Synthetic Studies of Crocynol

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Master of Science Thesis in Organic Chemistry
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Thesis Title	Synthetic Studies of Crocynol
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Major Program	Organic Chemistry

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The Graduate School, Prince of Songkla University, has approved this thesis as partial fulfillment of the requirement for the Master of Science degree in Organic Chemistry.

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Thesis Title Synthetic Studies of Crocynol
Author Miss Rapeeporn Suttirak
Major Programe Organic Chemistry
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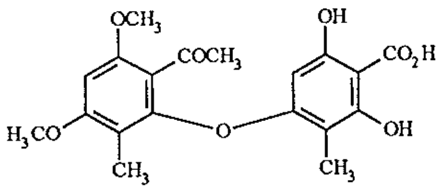
Abstract

The synthetic route to crocynol derivatives : 4-(2'-acetyl-3',5'-dimethoxy-6'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (57) and 4-(2'-acetyl-3',5'-dimethoxy-4'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (64) is described. The syntheses employed a novel Smiles rerrangement of precursor *para*-depsides (54) and (61) in the key step, to give the corresponding diphenyl ethers (55) and (62), respectively.



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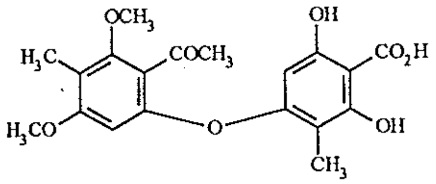

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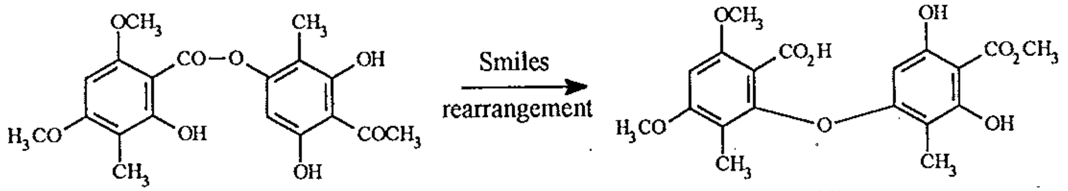

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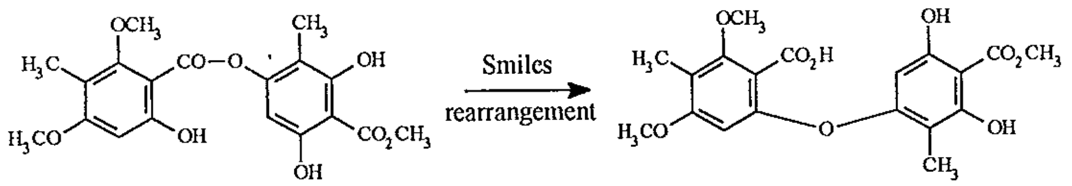
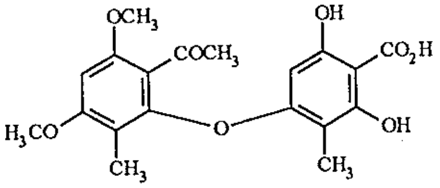


(61) (62)

ชื่อวิทยานิพนธ์ แนวทางการสังเคราะห์สารประกอบโครไซนอล
ผู้เขียน นางสาวระพีพร สุทธิรักษ์
สาขาวิชา เคมีอินทรีย์
ปีการศึกษา 2537

บทคัดย่อ

อธิบายแนวทางในการสังเคราะห์อนุพันธ์ของสารประกอบโครไซนอล : 4-(2'-acetyl-3',5'-dimethoxy-6'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (57) และ 4-(2'-acetyl 3',5'-dimethoxy-4'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (64) ขั้นตอนสำคัญในการสังเคราะห์ครั้งนี้คือ ปฏิกิริยาการจัดเรียงตัวแบบใหม่ของ Smiles (Smiles rearrangement) ของสารประกอบ *para*-depsides (54) และ (61) นำไปสู่สารประกอบ diphenyl ethers (55) และ (62) ตามลำดับ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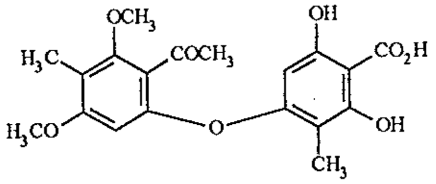
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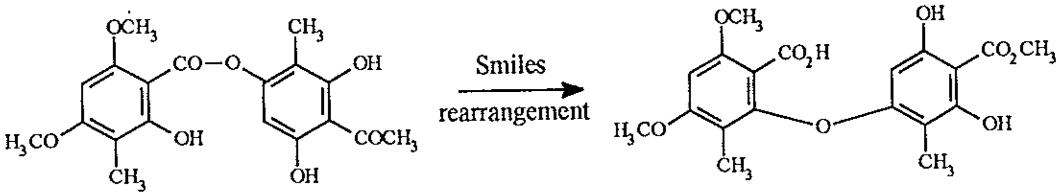

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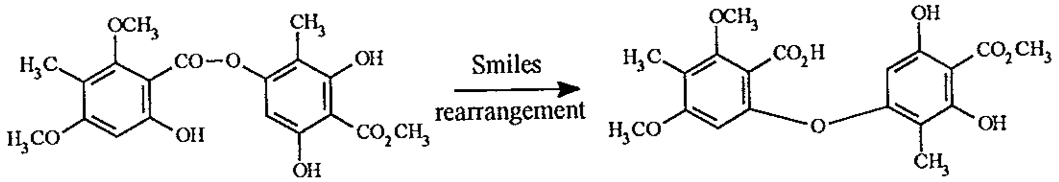

(61) (62)

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Rapeeporn Suttirak

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List of Schemes

Abbreviation and Symbol

DCC	N,N'-Dicyclohexylcarbodiimide
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMSO	Methyl sulfoxide (Dimethyl sulfoxide)
IR	Infrared
H' NMR	Proton nuclear magnetic resonance
NOE	Nuclear Overhauser effect enhancement
m.p.	Melting point
t.l.c.	Thin layer chromatrography
THF	Tetrahydrofuran

