To the Graduate Council:

I am submitting herewith a thesis written by Michael Sean Gaines entitled "Synthesis of Isobutyl and Pentyl C-4 Substituted Derivatives of Naturally Occurring (+)-Calanolide A and (−)-Calanolide B." I have examined the final copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

David C. Baker

Dr. David C. Baker, Major Professor

We have read this thesis
and recommend its acceptance:

Accepted for the council:

Associate Vice Chancellor
and Dean of The Graduate School

Synthesis of Isobutyl and Pentyl C-4 Substituted Derivatives of Naturally Occurring (+)-Calanolide A and (−)-Calanolide B

A Thesis

Presented for the

Master of Science

Degree

The University of Tennessee, Knoxville

Michael Sean Gaines

May 1997

DEDICATION

This thesis is dedicated to my parents

Ricky and Peggy Gaines.

ACKNOWLEDGMENTS

I would like to thank Dr. David Baker for his financial support and guidance that helped me achieve this degree. I am also very thankful to Shijia Yan and Neil Whittemore for their valuable help. I would like to thank my committee, Dr. David Baker, Dr. Ron Magid, and Dr. John Bartmess for their commitment to chemistry through teaching and research.

ABSTRACT

This research develops (+)-calanolide A and (−)-calanolide B derivatives that could potentially be used as drugs to inhibit HIV reverse transcriptase. The main emphasis of this research is the synthesis of isobutyl and pentyl C-4 substituted derivatives.

TABLE OF CONTENTS

CHAPTER PAGE

I. INTRODUCTION 1

II. STATEMENT OF PROBLEM 5

III. RESULTS AND DISCUSSION 7

IV. EXPERIMENTAL 20

LIST OF REFERENCES 39

APPENDIX 43

VITA 90

I. INTRODUCTION

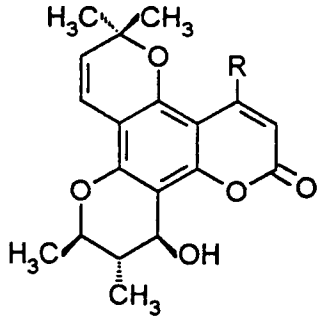
A. Background on Calanolides, Inophyllums, and HIV

Acquired immune deficiency syndrome (AIDS) is caused by human immunodeficiency virus (HIV); therefore, anti-HIV agents maintain a central role in the fight against the AIDS epidemic. AZT (3'-azido-3'-deoxythymidine) and ddI (2', 3'-dideoxyinosine) are useful anti-HIV compounds that function as inhibitors of HIV reverse transcriptase (HIV RT), an enzyme involved in the replication of the HIV genome. However, nucleoside analogs like AZT and ddI are only effective at slowing down the progress of AIDS[1,2] and produce serious side effects such as anemia and leukopenia. Also, these inhibitors are ineffective against recently developed resistant strains of HIV-1 RT.[3,4] Recently a new class of non-nucleoside HIV-1 RT inhibitors has emerged. Four members of this new class are: (+)-calanolide A,[5] (−)-calanolide B,[6] inophyllum B,[7] and soulattrolide.[8] They differ mechanistically in their mode of action from the chain terminators AZT and ddI.

Calanolide A was first isolated as the pure (+)-enantiomer from leaves and twigs of the Malaysian rainforest tree, *Calophyllum lanigerum* var. *austrocoriaceum*,[5] but now is also found as a scalemic mixture in the latex of *C. teysmannii*.[6] Calanolide B was first

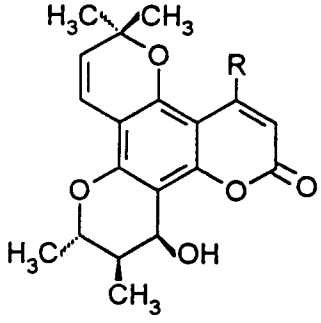
isolated as the (−)-enantiomer from the resin and bark of the Australian tree *C. costatum*,[9] but can also be found in *C. teysmannii* var. *inophylloide*.[10] Inophyllum B was isolated from *C. inophyllum*,[11] and soulattrolide was isolated from *C. soulattri*,[12] *C. moonii*,[13] and *C. teysmannii*.[8] (See Figure 1 for structures.) While (−)-calanolide B, (+)-calanolide A, inophyllum B, and soulattrolide are potent inhibitors of HIV-1 RT, their enantiomers, along with inophyllum A and calanolide C, are inactive against the virus. This suggests that the stereochemical orientation of the methyl groups and the hydroxyl group around the chromanol ring play an important role in the activity of these compounds.

Nucleoside and non-nucleoside HIV-1 RT inhibitors differ by where they attach on the RT and are, therefore, either competitive or noncompetitive inhibitors of the enzyme. Nucleoside inhibitors are competitive inhibitors of the deoxynucleoside triphosphate (dNTP) substrate and attach themselves to the dNTP binding site on RT.[14] It is generally accepted that non-nucleoside inhibitors attach to sites on RT other than the dNTP or template-primer binding sites and are noncompetitive inhibitors of dNTP.[15–18] There are, however, discrepancies regarding the mechanism of inhibition, noncompetitive or uncompetitive, within the class of non-nucleoside inhibitors with respect to template-primer as a subtrate. Inophyllum B inhibits template-primer uncompetitively, binds slowly to RT template-primer, and binds to a site which is adjacent or overlapping to the non-nucleoside inhibitors nevirapine/TIBO {(+)-(5*S*)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*j*,*k*][1,4]-benzodiazepin-2(1*H*)-thione} binding sites on RT.[7] It has also been reported that calanolide A and the non-nucleoside TBA {1*H*,^{3}*H*-thiazolo[3,4-a]benzimidazole (4*i*)} have partially overlapping binding sites.[19] These



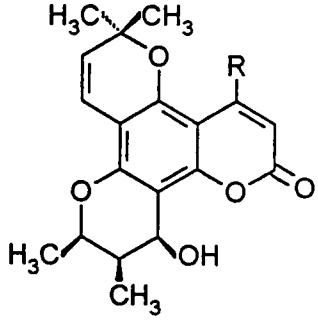
(+)-Calanolide A R = Propyl

Inophyllum B R = Phenyl



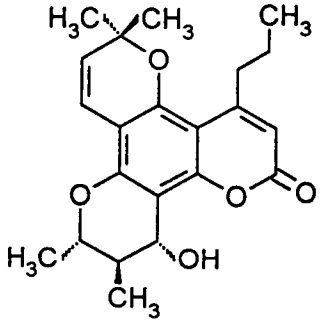
(-)-Calanolide B R = Propyl

Soulattrolide R = Phenyl

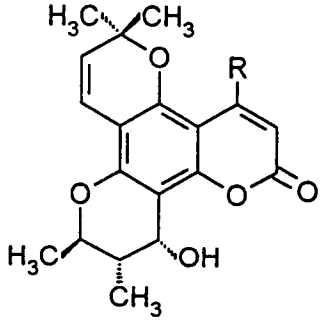


Calanolide C R = Propyl

Inophyllum A R = Phenyl



(-)-Calanolide A



(+)-Calanolide B R = Propyl

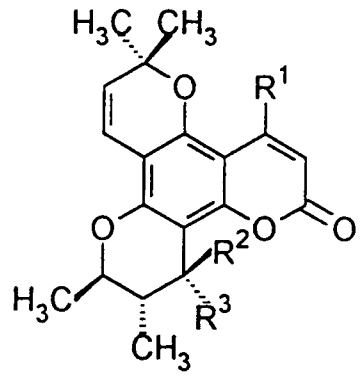
Inophyllum P R = Phenyl

Figure 1. Structures of Calanolides and Inophyllums

characteristics make the calanolides and inophyllum a novel class of chemotypes that could be used in combination chemotherapy with other diverse anti-HIV drugs.[7]

II. STATEMENT OF THE PROBLEM

The goal of this project is to synthesize isobutyl and pentyl C-4 substituted derivatives of naturally occurring (+)-calanolide A and (−)-calanolide B (as shown in Figure 2). Since these compounds are a new class of non-nucleoside HIV-1 RT inhibitors, their role as potential compounds that could be used in combination chemotherapy with other diverse anti-HIV drugs is quite promising. The reason for synthesizing the isobutyl and pentyl C-4 derivatives is to prepare compounds that have alkyl chains that could bind more effectively into the hydrophobic binding pocket of the RT enzyme.

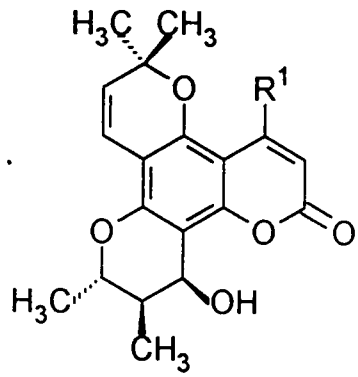


(+)-1a: R^1 = isobutyl, R^2 = OH, R^3 = H

(+)-1b: R^1 = pentyl, R^2 = OH, R^3 = H

(+)-2a: R^1 = isobutyl, R^2 = H, R^3 = OH

(+)-2b: R^1 = pentyl, R^2 = H, R^3 = OH



(-)-2a: R^1 = isobutyl

(-)-2b: R^1 = pentyl

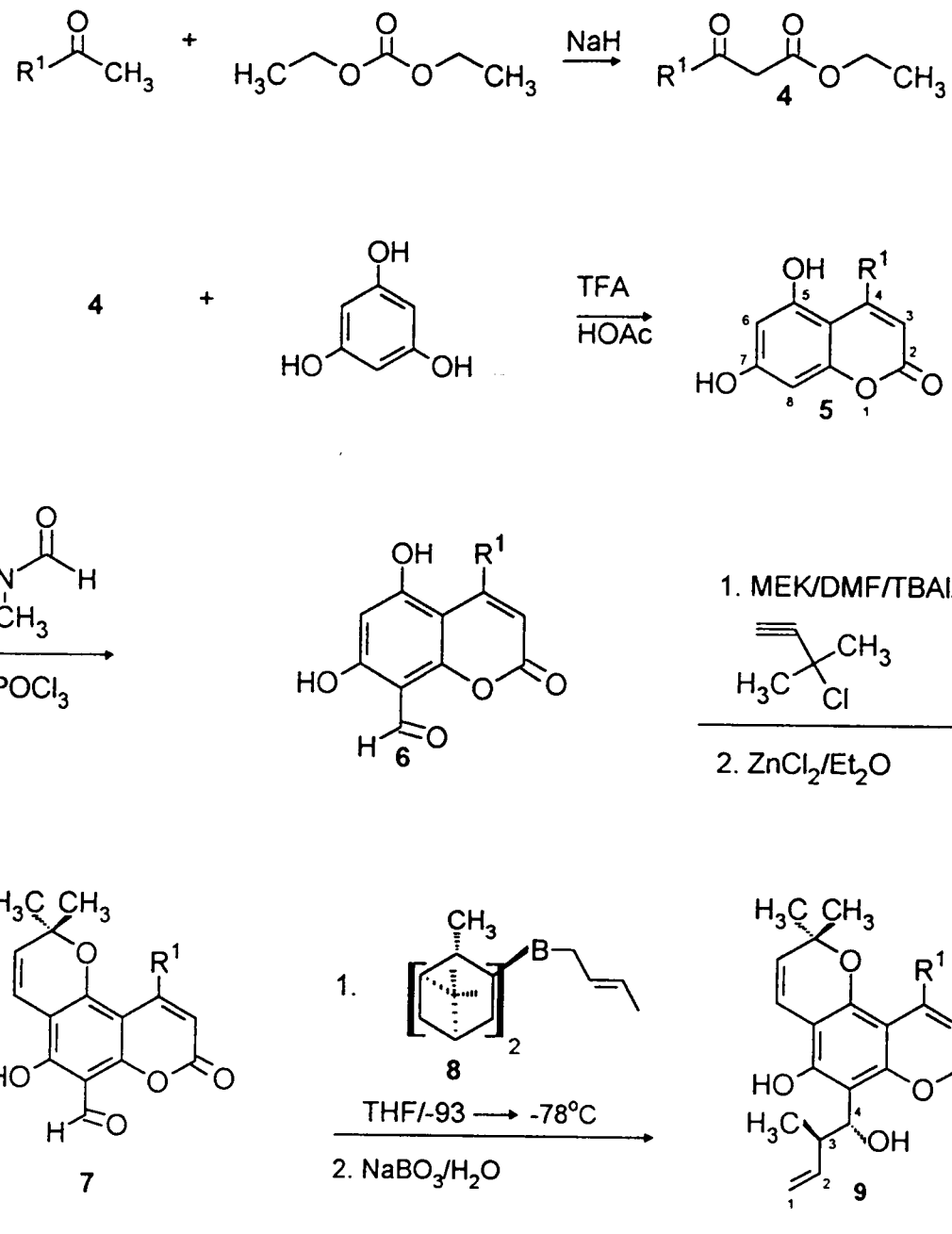
Figure 2. Analogs of (+)-calanolide A and (−)-calanolide B

III. RESULTS AND DISCUSSION

A. Chemical Synthesis

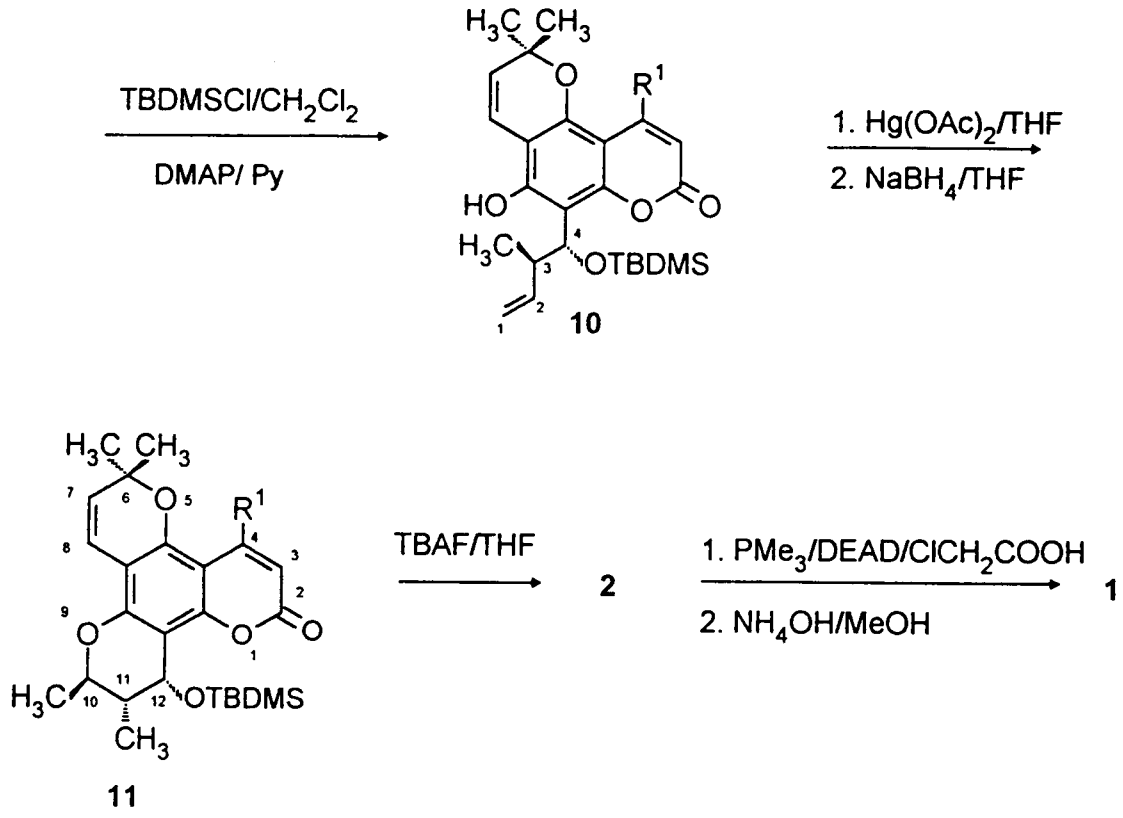
The calanolides and inophyllums share a common 4-alkyl or aryl-5,7-dioxygenated coumarin ring (coumarin = 2*H*-chromene-2-one), a chromene ring, and a 2,3-dimethylchroman-4-ol (3,4-dihydro-2*H*-benzo[*b*]pyran system). According to Baker and co-workers,[21] and based on the studies by Chenera et al.,[22] the crucial intermediate **6** was easily prepared through a regioselective Vilsmeier reaction[23] using a 5,7-dihydroxy-4-(alkyl)coumarin **(5)** as the starting material. Next, the dimethylchromene ring was introduced using the conditions also developed by Chenera et al.[22] Finally, the sensitive dimethylchromanol ring was introduced according to the procedures of Baker and co-workers[21] as shown in Scheme 1.

Following the procedures of Jackman and co-workers,[24] the β-ketoesters were prepared from the readily available alkyl methyl ketones by carbethoxylation with ethyl carbonate in the presence of sodium hydride as the condensing agent. Carbethoxylation occurred predominantly at the methyl group to give **4a** from 4-methyl-2-pentanone as a colorless liquid in 79% yield, bp 100 °C (20 torr). Compound **4b** from 2-heptanone was obtained as a colorless liquid in 66% yield, bp 126–130 °C (25 torr). A von Pechmann



Series a: R^1 = isobutyl Series b: R^1 = pentyl

Scheme 1a. Analogs of (+)-calanolide A and (−)-calanolide B



Series a: R^1 = isobutyl Series b: R^1 = pentyl

Scheme 1b. Analogs of (+)-calanolide A and (−)-calanolide B

reaction[25] on phloroglucinol with the β-ketoesters **4a** and **4b** in the presence of 3:1 acetic acid/trifluoroacetic acid gave **5a** as a white solid in 75% yield, mp 215–216 °C, and **5b** as a white solid in 80% yield, mp 232–234 °C.

Following the procedures of Baker and co-workers,[21] the formylated coumarins were prepared from **5a** and **5b** by a regioselective Vilsmeier reaction[23] that would place the aldehyde function at C-8. The reaction of **5a** and **5b** with *N*-methylformanilide and phosphorus oxychloride in 1,2-dichloroethane at 70 °C gave **6a** as a white solid in 70% yield, mp 209–210 °C, and **6b** as a white solid in 73% yield, mp 204–205 °C. The regiochemistry of the formylation was confirmed by Baker and co-workers[21] through NOE studies.

The dimethylchromene ring was introduced using the conditions developed by Chenera et al.[22] Due to a hydrogen-bond interaction between the phenolic hydroxy group at C-7 and the aldehyde function at C-8, a presumed propargyl ether formed at the phenolic hydroxyl group at C-5. The aryl propargyl ether underwent a presumed Claisen rearrangement to form an *o*-allenylphenol intermediate which cyclized to form the chromene ring. Compounds **6a** and **6b** were reacted with 3-chloro-3-methyl-1-butyne (prepared according to the procedures of Hennion and co-workers[26]), potassium carbonate, and tetrabutylammonium iodide in DMF and 2-butanone at 60 °C for 1 h, and then anhydrous zinc chloride in diethyl ether was added and the reaction mixture kept at 60 °C for 36 h. Compound **7a** was obtained as a yellow solid in 25% yield, mp 133–134 °C, and **7b** was obtained as a yellow solid in 30% yield, mp 104–105 °C.

The organoborane reagent (+)-(*E*)-crotyldiisopinocampheylborane **(+)-8** was

prepared according to the procedures of Brown and Bhat[27] and immediately treated with aldehydes **7a** and **7b** at −93 °C. The reaction mixture furnished the *threo*-β-methylhomoallylic alcohols **(+)-9a** as a syrup in 60% yield, $[\alpha]_D^{20} = +100°$ (*c* 1.0, $CHCl_3$), and **(+)-9b** as a white solid in 63% yield, mp 145–146 °C, $[\alpha]_D^{20} = +121°$ (*c* 1.0, $CHCl_3$). The boron–carbon bond was oxidized during the workup using sodium perborate[28] instead of the usual conditions (H_2O_2–3 N NaOH, reflux).

Due to a presumed steric interaction between the phenolic hydroxy group and the alkene proton at C-1, the silylation of both **(+)-9a** and **(+)-9b** gave monosilylation at the secondary homoallylic alcohol group as the major product. Compounds **(+)-9a** and **(+)-9b** were each reacted with *tert*-butylchlorodimethylsilane, 4-dimethylaminopyridine, and pyridine in dichloromethane from −30 °C to room temperature to give **(+)-10a** as a syrup in 85% yield, $[\alpha]_D^{20} = +28°$ (*c* 1.0, $CHCl_3$), and **(+)-10b** as a syrup in 81% yield, $[\alpha]_D^{20} = +27°$ (*c* 1.0, $CHCl_3$).

Based on the work of Tius and Busch-Petersen,[29] a bulky silyl group at C-4 controls the stereochemistry of the new chiral center (methyl group) at C-10, which was obtained via a mercury-assisted cyclization of the orthoalkenyl phenols[30] **(+)-10a** and **(+)-10b** using mercuric acetate[31] in THF. The organomercurial intermediate was reduced using sodium borohydride to furnish silyl protected **(+)-11a** as a glass in 80% yield, $[\alpha]_D^{20} = -48°$ (*c* 1.0, acetone), and **(+)-11b** as a glass in 75% yield, $[\alpha]_D^{20} = -17°$ (*c* 1.0, $CHCl_3$). Compounds **(+)-11a** and **(+)-11b** were each deprotected using tetrabutylammonium fluoride in THF to give **(+)-2a** as a white solid in 73% yield, mp 157–158 °C, $[\alpha]_D^{20} = +37°$ (*c* 1.0, acetone), and **(+)-2b** as a white solid in 70% yield, mp 119–120 °C, $[\alpha]_D^{20} =$

+36° (*c* 1.0, acetone).

Compounds **(+)-2a** and **(+)-2b** were converted into their epimers by a modified[32] Mitsunobu reaction.[33] Compounds **(+)-2a** and **(+)-2b** were reacted with diethyl azodicarboxylate, trimethylphosphine, and chloroacetic acid in THF and toluene, and the ester intermediate was saponified with ammonium hydroxide in methanol to give **(+)-1a** as a glass in 75% yield, $[\alpha]_D^{20} = +58°$ (*c* 0.5, $CHCl_3$), and **(+)-1b** as a glass in 70% yield, $[\alpha]_D^{20} = +54°$ (*c* 0.5, $CHCl_3$). The diastereomeric and enantiomeric purity of compounds **(+)-1a** and **(+)-1b** was found to be 79.6% and 68.8%, respectively, by chiral HPLC using a Regis no. 731221 Pirkle D-phenylglycine column (10 x 250 mm, 9:1 hexanes/2-propanol, 4 mL/min, UV_{285}).

The entire process in Scheme 1 was repeated using (−)-(*E*)-crotyldiisopinocampheylborane **(−)-8** in order to provide **(−)-2a** as a white solid, mp 157–158 °C, $[\alpha]_D^{20} = -37°$ (*c* 1.0, acetone), and **(−)-2b** as a white solid, mp 119–120 °C, $[\alpha]_D^{20} = -36°$ (*c* 1.0, acetone). The enantiomeric purity of compounds **(−)-2a** and **(−)-2b** was found to be 96.6% and 95.4%, respectively, by HPLC.

B. Molecular Modeling Studies

Using SYBYL, a molecular modeling program developed by Tripos Associates, each target compound [**(+)-1a, (+)-1b, (−)-2a,** and **(−)-2b**] was overlaid onto the corresponding calanolide model. The fit atoms command, which performs a least-squares fit between two molecules, was utilized to do the overlaying. The quality of the fit is

represented by the RMS value computed for the matched atoms: RMS = $(\sum d^2/n)^{½}$ where d is the distance between the matched atoms and n is the number of matched atoms selected.

The overlay of (+)-calanolide A and **(+)-1a** (Figure 3) has a RMS value of 0.046. The isobutyl group doesn't overlay with the propyl group and extends into a different direction. The overlay of (-)-calanolide B and **(-)-2a** (Figure 4) has a RMS value of 0.032. The isobutyl group follows the same pattern as the propyl group and almost overlays with it. The hydrogen of the hydroxyl group extends into a different direction relative to the hydrogen of the hydroxyl group of (-)-calanolide B. The overlay of (-)-calanolide B with another conformation of **(-)-2a** (Figure 5) has a RMS value of 0.037. The isobutyl group also comes close to overlaying with the propyl group, but unlike in (Figure 4) the hydrogens of the hydroxyl group match up.

The overlay of (+)-calanolide A and **(+)-1b** (Figure 6) has the best fit with a RMS value of 0.009. The pentyl chain in a staggered conformation aligns with the propyl group up to the second carbon in the chain. The overlay of (-)-calanolide B with **(-)-2b** (Figure 7) has a RMS value of 0.021. The pentyl group doesn't overlay with the propyl group and extends into a different direction. The overlay of (-)-calanolide B and another conformation of **(-)-2b** (Figure 8) with a RMS value of 0.068 shows the ability of the chromene ring to pucker in the opposite direction (a low energy barrier) and influence the direction the alkyl chain extends.

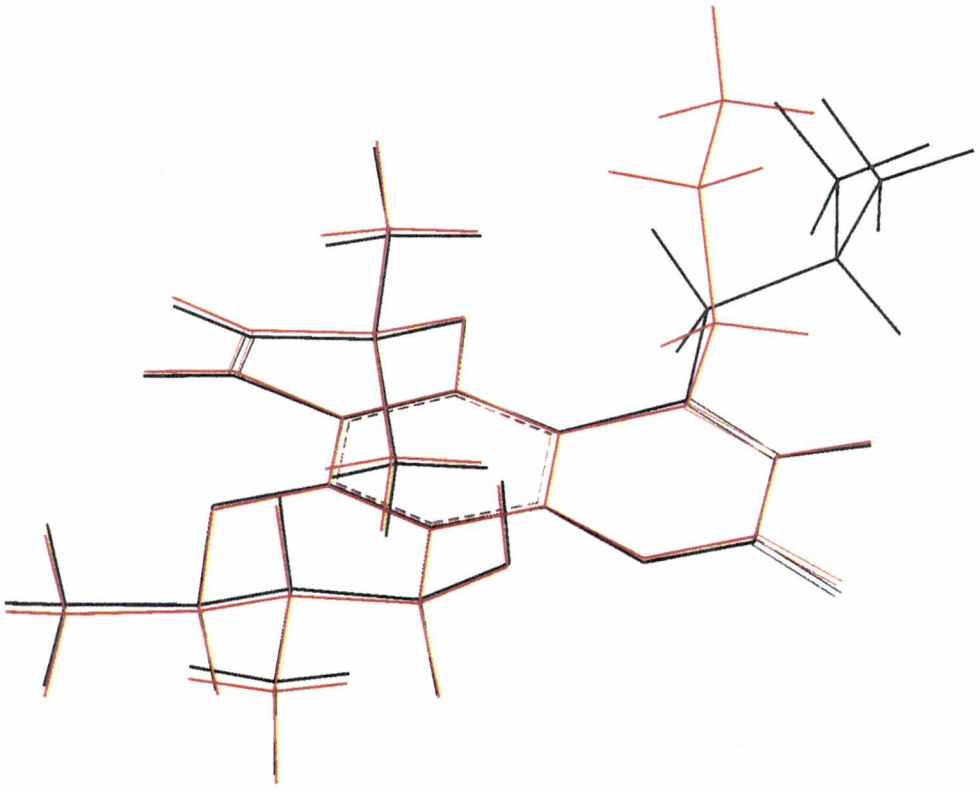


Figure 3. A Molecular Model of (+)-(10*R*,11*S*,12*S*)-12-Hydroxy-6,6,10,11-tetramethyl-4-isobutyl-6,10,11,12-tetrahydro-dipyrano[2,3-*f*;2',3'-*h*]chromene-2-one **[(+)-1a].**
red = (+)-Calanolide A, dark blue = **(+)-1a**

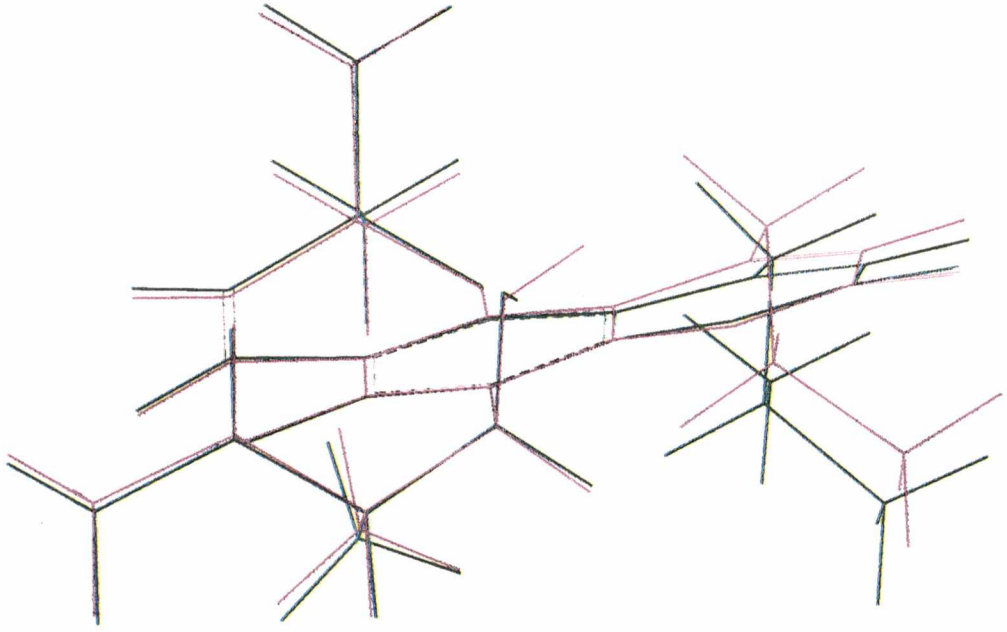


Figure 4. A Molecular Model of (−)-(10*S*,11*R*,12*S*)-12-Hydroxy-6,6,10,11-tetramethyl-4-isobutyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromen-2-one **[(−)-2a].** purple = (−)-Calanolide B, green = **(−)-2a**

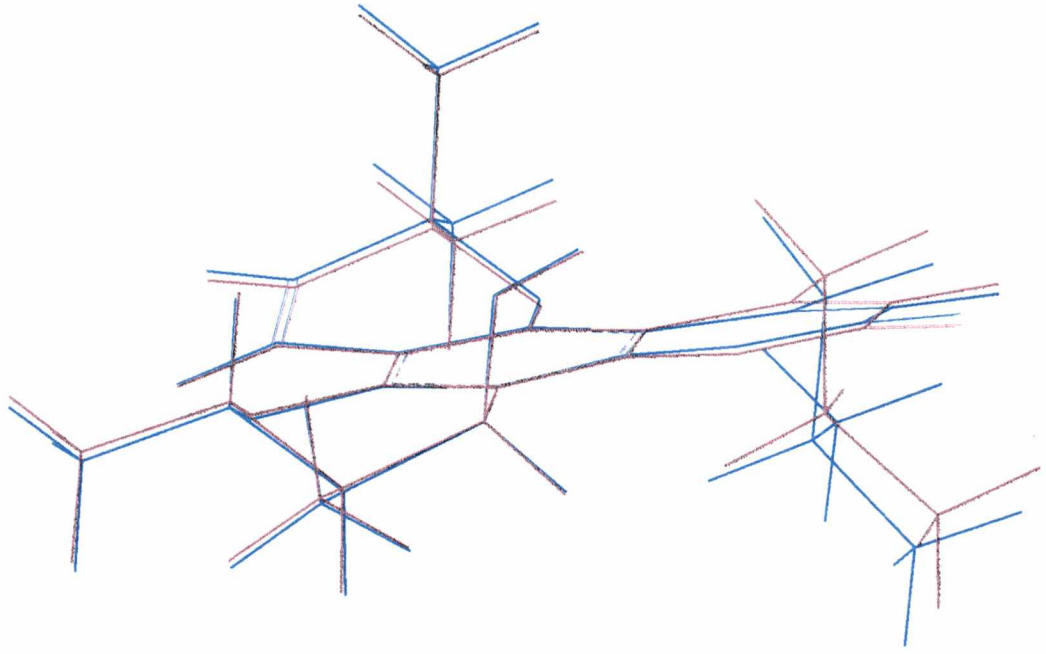


Figure 5. A Molecular Model of (−)-(10*S*,11*R*,12*S*)-12-Hydroxy-6,6,10,11-tetramethyl-4-isobutyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromen-2-one **[(−)-2a].** purple = (−)-Calanolide B, blue = **(−)-2a**

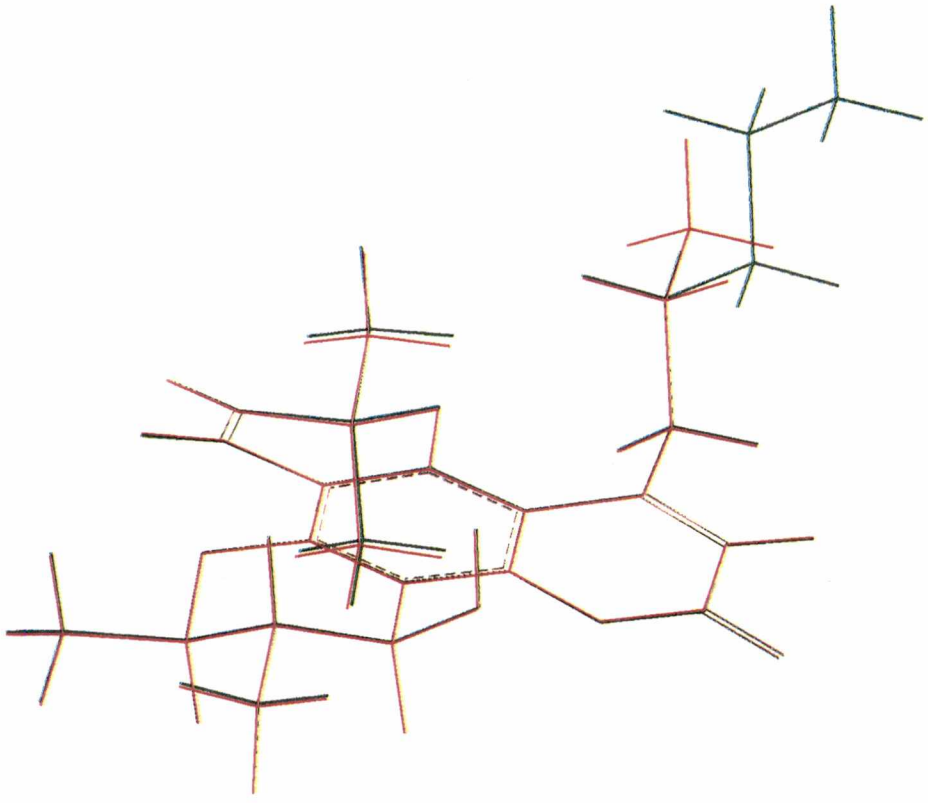


Figure 6. A Molecular Model of (+)-(10*R*,11*S*,12*S*)-12-Hydroxy-6,6,10,11-tetramethyl-4-pentyl-6,10,11,12-tetrahydro-dipyrano[2,3-*f*;2',3'-*h*]chromene-2-one **[(+)-1b].** red = (+)-Calanolide A, green = **(+)-1b**

