to decompose and lose HCl to produce 32 on standing for a half hour after the work-up, (Scheme 11). The fact that the gem-dichloromethoxy-cyclopropane 29 undergoes ring opening readily, demonstrates the importance of the methoxy group as a driving force in this reaction. The electron donating methoxy group stabilizes the incipient carboniumion which develops in the disrotatory concerted ring opening-chloride loss. The electronic effect of alkoxy groups on the unsaturated nature of the cyclopropane ring, has been reviewed extensively.[36] Further studies[37-39] have shown that the presence of lone pair electrons adjacent to the ring increases the rate of ring opening substantially. We also found in the literature that halo-substituents exert a strong effect on the nature of the cleavage of the cyclopropyl ethers.[40,41] In analogy with the solvolytic behavior of gem-dichlorocyclopropyl ethers, ester substituents also have been found[42,43] to accelerate the rate of such ring openings. The mechanism depicted for the transformation of 29 to 32 involves a concerted ring opening of the cyclopropane with loss of chloride ion to form an allylic carbocation. Subsequent reaction of this cation leads to the corresponding hemiacetal which gets converted to the observed product 32.

Scheme 11

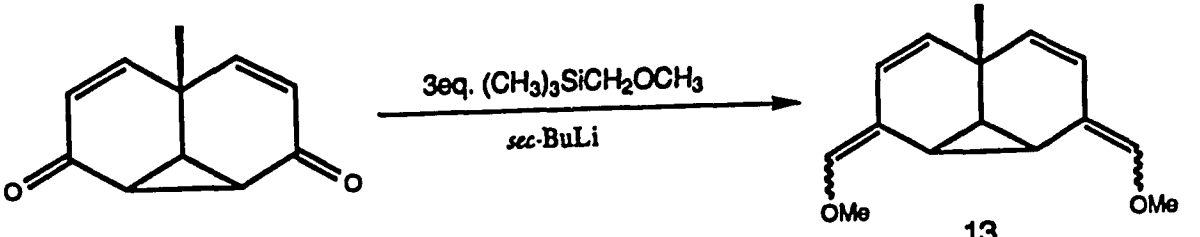


In the mass spectrum of 32, the base peak is indicated at a m/e value of 181. Since compound 32 contains two chlorine atoms, a distinct M + 4 peak can be observed at m/e value of 300, as well as an intense M + 2 peak at 298.

While our negative results can thus be reconciled with our previous ones, it also seems to establish model systems such as 17 and 21 as a synthetic dead end for our purposes. Therefore with compound 12 in hand, we decided to carry out the synthesis on the real system.

The very first step of the sequence in Scheme 1, i.e., the Wittig reaction of 12 to give 13, at first could not be accomplished. Compound 12 did not behave similarly towards the Wittig reaction as described for compound 4. Instead this reaction led to the formation of tar upon addition of compound 12 to the Wittig reagent. Several reactions were performed with variation of the Wittig reagent concentration to ascertain the scope of this olefination, unfortunately with unsuccessful results. However, 13 was synthesized successfully by a variation in Peterson's olefination as reported by Magnus[19], but only in less than 20% yield.

Due to the low yields of 13 and very little success with methylating reactions, we sought a significant change in the synthetic plan.

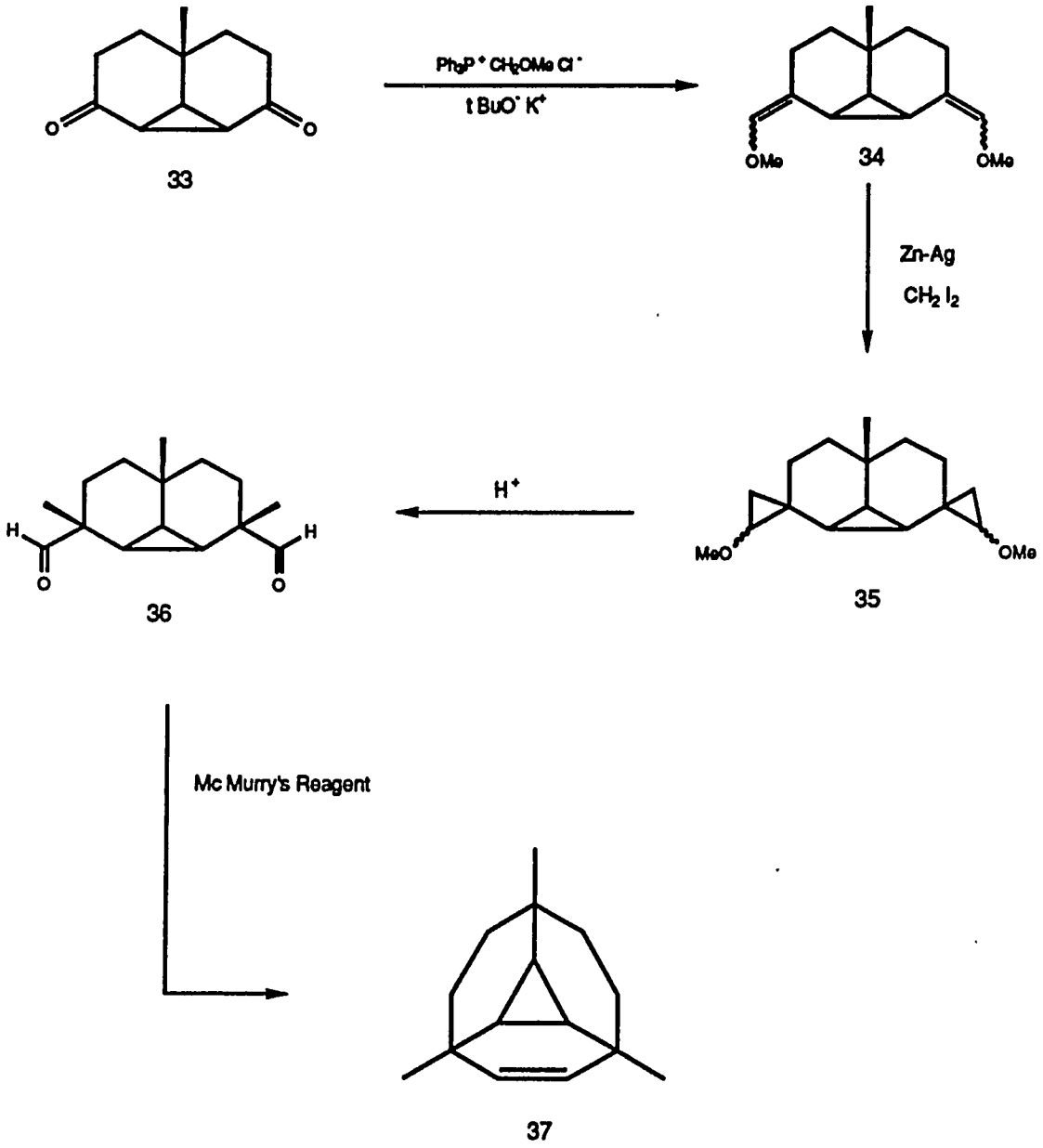


12 13

II.5 *Attempted synthesis of the tricyclic compound 33 from 12*

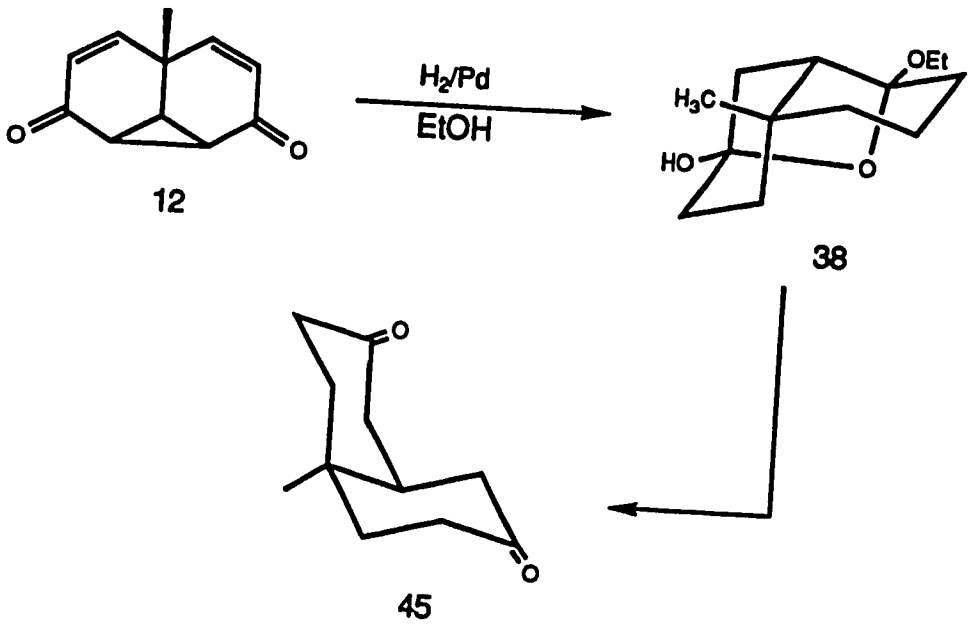
It was decided to make the saturated form of compound 12, namely 33, and carry out the synthesis towards the Truncamonoene 37 (Scheme 12). Free radical halogenation of 37 involving a preferential mono-bromination of the methylene hydrogens, followed by debromination can afford the desired triene 16. All the synthetic transformations envisioned in Scheme 12 seem attractive and are not expected to pose insurmountable problems. In the first step of the sequence, the olefination reaction of 33, which contains no double bonds, should proceed with a better yield than that of the olefination of 12. The next step, involving α-alkylation of 34 to 36 by the Simmons-Smith reaction has precedence in the literature.[1,2,3] However, for compound 34, unlike 13, there will be no danger of carbene insertion anywhere else in the molecule except the expected exocyclic enol double bonds. The latter sequence will be the primary reason for making 33 since we spent a great deal of time trying to alkylate at C_2 and C_7 positions in both 17 and 21.

Scheme 12


Ph3P+ CH2OMe Cl-
t BuO- K+
33
34
OMe
OMe
Zn-Ag
CH2 I2
H+
35
MeO
OMe
36
H
H
O
O
Mc Murry's Reagent
37

To achieve this goal, we hydrogenated 12 (Scheme 13) in the presence of a catalytic amount of palladium on charcoal (10%). After filtration of the charcoal and evaporation of the solvent (EtOH) a clear oily product was obtained with a very complex ^1H NMR spectrum. This stable oily residue was chromatographed on silica gel (10% ethyl acetate in hexane) giving a compound which by TLC showed only one spot. The ^1H NMR spectrum of this component was almost identical to that of the crude mixture. The chromatographed oil crystallized after standing on the bench for two days. Crystals were filtered and ^1H NMR showed this to be identical to the dione 45, which was synthesized separately from the decarboxylation of its precursor 42. Later we concluded that since ethanol was used as the solvent in this hydrogenation, a stable hemiketal was formed. This ketal on standing was converted to the dione 45 quantitatively. Compound 45 is a product of hydrogenolysis of the cyclopropane ring as well as the hydrogen addition to the double bonds. A similar observation, reported in the Ph. D. thesis of Watt, is mentioned in the first section of this thesis.

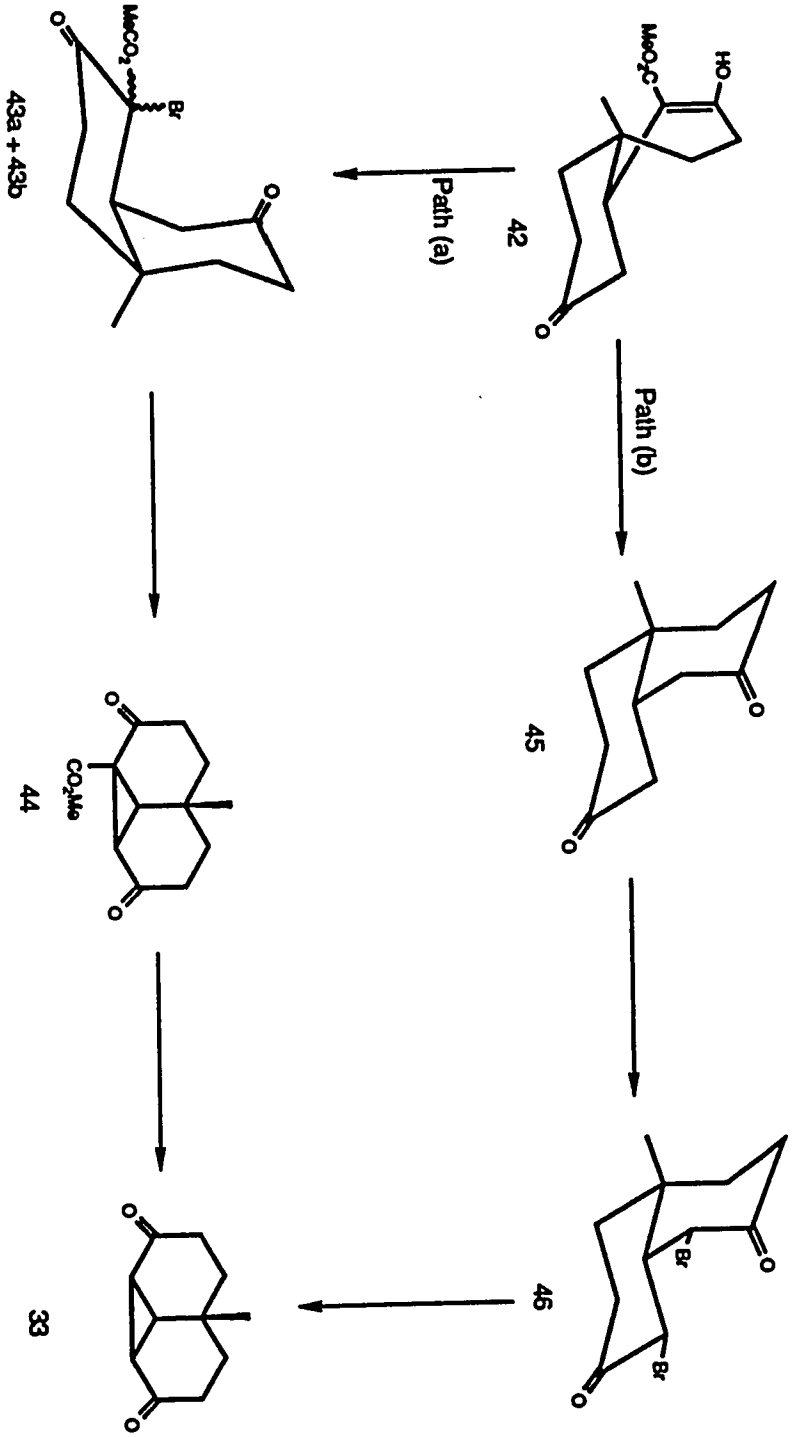
Scheme 13



III.1 *Attempted synthesis of compound 33 from either 42 or 45*

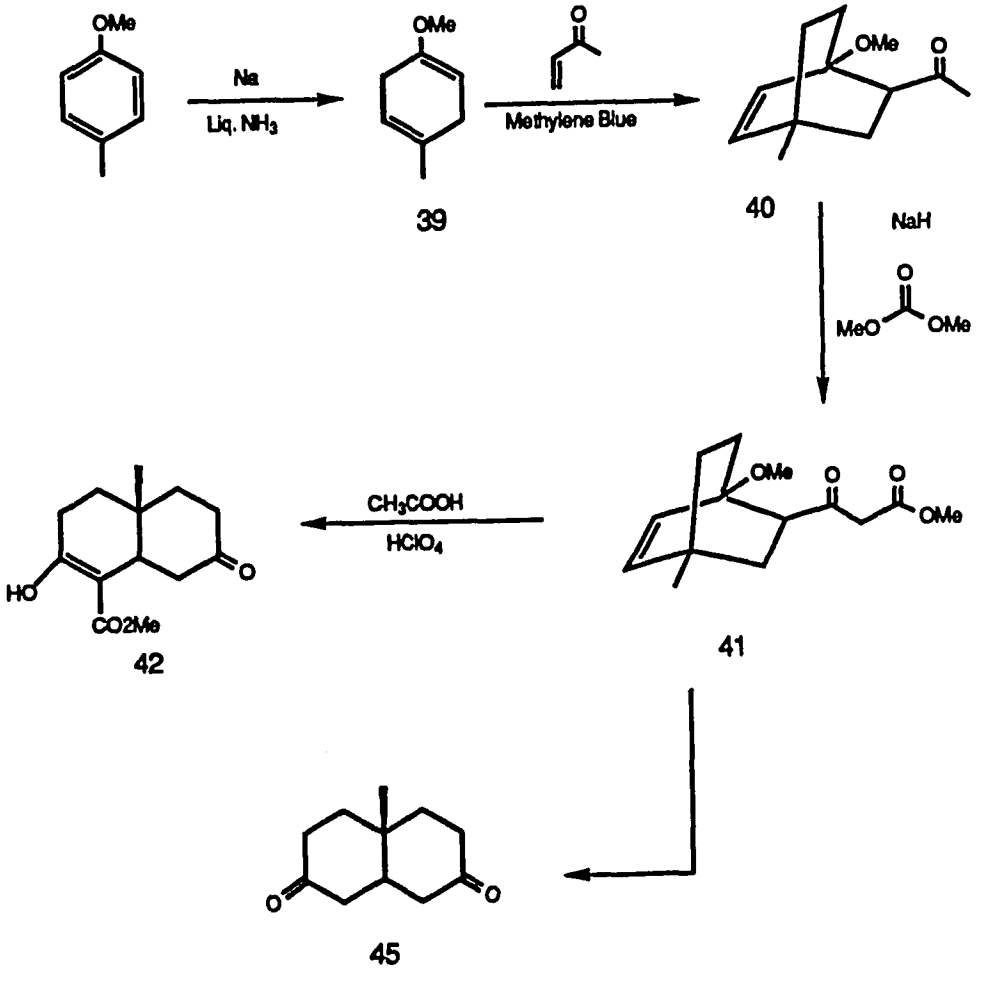
Alternatively with the β-keto ester 42 readily accessible,[44] we considered a possible strategy for its conversion to the tricyclic dione 33 *via* two independent pathways (scheme 14). Path (a) involves bromination of 42 at C_1 position followed by an intramolecular cyclopropanation to afford 44. Decarboxylation of 44 to 33 carries with it the possibility of cyclopropyl-carbinyl rearrangements, therefore defunctionalization at C_1 could be delayed to a later stage, possibly by perester decomposition. Path (b) on the other hand, shows bromination of the dione 45 derived from the decarboxylation of 42. The crucial reaction of 45 assumes bromination at C_1 and/or C_8 followed by either debromination, in the case of the dibrominated species 46, or dehydrobromination in the case of the mono-brominated compound, giving rise to 33.

Scheme 14



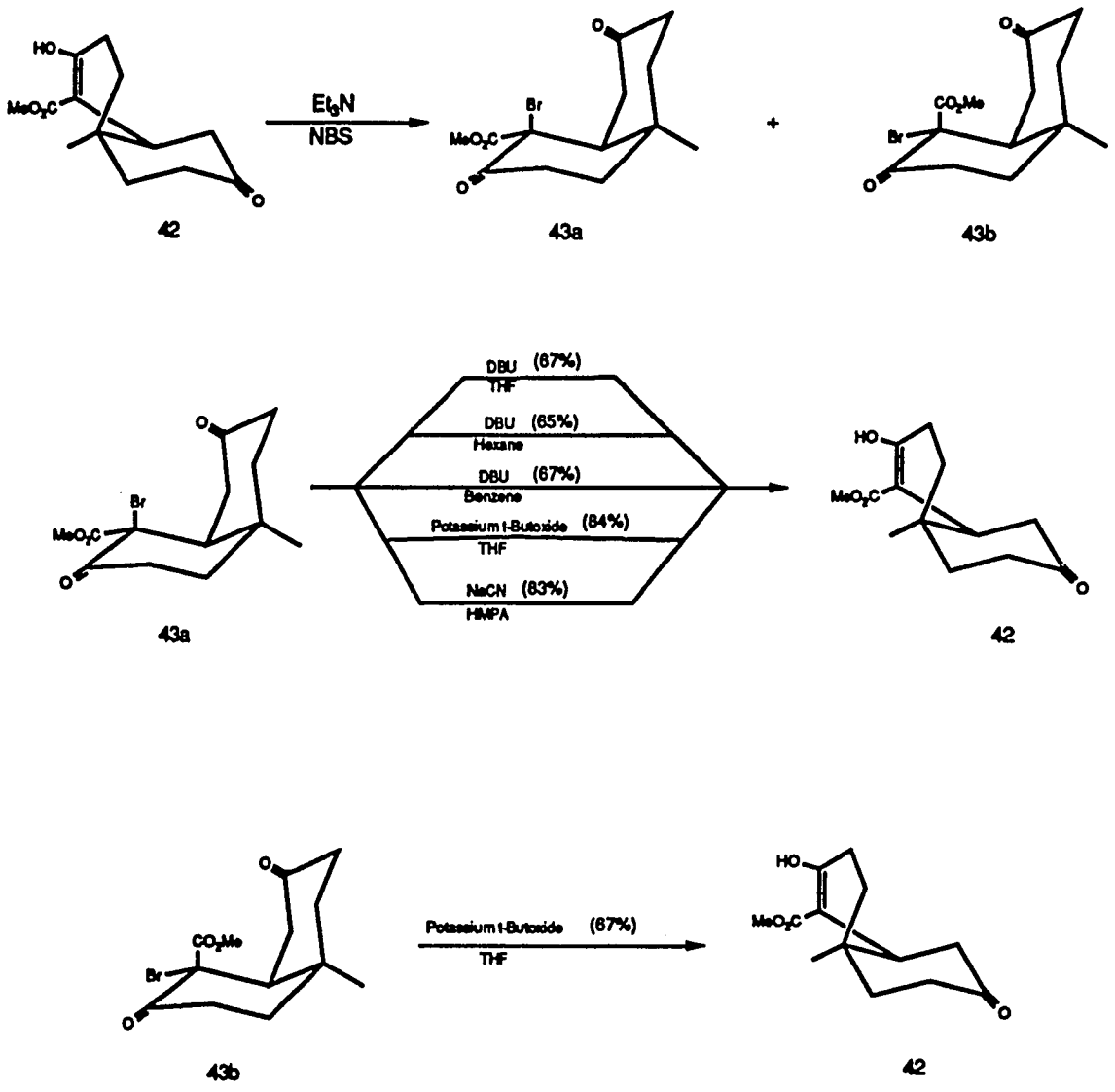
First, the preparation of 42 is described.[45] The Birch reduction of 4-methylanisole to the dihydroanisole 39 was accomplished in 85% yield. Compound 39 was isomerized to the conjugated diene in the presence of methylene blue, and its Diels-Alder reaction with methyl vinyl ketone gave 40 in 53% yield. Carbomethoxylation of 40 by dimethylcarbonate afforded 41 in 84% yield. Ester 41, treated with 70% perchloric acid in acetic acid, rearranged to give the crystalline 42 in 88% yield. Dione 45 was isolated in 70% yield, directly from the rearrangement followed by hydrolysis and decarboxylation of 41. The ^1H NMR, infrared, and melting point (91-93°C) of 45 were identical with those found in the literature.[7,46]

Scheme 15



We examined an approach aimed at direct bromination of the β-keto ester at the C_1 position. Compound 42 was treated with N-bromosuccinimide in the presence of triethylamine. This reaction produced two diastereomeric α–bromo-keto esters 43a and 43b in a 1:1 mixture (Scheme 16), and were separated chromatographically (silica gel, 20% ethyl acetate in hexane) to give a combined yield of 80%. The structures of these bromides were determined by ^1H, ^{13}C NMR spectroscopy and X-ray crystallography, as described in detail in the experimental section. Attempted cyclopropanation of these bromides through an intramolecular cyclization by use of various dehydrohalogenating agents and solvents led to the β-keto ester 42 as the only product (Scheme 16). The yields of 42 from these halo-derivatives are listed in Figure 3. A series of decarboxylation reactions of compounds 43a and 43b were tried. First, the mixture of bromo adducts, without purification, was treated with phosphoric acid / acetic acid in hope that ring closure would occur together with hydrolysis and decarboxylation. Unfortunately, the diketone 45 was the only product of this reaction. Another method of decarboxylation was undertaken, *via* S_N2 type dealkylation.[47] When 43a was directly treated with sodium cyanide in hexamethylphosphoramide at 160°C, we observed debromination and formation of the β-keto ester 42 as the sole product. Once again this reaction proceeds by an attack on the bromine, leaving behind the highly stabilized anion. These results demonstrate that attack of the base or nucleophile takes place on the bromine leaving an anion which is stabilized both by the ketone and the ester group. Therefore, these bromo derivatives act as if they were brominating agents. Like N-bromo succinimide, whose bromine atom is highly positive rather than being a leaving group, compounds 43a and 43b undergo debromination rather than dehydrobromination.

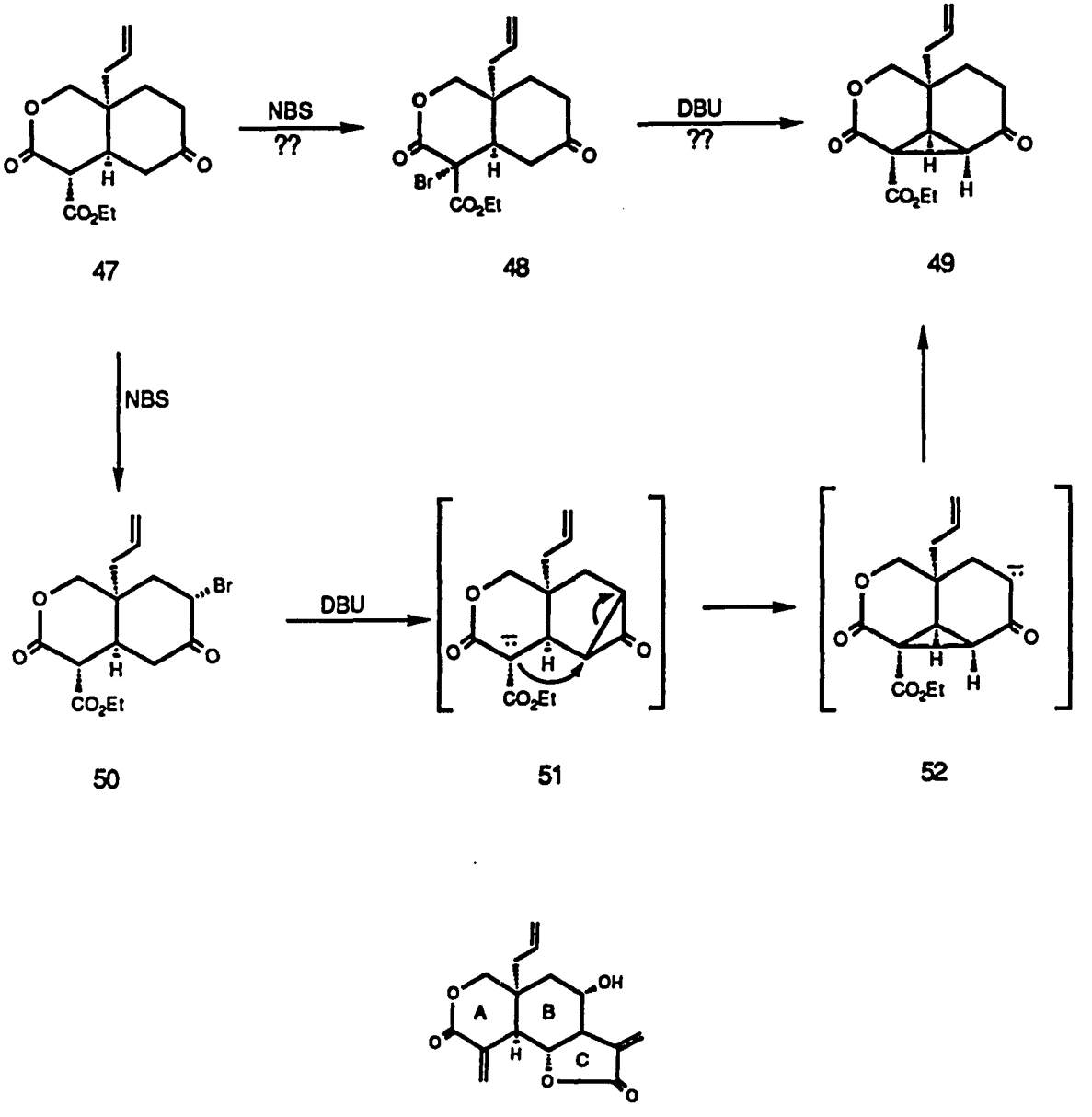
Scheme 16


HO
MeO2C
Et3N
NBS
Br
CO2Me
42
43a
43b
DBU (67%)
THF
DBU (65%)
Hexane
DBU (67%)
Benzene
Potassium t-Butoxide (84%)
THF
NaCN (83%)
HMPA
Potassium t-Butoxide (67%)
THF

III.2 *Bromination of 42 as opposed to bromination of 47 in the synthesis of Vernolepin*

During the continuing search for bromination of β-keto ester 42, the total synthesis of Vernolepin[48] was found (Scheme 17). This described the bromination of compound 47 at the C_4 and its conversion to the cyclopropane, a key intermediate for the synthesis of Vernolepin 53. On the elaboration of the cyclopropane ring to 49, Isobe[48] reported that compound 47 was mono-brominated at the C_4 position using 1 eq. of NBS in THF at 0°C. The brominated compound 48 was subjected, without purification, to treatment with DBU in isopropyl alcohol to afford the cyclopropane ketone 49 in 85% yield. However, there were no structural assignments provided to confirm C_4 as the location of the bromine atom in 48. In view of our results obtained for the bromination and dehydrobromination of 42 (see Schemes 18 and 19), we propose that the bromination of 47 occurs at C_8 to produce 50 instead of at C_4 position. Furthermore, attempted dehydrobromination of compounds 43a and 43b (see Scheme 16) demonstrate that, had the bromination of compound 47 under non-basic condition occurred at C_4, its subsequent treatment with DBU would have led to debromination rather than dehydrobromination. That the dehydrobromination of 50 to afford the key cyclopropyl intermediate 49, is rationalized by a mechanism that involves a cyclopropanone intermediate 51. Due to the large strain associated with the trigonal carbon, this intermediate is rapidly cleaved by the enolate ion from C_4 to give the product 49.

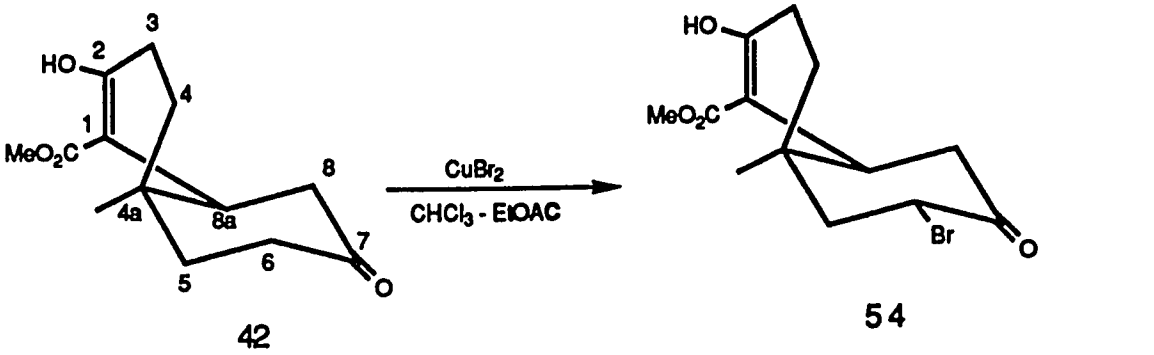
Scheme 17



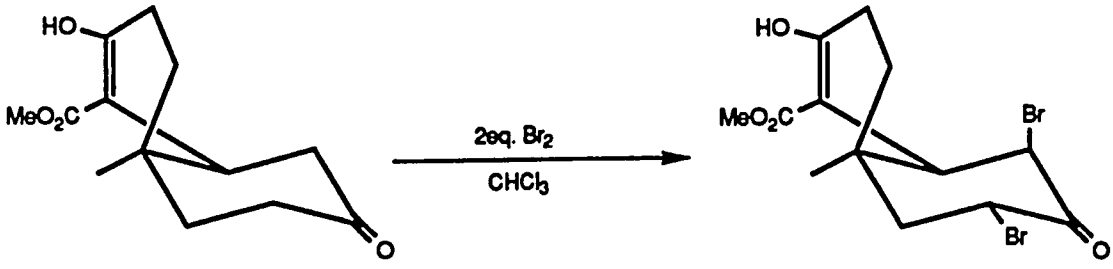
Vernolepin 53

The only other option remaining for the formation of 44 (Scheme 14), involves an acid catalyzed bromination of 42 at C_8 position, followed by dehydrobromination. To fulfill this goal, the β-keto ester 42 was brominated in a heterogeneous system containing two equivalents of copper (II) bromide in chloroform-ethylacetate.[49,50] This is one of the most direct and clean systems for selective bromination of ketones. Compound 42 was brominated exclusively in the undesired position at C_6 giving 54 in 80% yield (Scheme18). That the initial bromination had occured at C_6, instead of the expected C_8 position, was confirmed by both the ir and nmr spectra of 54. The carbonyl absorption of ketone 54 was shifted ~18 cm^{-1} from that of the parent ketone, indicating an equatorial configuration for the bromine atom.[51] Also, in the nmr spectrum of 54, the coupling pattern for the deshielded proton on C_6 ($J_{6(ax)-7(ax)}$ = 13.58 cps, $J_{6(ax)-7(eq)}$ = 5.83 cps; $J_{AX} + J_{BX}$ = 20 cps) is characteristic of the axial proton of an ABX-type system,[52] confirming C_6 as the position of the bromine atom. However when two equivalents of bromine were used instead of copper bromide, the second bromine atom was delivered in the desired position at C_8 and produced 55 in 80% yield (Scheme 18). The stereochemistry of 55 was assigned by examining its ^1H NMR spectrum. We first compared the position of the axial α-hydrogen adjacent to bromine on C_6 in both 54 and 55. In 55 the axial α-hydrogen on C_6 has moved downfield by 0.73 ppm. This downfield chemical shift difference shows that the other bromine atom in the molecule must be in the axial position. This causes deshielding due to a 1,3 diaxial interaction between the α-hydrogen and the axial bromine. Further proof of both the position and orientation of the bromine atom on C_8 was furnished unambiguously from its nmr spectral properties. A doublet at 4.7 ppm for the C_8 hydrogen atom in 55 confirmed the location of the bromine atom. Also, the value of its coupling constant ($J_{8(eq)-8a(ax)}$ = 5 cps) with the ring junction at C_{8a} is consistent for an equatorial-axial coupling. Further evidence for the structural proof of 54 and 55 was provided by X-ray crystallographic data.

Scheme 18



42 54

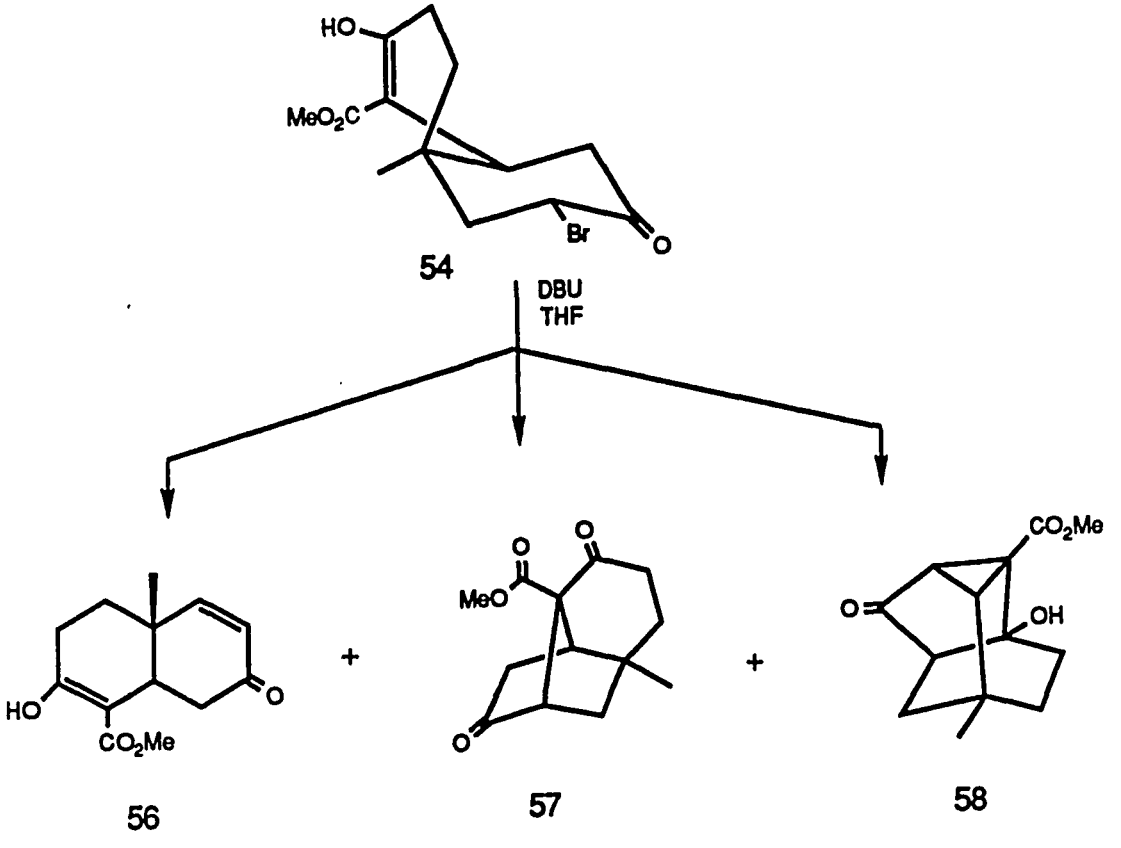


42 55

III.3 *Reaction of 54 with DBU*

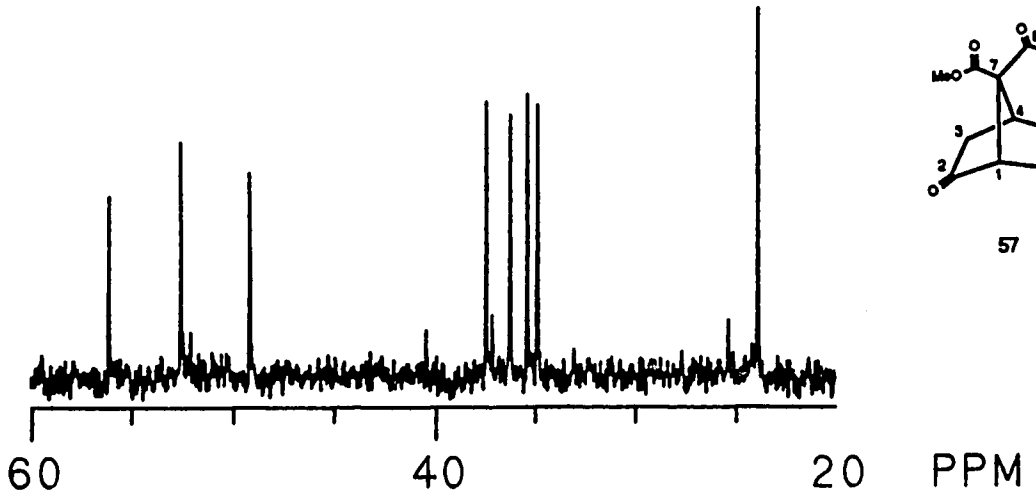
Before we sent compound 54 and 55 for X-ray analysis, we examined their reactions with both DBU and lithium halide-dimethyl formamide procedure.[53] The identity of these reaction products would then suggest the exact locations of the bromine atoms in both 54 and 55. When the monobromo β-keto ester 54 was treated with DBU, three compounds were obtained: 56, 57, and 58 in 18%, 40%, and 40% yields, respectively (Scheme 19). These three compounds were separated chromatographically by use of a Chromatotron eluting with 20% ethyl acetate in hexane. Monoene β-keto ester 56 is UV active and is the fastest moving band, followed by the non-UV active tricyclic diketone 57 and the tetracyclic keto-alcohol 58.

Scheme 19



The assignment of ^{13}C for CH, CH_2 and CH_3 groups in compound 57 was accomplished by using the INEPT method. INEPT (Insensitive Nuclei Enhanced by Polarization Transfer) is a new method in ^{13}C spectroscopy which generates separate spectra for CH, CH_2 and CH_3 groups. The information obtained by using INEPT is of the same kind traditionally acquired by off-resonance decoupling. However, both the sensitivity and resolution in INEPT are superior to the traditional method, because the polarization transfer spectra can be obtained with broadband decoupling. As pointed out by Derome[54] "an angle Θ is defined $\Theta = \pi J\Delta$. In order to distinguish the three kinds of carbon resonance, it is necessary to run three spectra with Δ adjusted to make Θ equal to $\pi/4$, $\pi/2$ and $3\pi/4$. The $\Theta = \pi/4$ spectrum contains all resonances, $\Theta = \pi/2$ gives CH's only, and $\Theta = 3\pi/4$ again shows all resonances, but with CH2's inverted. Suitable combining of these spectra then allows generation of CH, CH_2 and CH_3 subspectra."

When $\Theta = \pi/4$ and $\Theta = 3\pi/4$, the spectra differ only in the phase of the CH_2 signals. Therefore, by subtracting one from the other, a subspectrum of CH_2 is generated. Adding them generates a spectrum which contains only CH's and CH_3's.



57

Figure **3.** The figure above shows all the protonated carbons in 57.

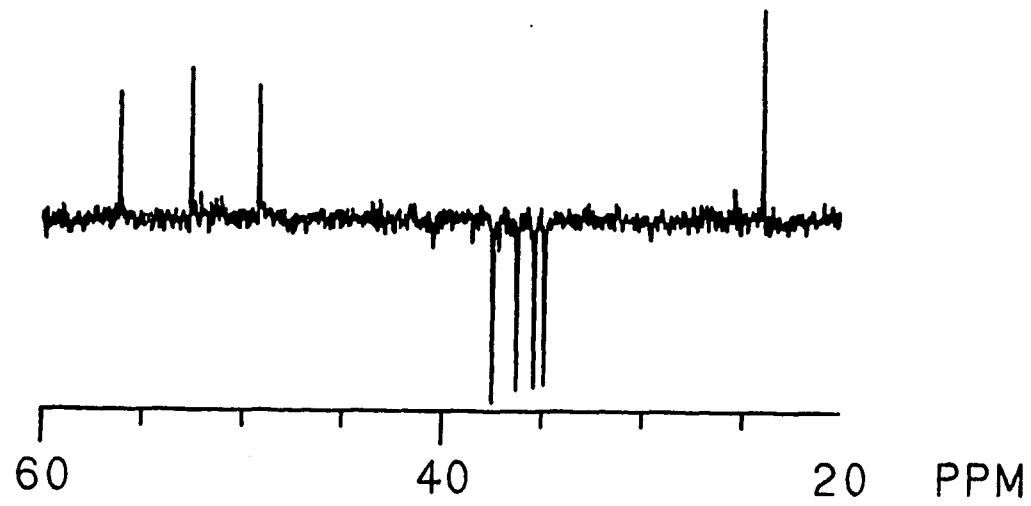


Figure **4.** In the spectrum above for compound 57, all the CH's and CH_3's are shown on one side (up), and the CH_2's are all inverted (down).

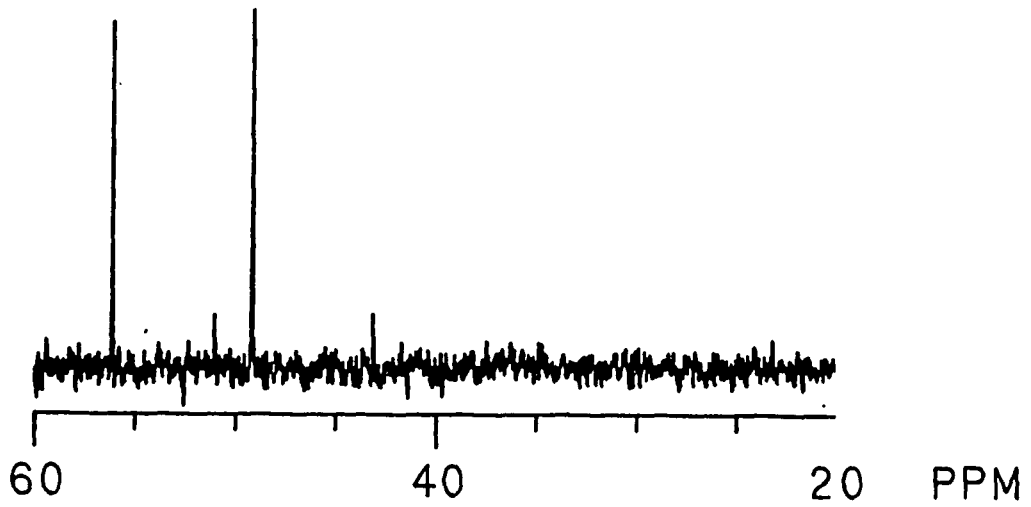
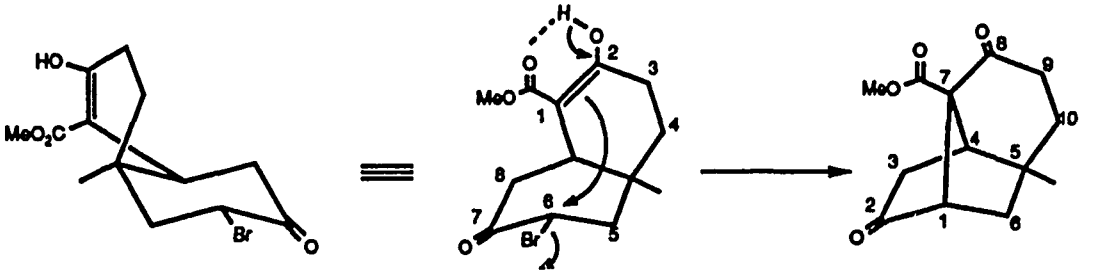


Figure **5.** The subspectrum above shows only the CH's in the molecule when $\Theta = \pi/2$.

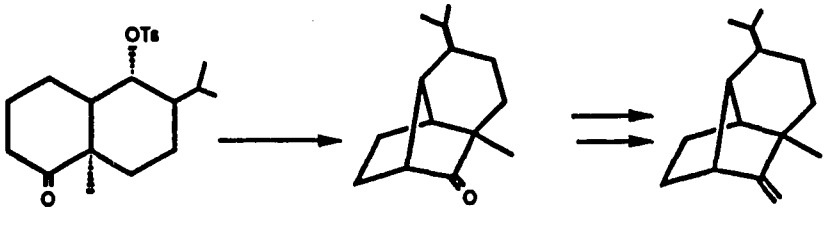
III.4 *Synthesis of 57 via transannular cyclization*

Compound 57 is formed *via* an intramolecular cyclization when DBU is used as the base. An examination of the model shows that the orbital in leading to the product, is placed directly to the rear of the bromine-bearing carbon C_6 and is oriented at the line of departure of this group. Several other condensed-ring systems were made[55] in connection with the synthesis of 57 (e.g. sativene and copaene shown in Scheme 20).

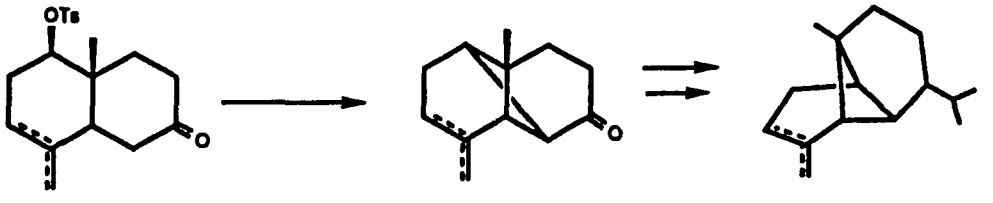
Scheme 20



54 57



Sativene

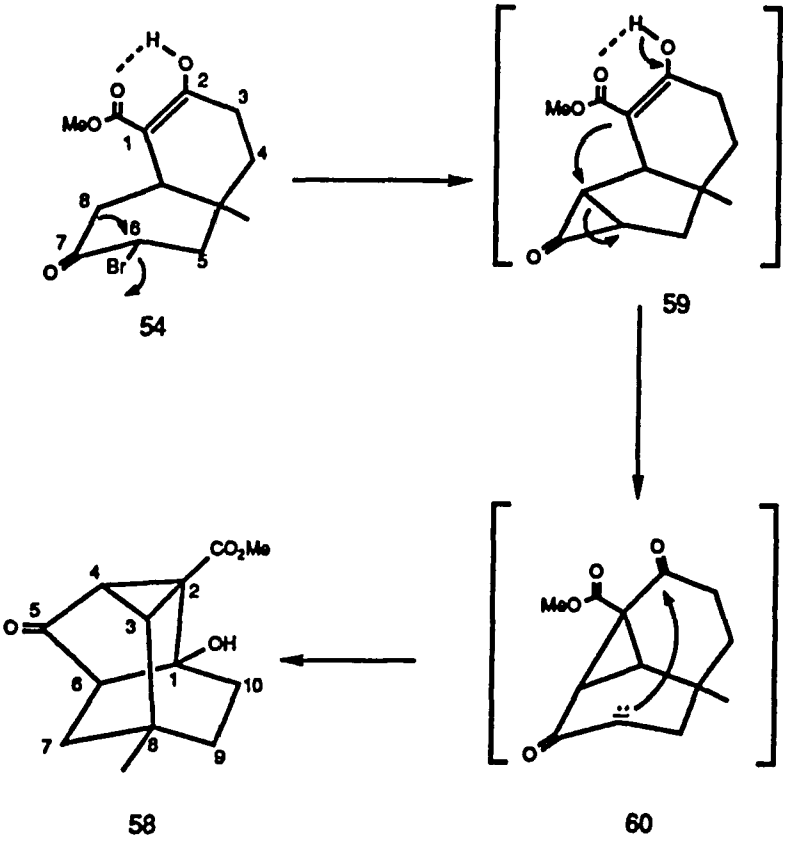


Copaene

III.5 *Synthesis of 58 via cyclopropanone intermediate*

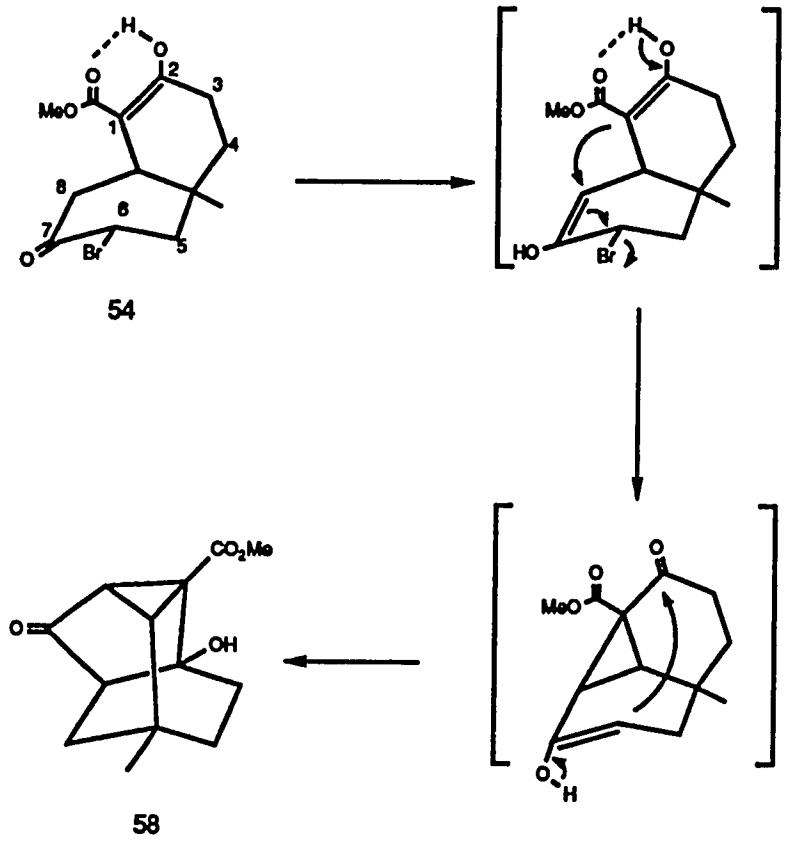
The third, tetracyclic compound 58 formed during this dehydrobromination reaction may involve a cyclopropanone intermediate. The reaction is initiated by an enolate ion, which carries out an intramolecular nucleophilic substitution to form a cyclopropanone ring. Due to the large strain associated with a trigonal carbon in a three-membered ring of cyclopropanone, nucleophilic attack by the enolate ion becomes feasible in order to relieve this strain. The three membered ring then opens to give a carbanion that attacks across the ring onto the ketone to give a transient oxygen anion that is protonated by the solvent to produce 58.

Scheme 21



Formation of 58 may also involve an S_N2' mechanism (Scheme 22). According to this view, in the presence of DBU, the initial step involves enolization between C_7 and C_8. Subsequent ejection of bromine is then feasible by an enolate attack at C_8 *via* S_N2' like mechanism as shown below.

Scheme 22

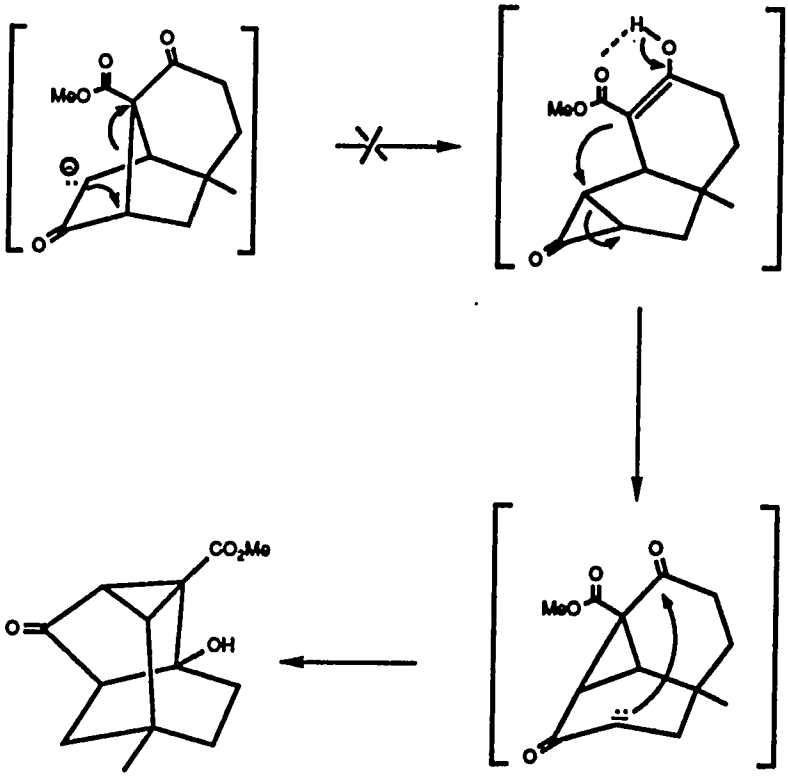


54

58

In order to rule out the possibility that 58 was not derived from 57 (Scheme 23), an independent reaction involving 57 with DBU was run. Under the same conditions (e.g. dehydrohalogenation of 54 with DBU) 57 remained unchanged.

Scheme 23

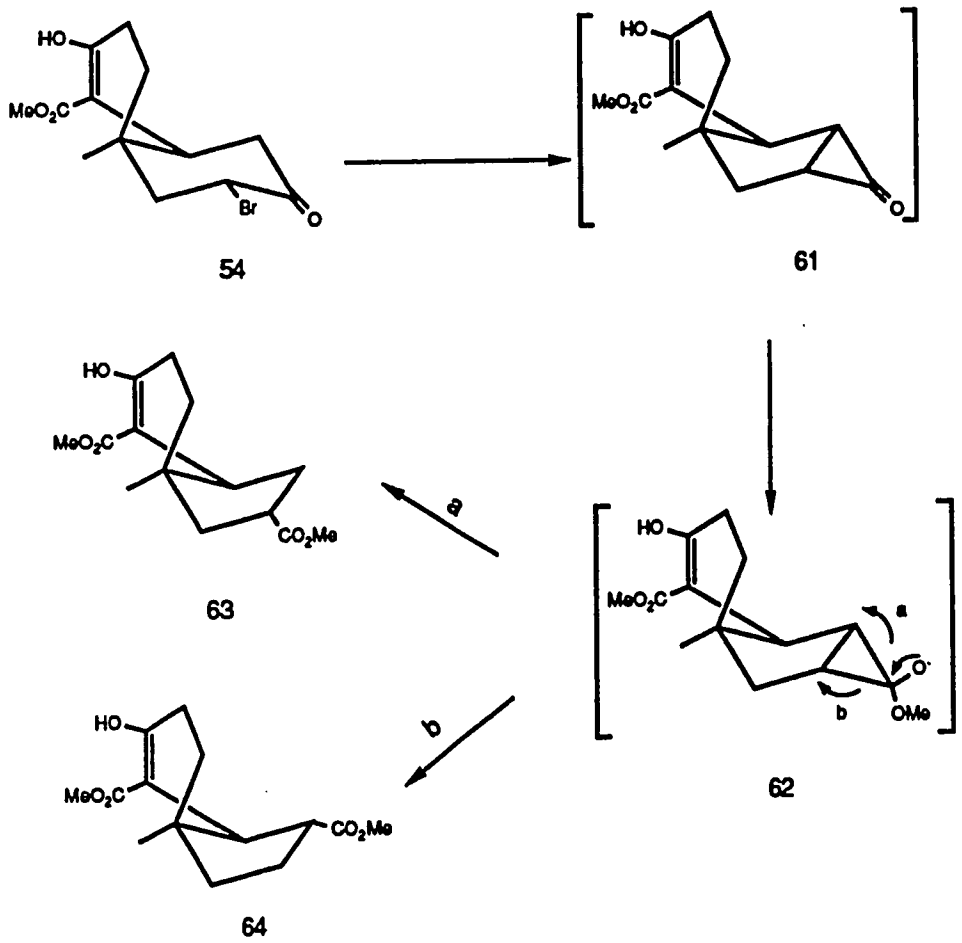


58

III.6 *Attempted Favorskii rearrangement of 54 to give 63 and 64*

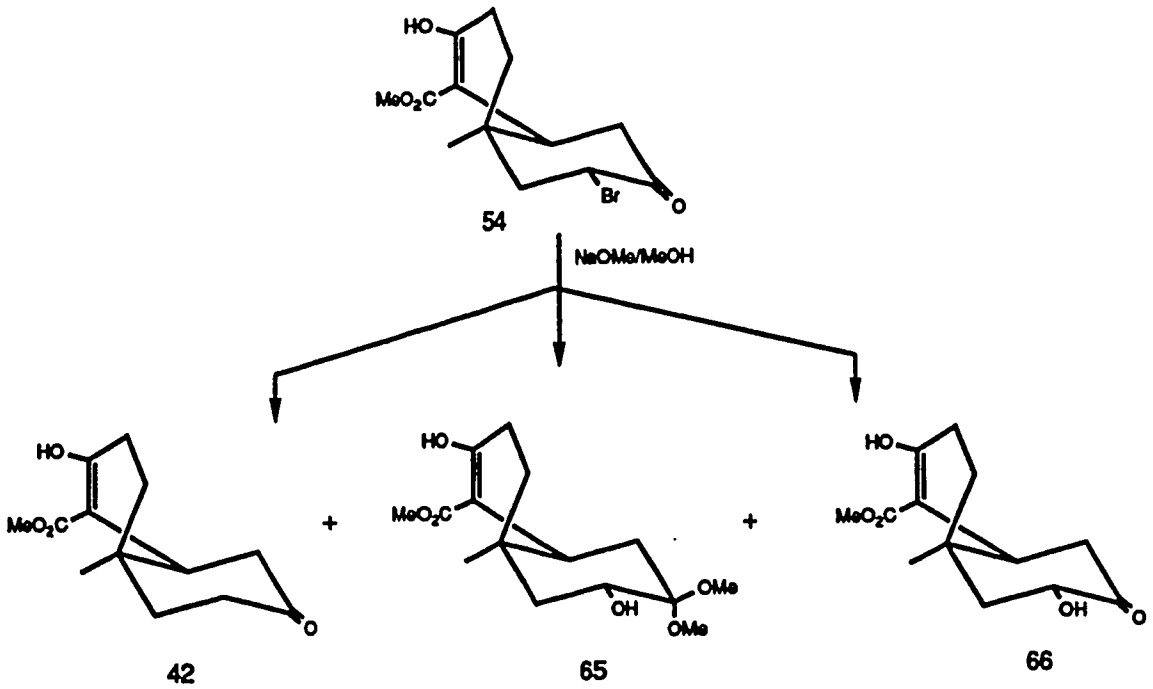
In order to prove that this reaction does in fact go through a cyclopropanone intermediate, compound 54 was treated with sodium methoxide in methanol. It was hoped that since sodium methoxide is a more nucleophilic base than DBU, 54 would undergo a Favorskii rearrangement either through path (a) or path (b) to the corresponding esters 63 and 64 (Scheme 24):

Scheme 24



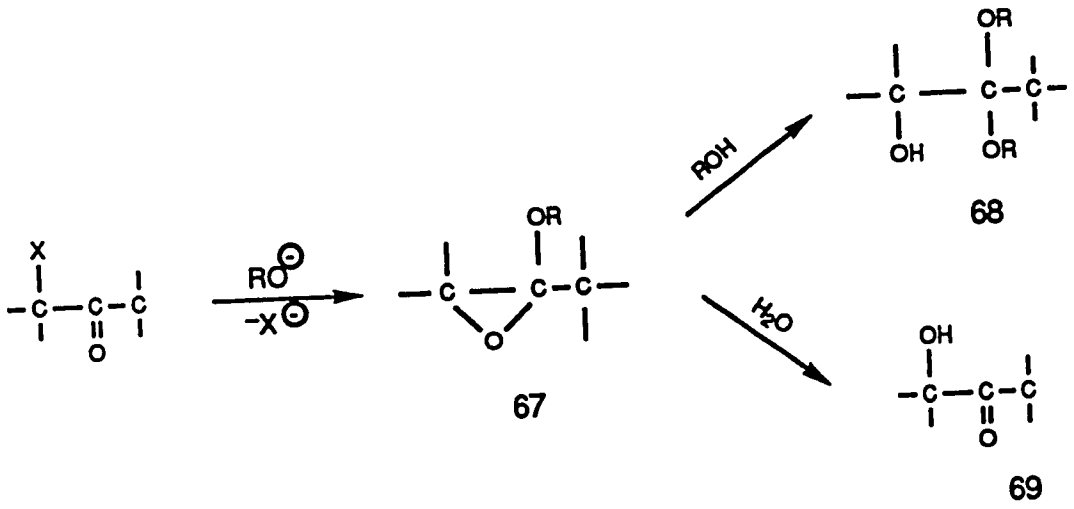
When the reaction mixture was purified, three UV active compounds were obtained. They were identified as 42, 65, and 66 in yields of 17, 47, and 8% respectively (Scheme 25). Compound 66 was easily identifiable since its ^1H NMR spectrum resembled closely to that of 54. The only observable difference in the ^1H NMR of 66 and 54 lies in the α- hydrogen attached to C_6. In 54, the α-H on C_6 appears at 4.8 ppm as a distinct doublet of a doublet whereas in 66 this proton shows up as a quintet at 4.3 ppm. Further structural proof for 66 was provided by X-ray crystallography. Compound 65, on the other hand, turned out to be a puzzle at first since we observed three methoxy signals in both its ^1H as well as its ^{13}C NMR spectra. This obstacle for 65 was eliminated by obtaining its X-ray structure.