Chapter 1

Introduction

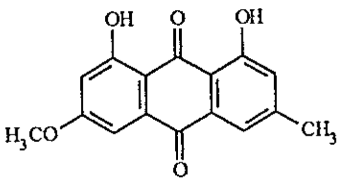
Lichen substances are metabolic products of lichens, which are symbiotic associations of algae and fungi. Some of these compounds occur only in lichens, whereas others are also found in fungi and higher plants. Under certain conditions, some lichen fungi are able to synthesize the compounds present in the corresponding lichens by themselves. Parietin (1), rhodocladonic acid (2), pulvinic acid (3), usninic acid (4), and didymic acid (5) can be established in cultures of lichen fungi. Lichen fungi are able to form depsides and depsidones in symbiosis with algae, however Hess (Hess, 1949) could not isolate any of these substances from their cultures. The mycelia of fungi generated only simple phenols, including oresellinic acid (6) and haematommic acid (7), which could not be established in the corresponding lichens. Obviously, by symbiosis, (a). the simple phenols synthesized by the fungus are interlinked into depsides and depsidones, and (b). the simple phenols are chemically changed before or after they have been linked. This means that the phycobiont not only generates the energy required by the fungus for forming the phenols but later also takes part in their metabolism. It would be interesting to investigate whether algae isolated from lichens are able to interlink with simple phenolic units to form depsides and depsidones.

The physiology of the isolated fungal and algal symbionts has been broadly dealt with by Ahmadjian (Ahmadjian, 1966).

As lichens are organisms which grow very slowly, lichen substances which possess antibiotic activity may have the function of protecting the organism from attack by other fungi. Harder and Uebelmesser (Harder and Uebelmesser, 1958) reported the retarding action of lichens on the growth of lower phycomycetes, and Hess (Hess, 1960) wrote about the retarding action of extracts of lichen fungi on the growth of *Neurospora crassa.*

Lichen substances have attracted the attention of chemists and botanists; as early as 1907, Zopf (Zopf, 1907) published a monograph on this class of natural substances. The two masters of lichen chemistry, Asahina and Shibata (Asahina and Shibata, 1954), published their standard work, *Chemistry of Lichen Substances,* in 1954 and later Shibata

(Shibata, 1958, 1963) wrote two further summarizing papers on the subject.



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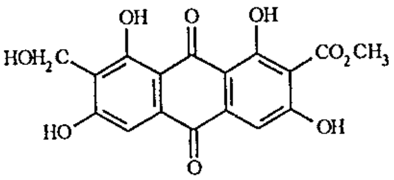

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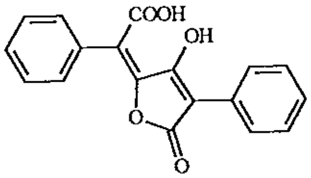

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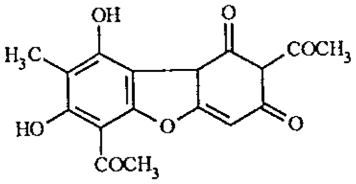

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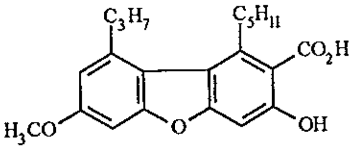

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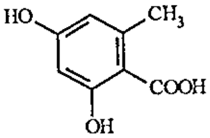

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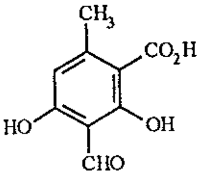

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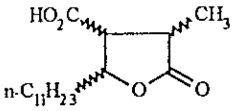
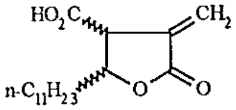
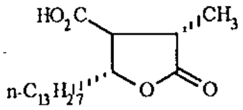
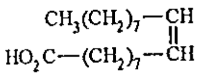
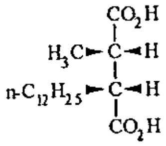
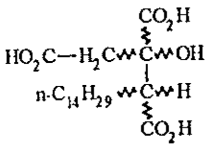
Classification of Lichen Substances

All the known lichen substances may be grouped as shown below (Huneck, 1972).

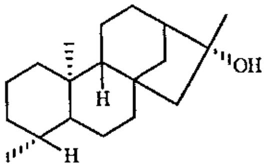
1. γ-Lactonic acid derivatives

Compounds	Structures	References
Nephrosteranic acid		Asahina and Shibata, 1954
Nephrosterinic acid		Asahina and Shibata, 1954
(+)-Roccellaric acid [(+)-neo-Dihydroprotolichesterinic acid]		Follmann and Huneck, 1967

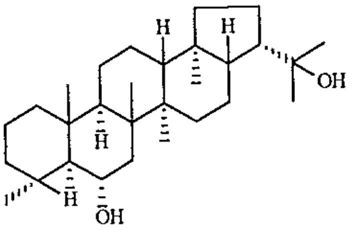
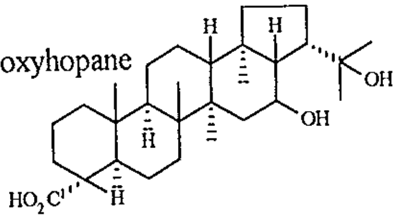
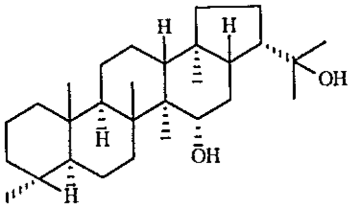
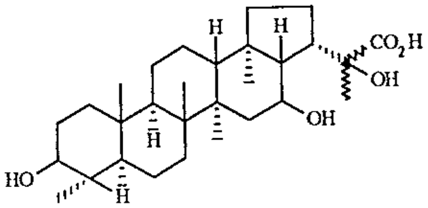
2. Mono-, di- and tribasic fatty acids