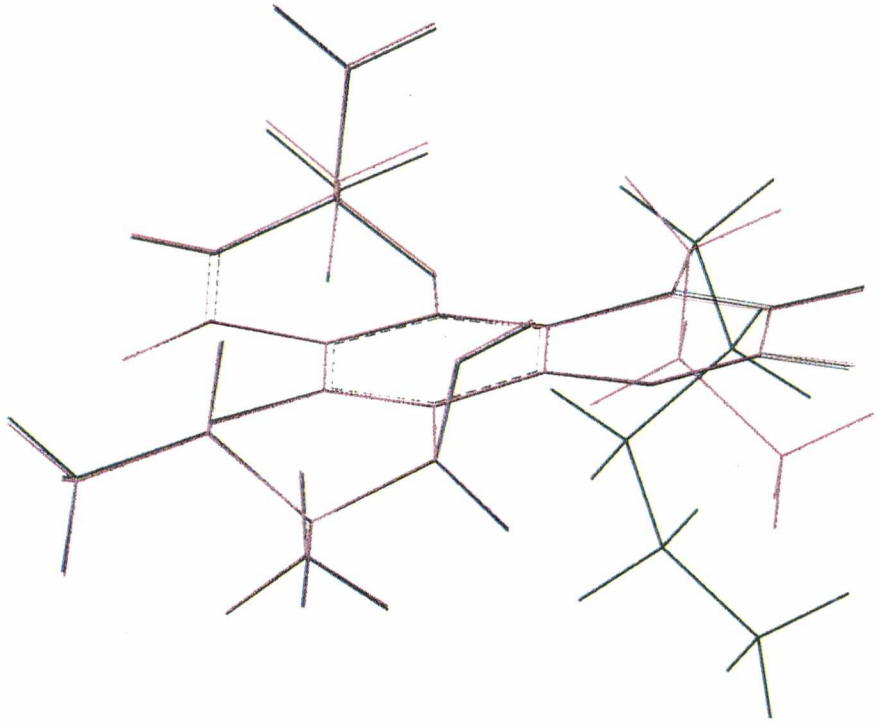


Figure 7. A Molecular Model of (−)-(10*S*,11*R*,12*S*)-12-Hydroxy-6,6,10,11-tetramethyl-4-pentyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromene-2-one **[(−)-2b].** purple = (−)-Calanolide B, green = **(−)-2b**

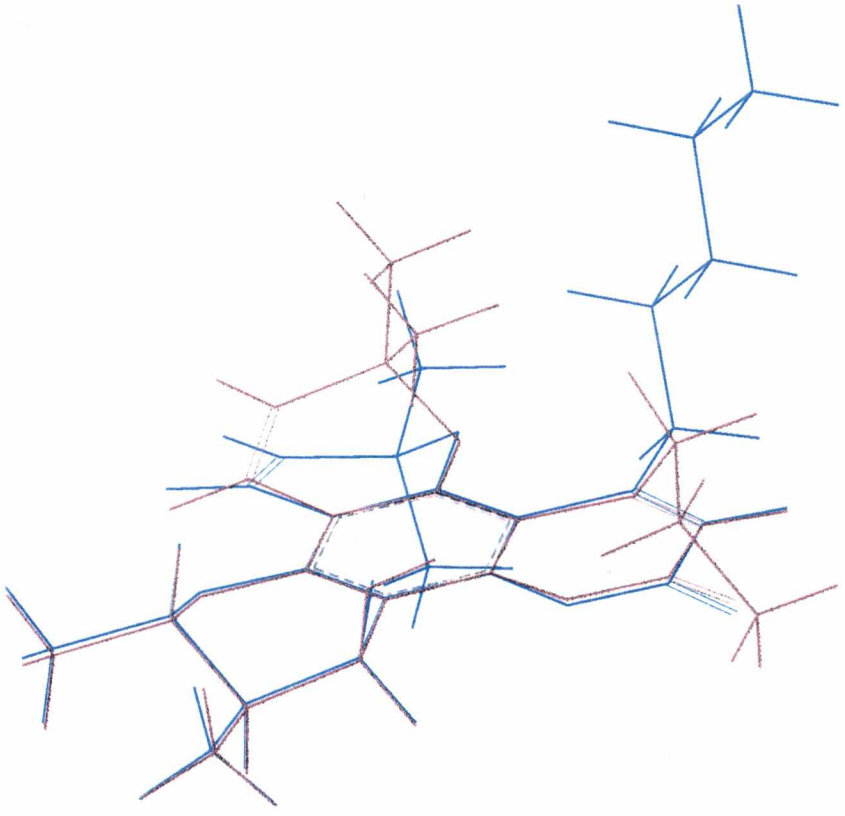


Figure 8. A Molecular Model of (−)-(10*S*,11*R*,12*S*)-12-Hydroxy-6,6,10,11-tetramethyl-4-pentyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromene-2-one **[(−)-2b].** purple = (−)-Calanolide B, blue = **(−)-2b**

IV. EXPERIMENTAL

A. General Methods

^{1}H and ^{13}C NMR spectra were obtained in the indicated solvent at 250 MHz and 62.5 MHz, respectively, as approximately 5–10% (w/v) solutions using a Bruker AM 250 instrument. ^{1}H NMR chemical shifts are reported as δ (ppm) downfield from an internal standard of tetramethylsilane. Peak multiplicities are first-order values in Hz and are recorded as: s, singlet; d, doublet; t, triplet; dd, doublet of doublet; m, multiplet. ^{13}C NMR chemical shifts are reported as δ (ppm) relative to $CDCl_3$ (77.0 ppm). Melting points were determined using a Thomas–Hoover "Unimelt" capillary melting point apparatus coupled with a Cole–Parmer 8520-50 Digi-Sense digital thermocouple. Optical rotations were measured with a Perkin–Elmer 241 automatic polarimeter at the sodium D line in a 0.1-dm cell at the indicated temperature. Elemental analyses were supplied by Atlantic Microlab, Inc. of Norcross, GA.

Anhydrous solvents were prepared by the following procedures. Diethyl ether and tetrahydrofuran (THF) were distilled at atmospheric pressure from lithium aluminum hydride and from sodium–benzophenone ketyl, respectively. *N*,*N*-Dimethylformamide (DMF) was distilled over calcium hydride under reduced pressure and stored over 4 Å

molecular sieves. Dichloromethane, pyridine, and toluene were distilled over calcium hydride at atmospheric pressure and stored over 4 Å molecular sieves. All reactions were carried out under a nitrogen atmosphere unless otherwise indicated. Solvents were evaporated at approximately 40 °C/30 torr unless otherwise indicated.

E. Merck Silica Gel 60 products were used to carry out adsorption chromatography. All reactions were monitored with 0.2-mm aluminum-backed thin-layer chromatography (TLC) plates. Column chromatography was carried out using 230–400 mesh silica gel. TLC plates were visualized by using a 254-nm UV light and by spray–heat development using an *p*-anisaldehyde–sulfuric acid reagent.[20]

Preparation of Ethyl 3-Oxo-5-methylhexanoate (4a). Following the procedures of Jackman and co-workers,[24] a 60% dispersion of sodium hydride in mineral oil (40.0 g, 1.00 mol) was added to diethyl carbonate (118 g, 1.00 mol) in a nitrogen-swept two-necked 500-mL flask fitted with a condenser and a dropping funnel. Then 4-methyl-2-pentanone (50.0 g, 0.500 mol) was added dropwise into the stirred mixture over a period of one h. During the course of the addition, the temperature rose from 25 to 60 °C. The reaction mixture was held at 60 °C for one h and then raised to 80 °C for one h. The following day the sodium salt was decomposed by the gradual addition of glacial acetic acid (65 mL). Upon the additon of water (150 mL) the precipitated sodium acetate dissolved and two phases separated. The aqueous phase was extracted twice with ether. The combined organic layers were washed twice with 5% sodium bicarbonate solution and dried over magnesium sulfate. The solution was distilled, first at atmospheric pressure to remove volatile materials, and then at reduced pressure to give **4a** (68 g, 79%), bp 100 °C

(20 torr). [Lit.[24] bp 93–96 °C (15 torr)].

Preparation of 5,7-Dihydroxy-4-isobutylcoumarin (5a). A solution of **4a** (66.0 g, 0.383 mol) and anhydrous phloroglucinol (43.8 g, 0.348 mol) in glacial acetic acid (200 mL) and trifluoroacetic acid (66 mL) was stirred at 75 °C for 24 h and then allowed to cool to room temperature. The reaction mixture was filtered and the solid was dried and recrystallized from ethanol/water to give **5a** (61 g, 75%) as a white solid: mp 215–216 °C; ^{1}H NMR (3:1 $CDCl_3/CD_3OD$): δ 0.964 [d, 6 H, J = 6.6 Hz, $CH(CH_3)_2$], 1.28 [m, 1 H, $CH(CH_3)_2$], 2.82 [d, 2 H, J = 6.6 Hz, $CH_2CH(CH_3)_2$], 5.83 (s, 1 H, H-3), 6.27 (d, 1 H, J = 2.3 Hz, H-6), 6.33 (d, 1 H, J = 2.3 Hz, H-8); ^{13}C NMR ($CDCl_3/CD_3OD$ 3:1): δ 21.69, 27.81, 44.83, 94.96, 99.29,102.44, 108.75, 156.66, 157.24, 159.59, 160.61, 162.91. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.52; H, 6.09.

Preparation of 5,7-Dihydroxy-2-oxo-4-isobutyl-2*H*-chromene-8-carbaldehyde (6a). A mixture of **5a** (46.2 g, 0.197 mol), *N*-methylformanilide (53.6 g, 0.400 mol), and phosphorus oxychloride (34.2 g, 0.223 mol) in 1,2-dichloroethane (200 mL) was stirred at 70 °C for four h and then allowed to cool to room temperature. The reaction solution was quenched by the dropwise addition of saturated aqueous sodium acetate and extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, concentrated, and submitted to silica gel chromatography (95:5 CH_2Cl_2/EtOAc) to provide **6a** (36.1 g, 70%) as a white solid: mp 209–210 °C; ^{1}H NMR (3:1 $CDCl_3/CD_3OD$): δ 0.976 [d, 6 H, J = 6.6 Hz, $CH(CH_3)_2$], 1.98 [m, 1 H, $CH(CH_3)_2$], 2.80 (d, 2 H, J = 6.6 Hz, $CH_2CH(CH_3)_2$], 5.93 (s, 1 H, H-3), 6.18 (s, 1 H, H-6), 10.26 (s, 1 H, CHO); ^{13}C NMR (3:1 $CDCl_3/CD_3OD$): δ 21.17, 27.54, 44.57, 98.35, 102.08, 102.93, 110.07, 158.41,

158.60, 159.57, 164.15, 165.61, 190.62. Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 63.91; H, 5.37.

Preparation of 3-chloro-3-methyl-1-butyne. Following the procedures of Hennion and co-workers,[26] calcium chloride (112.5 g) was added to HCl (420 mL, 12 M) at −5 °C. The reaction mixture was allowed to warm up to 20 °C and a mixture of 2-methyl-3-butyn-2-ol (85 g, 1.0 mol) and hydroquinone (1.6 g) was added. The reaction mixture was stirred for 40 min at 20 °C, and the organic layer was separated and dried over anhydrous potassium carbonate and calcium chloride. The organic layer was distilled over anhydrous potassium carbonate to give 3-chloro-3-methyl-1-butyne as a colorless liquid (50.8 g, 50%), bp 25 °C (90 torr). [Lit.[26] bp 72.6–75.8 °C (760 torr)].

Preparation of 5-Hydroxy-2,2-dimethyl-8-oxo-10-isobutyl-2*H*,8*H*-pyrano[2,3-*f*]chromene-6-carbaldehyde (7a). To a solution of **6a** (25.4 g, 96.9 mmol) in dry DMF (45 mL) and 2-butanone (550 mL) was added potassium carbonate (58.2 g, 421 mmol), tetrabutylammonium iodide (55.2 g, 150 mmol) and 3-chloro-3-methyl-1-butyne (50.7 g, 495 mmol). The stirring reaction mixture was heated at 60 °C for one h. Then anhydrous $ZnCl_2$ (72.0 mL, 1 M solution in ether) was added, and the reaction mixture was held at 60 °C for 12 h. Additional anhydrous $ZnCl_2$ (35.5 mL, 1 M solution in ether) was added, and the reation mixture was held at 60 °C for a further 24 h. The reaction mixture was allowed to cool down to room temperature and saturated aqueous ammonium chloride (650 mL) was added. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The residue obtained was purified by silica gel chromatography (98:2

hexane/EtOAc) and recrystallized from hexane to give **7a** (8.0 g, 25%) as a yellow solid: mp 133–134 °C; ^{1}H NMR ($CDCl_3$): δ 0.989 [d, 6 H, J = 6.5 Hz, $CH(CH_3)_2$], 1.56 [s, 6 H, $C(CH_3)_2$], 2.00 [m, 1 H, $CH(CH_3)_2$], 2.77 [d, 2 H, J = 7.0 Hz, $CH_2CH(CH_3)_2$], 5.61 (d, 1 H, J = 10.1 Hz, H-3), 5.97 (s, 1 H, H-9), 6.67 (d, 1 H, J = 10.0 Hz, H-4), 10.4 (s, 1 H, CHO), 12.8 (s, 1 H, ArOH); ^{13}C NMR δ 22.25, 27.64, 28.33, 45.63, 77.21, 80.34, 102.69, 103.90, 105.32, 112.60, 115.03, 126.61, 156.51, 158.18, 158.24, 158.67, 161.21, 192.09. Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.5; H, 6.14. Found C, 69.43; H, 6.17.

Preparation of (+)-5-Hydroxy-6-[(1*R*,2*R*)-1-hydroxy-2-methylbut-3-enyl]-2,2-dimethyl-10-isobutyl-2*H*-pyrano[2,3-*f*]chromene-8-one [(+)-9a]. The organoborane reagent (+)-**8** was prepared according to the procedure of Brown and Bhat.[27] To a stirred mixture of potassium *tert*-butoxide (1.30 g, 11.6 mmol) and *trans*-2-butene (1.30 g, 23.2 mmol) in THF (30 mL) at -78°C was added butyllithium (4.20 mL, 10.5 mmol, 2.5 M in hexane) and the reaction mixture was held at -78°C for two h. The reaction mixture was cooled down to -93 °C and (+)-β-methoxydiisopinocampheylborane (3.90 g, 12.3 mmol) in diethyl ether (14 mL) was added dropwise over a period of 25 min. The reaction mixture was brought up to -78°C and stirred for 30 min. The reaction mixture was cooled down to -93°C and boron trifluoride etherate (1.6 mL, 13 mmol) was added dropwise over a period of 5 min. The mixture was brought up to -78°C for 10 min and then cooled down to -93°C and **7a** (2.00 g, 6.10 mmol) in 1:1 Et_2O/THF (16 mL) was added dropwise over 10 min. The reaction mixture was held at -93°C for 30 min and then was held at -78°C for five h. Sodium perborate tetrahydrate (12.3 g, 80.0 mmol) and water (11.4 mL) were added and the reaction mixture was stirred at room temperature

for 15 h. Brine (31 mL) was added and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, concentrated, and submitted to silica gel chromatography (98:2 hexane/EtOAc) to give **(+)-9a** (1.4 g, 60%) as a syrup: $[\alpha]_D^{20}$ = + 100° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.949 [d, 6 H, *J* = 6.6 Hz, $CH(CH_3)_2$], 1.05 (d, 3 H, *J* = 6.9 Hz, $CHCH_3$), 1.48, 1.51 [2 s, 6 H, $C(CH_3)_2$], 2.00 [m, 1 H, $CH(CH_3)_2$], 2.67 (m, 1 H, $CHCH_3$), 2.74 [m, 2 H, $CH_2CH(CH_3)_2$], 4.30 (bs, 1 H, OH), 5.11–5.17 (m, 2 H, $CH=CH_2$), 5.38 (d, 1 H, *J* = 7.3 Hz, CHOH), 5.55 (d, 1 H, *J* = 9.9 Hz, H-3), 5.77 (s, 1 H, H-9), 5.86–6.00 (m, 1 H, $CH=CH_2$), 6.70 (d, 1 H, *J* = 9.9 Hz, H-4), 9.75 (s, 1 H, ArOH); ^{13}C NMR ($CDCl_3$): δ 16.21, 22.32, 27.64, 28.11, 44.63, 45.71, 72.51, 77.76, 102.99, 105.89, 107.17, 111.01, 116.55, 117.24, 126.86, 139.75, 151.24, 152.24, 155.75, 157.71, 160.92. Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found C, 71.73; H, 7.41.

Preparation of (+)-5-Hydroxy-6-[(1*R*,2*R*)-1-*tert*-butyldimethylsilyloxy-2-methylbut-3-enyl]-2,2-dimethyl-10-isobutyl-2*H*-pyrano[2,3-*f*]chromen-8-one [(+)-10a]. To a stirred solution of **(+)-9a** (1.30 g, 3.39 mmol) in dry dichloromethane at −30°C was added 4-dimethylaminopyridine (0.920 g, 7.56 mmol), pyridine (5.2 mL), and *tert*-butylchlorodimethylsilane (1.20 g, 7.76 mmol). The reaction mixture was allowed to warm up to room temperature and was stirred for 1.5 h or until all the starting material was consumed. Water (13 mL) was added and the reaction mixture was stirred for 15 min. The aqueous layer was extracted three times with dichloromethane. The combined organic layers were concentrated and the residue obtained was purified by column chromatography (98:2 hexane/EtOAc) to give **(+)-10a** (1.44 g, 85 %) as a syrup: $[\alpha]_D^{20}$ =

+28° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ -0.02, 0.17 (2s, 6 H, $SiCH_3$), 0.88 [s, 9 H, $C(CH_3)_3$], 0.98 [d, 9 H, *J* = 6.4 Hz $CHCH_3$, $CH(CH_3)_2$ overlapped], 1.49, 1.52 [2s, 6 H, $C(CH_3)_2$], 2.07 [m, 1 H, $CH(CH_3)_2$], 2.63 (m, 1 H, $CHCH_3$), 2.78 [m, 2 H, $CH_2CH(CH_3)_2$], 4.98–5.07 (m, 2 H, $CH=CH_2$), 5.31 [d, 1 H, *J* = 6.8 Hz, $CHOSi(CH_3)_2$-], 5.55 (d, 1 H, *J* = 10.0 Hz, H-3), 5.80–5.94 (m, 1 H, $CH=CH_2$), 5.87 (s, 1 H, H-9), 6.68 (d, 1 H, *J* = 9.9 Hz, H-4), 9.32 (s, 1 H, ArOH); ^{13}C NMR ($CDCl_3$): δ -0.42, -0.14, 16.28, 18.08, 22.38, 25.72, 27.60, 28.13, 44.57, 45.72, 74.25, 77.72, 102.87, 106.81, 106.93, 111.44, 115.73, 116.63, 126.79, 139.75, 151.14, 151.87, 155.46, 157.09, 160.34; Anal. Calcd for $C_{29}H_{42}O_5Si$: C, 69.84; H, 8.49. Found C, 70.03; H, 8.61.

Preparation of (+)-(10*R*,11*R*,12*R*)-12-*tert*-Butyldimethylsilyloxy-6,6,10,11-tetramethyl-4-isobutyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromen-2-one [(+)-11a]. To a stirred solution of **(+)-10a** (1.44 g, 2.89 mmol) in THF (110 mL) was added mercuric acetate (0.924 g, 2.90 mmol), and the reaction mixture was stirred for 20 min at room temperature. The reaction mixture was cooled down to 0 °C and sodium borohydride (0.72 g, 19 mmol) was added. The reaction mixture was allowed to warm up to room temperature and stir for 15 min. Hexanes (40 mL) and brine (75 mL) were added, and the organic layer was separated. The aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over magnesium sulfate, concentrated, and submitted to silica gel chromatography (98:2 hexane/EtOAc) to give **(+)-11a** (1.15 g, 80%) as a glass: $[\alpha]_D^{20}$ = -48° (*c* 1.0, acetone); ^1H NMR ($CDCl_3$): δ -0.11, 0.28 (2 s, 6 H, $SiCH_3$), 0.81 [s, 9 H, $C(CH_3)_3$], 0.95 [t, 6 H, $CH(CH_3)_2$], 1.08 (d, 3 H, *J* = 6.8 Hz, CH_3), 1.40 (d, 3 H, *J* = 6.3 Hz CH_3), 1.48, 1.50 [2 s, 6 H, $C(CH_3)_2$], 1.65

(m, 1 H, H-11), 2.03 [m, 1 H, C*H*(CH_3)$_2$], 2.77 [m, 2 H, CH_2CH(CH_3)$_2$], 4.41 (m, 1 H, H-10), 5.02 (d, 1 H, J = 2.0 Hz, H-12), 5.52 (d, 1 H, J = 10 Hz, H-7), 5.87 (s, 1 H, H-3), 6.65 (d, 1 H, J = 10 Hz, H-8); ^{13}C NMR ($CDCl_3$): δ -0.77, -0.53, 14.08, 18.51, 19.20, 22.39, 25.99, 27.67, 27.82, 39.03, 45.71, 62.66, 72.99, 102.89, 105.92, 106.84, 111.46, 116.69, 126.55, 151.21, 153.02, 153.09, 157.03, 160.35; Anal. Calcd for $C_{29}H_{42}O_5Si$: C, 69.84; H, 8.49. Found C, 69.94; H, 8.45.

Preparation of (+)-(10*R*,11*S*,12*R*)-12-Hydroxy-6,6,10,11-tetramethyl-4-isobutyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromen-2-one [(+)-2a]. To a stirred solution of **(+)-11a** (0.585 g, 1.17 mmol) in THF (25 mL) was added tetrabutylammonium fluoride (12 mL, 1 M solution in THF) and the reaction mixture was stirred for 20 min. Triethylamine (0.85 mL, 1 M in THF) and acetic acid (0.33 mL, 2 M in THF) was added and the reaction mixture was stirred for 2 h. The HOAc–Et_3N addition was repeated and the reaction mixture was stirred for 5 h. The THF was evaporated and EtOAc (25 mL) and water (25 mL) were added. The aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over magnesium sulfate, concentrated, and submitted to silica gel chromatography (90:10 hexane/EtOAc) to give **(+)-2a** (0.330 g, 73%) as a white solid: mp 157–158 °C; $[\alpha]_D^{20}$ = +37° (*c* 1.0, acetone); ^{1}H NMR ($CDCl_3$): δ 0.96 (dd, 6 H, J = 2.7 Hz, J = 3.8 Hz, CH(CH_3)$_2$], 1.12 (d, 3 H, J = 7.0 Hz, CH_3), 1.42 (d, 3 H, J = 6.3 Hz, CH_3), 1.48, 1.49 [2 s, 6 H, C(CH_3)$_2$], 1.73 (m, 1 H, H-11), 2.01 [m, 1 H, C*H*(CH_3)$_2$], 2.76 [m, 2 H, CH_2CH(CH_3)$_2$], 2.99 (bs, 1 H, OH), 4.26 (m, 1 H, H-10), 4.97 (d, 1 H, J = 3.1, H-12), 5.52 (d, 1 H, J = 10.0 Hz, H-7), 5.87 (s, 1 H, H-3), 6.63 (d, 1 H, J = 9.9 Hz, H-8); ^{13}C NMR ($CDCl_3$): δ 12.45, 18.81, 22.32, 27.66,

38.24, 45.59, 61.71, 72.91, 77.66, 103.53, 106.11, 106.40, 111.53, 116.57, 126.70, 151.32, 153.09, 153.96, 157.23, 160.64; Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found C, 71.93; H, 7.38.

Preparation of (+)-(10*R*,11*S*,12*S*)-12-Hydroxy-6,6,10,11-tetramethyl-4-isobutyl-6,10,11,12-tetrahydro-dipyrano[2,3-*f*;2',3'-*h*]chromene-2-one [(+)-1a]. To a solution of **(+)-2a** (0.200 g, 0.521 mmol) in toluene (40 mL) and THF (40 mL) at -78°C was added diethyl azodicarboxylate (1.99 g, 11.4 mmol), trimethylphosphine (11 mL, 1.0 M in THF), and chloroacetic acid (0.900 g, 9.52 mmol) in THF (3 mL). The stirred reaction mixture was allowed to warm up to -40°C to -30°C over a period of one h and maintained at -40°C to -30°C for 2 h. Then ammonium hydroxide (4 mL) was added and the solution was concentrated. The residue obtained was then treated with ammonium hydroxide (11 mL) in methanol (40 mL) and the reaction mixture was stirred for 12 h. A mixture of 1:1 EtOAc/hexane (80 mL) was added, and the mixture was stirred for 10 min and filtered, and the filtrate was washed with water (20 mL). The organic layer was separated, dried over magnesium sulfate, concentrated, and submitted to silica gel chromatography (90:10 hexane/EtOAc) to give **(+)-1a** (0.150 g, 75%) as a glass: $[\alpha]_D^{20}$ = +58° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.97 [dd, 6 H, *J* = 1.9 Hz, *J* = 4.7 Hz, $CH(CH_3)_2$], 1.15 (d, 3 H, *J* = 6.8 Hz, CH_3), 1.46 (d, 3 H, *J* = 6.4 Hz, CH_3), 1.46, 1.52 [2 s, 6 H, $C(CH_3)_2$], 1.95 (m, 1 H, H-11), 2.02 [m, 1 H, $CH(CH_3)_2$], 2.78 [m, 2 H, $CH_2CH(CH_3)_2$], 3.49 (d, 1 H, *J* = 2.9 Hz, OH), 3.92 (m, 1 H, H-10), 4.72 (dd, 1 H, *J* = 2.65 Hz, *J* = 5.1 Hz, H-12), 5.53 (dd, 1 H, *J* = 2.4 Hz, *J* = 7.6 Hz), 5.89 (s, 1 H, H-3), 6.62 (dd, 1 H, *J* = 3.3 Hz, *J* = 6.6 Hz, H-8); ^{13}C NMR ($CDCl_3$): δ 15.13, 18.92, 22.27,

27.50, 27.73, 28.06, 40.46, 45.75, 67.27, 77.19, 77.79, 104.17, 106.44, 111.48, 111.66, 116.58, 127.03, 151.22, 153.12, 154.63, 157.44, 160.06. Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34.

Preparation of (−)-5-Hydroxy-6-[(1*S*,2*S*)-1-hydroxy-2-methylbut-3-enyl]-2,2-dimethyl-10-isobutyl-2*H*-pyrano[2,3-*f*]chromene-8-one [(−)-9a]. The procedure for compound **(+)-9a** was repeated using (−)-(*E*)-crotyldiisopinocampheylborane **(−)-8** to give **(−)-9a** as a syrup: $[\alpha]_D^{20} = -100°$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.944 [dd, 6 H, *J* = 1.6 Hz, *J* = 5.0 Hz, $CH(CH_3)_2$], 1.06 (d, 3 H, *J* = 6.9 Hz, $CHCH_3$), 1.47, 1.51 [2 s, 6 H, $C(CH_3)_2$], 2.00 [m, 1 H, $CH(CH_3)_2$], 2.67 (m, 1 H, $CHCH_3$), 2.77 [m, 2 H, $CH_2CH(CH_3)_2$], 4.77 (bs, 1 H, OH), 5.11–5.14 (m, 2 H, $CH=CH_2$), 5.40 (d, 1 H, *J* = 7.3 Hz, CHOH), 5.55 (d, 1 H, *J* = 9.9 Hz, H-3), 5.73 (s, 1 H, H-9), 5.88-5.99 (m, 1 H, $CH=CH_2$), 6.69 (d, 1 H, *J* = 9.9 Hz, H-4), 9.93 (s, 1 H, ArOH); ^{13}C NMR ($CDCl_3$): δ 16.41, 22.34, 27.60, 28.05, 44.32, 45.68, 72.58, 77.73, 102.89, 106.23, 107.17, 110.72, 116.56, 116.69, 126.78, 139.62, 151.12, 151.99, 155.99, 157.96, 161.21. Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found C, 71.68; H, 7.40.

Preparation of (−)-5-Hydroxy-6-[(1*S*,2*S*)-1-*tert*-butyldimethylsilyloxy-2-methylbut-3-enyl]-2,2-dimethyl-10-isobutyl-2*H*-pyrano[2,3-*f*]chromen-8-one [(−)-10a]. By the same procedure as for compound **(+)-10a**, **(−)-10a** was obtained as a syrup: $[\alpha]_D^{20} = -28°$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ −0.02, 0.16 (2 s, 6 H, $SiCH_3$), 0.89 [s, 9 H, $C(CH_3)_3$], 0.98 [d, 9 H, *J* = 6.4 Hz, $CHCH_3$, $CH(CH_3)_2$ overlapped], 1.49, 1.52 [2 s, 6 H, $C(CH_3)_2$], 2.07 [m, 1 H, $CH(CH_3)_2$], 2.63 (m, 1 H, $CHCH_3$), 2.78 [m, 2 H, $CH_2CH(CH_3)_2$], 4.98–5.07 (m, 2 H, $CH=CH_2$), 5.31 [d, 1 H, *J* = 6.8 Hz, $CHOSi(CH_3)_2$],

5.55 (d, 1 H, J = 10.0 Hz, H-3), 5.80–5.90 (m, 1 H, C*H*=CH_2), 5.87 (s, 1 H, H-9), 6.68 (d, 1 H, J = 9.9 Hz, H-4), 9.32 (s, 1 H, ArOH); ^{13}C NMR ($CDCl_3$): δ -0.43, -0.17, 16.24, 18.05, 22.35, 25.69, 27.57, 28.09, 44.53, 45.69, 74.21, 77.69, 102.84, 106.78, 106.88, 111.41, 115.69, 116.60, 126.76, 139.71, 151.10, 151.84, 155.43, 157.06, 160.30; Anal. Calcd for $C_{29}H_{42}O_5Si$: C, 69.84; H, 8.49. Found C, 69.74; H, 8.54.

Preparation of (−)-(10*S*,11*S*,12*S*)-12-*tert*-Butyldimethylsilyloxy-6,6,10,11-tetramethyl-4-isobutyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromen-2-one [(−)-11a]. By the procedure used for compound **(+)-11a**, **(−)-11a** was obtained as a glass: $[\alpha]_D^{20}$ = +48° (*c* 1.0, acetone); ^{1}H NMR ($CDCl_3$): δ -0.11, 0.28 (2 s, 6 H, $SiCH_3$), 0.81 [s, 9 H, $C(CH_3)_3$], 0.95 [t, 6 H, $CH(CH_3)_2$], 1.08 (d, 3 H, J = 6.8 Hz, CH_3), 1.40 (d, 3 H, J = 6.3 Hz, CH_3), 1.48, 1.50 [2 s, 6 H, $C(CH_3)_2$], 1.65 (m, 1 H, H-11), 2.03 [m, 1 H, $CH(CH_3)_2$], 2.77 [m, 2 H, $CH_2CH(CH_3)_2$], 4.41 (m, 1 H, H-10), 5.02 (d, 1 H, J = 2.0 Hz, H-12), 5.52 (d, 1 H, J = 10 Hz, H-7), 5.87 (s, 1 H, H-3), 6.65 (d, 1 H, J = 10 Hz, H-8); ^{13}C NMR ($CDCl_3$): δ -0.85, -0.52, 14.08, 18.51, 19.20, 22.17, 22.38 25.99, 27.67, 27.84, 39.04, 45.71, 62.67, 72.99, 102.89, 105.92, 106.84, 111.47, 116.70, 126.55, 151.22, 153.03, 153.09, 157.02, 160.34; Anal. Calcd for $C_{29}H_{42}O_5Si$: C, 69.84; H, 8.49. Found C, 70.02; H, 8.60.

Preparation of (−)-(10*S*,11*R*,12*S*)-12-Hydroxy-6,6,10,11-tetramethyl-4-isobutyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromen-2-one [(−)-2a]. By the procedure for compound **(+)-2a**, **(−)-2a** was obtained as a white solid: mp 157–158 °C; $[\alpha]_D^{20}$ = −37° (*c* 1.0, acetone); ^{1}H NMR ($CDCl_3$): δ 0.96 (dd, 6 H, J = 2.7 Hz, J = 3.8 Hz, $CH(CH_3)_2$], 1.12 (d, 3 H, J = 7.0 Hz, CH_3), 1.42 (d, 3 H, J = 6.3 Hz, CH_3), 1.48, 1.50 [2

s, 6 H, $C(CH_3)_2$], 1.73 (m, 1 H, H-11), 2.01 [m, 1 H, $CH(CH_3)_2$], 2.76 [m, 2 H, $CH_2CH(CH_3)_2$], 3.00 (bs, 1 H, OH), 4.26 (m, 1 H, H-10), 4.97 (d, 1 H, J = 3.1, H-12), 5.52 (d, 1 H, J = 10.0 Hz, H-7), 5.87 (s, 1 H, H-3), 6.63 (d, 1 H, J = 9.9 Hz, H-8); ^{13}C NMR ($CDCl_3$): δ 12.43, 18.82, 22.33, 27.66, 27.78, 38.24, 45.59, 61.71, 72.91, 77.66, 103.53, 106.11, 106.38, 111.54, 116.57, 126.70, 151.32, 153.09, 153.96, 157.22, 160.64; Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found C, 72.04; H, 7.42.