Scheme 25



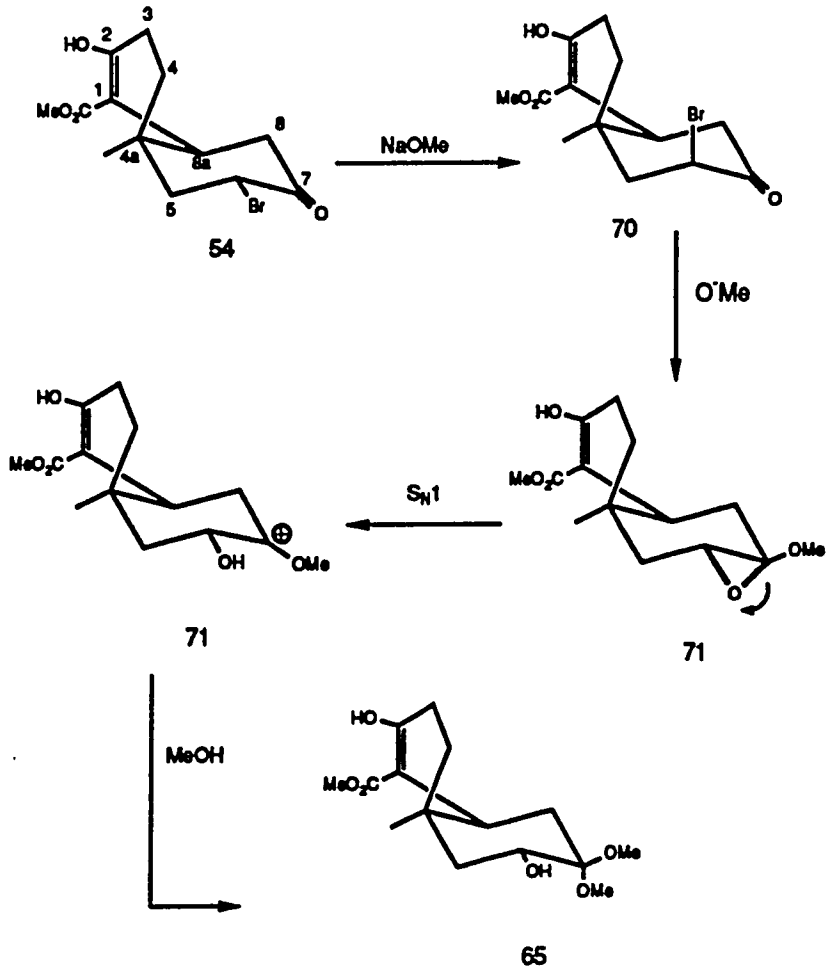
Surprisingly enough, the reaction chose a different pathway by which it provided us with 65 as the major compound. When we looked in the literature, we saw precedent that the main side reaction competing with rearrangement proceeds through nucleophilic attack of alkoxide to the carbonyl (first considered by Favorskii) forming a labile epoxyether 67. This intermediate can react further with alcohols or water to form the hydroxy ketal 68 or hydroxy ketone 69, respectively.[56-59]

Scheme 26



Based on the literature, therefore, the rearrangement of 54 to 65 first proceeds by addition of the methoxide to the carbonyl carbon C_7, followed by ejection of bromine, to produce the corresponding epoxyether (Scheme 27). This intermediate can react further with methanol to form hydroxy ketal 65 in 47% yield. The dimethoxy adduct 65, shows peaks in the mass spectrum at $M^{\cdot+}$ (m/e 300) and m/e 268 and 236. Separated by 32 mass units, they represent the loss of methanol in the molecule. It is important to point out that the stereochemistry of 65 at C_6 is retained, which indicates an initial enolization of the equatorial bromine in 54 to the axial position 70 followed by the epoxyether formation giving 71. The intermediate 71 can undergo ring opening under an S_N1 like condition, to give the methoxy stabilized carbocation, which gets trapped by methonol to afford 65.

Scheme 27



As noted by Kende,[60] "The principal side reactions encountered in the rearrangement of α-haloketones by alkoxides give rise to epoxyethers, α-hydroxy ketals and α-hydroxy ketones having the same carbon skeleton as the original haloketone. Less frequent by-products are α-alkoxyketones, unsaturated ketones, and acids resulting from secondary cleavage reactions."

Some of these epoxy ethers have been obtained through reaction of ethereal alkoxides on α-halopropiophenones and α-halocyclohexyl phenyl ketones.[61,62] These epoxyethers can then react with methanol or methanolic methoxide to form α-hydroxy ketals with no observable rearrangement to esters. Due to their lability, α-epoxyethers are not always isolated from Favorskii reaction mixtures. The major byproduct in the reaction of these epoxyethers in the presence of alcohol is the hydroxy ketal,[63,64] or sometimes the epoxydimer formed by reaction of hydroxyketal with the epoxyether.[57]

Hydroxy ketones are either made by reaction of α-haloketones with hydroxide,[65] or through hydrolysis of epoxyethers during reaction or isolation of the product.[66] In our case, since the reaction medium was free of hydroxide ion, compound 66 must have been formed either through hydrolysis of its epoxyether or during purification of the reaction mixture on the silica gel.

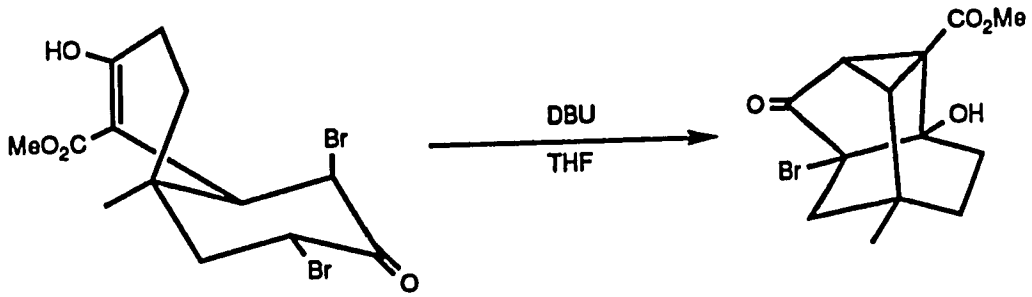
Sometimes such α-hydroxy ketones can undergo hydrolytic or oxidative cleavage to give carboxylic acids. When chloromethylcyclohexyl ketone is treated with sodium methoxide under anhydrous conditions, 21% of cyclohexanecarboxylic acid is formed a reaction which is ascribed to the hydrolysis of the hydroxymethyl ketone intermediate. Similarly, this type of reaction in steroids involves the reaction of hydroxy ketones as intermediates with oxygen in the presence of an alkoxide.[67]

The extent to which side reactions take preference over the normal Favorskii reaction depends on the rate of formation of epoxyether as opposed to the rate of rearrangement. The difference in reactivity depends largely on the structure of the haloketone and the nature of the halogen. There is also a dependence on polarity of the

reaction medium as well as the nature of alkoxide.[68] The effects that determine the course of these experimental results are discussed in detail by Kende.[60]

Having said all this, we have not yet found strong evidence that compound 54 produces 58 *via* cyclopropanone intermediate. We then decided to treat 55 with DBU under the same reaction conditions described for 54. This reaction produced 72 in 75% yield (Scheme 28) to be the only product.

Scheme 28



55 72

Direct evidence for the occurrence of the tetracyclic structure 72 was obtained through nmr spectroscopy and ir comparison with the tetracylic compound 58. The ^1H NMR spectrum of 72, contained a singlet at 3.8 ppm that integrated for one proton. It disappeared when D_2O was added. This signal was clearly assigned for the hydroxy group. The most striking feature observed in the comparison of the ir spectra of 58 and 72 was in the carbonyl absorption. Compound 58 gives absorption of ~1755 cm^{-1} whereas in 72 the same group has the absorption at 1770 cm^{-1}. All other bands are practically identical.

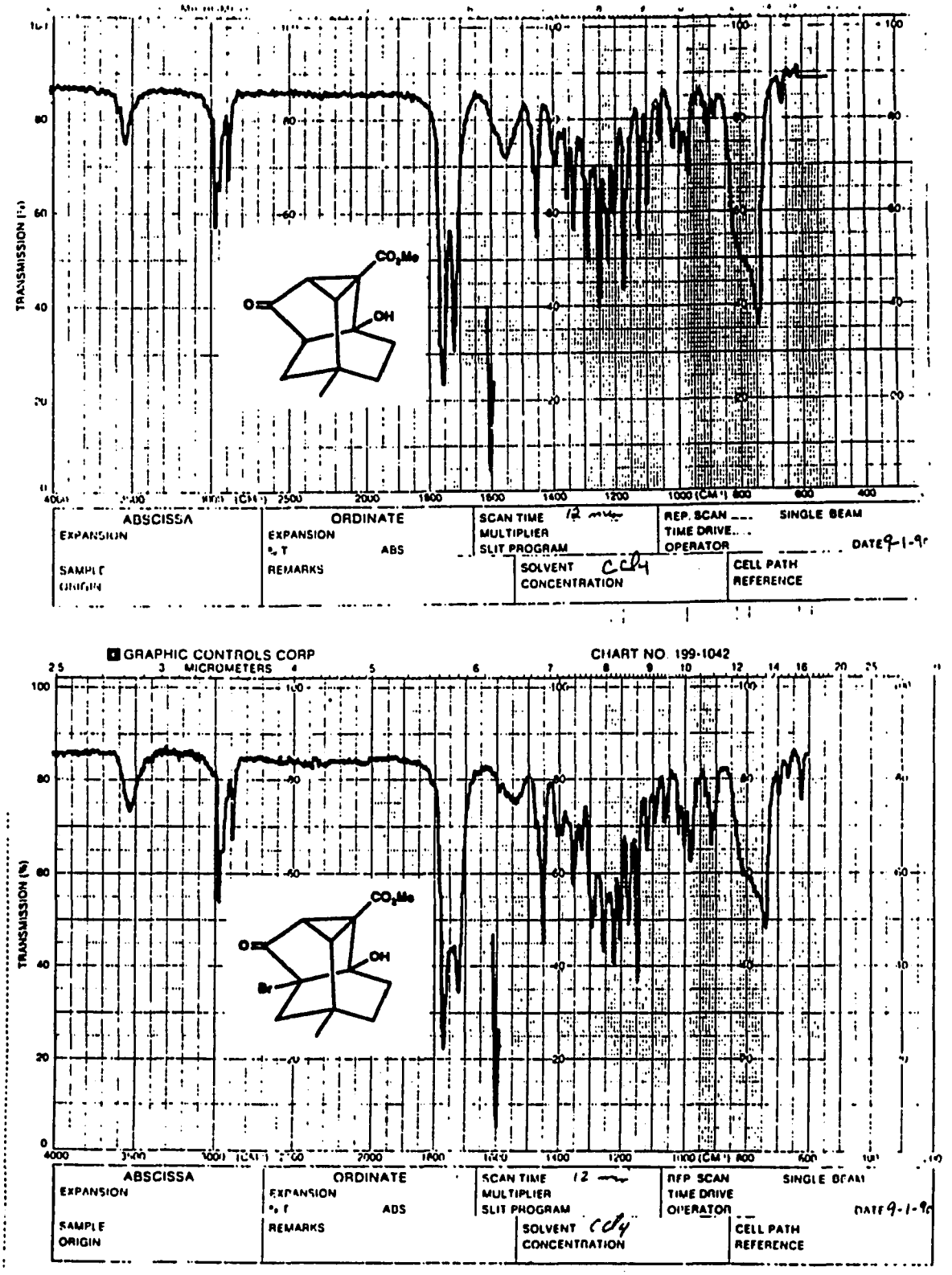


Figure **6**. Figure above shows the IR's for compounds 58 and 72.

The assignment of ^{13}C for CH, CH_2 and CH_3 groups in compound 72 was carried out by using the INEPT method in the same way that was described earlier for 57.

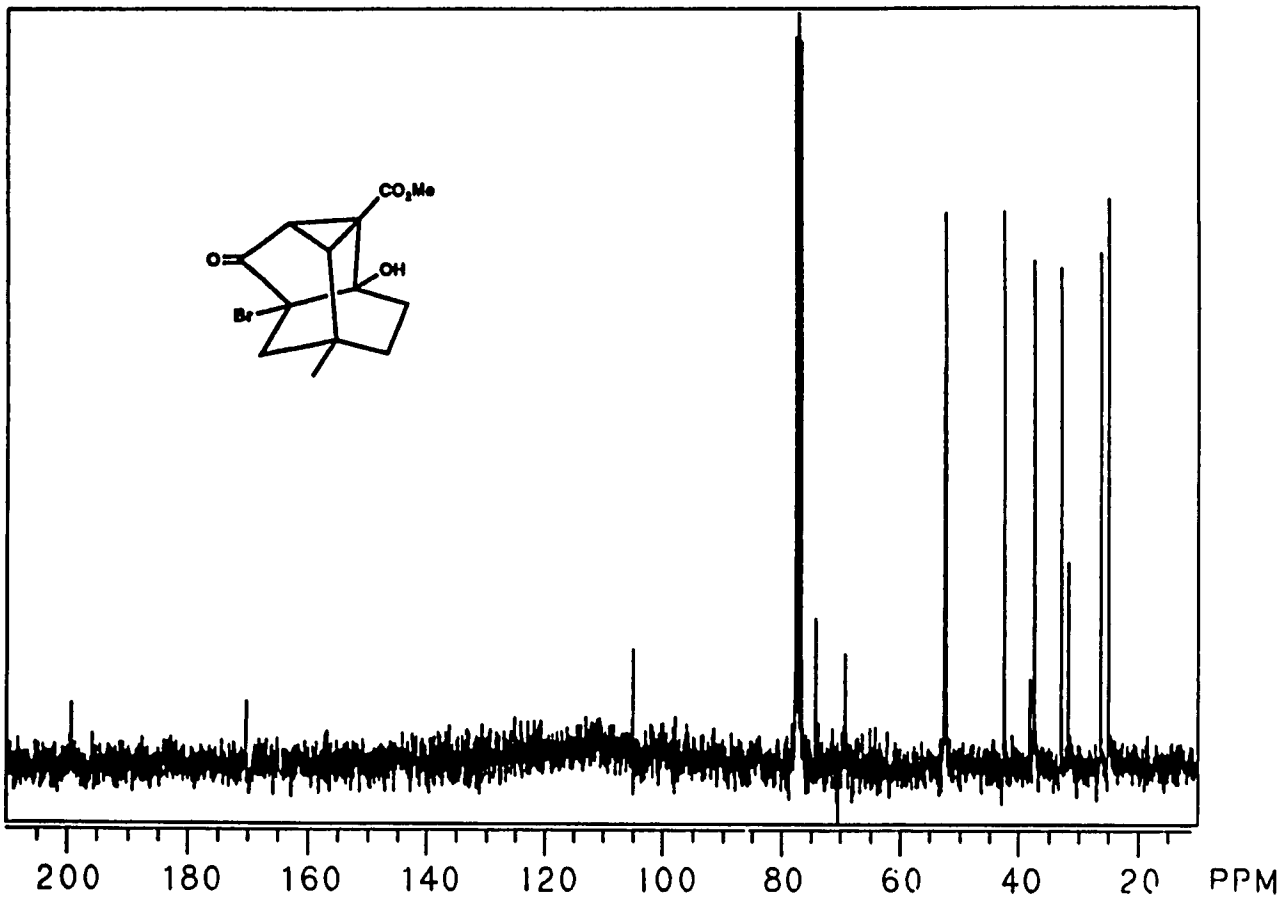


Figure 7. Spectrum above shows all the carbons in 72.

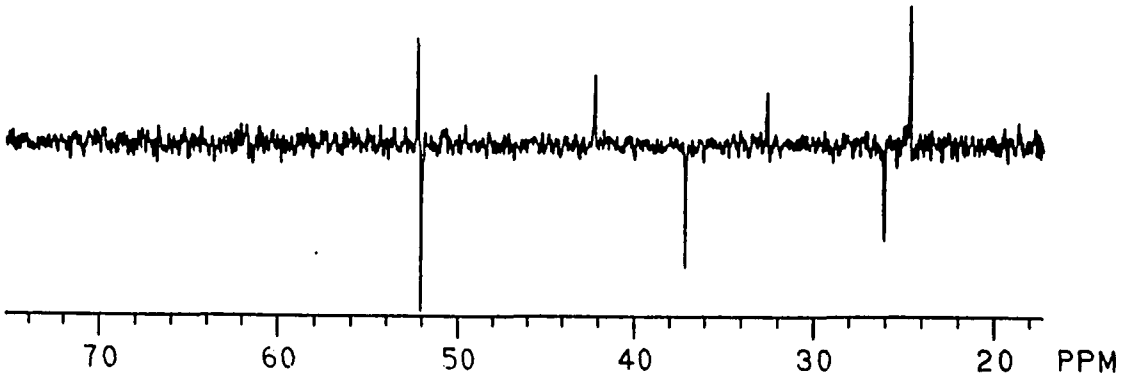


Figure **8.** In spectrum above positive signals refer to the CH_3's and the CH's. Negative (inverted) signals refer to the CH_2's for compound 72.

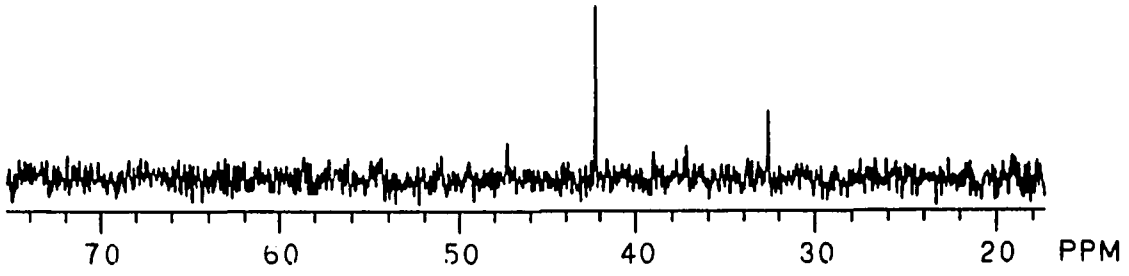
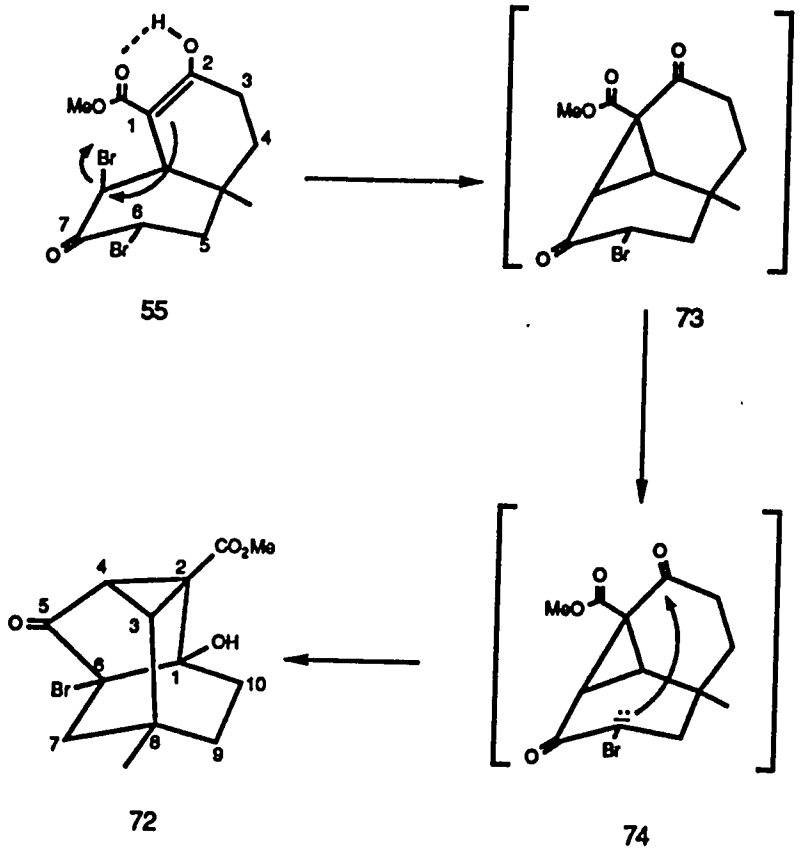


Figure **9.** The figure above shows only the CH subspectra for 72.

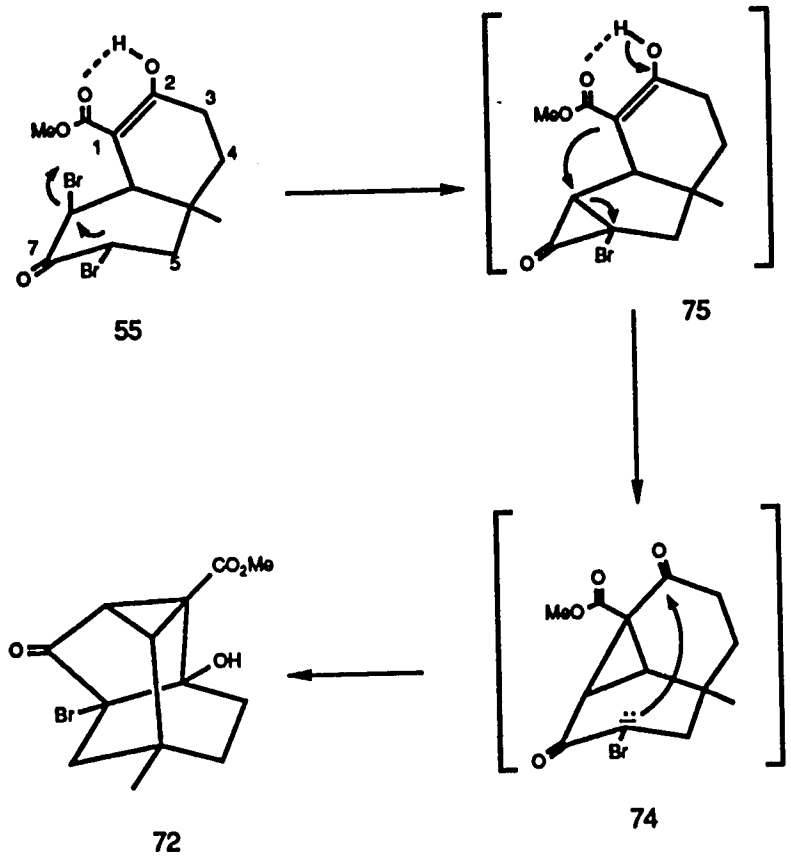
III. 7 *Synthesis of 72 via cyclopropane or cyclopropanone mechanism*

The transformation of 55 to 72 may involve: (a) Cyclopropanation by way of an enolate attack on C_8 forming a C_8-C_1 bond in 73 (Scheme 29). (b) Removal of the α-hydrogen from C_6 bearing bromine giving 74, followed by an intramolecular cyclization to 72. Alternatively, formation of 72 may be attributed to a mechanism that involves a cyclopropanone intermediate (Scheme 30). According to this view, the initial step is the removal of a proton from the α-carbon atom (C_8) to give the haloketone enolate anion. Subsequent ejection of halide ion from C_8, leads to a bromo cyclopropanone 75 which is rapidly cleaved by the enolate anion from the A ring to produce 74. The transient carbanion 74 attacks carbonyl C_2 across the ring to afford 72 before it β-eliminates.

Scheme 29



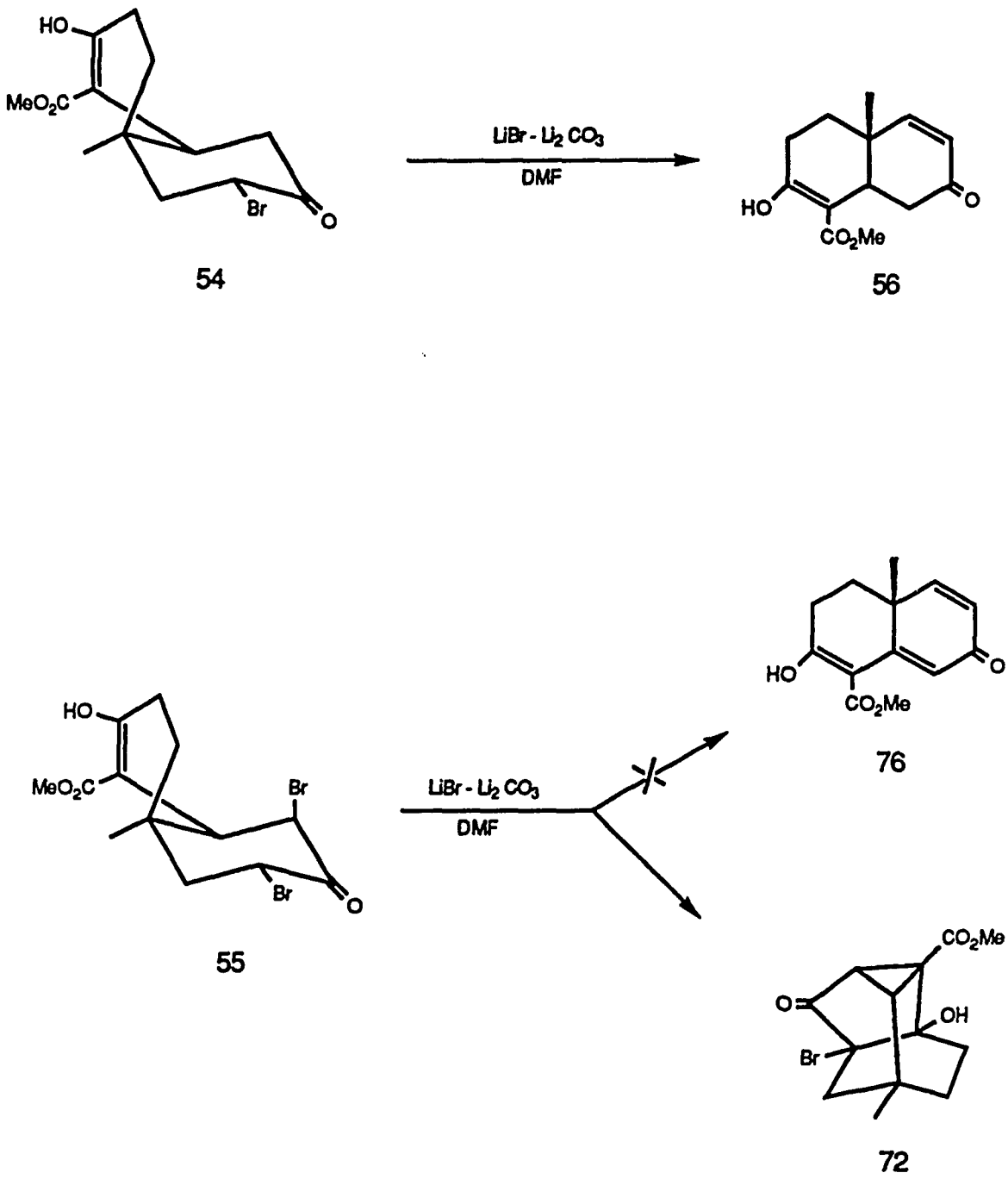
Scheme 30



III.8 *Dehydrohalogenation of 54 and 55 via lithium halide-dimethylformamide approach*

Literature affords an alternative dehydrohalogenation, the lithium halide-dimethylformamide, which was first reported by Holysz[53] and later employed in the preparation of steroidal Δ^1-3-ketones[69,70] gave excellent results. Treatment of 54 with LiBr-$LiCO_3$ in DMF at 120°C produced the monoene ester 56 in 64% yield (Scheme 31). When this method was used for the dibromide 55, an astonishing result was obtained. After examination of ^1H NMR spectrum, it turned out that 72 was the only product of dehydrohalogenation. This result suggests that even a weak base such as Li_2CO_3 brought about cyclopropanation and concomitant ring closure to the tetracyclic compound 72. Transformation of 55 into 72 suggests that the initial dehydrohalogenation leading to the cyclopropane is much faster than the β-elimination giving 76.

Scheme 31

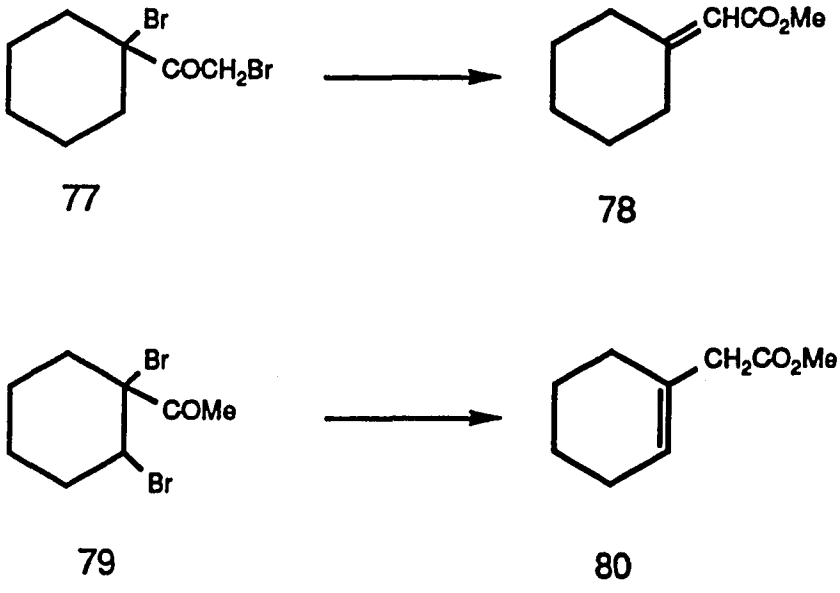

HO
MeO2C
Br
O
LiBr - Li2 CO3
DMF
HO
O
CO2Me
54
56
HO
MeO2C
Br
Br
O
LiBr - Li2 CO3
DMF
HO
O
CO2Me
76
55
CO2Me
O
OH
Br
72

III.9 *Dihaloketones*

The concept of cyclopropanone intermediates in the reactions of α-haloketones with bases is well documented in the German literature as of 1900.[71,72]

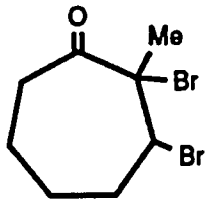
Dihaloketones have been studied by Wagner and it has been shown that rearrangement of a number of α,α' or α,β dihaloketones can be effected with sodium alkoxide. Thus it has been demonstrated[73] that α,α' dibromoketone 77 converts into an α,β unsaturated ester 78, while the products from an α,β dihaloketone 79 is a β,γ olefinic ester 80.

Scheme 32



The course of the above reaction is well accommodated by a cyclopropanone mechanism which is consistent with the stereochemistry of the rearranged olefinic products. Wagner also reported alkoxide-catalyzed rearrangement of several aliphatic α,α' and α,β dibromoketones.[74] The rearrangement of the endocyclic dibromoketone 81 to 2-methylcyclohexene-1-carboxylic acid is effected by sodium benzyloxide.[75]

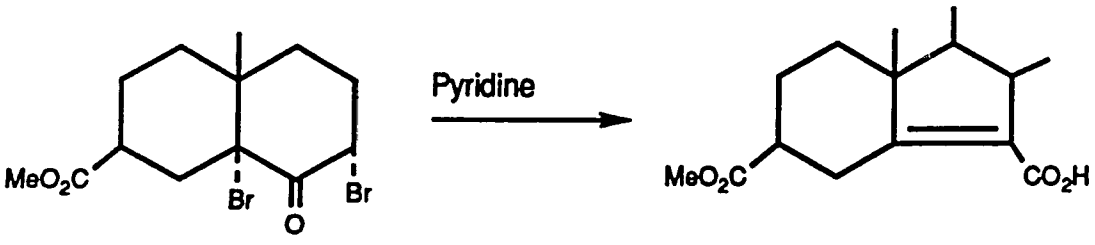
Scheme 33



81

Woodward, in 1941, showed that compound 82 is transformed into the olefinic acid 83 by refluxing in pyridine.[76]

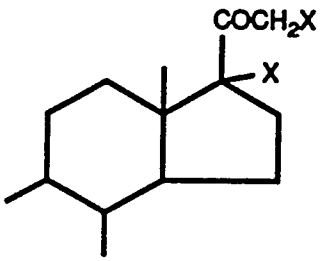
Scheme 34



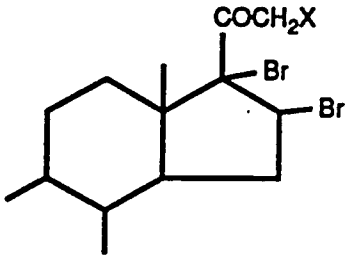
82 83

Steroidal 17,21-dihalo-20-ketones (X=Br, I) 84 and 16,17-dibromo-20-ketones 85 are converted by methanolic potassium hydroxide into the corresponding $\Delta^{17(20)}$-21-carboxylic acids.[77]

Scheme 35



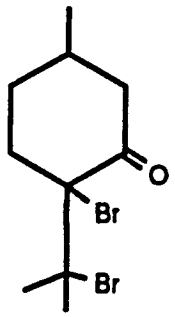
84



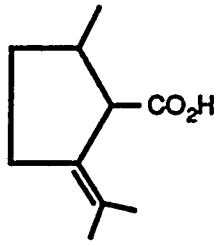
85

The rearrangement of some terpene dibromoketones by aqueous base is known as "Wallach degradation."[78] An example of this, is the transformation of pulegone dibromide 86 to "pulegenic acid"[79] known as 2-isopropylidene-5-methylcyclopentanecarboxylic acid 87.

Scheme 36



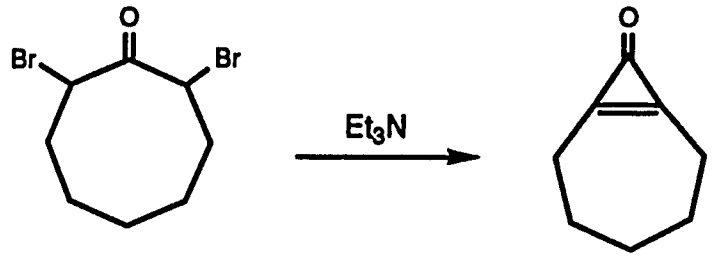
86



87

Breslow,[80] demonstrated that dehydrobromination in larger ring systems such as α,α dibromo cyclooctanone 88, results in interception of a stable cyclopropenone system 89.

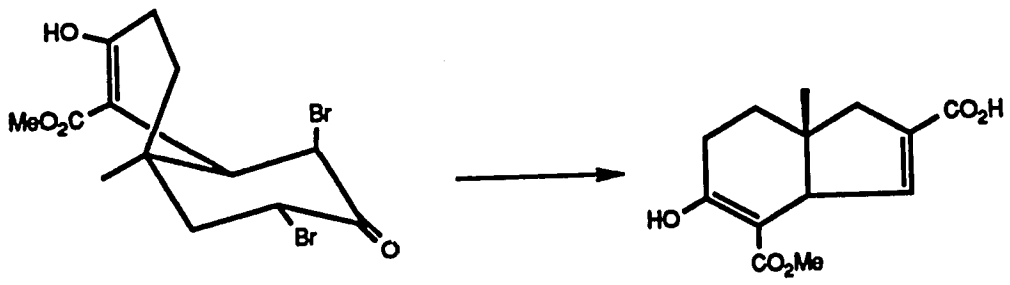
Scheme 37



88 89

Based on the examples illustrated above, we expected to find that the dibromide 55, under the appropriate experimental conditions, would undergo a Favorskii rearrangement to produce 90. However, knowing that 55, even under mild dehydrobromination condition (LiBr-$LiCO_3$ DMF method), produces 72 exclusively (Scheme 16), it will be a difficult task to find experimental conditions to convert 55 into 90. This would entail searching for a nucleophilic base that is even less nucleophilic than lithium carbonate! One way of achieving this goal may be to protect the enol hydroxy proton in 55 before subjecting it to rearrangement.

Scheme 38



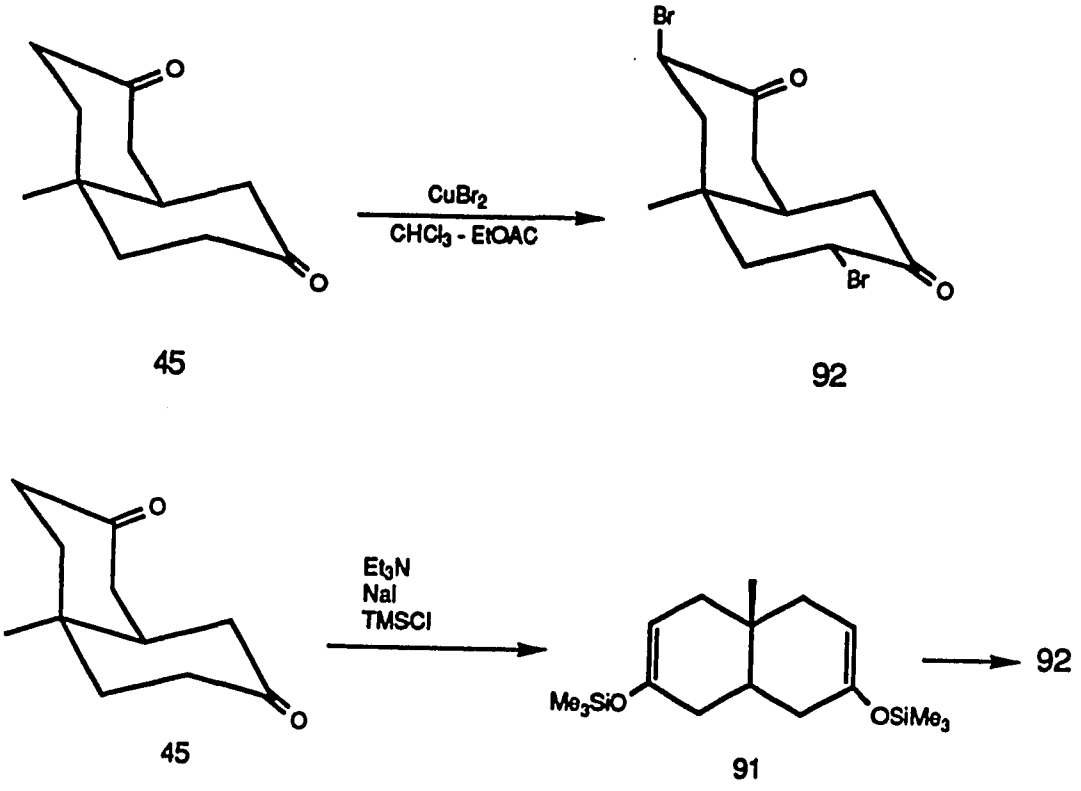
55 90

III.10 *Attempted bromination of 45 to 46 (Scheme 14)*

As the last alternative to achieve the synthesis of the intermediate 33, we pursued the following experiments. The ester 42 was decarboxylated to yield the dione 45 by the action of phosphoric acid in refluxing acetic acid giving the dione 45. Dione 45 was selectively brominated in the presence of copper (II) bromide in chloroform-ethylacetate.[49,50] Contrary to our prediction, proposed in Scheme 14, bromination of 45 (Scheme 39) resulted exclusively in the formation of 92 and none of 46 (Scheme 14). This was confirmed by the nmr of the crystalline product. The magnetically non-equivalent α-protons on C_3 and C_6 display two sets of doublets of doublets in the region near 4.9 ppm. The nmr coupling pattern for these downfield protons on the bromine-substituted carbons ($J_{3(ax)-4(ax)}$ and $J_{6(ax)-5(ax)}$ = 13 cps, $J_{3(ax)-4(eq)}$ and $J_{6(ax)-5(eq)}$ = 6.4 cps; $J_{AX} + J_{BX}$ = 20 cps) is characteristic of the axial α–protons of an ABX-type system,[52] thus confirming C_3 and C_6 as the location of the bromine atoms. When we looked in the literature for example of the bromination of decalones we found that exclusive equatorial bromination has been observed for both *trans*-decalone[81] and 3-keto steroid series.[82] As an alternative to the copper (II) bromide procedure, the diketone 45 was treated with liquid bromine in glacial acetic acid containing catalytic amounts of hydrogen bromide. This method too gave rise exclusively to the formation of 92. In order to clarify this, we decided to perform the bromination of 45 via its bis-silyl enol ether, hoping that enolization under basic condition would occur in the preferred orientation. Compound 91 was synthesized by the method of Doboudin[24,25] in quantitative yield. From the symmetry and the chemical shifts in the ^1H NMR spectrum of 91, one finds that enolization occurred in the undesired parallel position. This postulate was confirmed when, on treatment with NBS in THF, a pure sample of the di-brominated product 92 was obtained in 62% yield as the only product.We can therefore conclude that the position of enolization of 45 under both acidic and basic media, appears to be exclusively at C_3 and C_6, since the dibromide 92 was the only product of the reaction (Scheme 39). It should be noted that the latter method of brominating 45 is a cleaner way of

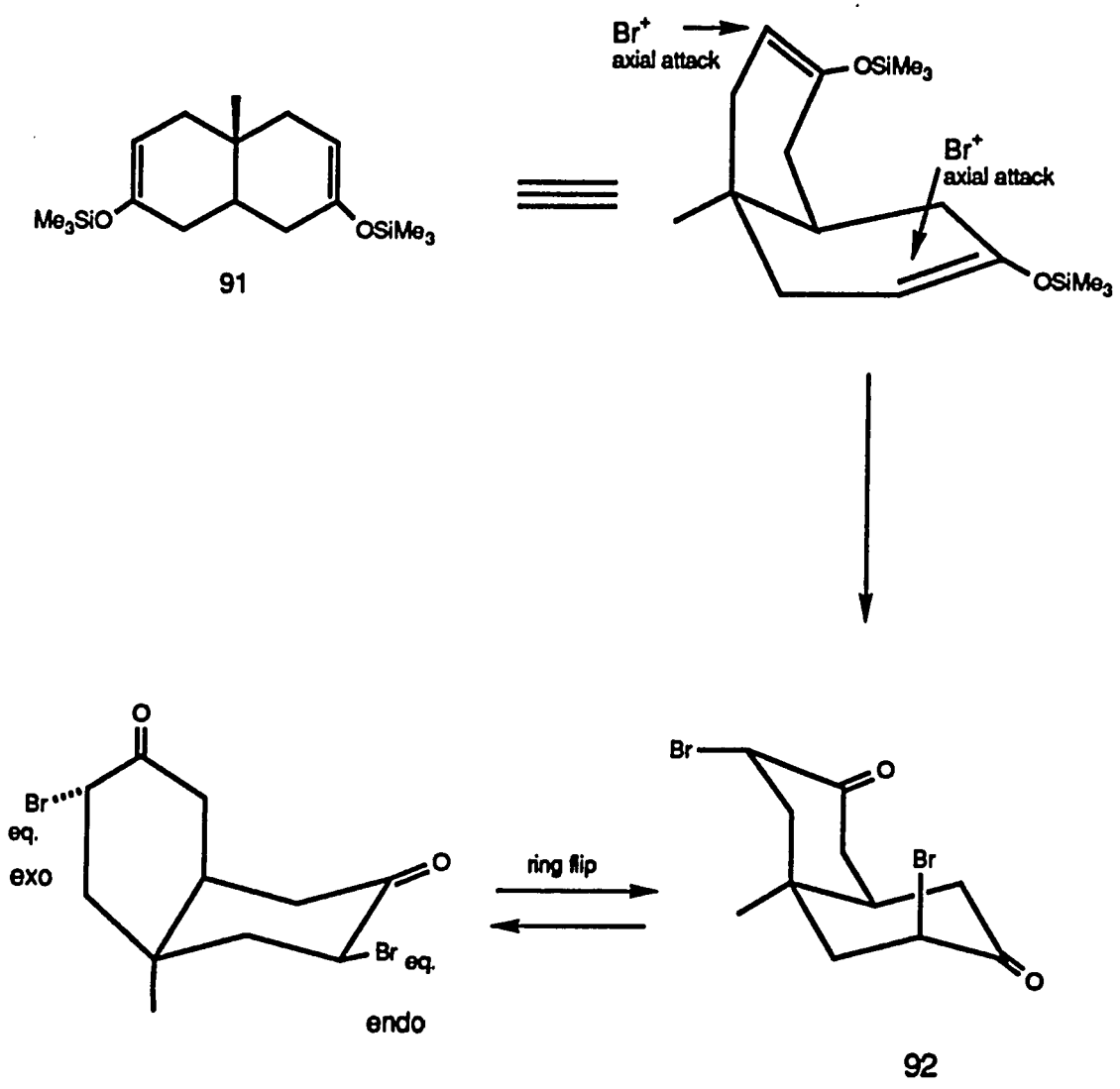
synthesizing 92 compared to a direct bromination of 45 using the copper (II) bromide procedure.

Scheme 39



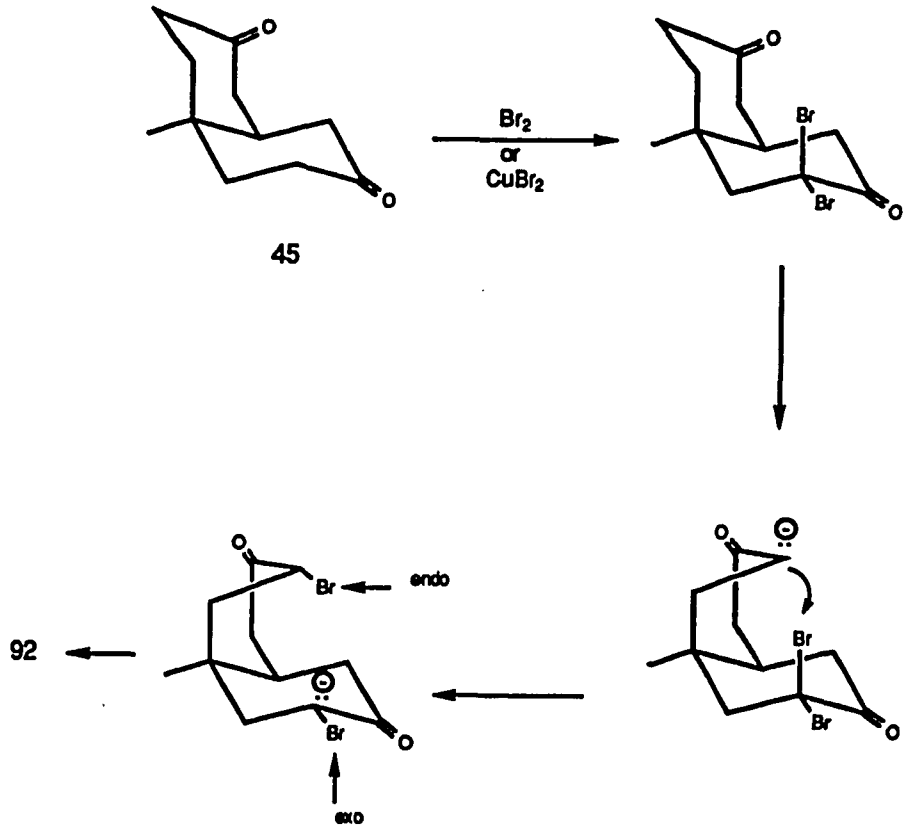
It is interesting to note the stereochemistry of the two bromine atoms in 92 as one *exo* and the other *endo*. This may be observed from a diaxial attack of the electrophilic bromine on the bis-(silyl enol) ether 91 which places the two bromines on the axial positions. The diaxial bromo-intermediate can undergo ring inversion to place one bromine *exo* and one *endo* in the more stable product.

Scheme 40



The idea of having both the *exo* and *endo* configuration of the two bromine atoms in 92, may be further supported *via* direct bromination of the dione 45 using copper (II) bromide (Scheme 41). This mechanism may involve the bromination of 45 giving an α-dibromoketone which is attacked by an enolate ion in an *endo* fashion to place one bromine *endo* and the other *exo* in the final product.

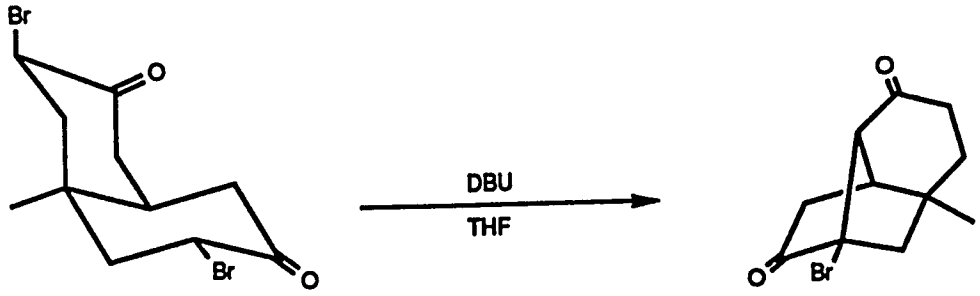
Scheme 41



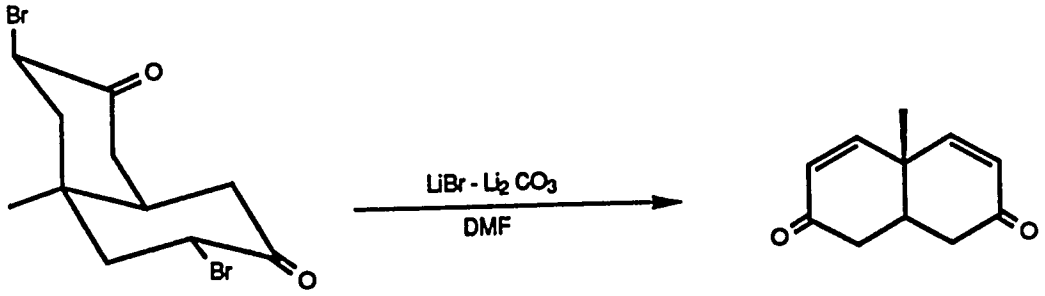
III.11 *A transannular cyclization of 92 to 93 via a cyclopropanone intermediate*

Further structural confirmation for 92 was obtained when it was treated with LiBr-$LiCO_3$ as the dehydrohalogenating agent. Under these conditions, dienedione 4 (whose synthesis was accomplished through a different route shown in Scheme 2) was isolated in 35% yield. On treatment with DBU, on the other hand, a product was obtained whose ^1H and ^{13}C NMR spectra resembled closely that of compound 57. The corresponding signal of α-protons on C_3 and C_6 was completely absent, even in the crude reaction product, demonstrating that a cyclization may have occurred between C_3 and C_6. Using mass spectrometry, we were able to find the one compound with a molecular ion at 256, the expected molecular weight of the cyclized product. The most important fragmentation involves loss of bromine to form the $C_{11}H_{13}O_2^+$ ion at m/e = 177. The intensity of the M+2 peak which is almost equal to the intensity of the molecular ion peak, demonstrates the presence of one bromine in this compound. However, the final structural assignment by X-ray crystallography confirmed 93 to be the cyclized product (Scheme 42). The formation of this product opened another entry into the ring system of sativene.

Scheme 42



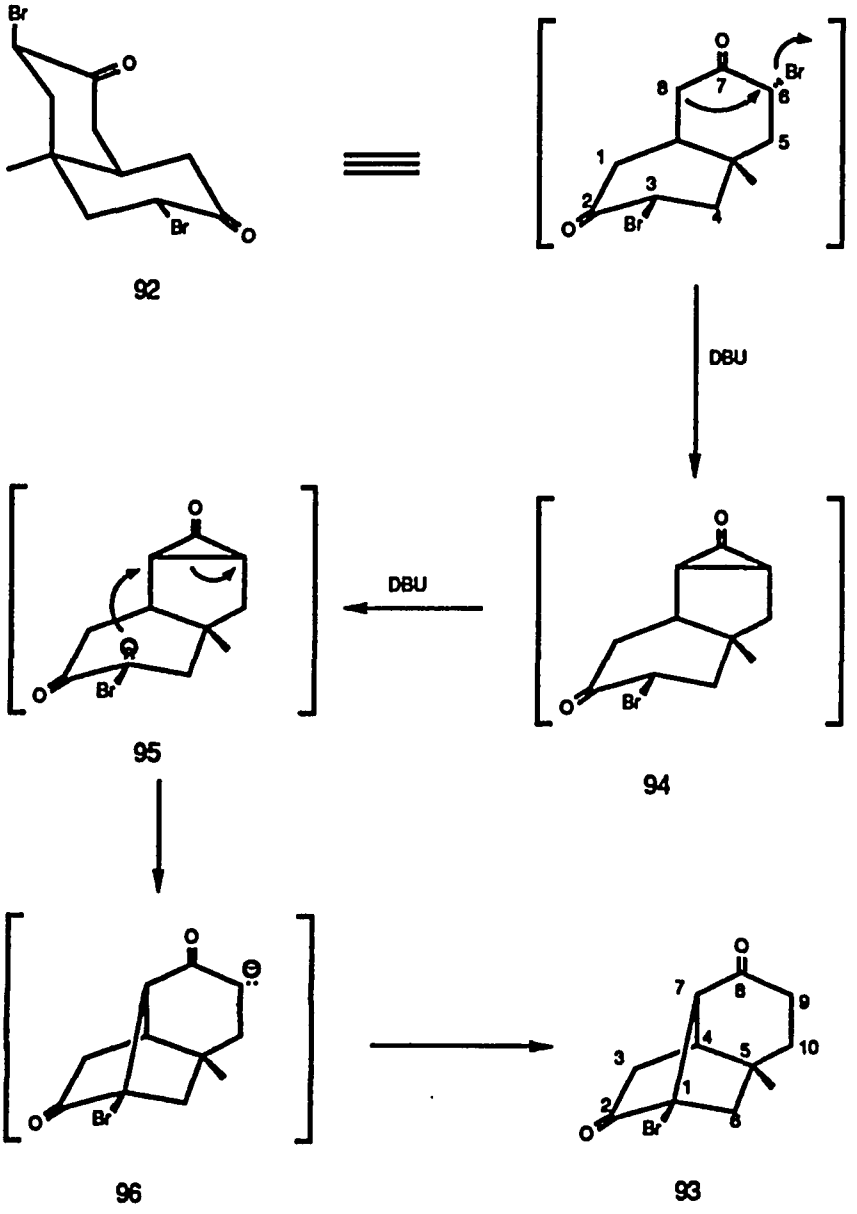
92 93



92 4

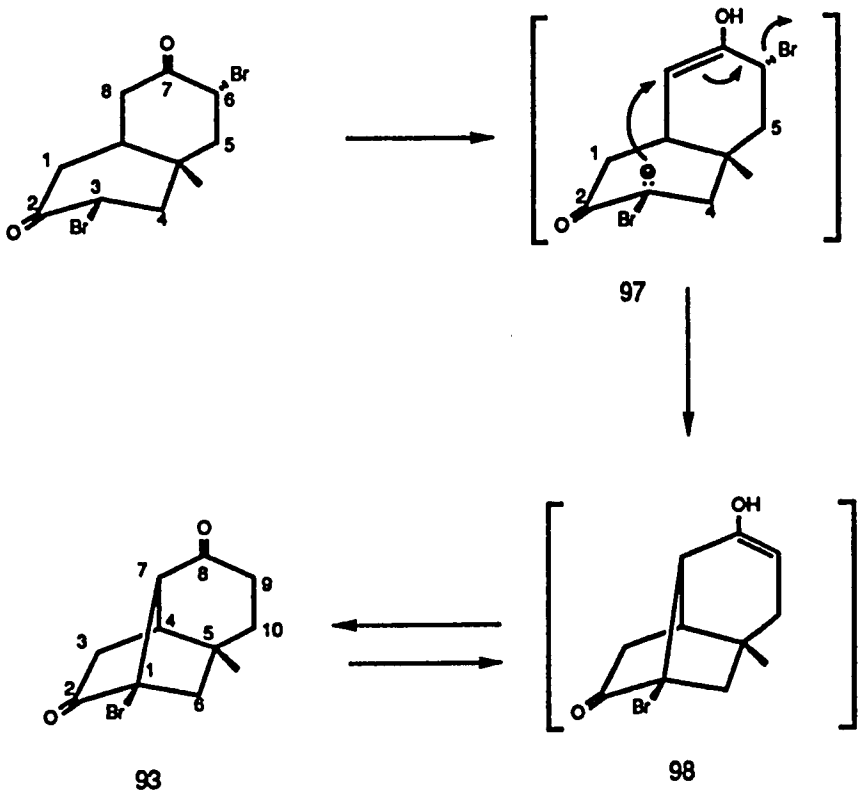
Mechanistically, the transformation of the dibromide 92 into 93 may entail one of the following three Schemes. Scheme 43 involves formation of a cyclopropanone intermediate 94 *via* an attack from C_8 enolate ion followed by ejection of the bromine (Scheme 43). This reactive intermediate is then rapidly cleaved by the haloketo-carbanion 95 to give 93, forming the new C_1-C_7 bond.

Scheme 43



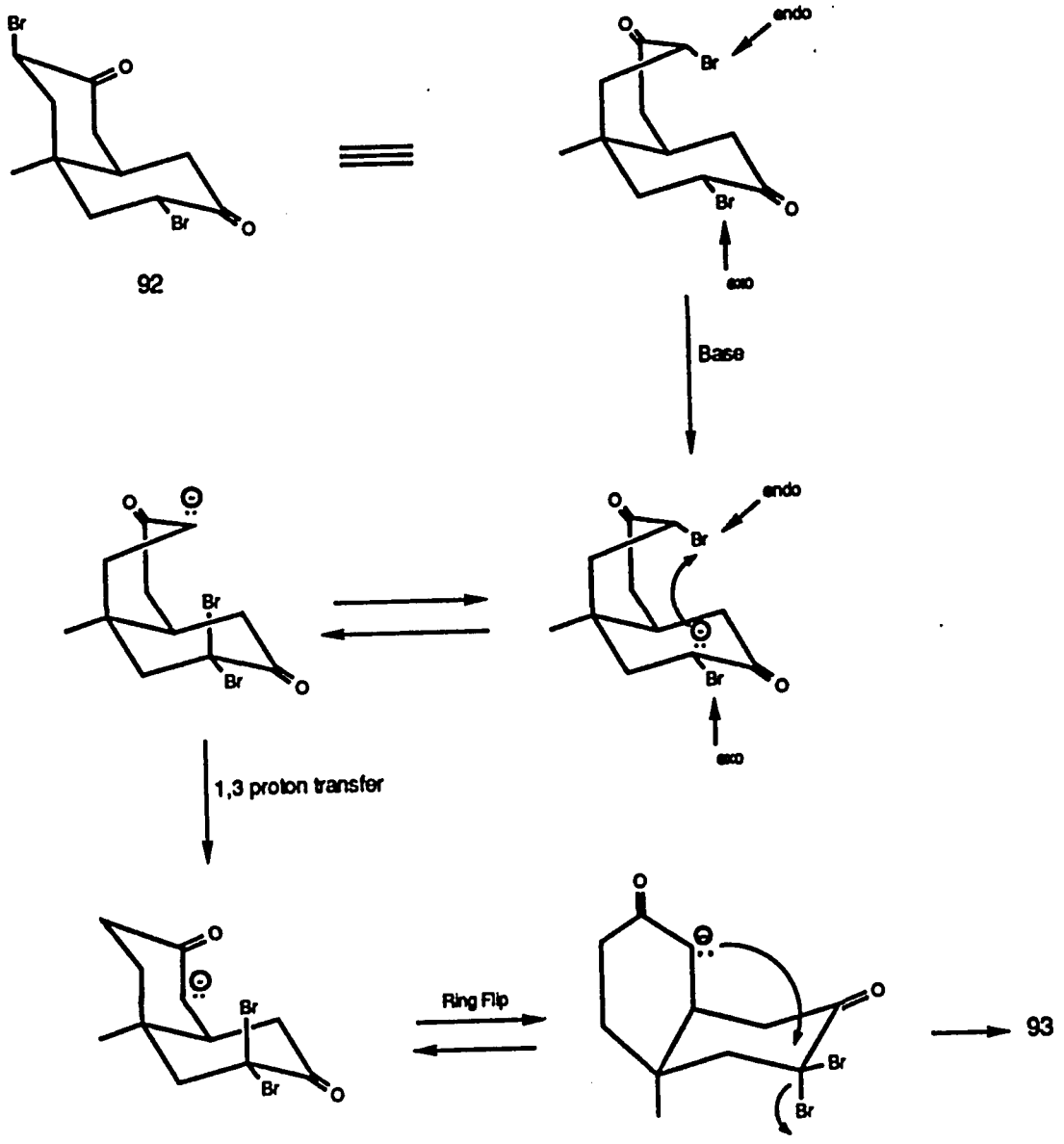
In Scheme 44, formation of 93 may be attributed to an S_N2' mechanism which initially in the presence of DBU, forms the enol between C_7 and C_8. This enol is attacked at C_8, by the haloketone enolate anion from C_3, in an S_N2' fashion to displace the bromine on C_6.

Scheme 44



Scheme 45 displays the formation of 93 through the *exo* and *endo* configuration of bromines in 92. In the presence of DBU, proton removal from the *exo*-bromoketone forms a haloketone enolate that can attack the *endo*-bromine to afford the α-dibromoketone enolate ion (in this step the bromine transfer may be reversible). The α-dibromoketone enolate can undergo proton transfer followed by a ring inversion to place one of the two bromines in an anti-periplanar orientation for departure.

Scheme 45

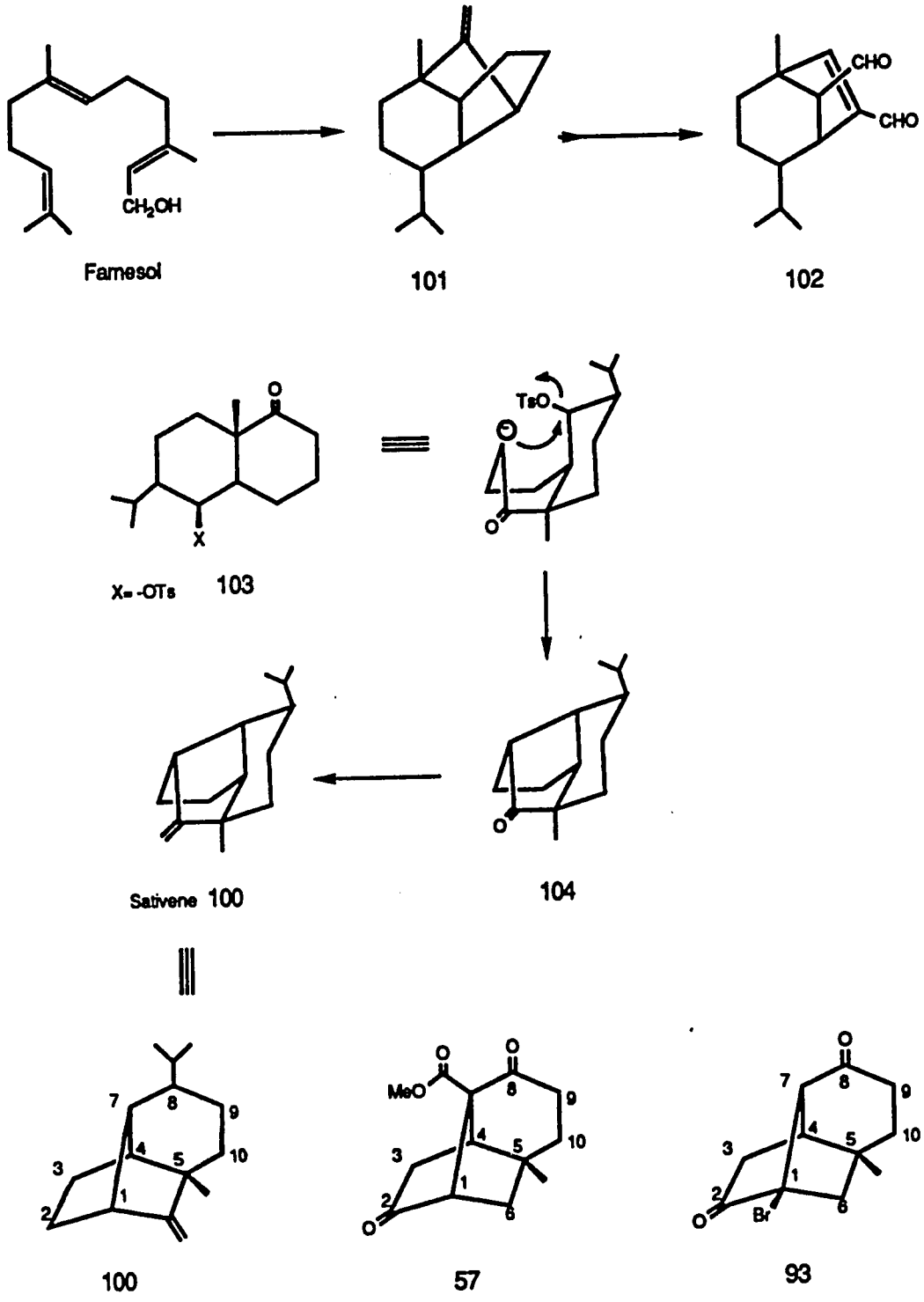


Both tricyclic compounds 57 and 93, appear to be of interest since their carbon skeleton resembled the tricyclic sesquiterpene hydrocarbon sativene 100. There are several reports in the literature of various successful intramolecular alkylations; nevertheless, the notable synthesis of sativene is the most similar case reported compared to the work discussed in this thesis.