Compounds	Structures	References
Oleic acid	 $\begin{array}{r}\mathrm{CH_3(CH_2)_7-CH}\\ \Vert\\ \mathrm{HO_2C-(CH_2)_7-CH}\end{array}$	Klima, 1932
(+)-Roccellic acid		Akermark, 1962
(-)-Caperatic acid		Asahina and Shibata, 1954

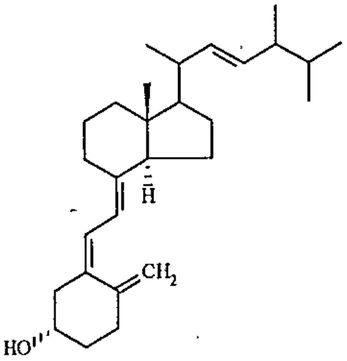
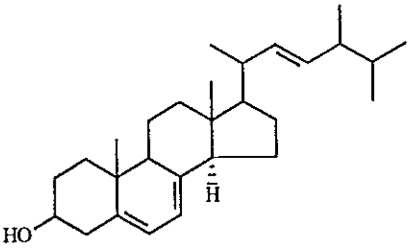
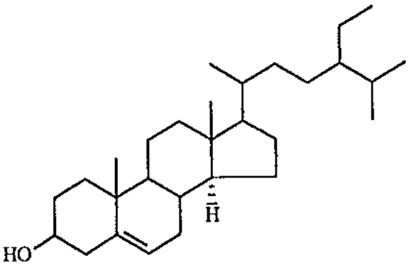
3. Diterpenes

Compounds	Structures	References
(-)-16 α-Hydroxykaurane		Follmann and Hunech, 1965 Hunech and Lehn, 1965

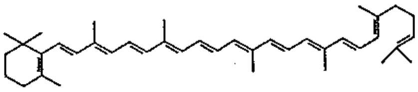
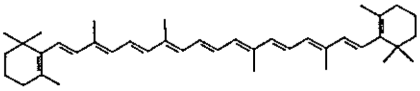
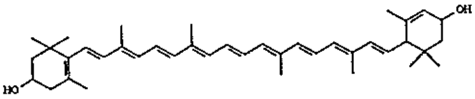
4. Triterpenes

Compounds	Structures	References
Zeorin		Hunech and Lehn, 1963
15 α, 22-Dihydroxyhopane		Corbett and Young, 1966
Leucotytic acid		Nakanishi, Tsucda and Yosioka, 1966
Pyxinic acid		Kitagawa, Matsuda and Yosioka, 1966

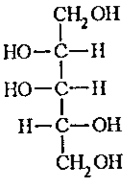
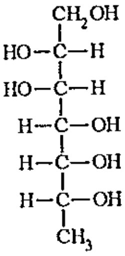
5. Steroids

Compounds	Structures	References
Vitamin D_2		Murty and Sankgra, 1959
Ergosterol		Alertsen, Brum and Hemmer, 1962
β-Sitosterol		Follmann and Huneck, 1965 Follmann and Huneck, 1966

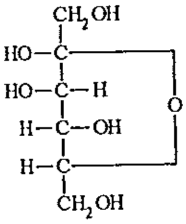
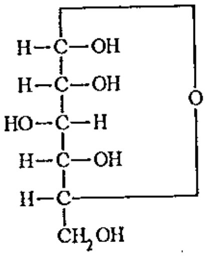
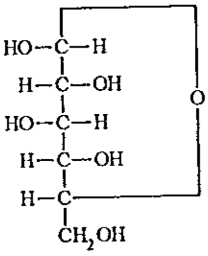
6. Carotenoids

Compounds	Structures	References
γ-Carotene		Murty and Subramanian, 1959
β-Carotene		Murty and Subramanian, 1959
Xanthophyll		Quillet, 1961

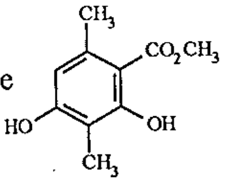
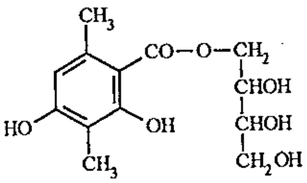
7. Polyhydric alcohols

Compounds	Structures	References
D-Arabitol	 $\begin{array}{c} CH_2OH \\ HO-C-H \\ HO-C-H \\ H-C-OH \\ CH_2OH \end{array}$	Lindberg, Misiorny and Washtmeister, 1953
D-Siphulitol	 $\begin{array}{c} CH_2OH \\ HO-C-H \\ HO-C-H \\ H-C-OH \\ H-C-OH \\ H-C-OH \\ CH_3 \end{array}$	Lindberg and Meier, 1962

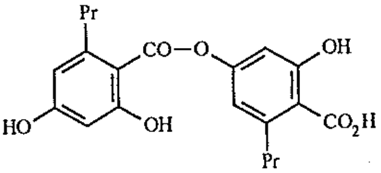
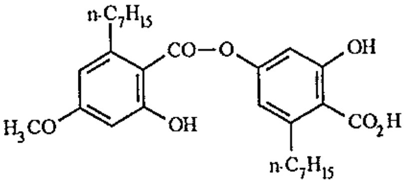
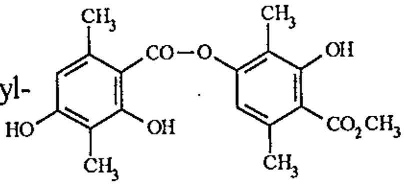
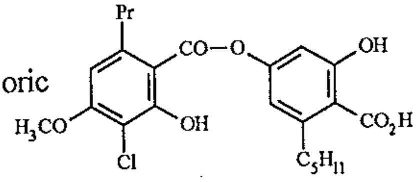
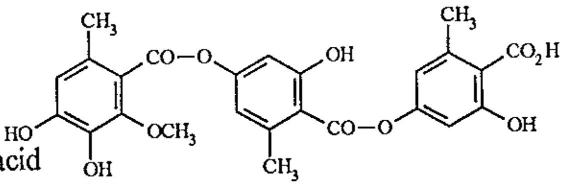
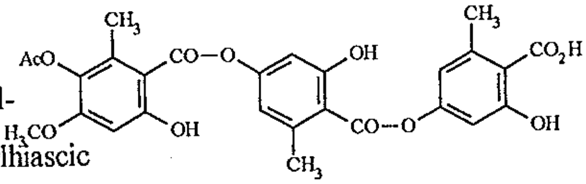
8. Carbohydrates