Preparation of Ethyl 3-Oxooctanoate (4b). By the same procedure as for compound **4a**, **4b** was obtained from 2-heptanone (57.0 g, 0.500 mol) as a colorless liquid (61.4 g, 66%), bp 126–130 °C (25 torr). [Lit.[34] bp 108–110 °C (11 torr)].

Preparation of 5,7-Dihydroxy-4-pentylcoumarin (5b). By the same procedure as for compound **5a**, **5b** was obtained from **4b** (31.6 g, 0.170 mol) as a white solid (39.7 g, 80%): mp 232–234 °C, (Lit.[35] mp 235–237 °C); ^1H NMR (3:1 $CDCl_3/CD_3OD$): δ 0.804 (t, 3 H, J = 6.9 Hz, CH_2CH_3), 1.27 (m, 4 H, CH_2CH_3, $CH_2CH_2CH_3$ overlapped), 1.54 (m, 2 H, $CH_2CH_2CH_2CH_3$), 2.85 (t, 2 H, J = 7.8 Hz, $CH_2CH_2CH_2CH_2CH_3$), 5.78 (s, 1 H, H-3), 6.14 (d, 1 H, J = 2.2 Hz, H-6), 6.23 (d, 1 H, J = 2.3 Hz, H-8); ^{13}C NMR (3:1 $CDCl_3/CD_3OD$): δ 13.59, 22.14, 29.12, 31.51, 35.91, 95.19, 99.38, 102.62, 107.81, 156.76, 157.33, 160.57, 161.24, 163.32. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.55; H, 6.55.

Preparation of 5,7-Dihydroxy-2-oxo-4-pentyl-2*H*-chromene-8-carbaldehyde (6b). By the same procedure as for compound **6a**, **6b** was obtained from **5b** (31.0g, 0.125 mol) as a white solid (25.2 g, 73%): mp 204–205 °C; ^1H NMR (3:1 $CDCl_3/CD_3OD$): δ 0.929 (t, 3 H, J = 6.9 Hz, CH_2CH_3), 1.40 (m, 4 H, $CH_2CH_2CH_3$,

CH_2CH_3 overlappped), 1.63 (m, 2 H, $CH_2CH_2CH_2CH_3$), 2.95 (t, 2 H, J = 7.9 Hz, $CH_2CH_2CH_2CH_2CH_3$), 6.00 (s, 1 H, H-3), 6.21 (s, 1 H, H-6), 10.3 (s, 1 H, CHO); ^{13}C NMR (3:1 $CDCl_3/CD_3OD$): δ 13.01, 21.72, 28.72, 31.09, 35.63, 98.41, 102.19, 103.05, 109.05, 158.57, 159.94, 160.08, 164.10, 165.65, 190.92. Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found C, 65.36; H, 5.89.

Preparation of 5-Hydroxy-2,2-dimethyl-8-oxo-10-pentyl-2*H*,8*H*-pyrano[2,3-*f*]chromene-6-carbaldehyde (7b). By the same procedure as for compound **7a**, **7b** was obtained from **6b** (21.6 g, 78.3 mmol) as a yellow solid (7.8 g, 30%): mp 104–105 °C; ^{1}H NMR ($CDCl_3$): δ 0.933 (t, 3 H, J = 6.9 Hz, CH_2CH_3), 1.41 (m, 4 H, $CH_2CH_2CH_3$, CH_2CH_3 overlapped), 1.55 [s, 6 H, $C(CH_3)_2$], 1.63 (m, 2 H, $CH_2CH_2CH_2CH_3$), 2.90 (t, 2 H, J = 7.8 Hz, $CH_2CH_2CH_2CH_2CH_3$), 5.61 (d, 1 H, J = 10.1 Hz, H-3), 6.03 (s, 1 H, H-9), 6.66 (d, 1 H, J = 10.1 Hz, H-4), 10.4 (s, 1 H, CHO), 12.8 (s, 1 H, ArOH); ^{13}C NMR ($CDCl_3$): δ 13.94, 22.54, 28.32, 29.49, 31.70, 36.54, 80.21, 102.64, 103.86, 105.26, 111.11, 115.02, 126.57, 158.15, 158.91, 161.18, 192.02. Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 69.95; H, 6.56.

Preparation of (+)-5-Hydroxy-6[(1*R*,2*R*)-1-hydroxy-2-methylbut-3-enyl]-2,2-dimethyl-10-pentyl-2*H*-pyrano[2,3-*f*]chromene-8-one [(+)-9b]. The procedure for compound **(+)-9a** was repeated using **7b** (3.50 g, 10.2 mmol) to give **(+)-9b** (2.57 g, 63%) as a white solid: mp 145–146 °C; $[\alpha]_D^{20}$ = +121° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$); δ 0.918 (t, 3 H, J = 6.9 Hz CH_2CH_3), 1.03 (d, 3 H, J = 6.8 Hz, $CHCH_3$), 1.38 (m, 4 H, $CH_2CH_2CH_3$, CH_2CH_3 overlapped), 1.46, 1.51 [2 s, 6 H, $C(CH_3)_2$], 1.58 (m, 2 H, $CH_2CH_2CH_2CH_3$), 2.64 (m, 1 H, $CHCH_3$), 2.86 (m, 2 H, $CH_2CH_2CH_2CH_2CH_3$), 4.21 (bs,

1 H, OH), 5.11–5.18 (m, 2 H, CH=CH_2), 5.36 (dd, 1 H, J = 2.6 Hz, J = 5.0 Hz, C*H*OH), 5.55 (d, 1 H, J = 9.9 Hz, H-3), 5.78 (s, 1 H, H-9), 5.90–6.00 (m, 1 H, C*H*=CH_2), 6.69 (d, 1 H, J = 10.0 Hz, H 4), 9.73 (s, 1 H, ArOH); ^{13}C NMR ($CDCl_3$): δ 14.04, 16.48, 22.63, 27.56, 28.11, 29.55, 31.92, 36.61, 44.56, 72.51, 77.67, 102.89, 105.97, 107.18, 109.41, 116.58, 117.13, 126.84, 139.84, 151.15, 151.88,155.78, 159.43, 161.57. Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found C, 72.19; H, 7.55.

Preparation of (+)-5-Hydroxy-6-[(1*R*,2*R*)-1-*tert*-butyldimethylsilyloxy-2-methylbut-3-enyl]-2,2-dimethyl-10-pentyl-2*H*-pyrano[2,3-*f*]chromen-8-one [(+)-10b]. By the same procedure as for **(+)-10a**, **(+)-10b** was obtained from **(+)-9b** (2.51 g, 6.32 mmol) as a syrup (2.62 g, 81%): $[\alpha]_D^{20}$ = +27° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ −0.11, 0.09 (2 s, 6 H, $SiCH_3$), 0.81 [s, 9 H, $C(CH_3)_3$], 0.85 (m, 3 H, CH_2CH_3), 0.91 (d, 3 H, J = 6.9 Hz, $CHCH_3$), 1.32 (m, 4 H, $CH_2CH_2CH_3$, CH_2CH_3 overlapped), 1.40, 1.44 [2 s, 6 H, $C(CH_3)_2$], 1.58 (m, 2 H, $CH_2CH_2CH_2CH_3$), 2.53 (m, 1 H, C*H*CH_3), 2.84 (m, 2 H, $CH_2CH_2CH_2CH_2CH_3$), 4.90–4.99 (m, 2 H, CH=CH_2) 5.22 [d, 1 H, J = 6.8 Hz, C*H*O$Si(CH_3)_2$], 5.47 (d, 1 H, J = 9.9 Hz, H-3), 5.72–5.83 (m, 1 H, C*H*=CH_2), 5.85 (s, 1 H, H-9), 6.60 (d, 1 H, J = 9.9 Hz, H-4), 9.25 (s, 1 H, ArOH); ^{13}C NMR ($CDCl_3$): δ −0.43, −0.16, 14.01, 16.25, 18.05, 22.61, 25.67, 27.57, 28.02, 29.60, 31.90, 36.61, 44.55, 74.18, 77.57, 102.80, 106.75, 106.84, 109.93, 115.70, 116.60, 126.73, 139.74, 151.10, 151.75, 155.42, 158.79, 160.62. Anal. Calcd for $C_{30}H_{44}O_5Si$: C, 70.27; H, 8.65. Found C, 70.52; H, 8.77.

Preparation of (+)-(10*R*,11*R*,12*R*)-12-*tert*-Butyldimethylsilyloxy-6,6,10,11-tetramethyl-4-pentyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromen-2-one

[(+)-11b]. By the same procedure as for **(+)-11a**, **(+)-11b** was obtained from **(+)-10b** (2.00 g, 3.91 mmol) as a glass (1.50 g, 75%): $[\alpha]_D^{20} = -17°$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ -0.11, 0.28 (2 s, 6 H, $SiCH_3$), 0.82 [s, 9 H, $C(CH_3)_3$], 0.91 (t, 3 H, CH_2CH_3), 1.07 (d, 3 H, J = 6.8 Hz, CH_3), 1.36 (m, 4 H, $CH_2CH_2CH_3$, CH_2CH_3 overlapped), 1.40 (d, 3 H, J = 6.4 Hz, CH_3), 1.48, 1.49 [2 s, 6 H, $C(CH_3)_2$], 1.63 (m, 4 H, H-11, $CH_2CH_2CH_2CH_3$ overlapped), 2.90 (m, 2 H, $CH_2CH_2CH_2CH_2CH_3$), 4.42 (m, 1 H, H-10), 5.00 (d, 1 H, J = 2.2 Hz, H-12), 5.51 (d, 1 H, J = 10.0 Hz, H-7), 5.92 (s, 1 H, H-3), 6.64 (d, 1 H, J = 9.9 Hz, H-8); ^{13}C NMR ($CDCl_3$): δ -0.89, -0.47, 14.03, 14.10, 18.53, 19.20, 22.63, 26.02, 27.82, 29.63, 31.58, 31.85, 36.58, 39.11, 62.69, 73.00, 102.90, 105.90, 106.84, 110.02, 116.72, 126.53, 151.27, 152.97, 153.11, 158.70, 160.67. Anal. Calcd for $C_{30}H_{44}O_5Si$: C, 70.27; H, 8.65. Found C, 70.19; H, 8.73.

Preparation of (+)-(10*R*,11*S*,12*R*)-12-Hydroxy-6,6,10,11-tetramethyl-4-pentyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromene-2-one [(+)-2b]. By the same procedure for **(+)-2a**, **(+)-2b** was obtained from **(+)-11b** (0.500 g, 0.977 mmol) as a white solid (0.272 g, 70%): mp 119–120 °C; $[\alpha]_D^{20} = +36°$ (*c* 1.0, acetone); ^1H NMR ($CDCl_3$): δ 0.92 (t, 3 H, J = 7.0 Hz, CH_2CH_3), 1.14 (d, 3 H, J = 7.0 Hz, CH_3), 1.39 (m, 4 H, CH_2CH_3, $CH_2CH_2CH_3$ overlapped), 1.43 (d, 3 H, J = 6.3 Hz, CH_3), 1.47, 1.49 [2 s, 6 H, $C(CH_3)_2$], 1.62 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.72 (m, 1 H, H-11), 2.50 (bs, 1 H, OH), 2.91 (m, 2 H, $CH_2CH_2CH_2CH_2CH_3$), 4.26 (m, 1 H, H-10), 4.97 (d, 1 H, J = 3.1 Hz, H-12), 5.53(d, 1 H, J = 10.0 Hz, H-7), 5.94 (s, 1 H, H-3), 6.63 (d, 1 H, J = 9.9 Hz, H-8); ^{13}C NMR ($CDCl_3$): δ 12.43, 13.97, 18.75, 22.57, 27.74, 29.65, 31.78, 36.51, 38.25, 61.66, 72.91, 77.57, 103.47, 106.06, 106.39, 110.03, 116.55, 126.67, 151.30, 153.09,

153.85, 159.00, 161.03; Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found C, 70.16; H, 7.67.

Preparation of (+)-(10*R*,11*S*,12*S*)-12-Hydroxy-6,6,10,11-tetramethyl-4-pentyl-6,10,11,12-tetrahydro-dipyrano[2,3-*f*;2',3'-*h*]chromene-2-one [(+)-1b]. By the same procedure for **(+)-1a**, **(+)-1b** was obtained from **(+)-2b** (0.143 g, 0.359 mmol) as a glass (0.100 g, 70%): $[\alpha]_D^{20} = +54°$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.92 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3), 1.15 (d, 3 H, *J* = 6.8 Hz, CH_3), 1.39 (m, 4 H, $CH_2CH_2CH_3$, CH_2CH_3 overlapped), 1.46 (d, 3 H, *J* = 6.4 Hz, CH_3), 1.46, 1.51 [2 s, 6 H, $C(CH_3)_2$], 1.62 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.95 (m, 1 H, H-11), 2.91 (m, 2 H, $CH_2CH_2CH_2CH_2CH_3$), 3.56 (d, 1 H, *J* = 3.1 Hz, OH), 3.92 (m, 1 H, H-10), 4.72 (dd, 1 H, *J* = 4.8 Hz, *J* = 3.0 Hz), 5.54 (d, 1 H, *J* = 9.9 Hz, H-7), 5.95 (s, 1 H, H-3), 6.62 (d, 1 H, *J* = 9.9 Hz, H-8); ^{13}C NMR ($CDCl_3$): δ . Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59.

Preparation of (−)-5-Hydroxy-6[(1*S*,2*S*)-1-hydroxy-2-methylbut-3-enyl]-2,2-dimethyl-10-pentyl-2*H*-pyrano[2,3-*f*]chromene-8-one [(−)-9b]. The procedure for compound **(+)-9a** was repeated using (−)-(*E*)-crotyldiisopinocampheylborane **(−)-8** to give **(−)-9b** as a white solid: mp 145–146 °C; $[\alpha]_D^{20} = -121°$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$); δ 0.918 (t, 3 H, *J* = 6.9 Hz CH_2CH_3), 1.03 (d, 3 H, *J* = 6.8 Hz, $CHCH_3$), 1.38 (m, 4 H, $CH_2CH_2CH_3$, CH_2CH_3 overlapped), 1.46, 1.51 [2 s, 6 H, $C(CH_3)_2$], 1.58 (m, 2 H, $CH_2CH_2CH_2CH_3$), 2.64 (m, 1 H, $CHCH_3$), 2.86 (m, 2 H, $CH_2CH_2CH_2CH_2CH_3$), 4.24 (bs, 1 H, OH), 5.11–5.18 (m, 2 H, $CH{=}CH_2$), 5.36 (dd, 1 H, *J* = 2.6 Hz, *J* = 5.0 Hz, CHOH), 5.55 (d, 1 H, *J* = 9.9 Hz, H-3), 5.78 (s, 1 H, H-9), 5.86–6.01 (m, 1 H, $CH{=}CH_2$), 6.69 (d, 1 H, *J* = 10.0 Hz, H 4), 9.74 (s, 1 H, ArOH); ^{13}C NMR ($CDCl_3$): δ 14.01, 16.46, 22.60,

27.46, 28.12, 29.48, 31.90, 36.57, 44.31, 72.58, 77.63, 102.89, 106.23, 107.17, 109.16, 116.61, 116.66, 126.77, 139.75, 151.15, 151.88,155.95, 159.57, 161.57. Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found C, 72.42; H, 7.60.

Preparation of (−)-5-Hydroxy-6-[(1*S*,2*S*)-1-*tert*-butyldimethylsilyloxy-2-methylbut-3-enyl]-2,2-dimethyl-10-pentyl-2*H*-pyrano[2,3-*f*]chromen-8-one [(−)-10b]. By the same procedure as for **(+)-10a**, **(−)-10b** was obtained as a syrup: $[\alpha]_D^{20}$ = −27° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ −0.11, 0.09 (2 s, 6 H, $SiCH_3$), 0.81 [s, 9 H, $C(CH_3)_3$], 0.85 (m, 3 H, CH_2CH_3), 0.91 (d, 3 H, *J* = 6.9 Hz, $CHCH_3$), 1.32 (m, 4 H, $CH_2CH_2CH_3$, CH_2CH_3 overlapped), 1.40, 1.44 [2 s, 6 H, $C(CH_3)_2$], 1.58 (m, 2 H, $CH_2CH_2CH_2CH_3$), 2.53 (m, 1 H, $CHCH_3$), 2.84 (m, 2 H, $CH_2CH_2CH_2CH_2CH_3$), 4.90–4.99 (m, 2 H, $CH=CH_2$), 5.22 [d, 1 H, *J* = 6.8 Hz, $CHOSi(CH_3)_2$], 5.47 (d, 1 H, *J* = 9.9 Hz, H-3), 5.72–5.83 (m, 1 H, $CH=CH_2$), 5.85 (s, 1 H, H-9), 6.60 (d. 1 H, *J* = 9.9 Hz, H-4), 9.25 (s, 1 H, ArOH); ^{13}C NMR ($CDCl_3$): δ −0.36, −0.17, 14.01, 16.24, 18.05, 22.60, 25.66, 27.57, 28.00, 29.60, 31.89, 36.61, 44.55, 74.18, 77.57, 102.79, 106.75, 106.84, 109.91, 115.69, 116.60, 126.71, 139.72, 151.09, 151.75, 155.42, 158.77, 160.61. Anal. Calcd for $C_{30}H_{44}O_5Si$: C, 70.27; H, 8.65. Found C, 70.26; H, 8.65.

Preparation of (−)-(10*S*,11*S*,12*S*)-12-*tert*-Butyldimethylsilyloxy-6,6,10,11-tetramethyl-4-pentyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromen-2-one [(−)-11b]. By the same procedure as for **(+)-11a**, **(−)-11b** was obtained as a glass: $[\alpha]_D^{20}$ = +17° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ −0.11, 0.28 (2 s, 6 H, $SiCH_3$), 0.82 [s, 9 H, $C(CH_3)_3$], 0.91 (t, 3 H, CH_2CH_3), 1.07 (d, 3 H, *J* = 6.8 Hz, CH_3), 1.36 (m, 4 H, $CH_2CH_2CH_3$, CH_2CH_3 overlapped), 1.40 (d, 3 H, *J* = 6.4 Hz, CH_3), 1.48, 1.49 [2 s, 6 H,

$C(CH_3)_2$], 1.63 (m, 4 H, H-11, $CH_2CH_2CH_2CH_3$ overlapped), 2.90 (m, 2 H, $CH_2CH_2CH_2CH_2CH_3$), 4.42 (m, 1 H, H-10), 5.00 (d, 1 H, J = 2.2 Hz, H-12), 5.51 (d, 1 H, J = 10.0 Hz, H-7), 5.92 (s, 1 H, H-3), 6.64 (d, 1 H, J = 9.9 Hz, H-8); ^{13}C NMR ($CDCl_3$): δ -0.87, -0.55, 14.01, 14.08, 18.51, 19.17, 22.60, 25.99, 26.05, 27.80, 29.60, 31.81, 36.55, 39.09, 62.68, 72.97, 102.88, 105.87, 106.81, 110.00, 116.70, 126.49, 151.24, 152.93, 153.09, 158.64, 160.61. Anal. Calcd for $C_{30}H_{44}O_5Si$: C, 70.27; H, 8.65. Found C, 70.02; H, 8.71.

Preparation of (−)-(10*S*,11*R*,12*S*)-12-Hydroxy-6,6,10,11-tetramethyl-4-pentyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromene-2-one [(−)-2b]. By the same procedure for **(+)-2a**, **(−)-2b** was obtained as a white solid: mp 119–120 °C; $[\alpha]_D^{20}$ = −36° (*c* 1.0, acetone); ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3 H, J = 7.0 Hz, CH_2CH_3), 1.14 (d, 3 H, J = 7.0 Hz, CH_3), 1.39 (m, 4 H, CH_2CH_3, $CH_2CH_2CH_3$ overlapped), 1.43 (d, 3 H, J = 6.3 Hz, CH_3), 1.47, 1.49 [2 s, 6 H, $C(CH_3)_2$], 1.62 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.72 (m, 1 H, H-11), 2.96 (bs, 1 H, OH), 2.91 (m, 2 H, $CH_2CH_2CH_2CH_2CH_3$), 4.26 (m, 1 H, H-10), 4.97 (d, 1 H, J = 3.1 Hz, H-12), 5.53(d, 1 H, J = 10.0 Hz, H-7), 5.94 (s, 1 H, H-3), 6.63 (d, 1 H, J = 9.9 Hz, H-8); ^{13}C NMR ($CDCl_3$): δ 12.49, 14.01, 18.85, 22.62, 27.68, 27.79, 29.69, 31.81, 36.54, 38.26, 61.73, 72.94, 77.60, 103.50, 106.08, 106.39, 110.11, 116.58, 126.70, 151.33, 153.11, 153.88, 158.97, 161.00; Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found C, 72.40; H, 7.63.

Molecular Modeling of (+)-1a, (+)-1b, (−)-2a, and (−)-2b. The modeling was accomplished at the University of Tennessee's Molecular Modeling Laboratory running SYBYL v. 6.2, a program by Tripos Associates. Compounds **(+)-1a, (+)-1b, (−)-2a,**

and **(−)-2b** were drawn freehand and minimized initially using Tripos's force-field approximation. Next, a simulated annealing run using SYBYL's dynamic module was performed. Each compound was heated up to 500 K and cooled down several times. Then, interesting comformations that occured at the start of a new interval and between the temperatures of 35 and 65° were analyzed and minimized. Next, a grid search, which allows selected bonds to be rotated at selected angles, was performed on a selected conformation so that a energy minima could be located. Once the grid search was completed on the selected conformation, there was a final minimization. Finally, each compound was overlaid onto the corresponding calanolide model that was developed by Kathy Bauerdorf (unpublished results). The compound's energy values were found to be 7.842 Kcal for **(+)-1a** (Figure 3), 6.020 and 5.230 Kcal for **(−)-2a** (Figures 4 and 5, respectively), 5.712 Kcal for **(+)-1b** (Figure 6), and 7.930 and 6.631 Kcal for **(−)-2b** (Figures 7 and 8, respectively). Kathy Bauerdorf's energy values were found to be 5.582 and 5.661 Kcal for (+)-calanolide A and (−)-calanolide B, respectively.

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LIST OF REFERENCES

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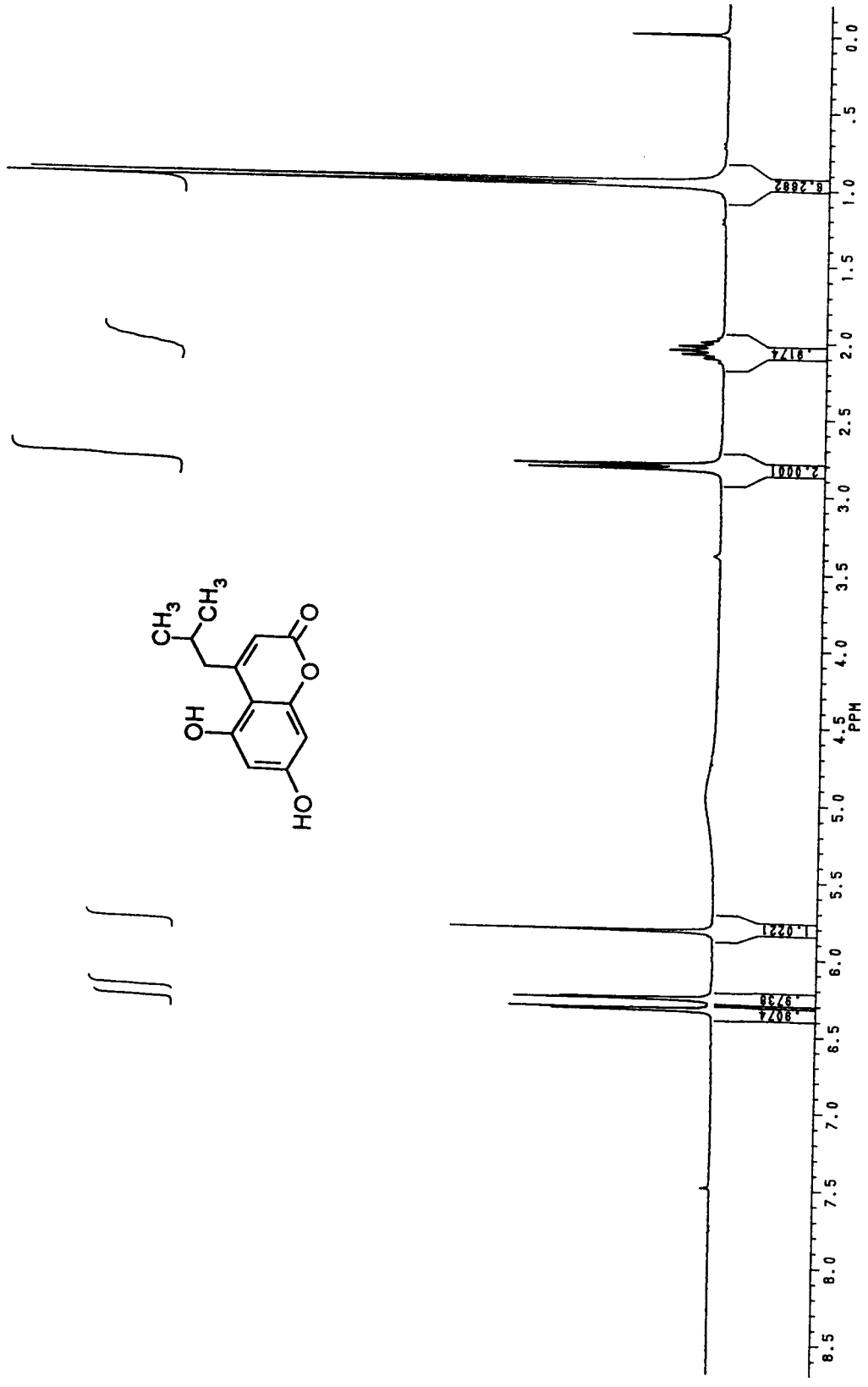
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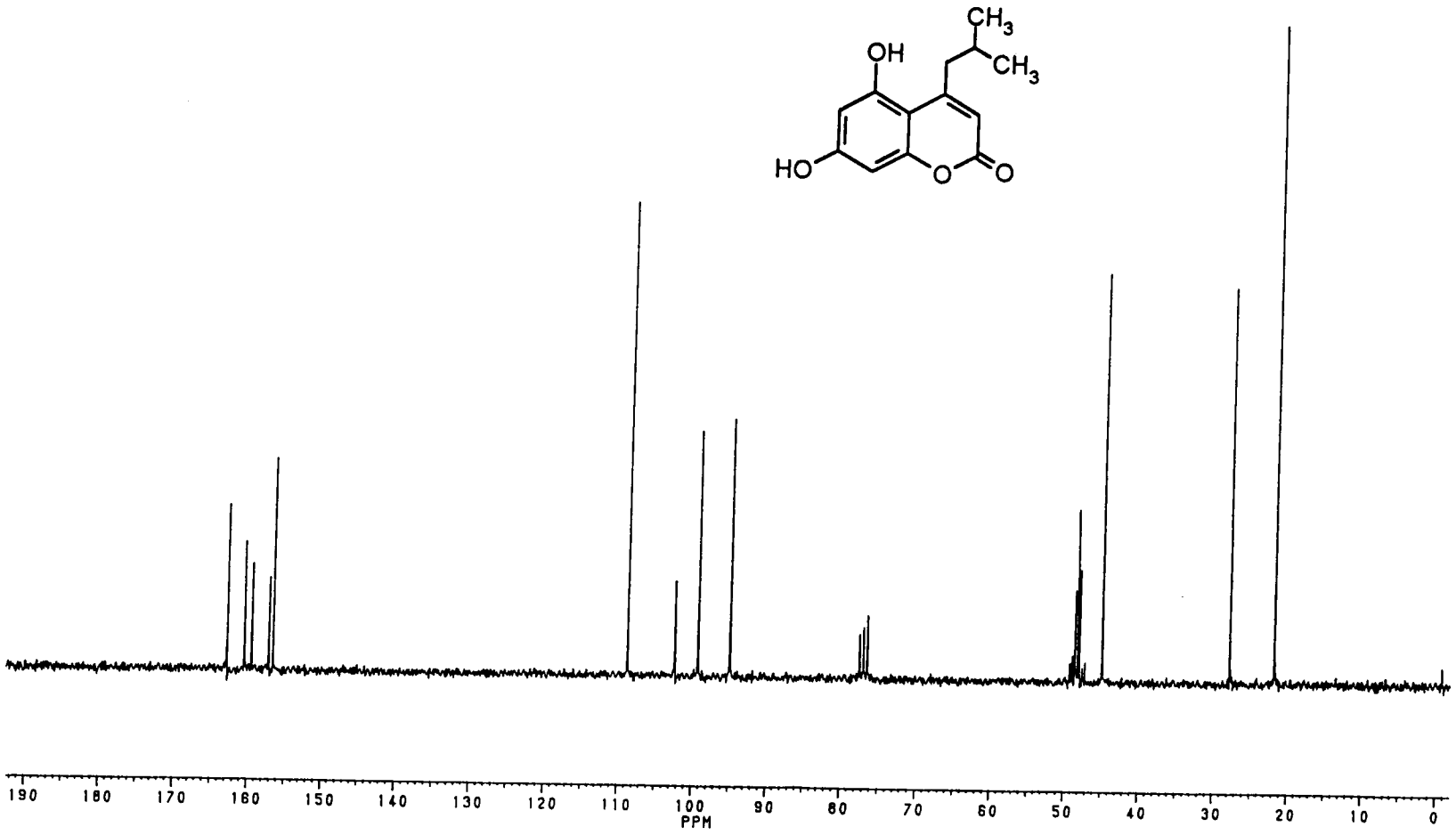
APPENDIX

^{1}H AND ^{13}C NMR SPECTRA FOR

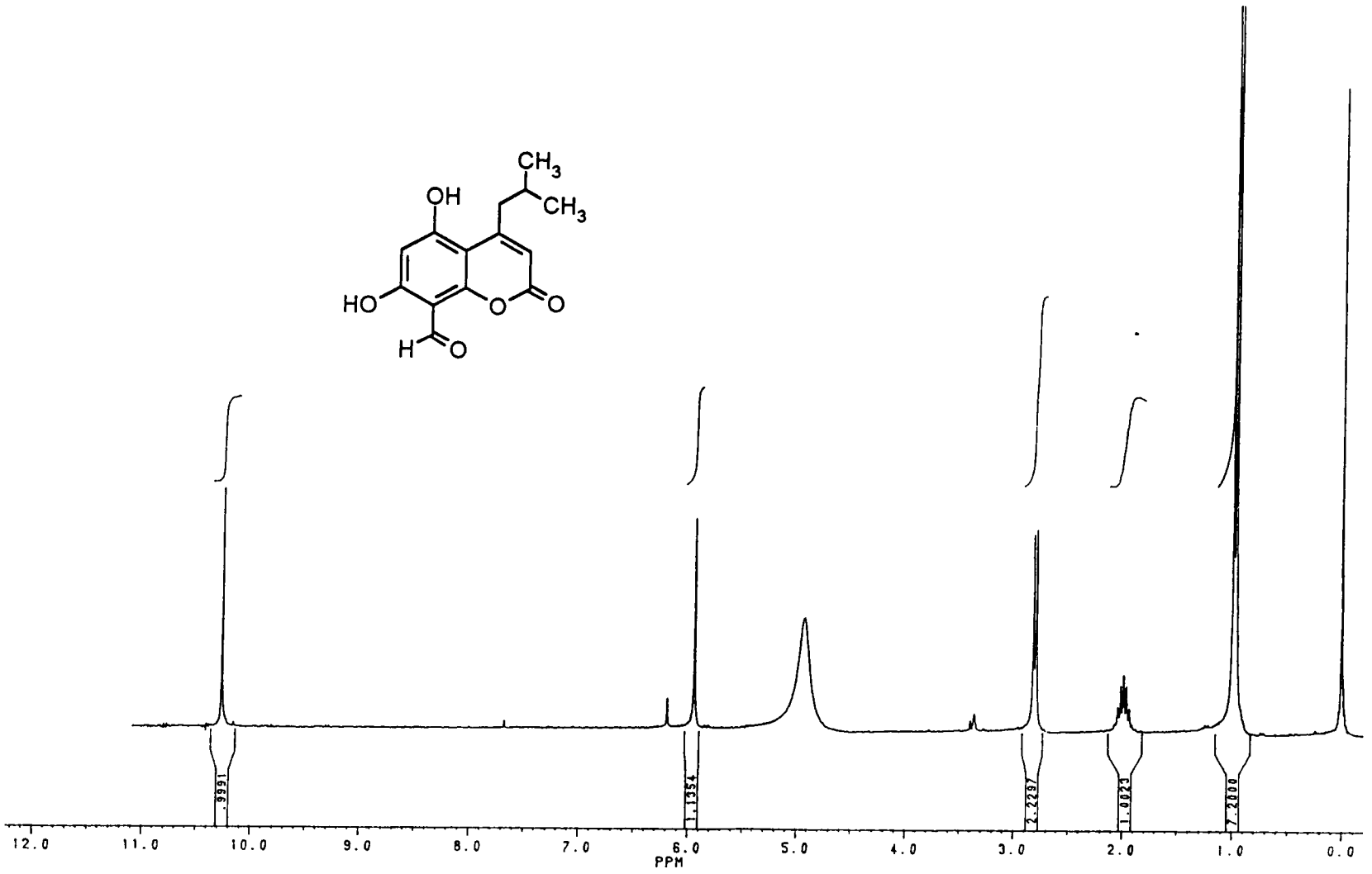
SELECTED INTERMEDIATE AND TARGET COMPOUNDS



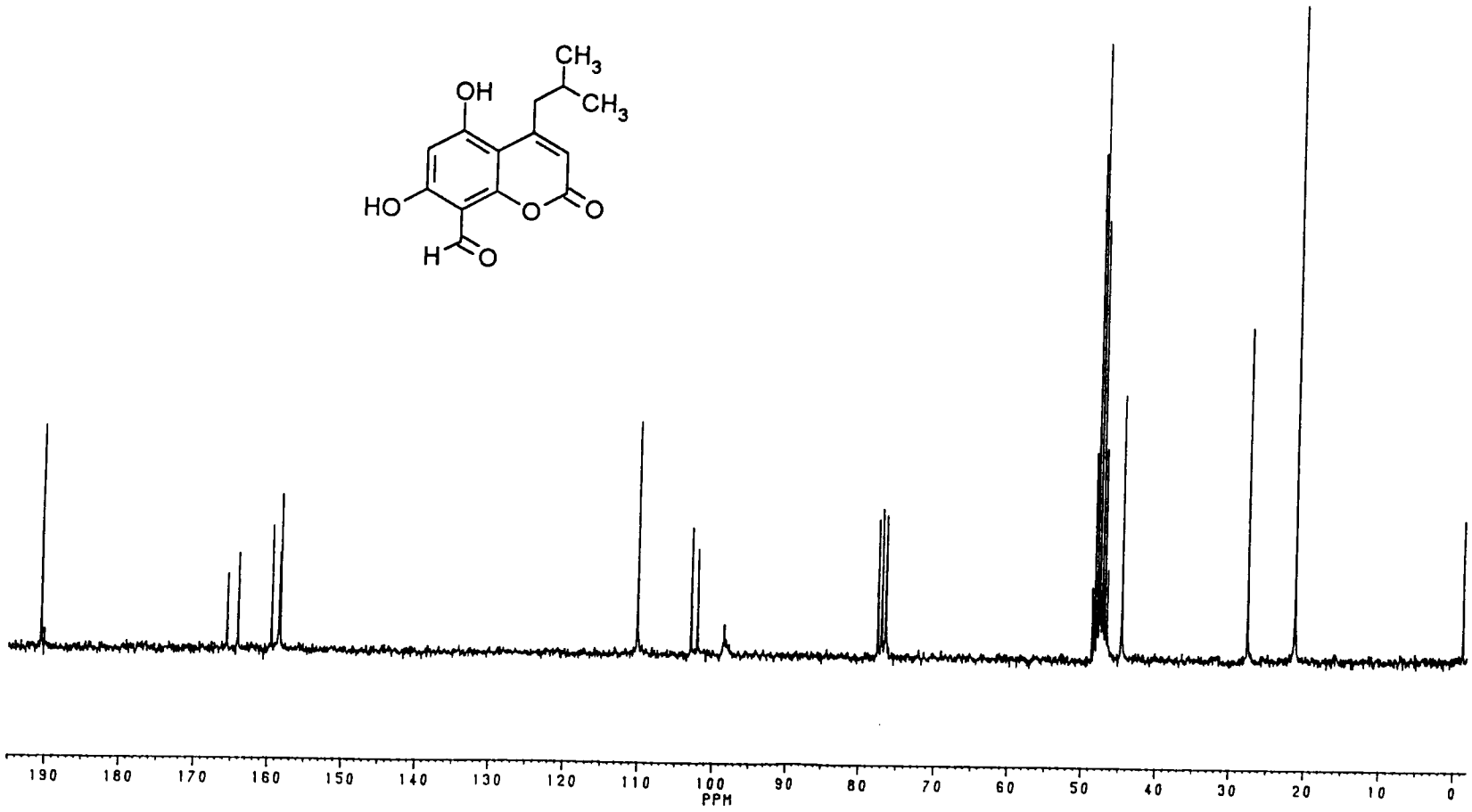
^{1}H NMR ($CDCl_3/CD_3OD$ 3:1) Spectrum of 5,7-Dihydroxy-4-isobutylcoumarin **(5a)**.