Sativene was isolated from a sesquiterpene, helminthosporal, the toxin form *Helminthosporium sativum*. The biogenesis pathway for sativene, was first proposed by de Mayo[83] in 1962. The proposed pathway involved farnesol through a simple cyclization to afford the hydrocarbon sativene 100. It was predicted that 100 can undergo oxidative cleavage of the carbon-carbon bond (Scheme 46) to afford helminthosporal 102. Later in 1965, de Mayo[84] and Williams isolated small amounts of sativene from *Helminthosporium sativum*, and proved that it fit the predicted structure.

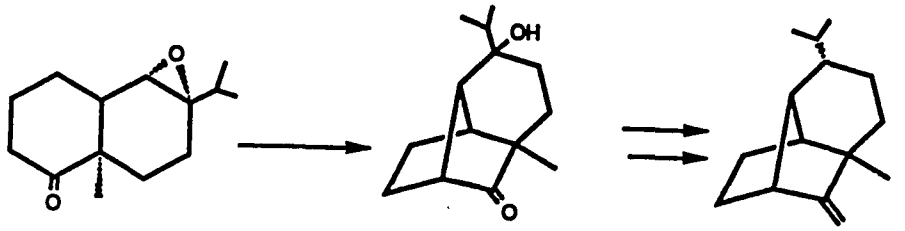
McMurry made an entry into the ring system of sativene,[85] via an alkylation on a substituted *cis*-decalone (Scheme 46). Examination of Dreiding models of *cis*-decalin show that when ring B is in a boat conformation, carbons 1 and 6 are close together. Therefore, it was decided to synthesize a molecule like 103 (where X = any leaving group) in order to make the requisite bond by an intramolecular alkylation. In sativene the ideal candidate for such a cyclization is the keto tosylate shown in Scheme 46.

Scheme 46

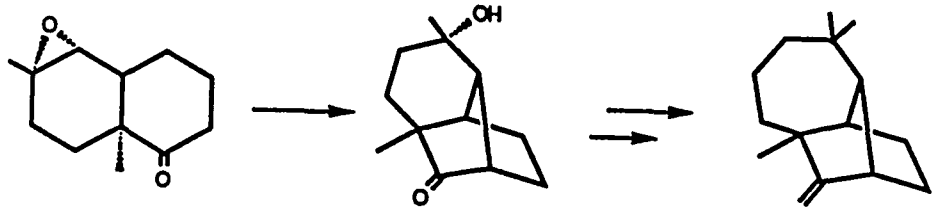

CH2OH
CHO
CHO
Farnesol
101
102
O
X
X= -OTs
103
TsO
O
O
Sativene 100
104
MeO
O
O
100
57
93
Br

McMurry also utilized this entry of intramolecular cyclization *via* an alkylation on substituted *cis*-α-decalones for copacamphene[86] 105 and longifolene[87]106 (Scheme 47).

Scheme 47



Copacamphene (105)



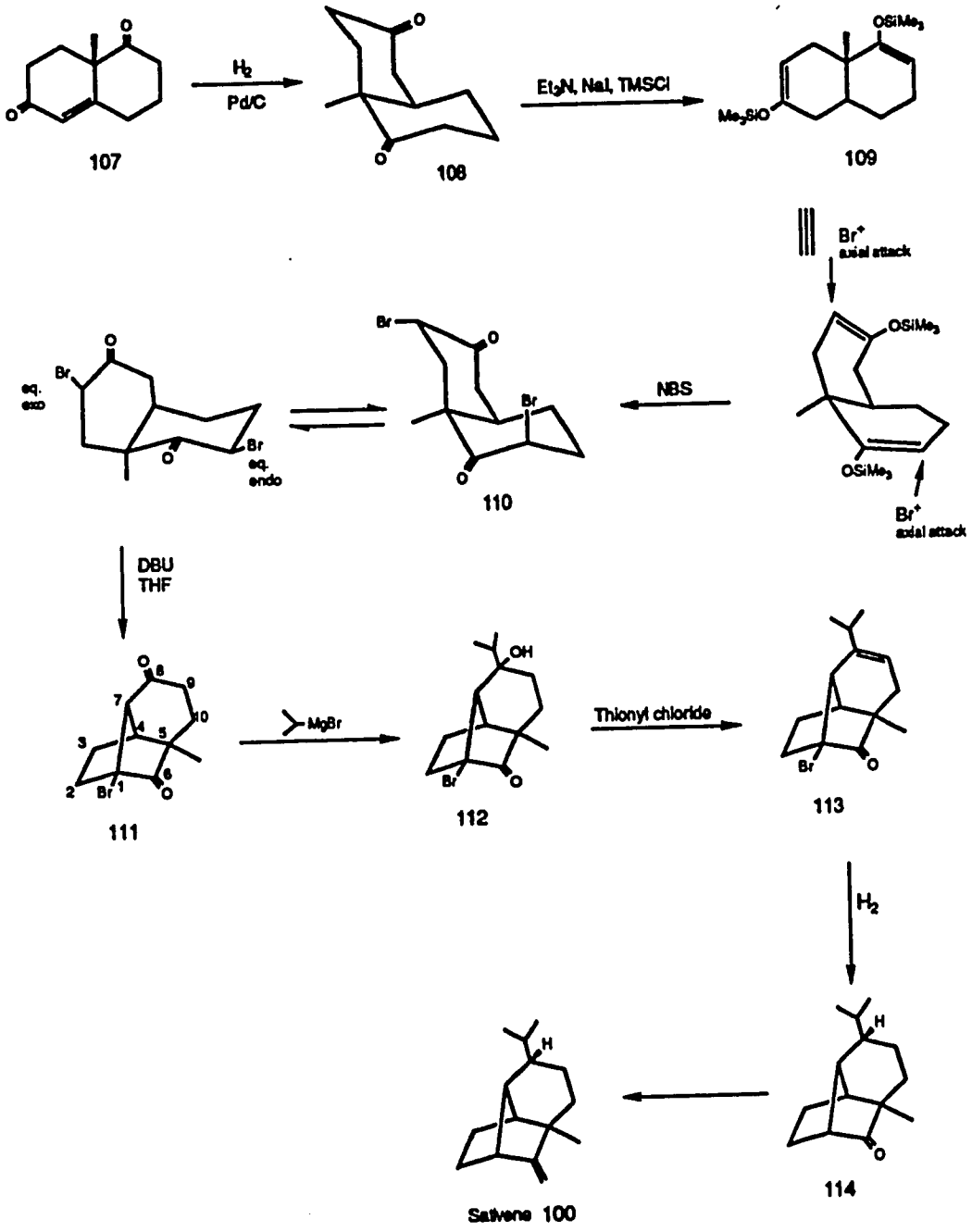
Longifolene (106)

This type of ring closure has also been used for a number of other compounds, such as Heathcock's copaene,[88] Piers seychellene,[89] and Gras's Iso and deoxynorpatchoulenol[90] syntheses. It is interesting to note that the entire skeleton of sativene,[91] copacamphor and ylangocamphor,[92] and both our compounds 57 and 93 is effected by the attachment of a cylopentane ring to an existing bicyclo [3.2.1] octane unit.

III.12 *A synthetic approach towards Sativene*

We now wish to describe a synthetic strategy for sativene 100, by application of our reaction conditions to appropriate haloketones (Scheme 48). The key reaction in the following scheme involves cyclization of 110 to 111 and was developed for the transformation of 92 to 93 in Scheme 42. McMurry has shown[85] that the *cis*-fusion of the decalin ring system can be easily established by catalytic hydrogenation of the Wieland-Miescher ketone 107 at atmospheric pressure over palladized charcoal. Assignment of the *cis*-fused stereochemistry, which has precedence in the literature[93] was determined from NMR studies of the line width at half-height of the angular methyl resonance.[94] The assignment of stereochemistry to *cis*/*trans* decalin is based on the fact that the angular methyl group in *trans*-decalin shows a slightly broader resonance line than in the *cis* compound. The transformation of 108 to 110, followed by an intramolecular cyclization to 111 could be accomplished based on the reaction conditions worked out for the conversion of 45 to 93. It should be noted that the stereochemistry of the two bromine atoms in compound 110 should be similar to compound 92, namely having one brimine in the *endo* and the other one in the *exo* configuration. The next step involves a selective Grignard reaction at carbonyl carbon C_8 instead of C_6, given the fact that C_6 is sterically more hindered due to the position of the methyl group at the ring junction. This suggestion is supported by the fact that in the total synthesis of sativene[85], compound 104 was completely inert on treatment with methylenetriphenylphosphorane in DMSO. Subjecting 111 to treatment with isopropylmagnesium bromide followed by acidic dehydration can give rise to compound 113. That the dehydration occurs in the desired direction to give 113 has been demonstrated by McMurry.[85] Catalytic hydrogenation and debromination of 113 could be achieved in one step to produce 114. Subsequent treatment of 114 with methyllithium followed by dehydration of the resulting tertiary alcohol with thionyl chloride in pyridine, should afford Sativene 100 in a fairly good yield.

Scheme 48


H2
Pd/C
Et3N, NaI, TMSCl
OSiMe3
Me3SiO
107
108
109
Br+
axial attack
NBS
eq.
exo
eq.
endo
110
DBU
THF
MgBr
OH
Thionyl chloride
111
112
113
H2
114
Sativene 100

III.13 *Summary and Conclusion*

The key intermediate 12 for the total synthesis of the title hydrocarbon 16 was prepared in seven steps from *p*-Cresol.

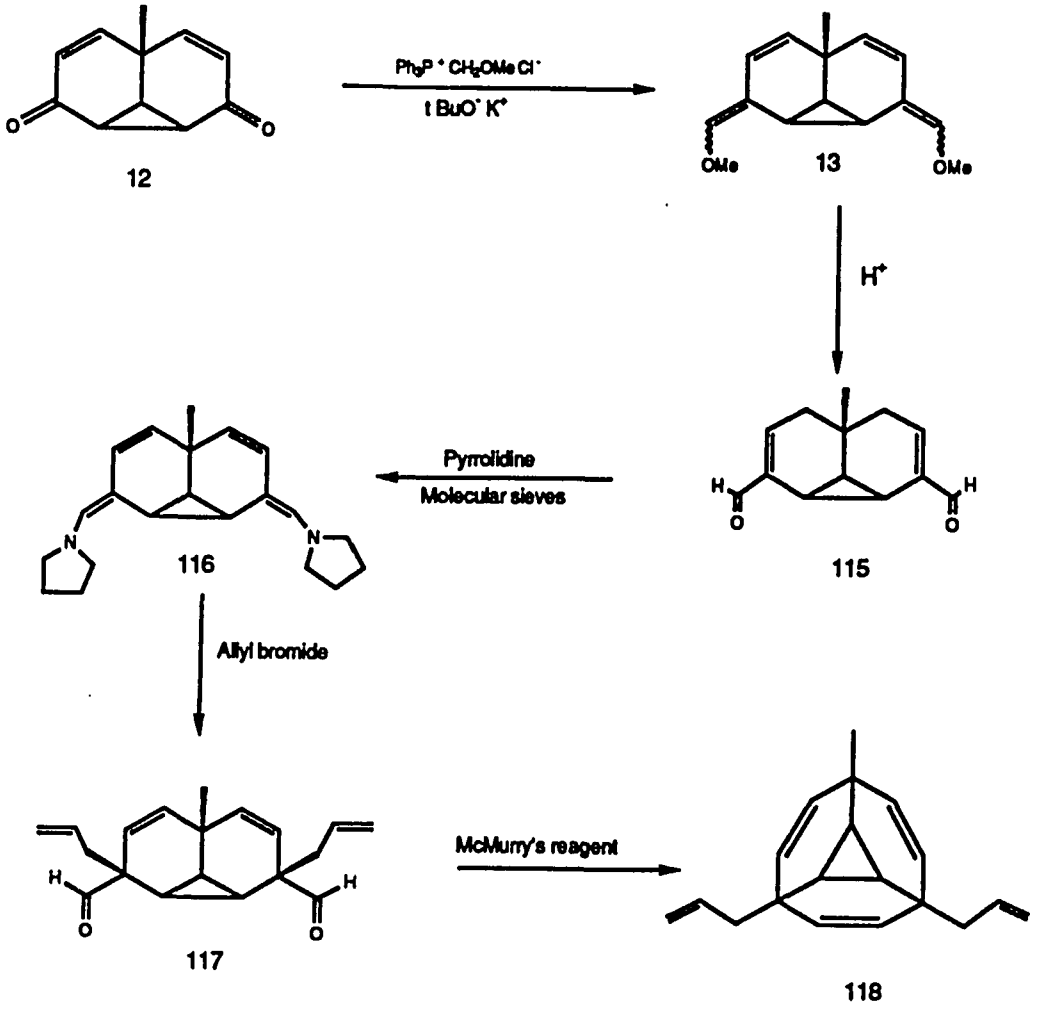
Several reactions of bromination and dehydrobromination of β-keto ester 42 and diketone 45 precursors, which possess a *cis*-fused decalin skeleton, have been examined for the attempted synthesis of intermediate 33. Upon treatment with Copper (II) bromide, β-keto ester 42 gave the selective bromination at C_3, forming 54 in 80% yield. When the diketone 45 was treated this way, the same selectivity was observed and gave 92 in 65% yield. With two equivalents of bromine, compound 42 was brominated at C_3, with the delivery of the second bromine in the desired C_1 position to give 55 in 80% yield. Dehydrobromination of 54, 55 and 92 has been accomplished with two reagents. Treatment of 54 with DBU resulted in a mixture of several products, the expected enone 56 as a minor product with the tricyclic keto-ester 57 and a tetracyclic keto alcohol 58 as the major components. Lithium halide DMF dehydrohalogenation of 54, gave the enone 56 as the only product. When the dibromo adduct 55 was used under both dehydrohalogenating conditions, the tetracyclic 72 was the sole isolable product of the reactions. Dehydrobromination of 92 with DBU afforded the single tricyclic isomer 93 similar in structure to that of compound 57. Under Lithium halide DMF method, compound 92 afforded an independent synthesis of dienedione 4 which is a precursor used in the synthesis of 12.

Mechanistically, while the keto-ester 57 was derived *via* an intramolecular cyclization, formation of the tetracyclic compounds 58 and 72 as well as the tricyclic bromo-ketone 93 may have involved a cyclopropanone or an S_N2' mechanism.

III.14 *Suggestions for future prospects*

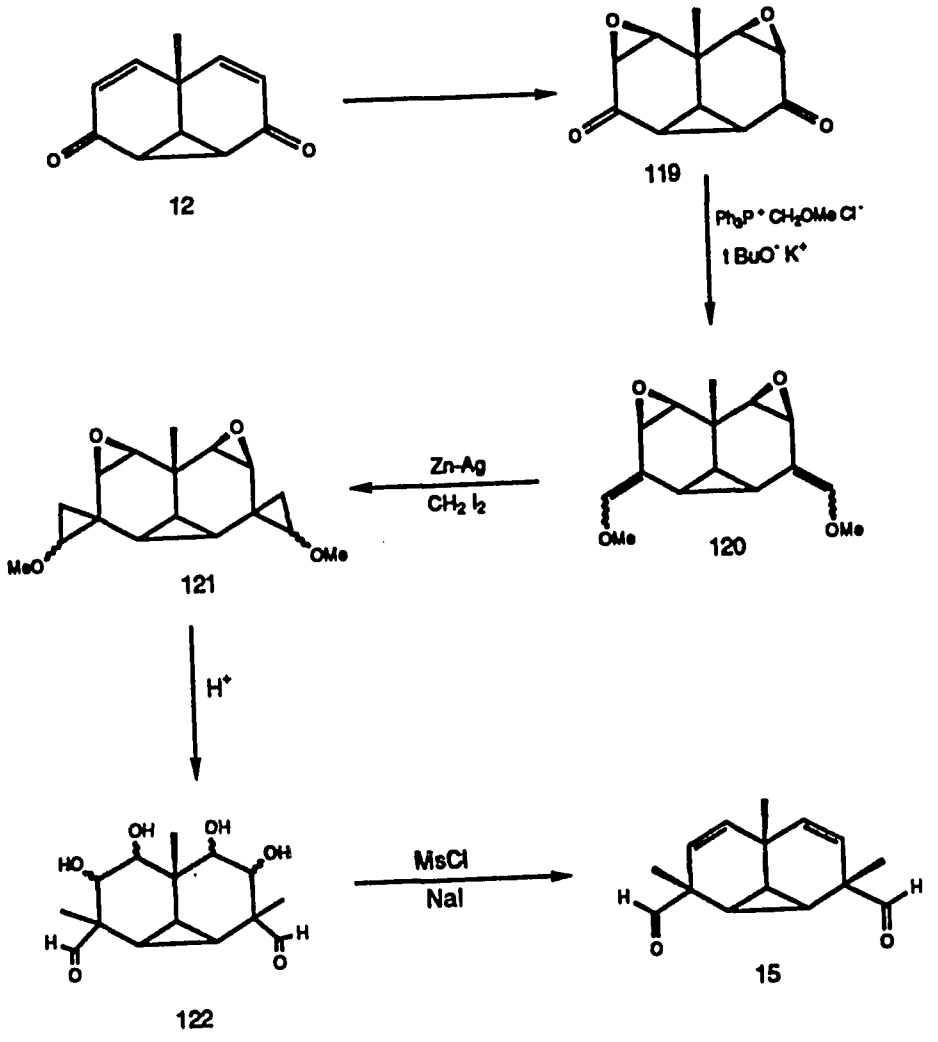
In an effort to develop an efficient synthetic method for angular methylation, we observed that the enamine 24 in the presence of allyl bromide underwent carbon-alkylation to produce 26 as a mixture of isomers. Thus, we outline the most probable path leading to the skeleton of the triene 16 in Scheme 49. An acid treatment of the enol ether 13 should give rise to the dialdehyde 115 (similar to that observed for compound 17) which on treatment with pyrrolidene can afford the enamine 116. Subsequent treatment of the desired enamine 116 with allyl bromide should result in C-alkylation giving 117 (similar to that observed for compound 24). The remaining step in the sequence is McMurry's coupling to permit formation of the triene 118.

Scheme 49



An alternative sequence to achieve the desired synthesis of 16 may initially involve protection of the double bonds in compound 12 either *via* epoxidation or bromination reaction. The protected double bonds in 12 can prevent both a premature Michael attack during the Wittig reaction and eliminate the possibility of an undesired carbene insertion during the Simmons-Smith cyclopropanation. Deprotection should allow the requisite double bonds in the final product. An example of protecting the doble bonds in 12 involving an epoxidation reaction is shown below (Scheme 50).

Scheme 50



IV.1 *General Experimental Information*

General procedure

Glassware used for air or moisture sensitive reactions was oven dried at 120°C overnight, then assembled and flushed under nitrogen or argon. In most reactions performed, a three necked round bottom flask was equipped with a pressure equalizing funnel or a condensor attached to a three way connecting tube for nitrogen inlet and drying tube. For larger reactions that required more efficient stirring, a mechanical stirrer with a ground glass shaft was used instead of a magnetic bar. The standard work-up procedure involved quenching the reaction mixture with water. If solvents like THF or acetone were used in the reaction, they would be removed by rotatory evaporator under reduced pressure and the residue was diluted with diethyl ether. Acidic reactions were neutralized with saturated aqueous sodium bicarbonate, or in some cases as solid sodium bicarbonate. Organic layers were dried over magnesium sulfate unless otherwise specified. Solvents were removed by using a Buchi rotatory evaporator at water aspirator pressure of ~13mm of Hg, and the remaining non-volatile residue was further dried by an oil pump under a reduced pressure of ~0.25 mm Hg.

Spectroscopy

Proton and carbon magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on a 300-MHz General Electric QE-300 spectrometer. Samples were prepared in chloroform-d (99.8% D, 0.03% V/V TMS, Aldrich). Chemical shifts were measured in parts per million (ppm) downfield from a tetramethylsilane internal standard (δ). Resonances are expressed in the following way: assignment; chemical shift; coupling constant (J in Hz). Multiplicities are expressed in abbreviation: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Infrared spectra were recorded on a Perkin-Elmer 1310 IR spectrometer and are reported in wave numbers ($\nu = Cm^{-1}$). Liquid samples were observed neat by placing them between sodium chloride plates (23 x 4 mm). Solid samples with low melting points were run as a melt on sodium chloride plates, all the others were dissolved in carbon tetrachloride and run in solution cells. All spectra were recorded during 12 minutes scans with a calibration band at 1601 cm^{-1} was recorded using a polystyrene film.

Mass spectra were determined by either electron impact (EI) ionization or chemical ionization (CI) using methane as the carrier gas on a HEWLETT PACKARD 5989A mass spectrometer. The data presented shows the parent ion where present, followed by some significant fragments or adducts.

X-ray

The intensity data were measured on an Enraf-Nonius CAD4 diffractometer (graphite-monochromated Cu Kα radiation, ω-2θ scans). The size of the crystal used for data collection was approximately 0.07 x 0.09 x 0.5 mm; the data were corrected for absorption. Of the 2736 independent reflections for $\theta < 75^{o}$, 2224 were considered observed [$I > 3.0\sigma(I)$].

The structure was solved by a multiple-solution procedure[1] and was refined by full-matrix least squares. In the final refinement, the nonhydrogen atoms were refined anisotropically. The hydrogen atoms were included in the structure-factor calculations but their parameters were not refined.

We are grateful to Mr. Louis Todaro at Hoffmann-La Roche for providing us with the X-ray analysis of compounds listed.

Melting points

Melting points were recorded on a Buchi Schmelzpunktbestimmungs instrument in soft glass capillaries and are uncorrected.

Chromatography

Thin layer chromatography (TLC) was performed using pre-coated plastic sheets of silica gel, with a thickness of 0.25 mm, supplied by Macherey-Nagel. UV active compounds were observed by 254 nm UV lamp. Non UV active compounds were either developed in iodine chambers or with a spray of phosphomolybdic acid in ethanol (230 gr PMA / 1 gal 95% ethanol).

Radial chromatography was carried out on a Chromatotron, model 7924T, made by Harrison Research. The plates were coated with silica gel 60 PF-254 containing calcium sulfate as binder, supplied by VWR Scientific, according to the procedure by Harrison.[2] The plate was first eluted with a non polar solvent (hexane), followed by introduction of the sample previously filtered through a short column. Polarity was later increased by the proper elutant, and the separation of compounds was followed by a UV irradiation. Plates were occasionally washed by a 30% methanol in methylene chloride.

Flash chromatography was performed according to the published procedure[3] using silica gel grade 60, available from Aldrich Chem. Co.

Reaction Solvents and Reagents

Solvents were ACS reagent grade and generally used as supplied; when required they were purified as follows:

Tetrahydrofuran:	distilled under nitrogen over potassium metal
Benzene:	distilled under nitrogen from calcium hydride
Dimethyl sulfoxide:	distilled under nitrogen from calcium hydride
Diisopropylamine:	distilled under nitrogen over sodium metal

Triethylamine:	distilled under nitrogen over sodium metal
Methanol:	distilled over magnesium metal
Acetonitrile:	distilled over phosphorus pentoxide
Methylene Chloride:	distilled from calcium hydride
Ethyl Acetate:	distilled from calcium hydride
Hexane:	distilled over calcium hydride
Trimethylsilyl Chloride:	distilled under nitrogen over calcium hydride

Potassium t-butoxide was sublimed at 180-200°C / 0.025 mm Hg.

n-Butyl lithium was titrated using either 1,3-diphenylacetone p-tosylhydrazone[4] or 2,5-dimethoxybenzyl alcohol[5] as indicator.

IV.2 *Experimentals and Procedures:*

cis-8,8a-dihydro-4a-methyl-2,7-(1H,4aH)-naphthalene-dione 4.

In a 1L three necked flask, potassium t-butoxide (14.55 g, 0.13 mol) was dissolved in dry DMSO (700 mL) under N_2, and was heated to 60°C before solid diketone 3 (18 g, 0.072 mol) was added all at once. After being stirred for 2 h at 60°C, the mixture was allowed to warm to RT, and then poured into cold water (2 L). The aqueous layer was extracted with chloroform (3 x 500 mL). The combined organic layers were washed with water (3 x 500 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The viscous oil (10.18 g) was 90% pure 4 based on its ^1H NMR spectrum. Purification by chromatography on alumina (activity III, elution first with toluene and then with methylene chloride) afforded dienedione 4 (5.8 g, 46%) as white solid.

4: ^1H NMR: δ 6.61 (d, 2H, J=10.15 Hz), 6.06 (d, 2H, J=10.13 Hz), 2.62 (m, 3H), 2.37 (m, 2H), 1.47 (s, 3H).

Racemic-3-[6-(dichloromethyl)-3-hydroxy-6-methyl-2-oxatricyclo-[3.3.1^{1,3,7}]-dec-1-yl]-8,8a-dihydro-4a-methyl-2,7-(1H,4aH)-naphthalene-dione 5.

Diketone 3 (6 g, 0.024 mol) was dissolved in of dry DMSO (100 mL) under N_2, and was heated to 60°C before solid potassium t-butoxide (3.2 g, 0.028 mole) was added all at once. After being stirred for 2 h at 60°C, the mixture was allowed to warm to RT, and then poured into of cold water (1 L). The aqueous layer was extracted with chloroform (3 x 300 mL). Some solid NaCl was occasionally needed for an efficient separation. The combined organic layers were washed with water (3 x 200 mL), brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on

alumina (activity III, elution first with toluene and then with methylene chloride) afforded dienedione 4 (1.6 g, 37%), and the dimer 5 (1.02 g, 20%) as white crystals.

5: ^{1}H NMR : δ 6.86 (s, 1H), 6.64 (d, 1H, J=10.1 Hz), 6.56 (s, 1H), 6.05 (d, 1H, J=10.03 Hz), 2.97 (s, OH), 2.63 (d, 1H, J=4.13 Hz), 2.43 (m, 8H), 2.12 (d, 2H, J=12.81 Hz), 1.64 (m, 2H), 1.46 (s, 3H), 1.31 (m, 2H), 1.32 (s, 3H)

Anal. Calcd for $C_{22}H_{26}Cl_2O_4$: C, 62.12; H, 6.16; Cl, 16.67; Found: C, 61.94; H, 6.13; Cl, 16.67.

cis-8,8a-dihydro-4a-methyl-7-(trimethylsiloxy)-(1H,4aH)-naphthalene-2-one 6.

To a magnetically stirred solution of 4 (176 mg, 1 mmol) in dry THF at -78°C, LDA (1.2 eq) was added dropwise *via* double sided needle under nitrogen pressure. After 20 minutes, chlorotrimethylsilane (0.14 mL, 1.2 mmol) was added, and the solution was allowed to warm to room temperature during 40 minutes. When the reaction mixture reached 0°C, it was quenched with aqueous cold saturated sodium bicarbonate, and diluted with ether (30 mL). The ether layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (Chromatotron, 10% ethyl acetate in hexane) afforded three compounds: 4: (23 mg, 13%), 6: (122 mg, 49%), 7: (112 mg, 35%).

6: ^{1}H NMR: δ 6.5 (d, 1H, J=10.09 Hz), 5.96 (d, 1H, J=10.09 Hz), 5.79 (dd, 1H, J= 9.78, 1.99 Hz), 5.56 (d, 1H, J=9.78 Hz), 4.81 (dd, 1H, J= 4.9, 1.72 Hz), 2.70 (m, 1H), 2.45 (d, 2H, J=7.26 Hz) , 1.25 (s, 3H), 0.21 (s, 9H).

cis-8,8a-dihydro-4a-methyl-2,7-(bis-trimethylsiloxy)-(1H,4aH)-naphthalene 7.

To a magnetically stirred solution of LDA (3 mmol) at -78°C under nitrogen, a solution of 4 (176 mg, 1mmol) in dry THF (15 mL) was added through a dropping funnel during 5 minutes. The mixture was left to stir for 20 minutes. Chlorotrimethylsilane (0.38 mL, 3 mmol) was added and the solution was allowed to warm to room temperature during 45 minutes. Some of the solvent was removed under reduced pressure and the mixture was quenched with a saturated aqueous sodium bicarbonate, and diluted with ether (50 mL). The ether-THF layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (Chromatotron, 10% ethyl acetate in hexane) gave compound 7 (294 mg, 92%) as colorless oil.

7: ^{1}H NMR: δ 5.64 (dd, 2H, J= 9.86, 1.97 Hz), 5.43 (d, 2H, J=9.86 Hz), 4.68 (dd, 2H, J= 4.5, 1.84 Hz), 3.2 (t, 1H, J=4.6 Hz), 1.22 (s, 3H), 0.22 (s, 18H).

cis-1-bromo-8,8a-dihydro-4a-methyl-2,7-(4aH,8H)-naphthalene-dione 8.

To a solution of 6 (248 mg, 1 mmol) in dry THF, bromine was added (0.06 mL, 1.2 mmol) at -78° C under nitrogen. The solution was stirred for 5 minutes more, and then allowed to warm to 0°C. The mixture was poured into a cold aqueous saturated sodium bicarbonate (40 mL), and diluted with ether. The organic layer was washed with sodium bisulfite (to decolorize excess bromine), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (Chromatotron, 20% ethyl acetate in hexane), gave compound 8 (168 mg, 66%) as white crystals.

8: ^{1}H NMR: δ 6.67 (d, 1H, J=10.05 Hz), 6.60 (dd, 1H, J= 10.05, 1.77 Hz), 6.16 (dd, 2H, J=10.12, 1.8 Hz), 5.23 (d, 1H, J=4.04 Hz), 2.96 (m, 2H), 2.22 (q, 1H), 1.6 (s, 3H).

cis-1(exo)-bromo-8-(endo)-bromo-8,8a-dihydro-4a-methyl-2,7-(1H,4aH)-naphthalene-dione 9.

A solution of 7 (320 mg, 1 mmol) in dry THF (20 mL) was brominated by rapid addition of bromine (0.15 mL, 3 mmol) dissolved in THF (10 mL) *via* syringe, under nitrogen at -78°C. After 5 minutes the mixture was quenched with water, and excess bromine was decolorized with a sufficient amount of sodium bisulfite. The layers were separated and the aqueous layer was extracted with ether (2 x 20 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by chromatography on silica gel (20% ethyl acetate in hexane) gave dibromo-adducts 9 (33.4 mg, 10%).

9: ^{1}H NMR: δ 6.73 (dd, 1H, J= 10.49, 1.31 Hz), 6.6 (d, 1H, J=10.3 Hz), 6.22 (d, 1H, J=10.5 Hz), 6.13 (dd, 1H, J= 10.3, 0.76 Hz), 4.5 (s, 1H), 4.43 (d, 1H, J=4.05 Hz), 3.4 (d, 1H, J=4.5 Hz), 1.8 (s, 3H).

cis-1,8-(exo)-dibromo-8,8a-dihydro-4a-methyl-2,7-(1H,4aH)-naphthalene-dione 10.

A solution of 7 (320 mg, 1 mmol) in dry THF (20 mL) was brominated by rapid addition of bromine (0.15 mL, 3 mmol) *via* syringe, dissolved in THF (10 mL) under nitrogen at -78°C. After 5 minutes the mixture was quenched with water, and excess bromine was decolorized with a sufficient amount of sodium bisulfite. The layers were separated and the aqueous layer was extracted with ether (2 x 20 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by chromatography on silica gel (20% ethyl acetate in hexane) gave 10 (177 mg, 53%).

10: ^{1}H NMR: δ 6.66 (d, 2H, J=10.27 Hz), 6.24 (dd, 2H, J= 10.27, 2.64 Hz), 4.9 (d, 2H, J=7.45 Hz), 3.16 (t, 1H, J=7.64 Hz), 1.93 (s, 3H).

Bromination of bis (silyl enol) ether 7 to 9 &10 using NBS.

To a solution of 7 (1.48 g, 4.62 mmol) in dry THF (50 mL) at 0°C under N_2 was added recrystallized ($CHCl_3$) NBS (1.8 g, 10.16 mmol) as solid. The reaction mixture was stirred for 15 minutes at 0°C and then quenched with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ether (2 x 75 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (20% ethyl acetate in hexane) of the crude residue gave 70% yield of the two dibromides 9: (0.65 g, 42%) and 10: (0.44 g, 28%) in a 1.5 : 1 ratio. This yield ratio was in agreement with NMR examination of the crude mixture which indicated 59% of 9 and 41% of 10.

9: ^{1}H NMR: δ 6.73 (dd, 1H, J= 10.49, 1.31 Hz), 6.6 (d, 1H, J=10.3 Hz), 6.22 (d, 1H, J=10.5 Hz), 6.13 (dd, 1H, J= 10.3, 0.76 Hz), 4.5 (s, 1H), 4.43 (d, 1H, J=4.05 Hz), 3.4 (d, 1H, J=4.5 Hz), 1.8 (s, 3H).

10: ^{1}H NMR: δ 6.66 (d, 2H, J=10.27 Hz), 6.24 (dd, 2H, J= 10.27, 2.64 Hz), 4.9 (d, 2H, J=7.45 Hz), 3.16 (t, 1H, J=7.64 Hz), 1.93 (s, 3H).

Synthesis of the tricyclodienedione 12 from the reaction of 8 with DBU.

1,8 Diazabicyclo [5.4.0] undec-7-ene (DBU, 0.3 mL, 2 mmol) was added *via* syringe to a solution of 8 (255 mg, 1 mmol) in dry THF (25 mL) under nitrogen. The solution was heated at reflux for 15 h. The reaction was quenched by addition of water. The aqueous layer was extracted with ether, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellowish oil. Purification by chromatography on silica gel (Chromatotron, 25% ethyl acetate in hexane) afforded compound 12 (35 mg, 20%).

12: ^{1}H NMR: δ 6.63 (d, 2H, J=9.91 Hz), 6.03 (d, 2H, J=9.91 Hz), 2.24 (s, 3H), 1.65 (s, 3H).

^{13}C NMR: δ 190.68 (C=O), 153.75 (C_4 or C_5), 128.1 (C_3 or C_6), 33.85 (C_{4a}), 29.22 (C_{8a}), 28.35 (CH_3), 27.02 (C_1 or C_8).

Compound 12 derived from sodium iodide reaction with 9.

Compound 9 (0.65 g, 1.95 mmol) was dissolved in dry acetone (50 mL) under N_2. To this was added 12.2 eq. excess of sodium iodide (3.5 g, 23.79 mmol) at RT and the reaction was left to stir for 3 h and refluxing was continued overnight. The solution was quenched with sufficient sodium bisulfite and then concentrated by rotary evaporation. To the residue was added cold saturated sodium bicarbonate (20 mL). The aqueous layer was extracted with ether (2 x 50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (30% ethyl acetate in hexane) gave compound 12 (0.1 g, 44%) as white crystals.

12: ^1H NMR: δ 6.63 (d, 2H, J=9.91 Hz), 6.03 (d, 2H, J=9.91 Hz), 2.24 (s, 3H), 1.65 (s, 3H).

^{13}C NMR: δ 190.68 (C=O), 153.75 (C_4 or C_5), 128.1 (C_3 or C_6), 33.85 (C_{4a}), 29.22 (C_{8a}), 28.35 (CH_3), 27.02 (C_1 or C_8).

Compound 12 derived from sodium iodide reaction with 10.

To a solution of 10 (0.44 g, 1.32 mmol) in acetone (40 mL, anhydrous), was added anhydrous sodium iodide (2.4 g, 16.1 mmol) under nitrogen. The mixture was stirred at RT for 3 h and then refluxed for 15 h under N_2. The solution was quenched with sufficient sodium bisulfite and then concentrated by rotary evaporation. To the residue was added cold saturated aqueous sodium bicarbonate (20 mL). The aqueous layer was extracted with ether (2 x 50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo.

Purification by chromatography on silica gel (30% ethyl acetate in hexane) gave compound 12 (0.16 g, 68%) as white crystals.

12: ^{1}H NMR: δ 6.63 (d, 2H, J=9.91 Hz), 6.03 (d, 2H, J=9.91 Hz), 2.24 (s, 3H), 1.65 (s, 3H).

^{13}C NMR: δ 190.68 (C=O), 153.75 (C_4 or C_5), 128.1 (C_3 or C_6), 33.85 (C_{4a}), 29.22 (C_{8a}), 28.35 (CH_3), 27.02 (C_1 or C_8).

Vinyl enol ether 13 *via* Peterson olefination of 12.

(Methoxymethyl) trimethylsilane (0.66 mL, 4.23 mmol) in dry THF (6 mL) was cooled to -78°C and sec-butyl lithium (3.25 mL, 4.23 mmol, 1.3 M in cyclohexane) was slowly added *via* syringe. The mixture was warmed to -25°C and held at this temperature for 0.5 h to ensure complete formation of methoxy (trimethylsilyl) methyl lithium. The above pale yellow solution was cooled to -35°C before 12 (0.332 g, 1.9 mmol) was added. After 1.5 h, to the above mixture potassium t-butoxide (0.47 g, 4.23 mmol) was added. The mixture was heated at 60°C for 1 h, and then quenched with saturated aqueous ammonium chloride. The organic extract was washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (Chromatotron, 10% ethyl acetate in hexane) afforded 13 (0.08 g, 18%) as colorless oil.

13: ^{1}H NMR: δ 6.25 (s, 1H), 6.20 (d, 1H, J=9.8 Hz), 5.7 (d, 1H, J=9.7 Hz), 5.65 (s, 1H), 5.4 (d, 1H, J= 9.9 Hz), 5.21 (d, 1H, J=9.9 Hz), 3.7 (s, 3H), 3.62 (s, 3H), 2.1 (d, 2H, J=9 Hz), 1.4 (s, 3H), 1.3 (tentative, 1H).

Vinyl enol ether 17 *via* Wittig reaction with 4.

A 50 mL 3 necked flask was fitted with a dropping funnel, nitrogen inlet, and a drying tube. Potassium t-butoxide (0.45 g, 4 mmol) was added to a suspension of methoxymethylenetriphenylphosphonium chloride (1.37 g, 4 mmol) in dry THF (25 mL) at -78°C. The mixture was warmed to RT over 2 h before it was cooled back to -40°C when 4 (0.176 g, 1 mmol) dissolved in THF (6 mL) was added. The reaction mixture was allowed to stand overnight at RT. The reaction mixture was quenched with of water (1 mL) and solvent was removed by rotatory evaporator. The viscous oil was diluted with diethyl ether (35 mL) and washed with water (35 mL). The aqueous phase was washed with diethyl ether (2 x 20 mL) and the combined etheral solution was dried and concentrated in vacuo down to ~30 mL before 1 mL of methyl iodide was added (addition of methyl iodide allowed a clean separation of enol ether 17 from the by-product triphenylphosphine, which has a very close R_f to 17, by converting it to the triphenylphosphinemethyl phosphonium chloride). After addition of methyl iodide, stirring was continued for 5 h, solvent was evaporated, and the resulting oily product was chromatographed on silica gel (10% ethyl acetate in hexane) to afford 17 (0.19 g, 81%) as colorless oil.

17: ^{1}H NMR: δ 6.36 (d, 1H, J=9.9 Hz), 6.05 (s, 1H), 5.83 (d, 1H, J=9.75 Hz), 5.79 (s, 1H), 5.42 (d, 1H, J=9.9 Hz), 5.3 (d, 1H, J=9.71 Hz), 3.63-3.62 (s, 6H), 2.5-2.24 (m, 4H), 1.77 (m, 1H), 1.17 (s, 3H).

Bis Simmons-Smith adduct 18 from the reaction of 17 with Zn-Ag couple.

To an etheral suspension of the Zn-Ag couple (1.71 g zinc and 55 mg silveracetate), diiodomethane (1.05 mL, 13.08 mmol) was added dropwise, with stirring, at such a rate as to maintain a gentle reflux. Stirring was continued for 1 h at RT. The enol ether 17 (0.76 g, 3.27 mmol) was added in ether dropwise over 15 minutes and the mixture was refluxed for 19 h. The mixture was then cooled to 0°C, followed by addition of pyridine (1.05 mL,

13.08 mmol). The mixture was stirred for 1 h. The resulting precipitate was removed by filtration and washed with ether. The filtrate was concentrated and purified by chromatography on silica gel (15% ethyl acetate in hexane) to give the colorless oil 18 (0.32 g, 37%).

18: ^{1}H NMR: δ 5.51 (d, 2H, J=10.01 Hz) , 4.76 (d, 2H, J=10.01 Hz), 3.3-3.56 (s, 6H), 3.03 (m, 2H, oxymethine), 2.2 (dd, 4H, J=13.2, 3.96 Hz), 1.68 (m, 1H), 1.35 (s, 3H), 0.57 (m, 4H).

Bis Simmons-Smith adduct 18 from the reaction of 17 with diethyl zinc.

Methylene iodide (0.64 mL, 8 mmol) was added dropwise during 30-60 minutes into a mixture of enol ether 17 (0.46 g, 2 mmol), diethyl zinc (6 mL, 6 mmol), and diethyl ether (15 mL) at RT. The reaction mixture was refluxed for 3 h and when cooled, it was poured slowly into 1% HCl aq. (10 mL). The organic layer was washed with water, dilute aqueous sodium bicarbonate, dried over $MgSO_4$, filtered, and concentrated in vacuo. The final oil obtained was purified by chromatography on silica gel (10% ethyl acetate in hexane) to give the colorless oil 18 (0.2 g, 39%).

18: ^{1}H NMR: δ 5.51 (d, 2H, J=10.01 Hz) , 4.76 (d, 2H, J=10.01 Hz), 3.3-3.56 (s, 6H), 3.03 (m, 2H, oxymethine), 2.2 (dd, 4H, J=13.2, 3.96 Hz), 1.68 (m, 1H), 1.35 (s, 3H), 0.57 (m, 4H).

α–β unsaturated dialdehyde 21.

The bis enol ether 17 (0.4 g, 1.72 mmol) was dissolved in THF (10 mL). To this was added of 5N HCl (5 mL) and the mixture was heated to 60° C for 1 h. TLC showed the disappearance of 16 completely. The reaction was then neutralized with saturated sodium

bicarbonate, extracted with diethyl ether (2 x 50 mL), dried over $MgSO_4$, and concentrated in vacuo to give 19 (0.35 g) in quantitative yield (m.p 88-90° C).

21: ^1H NMR: δ 9.45 (s, 2H), 6.7 (br s, 2H), 2.42-2.03 (m, 8H), 1.98-1.84 (m, 1H), 1.0 (s, 3H).

Compound 22 *via* silylation of 21 with trimethylsilyl chloride.

A three necked flask was fitted with a condenser, N_2 inlet, drying tube, and a magnetic bar. The dialdeyde 21 (0.2 g, 1 mmol) was dissolved in dry distilled acetonitrile (6 mL). Triethylamine (0.56 mL, 4 mmol), sodium iodide (0.6 g, 4 mmol), and trimethylsilyl chloride (0.5 mL, 4 mmol) were added sequentially. After stirring at RT for 15 minutes the reaction mixture was heated to 70° C for 1 h. Upon consumption of the aldehyde, 15 mL of cold saturated aqueous sodium bicarbonate was added. The organic layer was extracted with ether (20 mL). The aqueous phase was separated and extracted with an additional ether (2 x 20 mL). The combined organic extracts were washed with water (20 mL), saturated sodium chloride (20 mL), dried over potassium carbonate, and concentrated in vacuo to give a quantitative yield of the corresponding silyl enol ether 22 (0.32 g).

22: ^1H NMR: δ 6.31 (s, 2H), 5.87 (d, 2H, J=9.71), 5.32 (d, 2H, J=9.71), 2.47 (dd, 2H, J=15.6, 4.5 Hz), 2.29 (d, 1H, J=7.8 Hz), 2.25 (d, 1H, J=7.8 Hz), 1.77 (m, 1H), 1.17 (s, 3H), 0.23 (s, 18H).

Compound 23 *via* silylation of 21 with t-butyldimethylsilyl chloride.

A three necked flask was fitted with a condenser, N_2 inlet, drying tube, and a magnetic bar. The dialdeyde 21 (0.2 g, 1 mmol) was dissolved in dry distilled acetonitrile (6 mL). Triethylamine (0.56 mL, 4 mmol), sodium iodide (0.6 g, 4 mmol), and t-butyldimethylsilyl chloride (0.6 g, 4 mmol) were added sequentially. After stirring at RT for

15 minutes the reaction mixture was heated to 70° C for 1 h. Upon consumption of the aldehyde, cold saturated aqueous sodium bicarbonate (15 mL) was added. The organic layer was extracted with ether (20 mL). The aqueous phase was separated and extracted with an additional ether (2 x 20 mL). The combined organic extracts were washed with water (20 mL), saturated sodium chloride (20 mL), dried over potassium carbonate, and concentrated in vacuo. Purification by chromatography on silica gel (Chromatotron, 10% ethyl acetate in hexane) gave 23 (0.37 g, 93%).

23: ^{1}H NMR: δ 6.34 (s, 2H), 5.87 (d, 2H, J=9.68), 5.30 (d, 2H, J=9.74), 2.48 (dd, 2H, J=16, 4.5 Hz), 2.31 (d, 1H, J=6.7 Hz), 2.26 (d, 1H, J=7.2 Hz), 1.77 (m, 1H), 1.17 (s, 3H), 0.97 (s, 18H), 0.18 (s, 12H).

Pyrrolidine enamine 24.

A solution of the aldehyde 21 (0.2 g, 1 mmol), pyrrolidine (0.4 mL, 5 mmol), and anhydrous benzene (10 mL) containing molecular sieves (0.4 g) was heated at reflux for 15 h. The reaction mixture was filtered by gravity under N_2 , and solvent was evaporated off completely to give 24 (0.3 g) in quantitative yield as a mixture of *cis* and *trans* isomers.

Dialdehyde 26 derived from the reaction of enamine 24 with allyl bromide.

Dienamine 24 (0.15 g, 0.5 mmol) was treated with allyl bromide (0.2 mL, 2.5 mmol) in dry acetonitrile (10 mL). The mixture was refluxed overnight under N_2 atmosphere. Hydrolysis was effected by stirring (1h) a 0.5 M solution of the resulting imine in ether with an equal volume of a buffered (pH 4.5) aqueous acetic acid solution prepared from acetic acid (2.5 mL), water (2.5 mL), and sodium acetate (1.08 g). The layers were separated, and the aqueous layer was extracted with ether (3 x 25 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and

concentrated in vacuo. Purification by chromatography on silica gel (15% ethyl acetate in hexane) afforded 26 as a mixture of inseparable isomers.

Bis-t-butyl imine 27.

The dialdehyde 21 (0.2 g, 1 mmol) was dissolved in dry benzene (8 mL) containing molecular sieves (0.4 g). To this was added t-butylamine (0.42 mL, 4 mmol), and refluxing was effected under N_2 over 24 h. The reaction mixture was then gravity filtered followed by evaporation of the solvent to afford the imine 25 (0.32 g) in quantitative yield.

27: ^{1}H NMR: δ 7.78 (s, 2H), 5.98 (s, 2H), 2.42 (dd, 2H, J=17.9 Hz, J=1.6 Hz), 2.20 (d, 4H, J=19.53), 1.96-1.89 (dd, 2H, J=19.46, 2.67 Hz), 1.8 (m, 1H), 1.2 (s, 18H), 1.0 (s, 3H).

Transformation of 17 into 32.

A 50 mL, 2 necked, round bottom flask is fitted with a magnetic stirrer, a pressure-equal droping funnel, and a N_2 inlet. In the flask was dissolved enol ether 17 (0.46 g, 2 mmol), in anhydrous ether (10 mL). To this solution was added potassium t-butoxide (0.6 g, 5.32 mmol), under N_2, and the resulting suspension was cooled to -30°C with a dry ice / acetone bath and stirred effectively. While these conditions were maintained, a solution of chloroform (0.48 g, 0.32 mL) in ether (10 mL) was added dropwise during 90 min. The mixture is stirred for another 30 min at -30°C, and then the temperature was allowed to rise above 0°C. The reaction was quenched with water (5mL) and the layers were separated. The organic layer was washed with water (2 x 10 mL) while the aqueous layer was extracted with ether (2 x 5 mL). The ether extracts were combined and dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude brown solid (0.6 g) in quantitative yield. Purification by chromatography on silica gel (Chromatotron, 20% ethyl acetate in hexane) afforded 32 as a mixture of *cis* and *trans* isomers: mp 153-155°C.

32: ^{1}H NMR: δ 10 (s, H), 9.98 (s, H), 9.95 (s, H), 7.18 (d, 1H, J=10.11 Hz), 6.85 (dd, 1H, J=10, 2.9 Hz), 6.13 (d, 1H, J=10 Hz), 6.01 (d, 1H, J=10.12 Hz), 3.12 (dd, 1H, J=16.08, 4.3 Hz), 2.9 (m, 2H), 2.66 (dd, 1H, J=17.28, 7.9 Hz), 2.21 (m, 1H, J=4.2 Hz), 1.35 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H).

MS m/e 296 (M^+), 281 (M-CH_3, 15), 245 (-Cl, 36), 217 (-CO or -C_2H_4, 28); m/e 296 (M^+), 261 (-Cl, 35), 243 (-H_2O, 18), 181 (-80, base peak).

Hemiketal 38 from hydrogenolysis of 12.

To a solution of 12 (0.35 g, 2mmol) in absolute ethanol (50 mL) was added palladium on carbon (0.2 g, 10%). The reaction mixture was degassed, flushed under hydrogen, and stirred under a hydrogen atmosphere overnight. The black suspension was filtered through Celite, and the solvent was concentrated in vacuo. Purification by chromatography on silica gel (25% ethyl acetate in hexane) afforded 38 in nearly quantitative yield.

Dihydroanisole 39 derived from 4-methyl anisole.

To a 1L three necked flask, equipped with a gas inlet, dry ice / acetone condensor and mechanical stirrer was added 4-methyl anisole (20.6 g, 0.16 mol), ethanol (60 mL), liquid ammonia (600 mL) and sodium (18.5 g, 0.8 mol) cut in small pieces until the blue color persisted for 20 min. The condensor was removed and the ammonia was allowed to evaporate, and the residue was partitioned between saturated aqueous ammonium chloride (100 mL) and ether (100 mL). The aqueous layer was extracted with ether (3 x 100 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 39 (17.38 g, 85%) as a clear liquid.

39: ^{1}H NMR: δ 5.4 (s, 1H), 4.65 (s, 1H), 3.6 (s, 3H), 2.78 (br s, 4H), 1.78 (s, 3H).

2-acetyl-1-methoxy-4-methyl-bicyclo-[2.2.2]-oct-5-ene 40.

To the crude 39 (35.2 g, 0.28 mol) in a 250 ml flask was added methylvinyl ketone (58.87 g, 0.84 mol), methylene blue (400 mg) and chloroform (5 g). A water condensor was attached and the mixture refluxed under N_2 overnight. After cooling, $NaHCO_3$ (1 g) was added and the mixture was concentrated under reduced pressure. Distillation of the crude mixture under reduced pressure gave 40 (29.14 g, 53%).

40: ^{1}H NMR: δ 6.18 (d, 1H, J=8.7 Hz), 6 (d, 1H, J=8.7 Hz), 3.34 (s, 3H), 3.1 (m, 1H), 2.14 (s, 3H), 1.66-1.47 (m, 6H), 1.2 (s, 3H).

2-carbomethoxyacetyl-1-methoxy-4-methyl-bicyclo-[2.2.2]-oct-5-ene 41.

To a 300 ml flask equipped with a water condensor and charged with glyme (150 mL), (80%) sodium hydride (8.28 g), dimethyl carbonate (51.75 g, 0.57 mol), was added in one portion ketone 40 (25.14 g, 0.129 mol). The mixture was warmed to a reflux and evolution of H_2 gas was observed. After H_2 evolution subsided, the mixture was acidified with acetic acid (60 g), diluted with saturated aqueous sodium bicarbonate (200 mL) and taken up in ether (1L). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The final oil obtained was distilled under pressure to afford 41 (27.26 g, 84%) as a mixture of epimers. In the ^{1}H NMR of 41, δ values are expressed for both epimers.

41: ^{1}H NMR: δ 6.4-5.8 (two dd, 2H), 3.78-3.76 (two s, 3H), 3.6 (s, 2H), 3.38 (overlapping singlets, 3H), 3.2-3 (m, 1H), 1.8-1.2 (m, 6H), 1.19-1.17 (two s, 3H).

cis-8a,1,3,4,5,6-hexahydro-4a-methyl-2,7-dioxo-(6H,8H)-[1]-methyl-naphthoate 42.

Ester 41 (11.5 g, 45.63 mmol) was dissolved in acetic acid (100 mL). To this was added (70%) perchloric acid (10 mL) and the mixture was stirred at RT for 1.5 h. The acetic

acid solution was neutralized with excess solid sodium bicarbonate and the aqueous layer was extracted with ether. The ether layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give 42 (9.52 g, 88%).

42: ^1H NMR: δ 12.35 (s, 1H), 3.76 (s, 3H), 2.6 (dd, 2H, J=10.96, 2 Hz), 2.31 (m, 6H), 1.79 (m, 2H), 1.36 (s, 1H), 1 (s, 3H).

cis-8a,1,3,4,5,6-hexahydro-1(ax)-bromo-4a-methyl-2,7-dioxo-(6H,8H)-[1]-methyl-naphthoate 43a.

To a solution of the β-keto ester 42 (4.76 g, 0.02 mol) dissolved in dry methylene chloride (150 mL) was added (under N_2) triethyl amine (16.72 mL). To the resulting solution cooled to 0°C, N-bromo succinimide (7.83 g) dissolved in methylene chloride (300 mL) was added dropwise. The mixture was stirred at 0°C for 2h before it was quenched with 10% HCl. The layers were separated and the organic phase was washed with aqueous $NaHSO_4$ (5%), saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Purification by chromatography on silica gel (30% ethyl acetate in hexane) gave 43a (2.28 g, 36%) which was recrystallized from ether-hexane mixture as white needles: mp 108-110°C. Compound 43a was obtained together with 43b in a combined yield of 63%.

43a: ^1H NMR: δ 3.84 (s, 3H), 3.1 (m, 2H), 2.57 (m, 5H), 2.19 (dd, 2H), 1.81 (m, 1H), 1.62 (m, 1H), 1.16 (s, 3H).

^{13}C NMR: δ 208.53 (s, C=O, C_2), 198.69 (C=O, C_7), 167.68 (C=O of ester), 71.78 (C_1), 54.04 (OCH_3), 49.11 (C_{8a}), 41.34 (C_3 or C_6 or C_8), 36.44 (C_3 or C_6 or C_8), 35.17 (C_3 or C_6 or C_8), 33.75 (C_4 or C_5), 33.33 (C_4 or C_5), 33.12 (C_{4a}), 27.84 (CH_3).

IR (CCl_4) ν_{max}: 2960, 2930 (C-H), 1725 (C=O of ketone), 1740 (C=O of ester), 1270, 1250 (C-O of ester).

cis-8a,1,3,4,5,6-hexahydro-1(eq)-bromo-4a-methyl-2,7-dioxo-(6H,8H)-[1]-methyl-naphthoate 43b.

To a solution of the β-keto ester 42 (4.76 g, 0.02 mol) dissolved in dry methylene chloride (150 mL) was added (under N_2) triethyl amine (16.72 mL). To the resulting solution cooled to 0°C, N-bromo succinimide (7.83 g) dissolved in methylene chloride (300 mL) was added dropwise. The mixture was stirred at 0°C for 2h before it was quenched with 10% HCl. The layers were separated and the organic phase was washed with aqueous $NaHSO_4$ (5%), saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Purification by chromatography on silica gel (30% ethyl acetate in hexane) gave 43b (1.68 g, 27%) which was recrystallized from methylene chloride-hexane mixture as white needles: mp 115-116°C. Compound 43b was obtained together with 43a in a combined yield of 63%.

43b: ^1H NMR: δ 3.75 (s, 3H), 3.26 (dd, 1H, J=17.93, 1.6 Hz), 2.87 (ddd, 1H, J=6, 5.9, 6 Hz), 2.65 (m, 2H), 2.47 (m, 3H), 2.17 (m, 1H), 1.91 (m, 2H), 1.53 (m, 1H), 1.25 (s, 3H).

^{13}C NMR: δ 206.82 (C=O, C_2), 196.91 (C=O, C_7), 168.55 (C=O of ester), 72.31 (C_1), 54.51 (C_{8a}), 53.38 (OCH_3), 40.18 (C_3 or C_6 or C_8), 38.92 (C_3 or C_6 or C_8), 36 (C_3 or C_6 or C_8), 35.58 (C_4 or C_5), 35.16 (C_{4a}), 30.09 (C_4 or C_5), 27.46 (CH_3).

IR (CCl_4) ν_{max}: 2970, 2950 (C-H), 1740 (C=O of ketone and ester overlapping), 1255 (C-O of ester).

cis-3,4,5,6,8,8a-hexahydro-4a-methyl-2,7-(1H,3H)-naphthalene-dione 45.

A solution of 41 (2 g, 8 mmol), in acetic acid (35 mL) and phosphoric acid (3.5 mL), was stirred at RT for 1.5 h refluxed overnight. The mixture was allowed to cool and the acetic acid was evaporated under reduced pressure. The residue was poured into aqueous saturated sodium bicarbonate until neutral. The solution was partitioned between water (100 mL) and ether (100 mL), and the aqueous layer was extracted with ether (2 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Crystallization of the solid residue from ether-hexane gave the diketone 45 (1g, 70%): mp 91-93°C.

45: ^{1}H NMR: δ 2.47 (m, 6H), 2.15 (m, 5H), 1.69 (m, 2H), 1.34 (s, 3H).

^{13}C NMR: δ 209.88 (C=O, C_2 or C_7), 44.46 (C_1 and C_8 or C_3 and C_6), 43.74 (C_3 and C_6 or C_1 and C_8), 37.27 (C_4 and C_5), 34.19 (C_{8a}), 32 (C_{4a}), 25.73 (CH_3).

IR (CCl_4) ν_{max}: 2970, 2940 (C-H), 1725 (C=O).

cis-8a,1,3,4,5,6-hexahydro-6(eq)-bromo-4a-methyl-2,7-dioxo-(6H,8H)-[1]-methyl-naphthoate 54.

The copper (II) bromide was grounded in a mortar and pestle to ensure a large surface area for reaction. Copper (II) bromide (0.45 g, 2.01 mmol) was placed in a round bottom flask fitted with a reflux condensor. Ethyl acetate (10 mL) was added and brought to reflux on a hot plate. Compound 42 (0.24 g, 1 mmol) was dissolved in hot chloroform (10 mL) and added to the flask. The resulting reaction mixture was refluxed with stirring for 1h to ensure complete exposure of the copper (II) bromide to the reaction medium until the reaction changed color from green to amber. The mixture was then gravity filtered in order to remove copper (I) bromide and worked up first with sodium thiosulfate, sodium

bicarbonate, and then water (2 x 30 mL). The aqueous layer was extracted with ether (2 x 30 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 54 (0.32 g) in quantitative yield. Compound 54 was recrystallized from methylene chloride-hexane mixture into colorless needles: mp 179-181°C.

54: ^1H NMR: δ 12.37 (s, 1H), 4.8 (dd, 1H, J=13.58, 5.83 Hz), 3.77 (s, 3H), 2.93 (dd, 1H, J=14.17, 4.7 Hz), 2.71 (m, 1H), 2.45 (m, 3H), 2.23 (m, 3H), 1.52 (m, 1H), 1.04 (s, 3H).

^{13}C NMR: δ 200.33 (C=O, C_7), 172.2 (C_2), 171.87 (C=O of ester), 100.03 (C_1), 52.76 (C_6), 51.79 (C_8 or OCH_3), 51.39 (C_8 or OCH_3), 44.87 (C_{8a}), 41.75 (C_3), 35.09 (C_{4a}), 26.17 (C_5), 26.08 (C_4), 25.08 (CH_3).

IR (CCl_4) ν_{max}: 2950 (C-H), 1620 (C-OH of enol), 1740 (C=O of ester), 1660 (C=O of ketone).

cis-8a,1,3,4,5,6-hexahydro-6(eq),8(ax)-dibromo-4a-methyl-2,7-dioxo-(6H,8H)-[1]-methyl-naphthoate 55.

A solution of bromine (0.4 g, 2.5 mmol) in chloroform (10 mL) was slowly added to β-keto ester 42 (0.24 g, 1 mmol) dissolved in chloroform (10 mL) over a period of 15 minutes. The solution was left to stir overnight at RT. The reaction was quenched with sodium bisulfite (5%), and the layers were separated. The organic layer was washed with aqueous saturated sodium bicarbonate, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (20% ethyl acetate in hexane) gave 55 (0.32 g, 80%): mp 178-179°C.

55: ^{1}H NMR: δ 12.59 (s, 1H), 5.53 (dd, 1H, J=14.27, 5.62 Hz), 4.79 (d, 1H, J=5 Hz), 3.79 (s, 3H), 2.92 (d, 1H, J=4.86 Hz), 2.78 (m, 1H), 2.47 (m, 3H), 2.2 (t, 1H), 1.39 (m, 1H), 1.01 (s, 3H).

^{13}C NMR: δ 195.53 (C=O, C_2), 174.88 (C_7), 171.36 (C=O of ester), 96.84 (C_8), 53.75 (C_1 or C_3), 51.91 (C_1 or C_3), 51.00 (OCH_3), 47.9 (C_{8a}), 44.71 (C_6), 35.21 (C_{4a}), 27.78 (C_4), 27.23 (C_5), 25.96 (CH_3).

cis-8a,1,3,4-tetrahydro-4a-methyl-2,7-dioxo-(4aH,8H)-[1]-methyl-naphthoate 56.