Compounds	Structures	References
D-Fructose		Pueyo, 1963
D-Glucose	 α-form  β-form	Pueyo, 1963

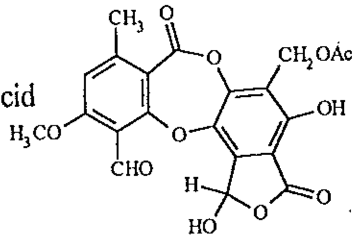
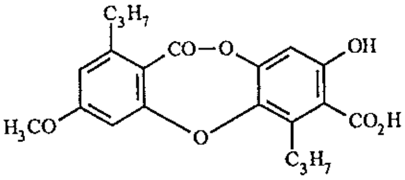
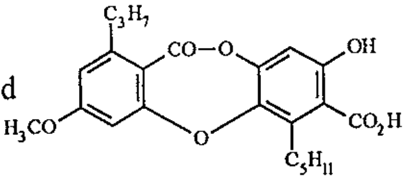
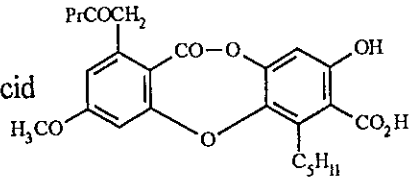
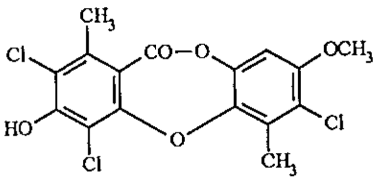
9. Orcinol derivatives

Compounds	Structures	References
Methyl β-orcinolcarboxylate		Murty, 1960
Montagnetol (Picroerythrin)		Neelakantan, Manaktala and Seshadri, 1966

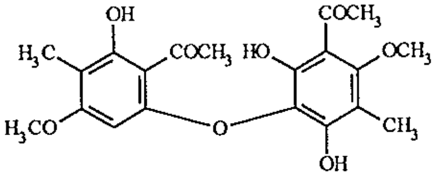
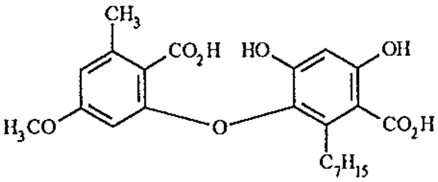
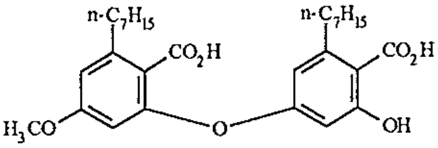
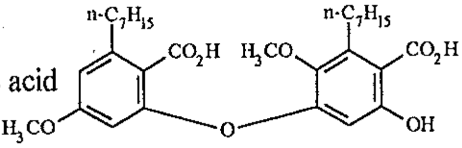
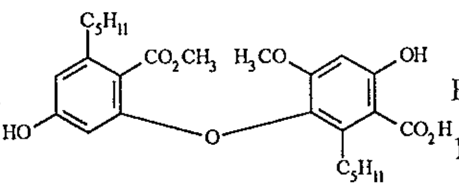
10. Depsides

Compounds	Structures	References
Nordivaricatic acid		Elix and Tearne, 1977
Prasinic acid		Coppins, *et al.*, 1984
Methyl 4-*o*-demethyl-barbatate		Arvidsson, *et al.* 1987
3-Chlorostenosporic acid		Elix, Evans and Nash, 1988
3-Hydroxy-umbilicaric acid		Alder, Elix and Yu, 1989
5-*o*-Acetyl-4-*o*-methylhiascic acid		Elix, Tonsberg and Yu, 1990

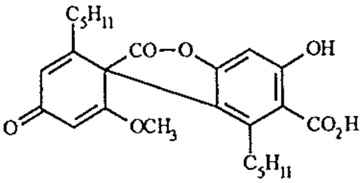
11. Depsidones

Compounds	Structures	References
a-Acetylconstictic acid		Elix, *et al.*, 1987
Divaronic acid		Elix, Jenie and Parker, 1987
Stenosporonic acid		Elix, Jenie and Parker, 1987
Glomelliferonic acid		Elix, Jenie and Jenkins, 1987
Isofulgidin		Birkbeck, Elix and Sargent, 1990

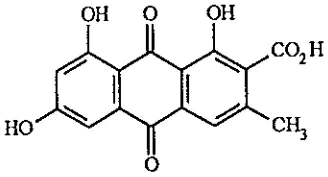
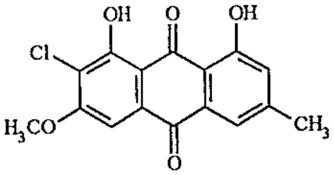
12. Diphenyl ethers

Compounds	Structures	References
Leprolomin		Elix, *et al.*, 1978
Congrayanic acid		Chester and Elix, 1980
Micareic acid		Coppins, *et al.*, 1984
Methoxymicareic acid		Coppins, *et al.*, 1984
Epiphorellic acid 1		Elix and Jenie, 1989

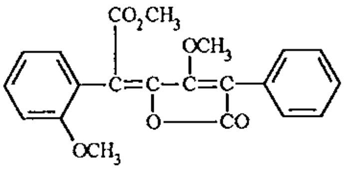
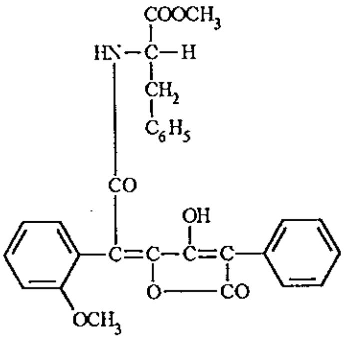
13. Depsones