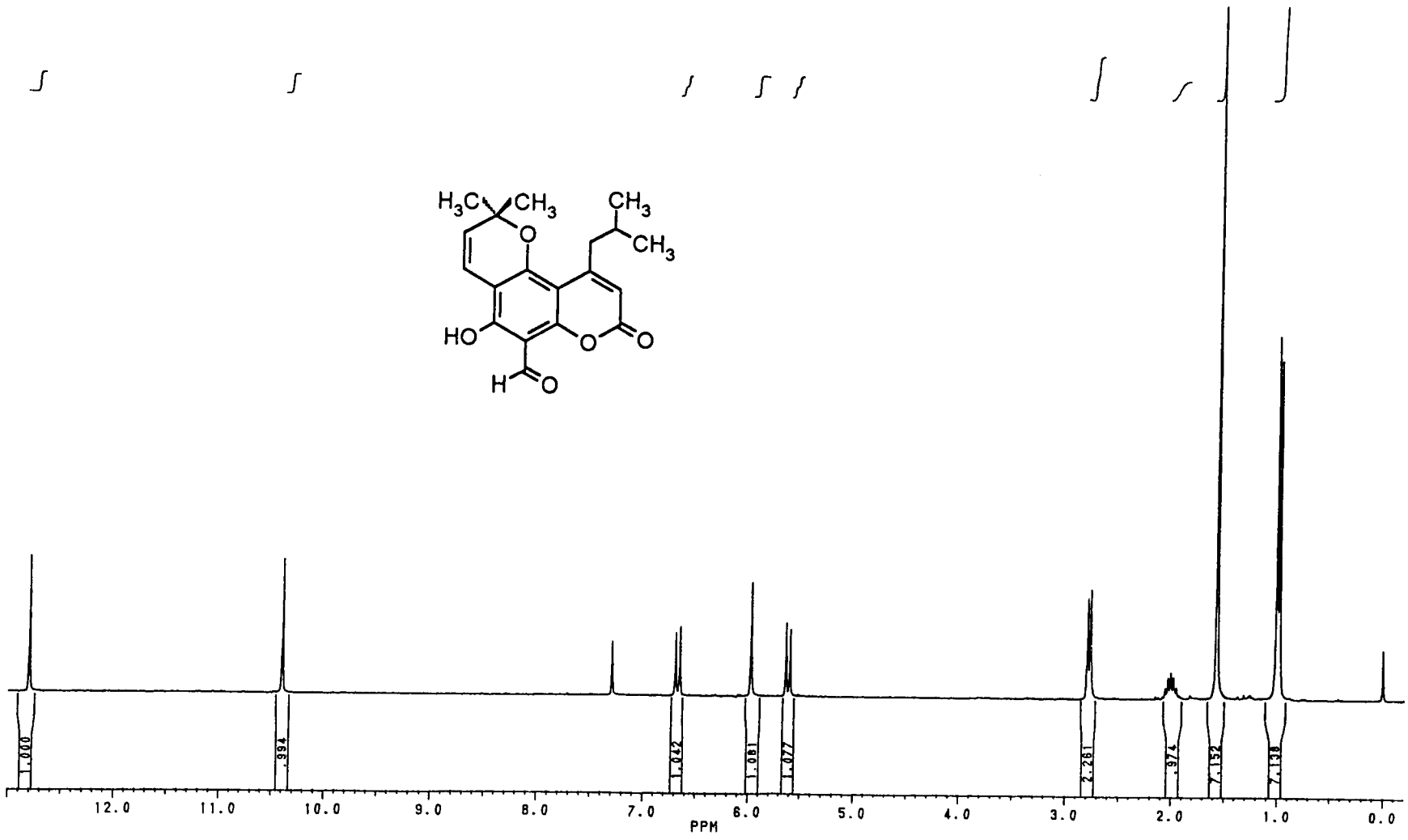
^{13}C NMR ($CDCl_3/CD_3OD$ 3:1) Spectrum of 5,7-Dihydroxy-4-isobutylcoumarin **(5a).**



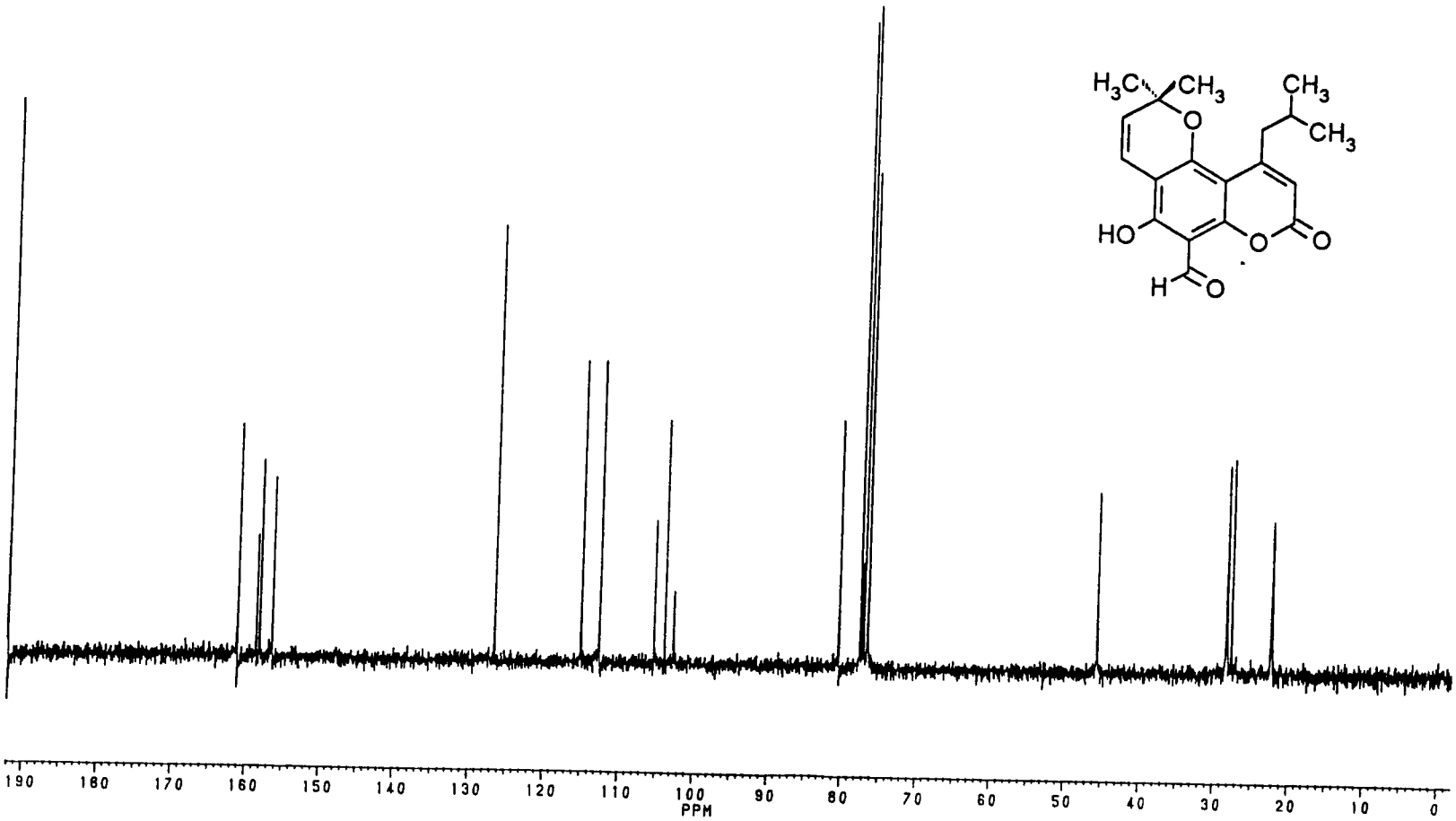
^{1}H NMR ($CDCl_3/CD_3OD$ 3:1) Spectrum of 5,7-Dihydroxy-2-oxo-4-isobutyl-2*H*-chromene-8-carbaldehyde **(6a).**



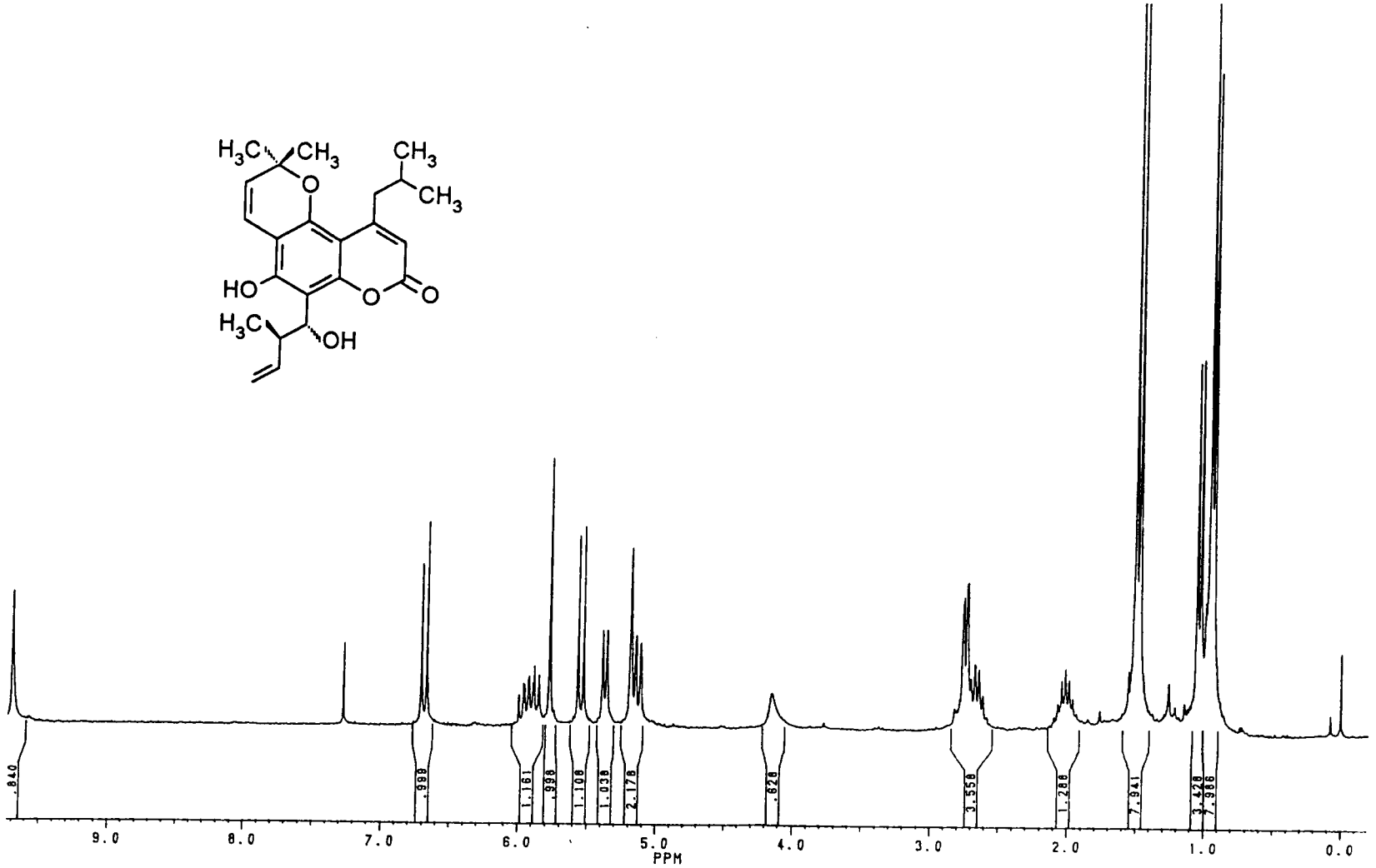
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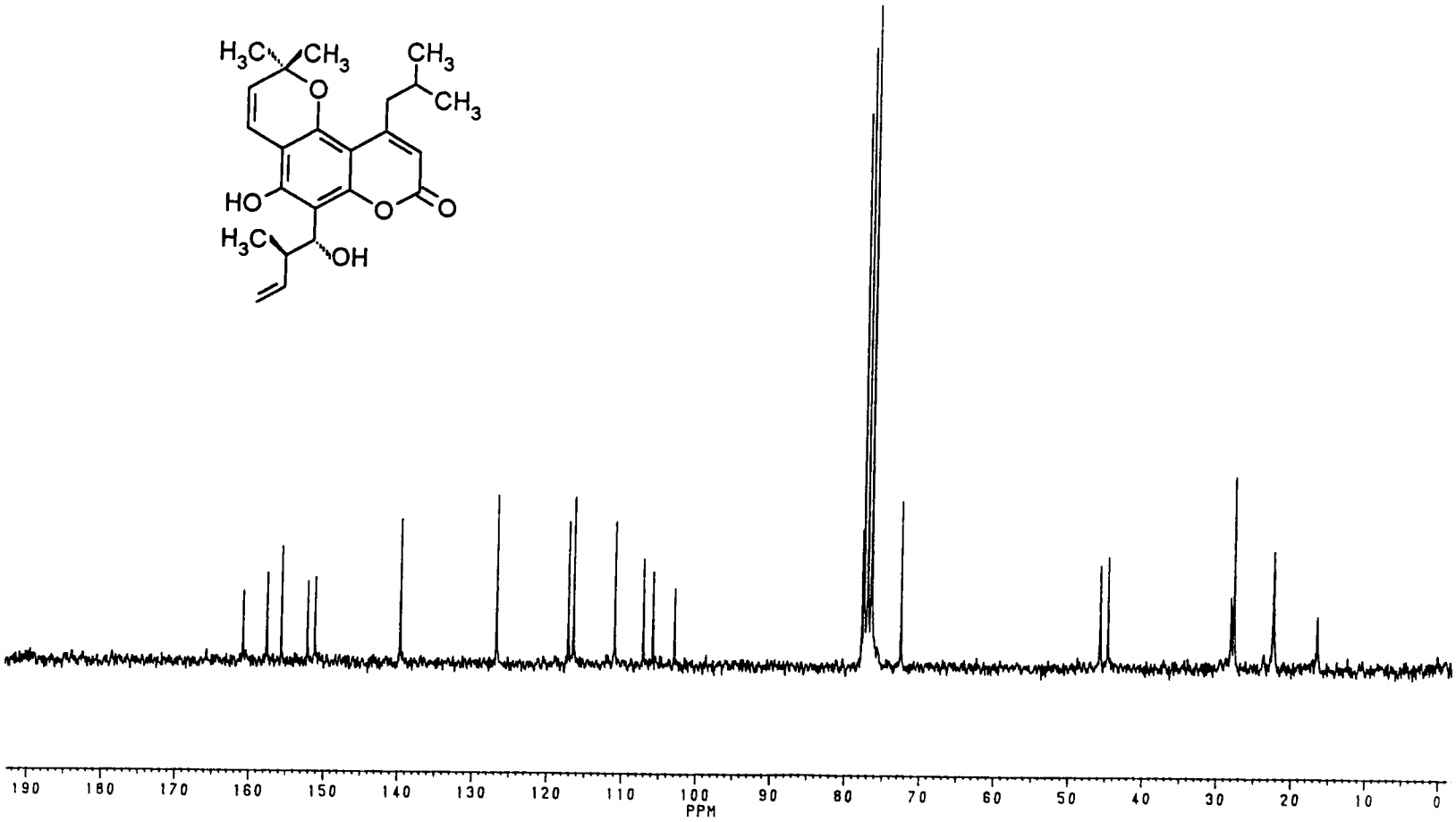
^{1}H NMR ($CDCl_3$) Spectrum of 5-Hydroxy-2,2-dimethyl-8-oxo-10-isobutyl-2*H*,8*H*-pyrano[2,3-*f*]chromene-6-carbaldehyde (**7a**).



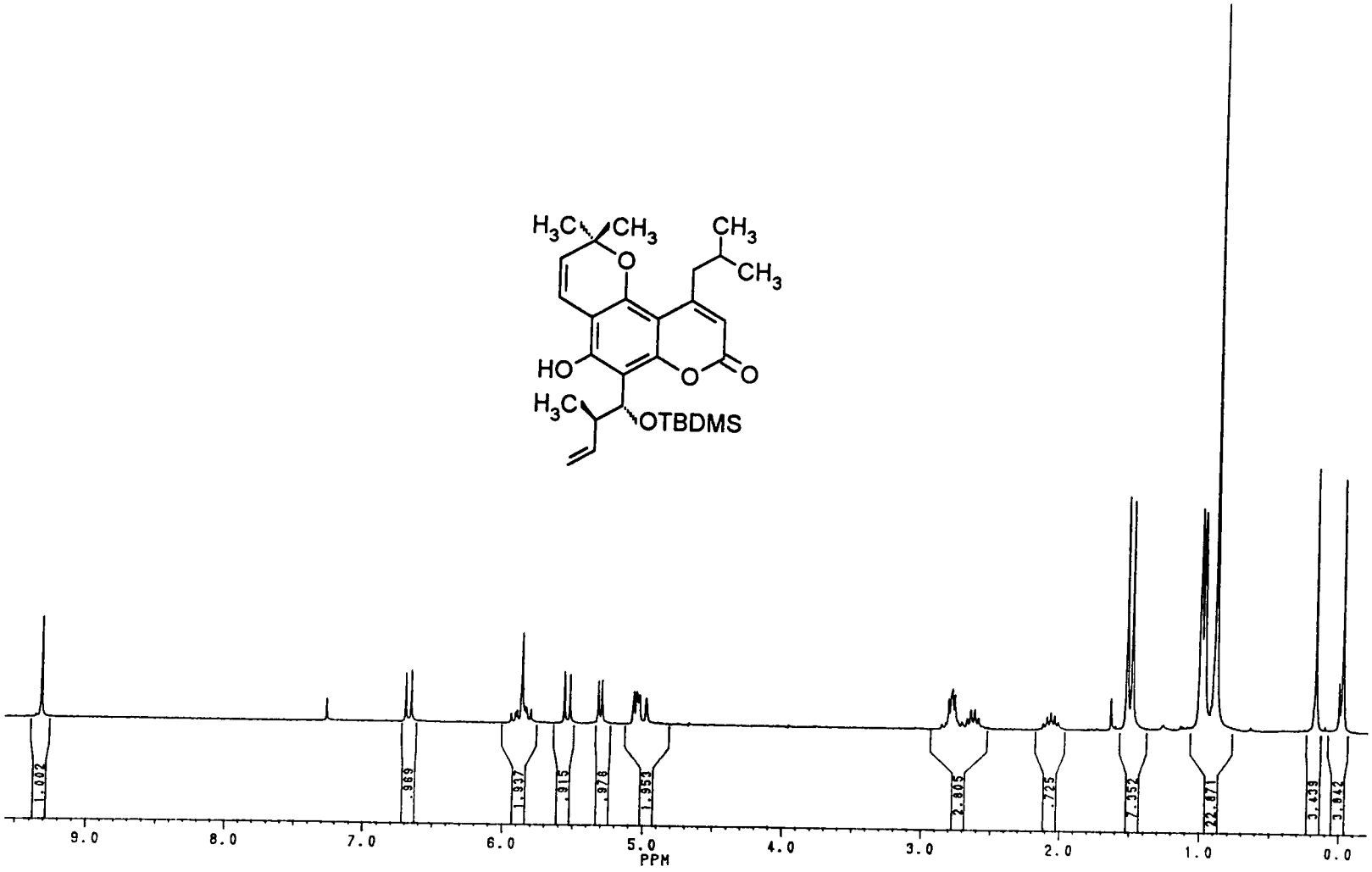
^{13}C NMR ($CDCl_3$) Spectrum of 5-Hydroxy-2,2-dimethyl-8-oxo-10-isobutyl-2*H*,8*H*-pyrano[2,3-*f*]chromene-6-carbaldehyde **(7a)**.



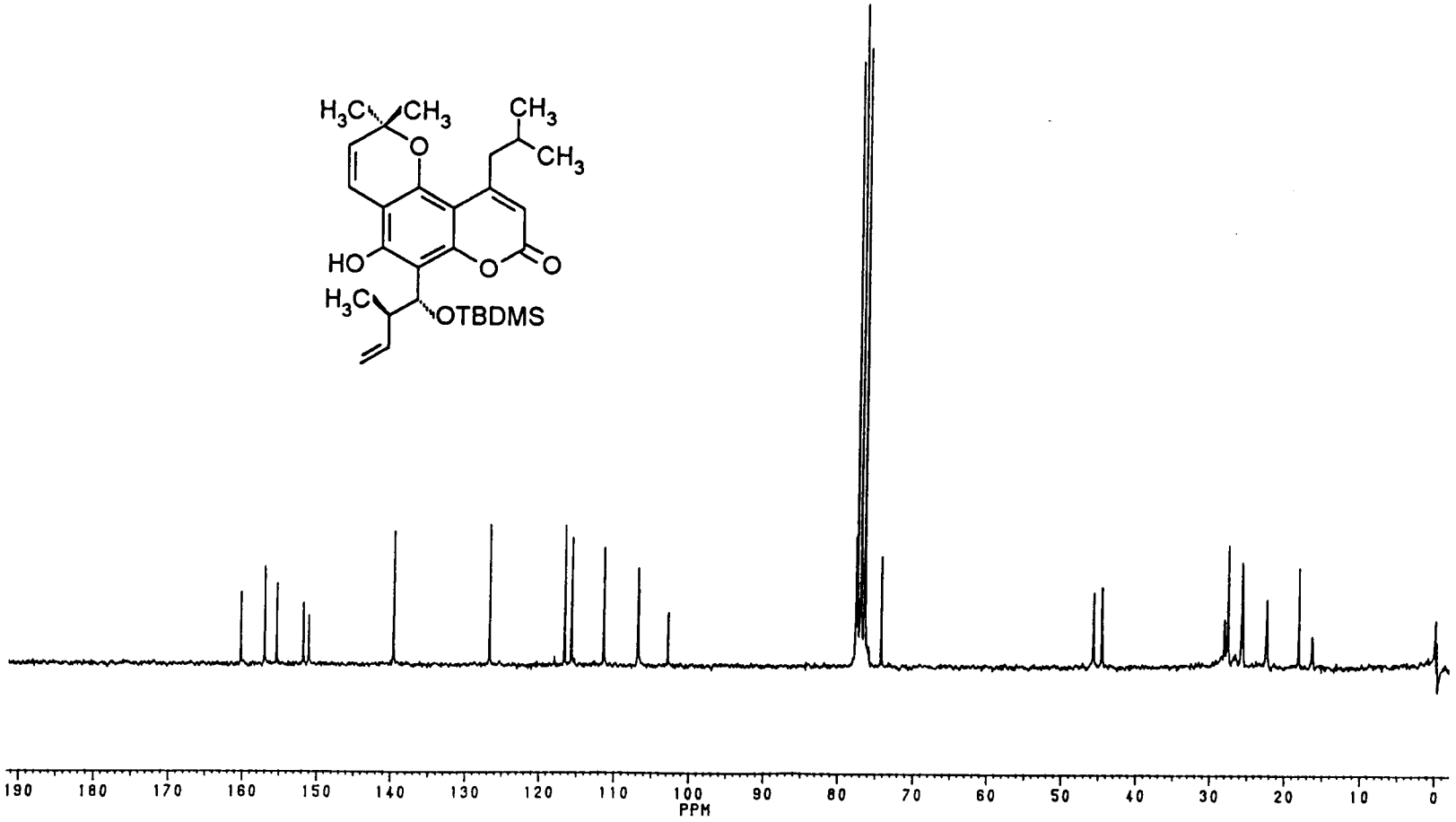
^{1}H NMR ($CDCl_3$) Spectrum of (+)-5-Hydroxy-6-[(1*R*,2*R*)-1-hydroxy-2-methylbut-3-enyl]-2,2-dimethyl-10-isobutyl-2*H*-pyrano[2,3-*f*]chromene-8-one **[(+)-9a].**