Monobromide 54 (0.64 g, 2 mmol) was dissolved in THF (20 mL) under N_2. To this solution DBU (0.6 mL, 4 mmol) was added and the mixture was heated to 60°C for 15 h. The mixture was allowed to cool slowly to RT, before it was quenched with HCl (1N). The mixture was diluted with ether (2 x 30 mL), and the organic layer was washed with saturated aqueous sodium bicarbonate, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (Chromatotron, 20% ethyl acetate in hexane) afforded the monoene 56 (0.08 g, 17%): mp 97-100°C.

56: ^{1}H NMR: δ 12.41 (s, 1H), 6.66 (d, 1H, J=10.12 Hz), 5.93 (d, J=10.16 Hz), 3.78 (s, 3H), 2.84 (dd, 1H, J=13.2, 4 Hz), 2.72 (dd, 1H, J=17, 4.33 Hz), 2.42 (m, 2H), 2.2 (q, 1H, J=13.25 Hz), 1.88 (m, 1H), 1.56 (m, 1H), 1.15 (s, 3H).

Synthesis of *56* by lithium-bromide lithium-carbonate dimethylformamide dehydrobromination.

To a stirred suspension of dry LiBr (0.14 g, 1.57 mmol) and $LiCO_3$ (0.18 g, 2.46 mmol) in dry DMF (10 mL) at 120°C under N_2, was added solid 54 (0.32 g, 1 mmol). Stirring was continued for 75 minutes at the same temperature. The reaction was then

cooled, poured into dilute acetic acid, and extracted with ether. The ether extracts were washed with water, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give monoene 56 as the only product (0.15 g, 64%).

56: ^1H NMR: δ 12.41 (s, 1H), 6.66 (d, 1H, J=10.12 Hz), 5.93 (d, J=10.16 Hz), 3.78 (s, 3H), 2.84 (dd, 1H, J=13.2, 4 Hz), 2.72 (dd, 1H, J=17, 4.33 Hz), 2.42 (m, 2H), 2.2 (q, 1H, J=13.25 Hz), 1.88 (m, 1H), 1.56 (m, 1H), 1.15 (s, 3H).

7-carbomethoxy-5-methyl-tricyclo-[4.4.0.$0^{1,7}$]-decane-2,8-dione 57.

Monobromide 54 (0.64 g, 2 mmol) was dissolved in THF (20 mL) under N_2. To this solution DBU (0.6 mL, 4 mmol) was added and the mixture was heated to 60°C for 15 h. The mixture was allowed to cool slowly to RT before it was quenched with HCl (1N). The mixture was diluted with ether (2 x 30 mL), and the organic layer was washed with saturated aqueous sodium bicarbonate, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (Chromatotron, 20% ethyl acetate in hexane) afforded the keto-ester 57 (0.19 g, 40%) which was recrystallized from hexane: mp 107-108°C.

57: ^1H NMR: δ 3.73 (s, 3H), 2.94 (d, 1H, J=5.44 Hz), 2.74 (m, 2H), 2.53 (m, 1H), 2.44 (d, 1H, J=18.92 Hz), 2.05 (m, 3H), 1.81 (m, 1H), 1.44 (d, 1H, J=14.6 Hz), 1.2 (s, 3H).

^{13}C NMR: δ 210.08 (C=O, C_2), 206.18 (C=O, C_8), 169.87 (C=O of ester), 71.15 (C_7), 56.25 (C_1), 52.71 (OCH_3), 49.31 (C_4), 38.17 (C_5), 37.55 (C_3 or C_9), 36.32 (C_3 or C_9), 35.47 (C_6 or C_{10}), 34.96 (C_6 or C_{10}), 23.99 (CH_3).

IR (CCl_4) ν_{max}: 2970, 2890 (C-H), 1770 Cm-1 (C=O of C_3 β-keto ester), 1750 (C=O of ester), 1720 (C=O of ketone, C_9)

2-carbomethoxy-1-hydroxy-8-methyl-tetracyclo-[4.4.0.0^{1,6}.0^{2,4}]-decane-5-one 58.

Monobromide 54 (0.64 g, 2 mmol) was dissolved in THF (20 mL) under N_2. To this solution DBU (0.6 mL, 4 mmol) was added and the mixture was heated to 60°C for 15 h. The mixture was allowed to cool slowly to RT, before it was quenched with HCl (1N). The mixture was diluted with ether (2 x 30 mL), and the organic layer was washed with saturated aqueous sodium bicarbonate, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (Chromatotron, 20% ethyl acetate in hexane) afforded the tetracyclic 58 (0.19 g, 40%) which was recrystallized from hexane into colorless crystals: mp 104-105°C.

58: ^{1}H NMR: δ 3.76 (s, 3H), 2.4 (dd, 1H, J=7.62, 1.88 Hz), 2.26 (dd, 1H, J=7.62, 2.74 Hz), 2.16 (dd, 1H, J=7.85, 1.62 Hz), 2.08 (d, 1H, J=10.78 Hz), 1.93 (m, 2H), 1.68 (m, 1H), 1.58 (m, 3H), 1.16 (s, 3H).

^{13}C NMR: δ 207.85 (C=O, C_5), 171.22 (C=O of ester), 74.2 (C_1), 52.2 (OCH_3), 51.14 (C_{10}), 43.29 (C_6), 40.59 (C_4), 38.58 (C_2), 37.26 (C_7), 35.80 (C_3), 29.12 (C_8), 27.79 (C_9), 25.47 (CH_3).

IR (CCl_4) ν_{max}: 3540 (OH), 2970, 2940, 2890 (C-H), 1720 (C=O of ester), 1755 (C=O of ketone).

cis-8a,1,3,4,5,6,7,8-octahydro-2,2-dimethoxy-6-hydroxy-4a-methyl-[1]-methyl-naphthoate-2-one 65.

To a solution of sodium (0.06 g, 2.6 mmol) dissolved in dry methanol (15 mL) under N_2 at RT, was added solid mono bromide 54 (0.32 g, 1 mmol). The mixture was heated at 60°C for 15 h, and the reaction was quenched with HCl (10%). The mixture was diluted with ether (2 x 20 mL), and the organic layer was washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (Chromatotron, 20% ethyl acetate in hexane) gave 65 (0.14 g, 47%) as white crystals.

65: ^{1}H NMR: δ 12.23 (s, 1H), 3.77 (s, 3H), 3.40 (s, 3H), 3.35 (s, 3H), 2.3 (m, 4H), 2.07 (m, 2H), 1.64 (m, 2H), 1.18 (m, 2H), 0.94 (s, 3H).

^{13}C NMR: δ 172.74 (C_2), 171.81 (C=O of ester), 99.99 (C_1), 99.12 (C_7), 71.77 (C_6), 51.38 (OCH_3 of ester), 51.05 (OCH_3 on C_7), 48.45 (OCH_3 on C_7), 46.60 (C_{8a}), 36.71 (C_3), 36.02 (C_8), 32.79 (C_{4a}), 26.51 (C_5), 26.27 (C_4), 26 (CH_3).

cis-8a,1,3,4,5,6-hexahydro-6-hydroxy-4a-methyl-2,7-dioxo-(6H,8H)-[1]-methyl-naphthoate 66.

To a solution of sodium (0.06 g, 2.6 mmol) dissolved in dry methanol (15 mL) under N_2 at RT, was added solid mono bromide 54 (0.32 g, 1 mmol). The mixture was heated at 60°C for 15 h, before the reaction was quenched with HCl (10%). The mixture was diluted with ether (2 x 20 mL), and the organic layer was washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (Chromatotron, 20% ethyl acetate in hexane) gave 66 (0.02 g, 8%) as white crystals.

66: ^{1}H NMR: δ 12.36 (s, 1H), 4.32 (q, 1H, J=6.4, 3.3 Hz), 3.78 (s, 3H), 3.47 (d, 1H, J=3.6 Hz), 2.82 (dd, 1H, J=13.95, 4.6 Hz), 2.65 (dd, 1H, J=12.3, 4.3 Hz), 2.47 (m, 2H), 2.25 (m, 3H), 1.64 (m, 2H), 1.03 (s, 3H).

^{13}C NMR: δ 210.06 (C_7), 172.27 (C_2), 172.07 (C=O of ester), 100.28 (C_1), 71.49 (C_6), 51.65 (OCH_3), 48.94 (C_{8a}), 43.47 (C_8), 42.48 (C_3), 33.48 (C_{4a}), 26.67 (C_5), 26.37 (C_4), 25.24 (CH_3).

6-bromo-2-carbomethoxy-1-hydroxy-8-methyl-tetracyclo-[4.4.0.0^{1,6}.0^{2,4}] decane-5-one 72.

To a solution of dibromo ketone 55 (0.2 g, 0.5 mmol) dissolved in dry THF (10 mL) under N_2, was added DBU (0.08 g, 1 mmol) dropwise using a syringe. Stirring was continued overtnight at 55^{o}C before the reaction was quenched with HCl (10%). The mixture was diluted with ether (2 x 20 mL), and the organic layer was washed with saturated sodium bicarbonate, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give 72 (0.11 g, 70%) as pale yellow crystals. Recrystallization afforded pure 72 as colorless needles: mp 114-116^{o}C.

72: ^{1}H NMR: δ 3.81 (s, 1H), 3.75 (s, 3H), 2.56 (d, 1H, J=7.58 Hz), 2.27 (dd, 1H, J=7.53, 2.45 Hz), 2.11 (m, 4H), 1.81 (q, 1H, J=2 Hz), 1.67 (m, 1H), 1.16 (s, 3H).

^{13}C NMR: δ 199.3 (C_5), 170.14 (C=O of ester), 74.22 (C_1), 69.15 (C_6), 52.53 (OCH_3), 52.33 (C_{10}), 42.47 (C_4), 38.06 (C_2), 37.41 (C_7), 32.82 (C_3), 31.65 (C_8), 26.30 (C_9), 24.92 (CH_3).

IR (CCl_4) ν_{max}: 3540 (OH), 2970, 2940, 2890 (C-H), 1770 (C=O, C5), 1720 (C=O of ester).

Synthesis of 72 by lithium-bromide lithium-carbonate dimethylformamide dehydrobromination.

To a stirred suspension of dry LiBr (0.14 g, 1.57 mmol) and $LiCO_3$ (0.18 g, 2.46 mmol) in dry DMF (10 mL) at 120°C under N_2, was added 55 (0.2 g, 0.5 mmol) as solid. Stirring was continued for 75 minutes at the same temperature. The reaction was then cooled, poured into dilute acetic acid, and extracted with ether. The ether extracts were washed with water, brine, and dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford the tetracyclic compound 72 as the only product (80 mg, 50%).

72: ^1H NMR: δ 3.81 (s, 1H), 3.75 (s, 3H), 2.56 (d, 1H, J=7.58 Hz), 2.27 (dd, 1H, J=7.53, 2.45 Hz), 2.11 (m, 4H), 1.81 (q, 1H, J=2 Hz), 1.67 (m, 1H), 1.16 (s, 3H).

^{13}C NMR: δ 199.3 (C_5), 170.14 (C=O of ester), 74.22 (C_1), 69.15 (C_6), 52.53 (OCH_3), 52.33 (C_{10}), 42.47 (C_4), 38.06 (C_2), 37.41 (C_7), 32.82 (C_3), 31.65 (C_8), 26.30 (C_9), 24.92 (CH_3).

IR (CCl_4) ν_{max}: 3540 (OH), 2970, 2940, 2890 (C-H), 1770 (C=O, C5), 1720 (C=O of ester).

(Silyl enol) ether 91 derived from silylation of 45.

Dione 45 (0.36 g, 2 mmol) was dissolved in dry acetonitrile (12 mL). Triethylamine (1.2 mL, 8 mmol), sodium iodide (1.2 g, 8 mmol) and trimethylsilyl chloride (1 mL, 8 mmol) were added sequentially. After 15 minutes at RT, the reaction mixture was heated to 70°C for 1h. Upon consumption of the aldehyde, a cold aqueous saturated $NaHCO_3$ (15 mL) and ether were added (20 mL). The aqueous phase was separated and extracted with ether (2 x 20 ml). The organic layer was dried over K_2CO_3, filtered, and concentrated in

vacuo to afford (silyl enol) ether 91 (0.65 g) in quantitative yield. The product was carried out to the next step without purification.

91: ^{1}H NMR: δ 4.7 (br s, 2H), 2.05 (m, 4H), 1.81 (m, 4H), 1.5 (d, 1H, J=10.93 Hz), 0.96 (s, 3H), 0.17 (s, 9H), 0.16 (s, 9H).

cis-3,6-(eq)-dibromo-3,4,5,6,8a,8-hexahydro-4a-methyl-2,7-(1H,3H) naphthalene dione 92 *via* reaction of 91 with NBS.

To a solution of the (silyl enol) ether 91 (0.65 g, 2 mmol) in THF (15 mL), was added recrystallized ($CHCl_3$) NBS (0.73 g, 4.1 mmol) and the reaction was stirred at RT under N_2 for 1h. The reaction was quenched with water and diluted with ether (2 x 30 mL). The organic layer was washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography (30% ethyl acetate in hexane) afforded 92 (0.49 g, 62%) as white crystals: mp 127-129°C

92: ^{1}H NMR: δ 4.9 (dd, 1H, J=13, 6.4 Hz), 4.75 (dd, 1H, J=13.63, 6.13 Hz), 2.92 (dd, 1H, J=14.5, 4.5 Hz), 2.76 (t, 1H, J=13.35), 2.6 (d, 1H, J=10.14), 2.51 (dd, 1H, J=13.91, 6.18 Hz), 2.4 (m, 3H), 2.19 (t, 1H, J=13.78), 1.45 (s, 3H).

^{13}C NMR: δ 199 (C_2 or C_7), 198.76 (C_2 or C_7), 51.92 (C_3 or C_6), 51.38 (C_3 or C_6), 50.24 (C_1 or C_8), 45.46 (C_{8a}), 43.74 (C_1 or C_8), 42.71 (C_4 or C_5), 38.53 (C_4 or C_5), 25.82 (C_{4a}), 25.56 (CH_3).

Compound 92 derived from the reaction of 45 with copper bromide.

The copper (II) bromide was grounded in a mortar and pestle to ensure a large surface area for reaction. Copper (II) bromide (0.78 g, 3.5 mmol) was placed in a round bottom flask fitted with a reflux condensor. Ethyl acetate (20 mL) was added and brought to

reflux on a hot plate. Compound 45 (0.18 g, 1 mmol) was dissolved in hot chloroform (20 mL) and added to the flask. The resulting reaction mixture was refluxed with stirring for 1h to ensure complete exposure of the copper (II) bromide to the reaction medium until the reaction changed color from green to amber. The mixture was then gravity filtered in order to remove copper (I) bromide and worked up first with sodium thiosulfate, sodium bicarbonate, and then water (2 x 60 mL). The aqueous layer was extracted with ether (2 x 60 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 92 in quantitative yield. Compound 92 was digested with ether and placed in the refrigerator overnight to yield pure dibromo diketone 92 as needles: mp 127-129°C.

92: ^1H NMR: δ 4.9 (dd, 1H, J=13, 6.4 Hz), 4.75 (dd, 1H, J=13.63, 6.13 Hz), 2.92 (dd, 1H, J=14.5, 4.5 Hz), 2.76 (t, 1H, J=13.35), 2.6 (d, 1H, J=10.14), 2.51 (dd, 1H, J=13.91, 6.18 Hz), 2.4 (m, 3H), 2.19 (t, 1H, J=13.78), 1.45 (s, 3H).

^{13}C NMR: δ 199 (C_2 or C_7), 198.76 (C_2 or C_7), 51.92 (C_3 or C_6), 51.38 (C_3 or C_6), 50.24 (C_1 or C_8), 45.46 (C_{8a}), 43.74 (C_1 or C_8), 42.71 (C_4 or C_5), 38.53 (C_4 or C_5), 25.82 (C_{4a}), 25.56 (CH_3).

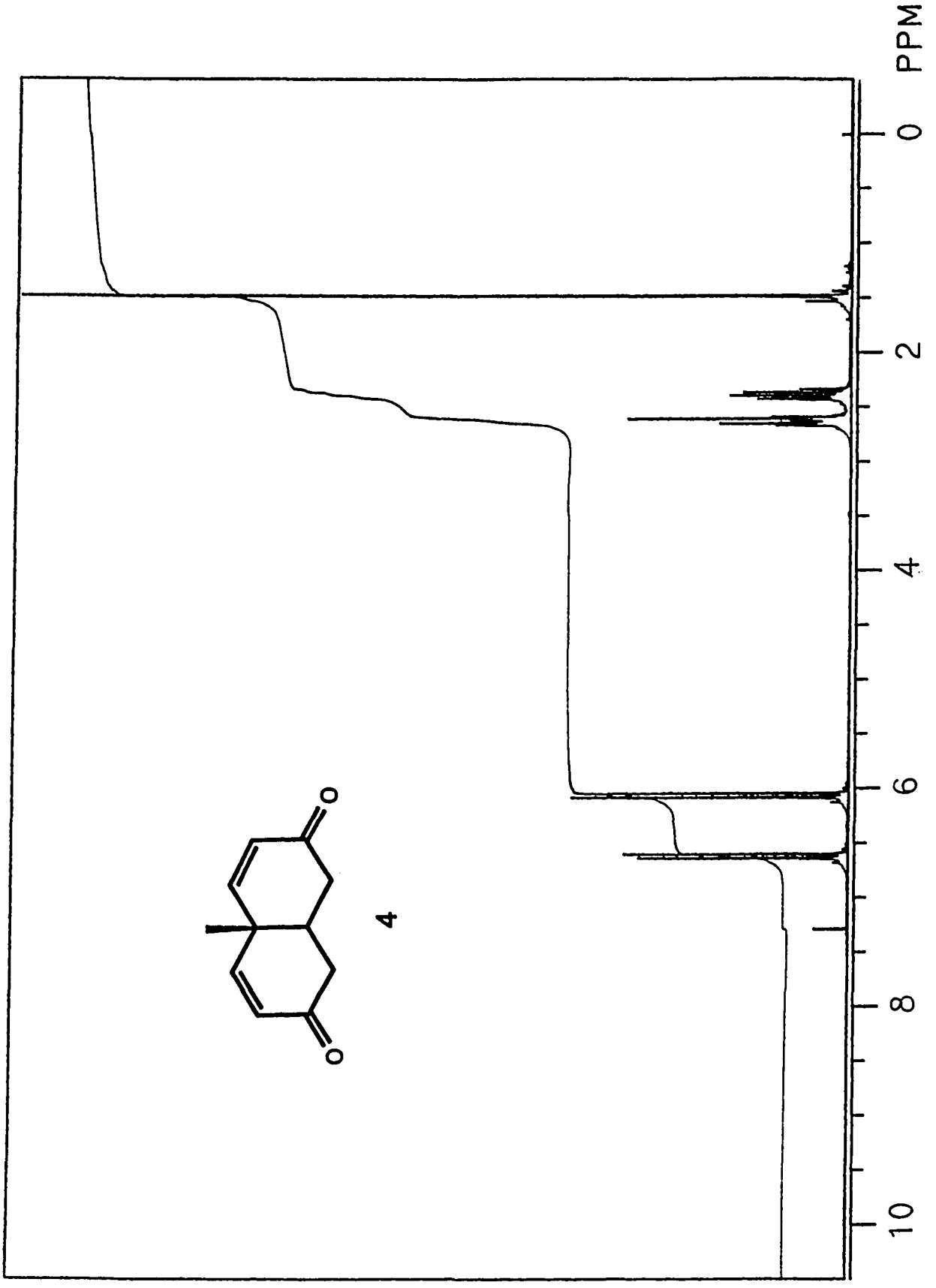
1-bromo-5-methyl-tricyclo-[4.4.0.0^{1,7}]-decane-2,8-dione 93.

To a solution of dibromide 92 (0.13 g, 0.385 mmol) dissolved in dry THF (10 mL) under N_2 was added DBU (0.15 mL) and the mixture was stirred at 50°C overnight. The reaction was quenched with HCl (10%) and diluted with ether (2 x 20 mL). The organic layer was washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography (15% ethyl acetate in hexane) afforded 93 (47 mg, 48%) as white crystals.

93: ^{1}H NMR: δ 2.82 (s, 1H), 2.66 (m, 2H), 2.48 (m, 3H), 2.26 (dd, 1H, J=18.77, 5.2 Hz), 1.8 (m, 3H), 1.25 (s, 3H).

^{13}C NMR: δ 205.7 (C_2), 202.28 (C_8), 66.6 (C_1), 64.85 (C_7), 46.41 (C_4), 42.7 (C_3), 41.21 (C_5), 37.75 (C_9), 37.04 (C_6), 36.76 (C_{10}), 22.79 (CH_3).

^{1}H NMR Spectra of selected compounds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O
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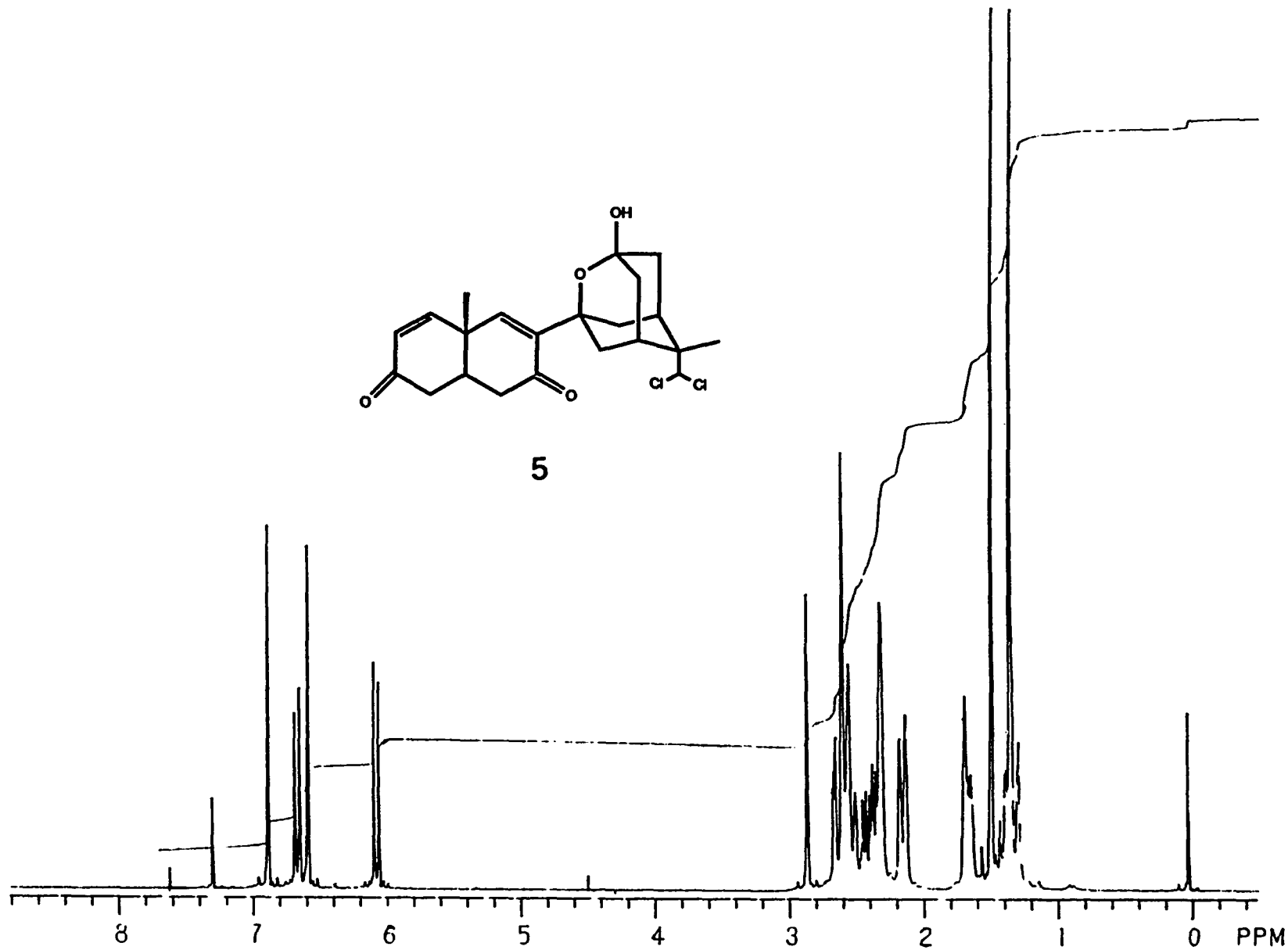
4



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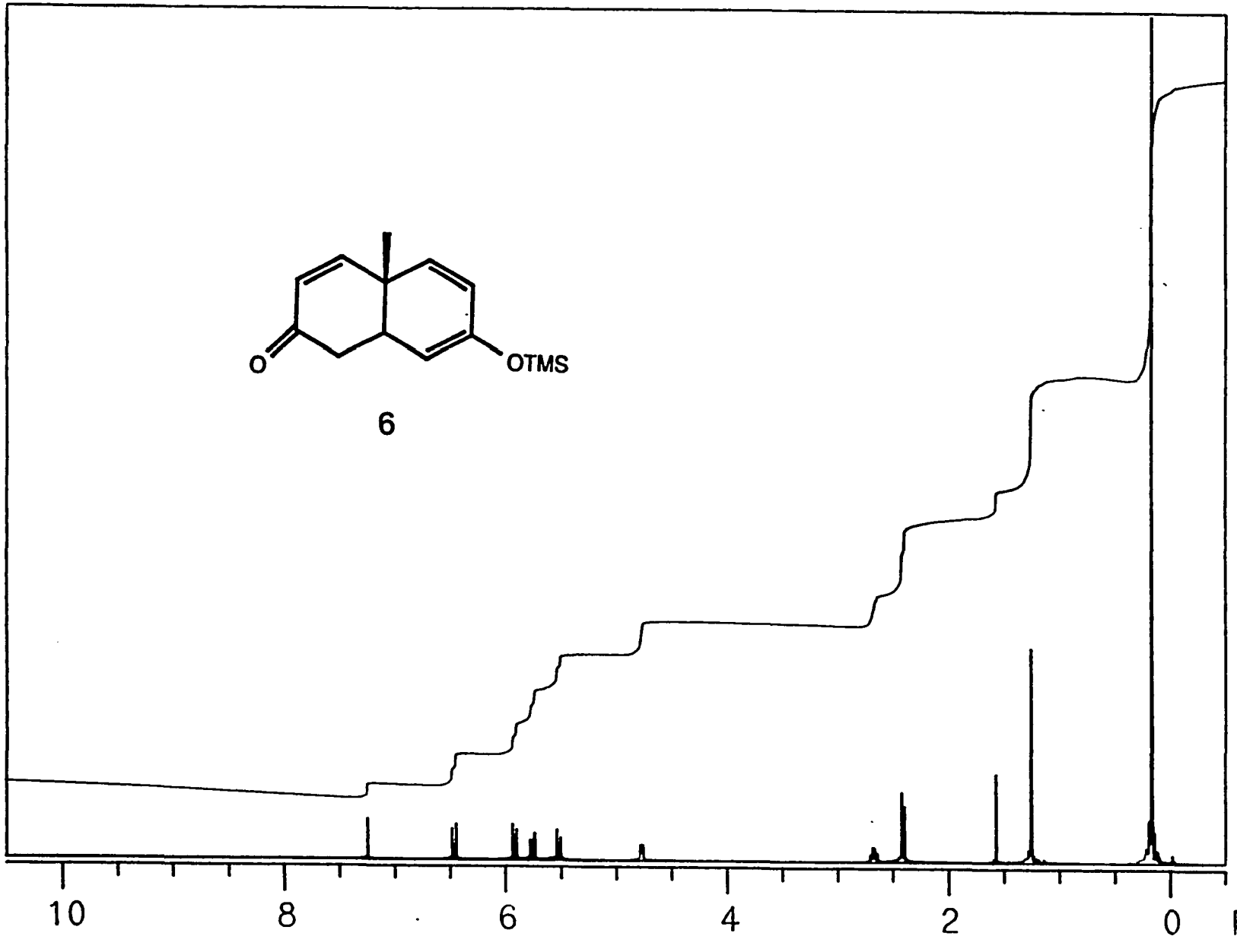

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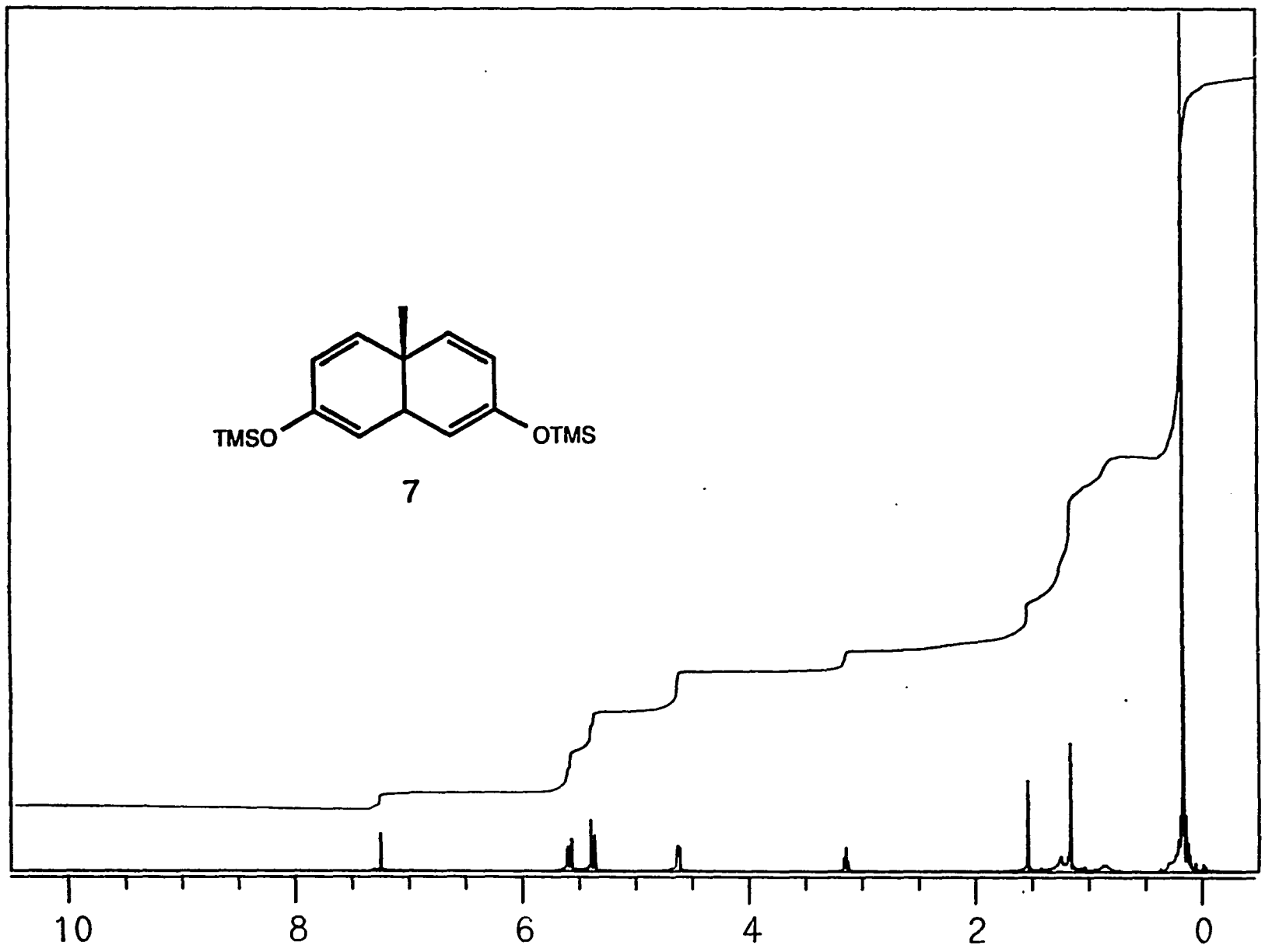
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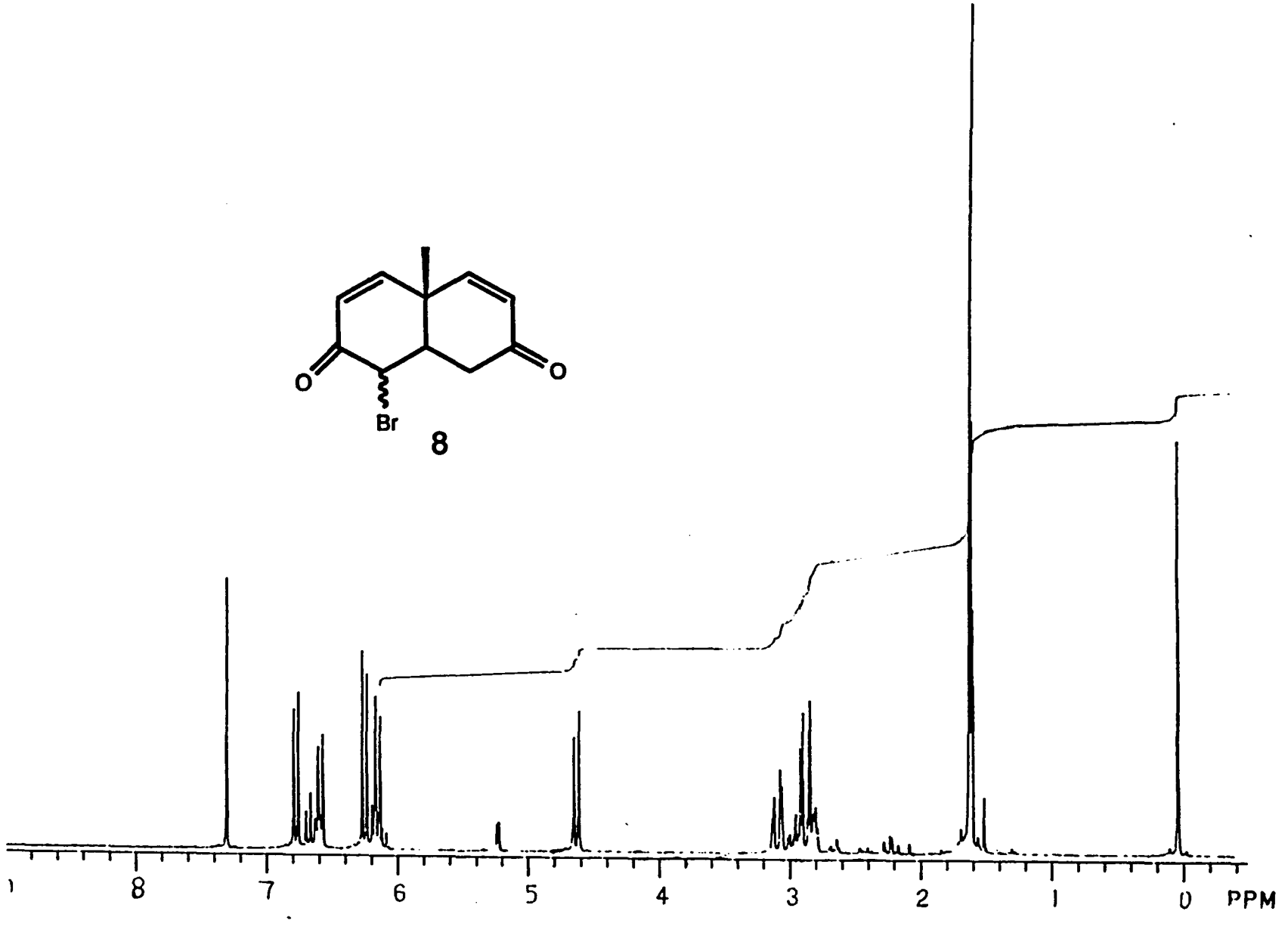
6
4
2
0
PPM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Br
8
8
7
6
5
4
3
2
1
0
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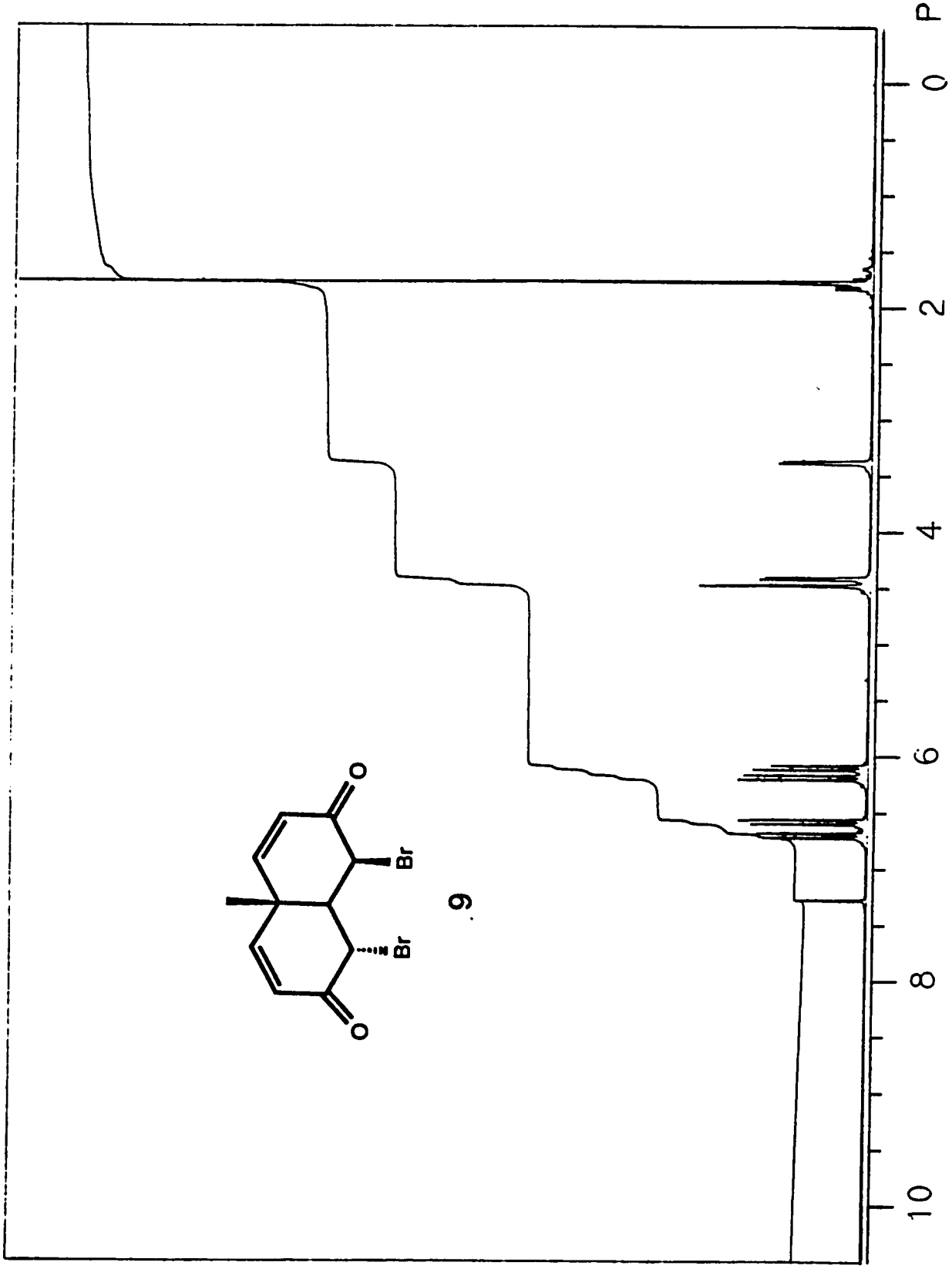

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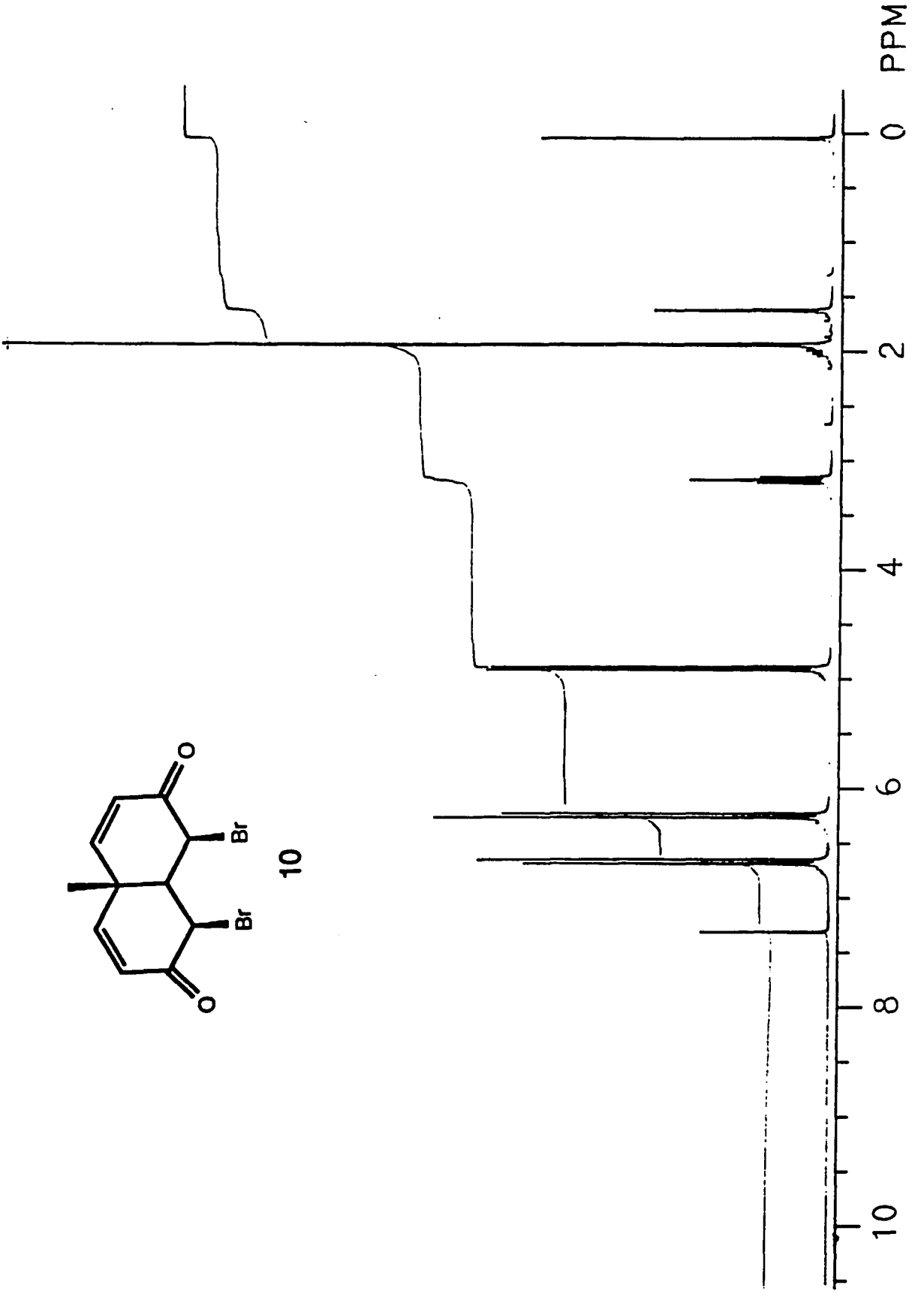

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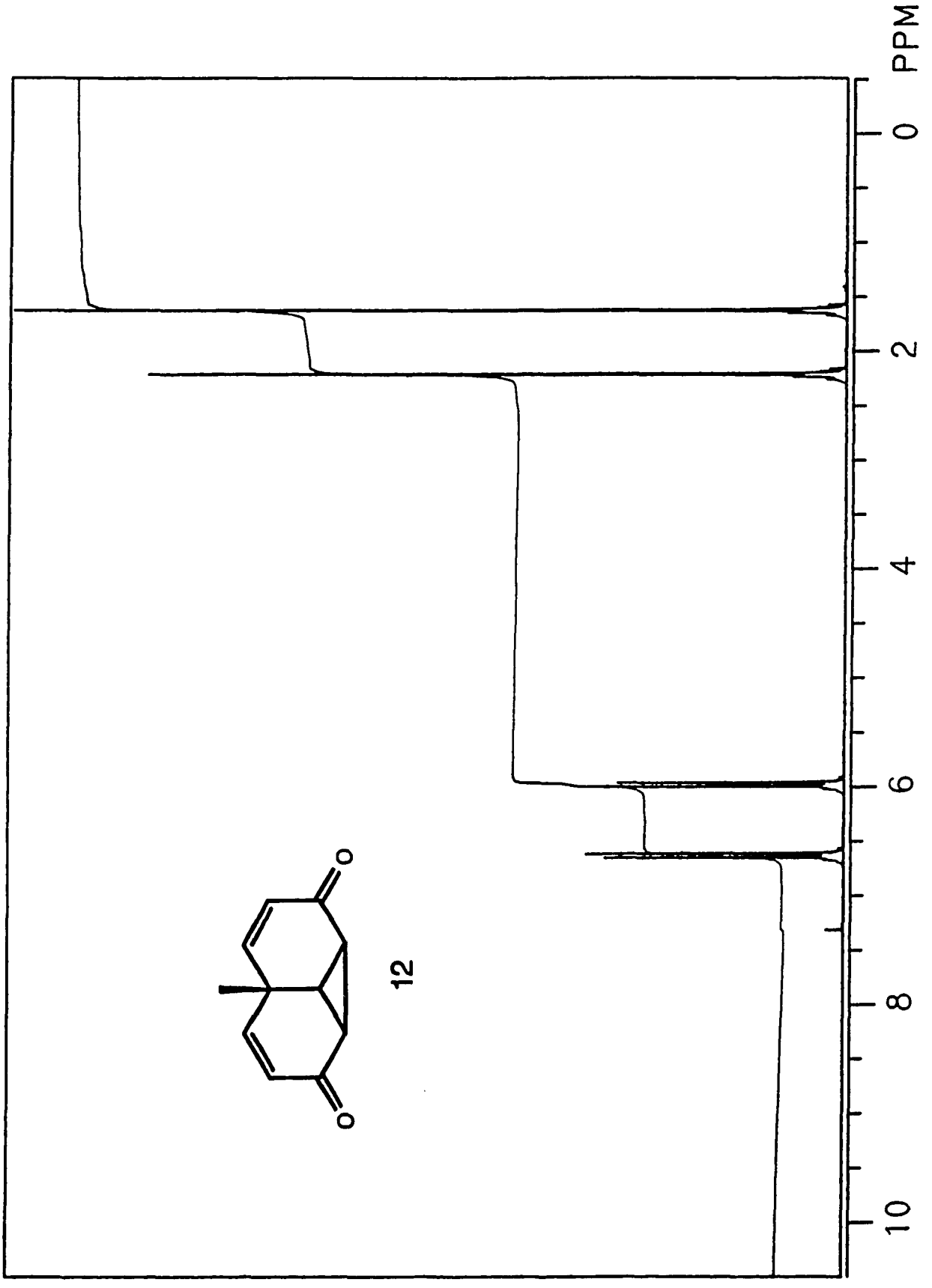
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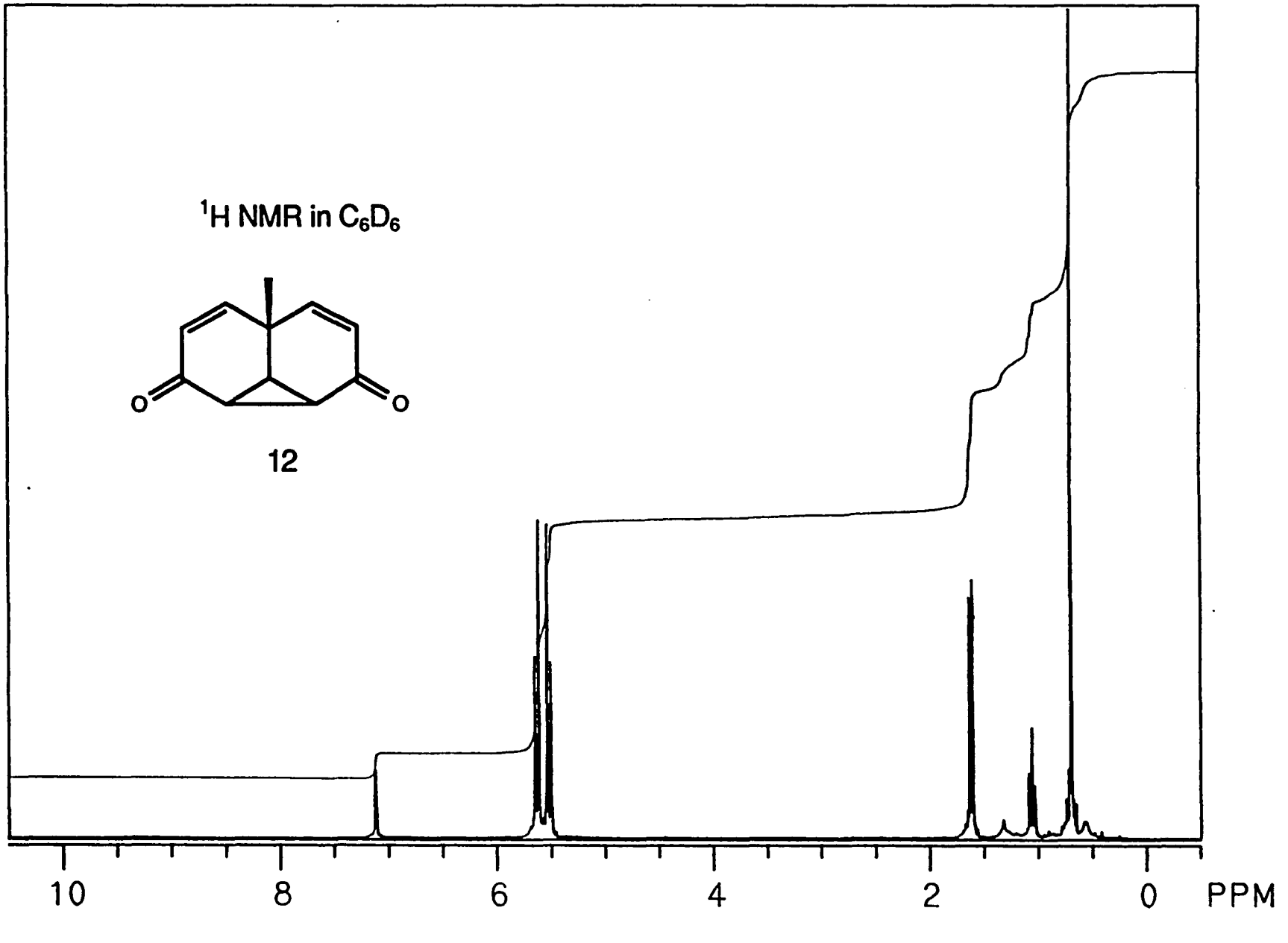
0
2
4
6
8
10
O
O
12


^{1}H NMR in C_6D_6
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O
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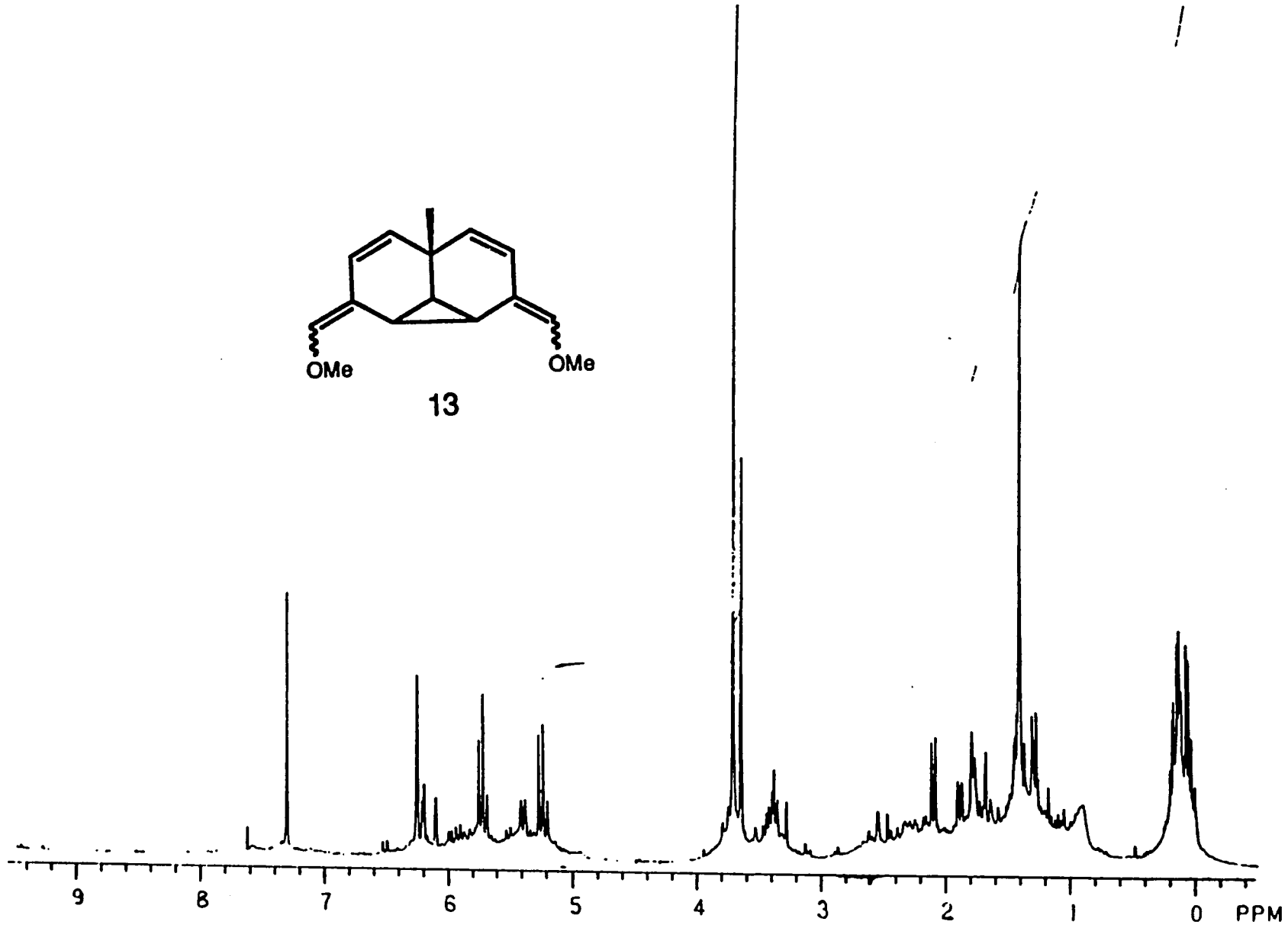
10
8
6
4
2
0
PPM



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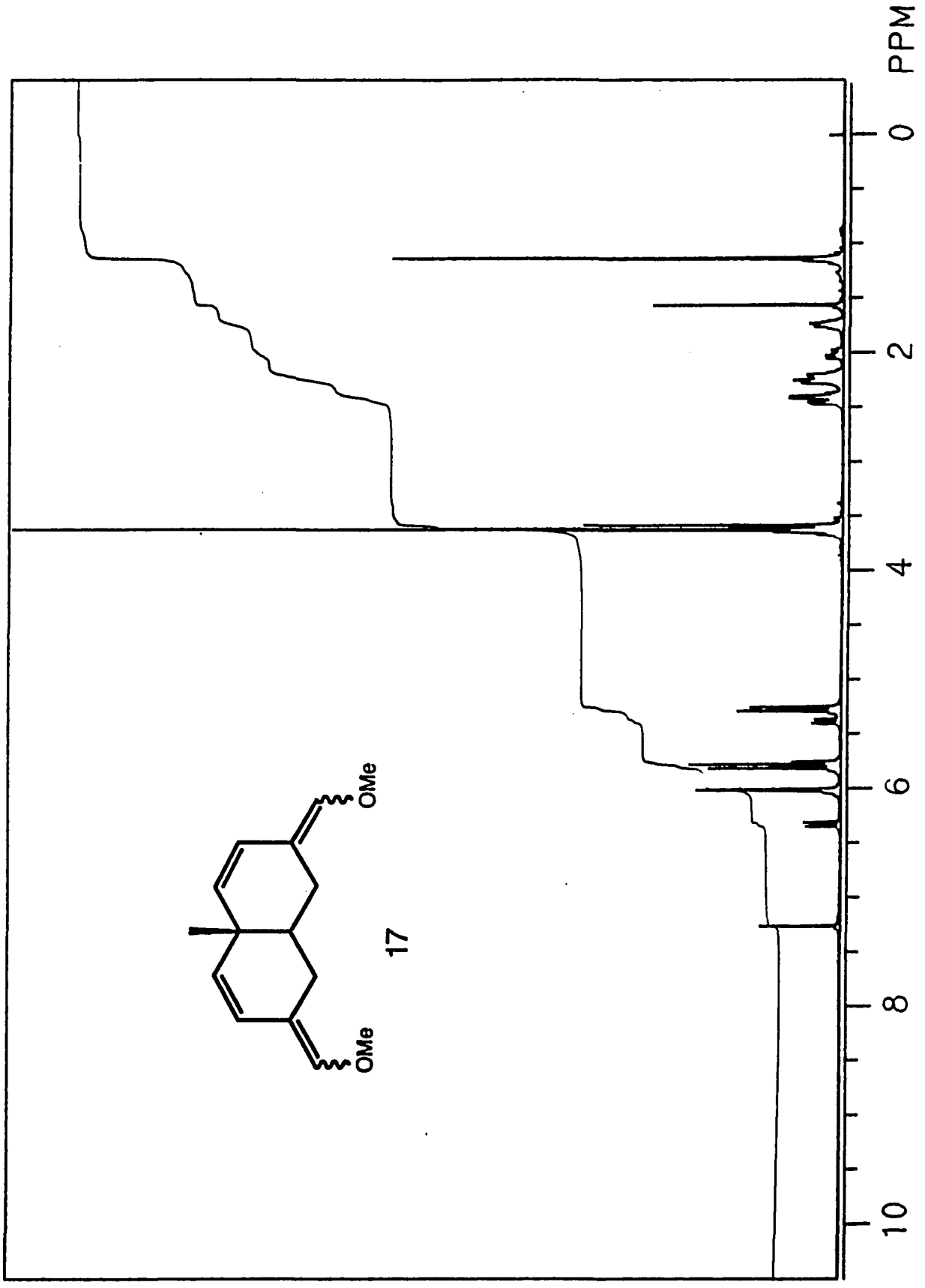
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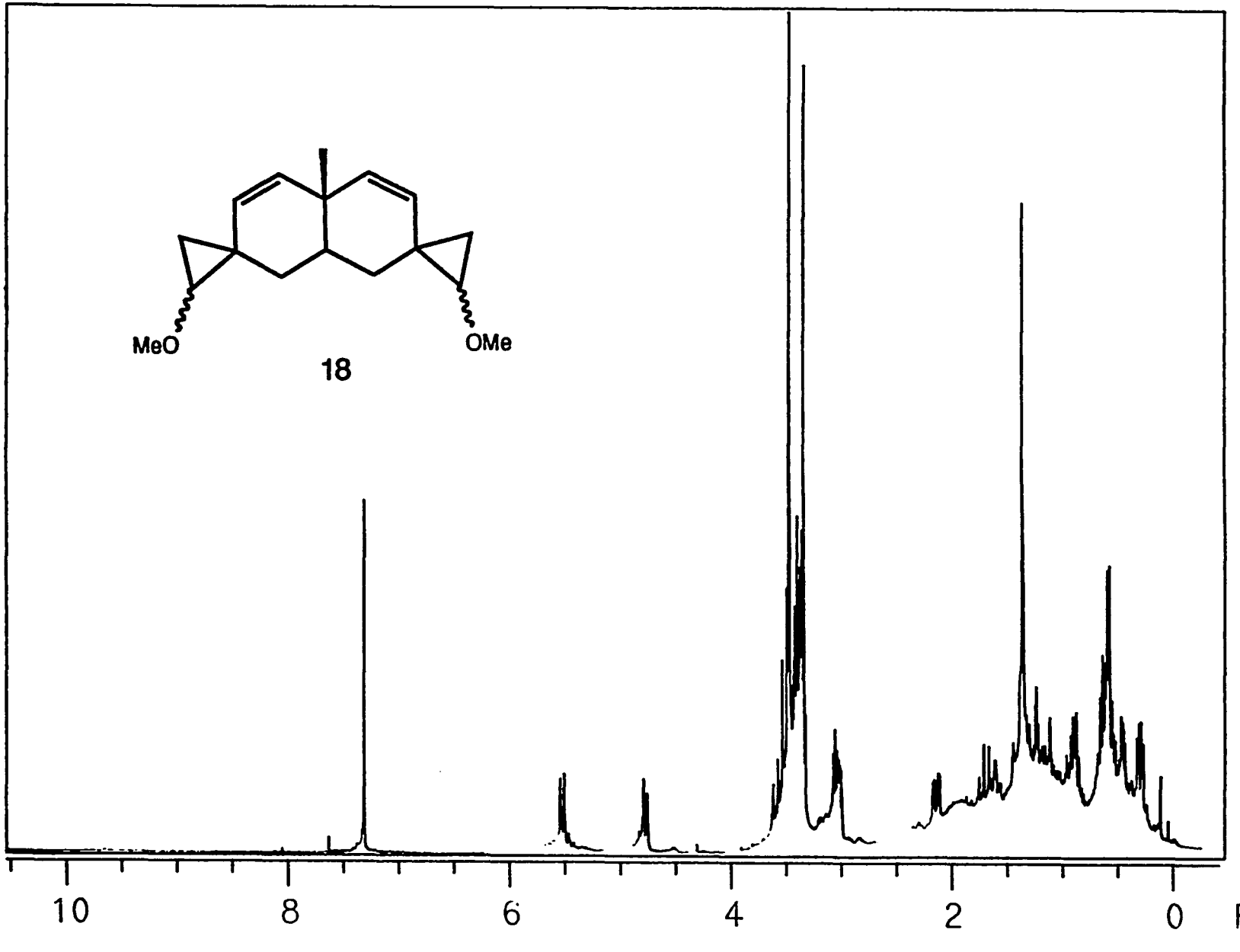
0
2
4
6
8
10
OMe
OMe
17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OMe
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10
8
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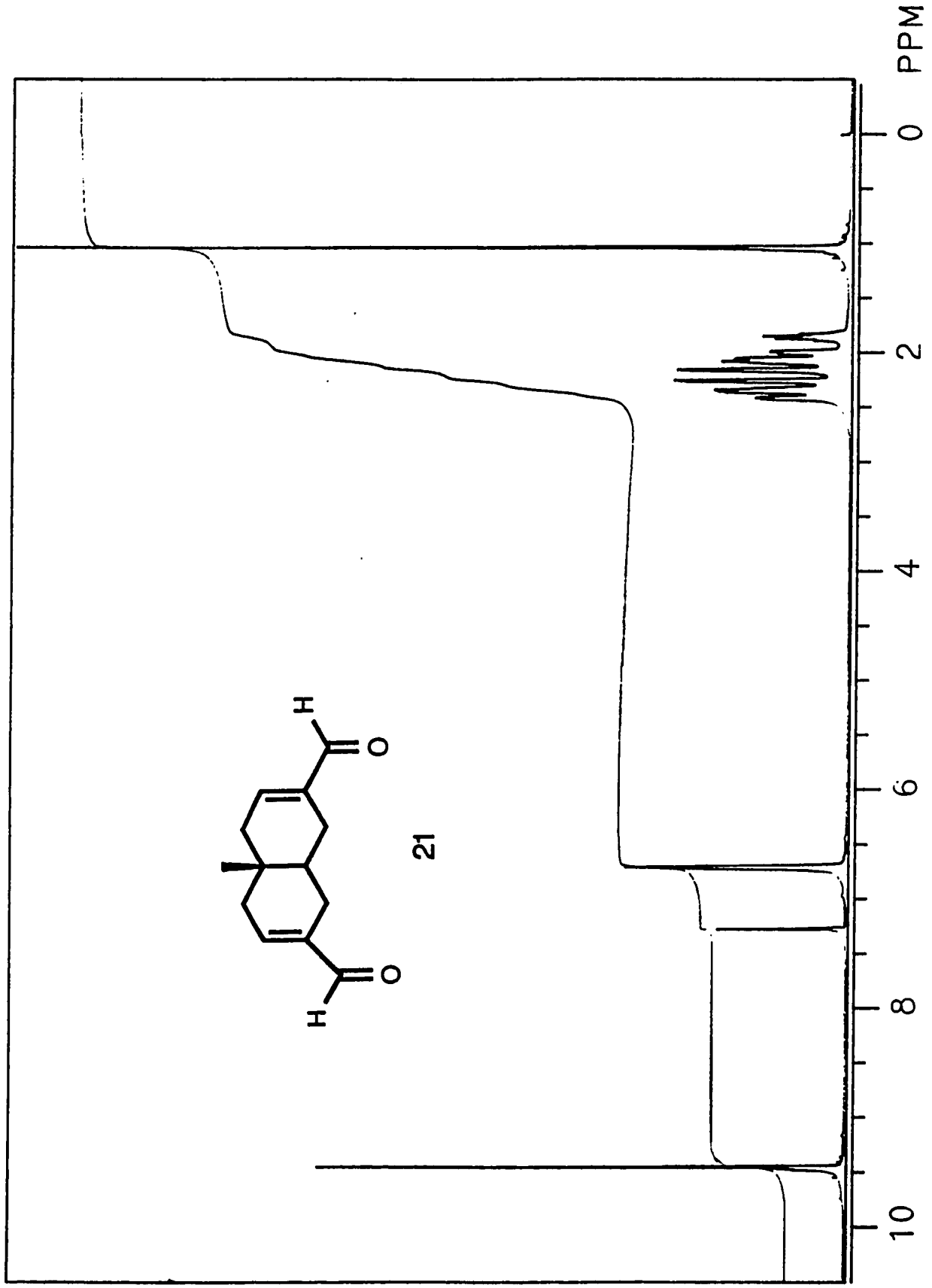
4
2
0
PPM