Compounds	Structures	References
Picrolicheninic acid (Picrolichenic acid)		Harper and Letcher, 1966

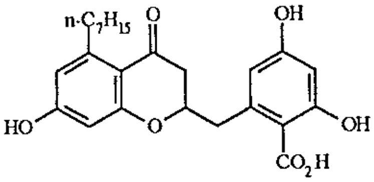
14. Quinones

Compounds	Structures	References
Endocrocin		Joshi, Ramanathan and Venkataraman, 1962
Fragilin		Bruun, Hollis and Ryhage, 1965

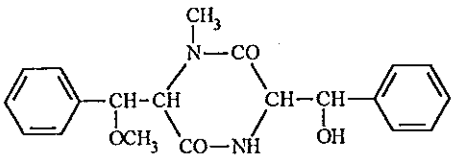
15. Pulvinic acid derivatives

Compounds	Structures	References
Leprapinic acid methyl ether		Agarwal and Seshadri, 1965
Rhizocarpic acid		Huneck, 1966

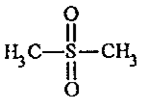
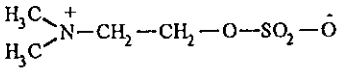
16. Chromanone derivatives

Compounds	Structures	References
Siphulin		Bruun, 1960

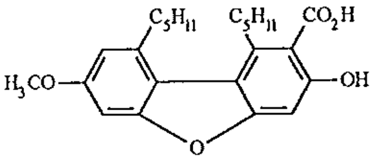
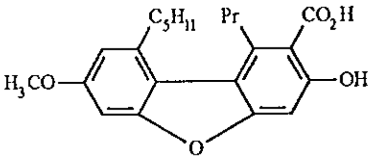
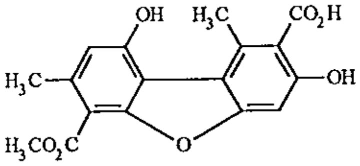
17. Nitrogen-containing compounds

Compounds	Structures	References
Picroroccellin		Asahina and Shibata, 1954

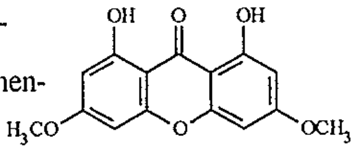
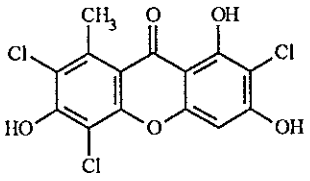
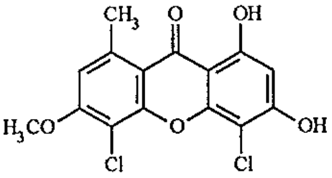
18. Sulphur-containing compounds

Compounds	Structures	References
Dimethyl sulphone	 $H_3C-\overset{\overset{O}{\Vert}}{\underset{\underset{O}{\Vert}}{S}}-CH_3$	Bruun and Sörensen, 1954
Cholinesulphuric acid	 $\begin{matrix}H_3C\\H_3C\end{matrix}\!>\overset{+}{N}-CH_2-CH_2-O-SO_2-\overset{-}{O}$	Harper and Letcher, 1966

19. Dibenzofuran derivatives

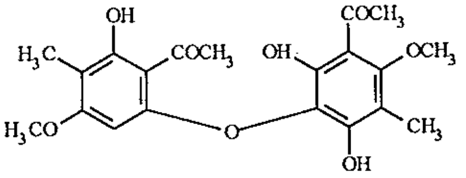
Compounds	Structures	References
Condidymic acid		Chester and Elix, 1981
Isodidymic acid		Chester, Elix and Kennedy, 1986
Pannaric acid 6-methyl ester		Elix, Laundon and Pratt, 1990

20. Xanthone derivatives

Compounds	Structures	References
1, 8-Dihydroxy-3, 6-dimethoxy-9*H*-xanthen-9-one		Elix, Gaul and Lumbsch, 1987
2, 5, 7-Trichloro-norlichexanthone		Elix, Jiang and Portelli, 1990
4, 5-Dichloro-6-*o*-methylnorlichen-xanthone		Bennett, Elix and Jiang, 1991

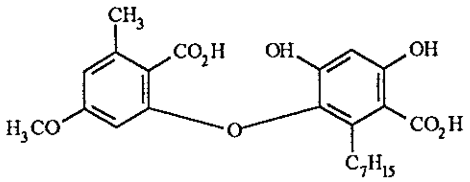
2. Structures and Syntheses of Diphenyl Ethers

John A. Elix and co-workers isolated 3-(2'-acetyl-3'-hydroxy-5'-methoxy-4'-methylphenoxy)-2,4-dihydroxy-6-methoxy-5-methylacetophenone (leprolomin) (8), a novel diphenyl ether from the lichen *Psoroma leprolomum* (Elix, *et al,* 1978). The structure of leprolomin (8) was determined by the spectroscopic data including X-ray diffraction.



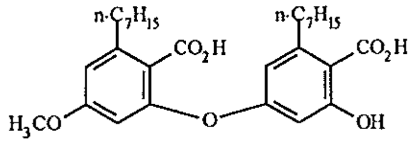
(8)

Diphenyl ether congrayanic acid (2-(3'-carboxy-2'-heptyl-4',6'-dihydroxyphenoxy)-4-methoxy-6-methylbenzoic acid) (9) was shown to be a constituent of the Australian lichen *Gymnoderma melacarpum* (Wils.) Yoshim (Chester and Elix, 1980).

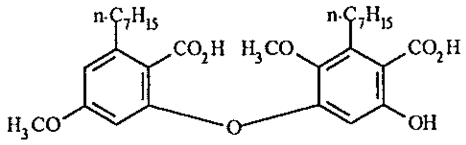


(9)

In 1984, two diphenyl ethers, 4-(2'-carboxy-3'-heptyl-5'-methoxyphenoxy)-2-heptyl-6-hydroxybenzoic acid (micareic acid) (10) and 4-(2'-carboxy-3'-heptyl-5'-methoxyphenoxy)-2-heptyl-6-hydroxy-3-methoxybenzoic acid (methoxymicareic acid) (11) were isolated from the lichen *Micarea prasina* Fr. (Coppins, *et al.*, 1984). The structure of the compounds (10) and (11) were confirmed by total syntheses as shown in **Scheme 1** and **2**.