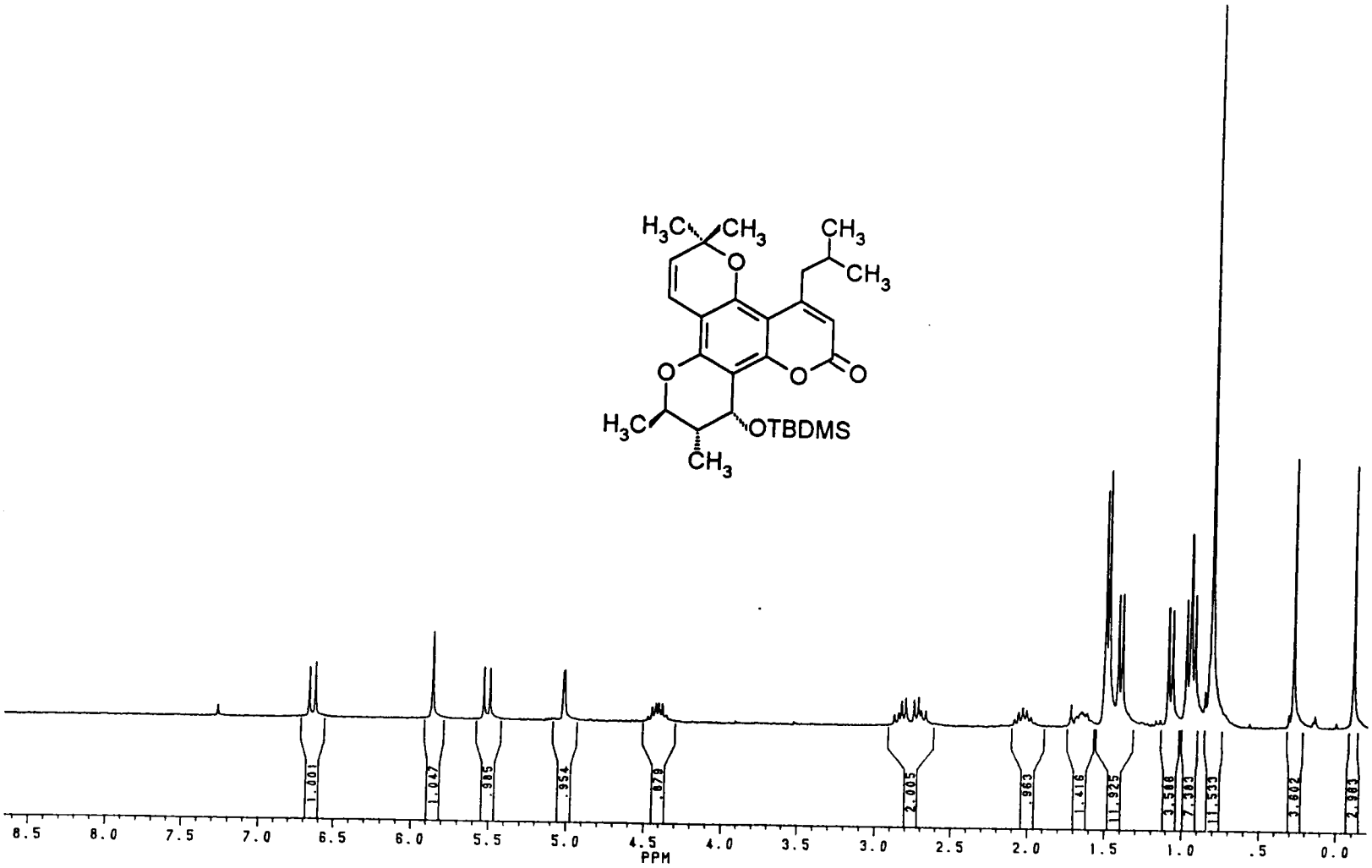
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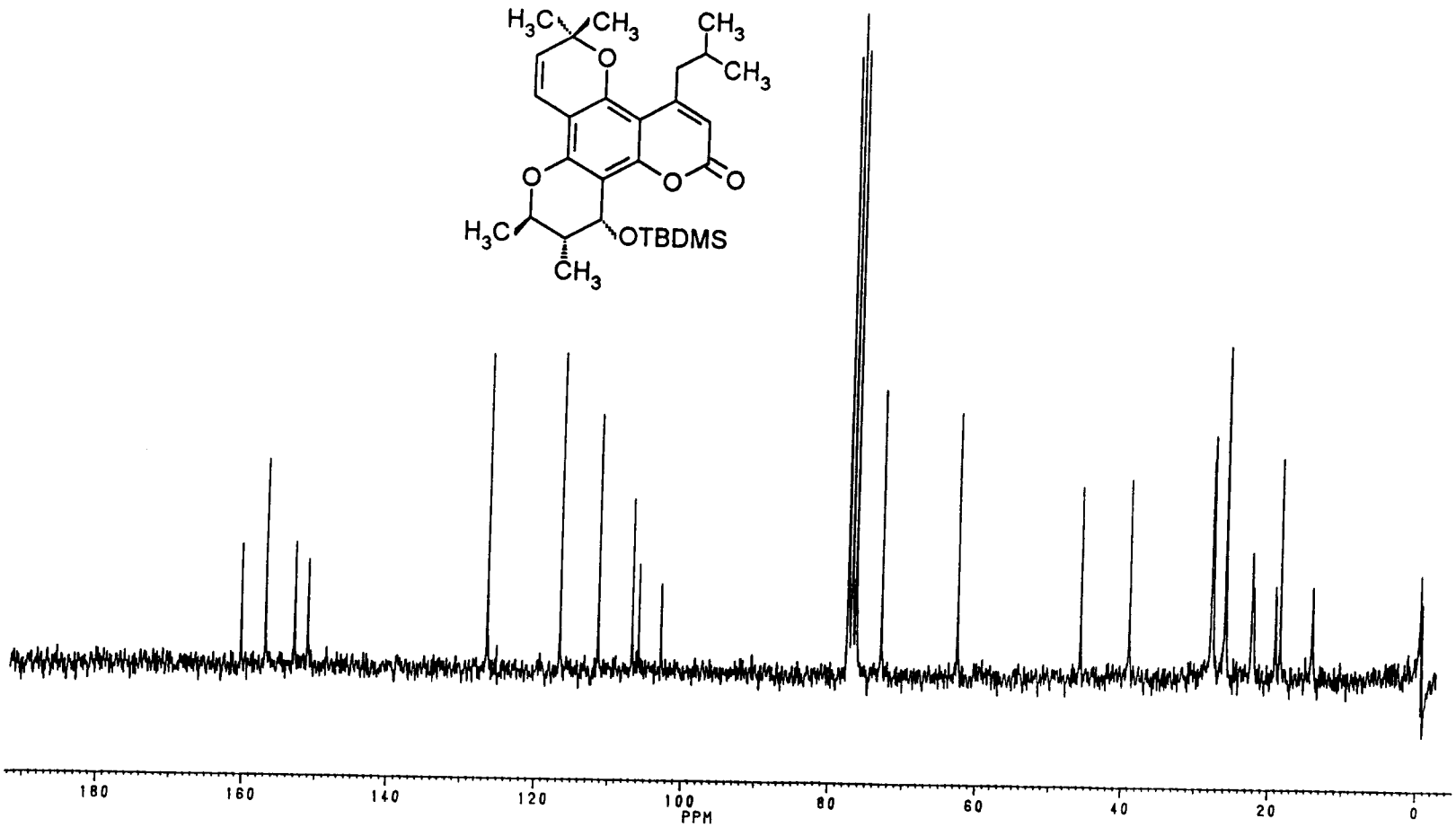
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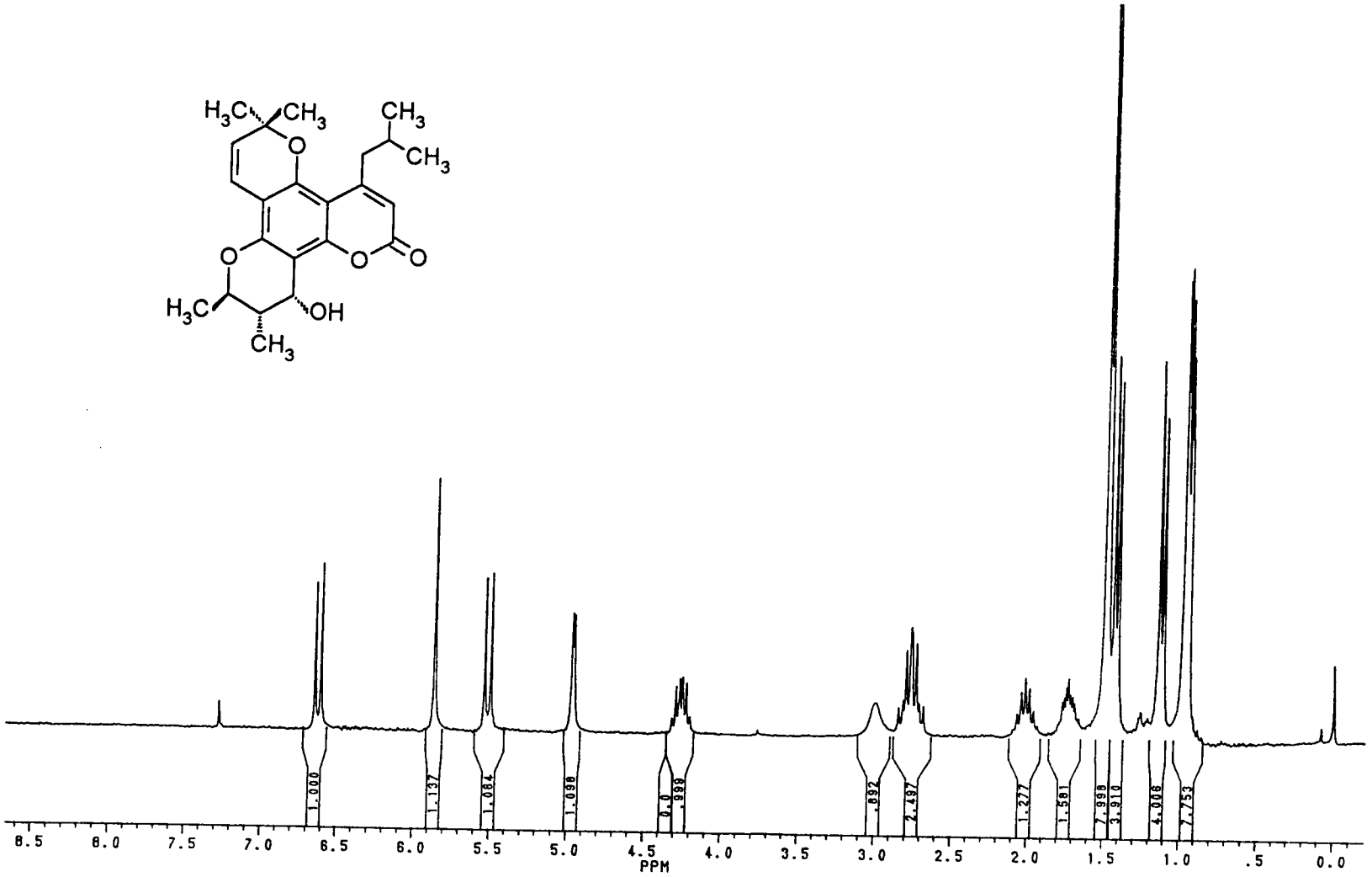
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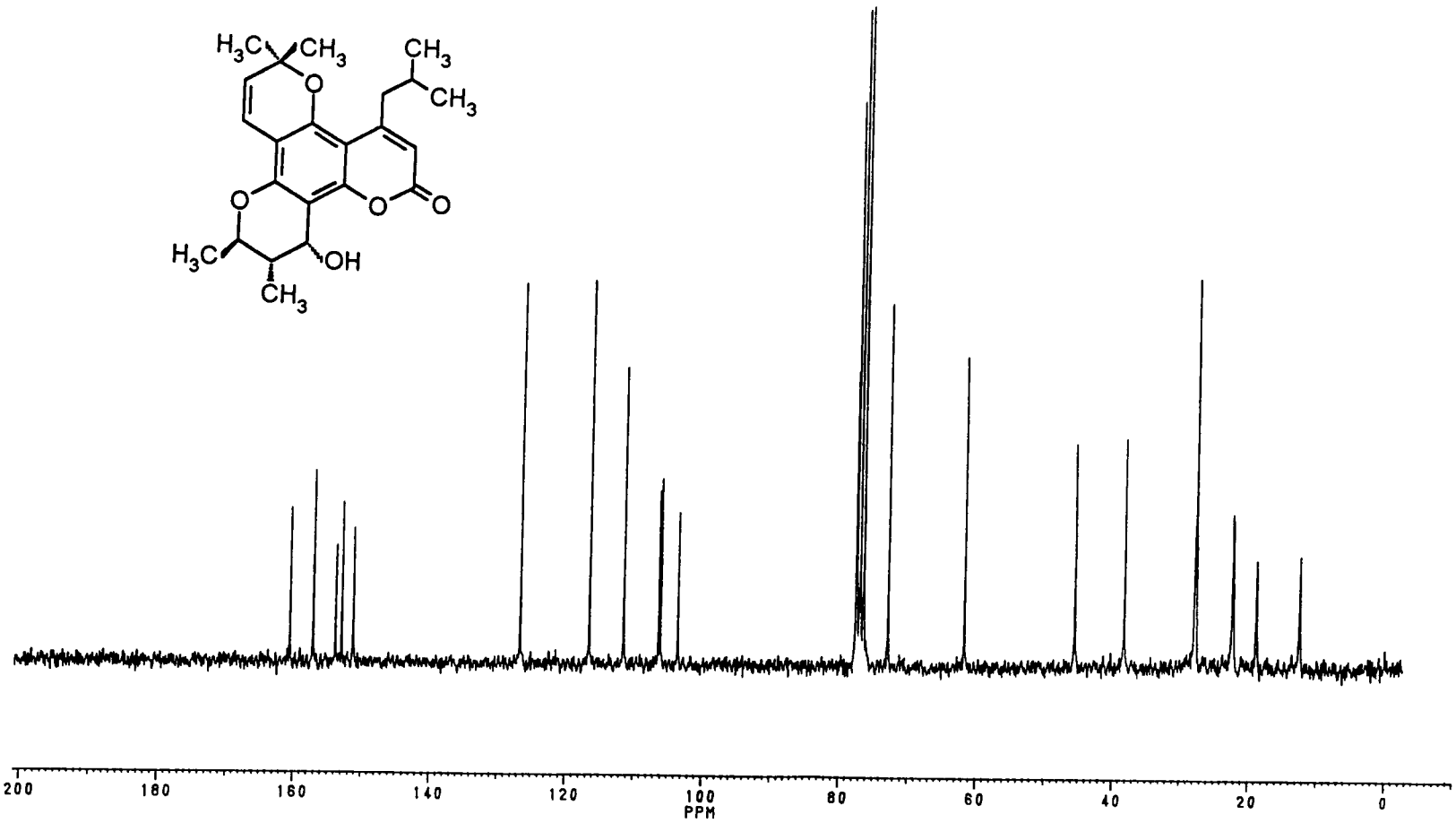
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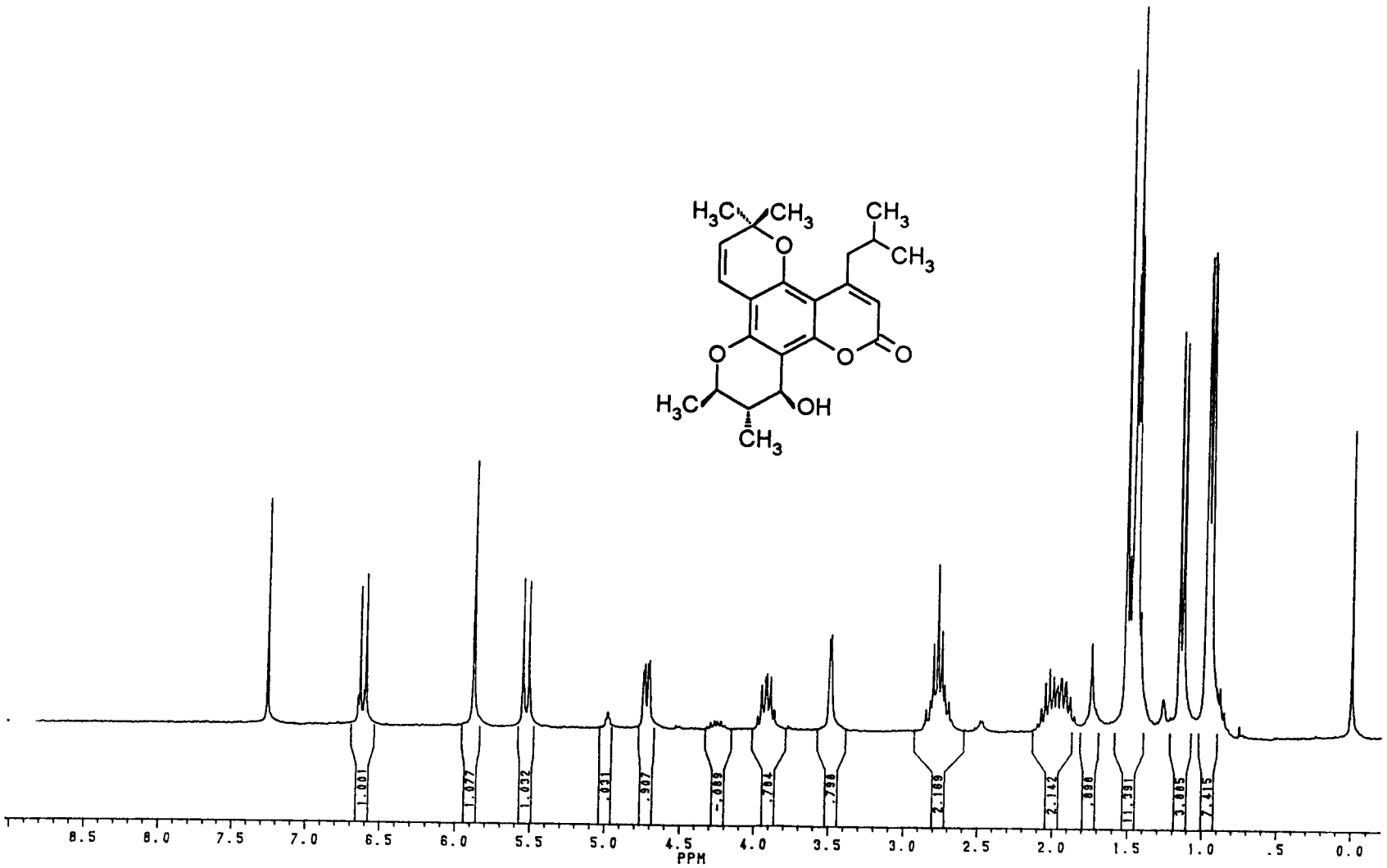
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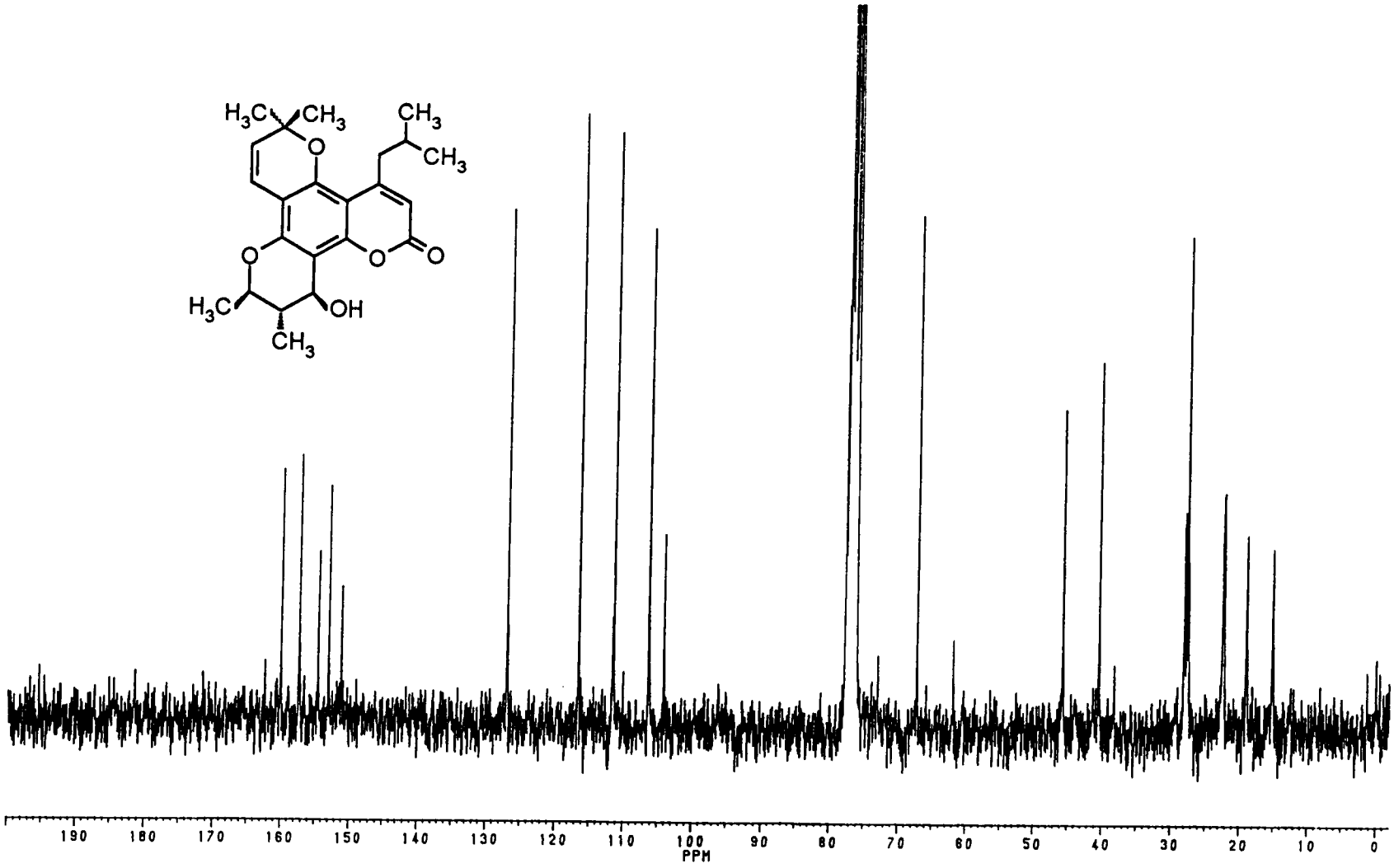
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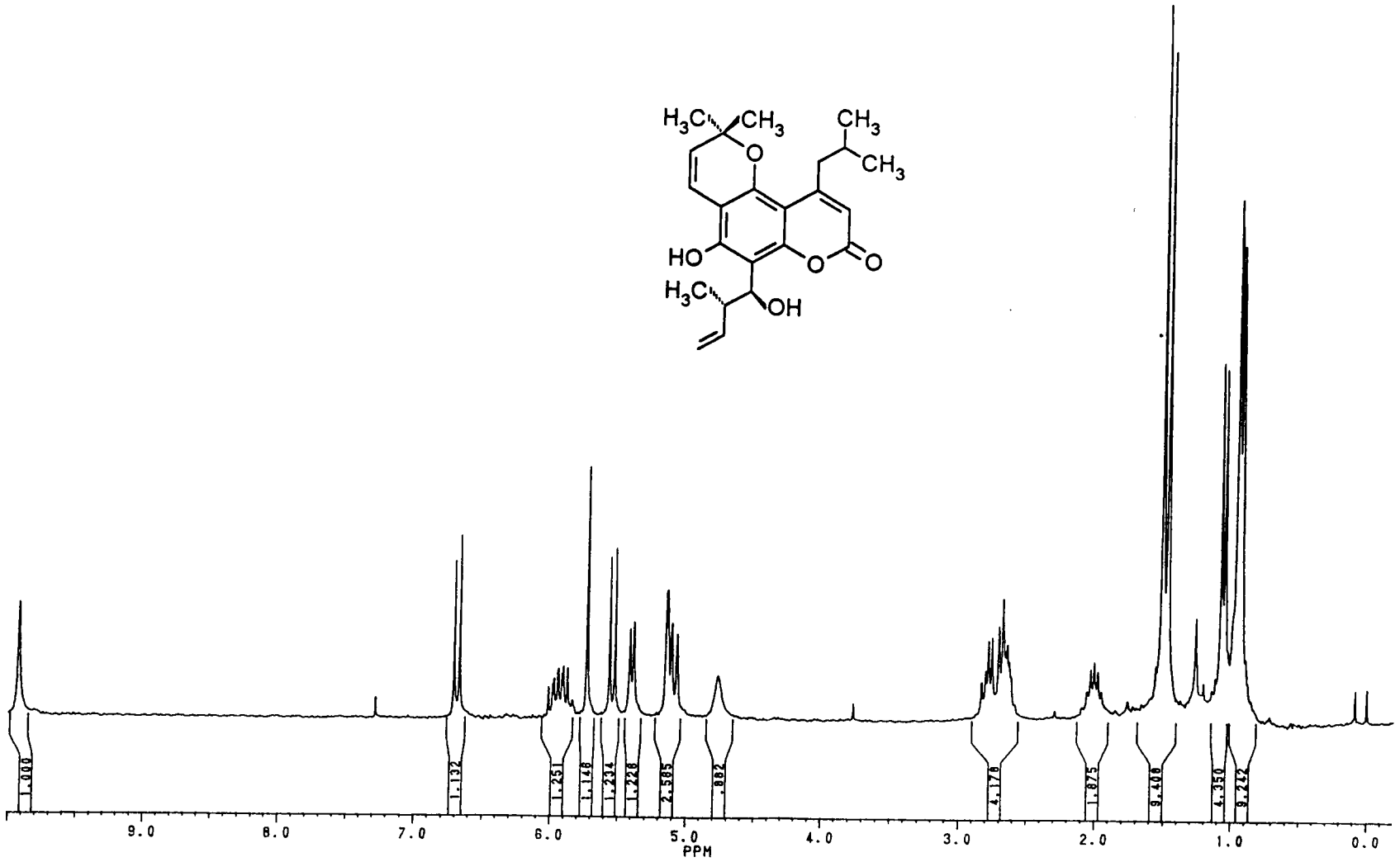
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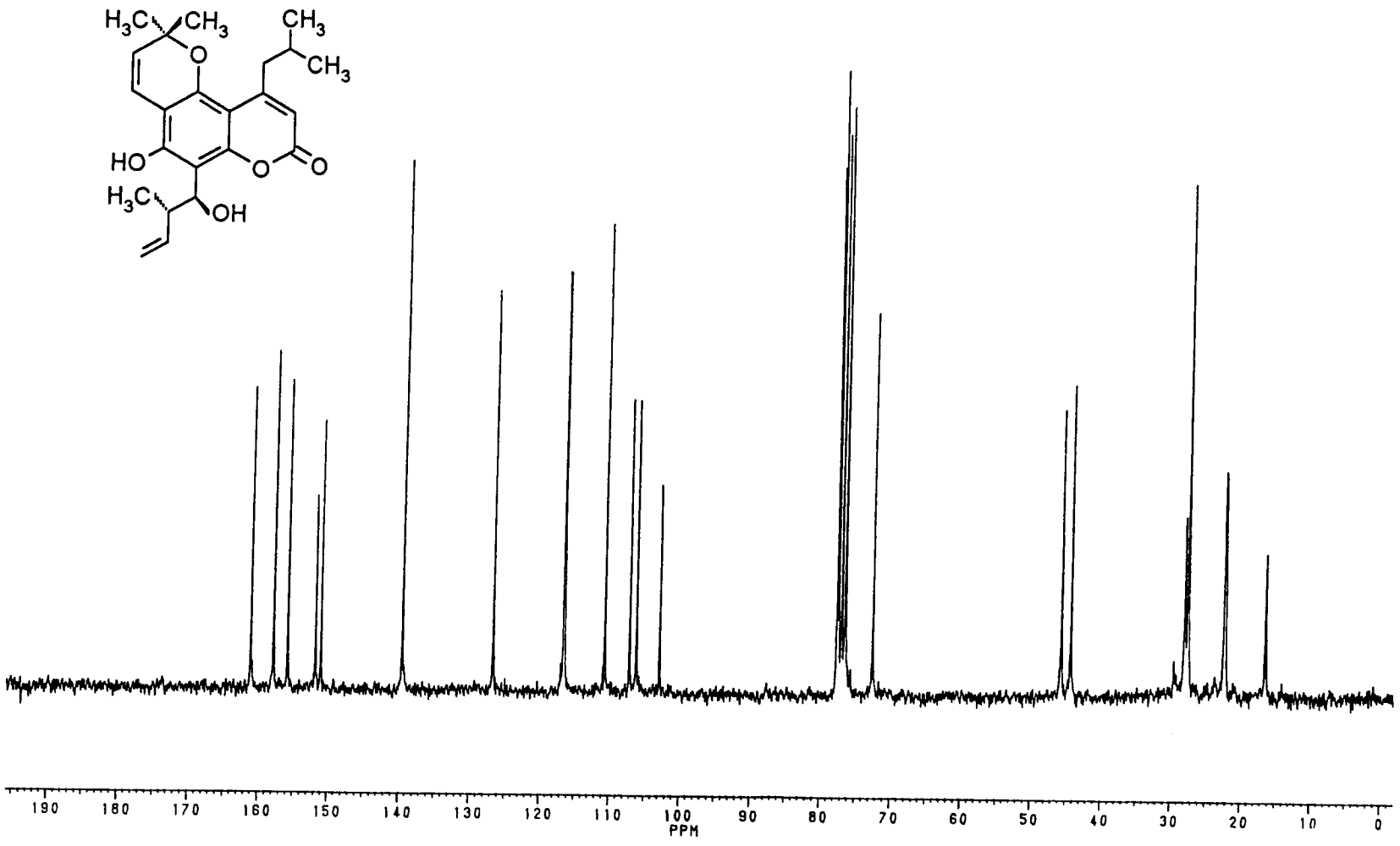
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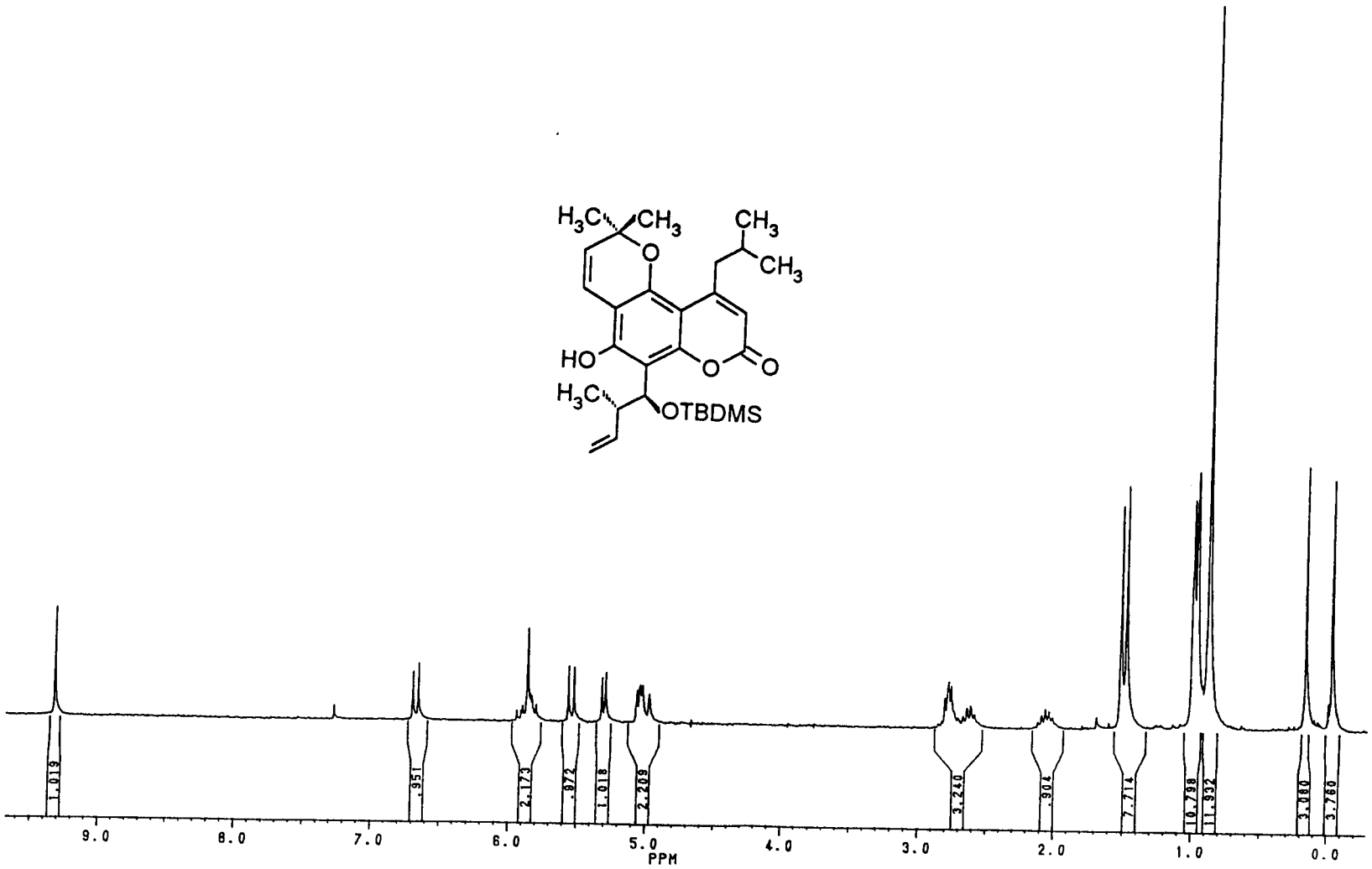
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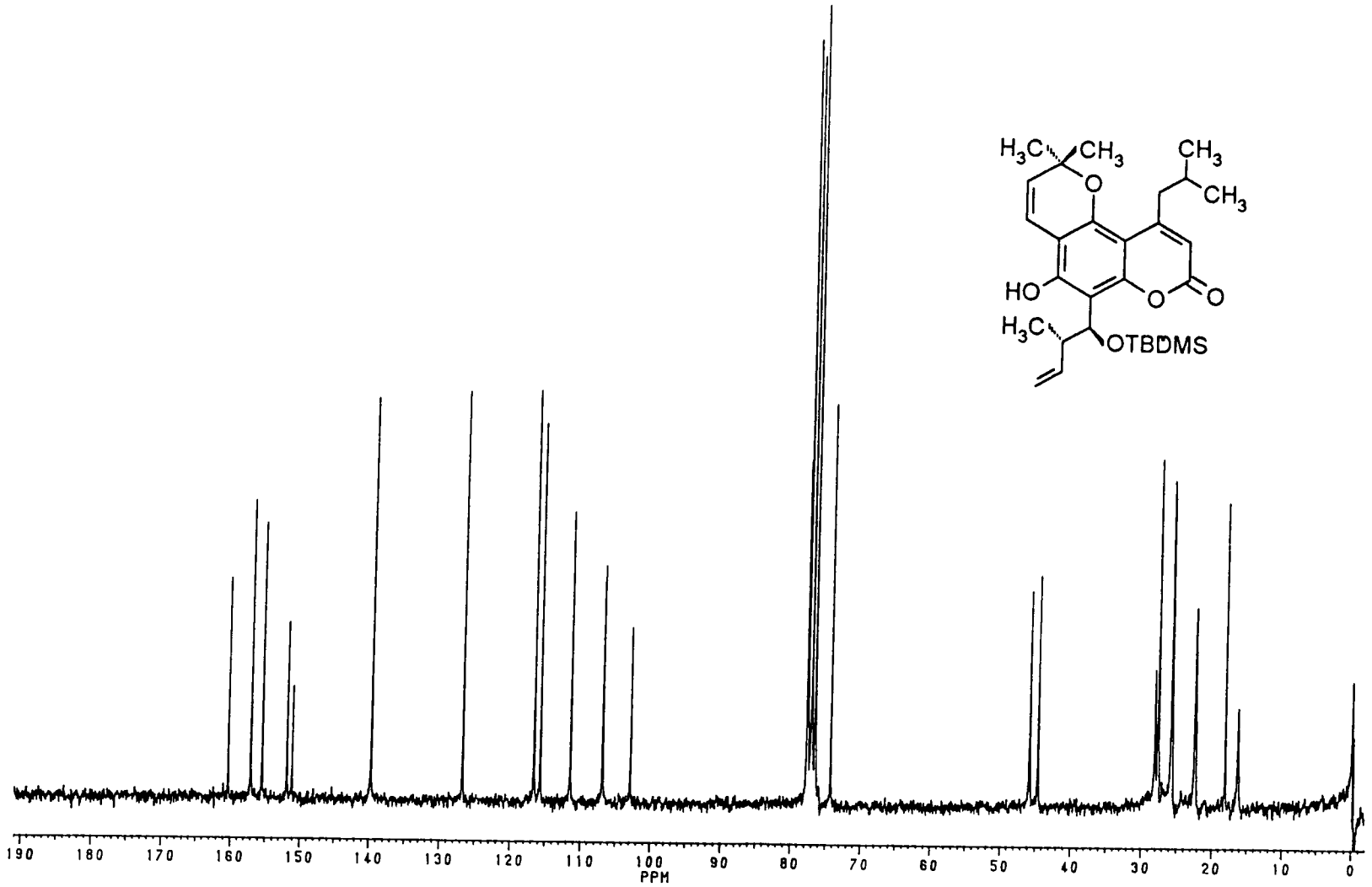
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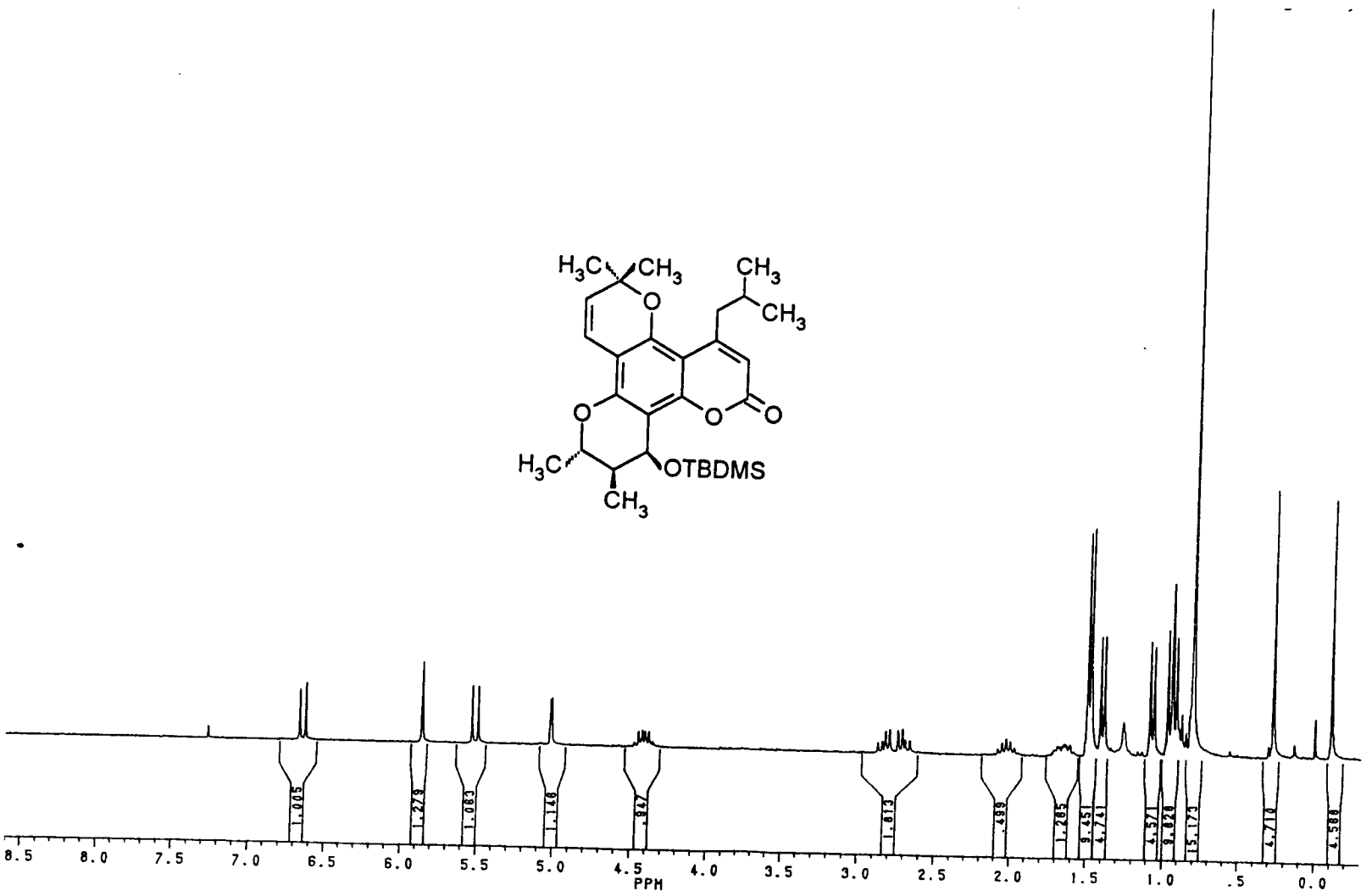
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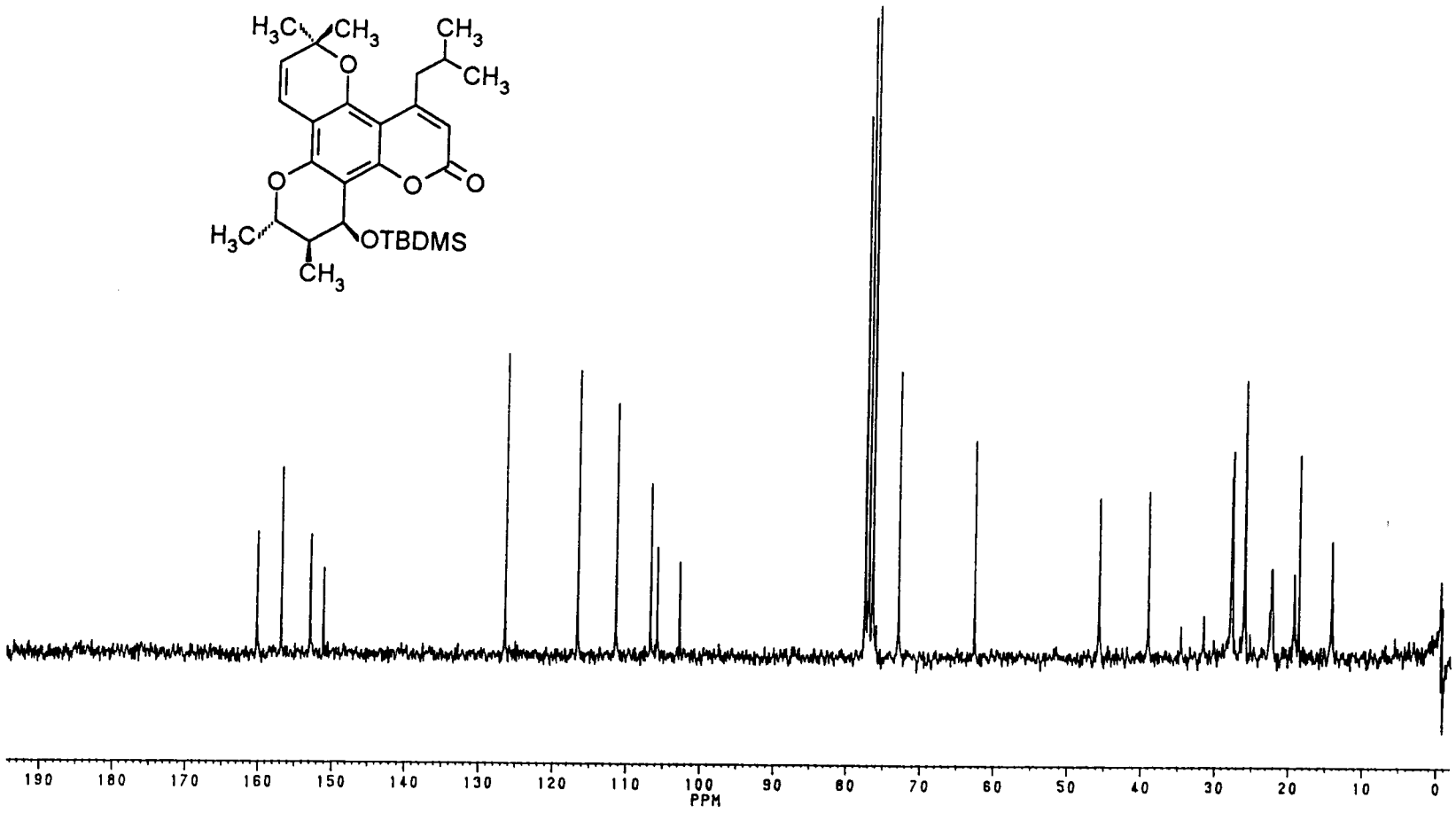
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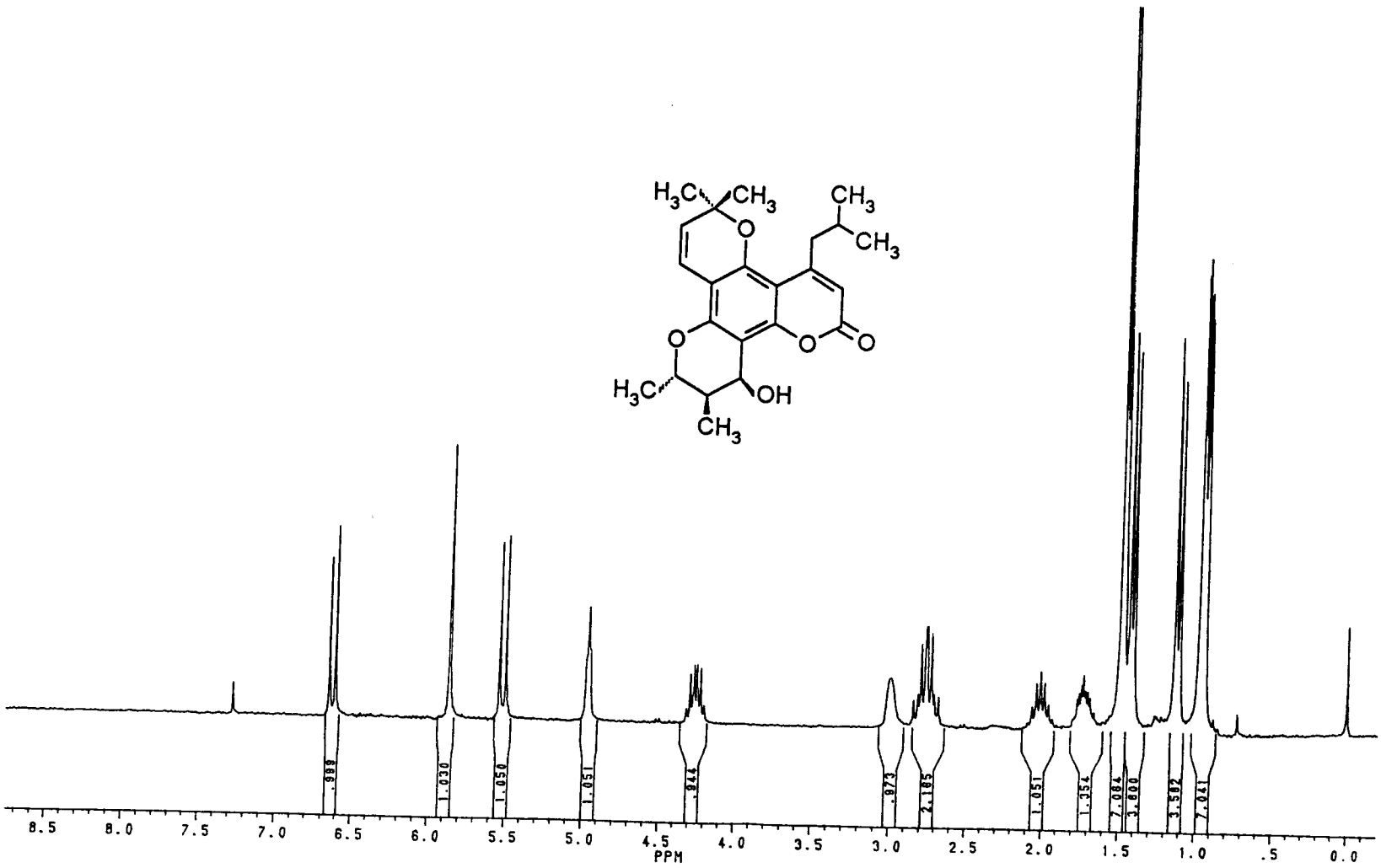
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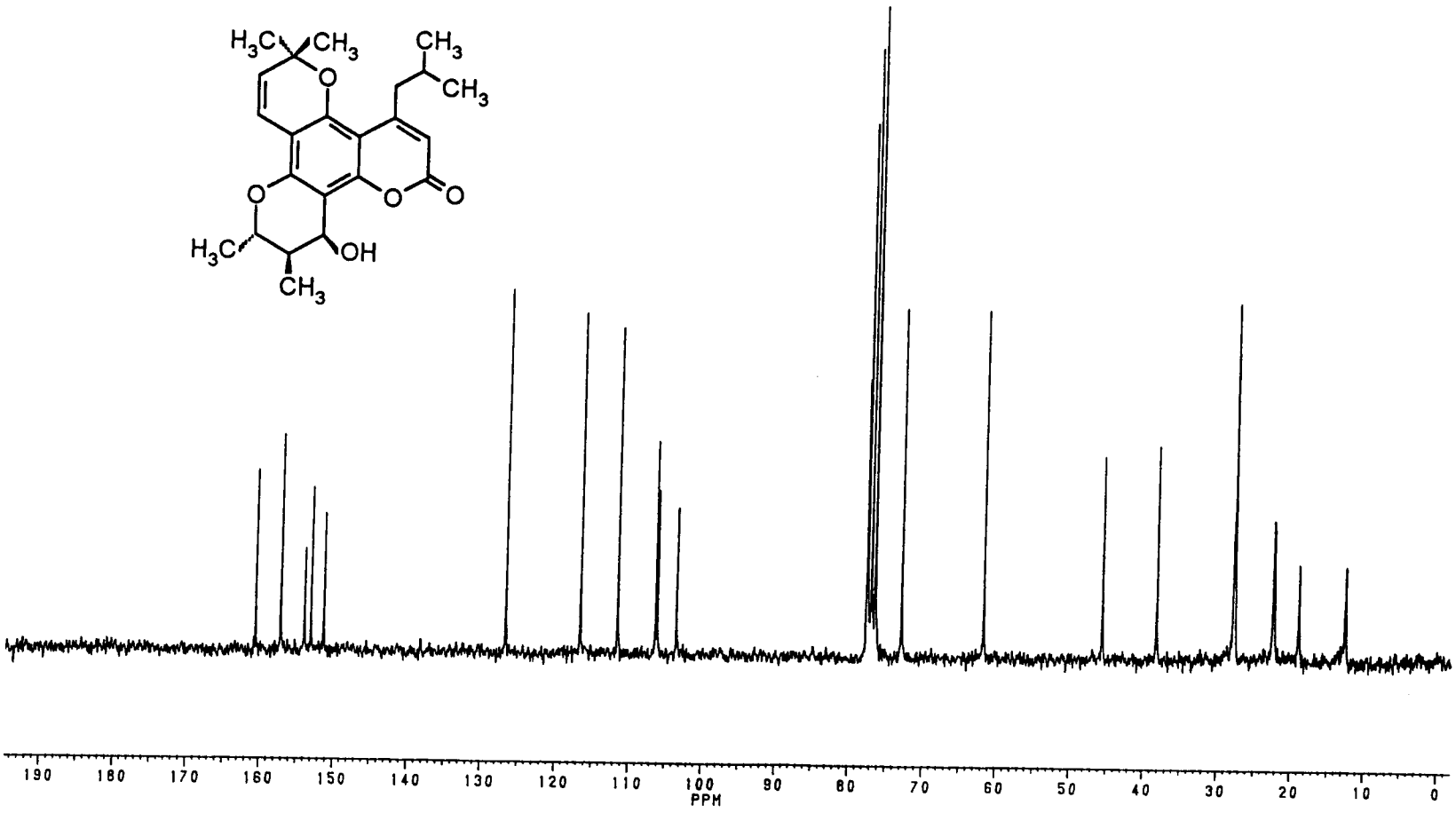
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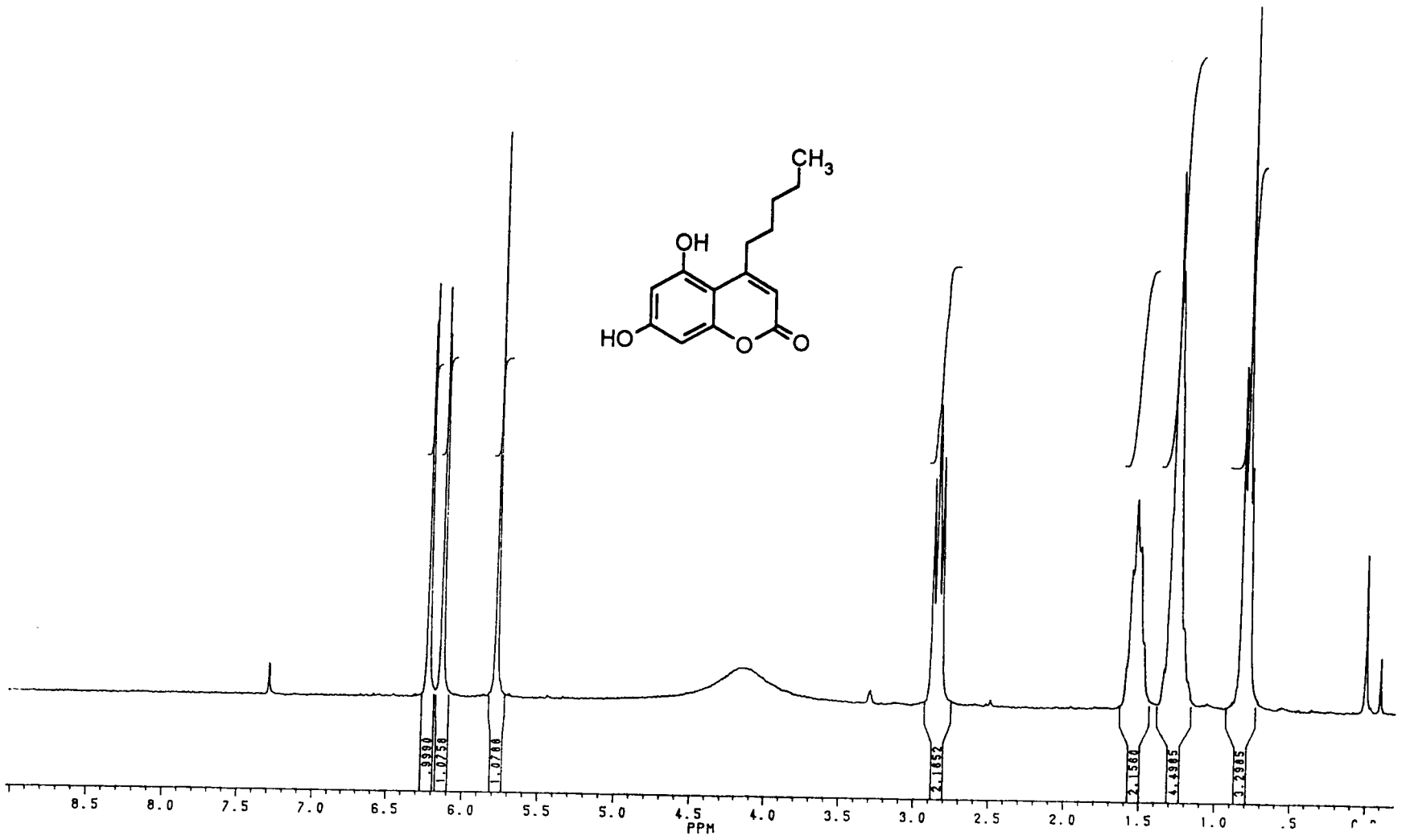
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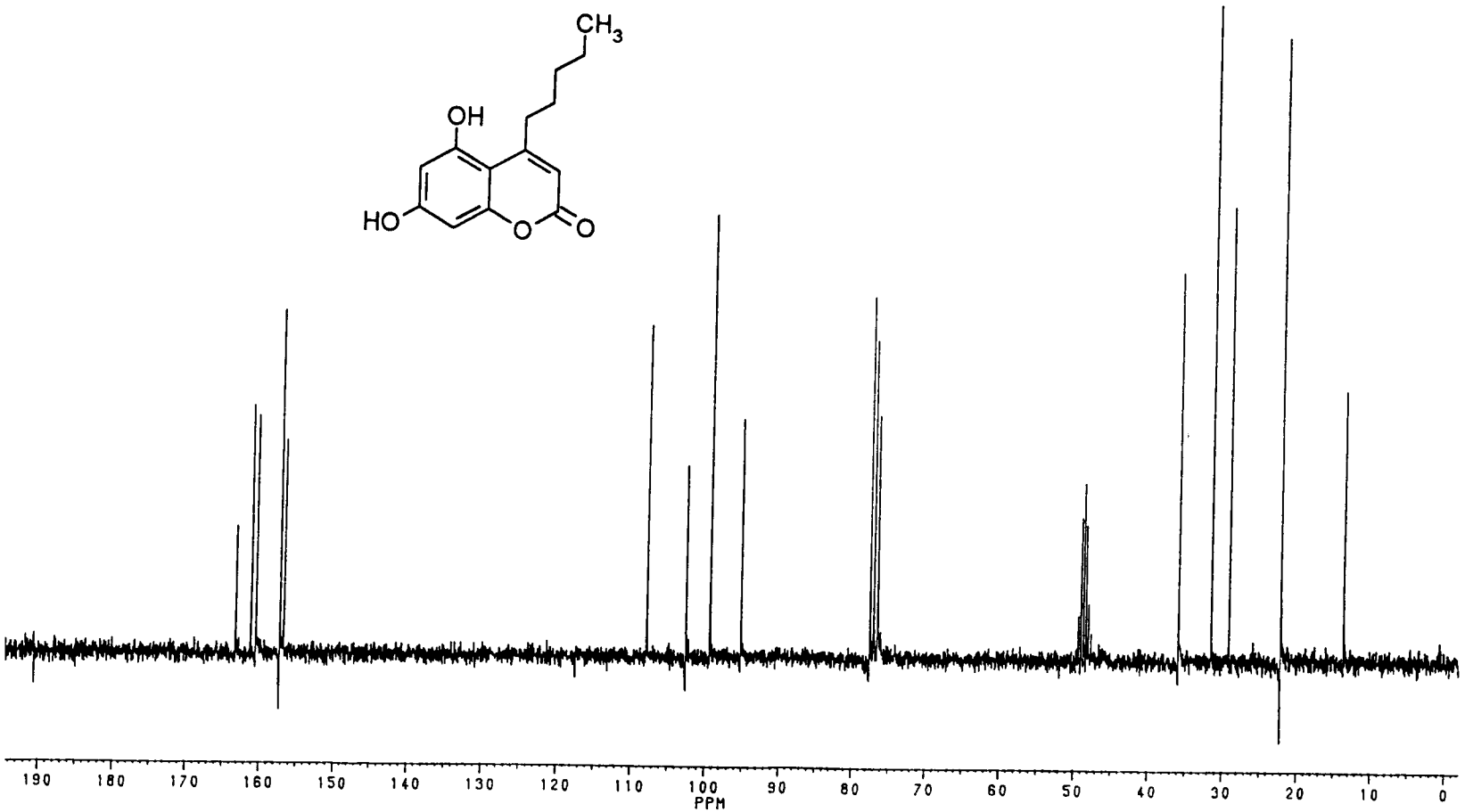
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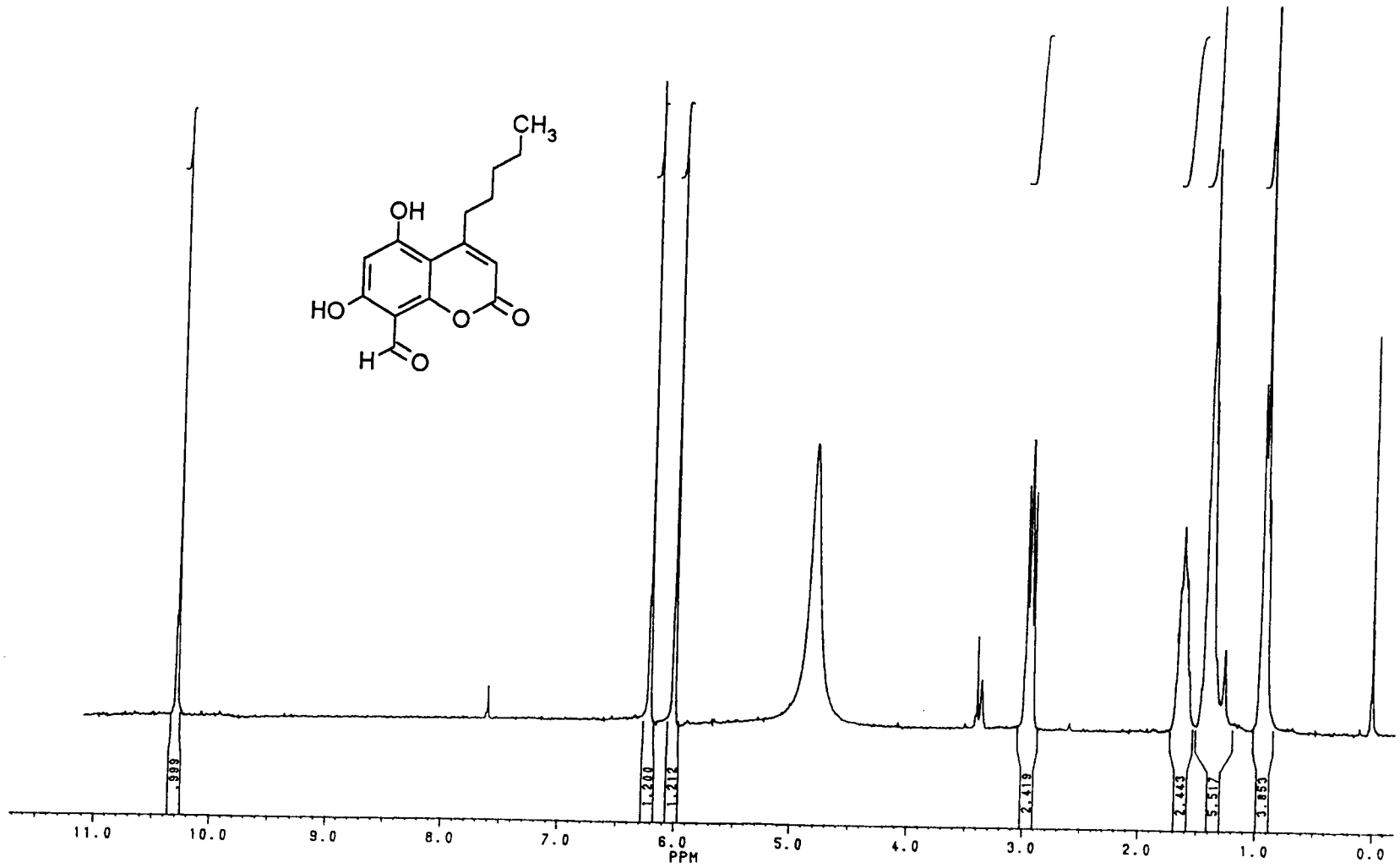
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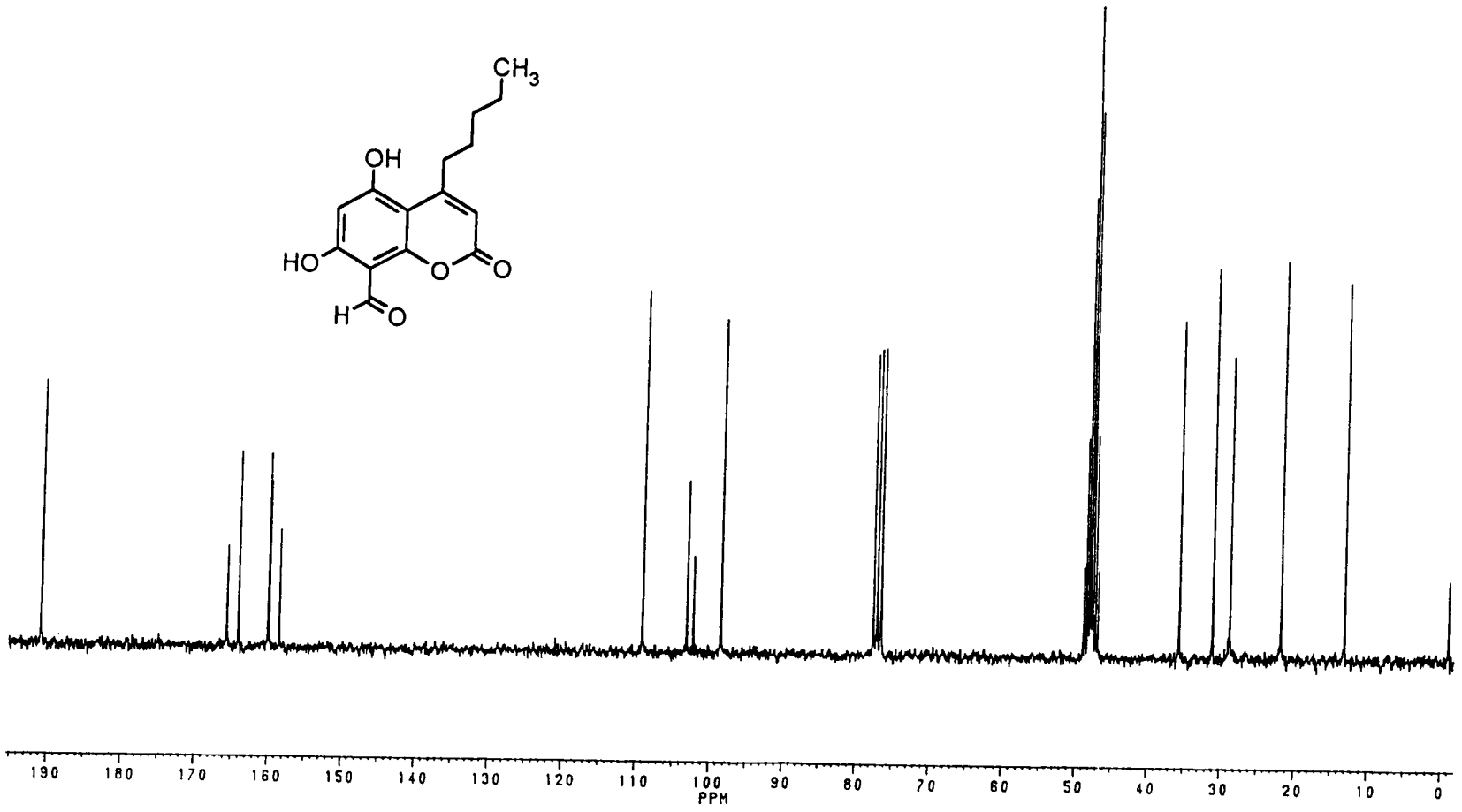
^{1}H NMR ($CDCl_3/CD_3OD$ 3:1) Spectrum of 5,7-Dihydroxy-4-pentylcoumarin **(5b).**