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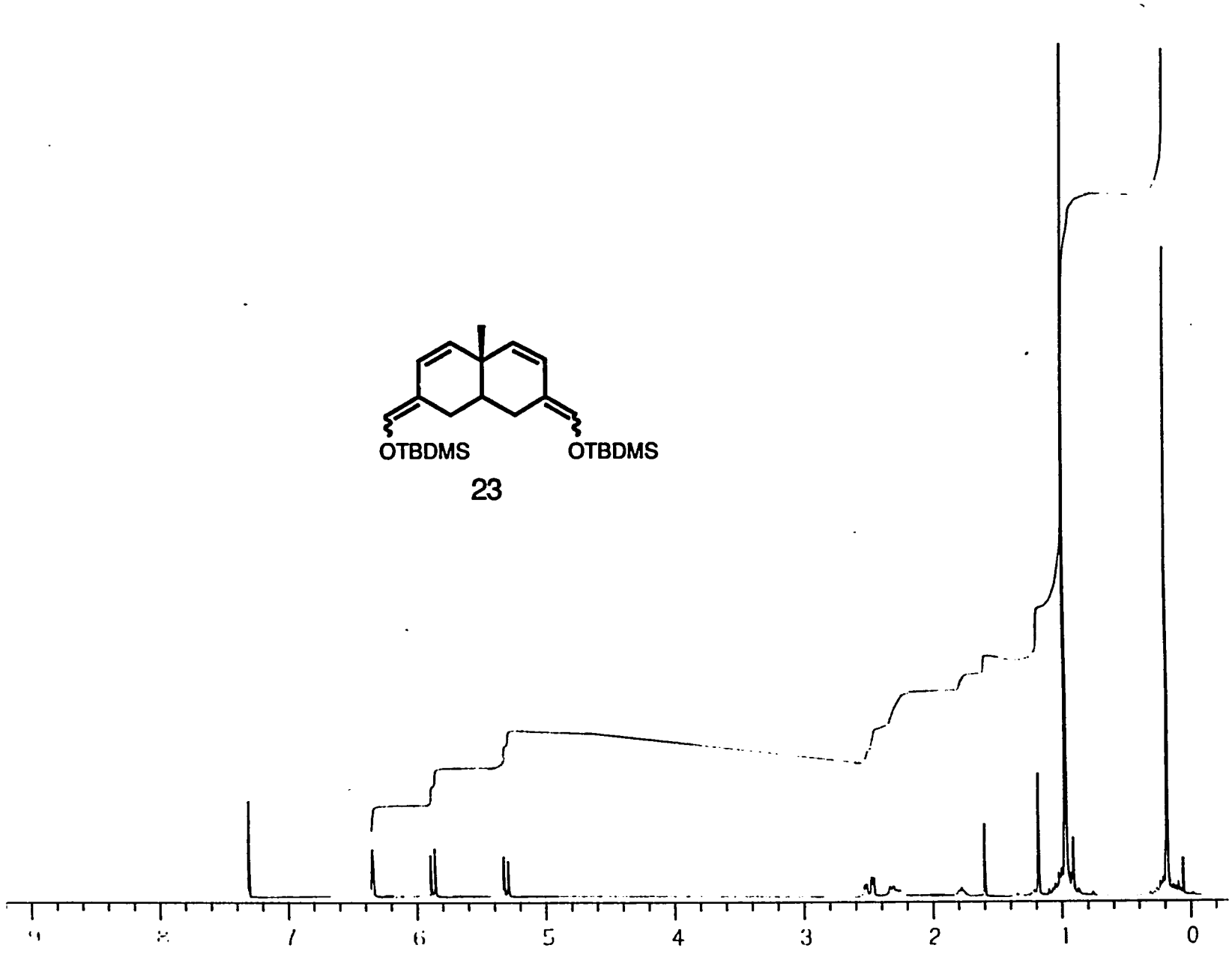
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OTBDMS
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6
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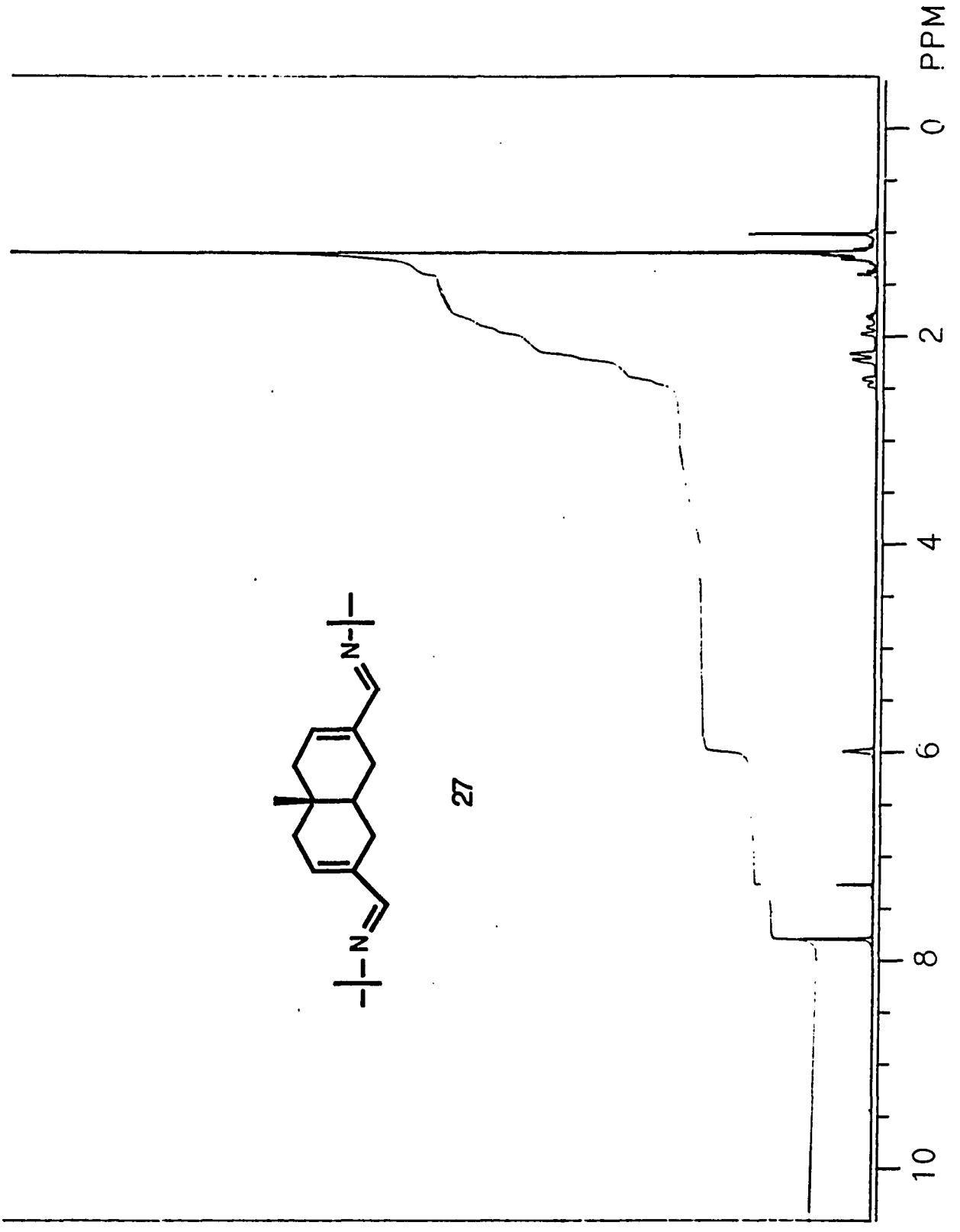
4
3
2
1
0



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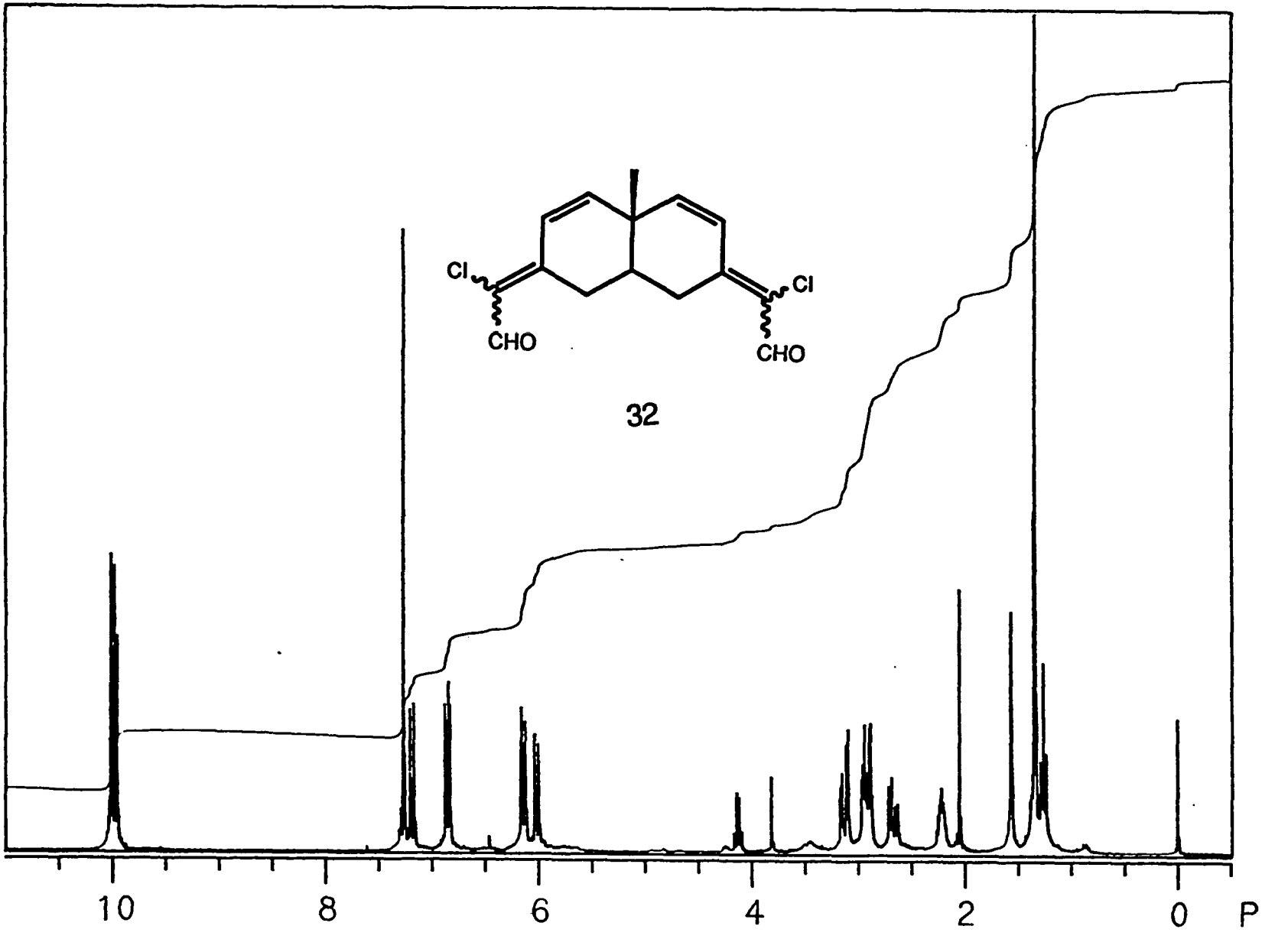
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Cl
CHO
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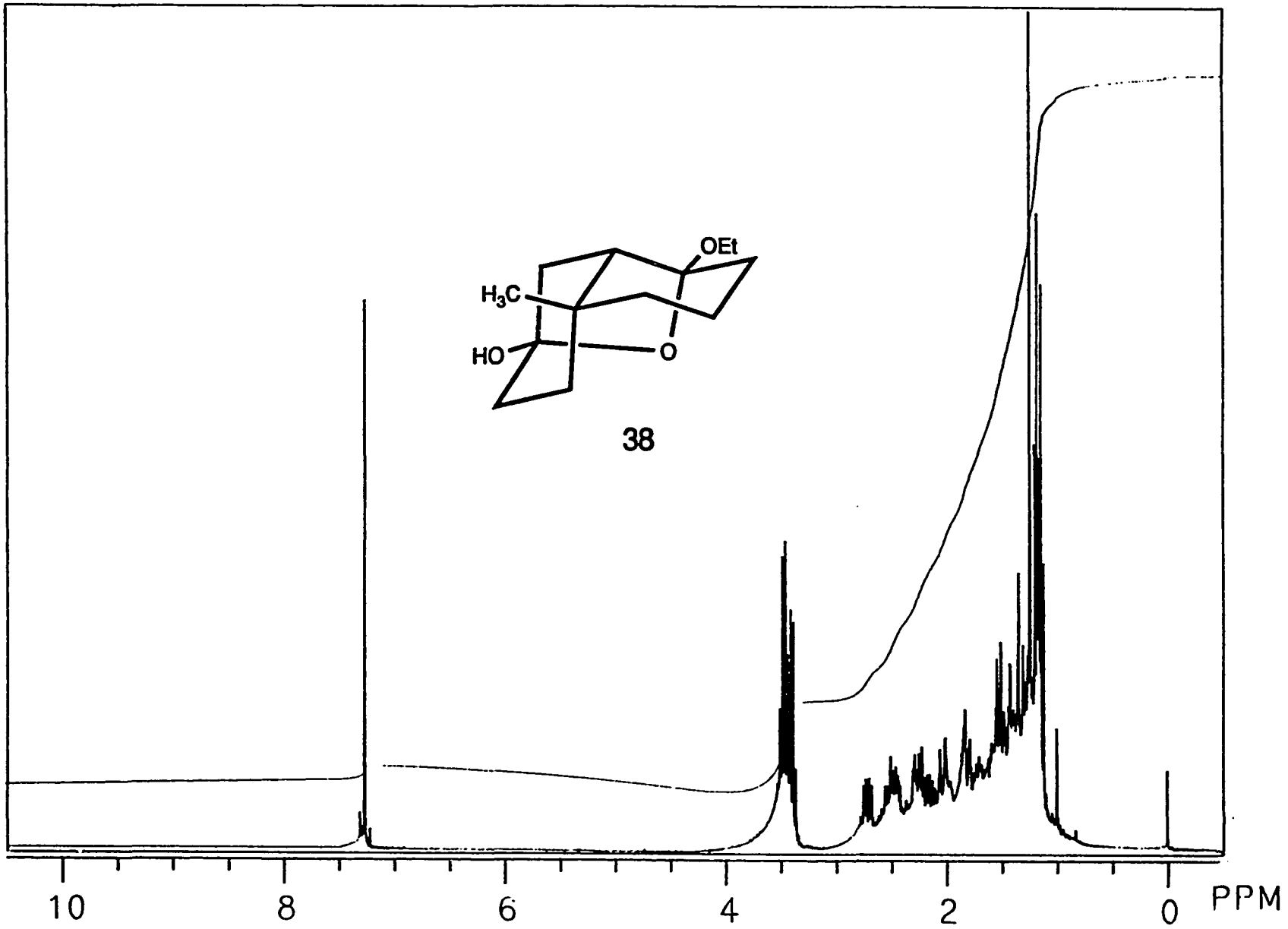
PPM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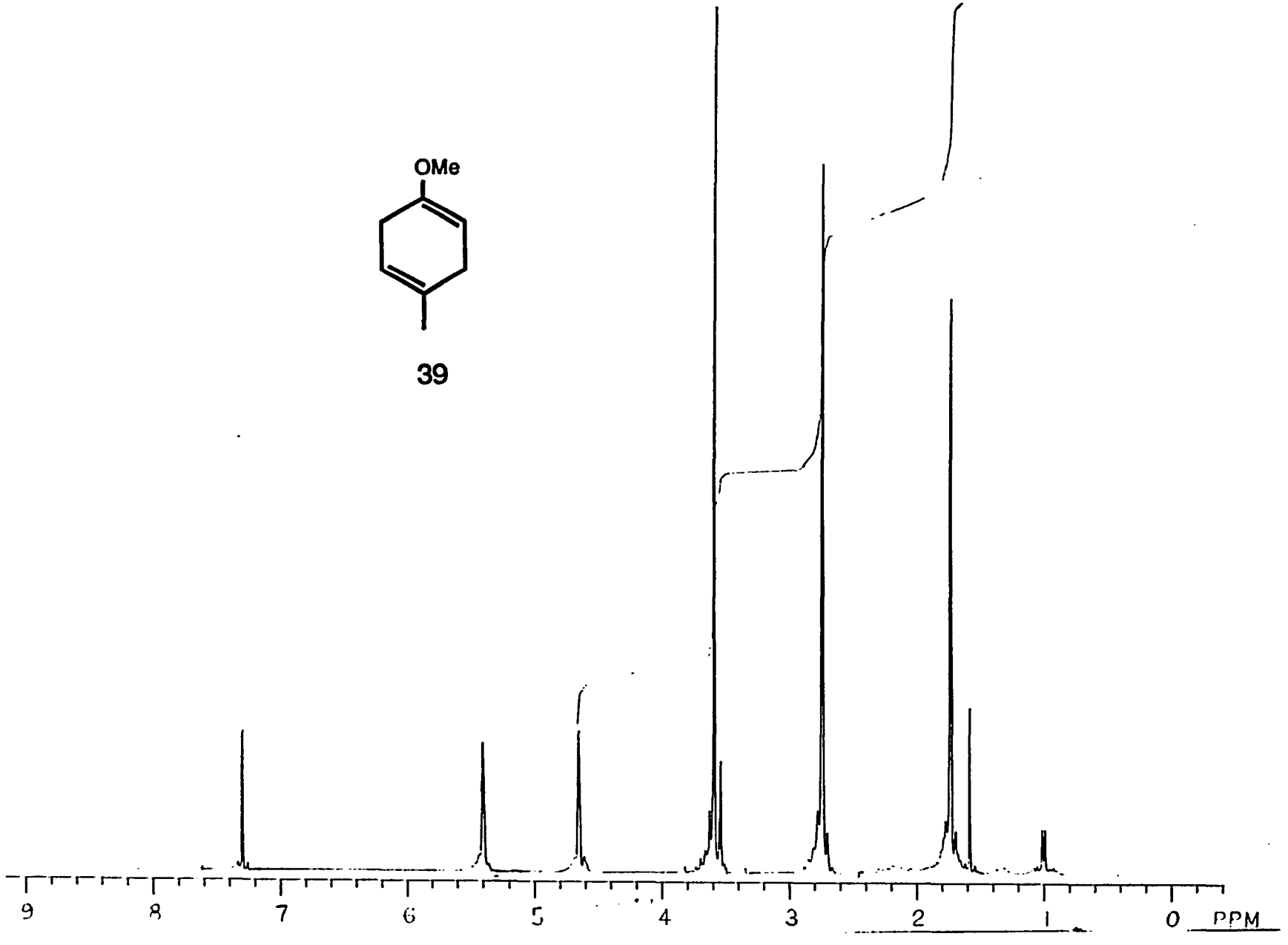

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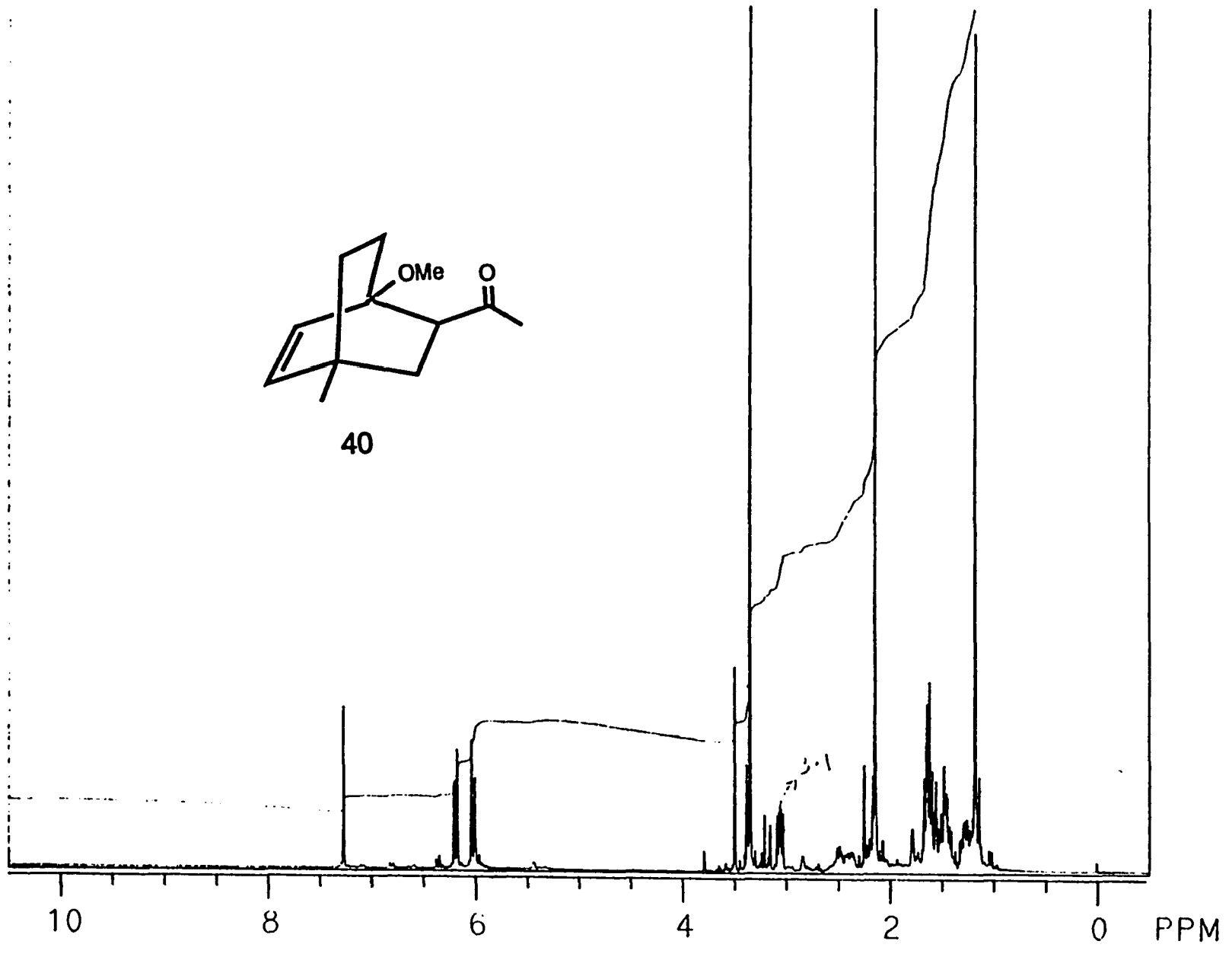
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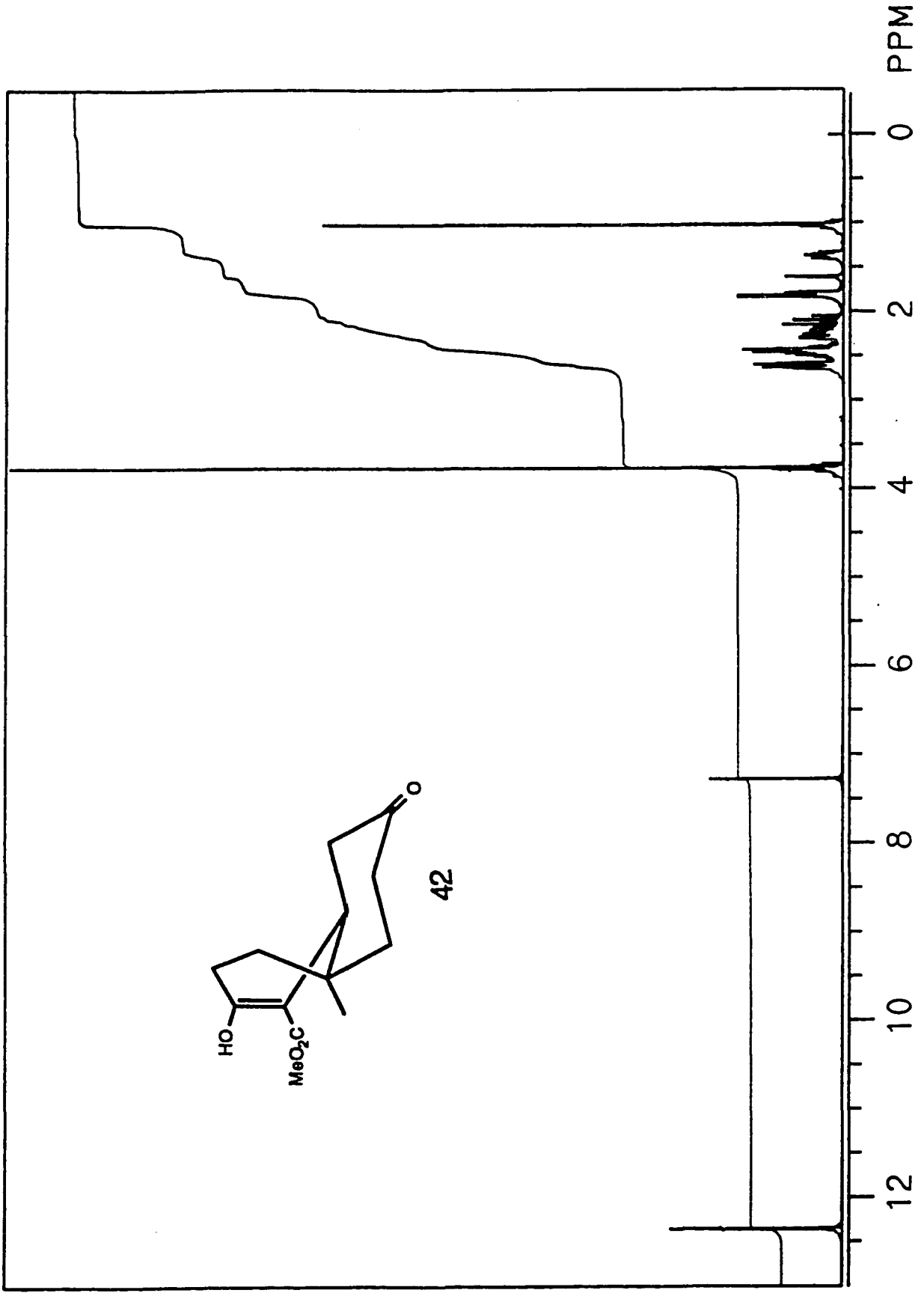
PPM



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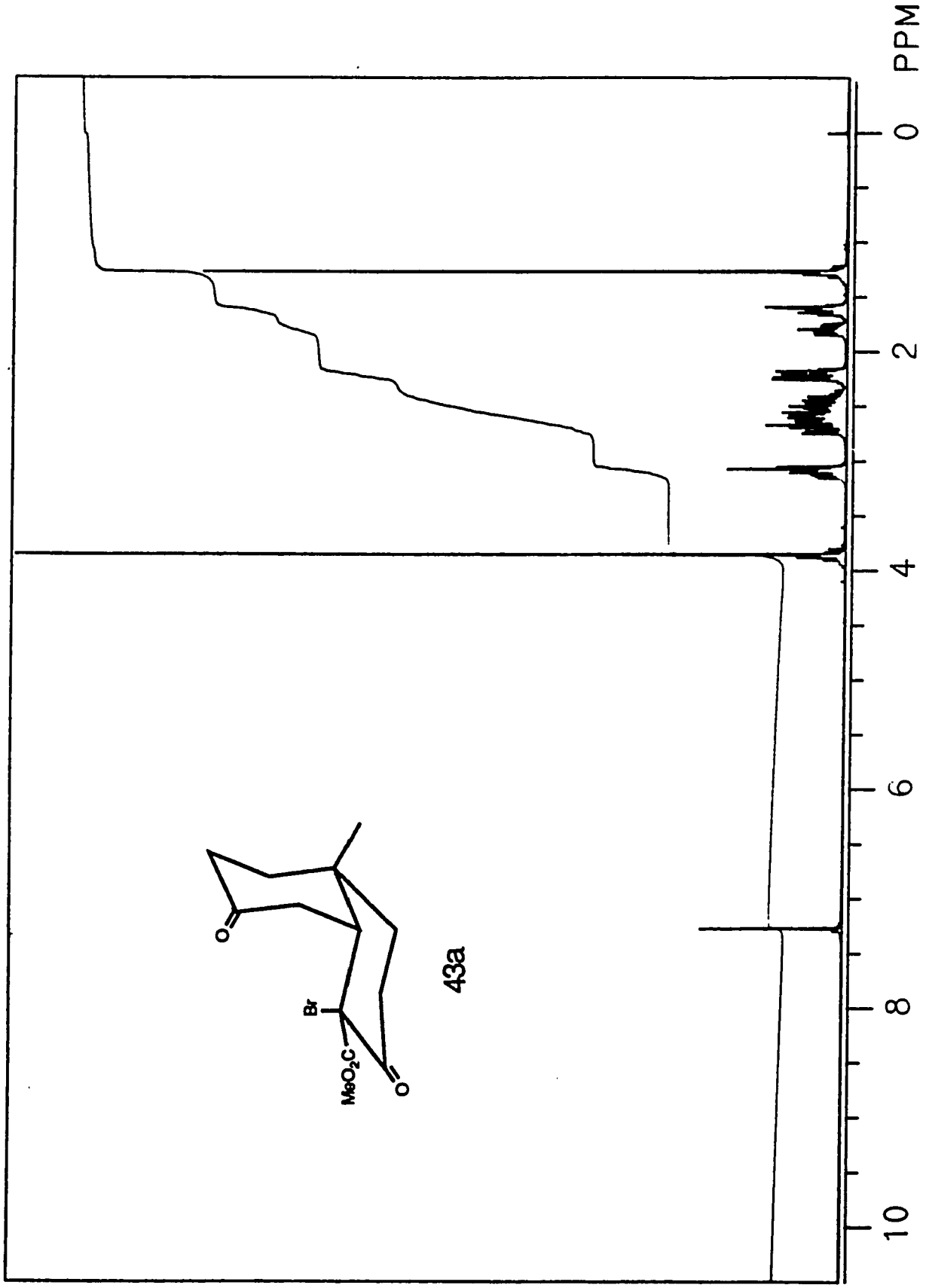
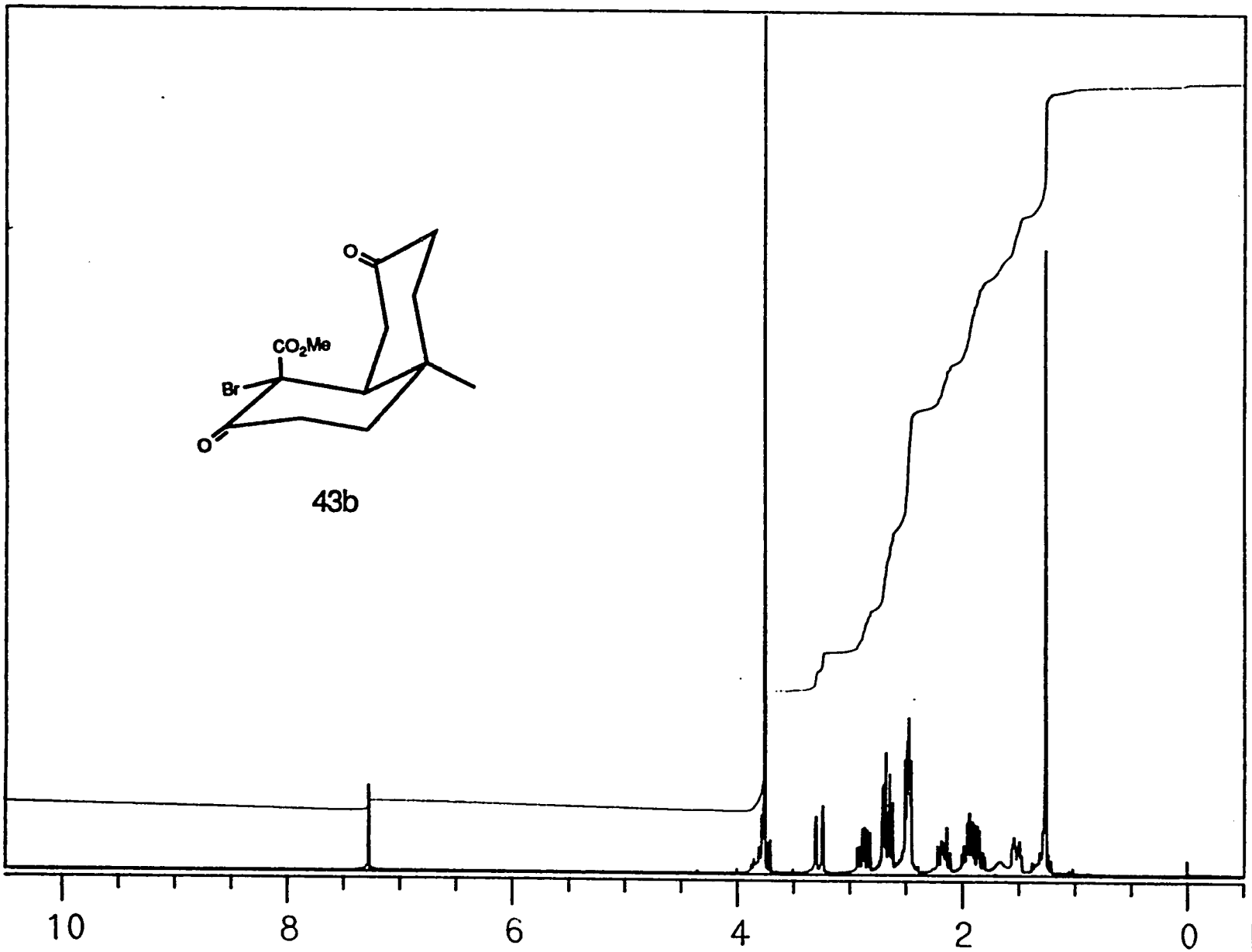


43a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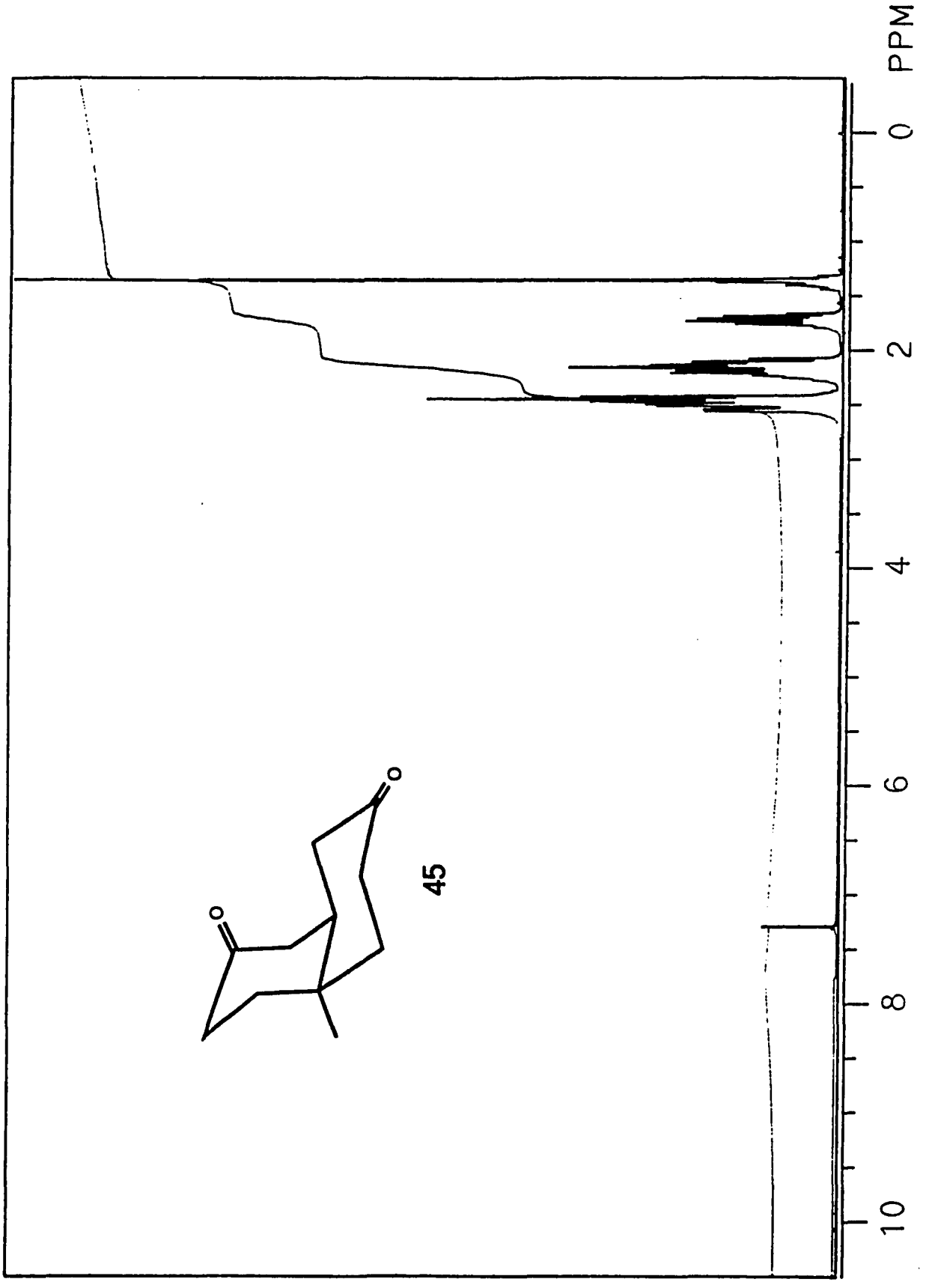
CO2Me
Br
O
43b
10
8
6
4
2
0
PPM


PPM
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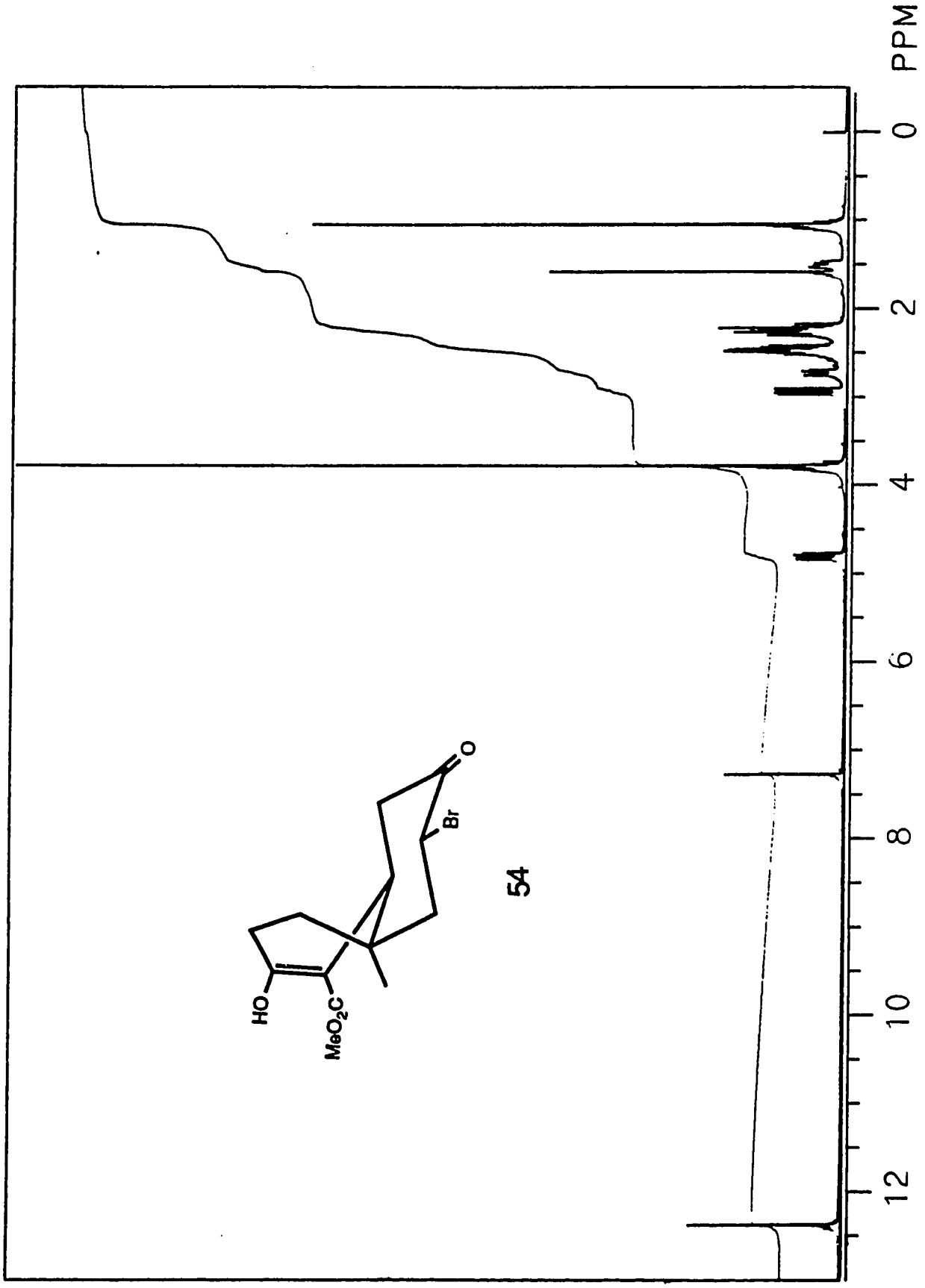
2
4
6
8
10
45



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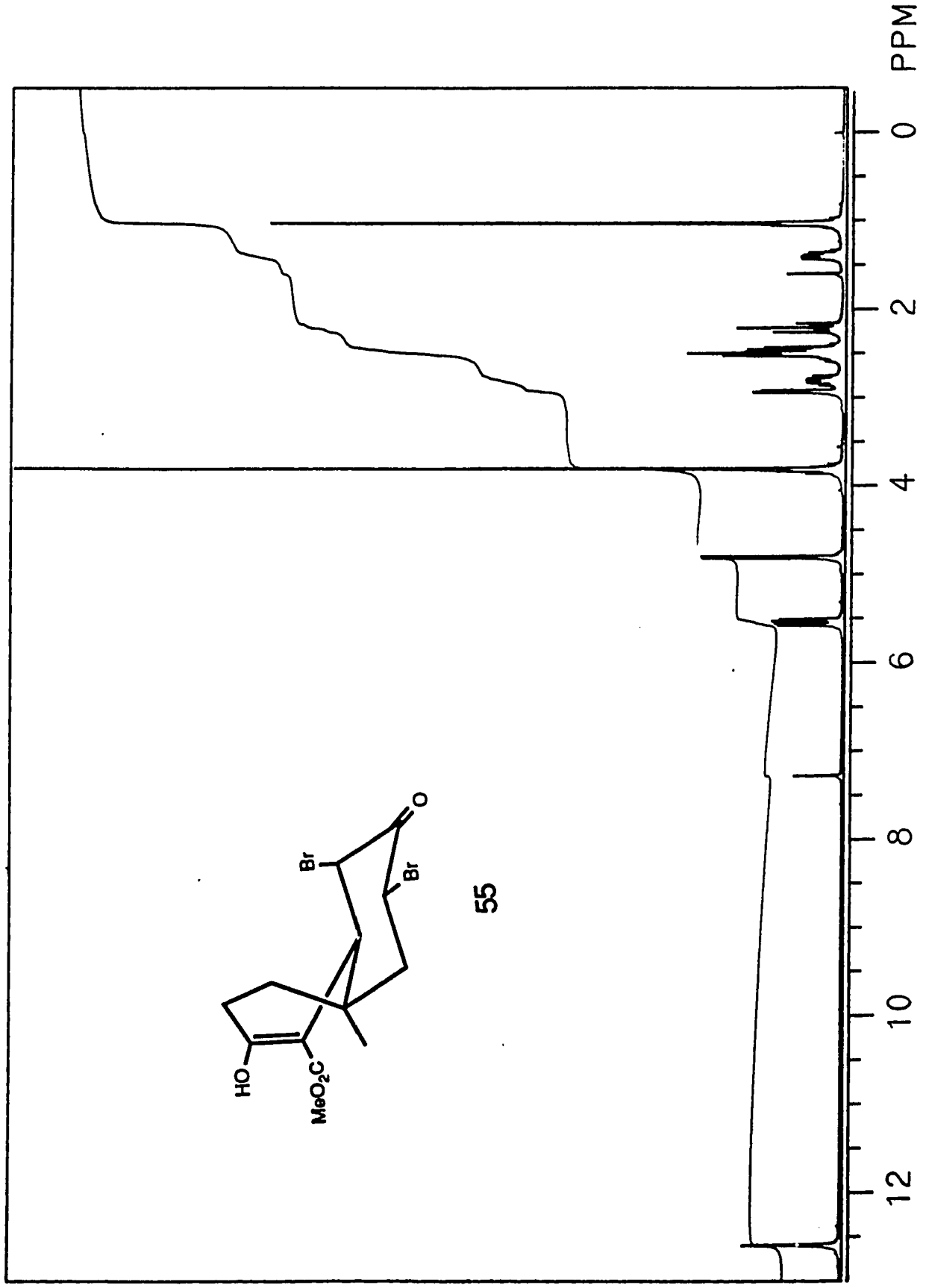

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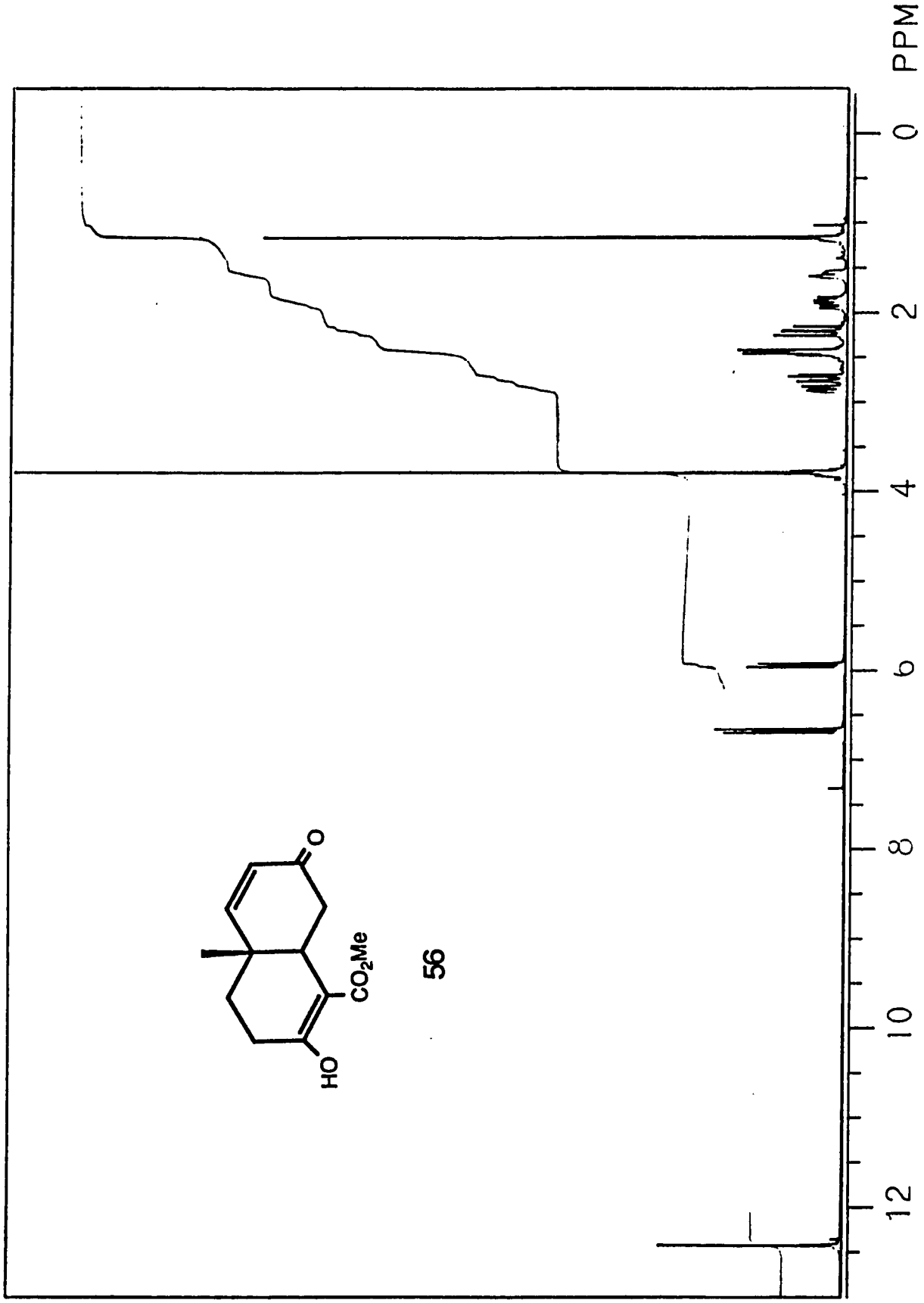

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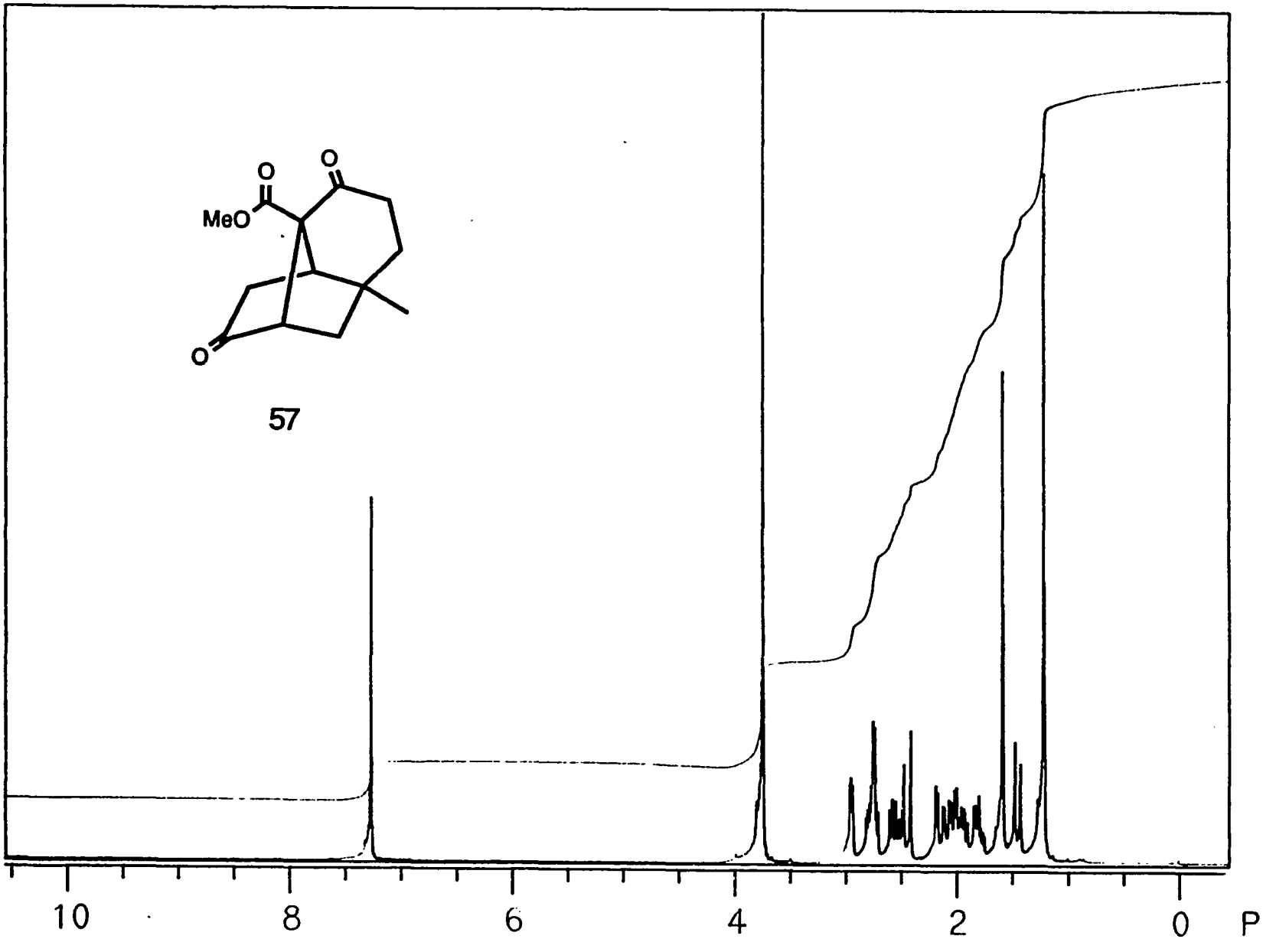

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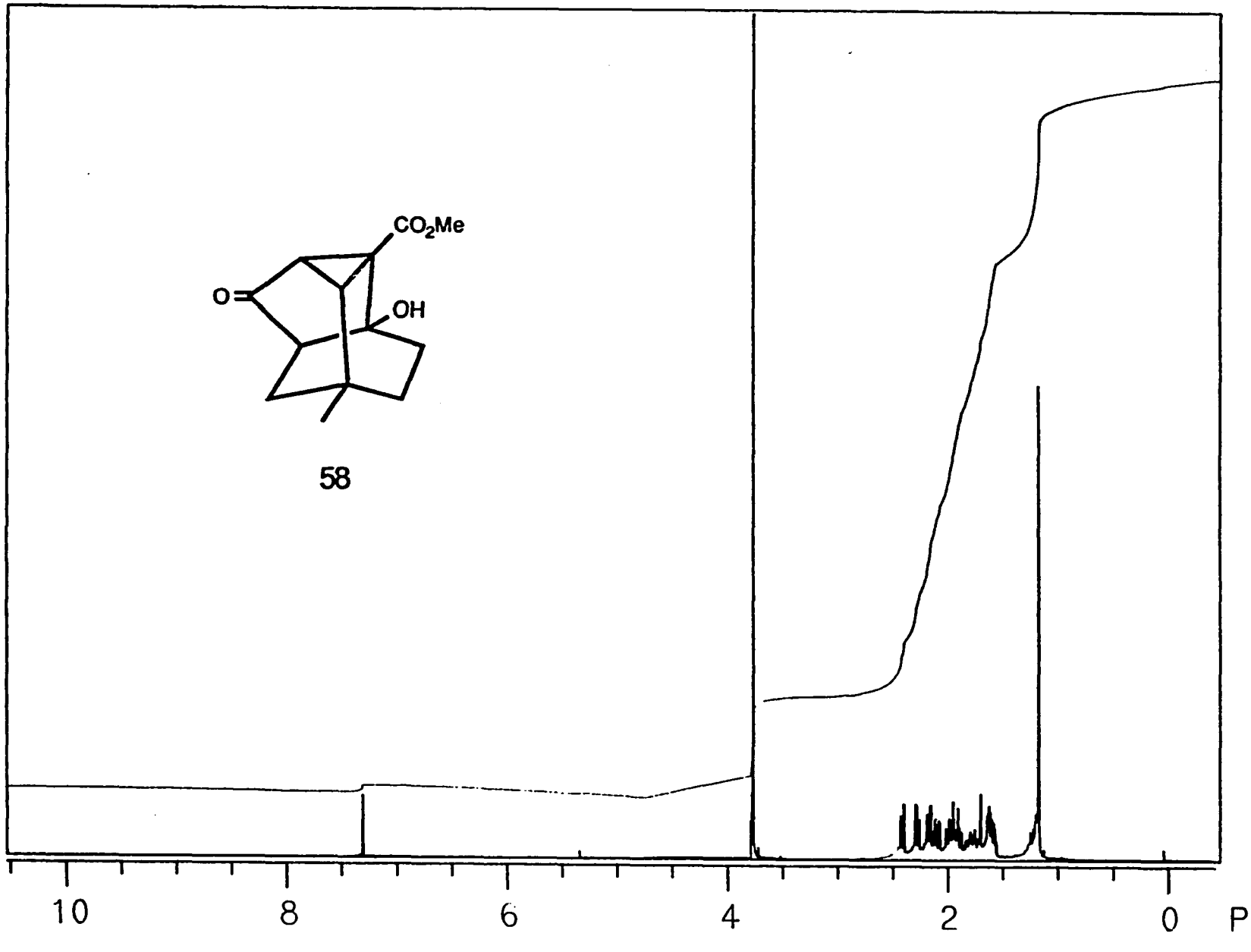

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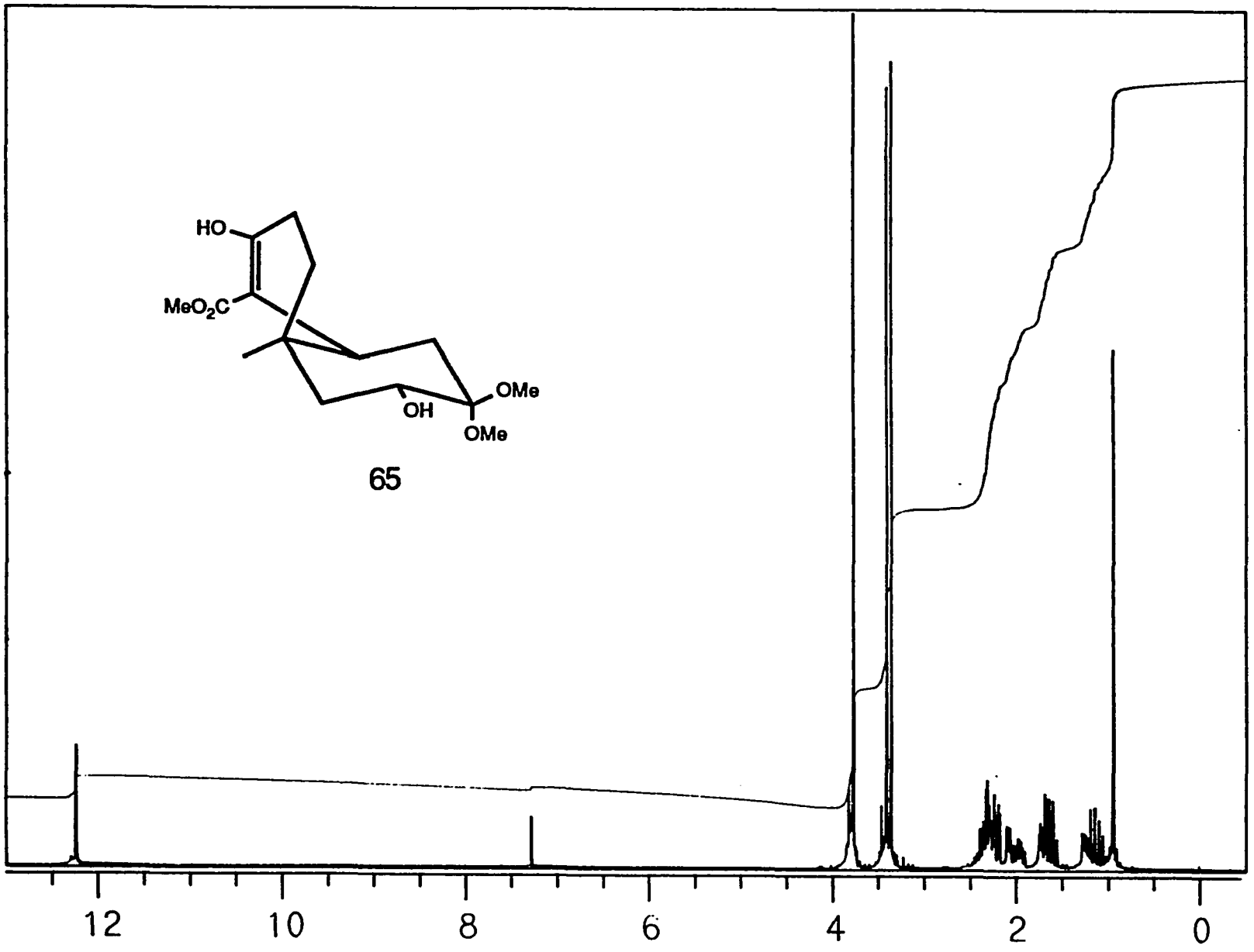