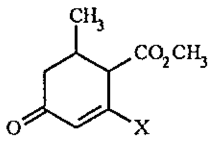


(10)

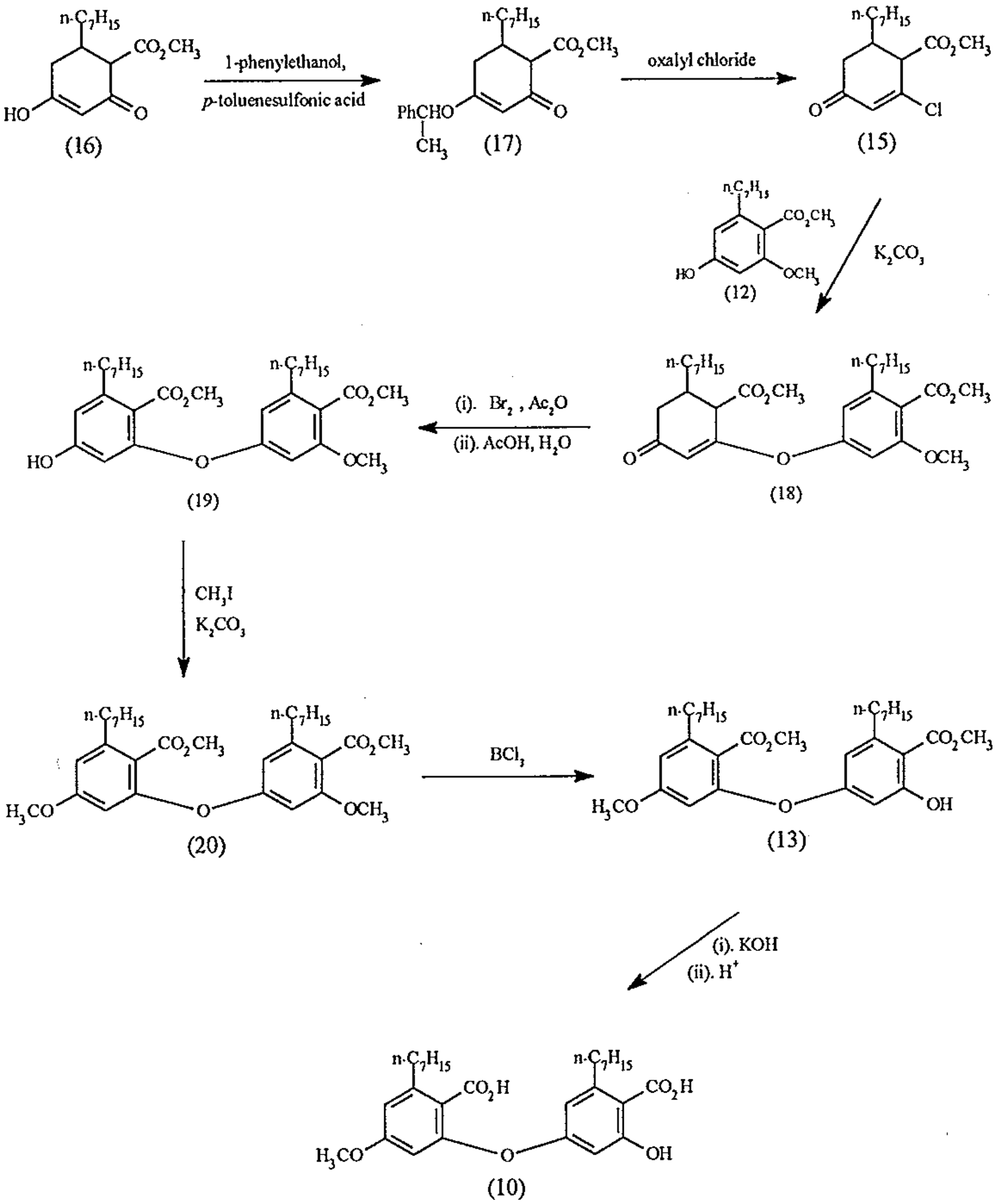


(11)