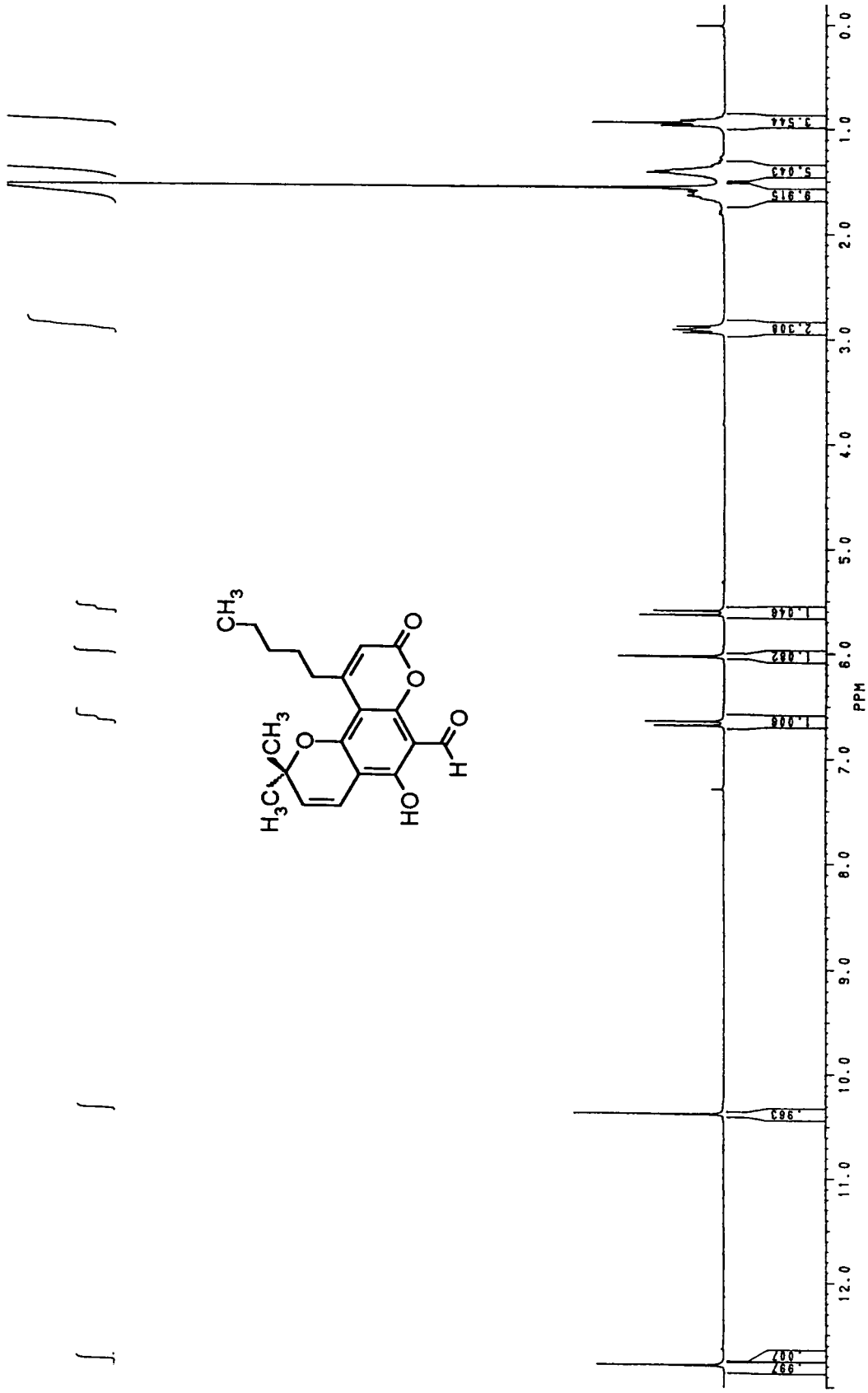
^{13}C NMR ($CDCl_3$/ CD_3OD 3:1) Spectrum of 5,7-Dihydroxy-4-pentylcoumarin **(5b).**