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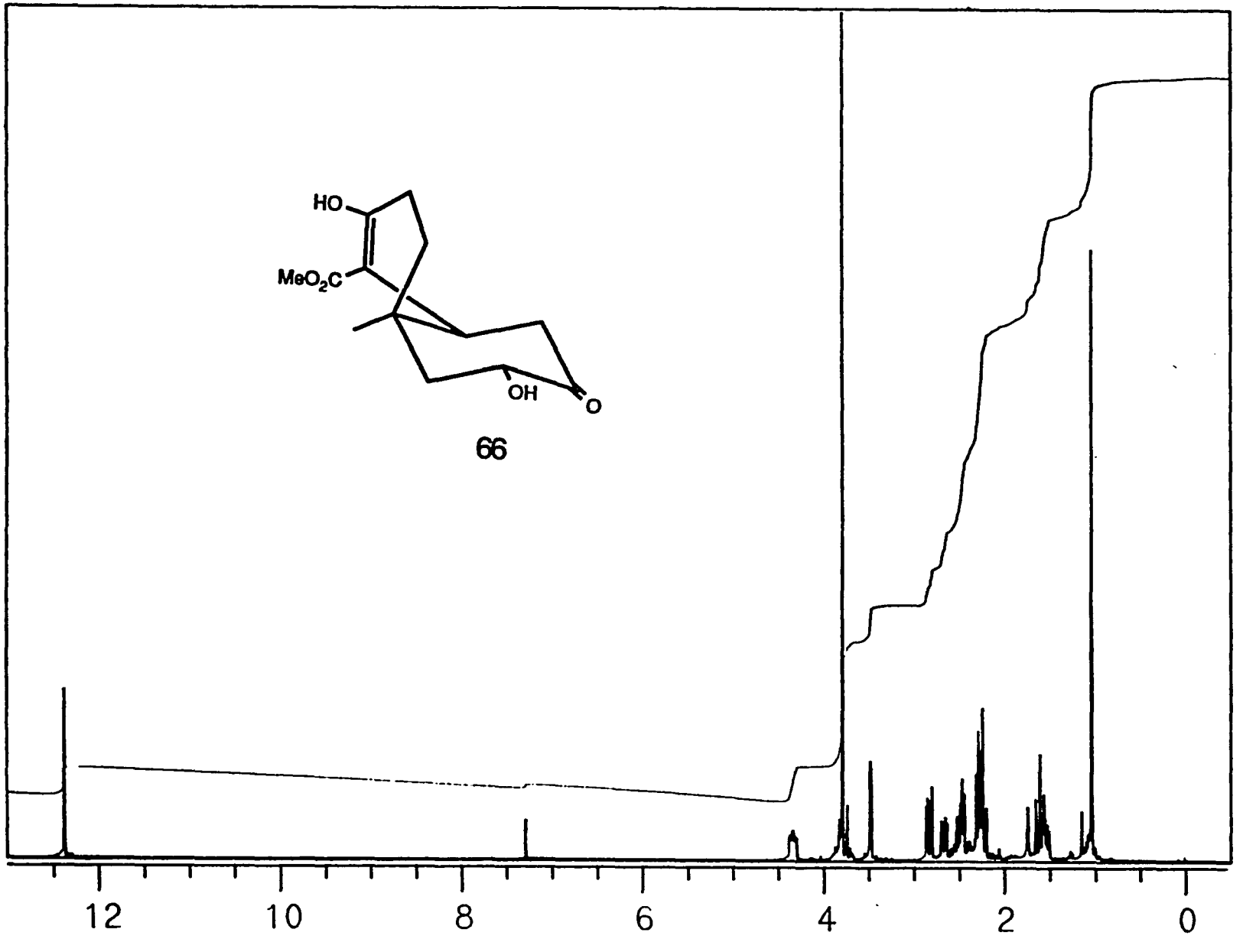
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OH
O
66
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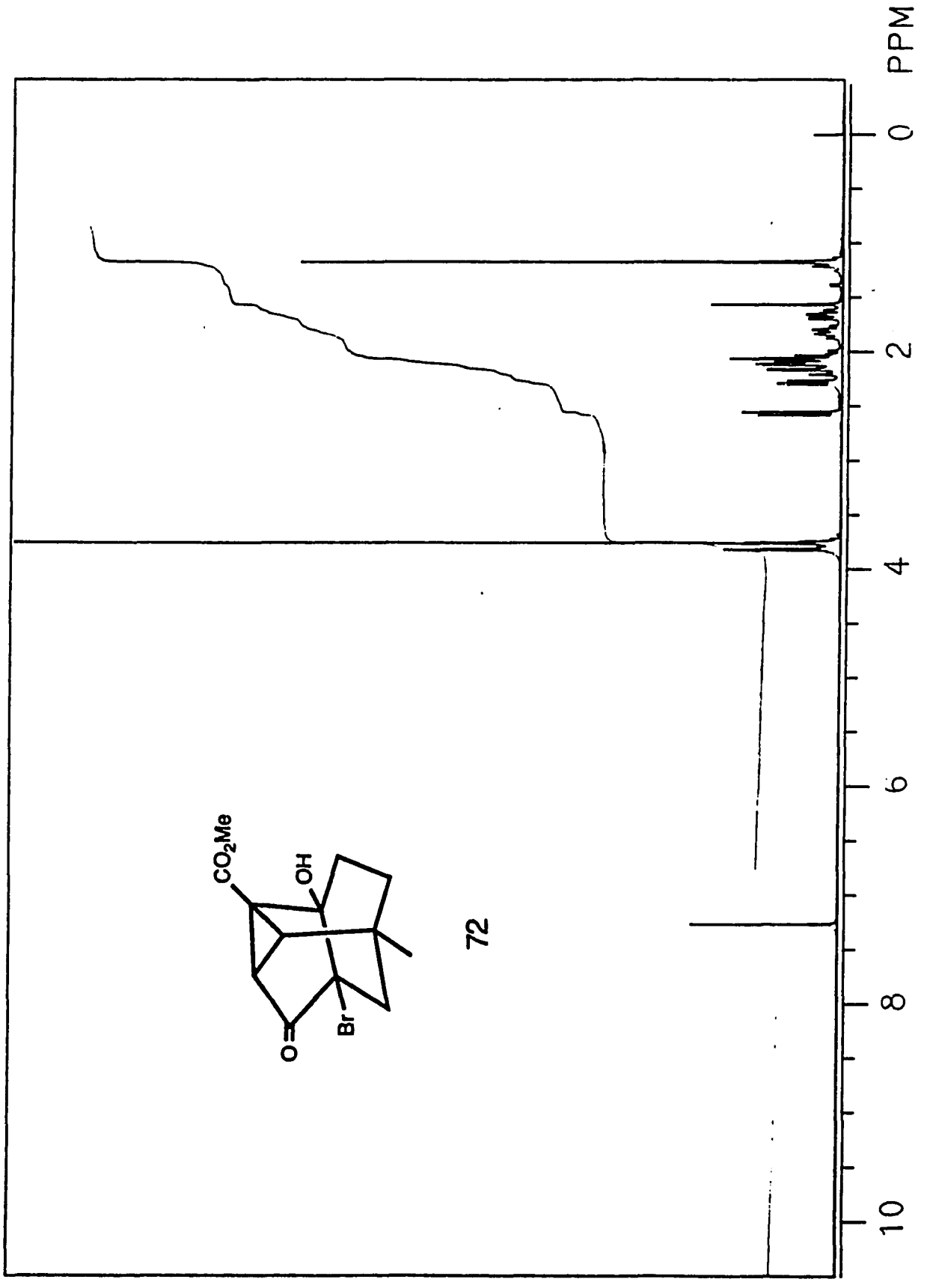
10
8
6
4
2
0
PPM



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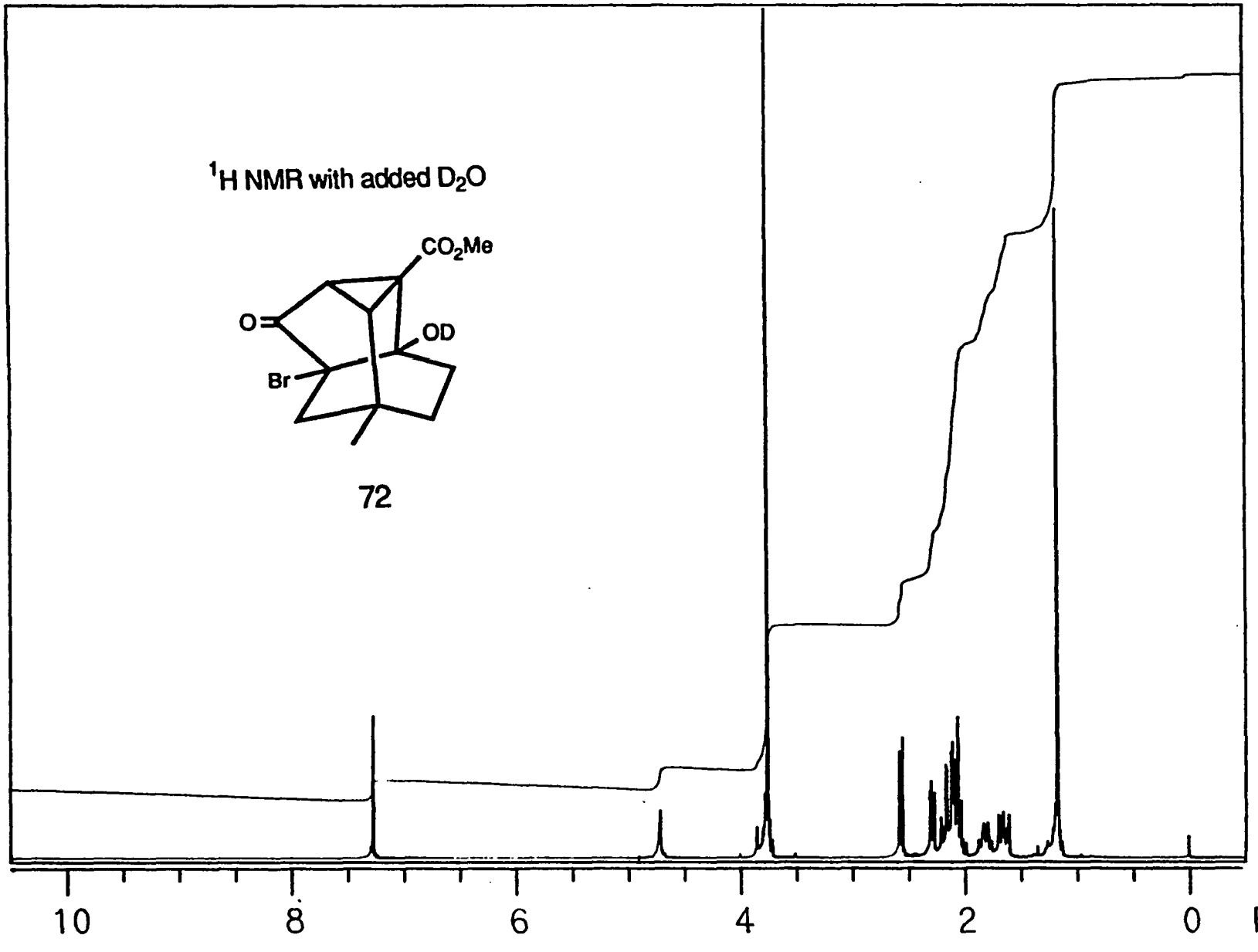
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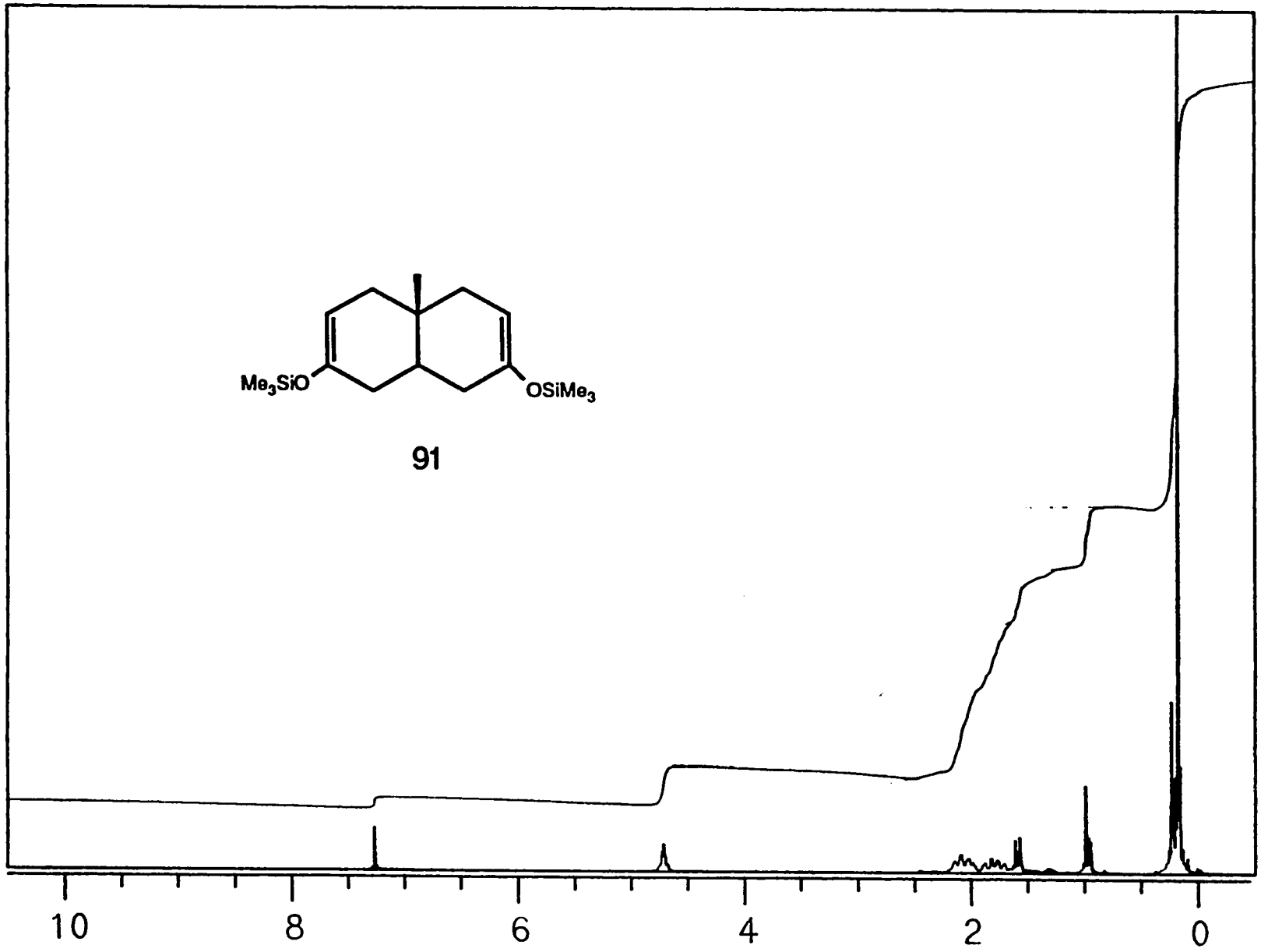
OD
Br
72
10
8
6
4
2
0
PPM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OSiMe3
91
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8
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2
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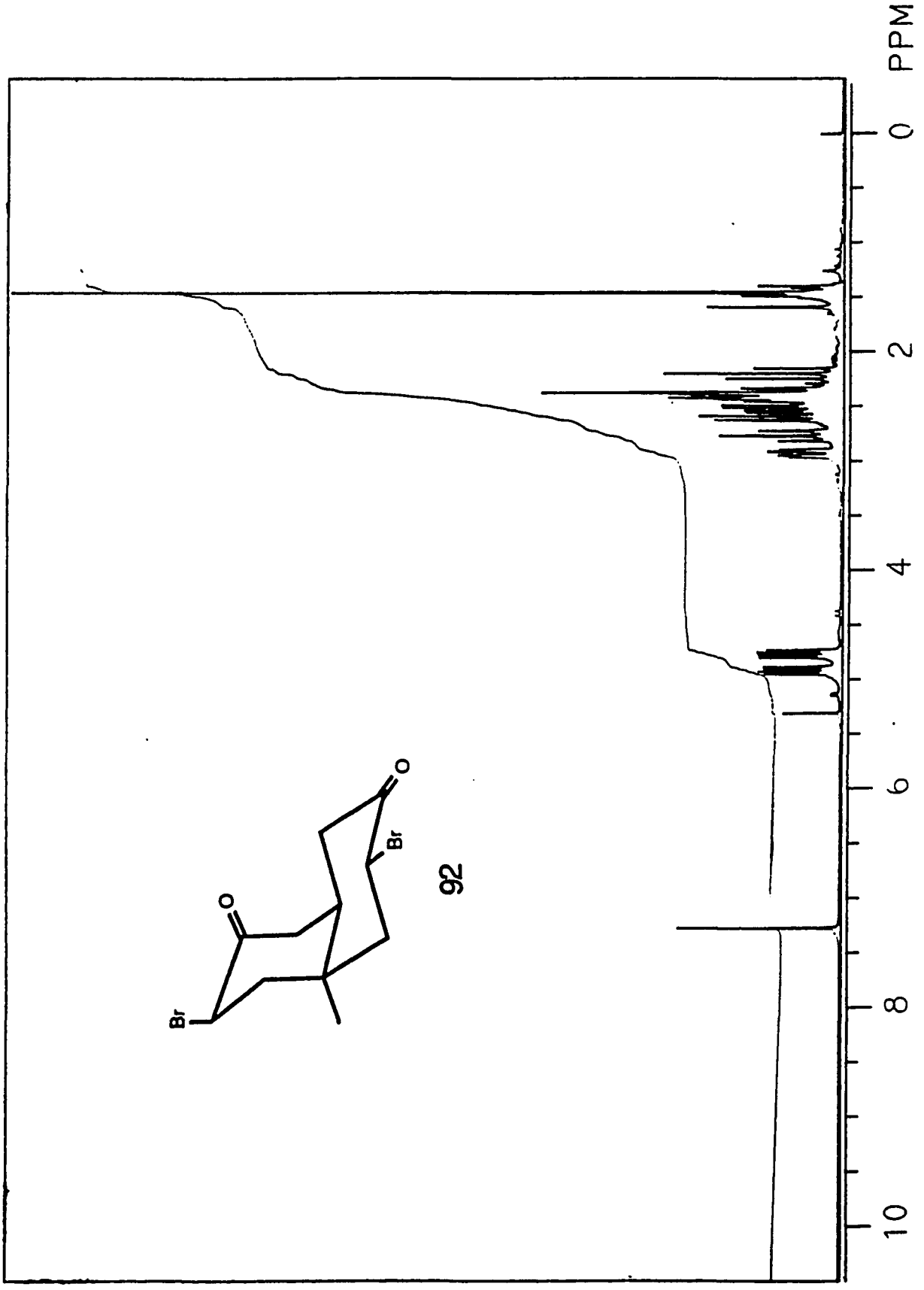
PPM



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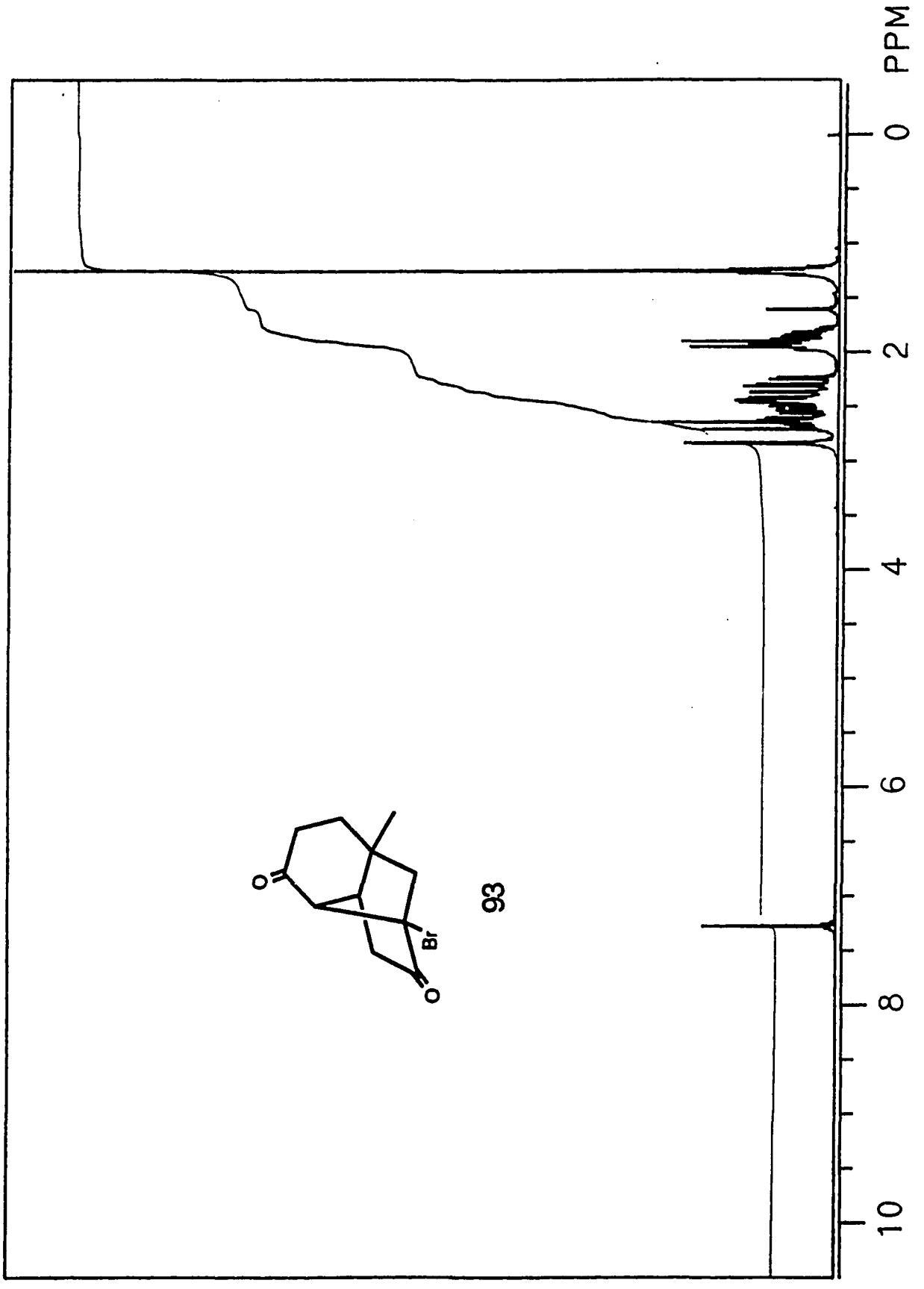
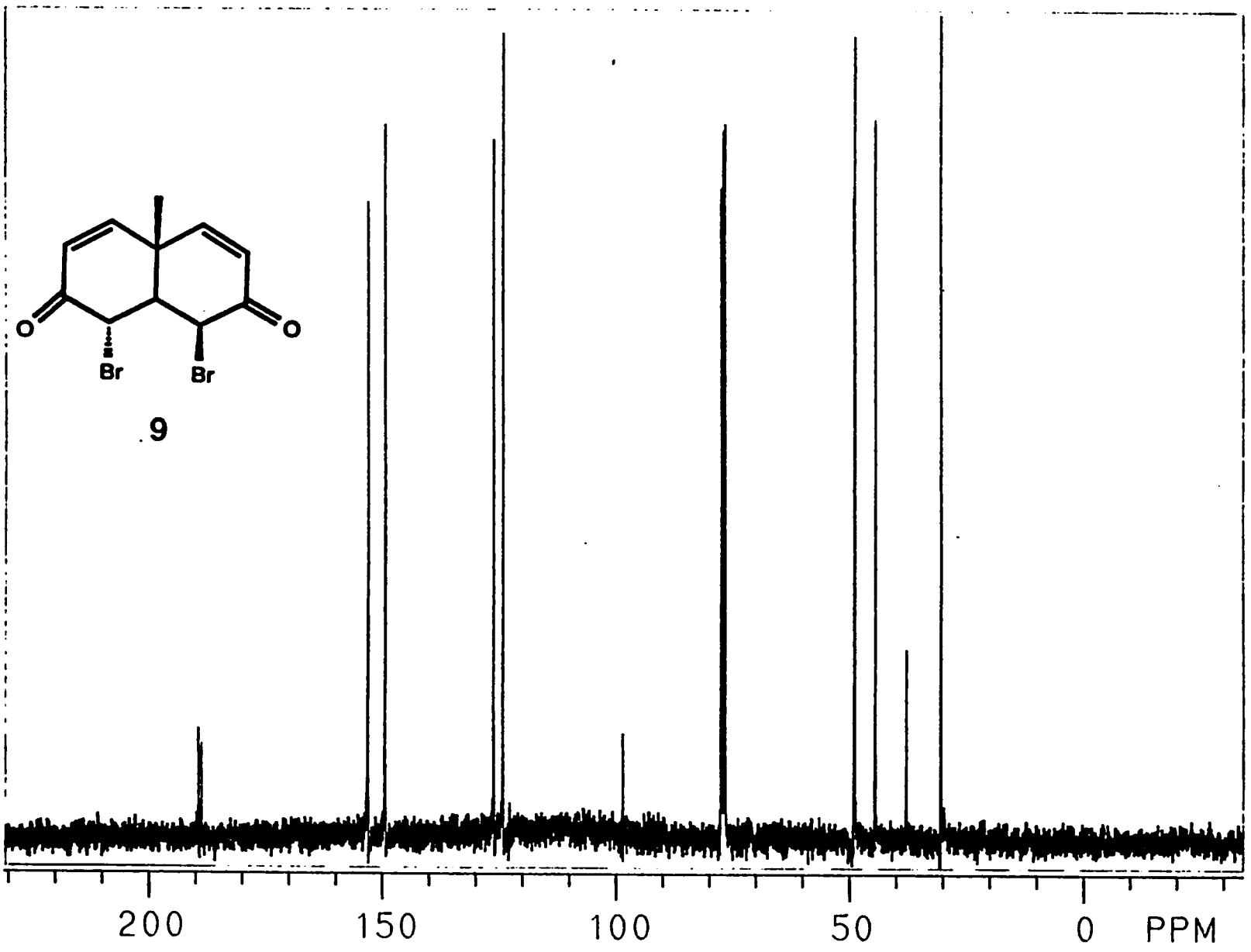


93

^{13}C NMR Spectra of selected compounds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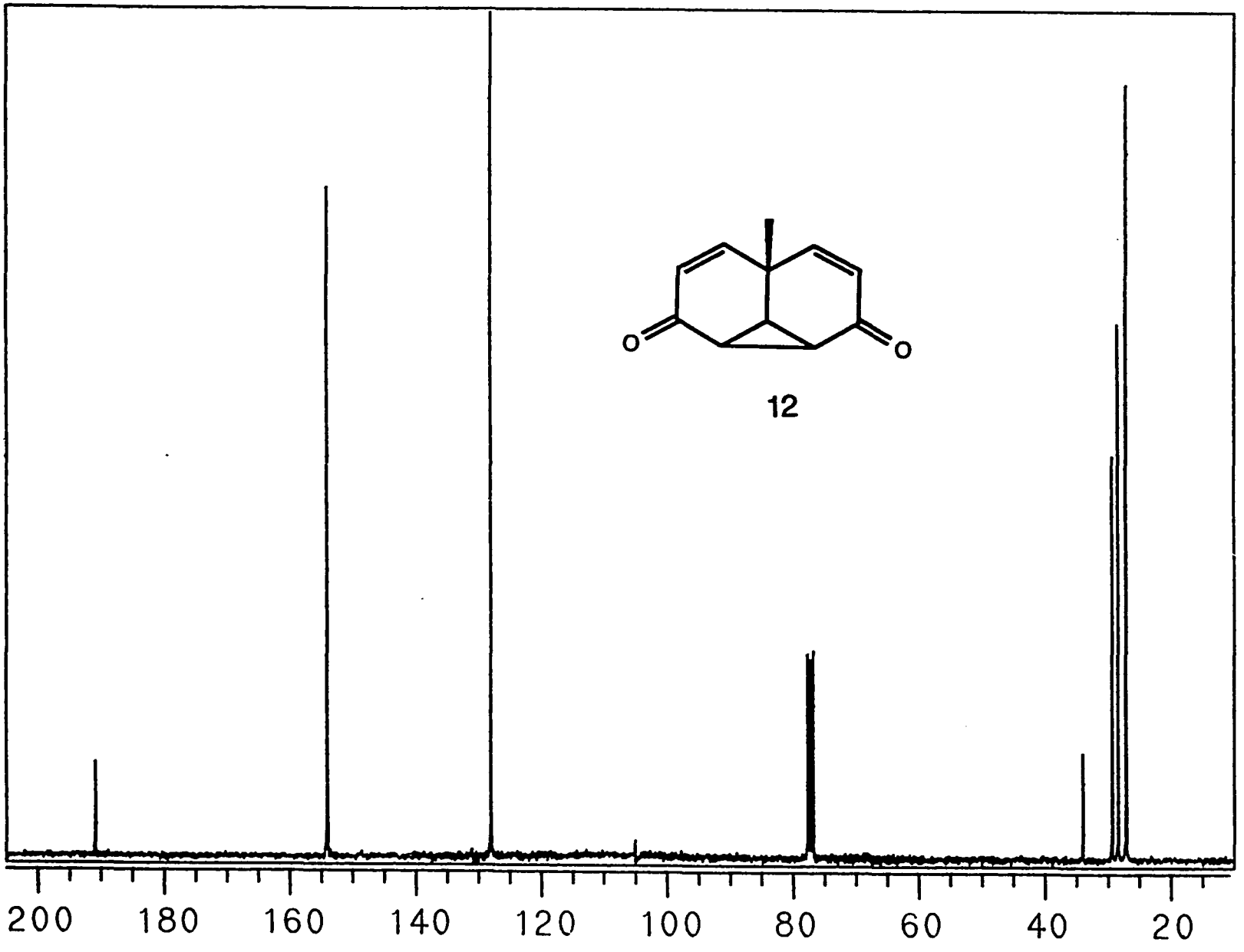
Br
Br
9
200
150
100
50
0
PPM



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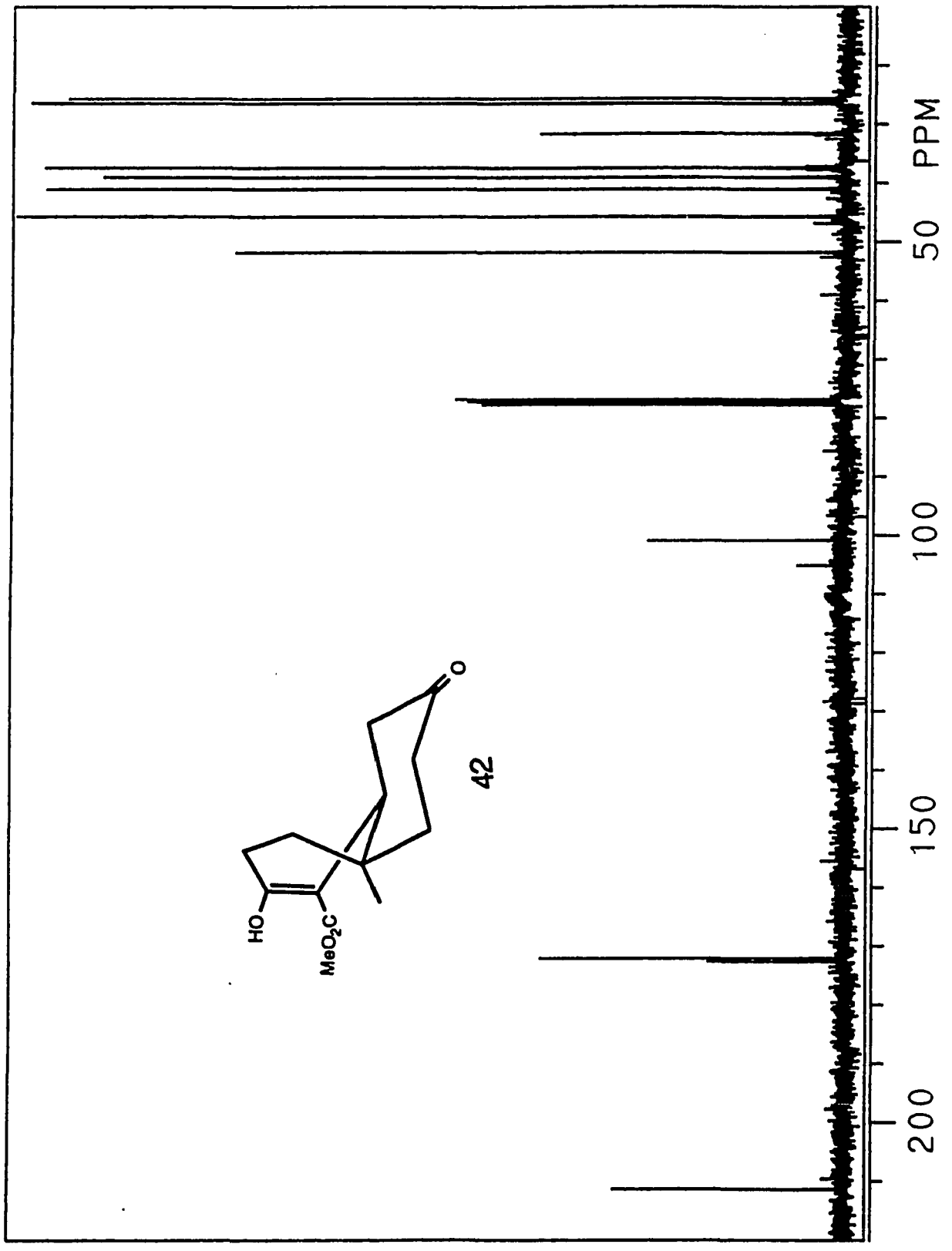

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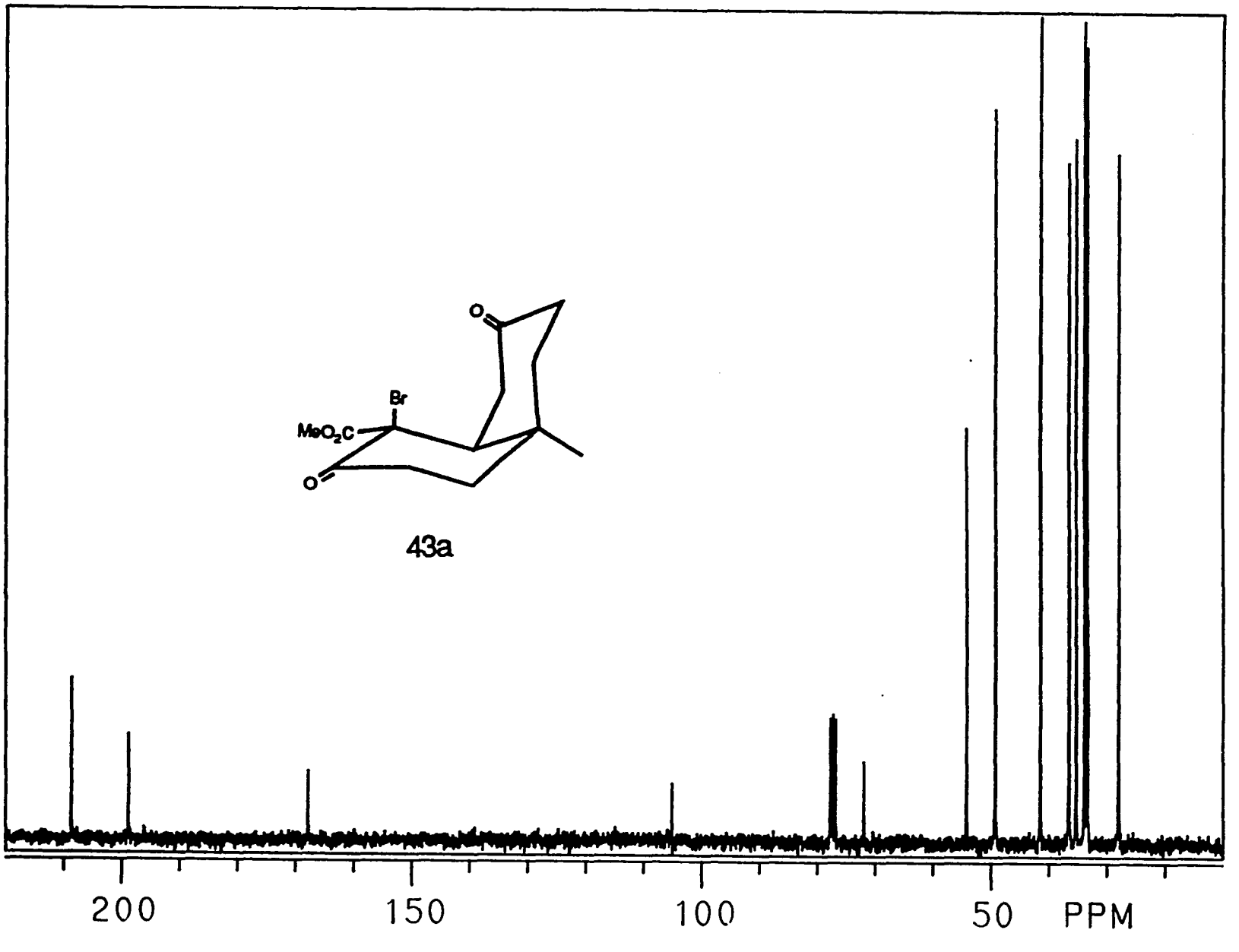
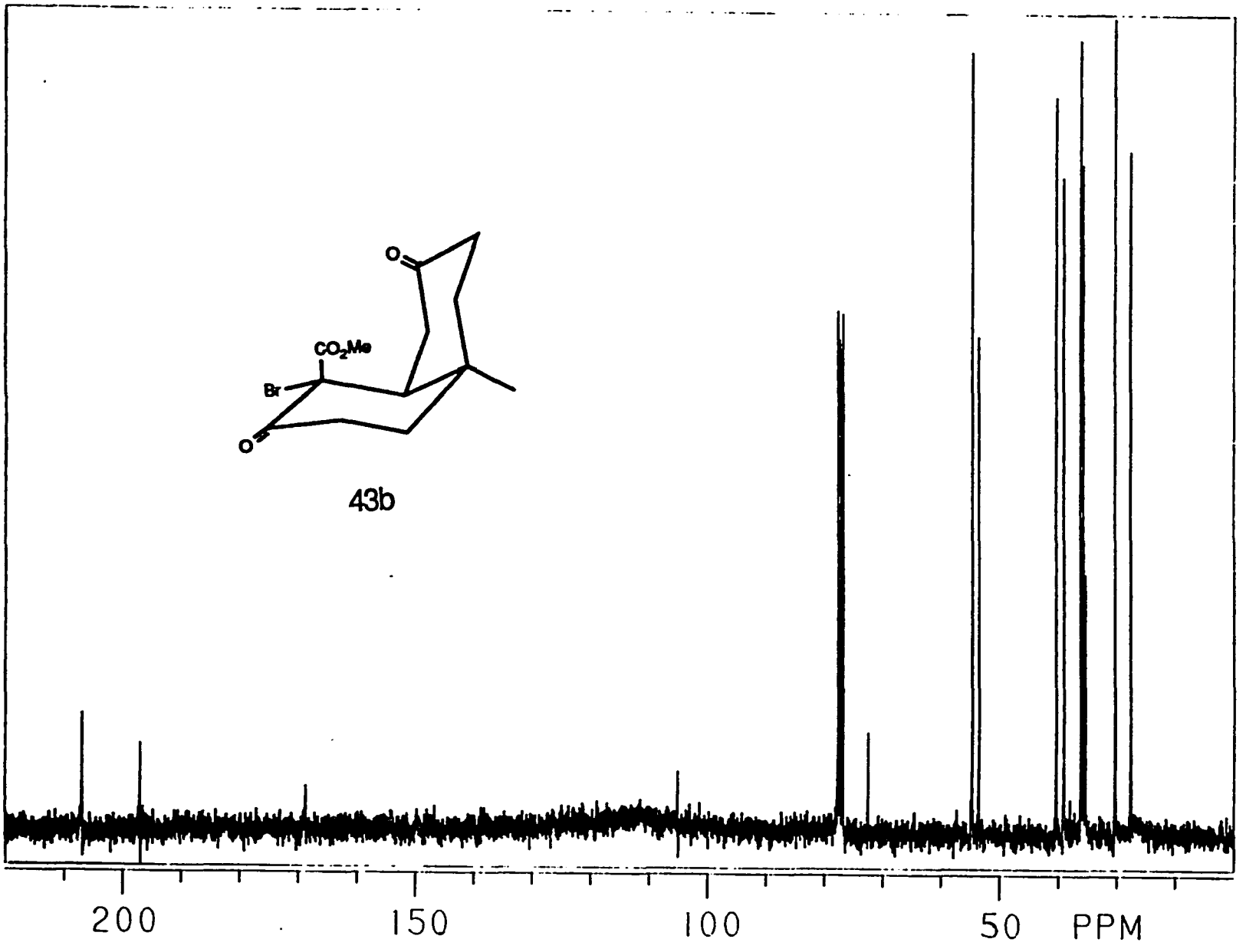


43a



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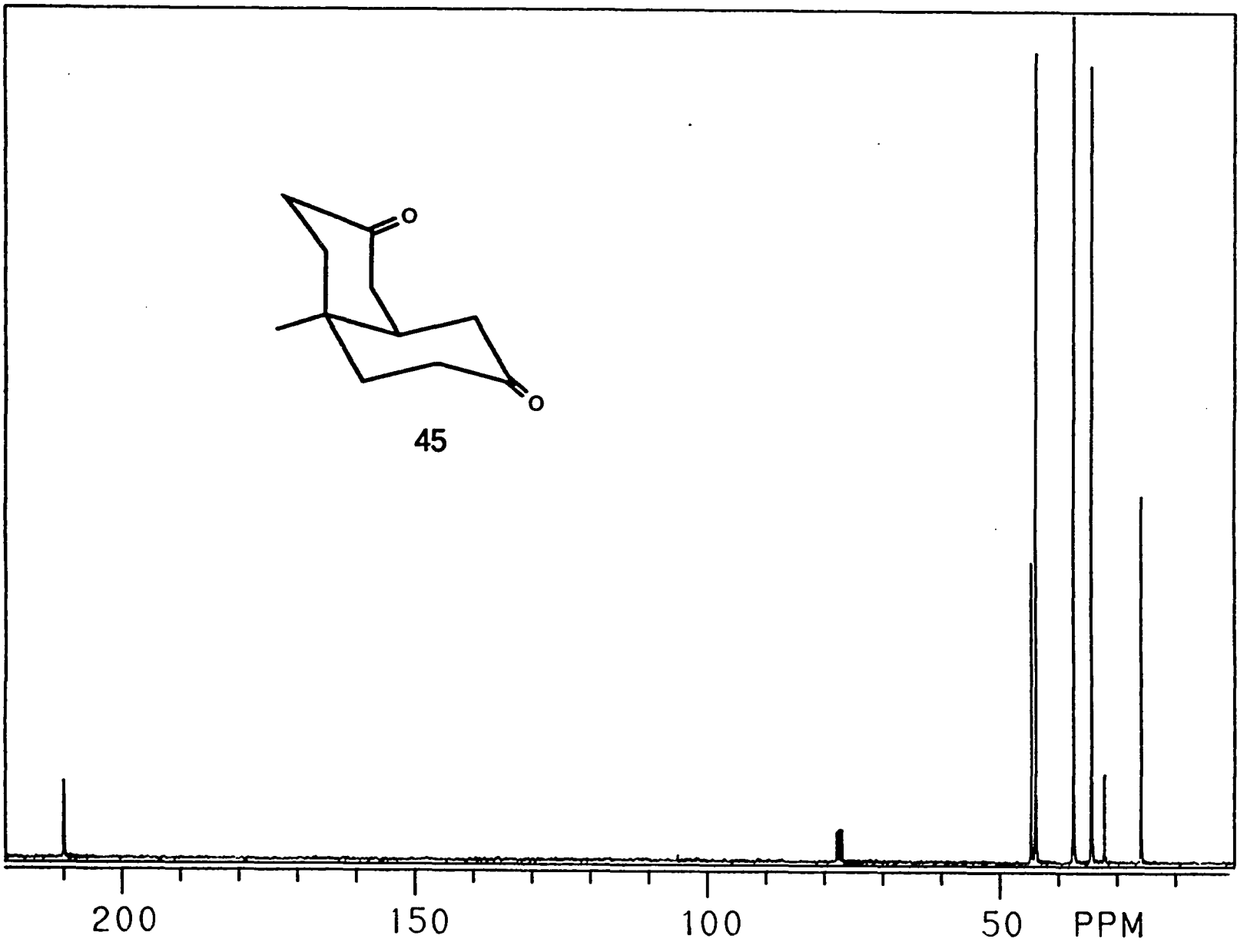

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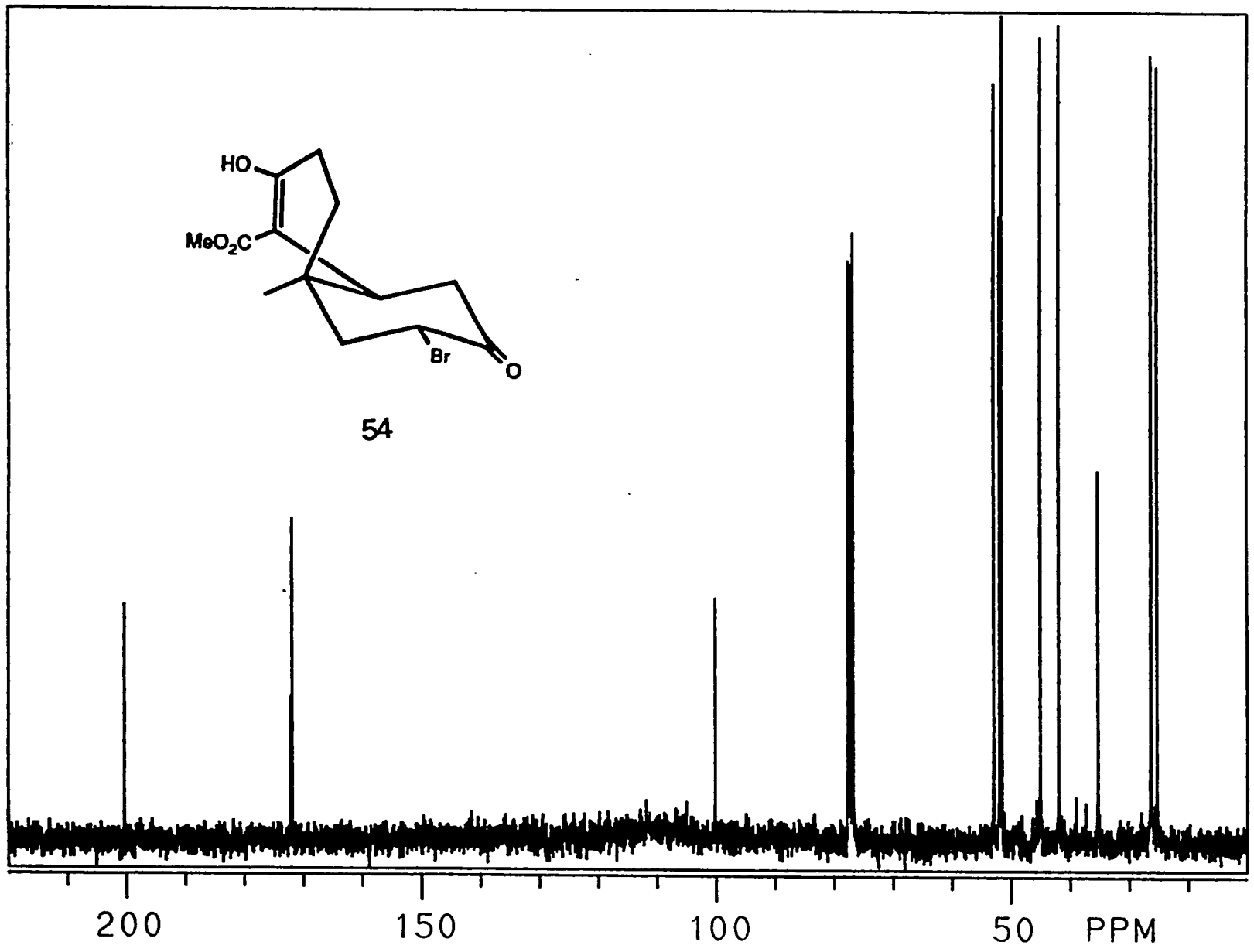

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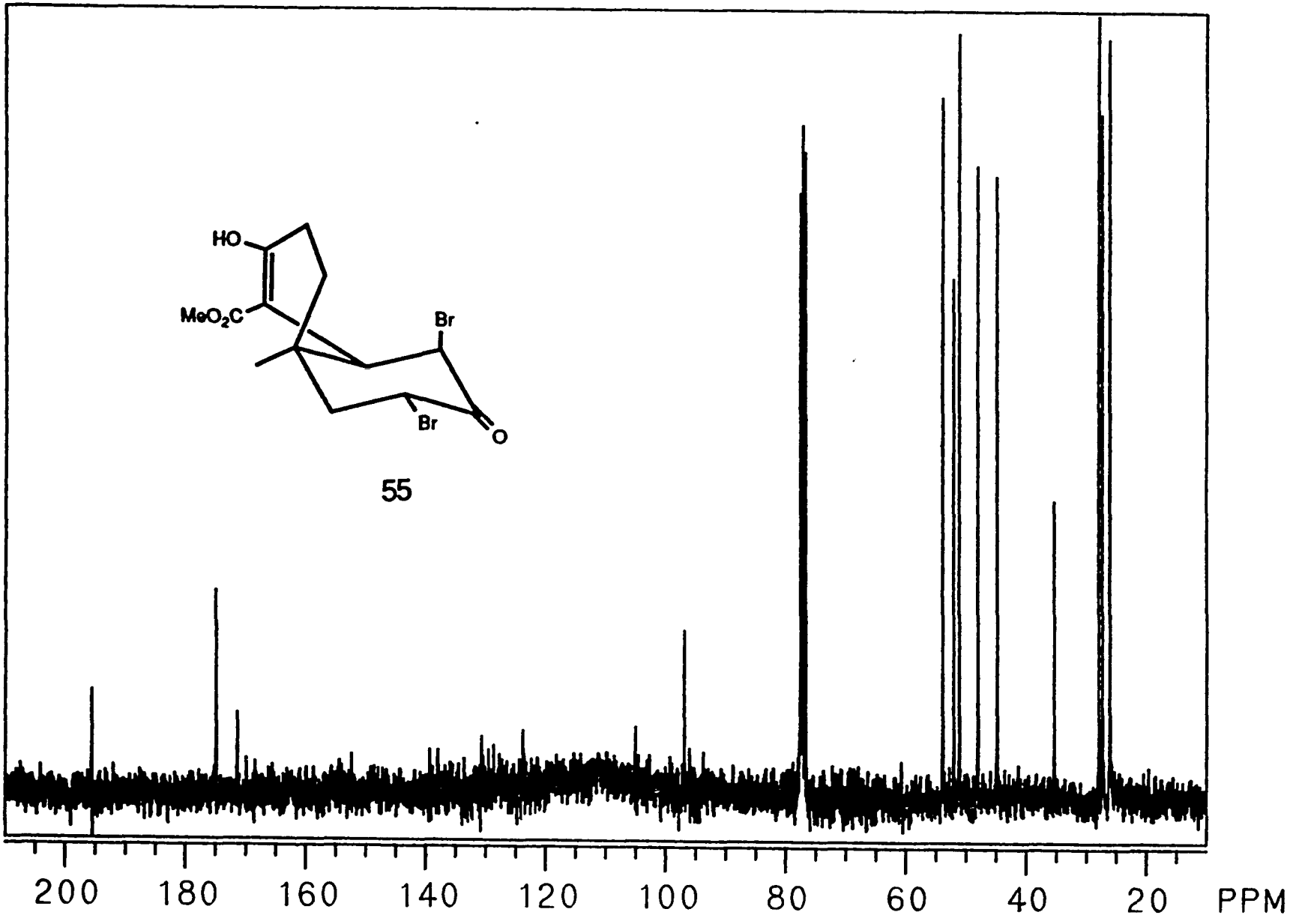
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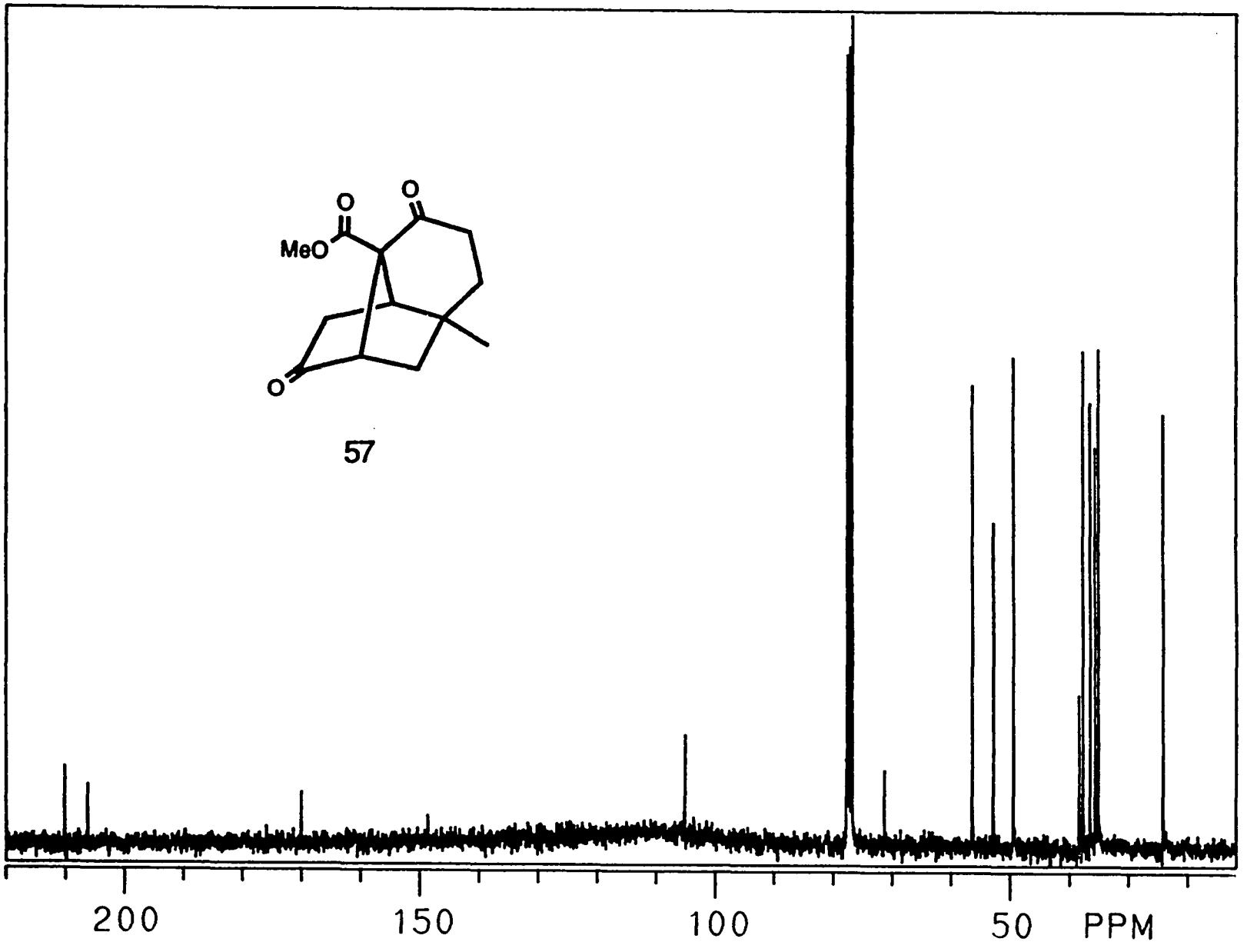
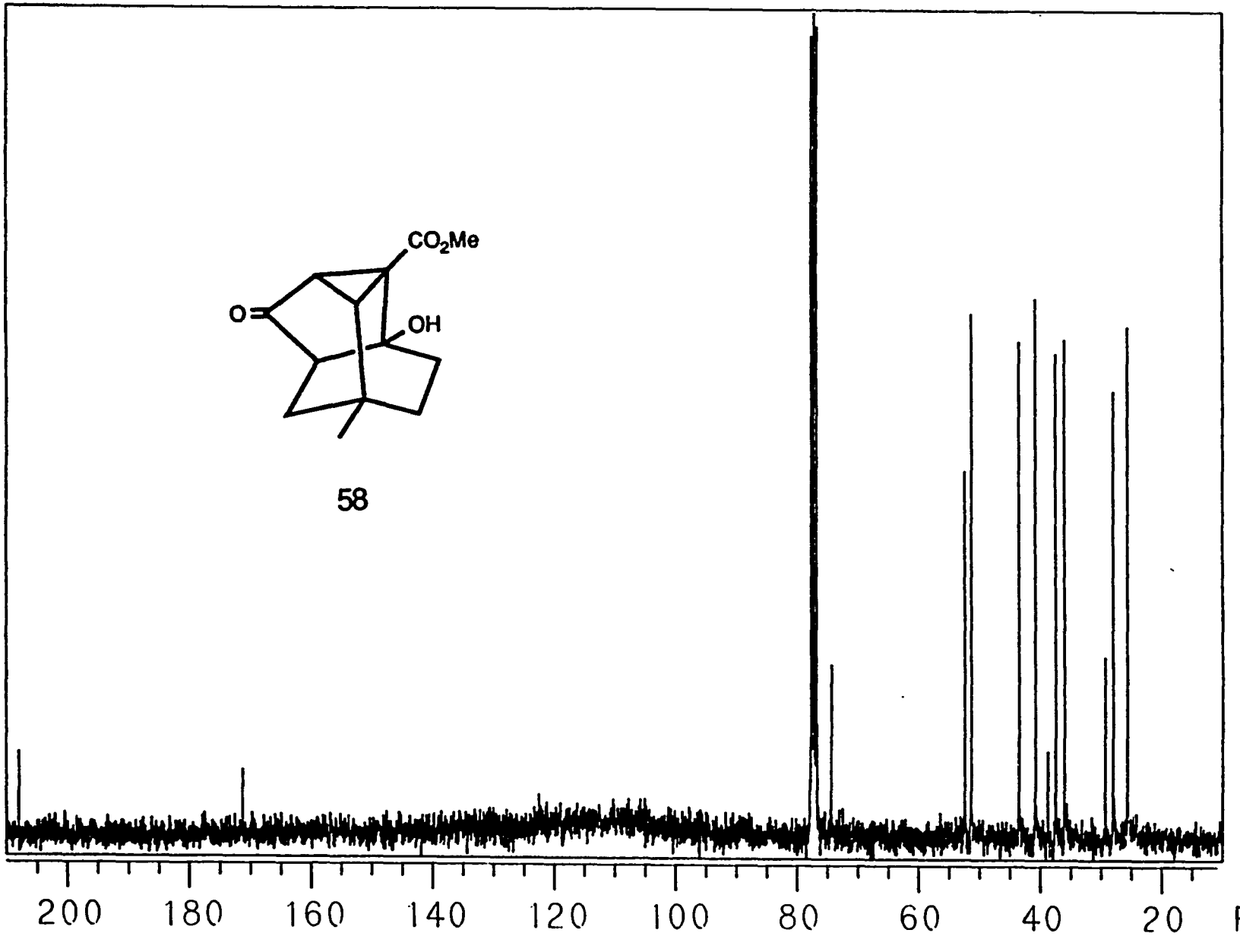
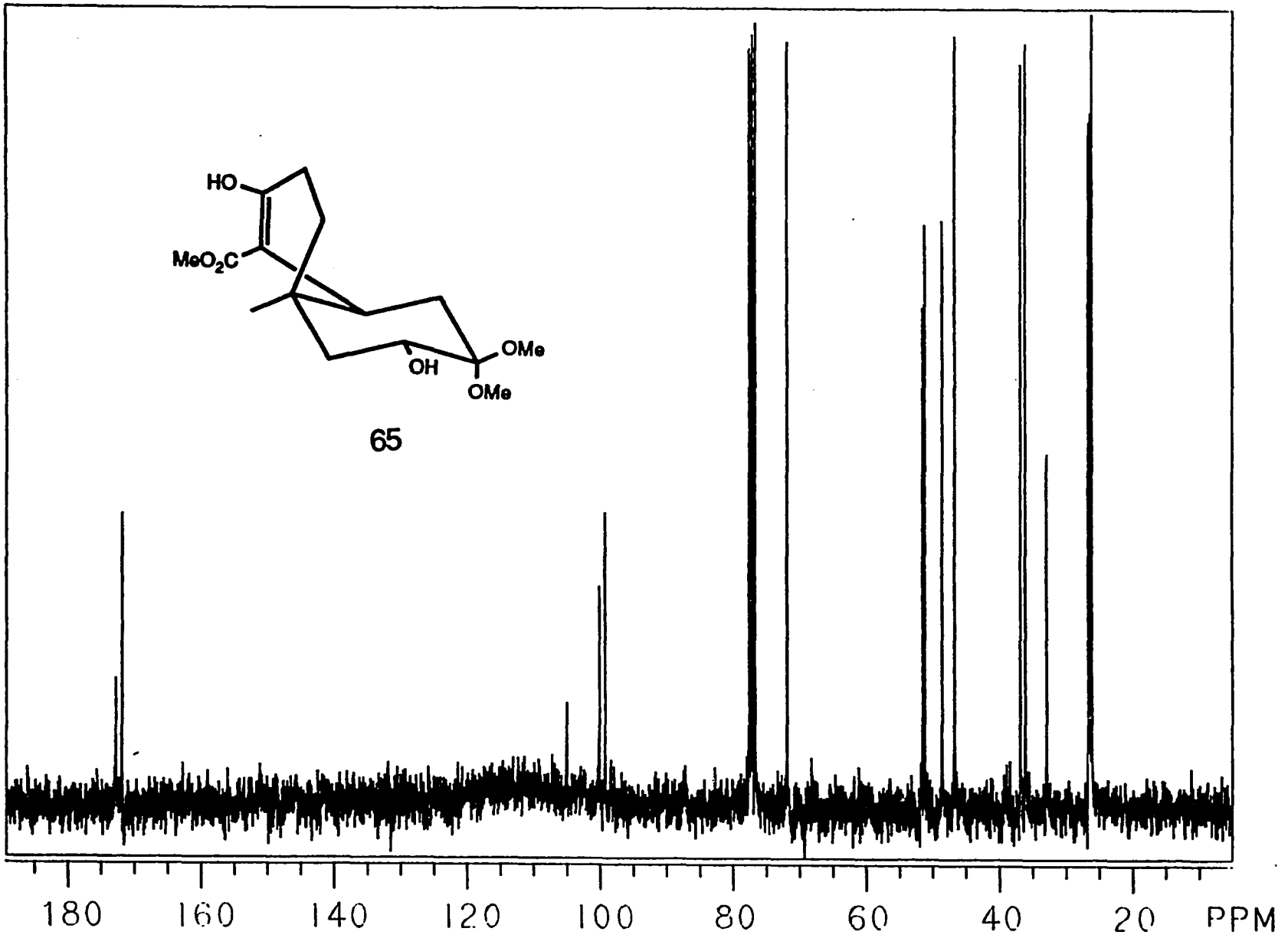
MeO2C
Br
Br
O
55
200
180
160
140
120
100
80
60
40
20
PPM