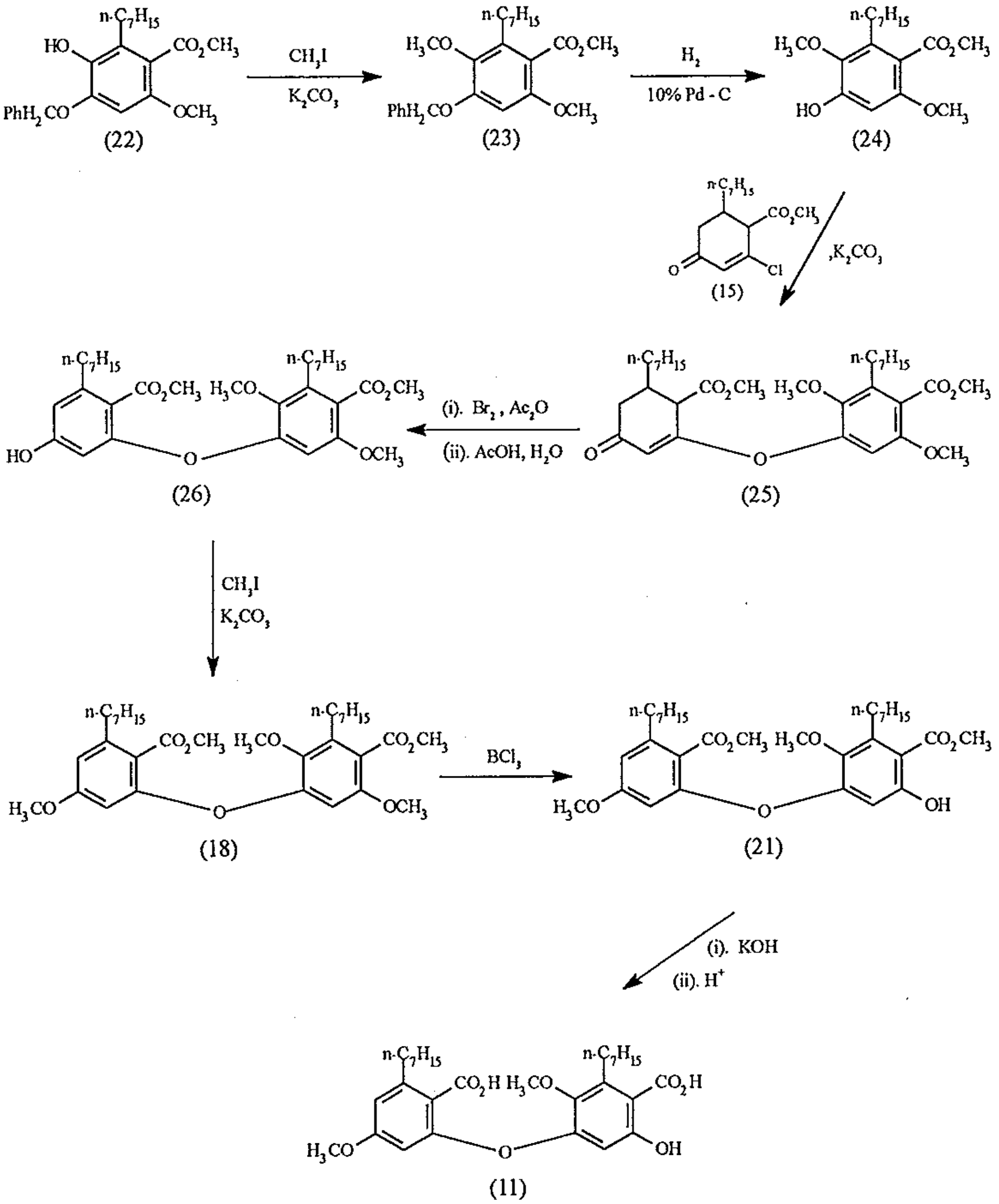
In general, diphenyl ethers have normally been prepared by the Ullmann ether synthesis (Moroz and Shvartsberg, 1974) involving the reaction between a phenol (or phenolate salt) and a halobenzene in the presence of a tertiary amine and catalysed by copper, cuprous or cupric salts. Such a synthetic approach to a highly substituted diphenyl ether such as (13) is feasible but the preparation of substituted halobenzene involves numerous step (Djura and Sargent, 1976). Recently, Büchi and co-workers (Büchi and Willard, 1978) have circumvented this difficulty by utilizing the more accessible methyl-2-halo-4-oxo-6-methylcyclohex-2-enecarboxylates (14 ; x = Br, Cl) in an Ullmann-type reaction with the appropriate phenol. Therefore, the key steps in the syntheses of the diphenyl ethers (13) and (21) involved Ullmann-like condensation between the 3-chloro-2-enone (15) and the phenols (12), (24) and subsequent aromatization of the enol ethers (18) and (25) **(Scheme 1** and **2)**.



(14)

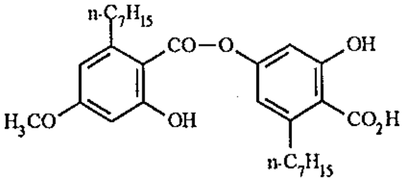


Scheme 1 Synthesis of micareic (10)

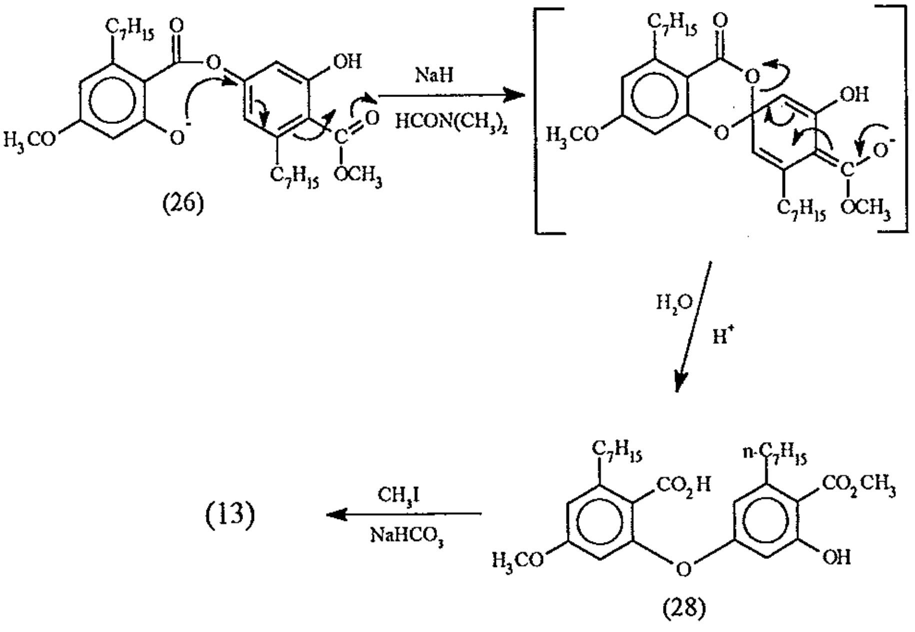


Scheme 2 Synthesis of methoxymicareic acid (11)

Micareic acid (10) and methoxymicareic acid (11) have a distinctly different substitution pattern and presumably biogenetic origin. One intriguing possibility is that micareic acid (10) arises by an enzymatically induced Smiles rearrangement of the depside, prasinic acid (27). When methyl prasinate (26) was made to react with sodium hydride in dimethylformamide to give methyl micareate (28) **(Scheme 3)**, this rearrangement was accompained by a minor amount of depside cleavage. Subsequent methylation of the acid (28) gave dimethyl micareate (13), identical in all respects with the authentic material. This synthesis gives credence to the proposal that Smiles rearrangement (Brand, Kreider and Truce, 1971) of the appropriate depside provides a viable biosynthetic pathway to these uniquely substituted diphenyl ethers.