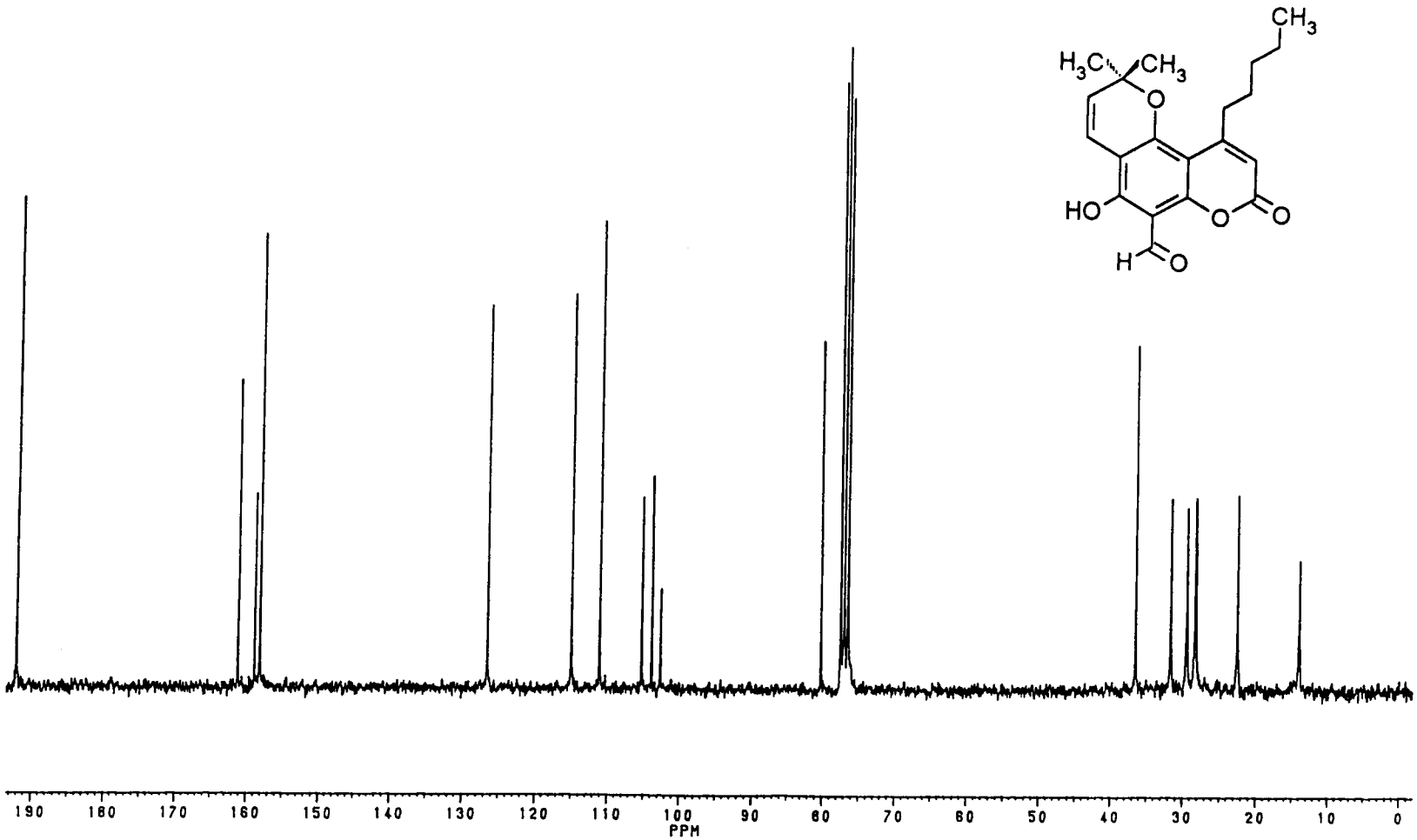
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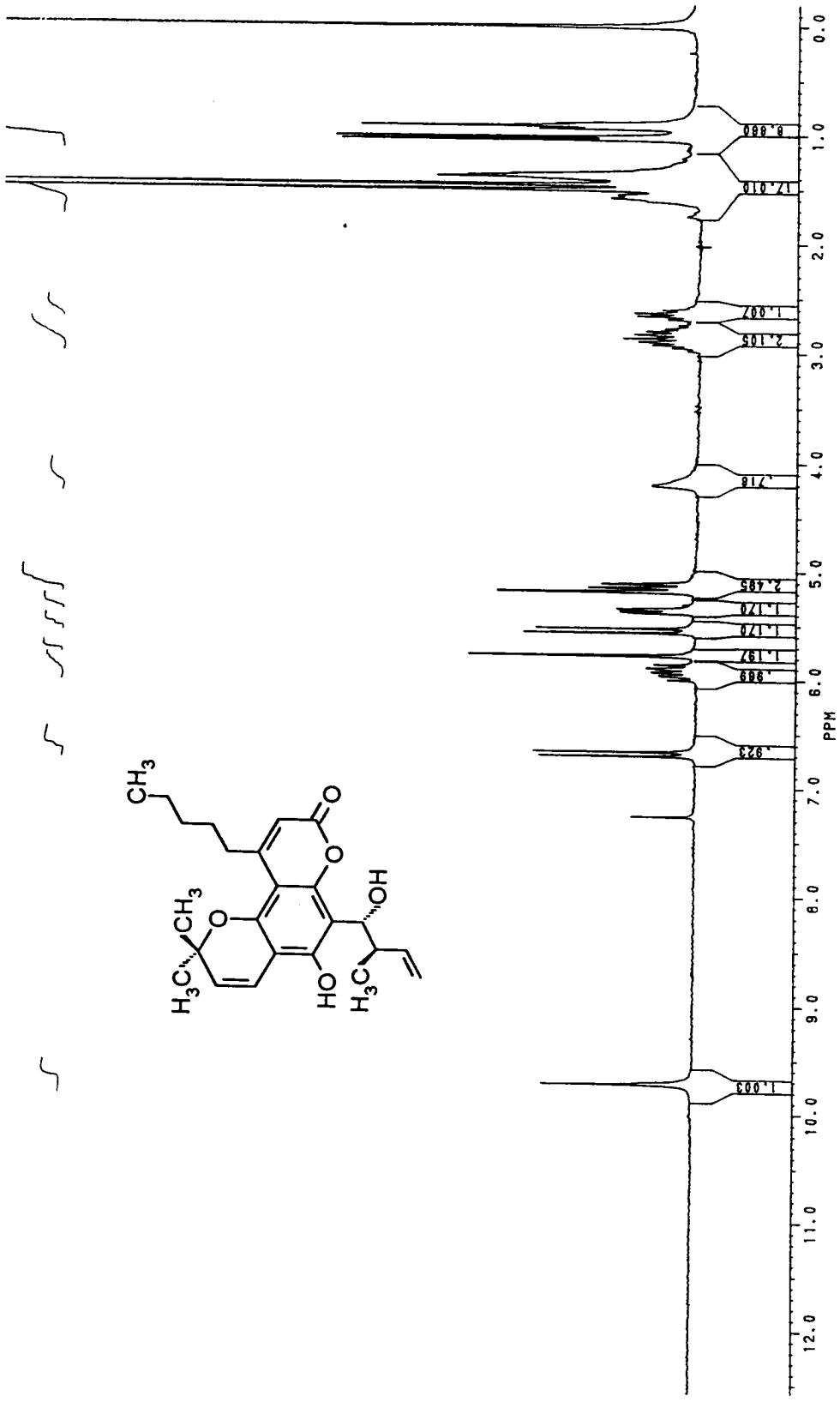
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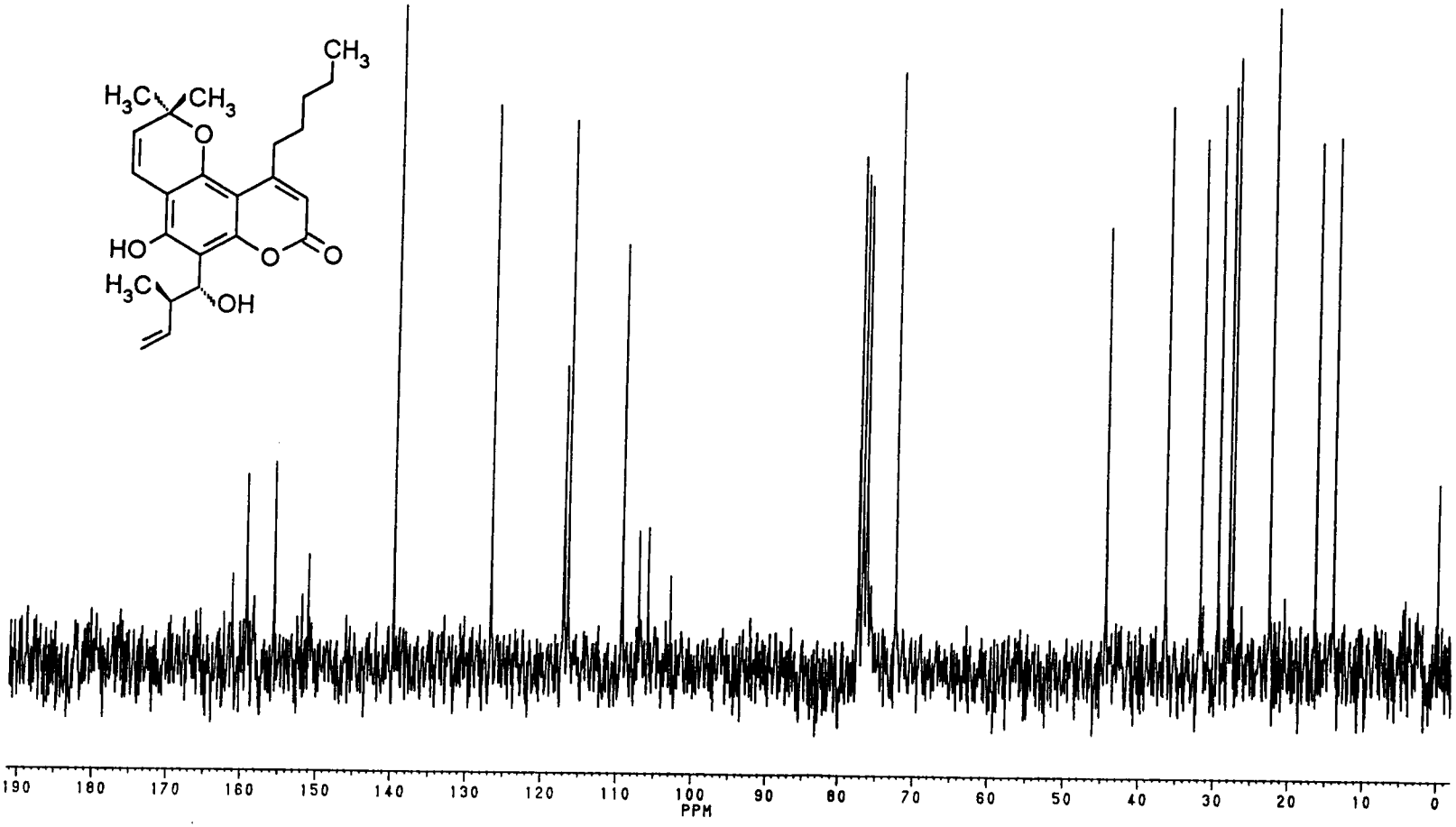
^{1}H NMR ($CDCl_3$) Spectrum of 5-Hydroxy-2,2-dimethyl-8-oxo-10-pentyl -2*H*,8*H*-pyrano[2,3-*f*]chromene-6-carbaldehyde (**7b**).



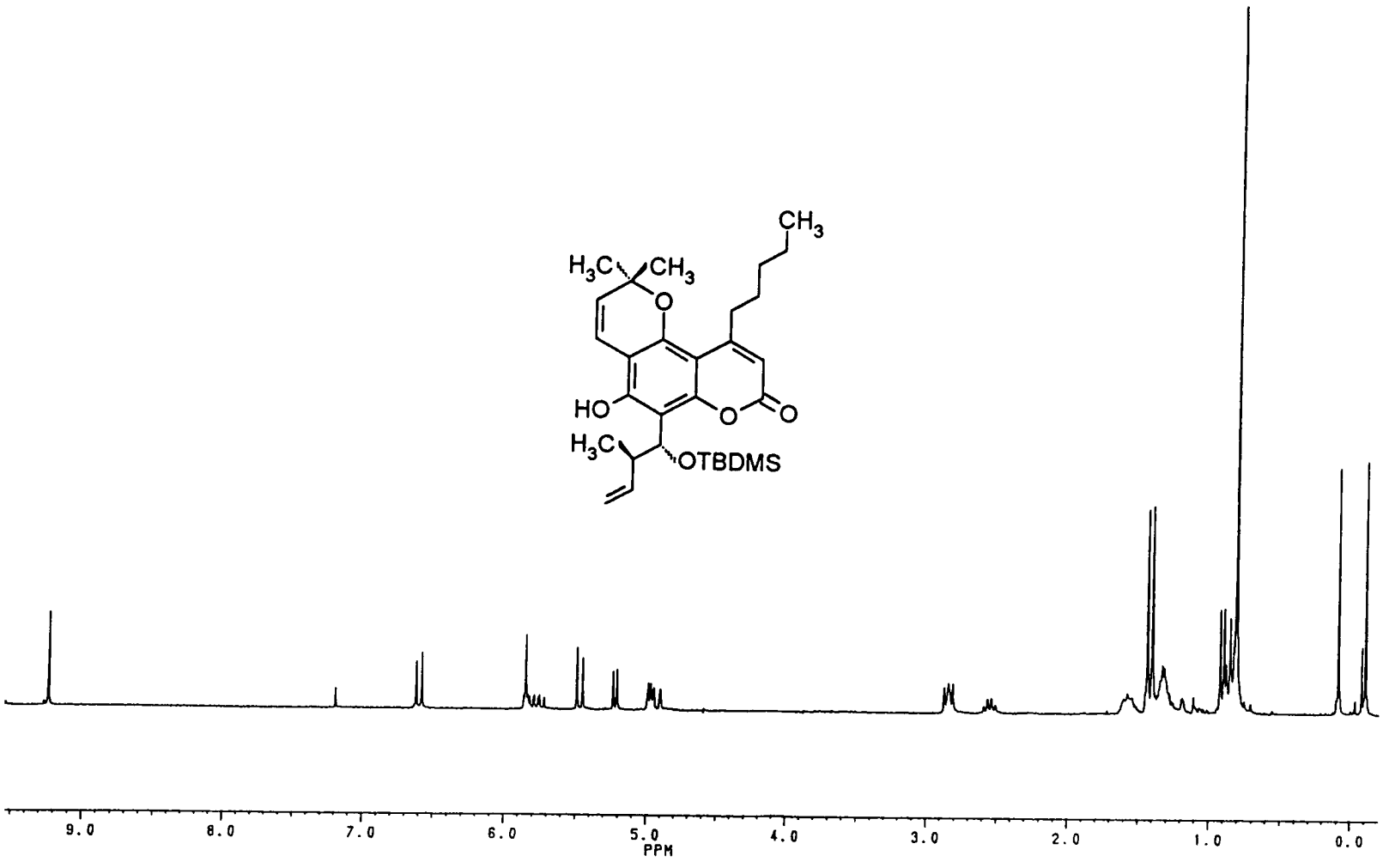
^{13}C NMR ($CDCl_3$) Spectrum of 5-Hydroxy-2,2-dimethyl-8-oxo-10-pentyl -2*H*,8*H*-pyrano[2,3-*f*]chromene-6-carbaldehyde **(7b).**



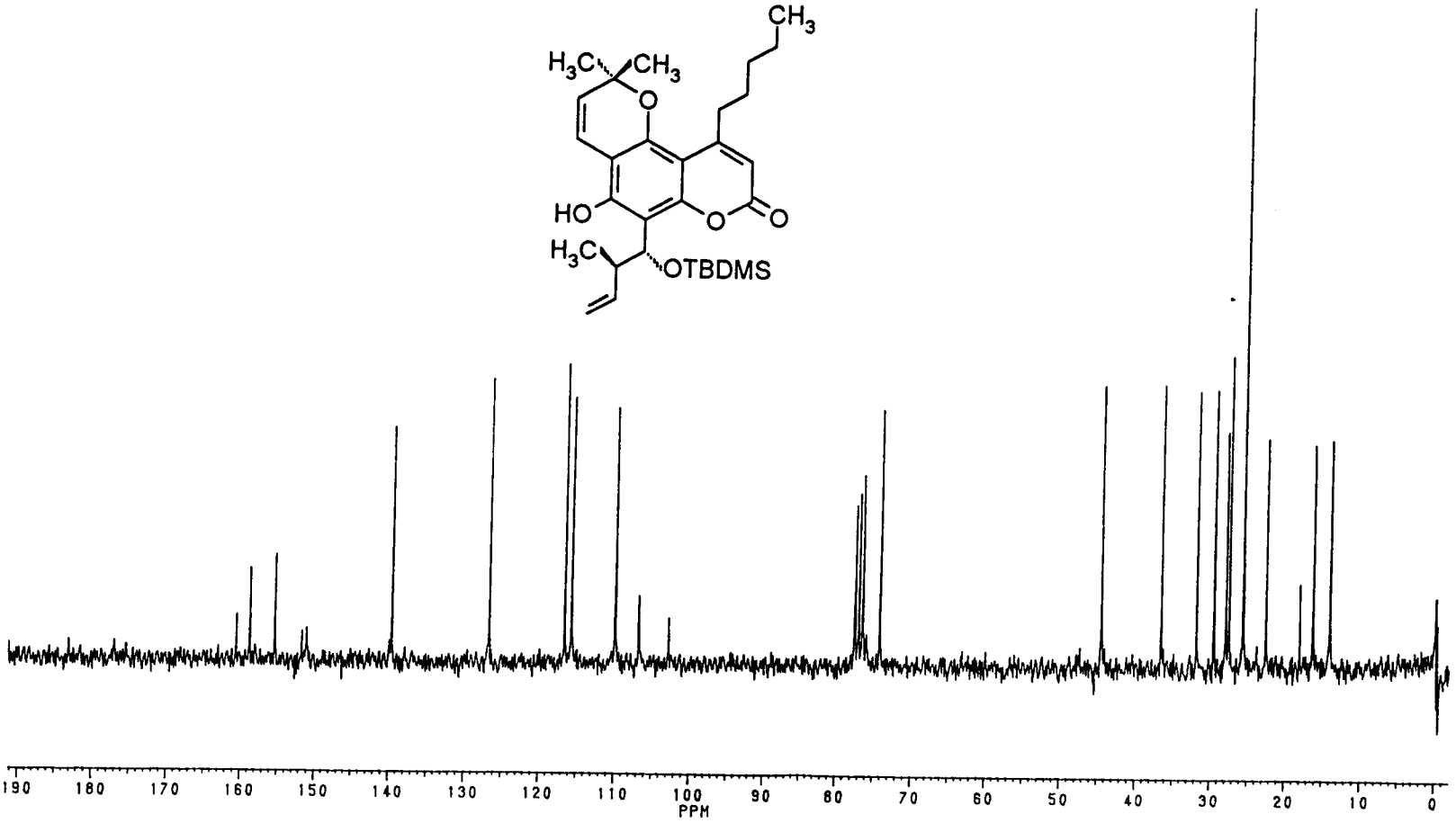
^{1}H NMR ($CDCl_3$) Spectrum of (+)-5-Hydroxy-6[(1*R*,2*R*)-1-hydroxy-2-methylbut-3-enyl]-2,2-dimethyl-10-pentyl-2*H*-pyrano[2,3-*f*]chromene-8-one **[(+)-9b]**.



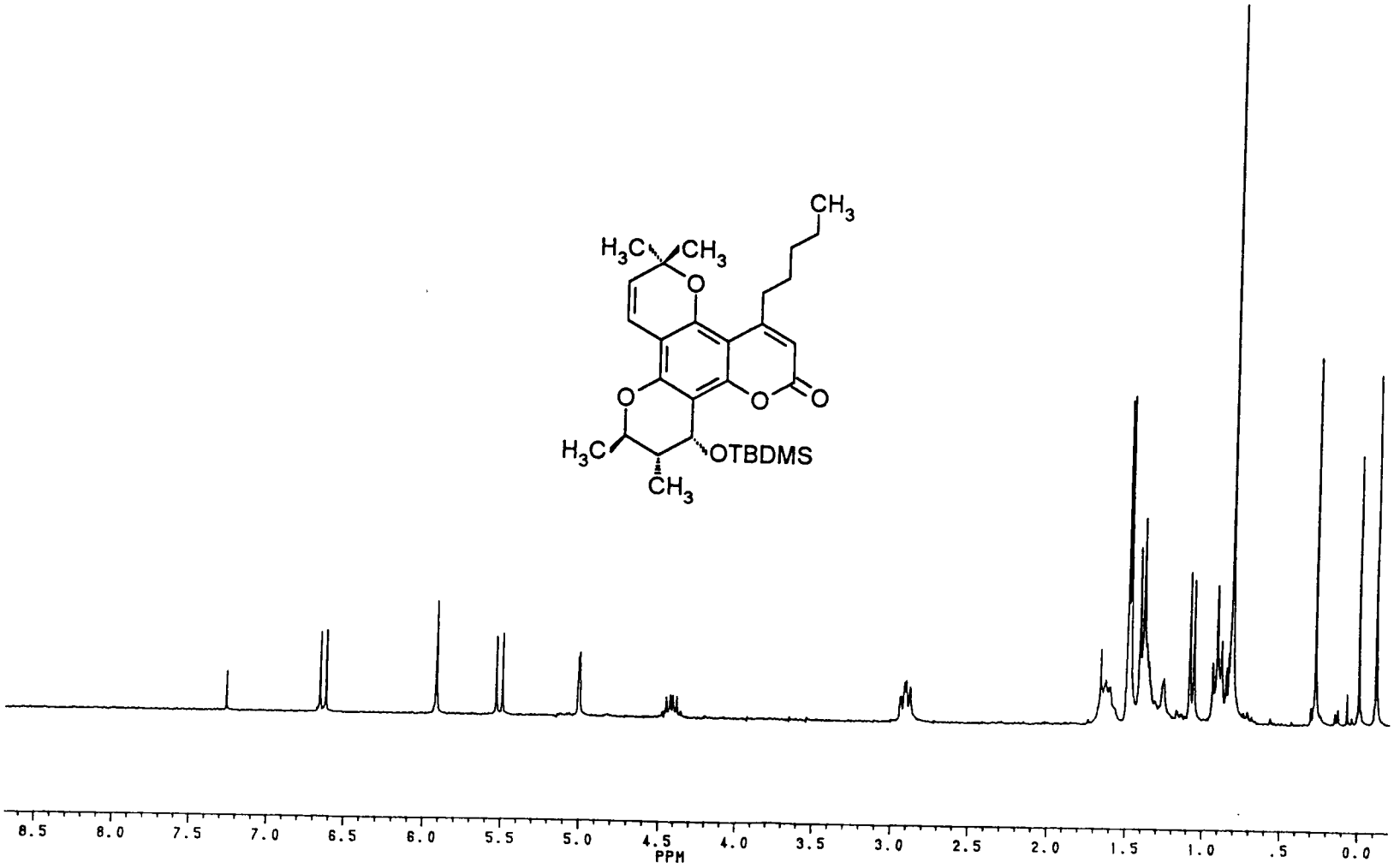
^{13}C NMR ($CDCl_3$) Spectrum of (+)-5-Hydroxy-6[(1*R*,2*R*)-1-hydroxy-2-methylbut-3-enyl]-2,2-dimethyl-10-pentyl-2*H*-pyrano[2,3-*f*]chromene-8-one **[(+)-9b].**



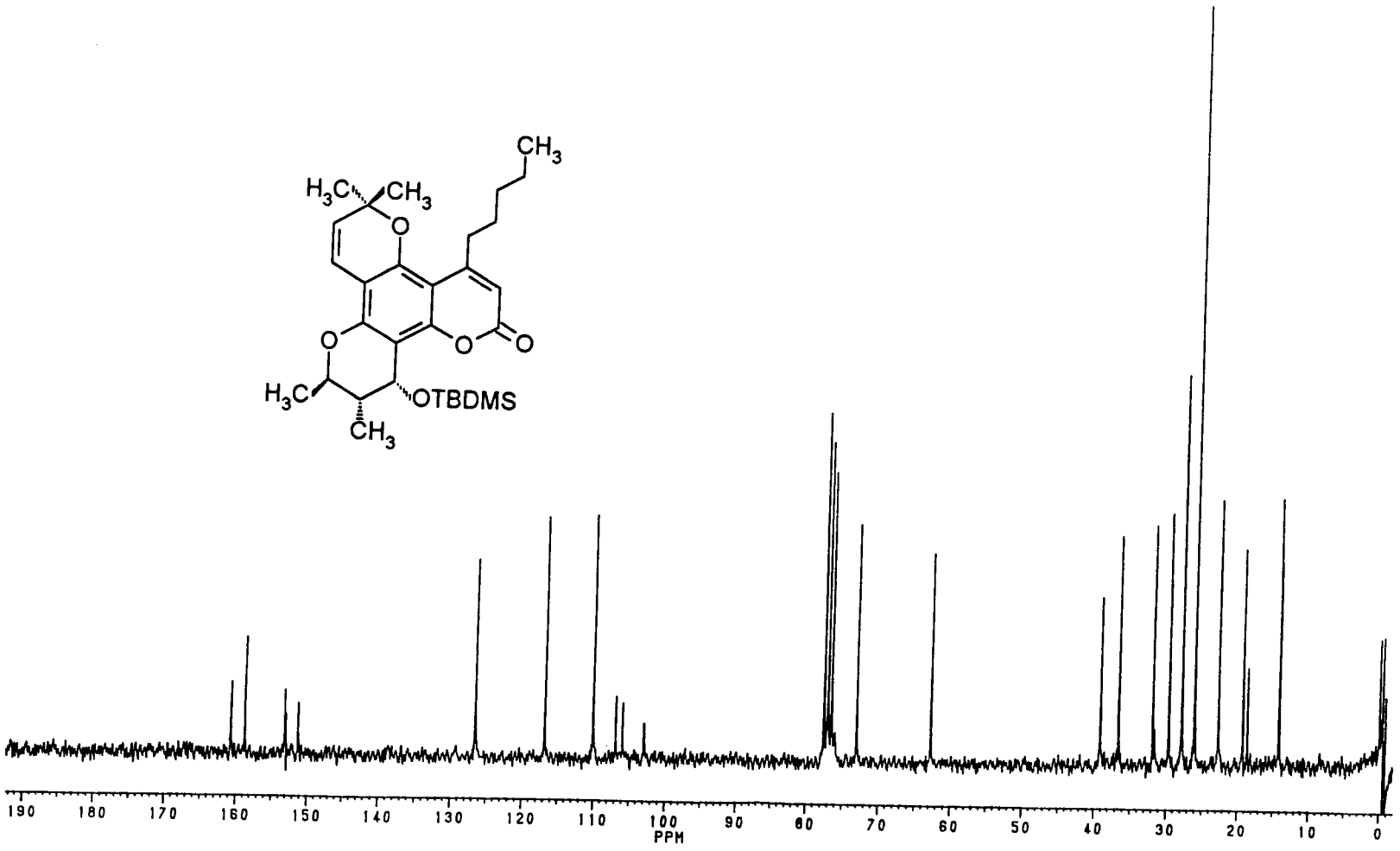
^{1}H NMR ($CDCl_3$) Spectrum of (+)-5-Hydroxy-6-[(1*R*,2*R*)-1-*tert*-butyldimethylsilyloxy-2-methylbut-3-enyl]-2,2-dimethyl-10-pentyl-2*H*-pyrano[2,3-*f*]chromen-8-one **[(+)-10b].**



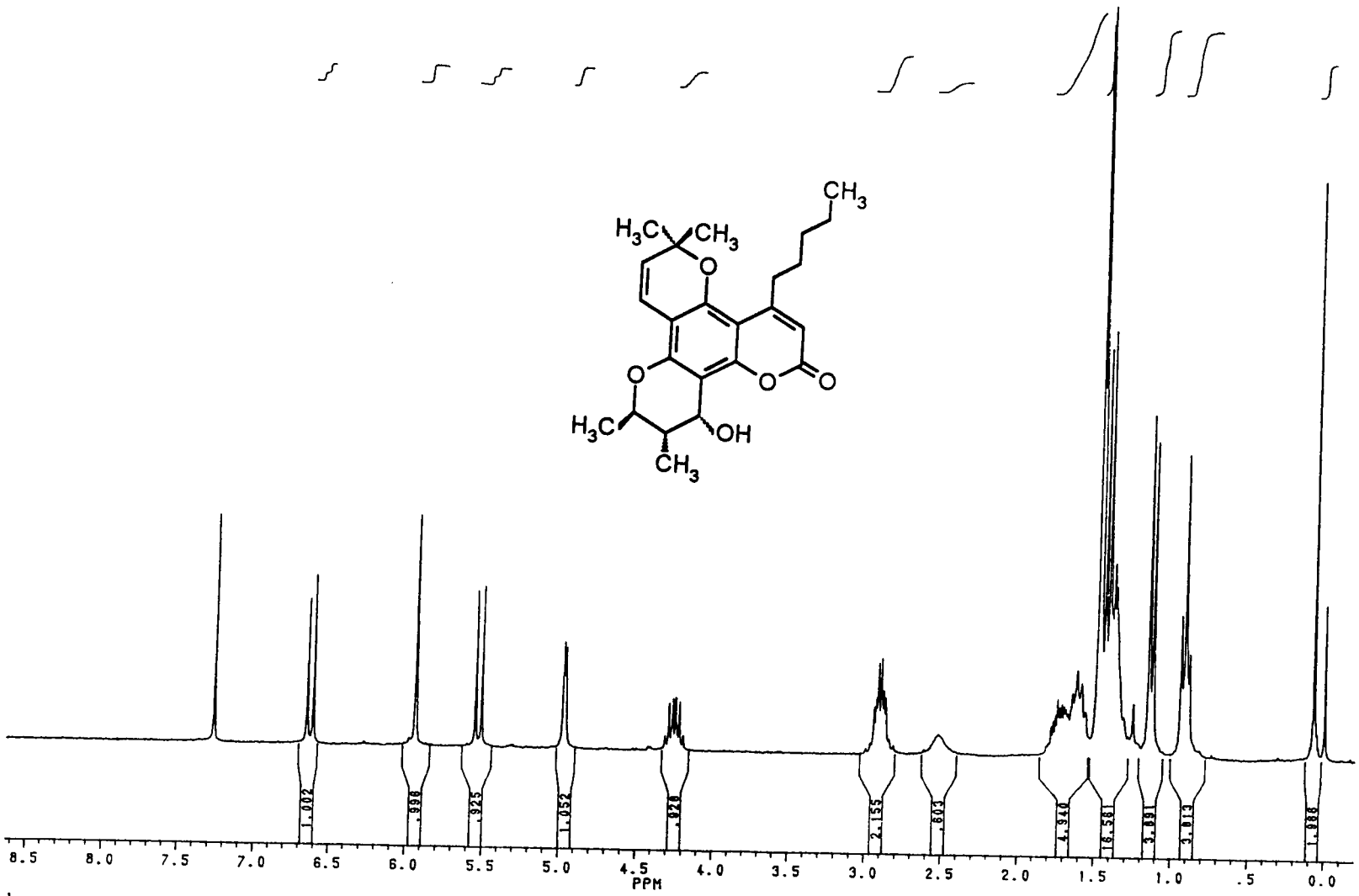
^{13}C NMR ($CDCl_3$) Spectrum of (+)-5-Hydroxy-6-[(1*R*,2*R*)-1-*tert*-butyldimethylsilyloxy-2-methylbut-3-enyl]-2,2-dimethyl-10-pentyl-2*H*-pyrano[2,3-*f*]chromen-8-one **[(+)-10b].**



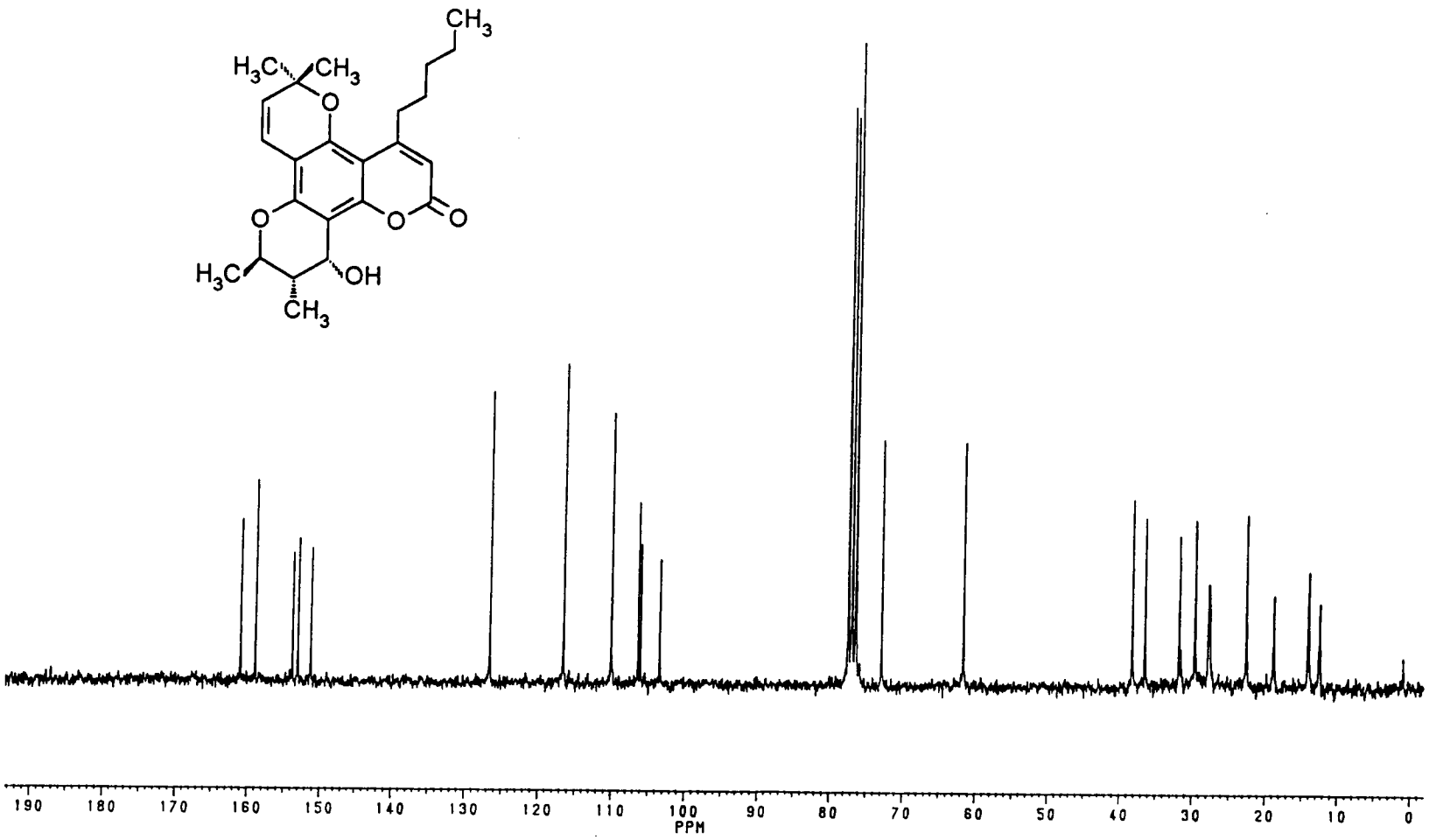
^{1}H NMR ($CDCl_3$) Spectrum of (+)-(10*R*,11*R*,12*R*)-12-*tert*-Butyldimethylsilyloxy-6,6,10,11-tetramethyl-4-pentyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromen-2-one **[(+)-11b].**



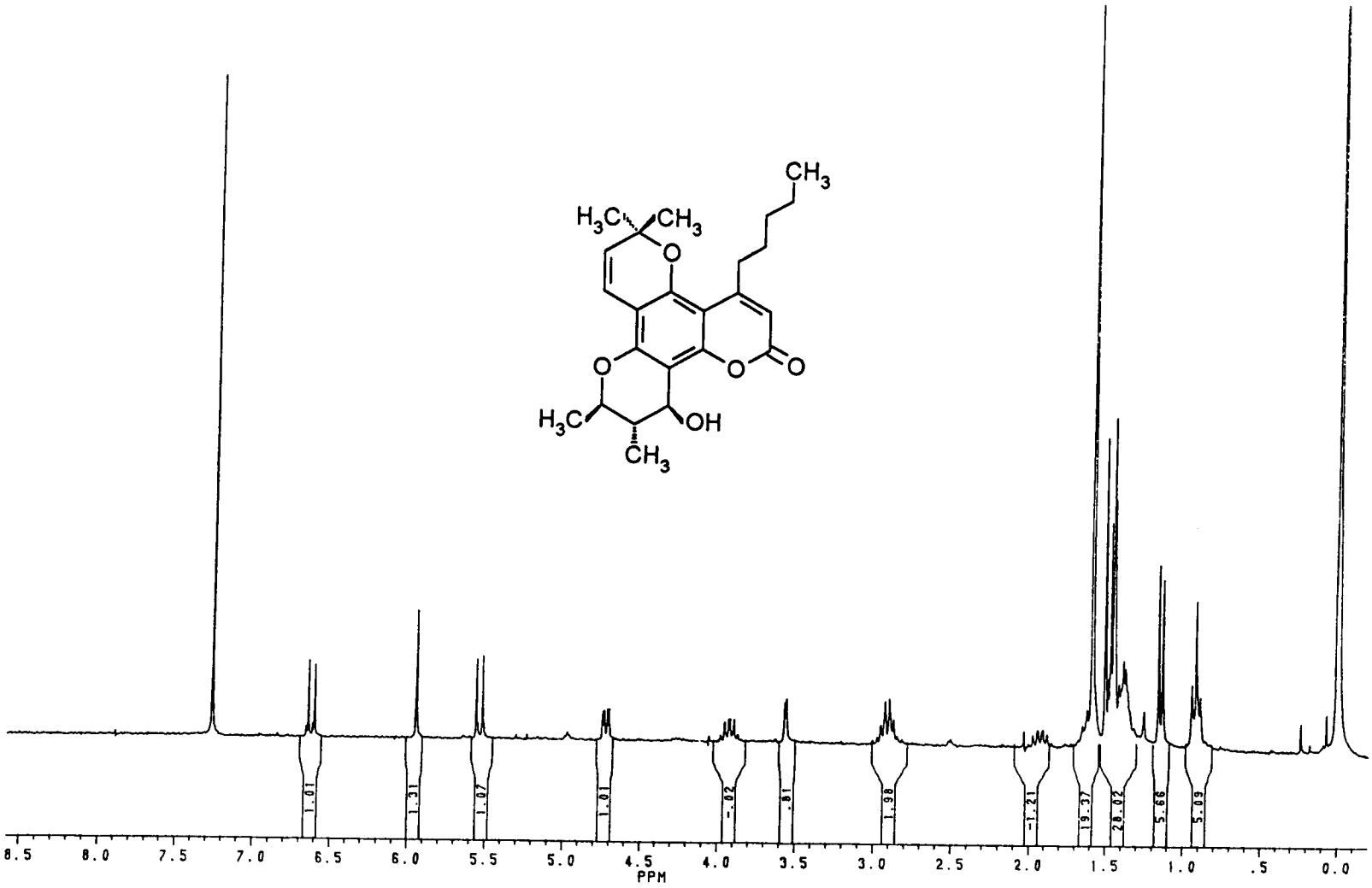
^{13}C NMR ($CDCl_3$) Spectrum of (+)-(10*R*,11*R*,12*R*)-12-*tert*-Butyldimethylsilyloxy-6,6,10,11-tetramethyl-4-pentyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromen-2-one **[(+)-11b].**