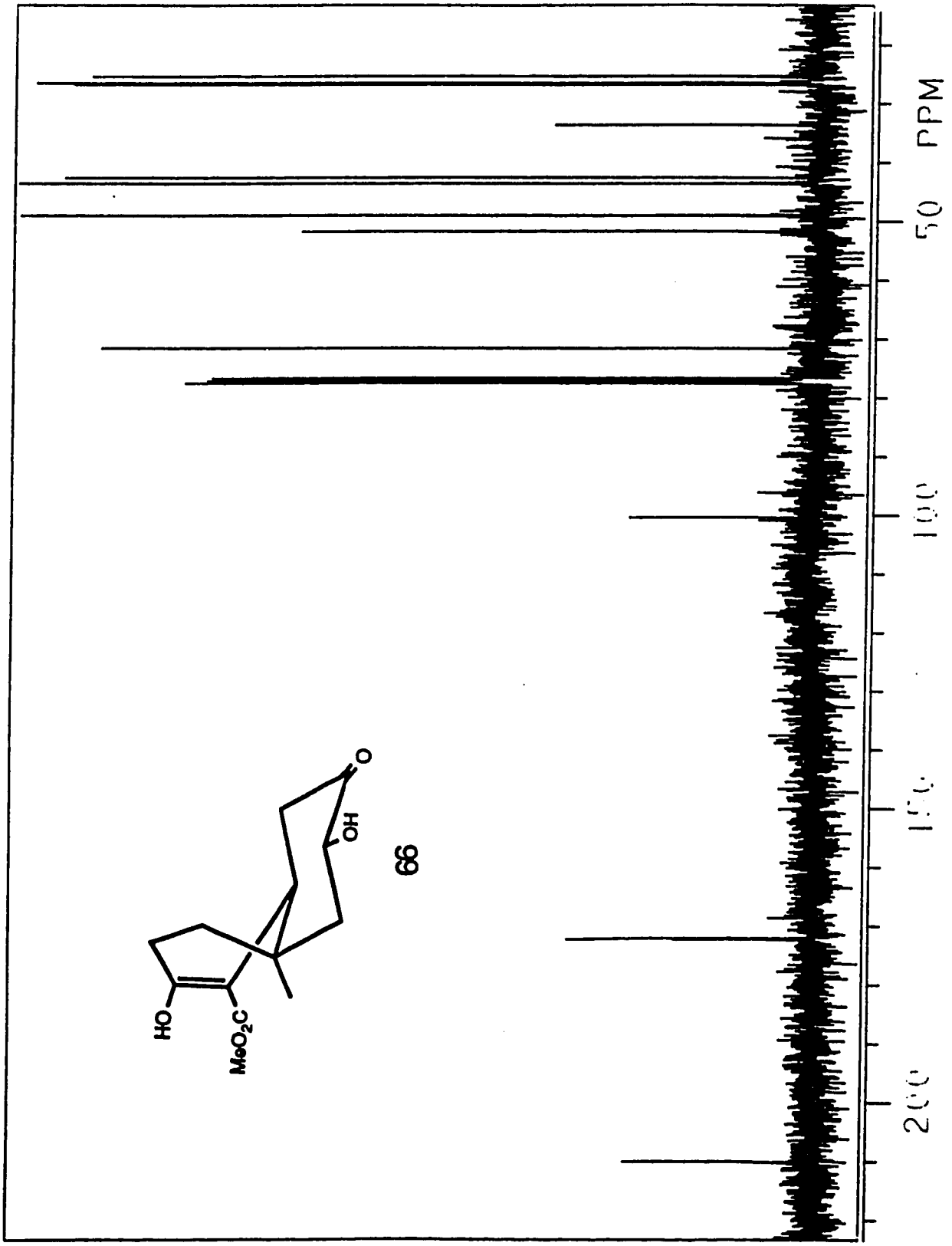


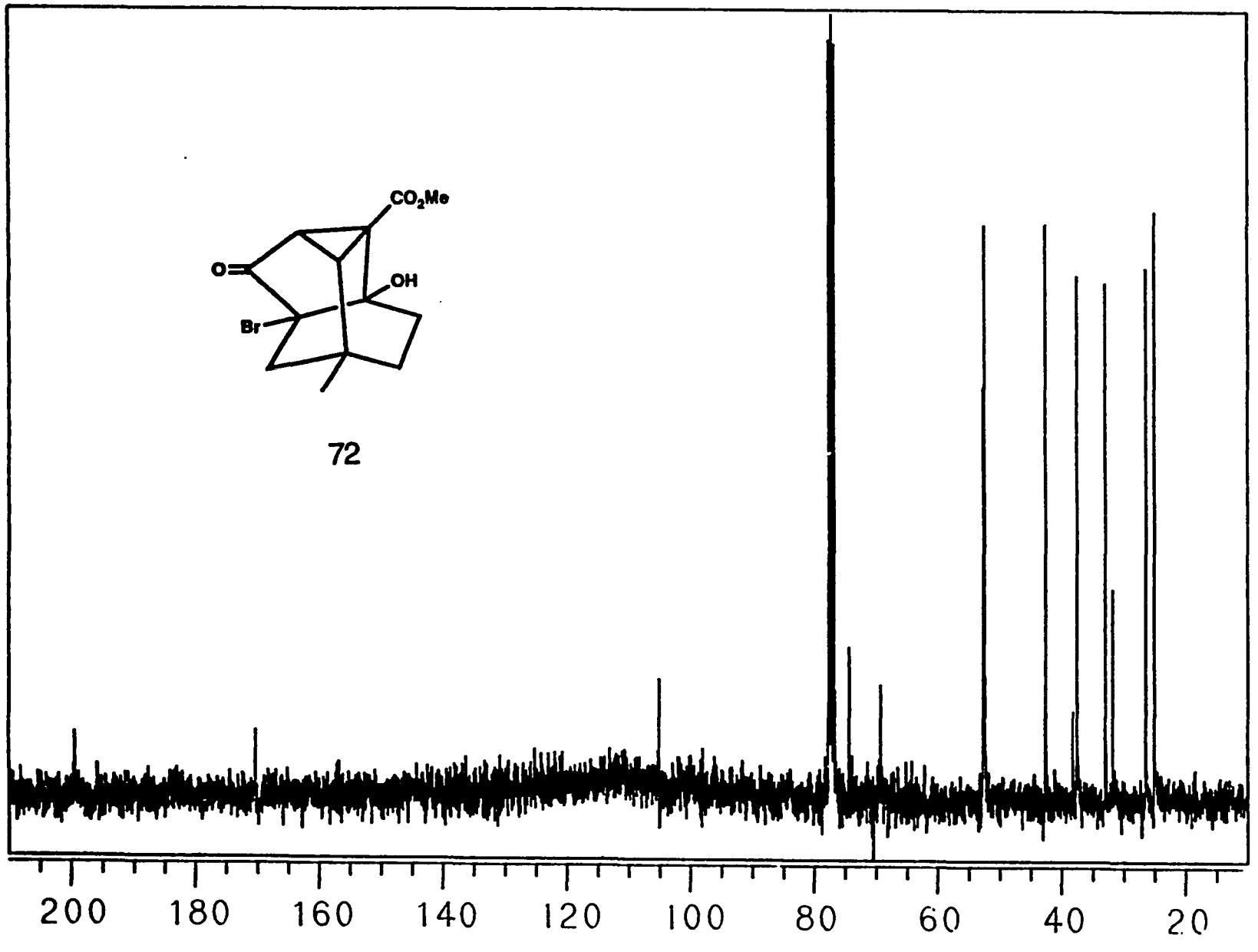
57



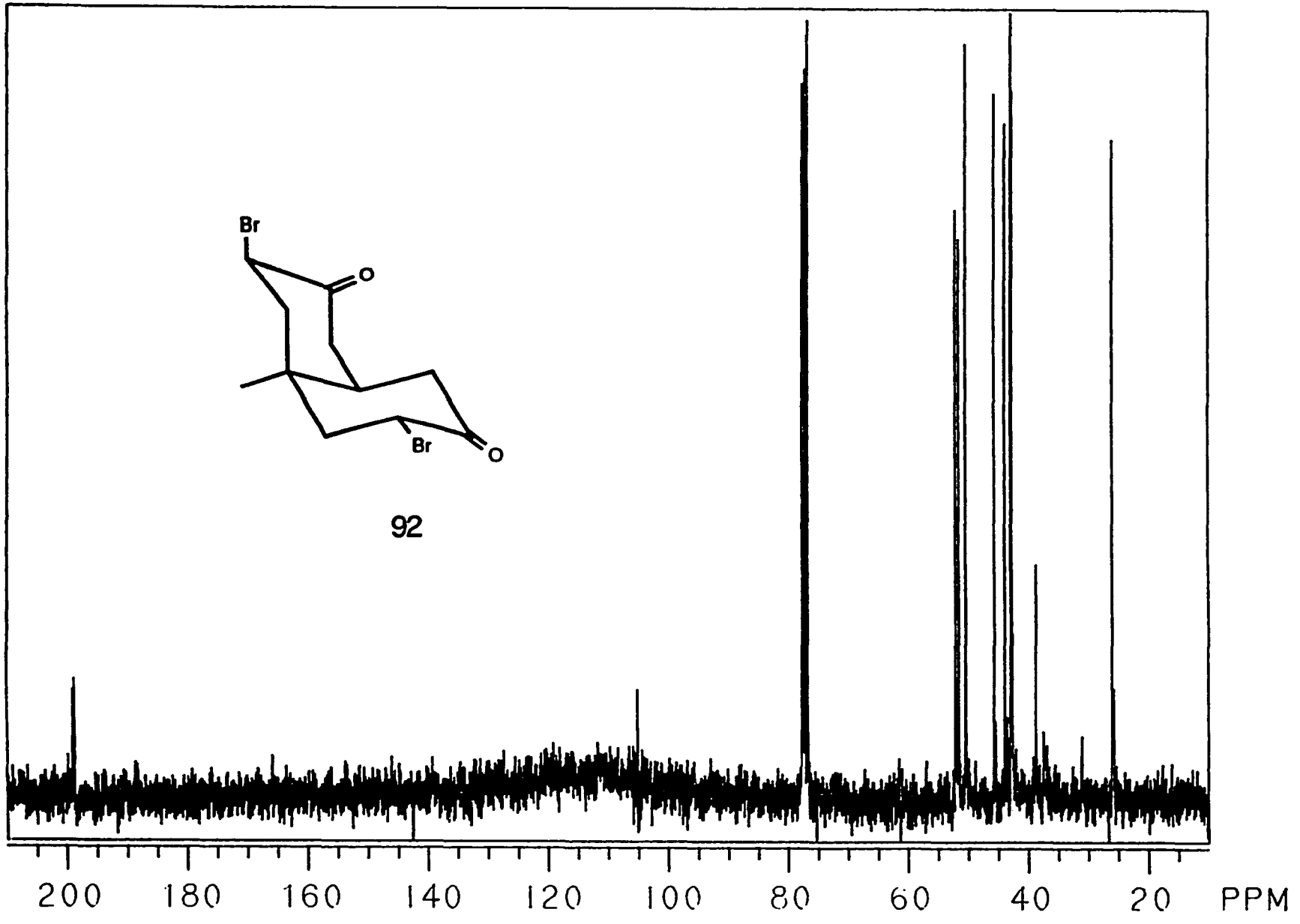
58

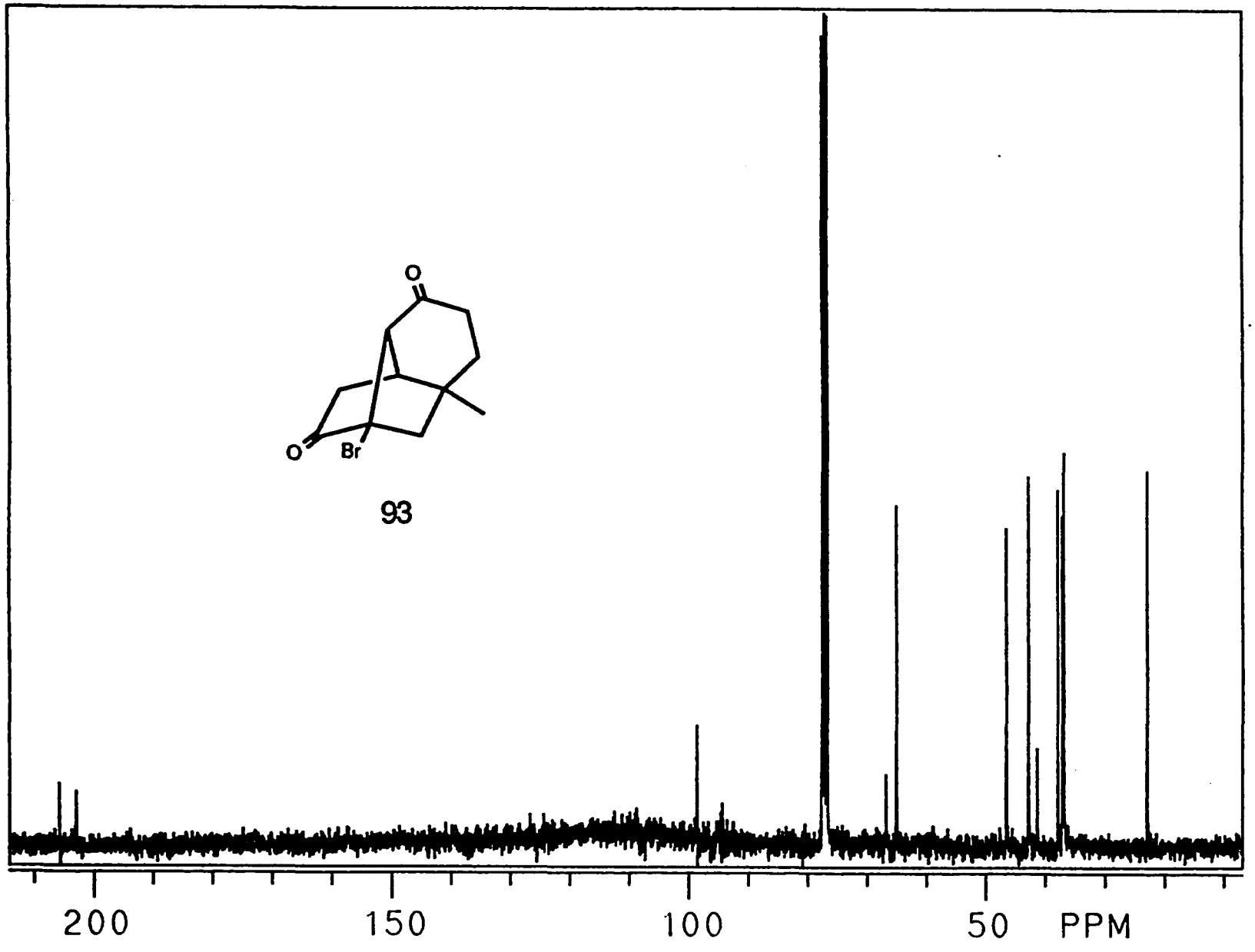

HO
MeO2C
OMe
OH
OMe
65
180
160
140
120
100
80
60
40
20
PPM


HO
MeO2C
OH
O
66
50 PPM



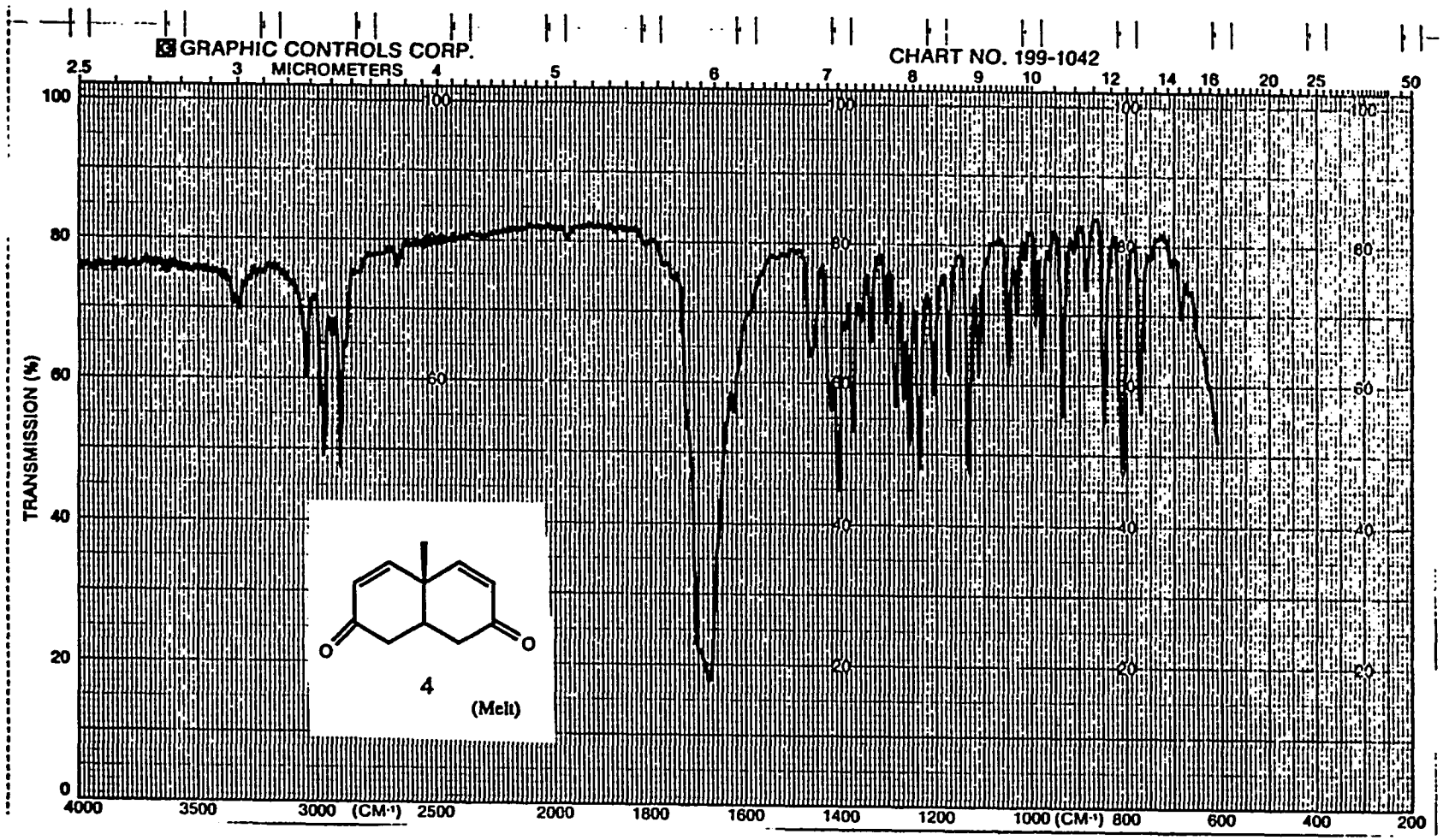
72

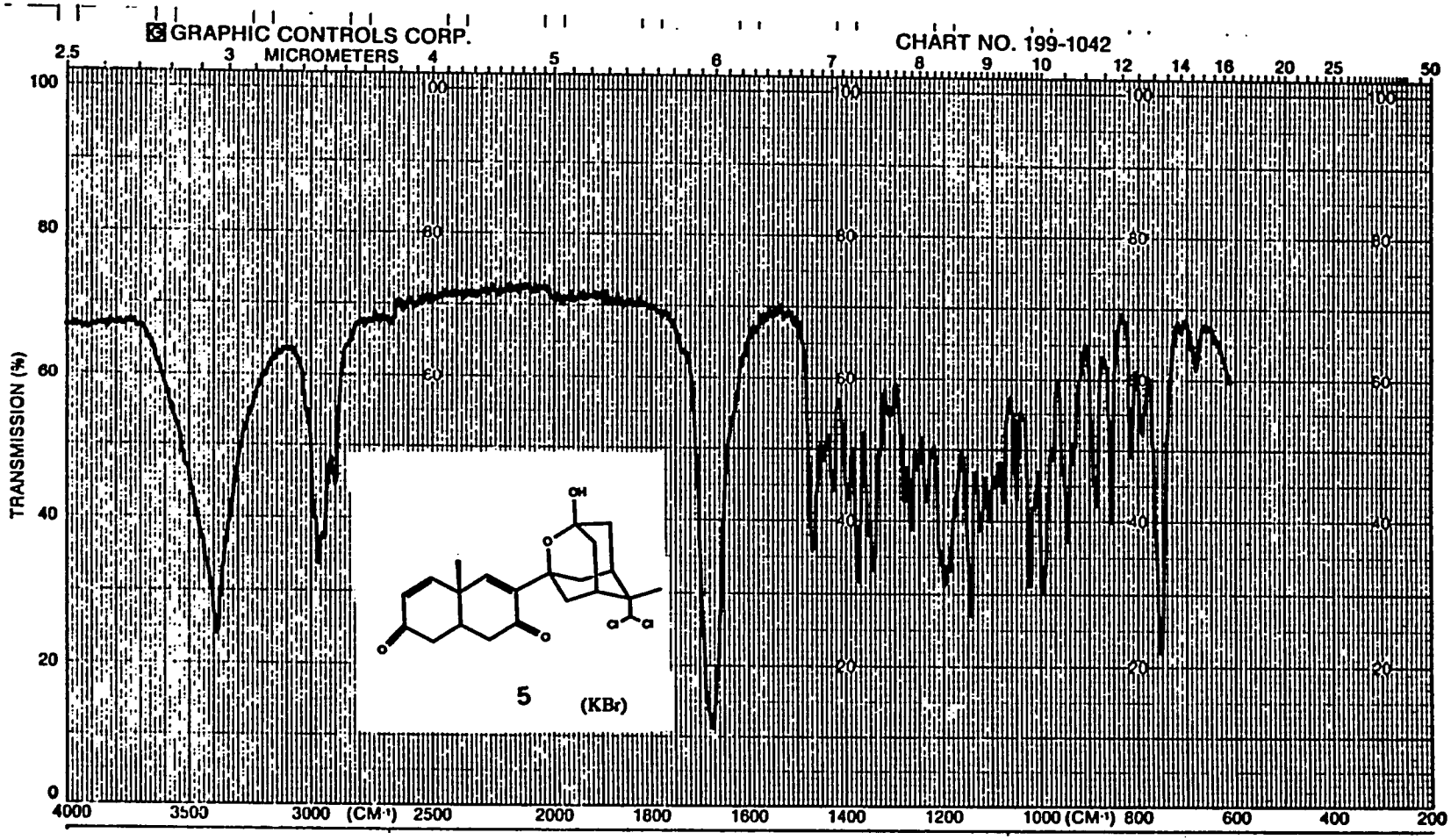

Br
O
Br
O
92
200
180
160
140
120
100
80
60
40
20
PPM

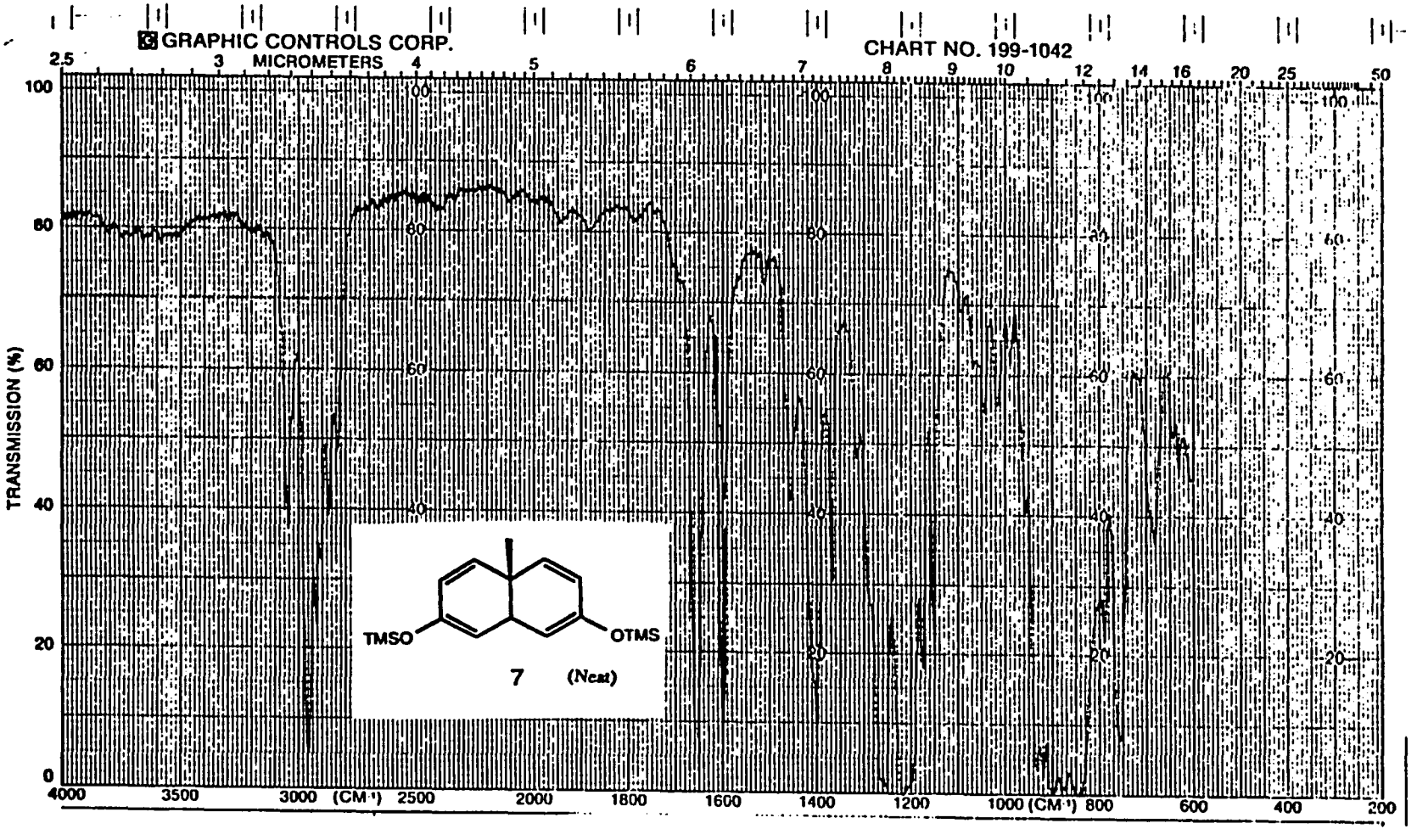


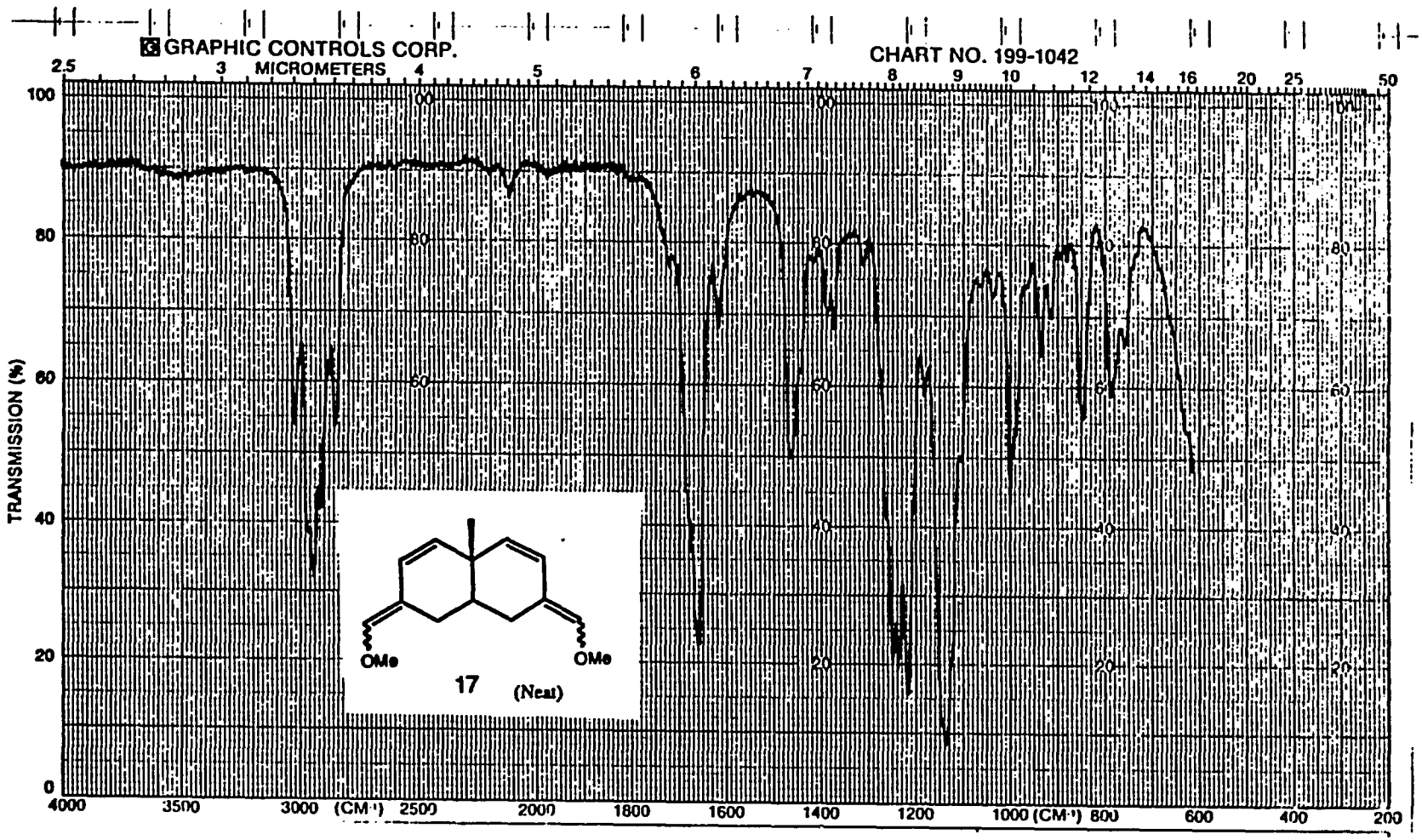
93

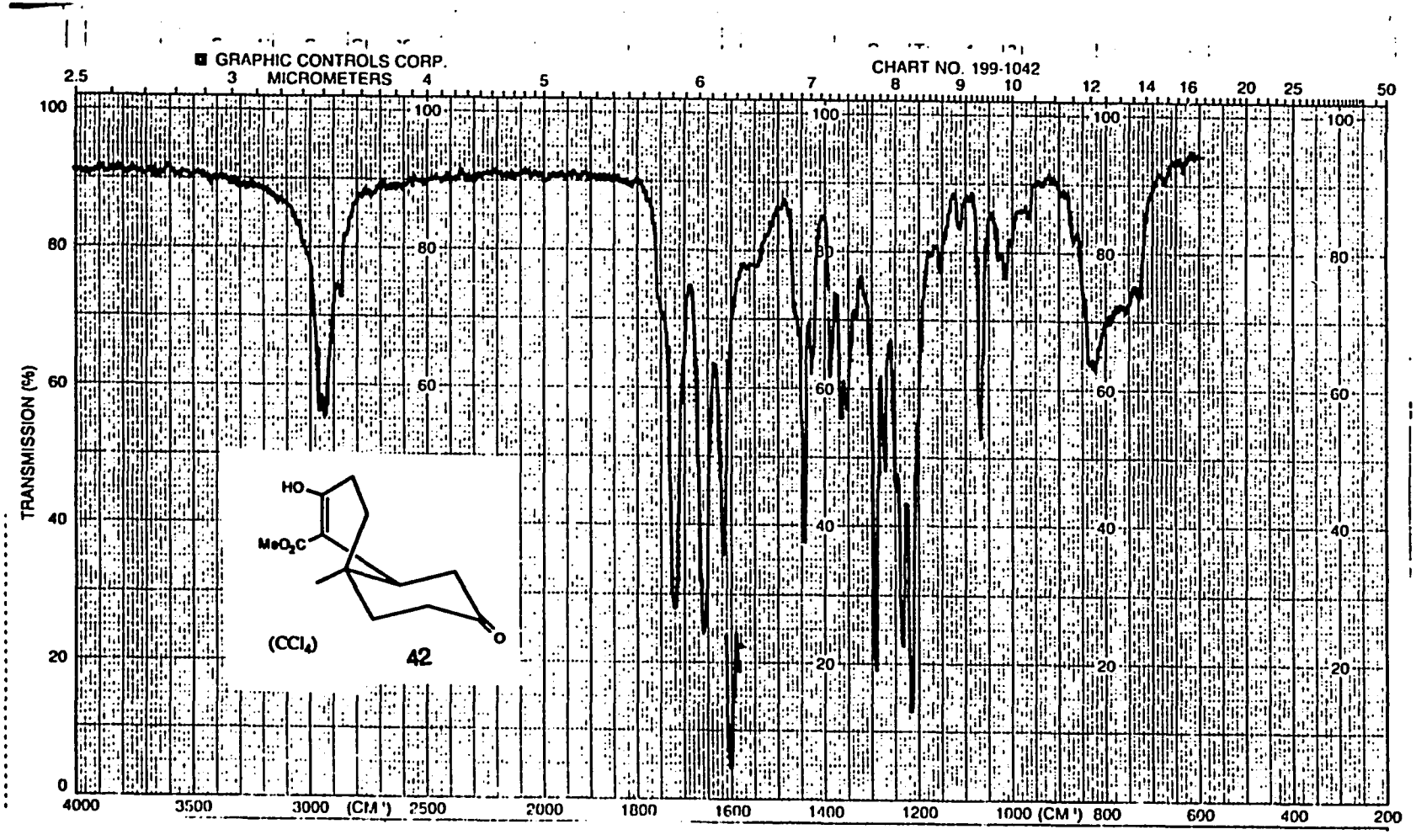
IR Spectra of selected compounds

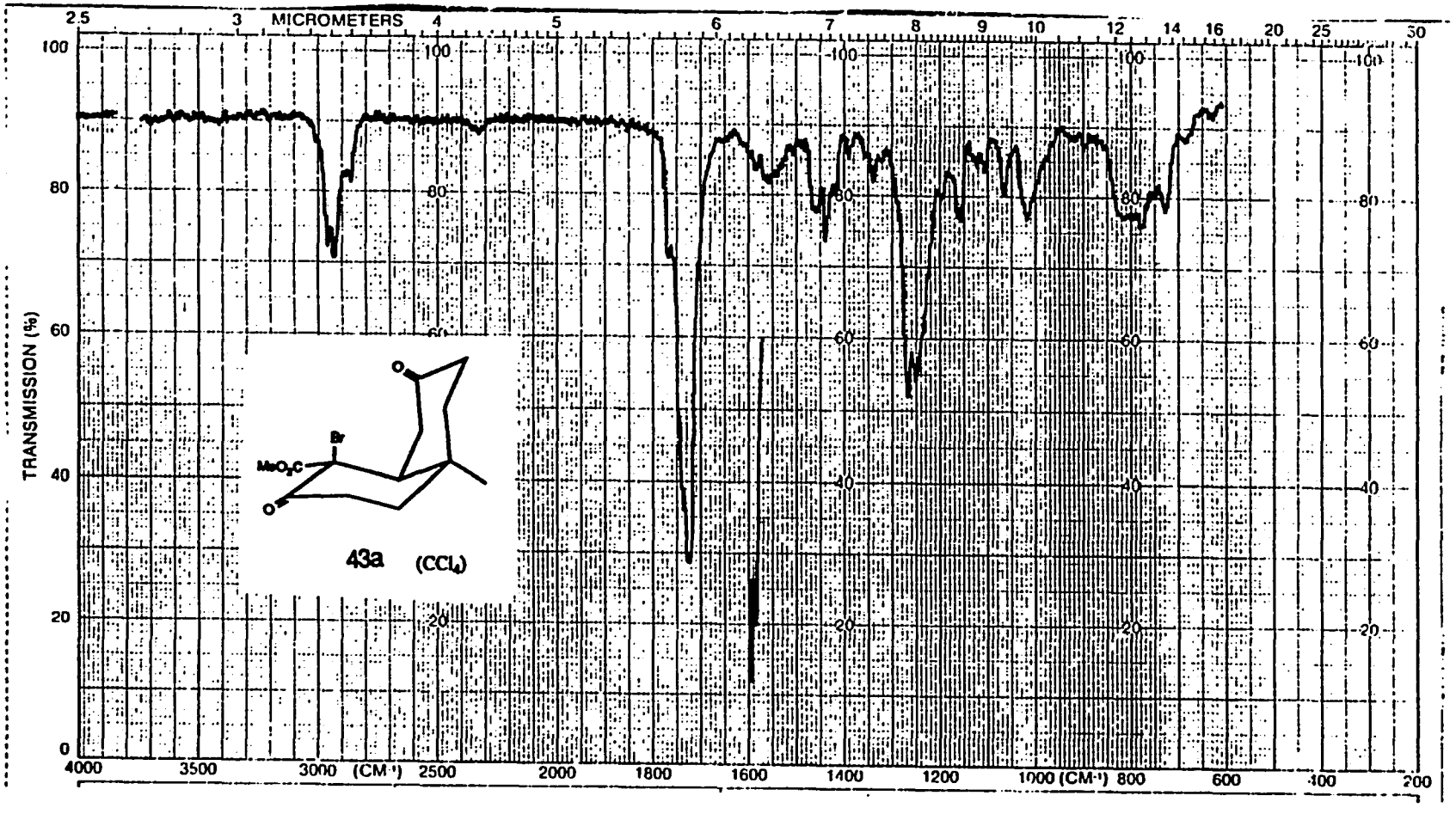

GRAPHIC CONTROLS CORP.
CHART NO. 199-1042
MICROMETERS
TRANSMISSION (%)
(CM-1)
4
(Melt)

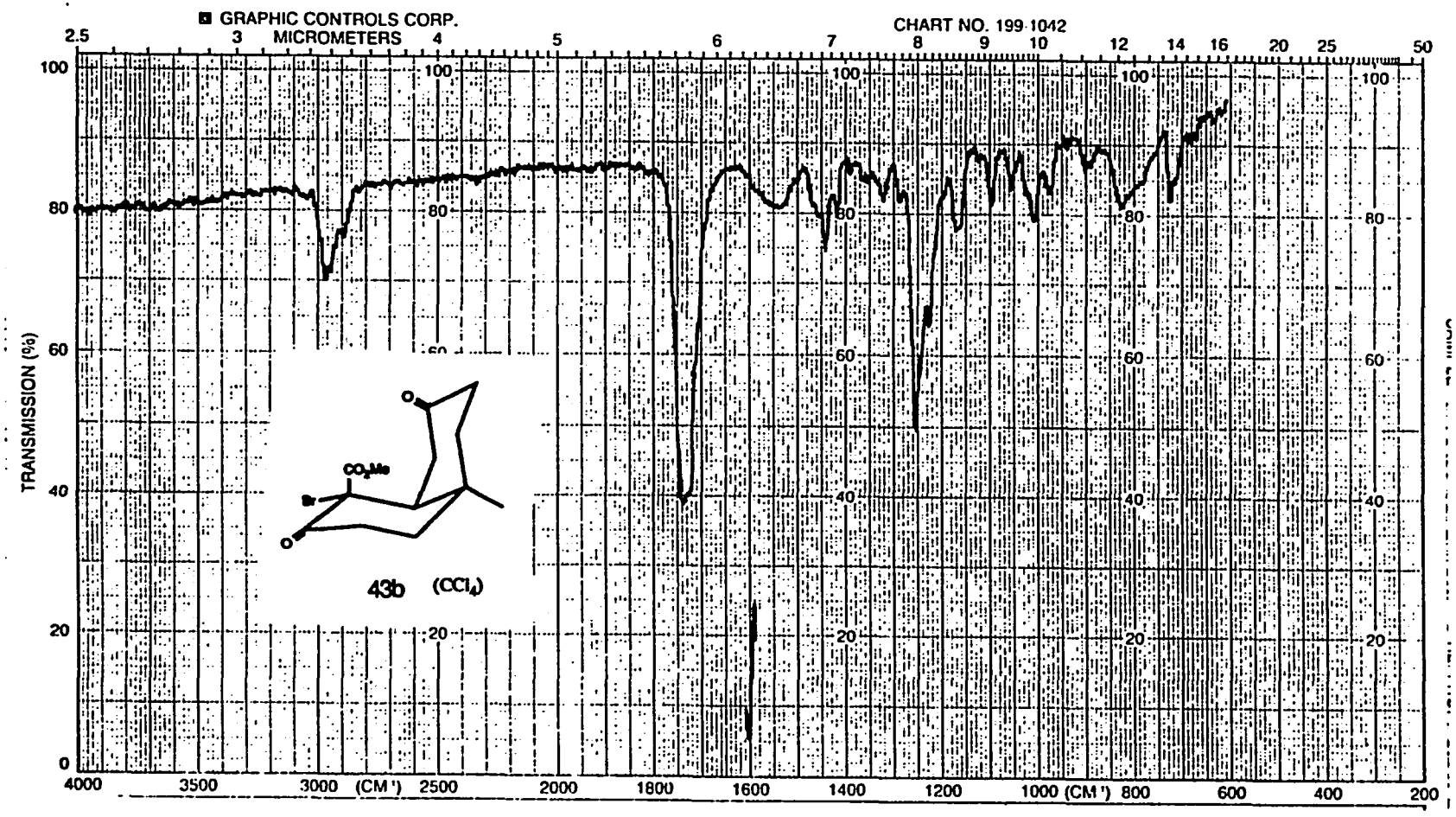

GRAPHIC CONTROLS CORP.
CHART NO. 199-1042
MICROMETERS
TRANSMISSION (%)
(CM-1)
5
(KBr)

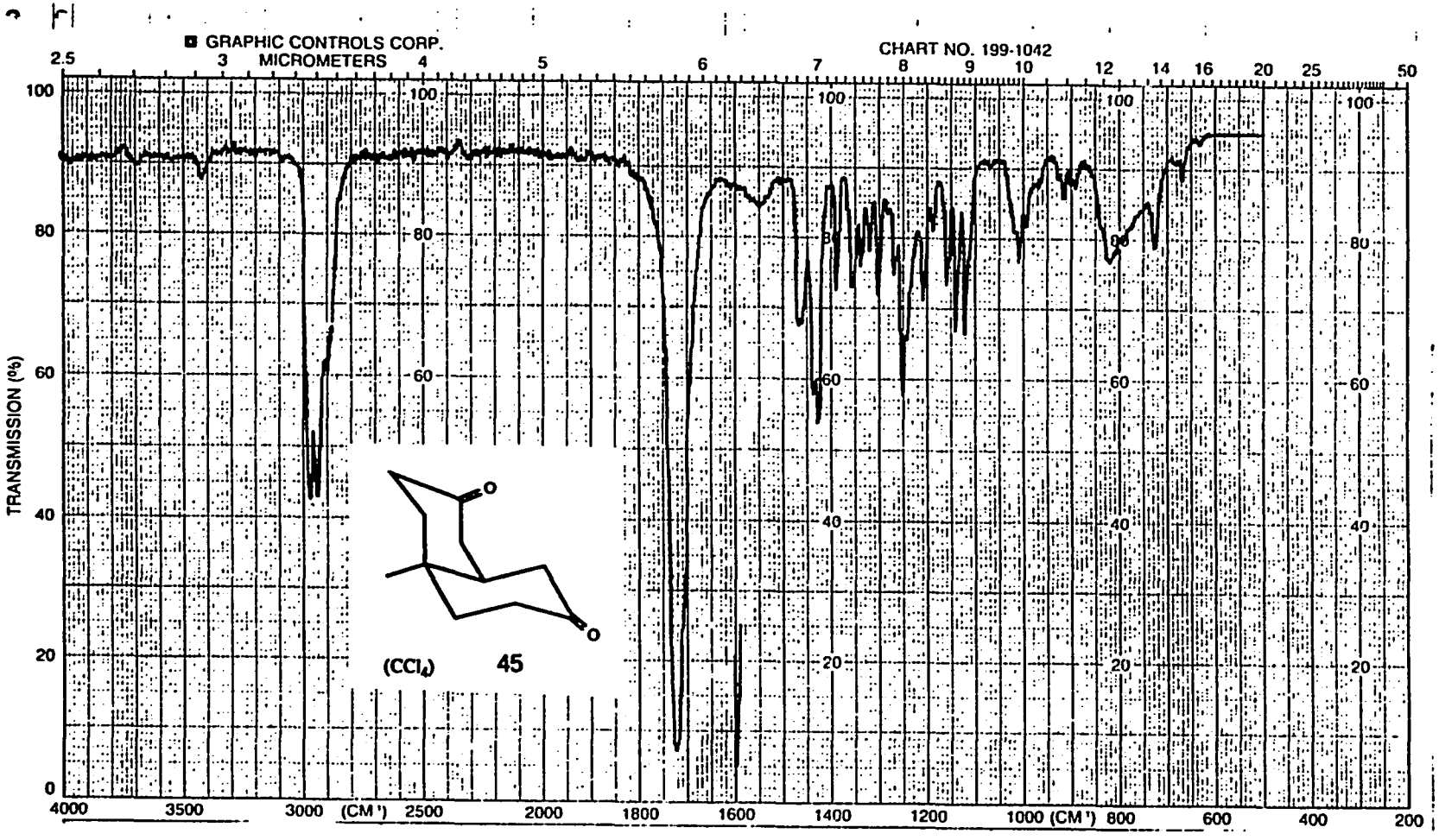

GRAPHIC CONTROLS CORP.
CHART NO. 199-1042
MICROMETERS
TRANSMISSION (%)
(CM⁻¹)
TMSO
OTMS
7 (Neat)

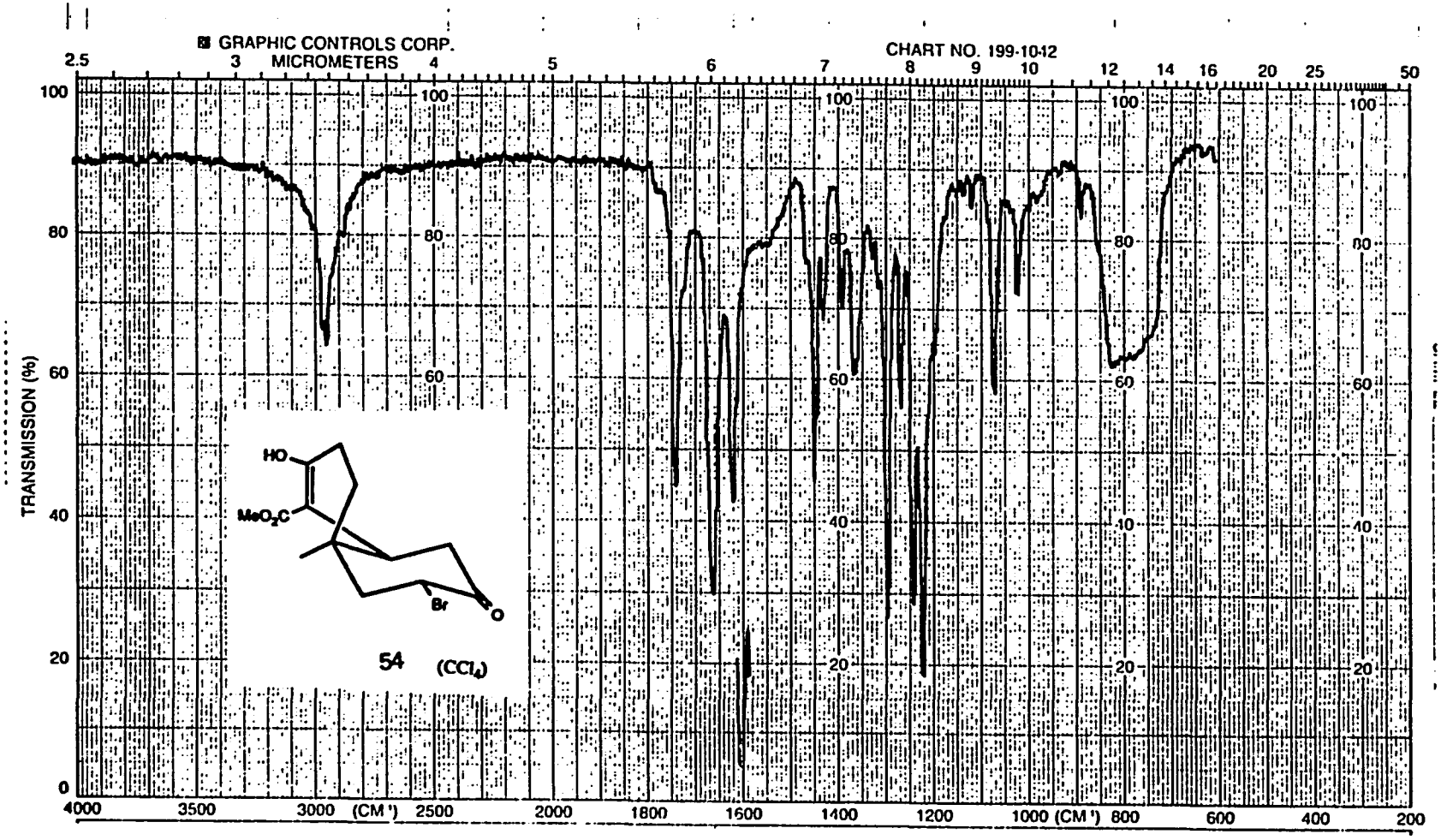

GRAPHIC CONTROLS CORP.
CHART NO. 199-1042
MICROMETERS
TRANSMISSION (%)
(CM⁻¹)
OMe
OMe
17
(Neat)

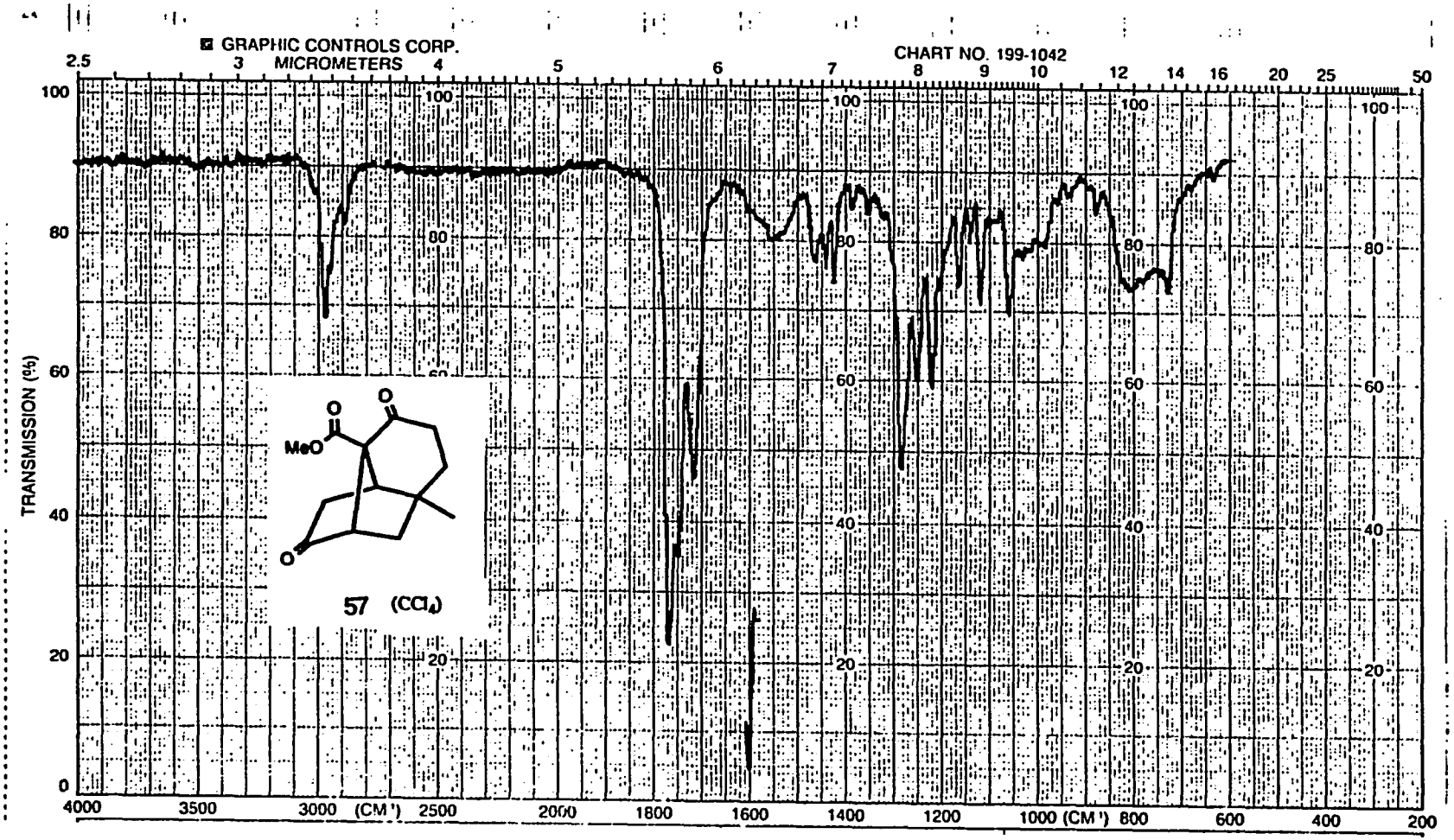

GRAPHIC CONTROLS CORP.
CHART NO. 199-1042
MICROMETERS
TRANSMISSION (%)
HO
MeO2C
O
(CCl4)
42
(CM ')

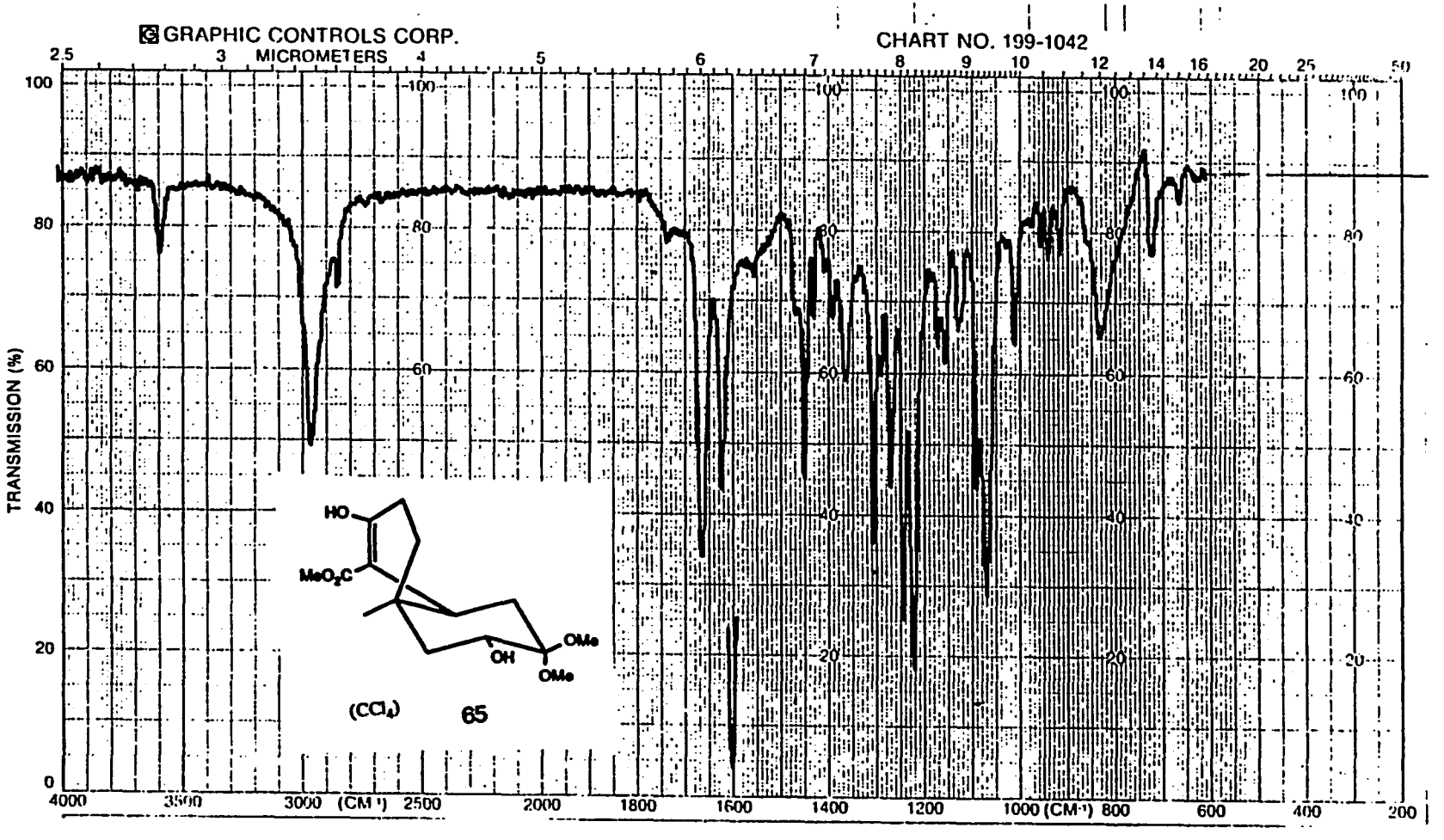

MICROMETERS
TRANSMISSION (%)
(CM⁻¹)
43a (CCl4)
Br
MeO2C
O

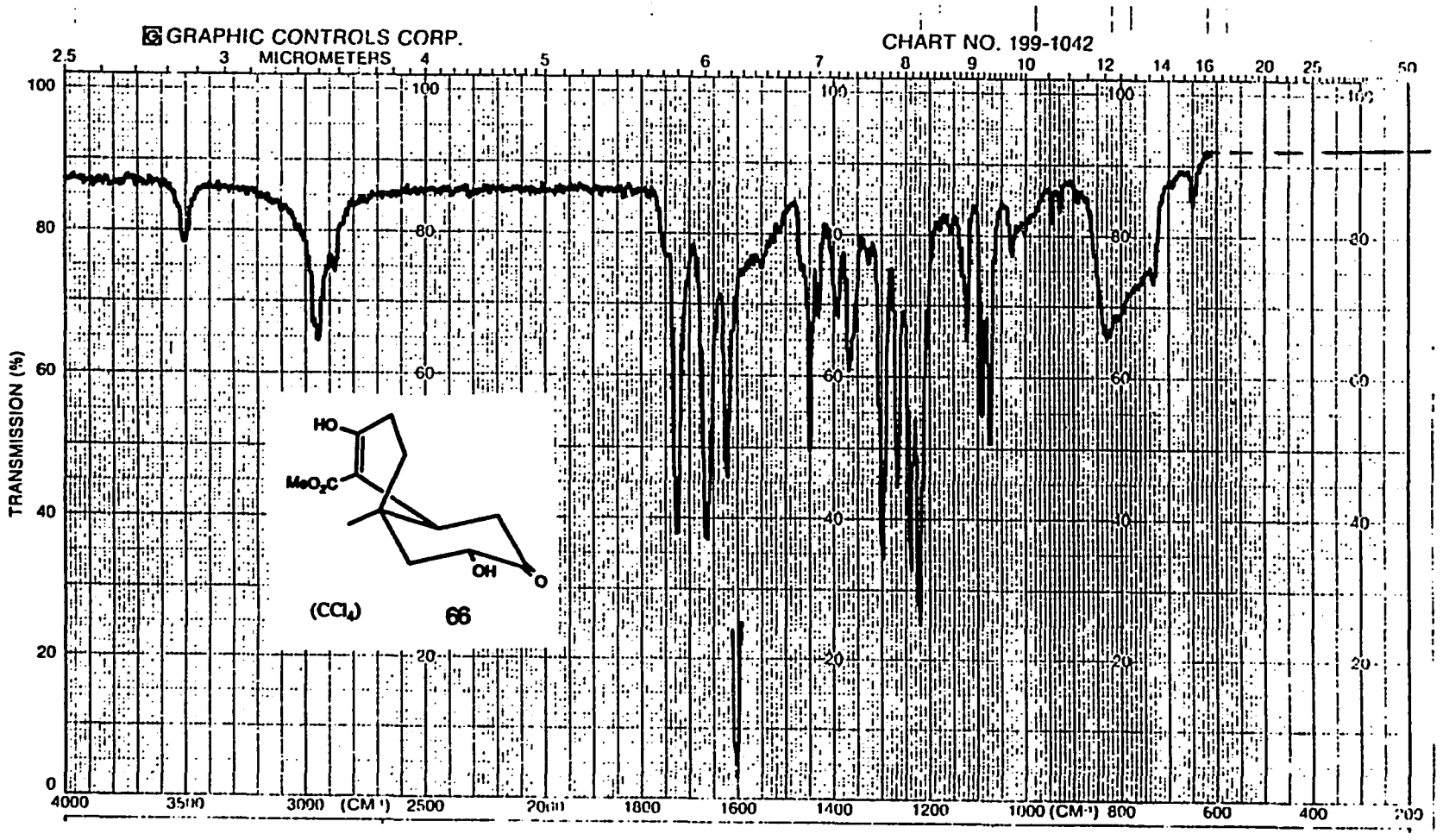

GRAPHIC CONTROLS CORP.
CHART NO. 199-1042
MICROMETERS
TRANSMISSION (%)
(CM ')
CO2Me
Br
O
O
43b (CCl4)


GRAPHIC CONTROLS CORP.
CHART NO. 199-1042
MICROMETERS
TRANSMISSION (%)
(CM ')
(CCl4)
45

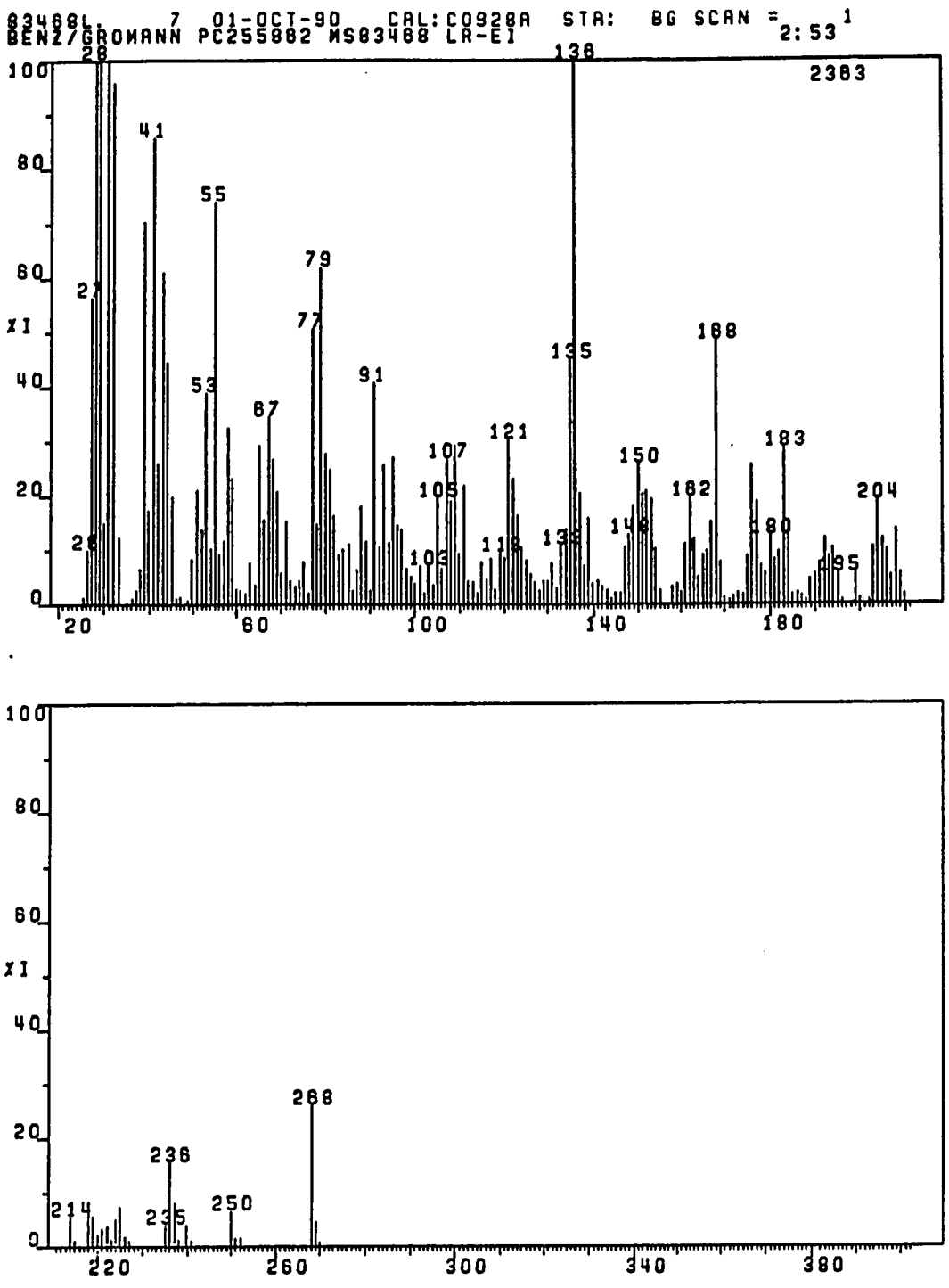

GRAPHIC CONTROLS CORP.
CHART NO. 199-10-12
MICROMETERS
TRANSMISSION (%)
(CM ')
HO
MeO2C
Br
O
54 (CCl4)


GRAPHIC CONTROLS CORP.
CHART NO. 199-1042
MICROMETERS
TRANSMISSION (%)
(CM⁻¹)
MeO
O
O
O
57 (CCl4)

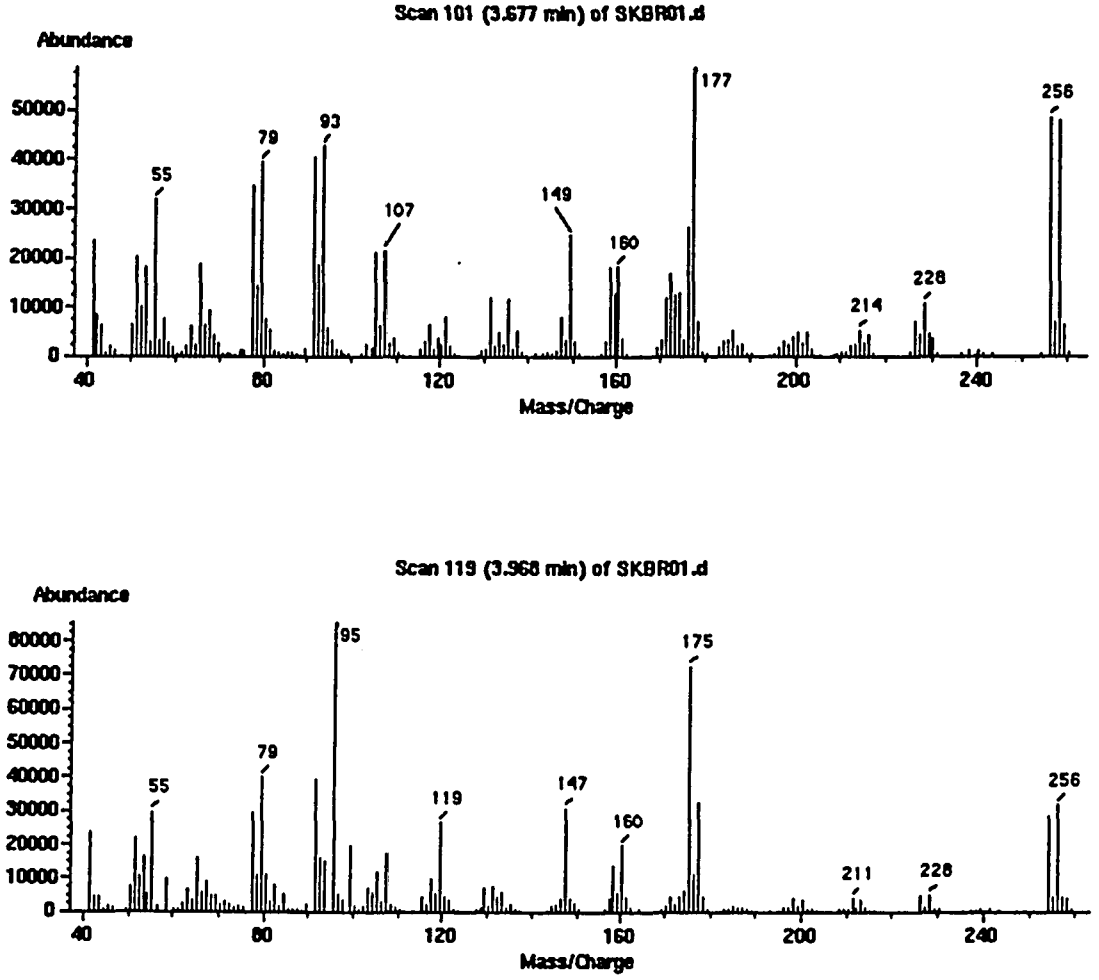

GRAPHIC CONTROLS CORP.
CHART NO. 199-1042
MICROMETERS
TRANSMISSION (%)
(CM⁻¹)
HO
MeO2C
OMe
OH
OMe
(CCl4)
65


GRAPHIC CONTROLS CORP.
CHART NO. 199-1042
MICROMETERS
TRANSMISSION (%)
(CM⁻¹)
HO
MeO2C
OH
O
(CCl4)
66

Mass Spectra of selected compounds

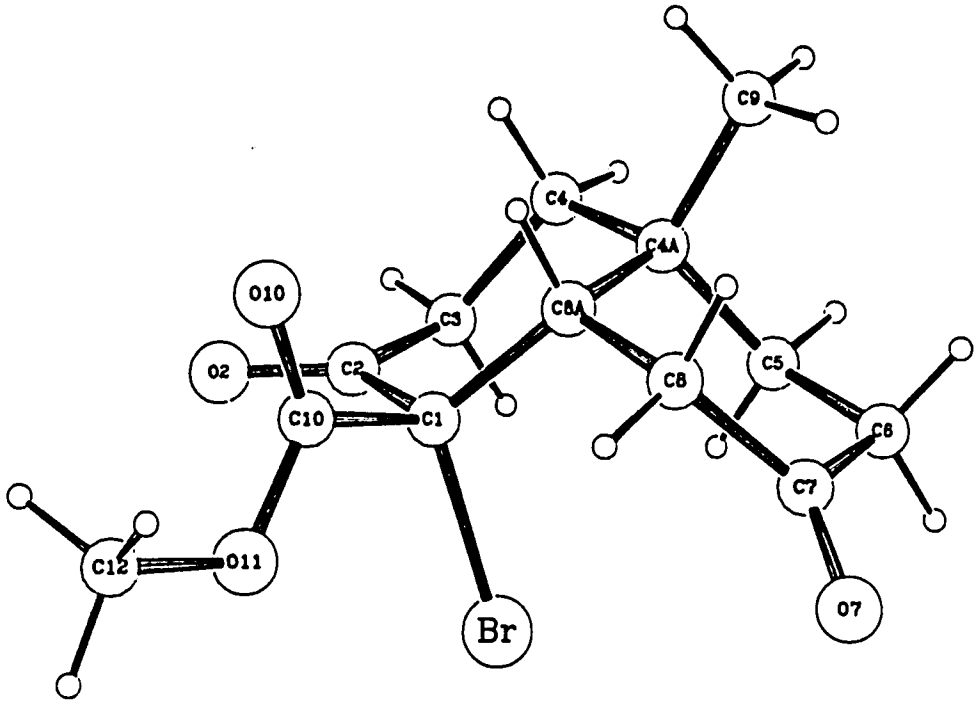


Mass spectrum of compound 65

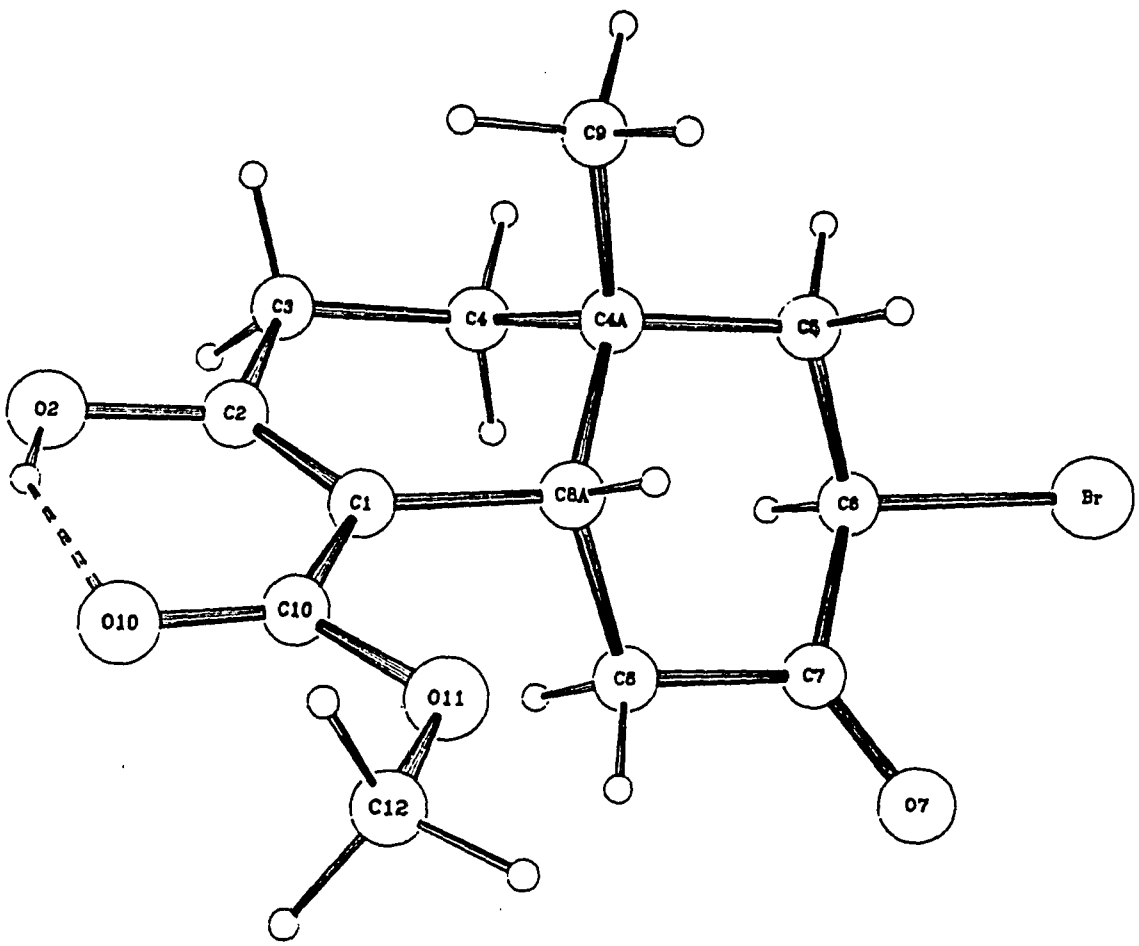


Mass spectrum of compound 93

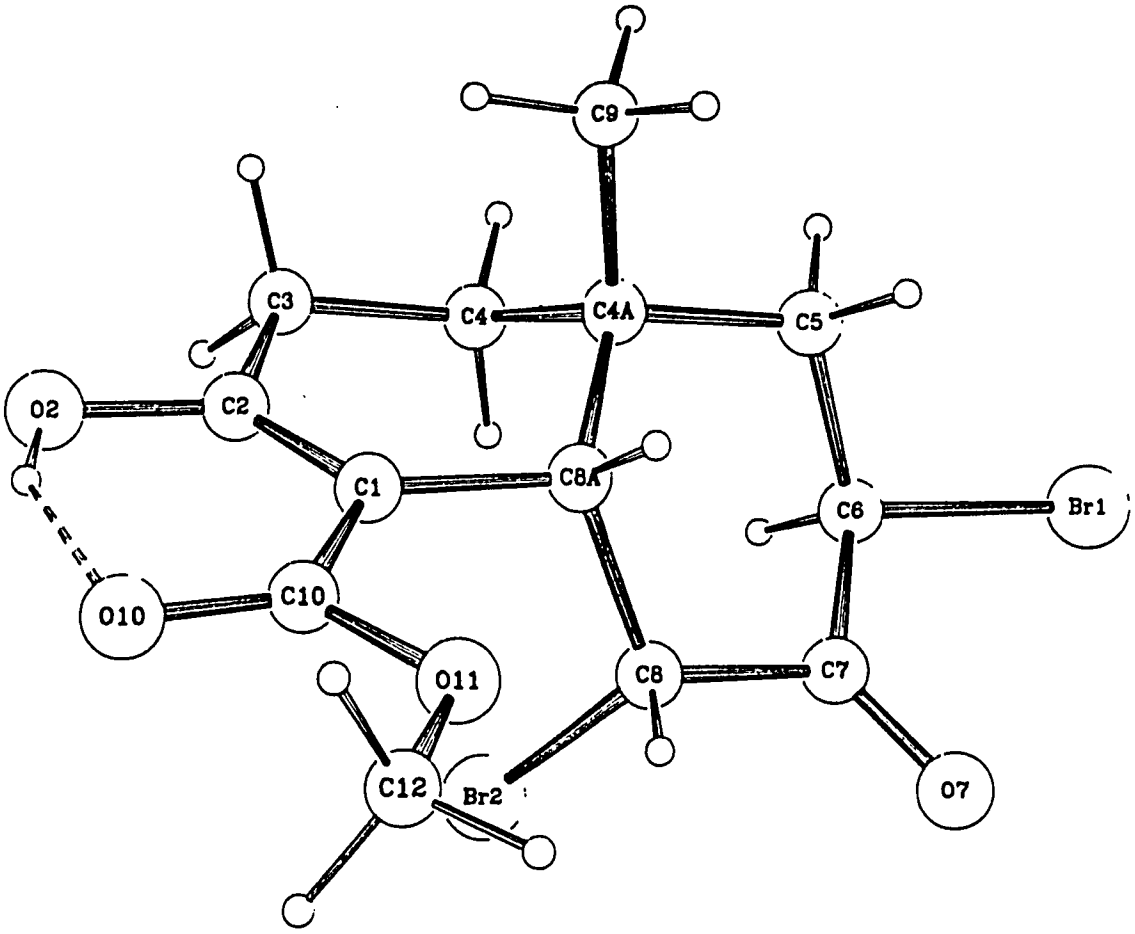
X-ray of selected compounds



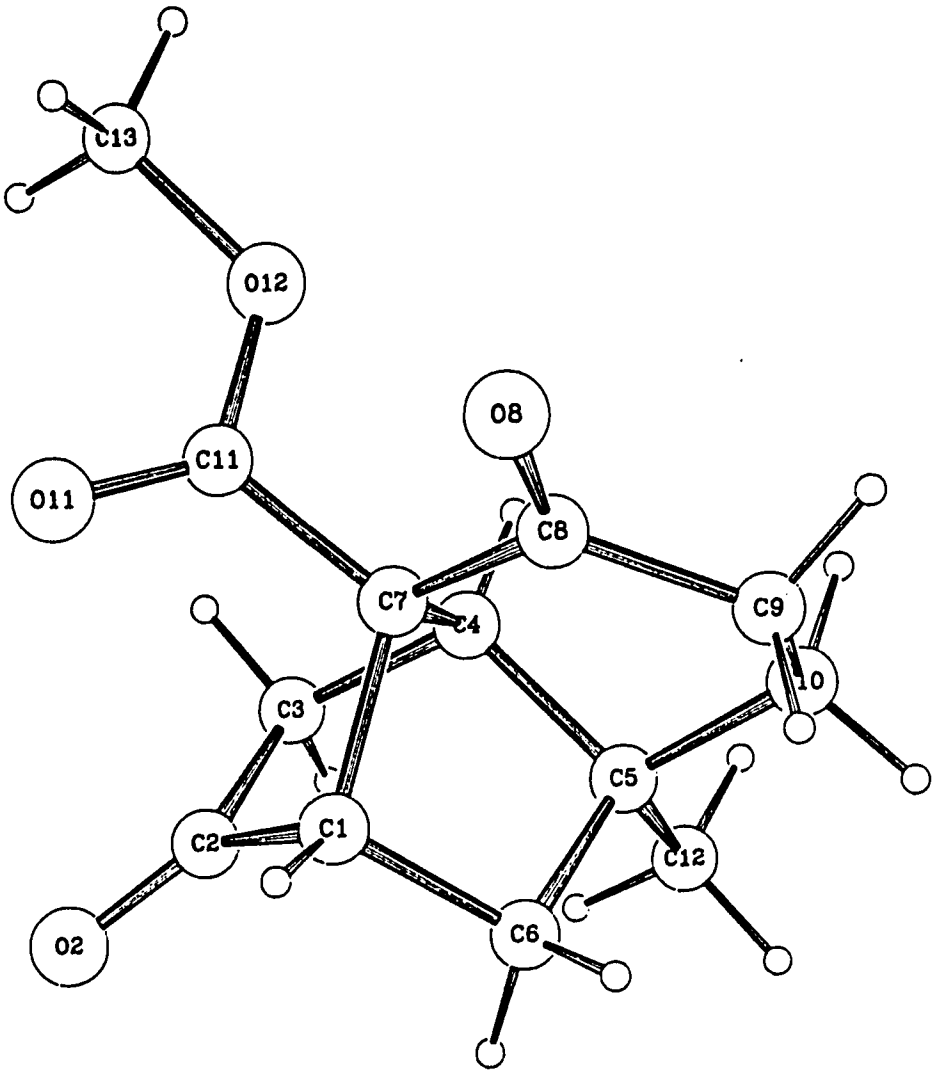
X-ray of compound 43a



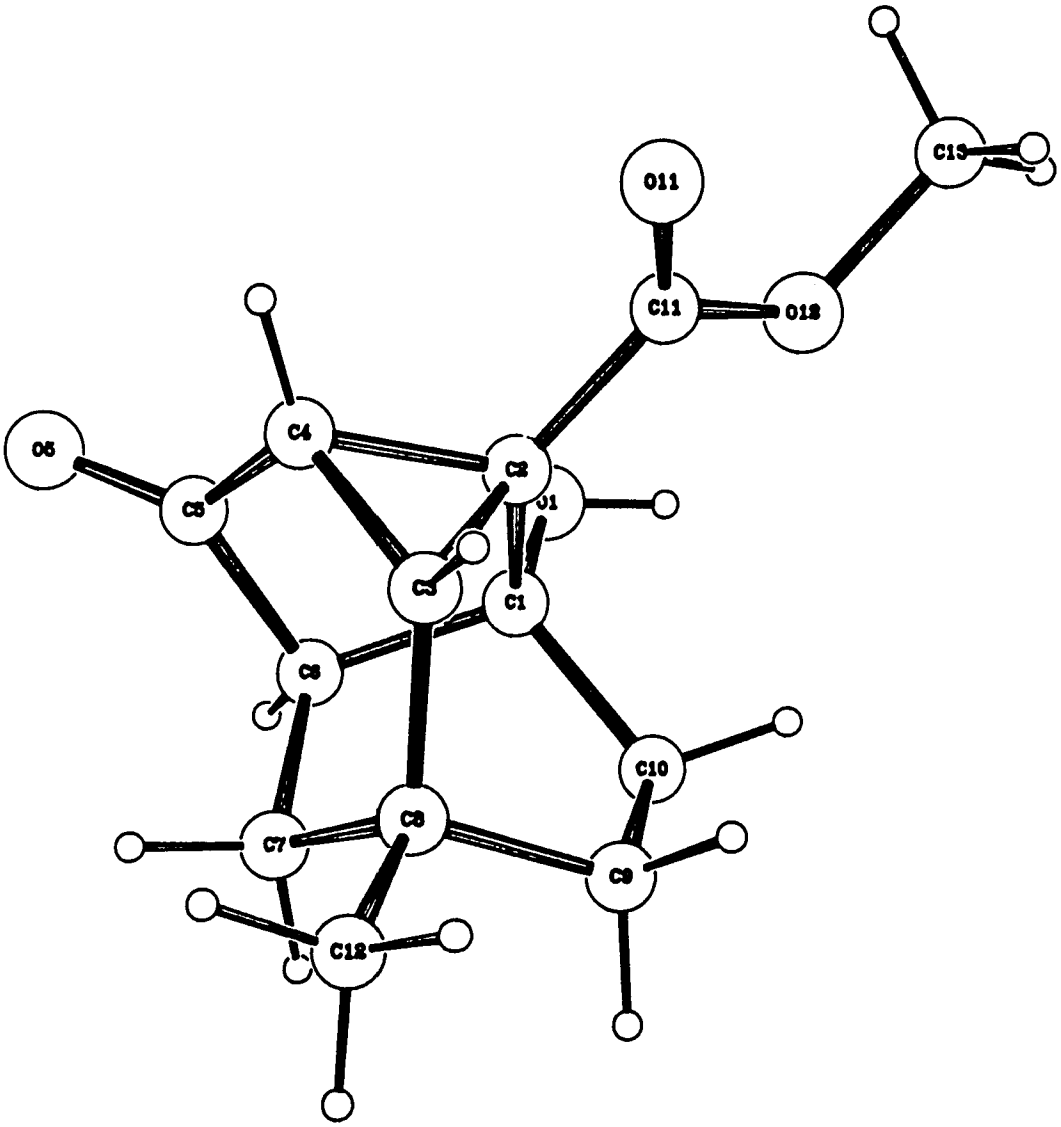
X-ray of compound 54



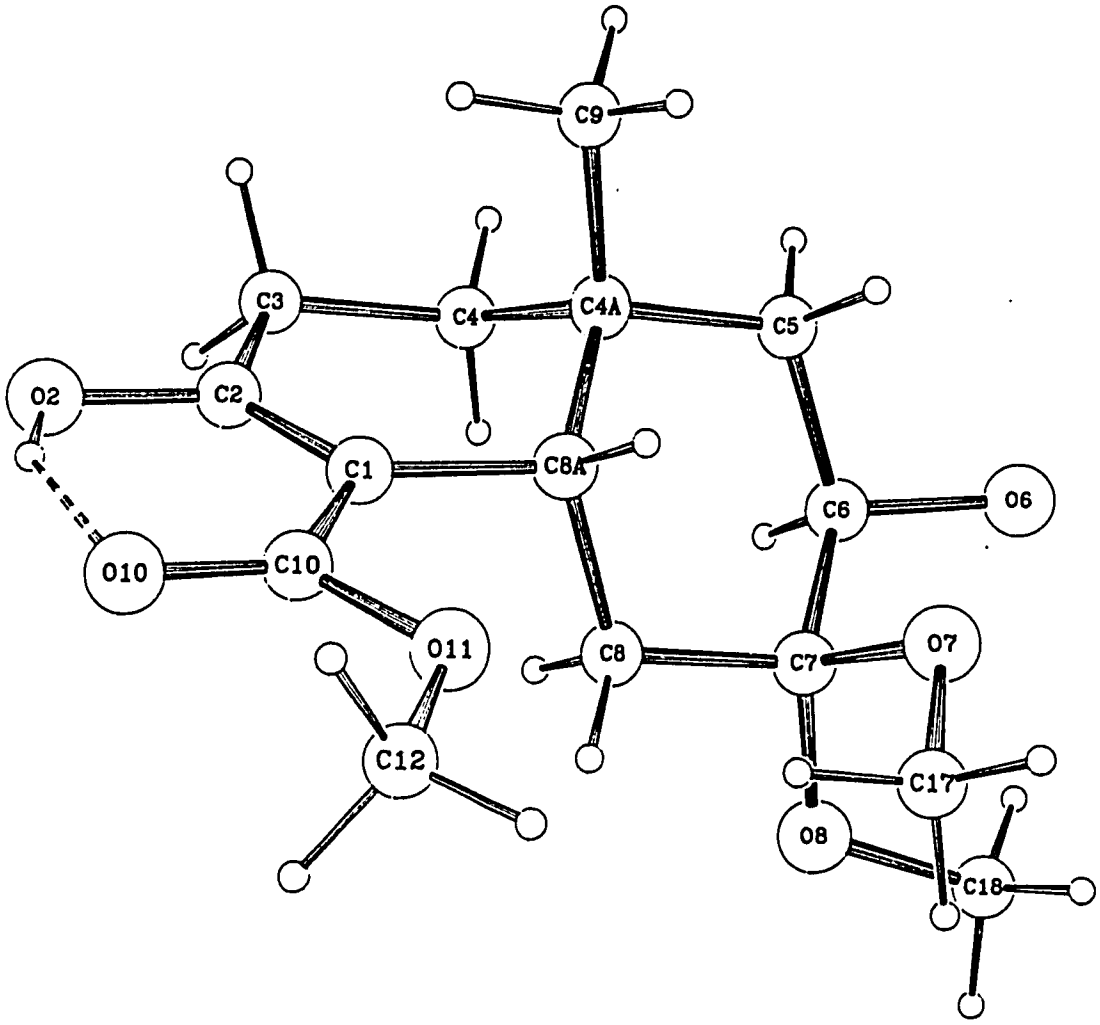
X-ray of compound 55



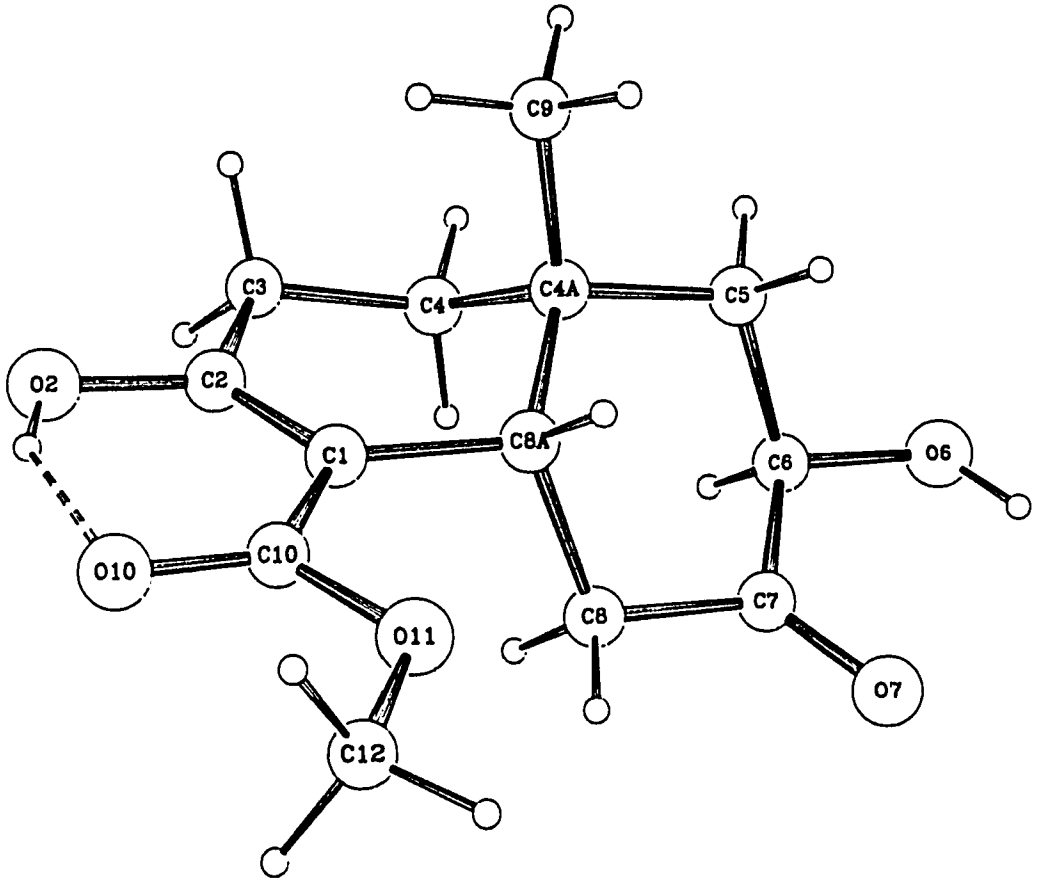
X-ray of compound 57



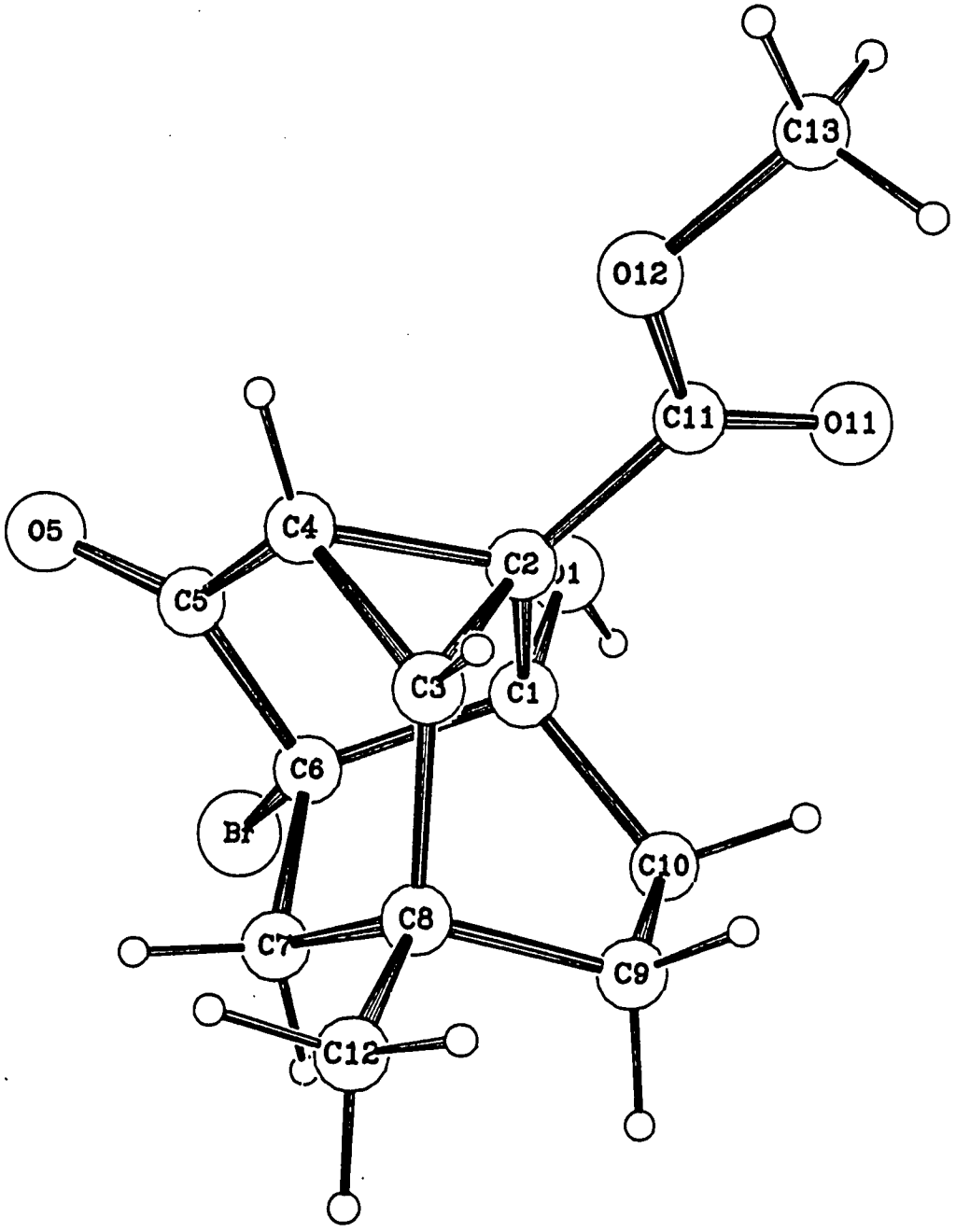
X-ray of compound 58



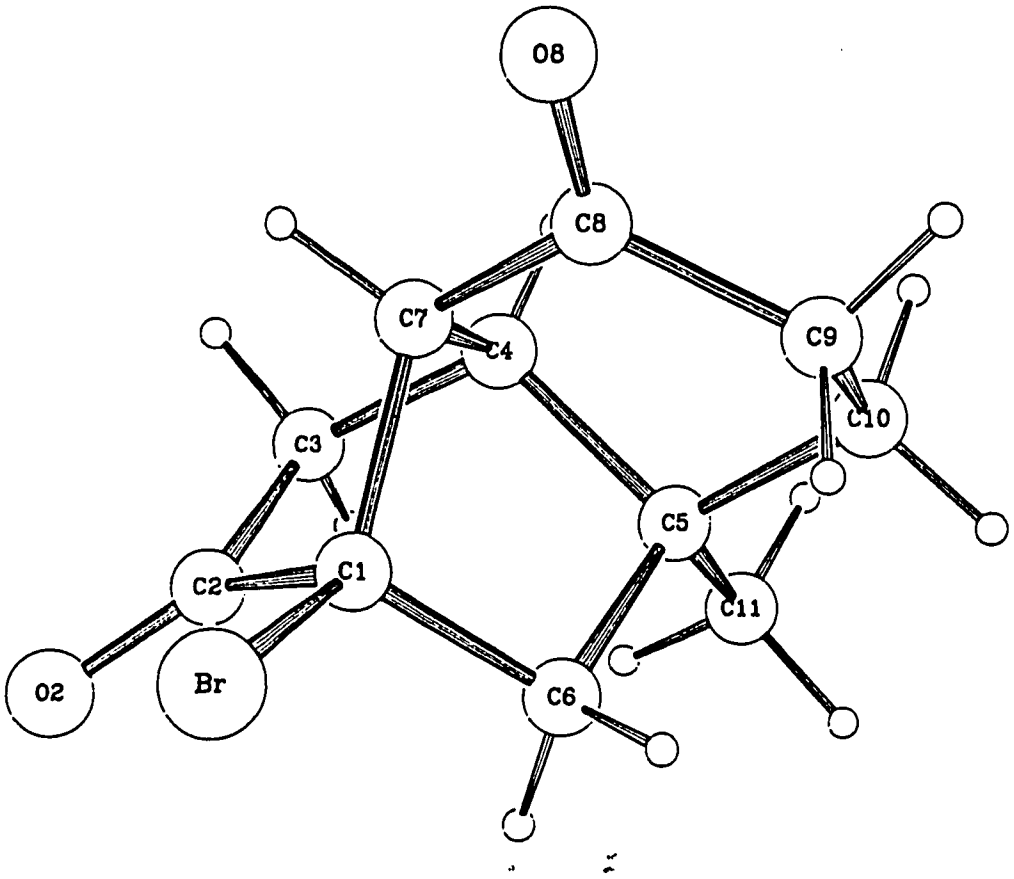
X-ray of compound 65



X-ray of compound 66



X-ray of compound 72



X-ray of compound 93

X-ray data given for compound 57

Crystal Data for 57

Formula	$C_{13}H_{16}O_4$
Formula weight	236.27
Crystal system	monoclinic
Space group	$P2_1/c$
a	12.925(3) Å
b	6.184(5) Å
c	16.257(4) Å
β	113.10(2)°
Z	4
d_{calc}	1.313 g cm^{-3}
μ(Cu Kα)	7.6 cm^{-1}

Table I. Final Atomic Parameters for 57

Atom	x	y	z	B(A2)
O2	0.1264(2)	0.5514(3)	0.4820(1)	5.63(5)
O8	0.5032(1)	0.1095(3)	0.7120(1)	4.59(4)
O11	0.3556(2)	0.2406(3)	0.4981(1)	5.75(5)
O12	0.3438(2)	-0.0960(3)	0.5423(1)	4.41(4)
C1	0.2680(2)	0.4158(4)	0.6220(2)	3.19(5)
C2	0.1651(2)	0.4082(4)	0.5359(2)	3.62(5)
C3	0.1145(2)	0.1840(5)	0.5317(2)	3.87(6)
C4	0.1958(2)	0.0800(4)	0.6196(1)	3.05(4)
C5	0.1838(2)	0.1823(4)	0.7016(2)	3.56(5)
C6	0.2180(2)	0.4211(4)	0.6946(2)	3.92(6)
C7	0.3101(2)	0.1791(4)	0.6269(1)	2.78(4)
C8	0.4105(2)	0.1295(4)	0.7130(2)	3.38(5)
C9	0.3919(2)	0.1138(5)	0.7984(2)	4.55(7)
C10	0.2695(2)	0.0735(5)	0.7851(2)	4.27(6)
C11	0.3400(2)	0.1178(4)	0.5491(2)	3.42(5)
C12	0.0661(2)	0.1578(6)	0.7026(2)	5.62(7)
C13	0.3612(3)	-0.1844(6)	0.4665(2)	5.78(7)
H1	0.324	0.533	0.628	3.8
H3A	0.114	0.102	0.478	4.6
H3B	0.036	0.193	0.530	4.6
H4	0.185	-0.080	0.619	3.7
H6A	0.151	0.518	0.676	4.7
H6B	0.276	0.472	0.753	4.7
H9A	0.417	0.253	0.832	5.5
H9B	0.439	-0.008	0.834	5.5
H10A	0.255	-0.086	0.780	5.1
H10B	0.258	0.130	0.839	5.1
H12A	0.050	0.001	0.707	6.8
H12B	0.063	0.237	0.755	6.8
H12C	0.009	0.219	0.646	6.8
H13A	0.362	-0.346	0.470	6.9
H13B	0.299	-0.137	0.410	6.9
H13C	0.434	-0.132	0.467	6.9

The parameters of the hydrogen atoms were not refined.

Standard deviations are in parentheses.

Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as:
(4/3) * [a2*B(1,1) + b2*B(2,2) + c2*B(3,3) + ab(cos gamma)*B(1,2) + ac(cos beta)*B(1,3) + bc(cos alpha)*B(2,3)]

Table II. Final Anisotropic Thermal Parameters (U's) for 57

Atom	U(1,1)	U(2,2)	U(3,3)
O2	0.060(1)	0.064(1)	0.075(1)
O8	0.0471(8)	0.054(1)	0.064(1)
O11	0.117(1)	0.051(1)	0.0754(8)
O12	0.090(1)	0.0345(9)	0.0539(7)
C1	0.042(1)	0.026(1)	0.049(1)
C2	0.041(1)	0.042(1)	0.051(1)
C3	0.043(1)	0.050(1)	0.046(1)
C4	0.047(1)	0.030(1)	0.0386(9)
C5	0.058(1)	0.034(1)	0.049(1)
C6	0.062(1)	0.030(1)	0.058(1)
C7	0.043(1)	0.025(1)	0.0360(9)
C8	0.049(1)	0.028(1)	0.044(1)
C9	0.069(2)	0.055(2)	0.039(1)
C10	0.080(1)	0.044(1)	0.042(1)
C11	0.050(1)	0.037(1)	0.0429(9)
C12	0.073(1)	0.077(2)	0.081(1)
C13	0.112(2)	0.060(2)	0.065(1)

Atom	U(1,2)	U(1,3)	U(2,3)
O2	0.011(1)	0.0107(9)	0.0361(9)
O8	0.0103(9)	0.0119(7)	0.0029(9)
O11	0.013(1)	0.0649(6)	0.0205(9)
O12	-0.0043(8)	0.0399(6)	-0.0074(7)
C1	0.0012(9)	0.0130(8)	0.003(1)
C2	0.002(1)	0.0146(8)	0.011(1)
C3	-0.010(1)	0.0102(9)	0.002(1)
C4	-0.0063(9)	0.0159(7)	-0.0005(9)
C5	-0.000(1)	0.0265(8)	0.001(1)
C6	0.003(1)	0.0250(9)	-0.001(1)
C7	0.0017(8)	0.0131(7)	0.0022(8)
C8	0.003(1)	0.0105(9)	-0.0008(9)
C9	0.011(1)	0.011(1)	0.006(1)
C10	0.004(1)	0.0276(9)	0.004(1)
C11	0.001(1)	0.0177(8)	0.003(1)
C12	0.001(2)	0.0485(9)	0.007(2)
C13	-0.004(2)	0.053(1)	-0.020(1)

The form of the anisotropic displacement parameter is:
exp[-2PI2(h2a2U(1,1) + k2b2U(2,2) + l2c2U(3,3) + 2hkabU(1,2) + 2hlacU(1,3) + 2klbcU(2,3))] where a,b, and c are reciprocal lattice constants.

Table III. Bond Distances (Å) for 57

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
O2	C2	1.208(3)	C4	C5	1.538(4)
O8	C8	1.210(3)	C4	C7	1.560(3)
O11	C11	1.199(3)	C5	C6	1.558(4)
O12	C11	1.330(3)	C5	C10	1.530(3)
O12	C13	1.444(4)	C5	C12	1.535(4)
C1	C2	1.507(3)	C7	C8	1.521(3)
C1	C6	1.553(4)	C7	C11	1.509(4)
C1	C7	1.552(3)	C8	C9	1.502(4)
C2	C3	1.523(4)	C9	C10	1.531(4)
C3	C4	1.543(3)			

Table IV. Bond Angles (°) for 57

Atom 1	Atom 2	Atom 3	Angle
C11	O12	C13	118.1(2)
C2	C1	C6	103.1(2)
C2	C1	C7	100.5(2)
C6	C1	C7	102.9(2)
O2	C2	C1	127.9(2)
O2	C2	C3	125.9(2)
C1	C2	C3	106.1(2)
C2	C3	C4	102.3(2)
C3	C4	C5	111.6(2)
C3	C4	C7	100.8(2)
C5	C4	C7	100.7(2)
C4	C5	C6	101.5(2)
C4	C5	C10	107.7(2)
C4	C5	C12	113.9(2)
C6	C5	C10	110.8(2)
C6	C5	C12	113.9(2)

Atom 1	Atom 2	Atom 3	Angle
C1	C6	C5	104.5(2)
C1	C7	C4	93.7(2)
C1	C7	C8	113.1(2)
C1	C7	C11	113.2(2)
C4	C7	C8	115.6(2)
C4	C7	C11	112.6(2)
C8	C7	C11	108.2(2)
O8	C8	C7	120.0(2)
O8	C8	C9	121.6(2)
C7	C8	C9	118.3(2)
C8	C9	C10	114.3(2)
C5	C10	C9	113.7(2)
O11	C11	O12	123.4(3)
O11	C11	C7	126.1(2)
O12	C11	C7	110.5(2)

Standard deviations are in parentheses.

REFERENCES

REFERENCES FOR PART I

1. L. T. Scott and M. Jones, Jr., Chem. Rev., 72, 181 (1972); S. Masamune and N. Darby, Acc. Chem. Res., 5, 272 (1972), and the references therein.

2. A. T. Balaban, Rev. Roum. Chim., 11, 865 (1972)

3. G. Schroeder and W. Martin, Angew. Chem., Int. Ed. Engl., 5, 130 (1966); G.Schroeder, ibid., 2, 481 (1963); G.Schroeder, Chem. Ber., 97, 3131 (1964)

4. W. V. E. Doering and H. Krouch, Angew. Chem., 68, 661 (1956)

5. M. E. Volpin, I. S. Akhrem, and D. N. Kusanov, Zh. Obshch. Khim, 28, 330 (1958)

6. L. A. Paquette and M. J. Kukla, J. Chem. Soc., Chem. Commun., 409 (1973); L. A. Paquette and J. C. Stowel, ibid., 93, 5735 (1971); L. A. Paquette and J. C. Stowell, Tet. Lett., 4159 (1969)

7. J. A. Berson and R. F. Davis, J. Am. Chem. Soc., 94, 3658 (1972)

8. J. F. M. Oth, H. M. Gilles, and G. Schroeder, Tet. Lett., 67 (1970)

9. S. Raghu, "Synthetic approaches to truncated tetrahedrane and other $(CH)_{12}$ hydrocarbons", Ph. D. thesis, Michigan state University (1972)

10. E. Vedejs and R. A. Shepherd , J. Org. Chem. 41, 742 (1976)

11. E. Vedejs, W. R. Wilber, R. Tweig, J. Org. Chem. 42, 401 (1977)

12. W. R. Wilber "Synthetic approaches to the tetrahedral molecule heptacyclo $[5.5.0.0.^{2,12}.0^{3,5}.0^{4,10}.0^{6,8}.0^{9,11}]$ dodecane", Ph. D. thesis, Wisconsin-Madison University (1974)

13. L. A. Wade, "Synthetic approaches to bicyclo [5.5.0] dodecane", Ph. D. thesis, Harvard University (1974)

14. J. E. Baldwin and F. al-Barkawi, "Truncated tetrahedrane" Abstracts of the 159th ACS national meeting, division of petroleum chemistry , Houston, Texas, **(1970)**

15. R. J. Brousseau, Ph. D. thesis, Harvard University, **(1977)**

16. H. Park, Ph. D. thesis, Ohio State University **(1980)**

17. L. T. Scott, Ph. D. thesis, Harvard University **(1970)**

18. P. Mukharjee, postdoctoral research report **(1971)**

19. R. B. Woodward, R. Hoffmann, "The conservation of orbital symmetry" Academic press, New York, N.Y., **(1970)**

20. P. Bischof, R. Gleiter, and E. Heilbronner, Helv. Chim. Acta 53, 1425 **(1970)**

21. S. Winstein, J. Am. Chem. Soc., 81, 6524 **(1959)**; R. Adams, S. Winstein, ibid., 70, 838 **(1948)**

22. H. Prinzbach, D. Stuscher, J. Market, H. H. Limbach., Chem. Ber. 109, 3505 **(1976)**

23. P. Radlick, S. Winstein, J. Am. Chem. Soc., 85, 344 **(1963)**; K. G. Unch, ibid., 85, 345 **(1963)**; W. R. Roth, Justus Liebig Ann. Chem., 671, 10 **(1964)**

24. R. B. Woodward, T. Fukunaya, R. C. Kelly, J. Am. Chem. Soc., 86, 3162 **(1964)**; I. T. Jacobson, Acta. Chem. Scand., 21, 2235 **(1967)**; C. Mercier, P. Soucy, W. Rosen, P. Deslongchamps, Synth. Commun., 3, 161 **(1973)**; M. J. Wyvrat, L. A. Paquette, Tet. Lett., 2433 **(1974)**

25. A. de Meijere, D. Kaufmann, O. Schallner, Angew. Chem. Intern. Ed., 10, 417 **(1971)**

26. L. A. Paquette, R. A. Snow, J. L. Muthard, T. Cynkowski, J. Am. Chem. Soc., 100, 1600 **(1978)**

27. W. R. Roth, W. B. Bang, P. Goehel, R. L. Sass, R. B.Turner, A. P. Yu, J. Am. Chem. Soc., 86, 3178 **(1964)**

28. L. I. Smith, J. R. Holum, J. Am. Chem. Soc., 78, 3417 (1956); J. Armond, L. Boulares, Can. J. Chem., 54, 1197 (1976)

29. J. Aihara, J. Am. Chem. Soc., 98, 2750 (1976)

30. L. A. Paquette, T. G. Wallis, T. Kempe, G. G. Christoph, J. P. Springer, J. Clardy, J. Am. Chem. Soc., 99, 6946 (1977)

31. E. Heilbronner, R. Gleiter, T. Hoshi, A. de Meijere, Helv.Chim. Acta 56, 1594 (1973)

32. J. F. Liebman, L. A. Paquette, J. R. Peterson, D. W. Rogers, J. Am. Chem. Soc., 108, 8267 (1986)

33. M. A. Miller, J. M. Schulman, R. L. Disch, J. Am. Chem. Soc., 110, 7681 (1988)

34. J. M. Schulman, M. L. Miller, R. L. Disch, Theochem , 169, 563 (1988)

35. M. J. S. Dewar, A. J. Holder, J. Am. Chem. Soc., 111, 5384 (1989)

36. S. W. Benson, F. R. Cruickshank, D. M. Goleden, G. R. Haugen, H. E. O'Neal, A.S. Rodgers, R. Shaw, and R. Walsh, Chemical Reviews 69, 279 (1969)

37. J. M. Schulman, R. L. Disch, M. L. Sabio, J.Am. Chem. Soc., 108, 3258 (1986); J. M. Schulman, R. L.Disch, Tetrahedron Lett., 26, 5647 (1985)

38. R. B.Woodward, T. Fukunaya, O. Schallner, J. Am. Chem. Soc., 86, 3162 (1964)

39. M. Jones, Jr., S. D. Reich, and L. T. Scott, J. Am. Chem. Soc., 92, 3118 (1970)

40. L. A. Paquette, J. Dressel, K. L. Chasey, J. Am. Chem. Soc., 108, 512 (1986); ibid. 110, 5479 (1988); L. A. Paquette, J. Dressel, P. D. Pansegrau, Tetrahedron Lett., 4965 (1987)

41. H. Rottle, W. Martin, J. F. M. Oth, and G. Schroeder, Chem. Ber., 102, 3985 (1969)

42. W. L. Mock, C. M. Sprecher, R. F. Stewart, and M. G. Northolt, J. Am. Chem. Soc., 94, 2015 **(1972)**

43. P. Radlick and W. Fenical, J. Am. Chem. Soc., 91, 1560 **(1969)**

44. E. Vogel, W. Wiedemann, H. Roth, J. Eimer, H. Gounther, Justus Liebigs Ann. Chem., 759, 1 **(1972)**

45. P. Warner, S. L. Lu, J. Org. Chem., 41, 1459 **(1976)**

46. E. J. Corey, A. G. Hostmann, J. Am. Chem. Soc., 87, 5736 **(1965)**

47. D. Ginsburg, "Propellanes; Structure and Reactions" p.119 **(1975)**

48. R. Breslow, J. M. Hoffmann Jr, J. Am. Chem. Soc., 94, 2110 **(1972)**; R. Breslow, J. M. Hoffmann Jr, C. Perchonock, Tetrahedron Lett. 3723 **(1973)**

49. S. Hirano, T. Hiyama, H. Nozaki, Tetrahedron, 32, 2381 **(1976)**

50. L. A. Paquette, M. J. Wyvratt, J. Am. Chem. Soc., 96, 4671 **(1974)**; M. J. Wyvratt, L. A. Paquette, Tetrahedron Lett., 2433 **(1974)**

51. R. A. Snow, C. R. Degenhardt, L. A. Paquette, Tetrahedron lett. 4447 **(1976)**

52. L. A. Paquette, M. J. Wyvratt, H. C. Berk, R. E. Moerck, J. Am. Chem. Soc., 100, 5845 **(1978)**

53. C. I. F. Watt, "The synthesis of some intermediates directed toward the preparation of pentacyclo [5.3.2.$0^{4,11}$.$0^{10,8}$] dodecatriene", Ph. D. thesis, Carnegie-Melon University **(1972)**

54. H. Bohme and K. Hartke, Chem. Ber., 93, 1305 **(1960)**

REFERENCES FOR PART II and III

1. S. G. Levine, J. Am. Chem. Soc., 80, 6150 (**1958**); G. Wittig, Angew. Chem. 71, 127 (**1959**); Chem. Ber. 94, 1373 (**1961**); M. E. Jung, M. A. Mazurek, R. M. Lim, Synthesis, 588 (**1978**); G. R. Pettit, B. Green, G. L. Dunn, and P. Sunder-Plassmann, J. Org. Chem., 35, 1385 (**1970**)

2. H. E. Simmons and R. D. Smith J. Am. Chem. Soc. 81, 4256 (**1959**)

3. E. Wenkert, D. A. Berges, J. Am. Chem. Soc., 89, 2507 (**1967**); E. Wenkert, R. A. Mueller, E. J. Reardon, Jr., S. S. Sathe, D. J. Scharf, and G.Tosi, ibid., 92, 7428 (**1970**); E. Wenkert, C. A. Mc Pherson, E. L. Sanchez, and R. L. Webb, Synth. Commun., 3, 255 (**1973**)

4. J. E. McMurry and M. P. Fleming, J. Org. Chem., 41, 896 (**1976**); J. E. McMurry, M. P. Fleming, K. L. Kees, and L. R. Krepski, ibid. 43, 3255 (**1978**); J. E. McMurry, T. Lectka, and J. G. Rico. ibid., 54, 3748 (**1989**)

5. L. Stehelin, L. Kanellias, and G. Ourisson, J. Org. Chem., 38, 851 (**1973**)

6. H. Setetter and J. Mayer, Chem. Ber., 92, 2664 (**1959**)

7. E. Wenkert, F. Haviv and A. Zeithin, J. Am. Chem. Soc., 91, 2299 (**1969**)

8. W. Haung, Ph. D. Thesis, City University of New York (**1990**)

9. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M.C. Pirrung, J. E. Sohn, and J. Lampe, J. Org. Chem., 45, 1066 (**1980**)

10. H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, J. Org. Chem., 34, 2324 (**1969**)

11. K. A. Hill, P. L. Stotter, J. Org. Chem., 38, 2576 (**1973**)

12. A. W. P. Jarvie, Organometal. Chem. Rev., Sect.A, 6, 153 (**1970**); S. Murai, Y. Kuroki, T. Aya, N. Sonoda and S. Tsutsumi, J. Chem. Soc. Chem. Commun., 741 (**1972**)

13. R. Gleiter, G. Jaehne, Angew. Chem. Int. Ed. Engl., 22, 488 (**1983**)

14. E. Ghera, Y. Gaoni, S. Shoua, J. Am. Chem. Soc., 93, 524 (1971)

15. H. Quast, J. Christ, E. M. Peters, K. Peters, and H. G. V. Schnering, Chem. Ber. 118, 1154 (1985)

16. H. Finkelstein, Ber., 43, 1528 (1910); M. Hojo, R. Masuda, E. Saeki, S. Uyeda, Synthesis, 697 (1976); M. Schlosser, B. Spahic, C. Tarchini, and L. Van Chau, Angew. Chem. Internat. Ed., 14, 365 (1975)

17. J. V. Hatton and R. E. Richards, Mol. Phys., 5, 153 (1962)

18. R. E. Irland and P. W. Shiess, J. Org. Chem., 28, 6 (1963); G. R. Pettit, G. L. Dunn, P. Sunder-Plassmeimn J. Org. Chem., 35, 1385 (1970)

19. P. Magnus, G. Roy., Organometallics, 1, 553 (1982)

20. H. E. Simmons and R. D. Smith J. Am. Chem. Soc., 80, 5323 (1958)

21. J. M. Dennis, C. Girard, and J. M. Conia Synthesis, 549 (1972)

22. J. Furukawa, N. Kawabata and J. Nishimura, Tetrahedron, 53 (1967)

23. C. Girard and J. M. Conia , Tetrahedron Lett., 37, 3333 (1974)

24. P. Cazeau, F. Mouline, O. Laporte, F. J. Duboudin, Organomet. Chem. 201, C9-C13 (1980)

25. T. K. Jones and S. E. Denmark, J. Org. Chem., 50, 4037 (1985)

26. P. Boldt, H. Militzen, W. Thielecke and L. Schultz, Liebigs Ann. Chem., 718, 101 (1968)

27. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkorucz and R. Terrell, J. Am. Chem. Soc., 85, 207 (1963)

28. K. Taguchi, F. H. Westheimer, J. Org. Chem., 36, 1570 (1971)

29. D. P. Roelofsen, H. Van Bekkum, Recl. Trav. Chim. Pays-Bas 91, 605 (1972)

30. J. K. Whitesell, S. W. Felman, J. Org. Chem., 42, 1663 (1977)

31. E. Elkik, Bull. Soc. Chim. France., 972 (1960); G. Optiz, Angew. Chem., 73, 437 (1961); G. Optiz and H. Mildenberger Ann., 649, 26 (1961)

32. K. C. Brannock and R. C. Burpitt, J. Org. Chem., 26, 3576 (1961); G. Optiz, H. Hellmann, H. Mildenberger and H. Suhr, Ann., 649, 36 (1961); G. Optiz. ibid 650, 122 (1961)

33. G. Stork and S. R. Dowd, J. Am. Chem. Soc., 85, 2178 (1963)

34. G. R. Kieczykowski, R. H. Schlessinger, and R. B. Sulsky Tetrahedron Lett. 8, 597 (1976)

35. E. Vogel, W. Klug, and A. Breuer, Org. Synth. Vol. 54 page 11 (1974)

36. M. Yu Lukina, Russ. Chem. Rev., 31, 419 (1962)

37. C. H. Depuy and F. W. Breitbeil, J. Am. Chem. Soc., 85, 2176 (1963)

38. C. Kaiser, A. Burger, L. Zirngibl, C. S. Davis, and C. L. Zirkle, J. Org. Chem., 27, 768 (1962)

39. C. L. Bumgardner and J. P. Freeman, Tetrahedron Lett., 737 (1964)

40. A. J. Birch, J. M. H. Graves, and J. B. Siddall, J. Chem. Soc., 4234 (1963)

41. W. E. Parham, R. W. Soeder, J. R. Throckmorton, K. Kuncl, and R. M. Dodson, J. Am. Chem. Soc., 87, 321 (1965); L. Skattebol, J. org. Chem., 31, 1554 (1966)

42. R. C. Selms, Tetrahedron Lett., 1965 (1966)

43. G. Stork, M. Nussim, and B. August, Tetrahedron Suppl., 8, 105 (1966)

44. D. F. Taber, Ph. D. thesis, Columbia University (1974)

45. A. J. Birch and J. S. Hill, J. Chem. Soc. (C), 419 (1966)

46. S. Danishefsky, S. Chackalamannil, B. J. Uang, J. Org. Chem., 47, 2231 (1982)

47. A. P. Krapcho, G. A. Glynn, and B. J. Grenon, Tet. Lett., 215 (1967)

48. M. Isobe, H. Ito, T. Kawai and T. Goto, Tetrahedron, 35, 941 (1979)

49. R. Gleiter, G. Jauhne., Angew. Chem. Suppl., 661-667 (1983)

50. L. C. King, G. K. Ostrum, J. Org. Chem., 29, 3459 (1964)

51. L. F. Fieser and M. Fieser, "Steroids", Reinhold Publishing Corp., New York, N. Y p 170 (1959)

52. N. S. Baccha and D. S. Williams, Applications of NMR Spectroscopy in Organic Chemistry, Holden-Day, Inc., San Francisco, Calif., 51 (1964)

53. R. P. Holysz, J. Am. Chem. Soc., 75, 4432 (1953)

54. A. E. Derome, Modern NMR Techniques for Chemistry Research, Pergamon press, 133 (1987)

55. Tse-Lok Ho, Carbocycle Construction in Terpene Synthesis, VCH publishers, Inc., 204 (1988)

56. Mousseron, Jacquier, and Fontaine, Bull. Soc. Chim. France, [5] 19, 767, (1952)

57. R. B. Loftfield and L. Schaad, J. Am. Chem. Soc., 76, 35 (1954)

58. C. L. Stevens and J. Tazuma, J. Am. Chem. Soc., 76, 715 (1954)

59. M. Bergmann and A. Miekeley, Ber., 64, 802 (1931)

60. A. S. Kende, Org. Reactions, 11, 261 (1960)

61. C. L. Stevens, W. Malik, R. Pratt, J. Am. Chem. Soc., 72, 4758 (1950)

62. C. l. Stevens and E. Farkas, J. Am. Chem. Soc., 74, 618 (1952)

63. J. G. Aston and R.B. Greenburg, J. Am. Chem. Soc., 62, 2590 (1940)

64. R. B. Wagner and J. A. Moore, J. Am. Chem. Soc., 72, 2884 (1950)

65. A. A. Sacks and J. G. Aston, J. Am. Chem. Soc., 73, 3902 (1951)

66. R. B. Wagner and J. A. Moore, J. Am. Chem. Soc., 72, 3655 (1950)

67. B. B. Smith and H. R. Nace, J. Am. Chem. Soc., 76, 6119 (1954)

68. R. B. Loftfield, J. Am. Chem. Soc., 72, 632 (1950); ibid., 73, 4707 (1951)

69. R. Joly, J. Warnant, G. Nomine, and D. Bertin, Bull. Soc. Chim. France, 366 (1958)

70. R. Joly and J. Warnant, Ibid., 367 (1958)

71. L. Wolff, Ann., 260, 79 (1890); Ber., 26, 2220 (1893)

72. M. Conrad, Ber., 32, 1005 (1899)

73. R. B. Wagner and J. A. Moore, J. Am. Chem. Soc., 72, 974 (1950)

74. R. B. Wagner, J. Am. Chem. Soc., 71, 3214 (1949)

75. G. Stork and I. Borowitz, J. Am. Chem. Soc., 82 (1960)

76. R. B. Woodward and A. F. Clifford, J. Am. Chem. Soc., 63, 1123, 2727 (1941)

77. J. Romo and A. Romo de Vivar, J. Am. Chem. Soc., 79, 1118 (1957)

78. O. Wallach, Ann., 414, 271 (1918)

79. O. Wallach, Ann., 327, 125 (1903); ibid., 414, 233 (1918)

80. R. Breslow, J. Posner, A. Krebs, J. Am. Chem. Soc., 85, 234 (1963)

81. M. Yanagita and Tahara, J. Org. Chem. 18, 792 (1953); M. Yanagita and K. Yamakawa, ibid., 21, 500 (1956); J. A. Marshall, G. L. Bundy, and W. I. Fanta, ibid., 33, 3913 (1968)

82. A. Butenandt and A. Wolff, Chem. Ber., 68, 2091 (1935); E. J. Corey, J. Amer. Chem. Soc., 75, 4832 (1953)

83. P. de Mayo, R. Robinson, E. Y. Spencer, And R. W. White, Experientia, 18, 359 (1962)

84. P. de Mayo and R. E. Williams, J. Am. Chem. Soc., 87, 3275 (1965)

85. J. E. McMurry, J. Am. Chem. Soc., 90, 6821 (1968)

86. J. E. McMurry, J. Org. Chem., 36, 2826 (1971)

87. J. E. McMurry, S. J. Isser, J. Am. Chem. Soc., 94, 7132 (1972)

88. C. H. Heathcock, R. A. Badger, and J. W. Patterson, Jr. J. Am. Chem. Soc., 89, 4133 (1967)

89. E. Piers, R. W. Britton and W. de Waal, Chem. Commun., 1069 (1969)

90. J. L. Gras, Tetrahedron Lett., 47, 4117 (1977)

91. M. Yanagiya, K. Kaneko, T. Kaji, T. Matsumoto, Tetrahedron Lett., 1761 (1979)

92. E. Piers, R. W. Britton, R. J. Keziere, R. D. Smillie, Can. J. Chem. 49, 2620 (1971); E. Piers, R. W. Britton, M. R. Geraphty, R. J. Keziere, R. D. Smillie, ibid. 53, 2827 (1975)

93. C. B. C. Boyce and J. S. Whitehurst, J. Chem. Soc., 2680 (1960)

94. K. L. Williamson, T. Howell, and T. A. Spencer, J. Am. Chem. Soc., 88, 325 (1966)

REFERENCES PART IV

1. P. Main, S. Fiske, S. Hull, L. Lessinger, G. Germain, J. P. Declercq, M. Woolfson, (1982). MULTAN 11/82. University of York, England and University of Louvain, Belgium.

2. Instruction manual for Chromatotron model 8924, Harrison Research, CA (1988)

3. W. C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 43, 2923 (1978)

4. M. F. Lipton, C. M. Sorensen, A. C. Sadler, and R. H. Shapiro, J. Organometal. Chem., 186, 155 (1980)

5. M. R. Winkle, J. M. Lasinger, and R. C. Ronald, J. C. S. Chem. Comm., 87 (1980)