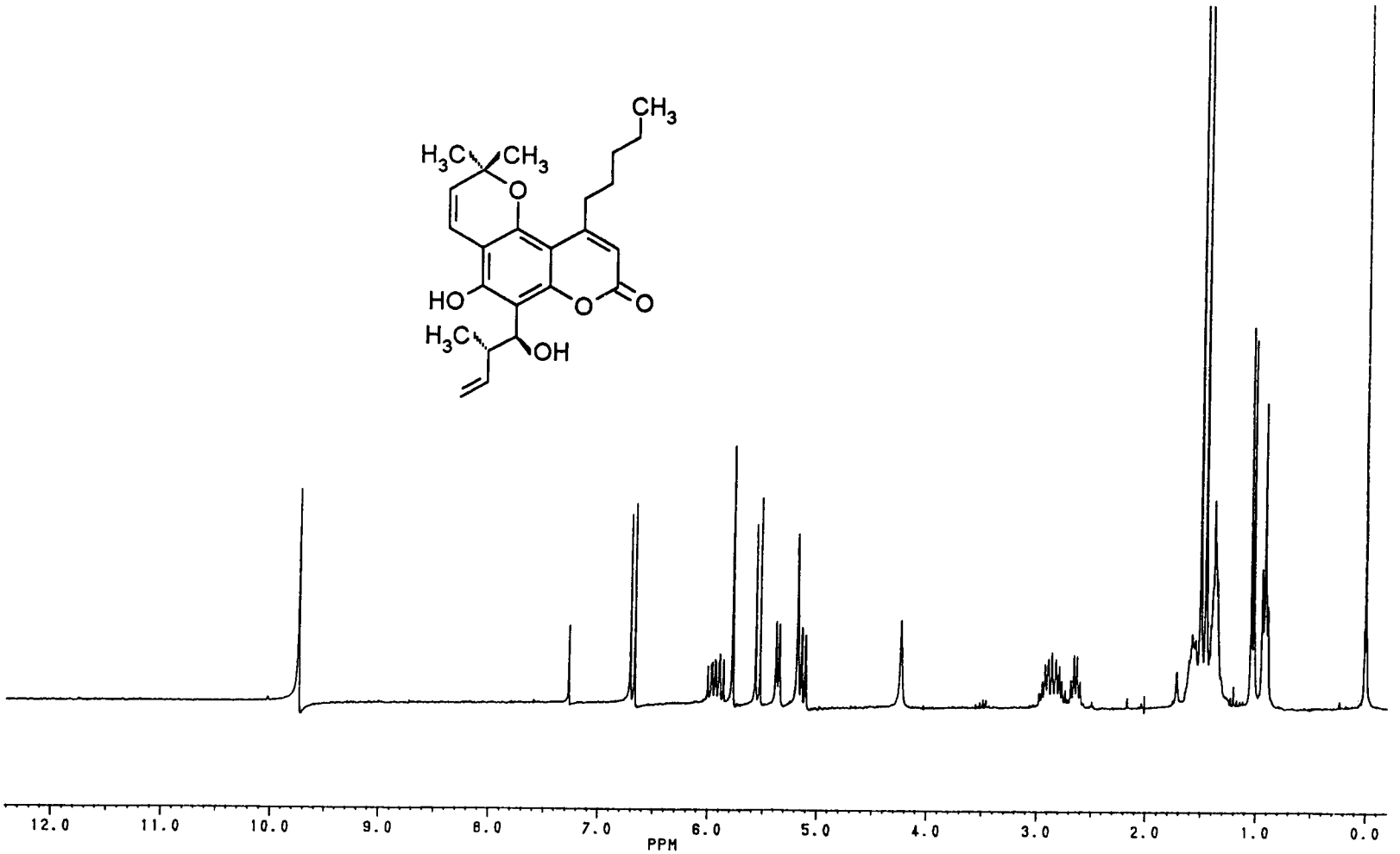
^{1}H NMR ($CDCl_3$) Spectrum of (+)-(10*R*,11*S*,12*R*)-12-Hydroxy-6,6,10,11-tetramethyl-4-pentyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromene-2-one **[(+)-2b].**



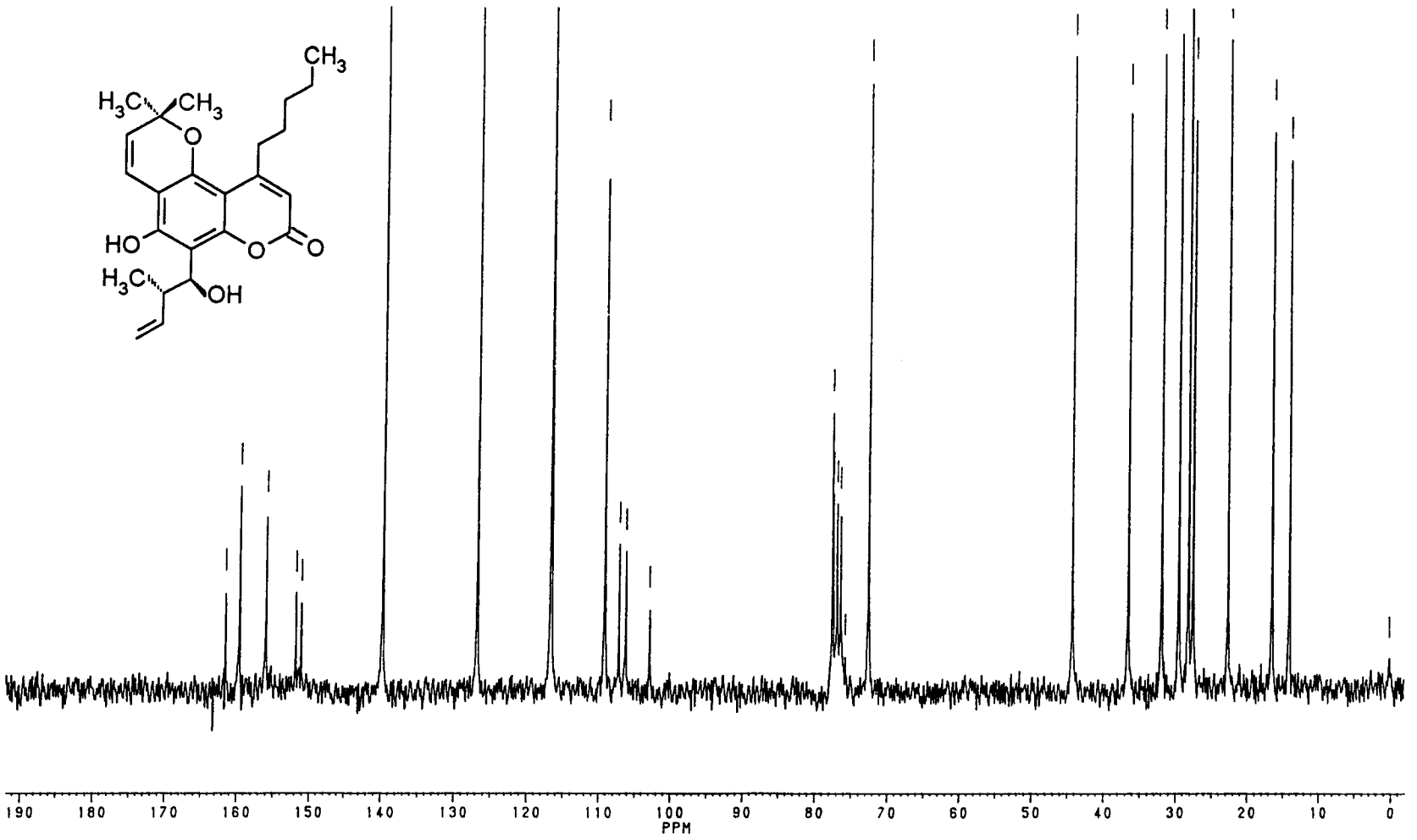
^{13}C NMR ($CDCl_3$) Spectrum of (+)-(10*R*,11*S*,12*R*)-12-Hydroxy-6,6,10,11-tetramethyl-4-pentyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromene-2-one **[(+)-2b].**



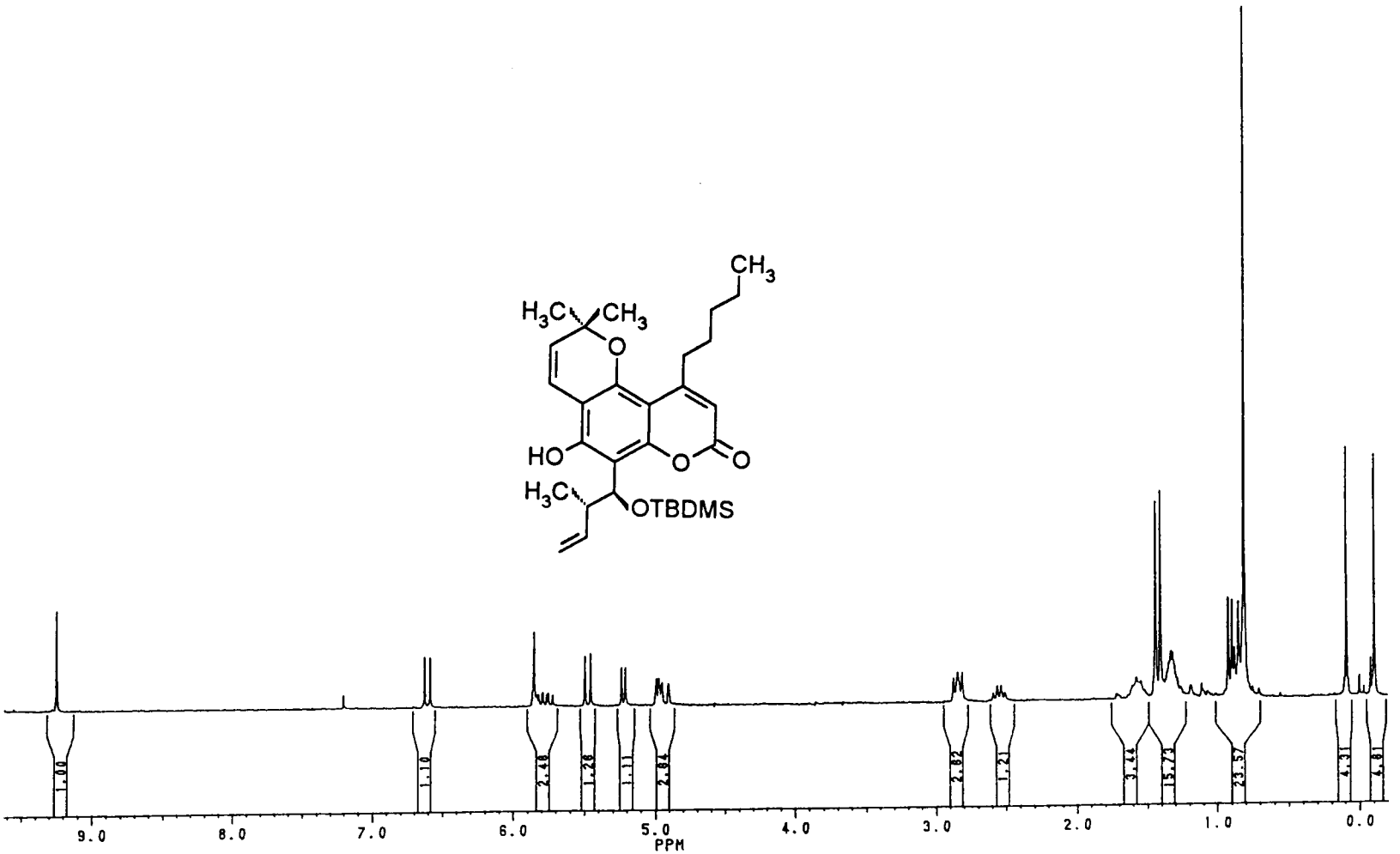
^{1}H NMR ($CDCl_3$) Spectrum of (+)-(10*R*,11*S*,12*S*)-12-Hydroxy-6,6,10,11-tetramethyl-4-pentyl-6,10,11,12-tetrahydro-dipyrano[2,3-*f*;2',3'-*h*]chromene-2-one **[(+)-1b]**.



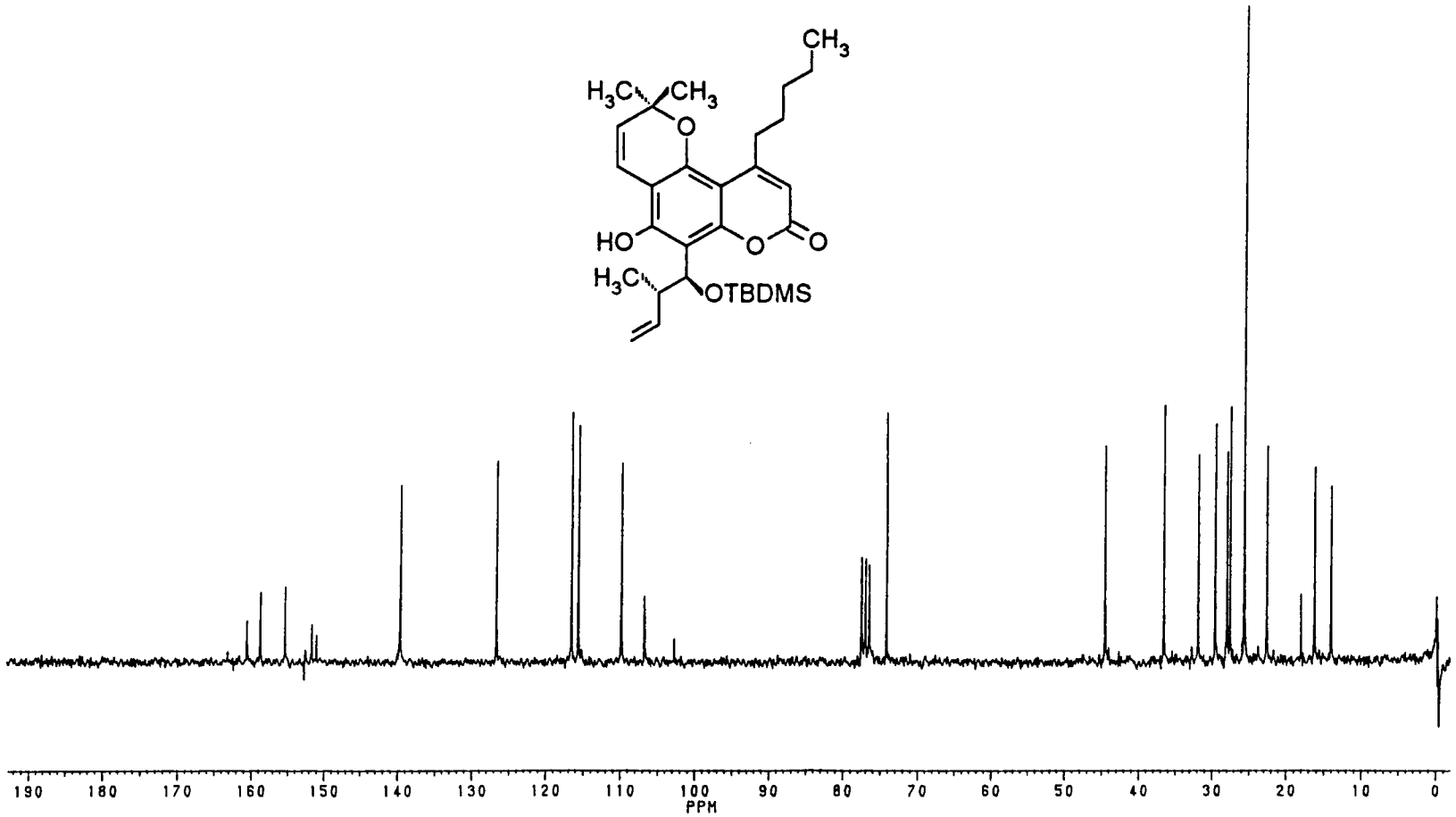
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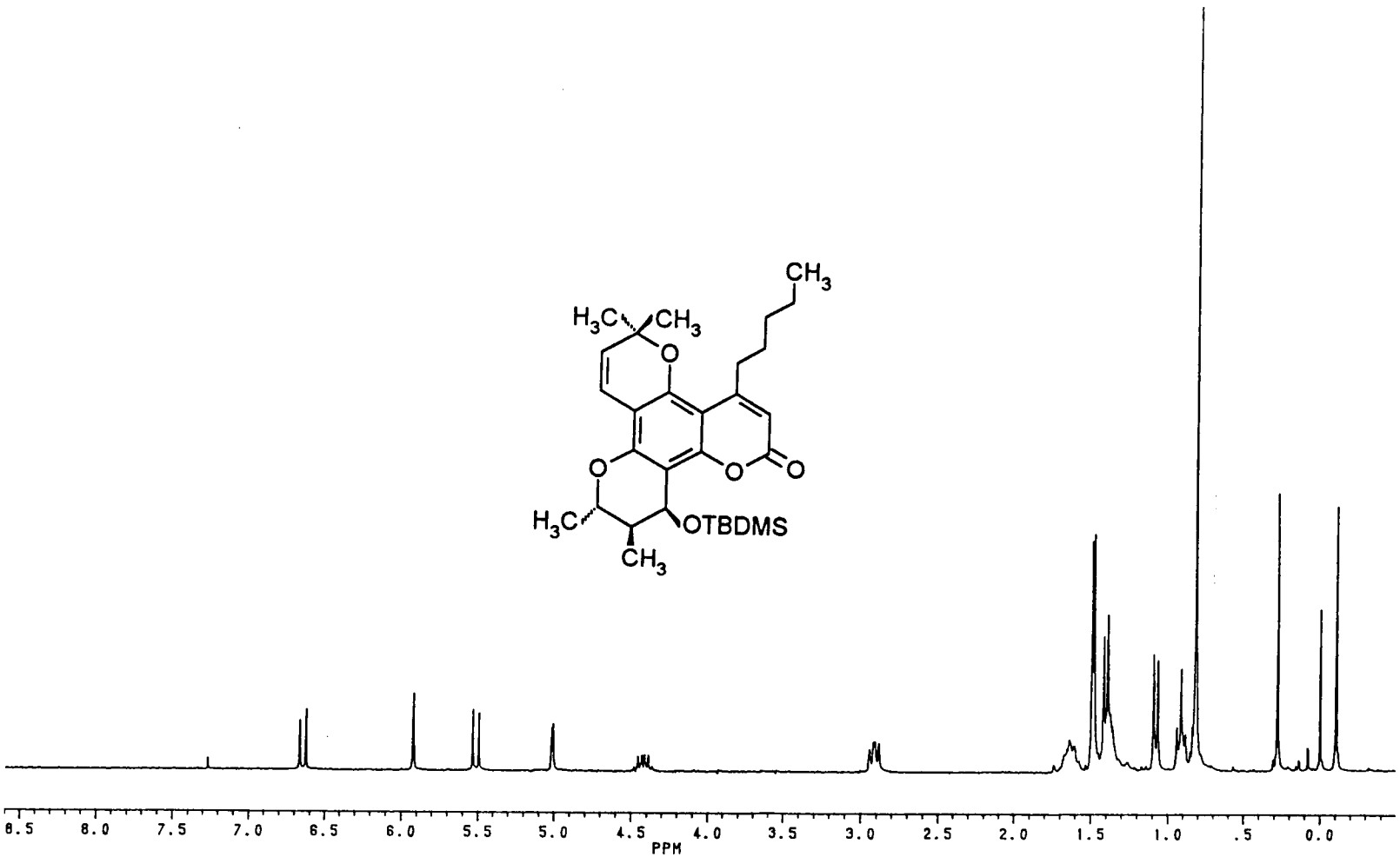
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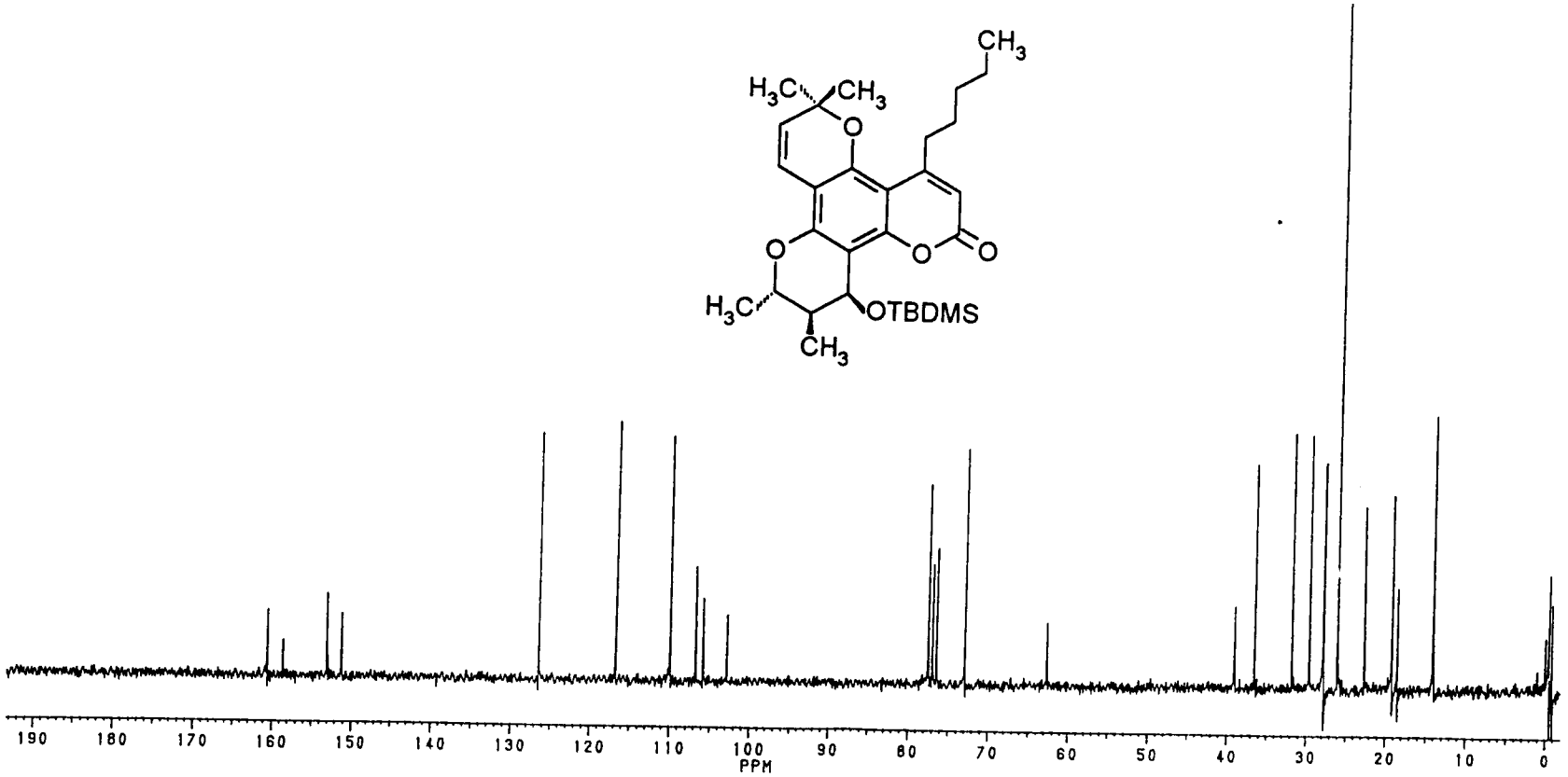
^{1}H NMR ($CDCl_3$) Spectrum of (−)-5-Hydroxy-6-[(1*S*,2*S*)-1-*tert*-butyldimethylsilyloxy-2-methylbut-3-enyl]-2,2-dimethyl-10-pentyl-2*H*-pyrano[2,3-*f*]chromen-8-one **[(−)-10b].**



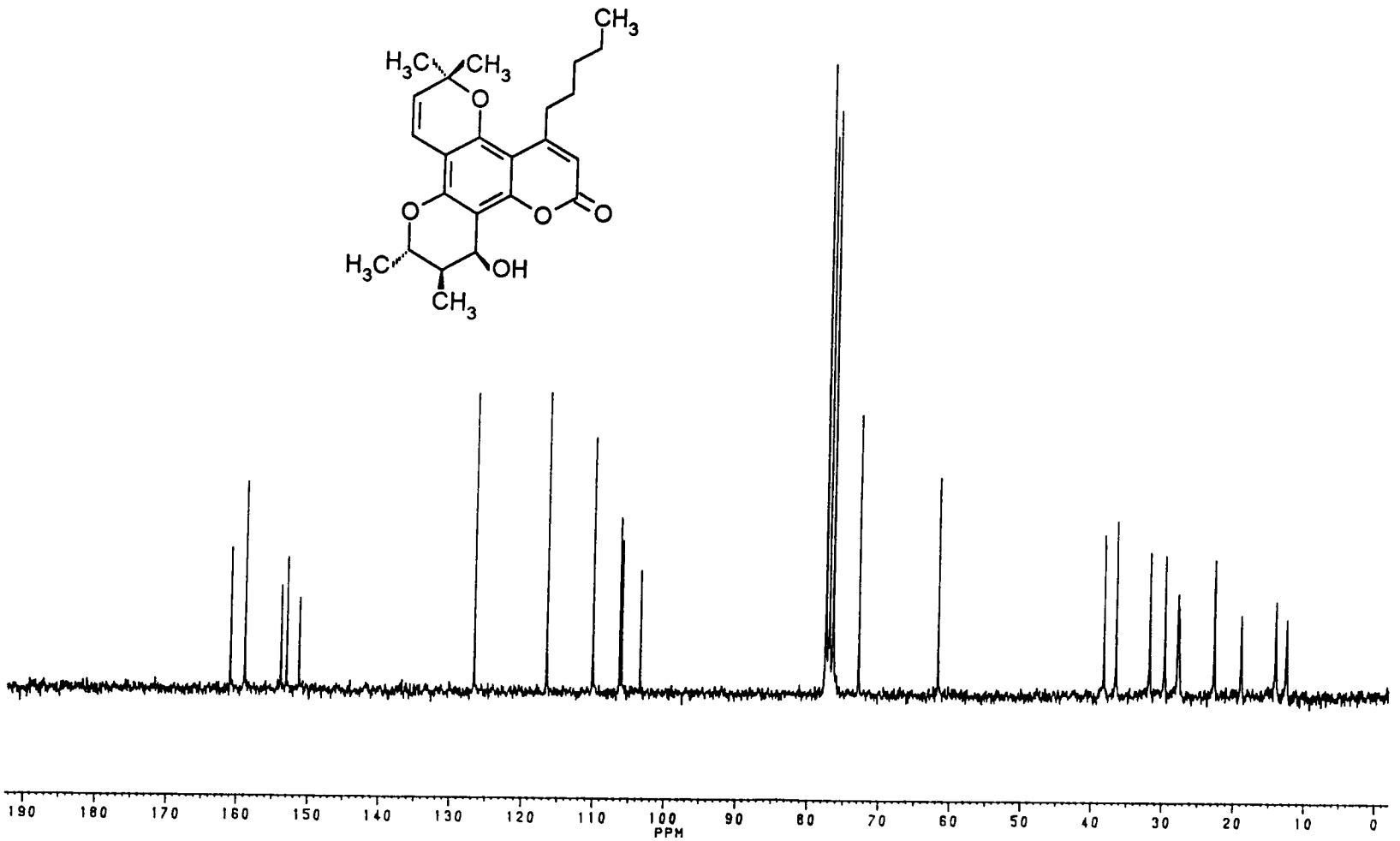
^{13}C NMR ($CDCl_3$) Spectrum of (−)-5-Hydroxy-6-[(1*S*,2*S*)-1-*tert*-butyldimethylsilyloxy-2-methylbut-3-enyl]-2,2-dimethyl-10-pentyl-2*H*-pyrano[2,3-*f*]chromen-8-one **[(−)-10b].**



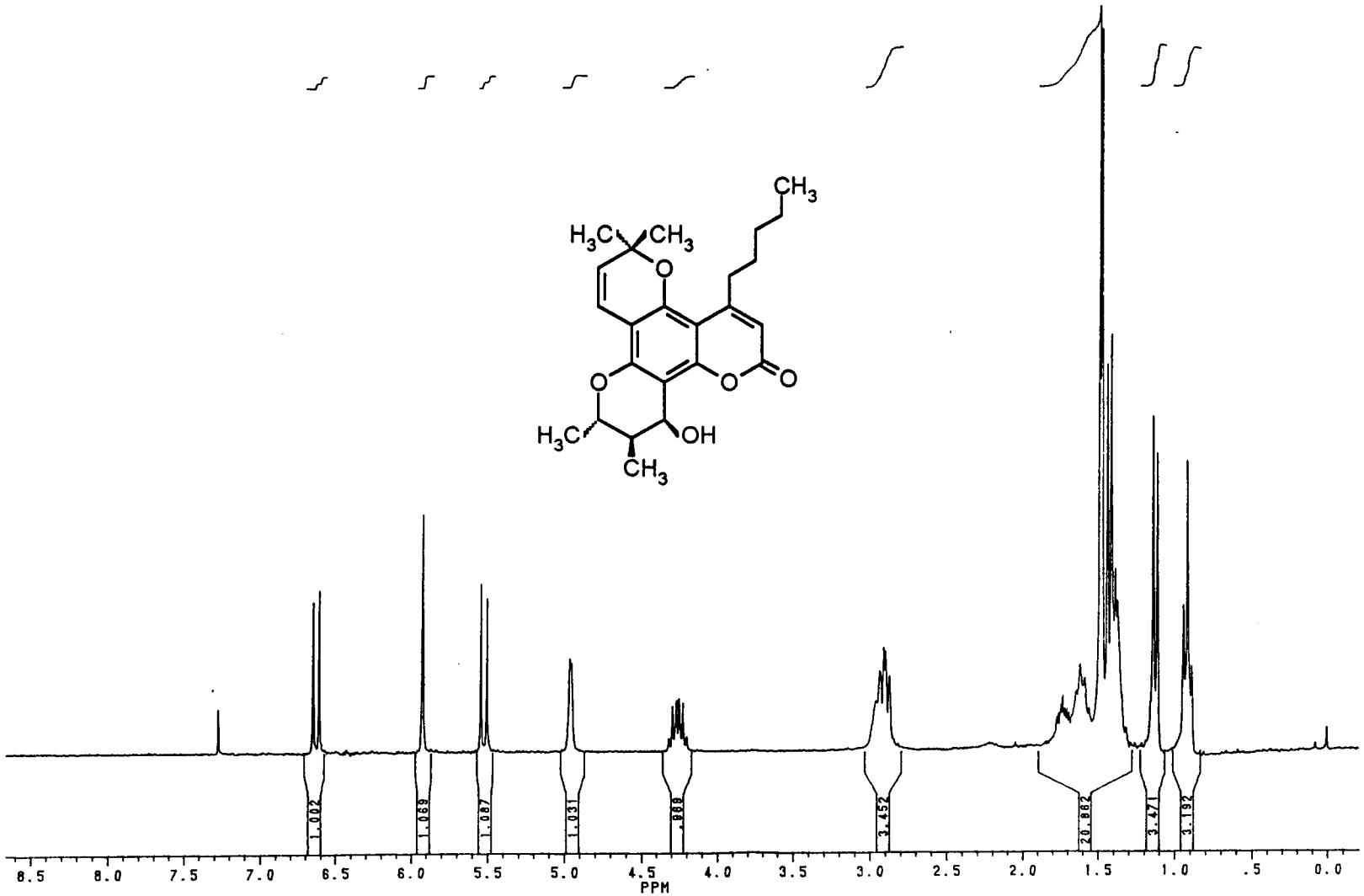
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^{13}C NMR ($CDCl_3$) Spectrum of (−)-(10*S*,11*R*,12*S*)-12-Hydroxy-6,6,10,11-tetramethyl-4-pentyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromene-2-one **[(−)-2b].**



^{1}H NMR ($CDCl_3$) Spectrum of (−)-(10*S*,11*R*,12*S*)-12-Hydroxy-6,6,10,11-tetramethyl-4-pentyl-6,10,11,12-tetrahydrodipyrano[2,3-*f*;2',3'-*h*]chromene-2-one **[(−)-2b].**

VITA

Michael S. Gaines was born in Wynne, Arkansas on June 21, 1972. He attended the public schools of Marion, Arkansas and graduated from Marion High School in May of 1990. The following August he entered Christian Brothers University, Memphis, Tennessee, and in May, 1994, was graduated with a Bachelor of Science in Chemistry. He entered the University of Tennessee Graduate School in August, 1994; he was the holder of a graduate teaching assistantship in the department of chemistry from 1994–1996.