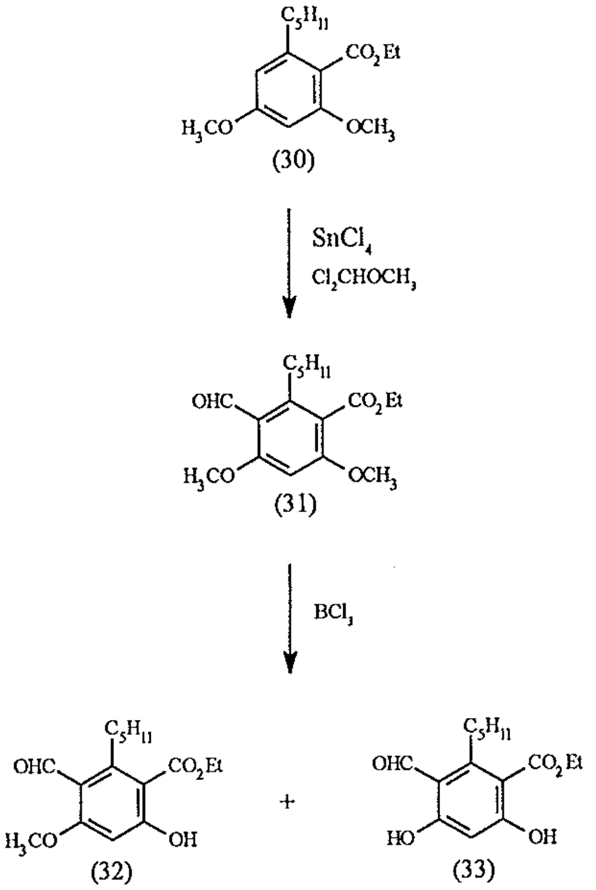


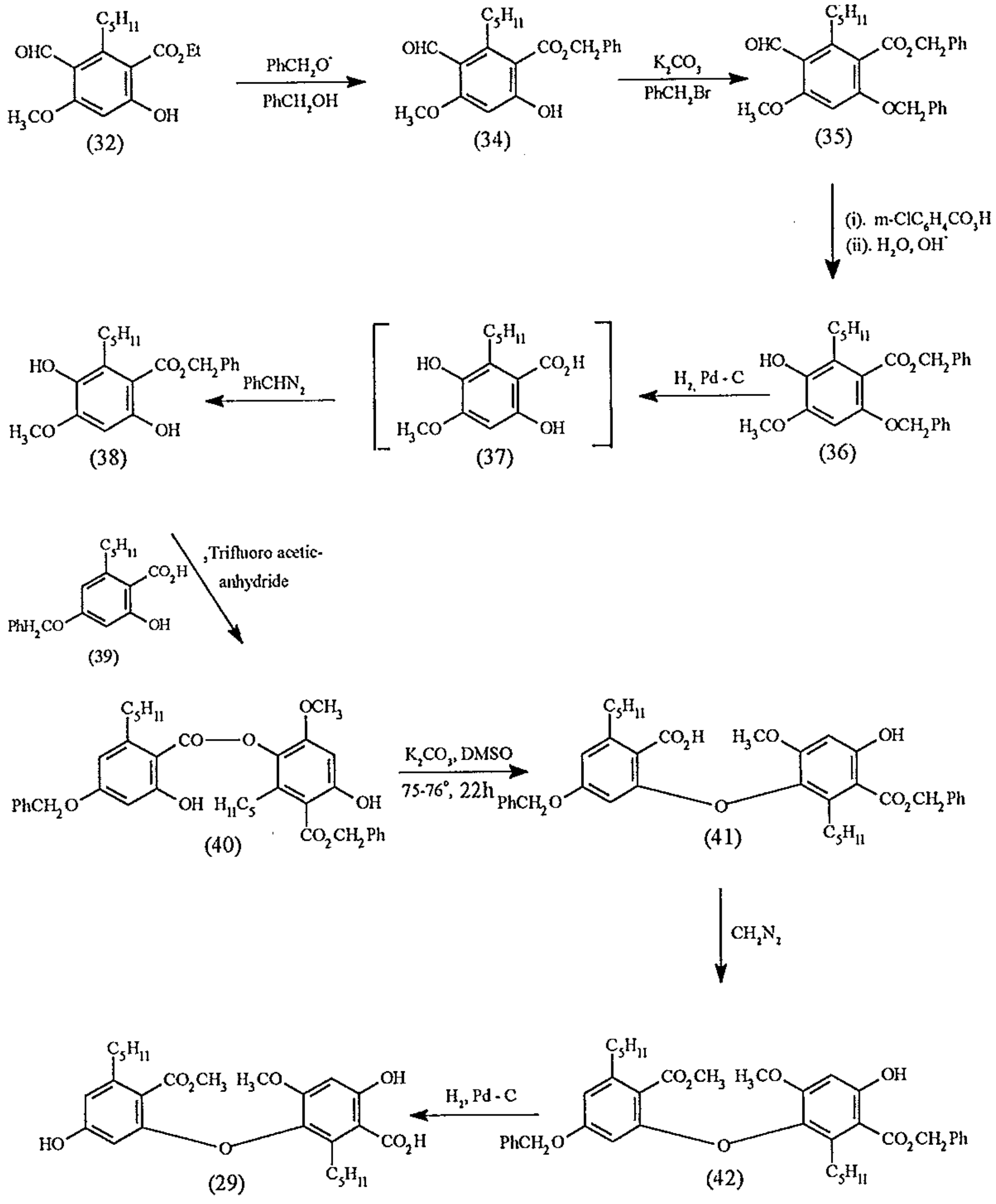
(27)



Scheme 3 Synthesis of dimethyl micareate (13) via Smiles rearrangement

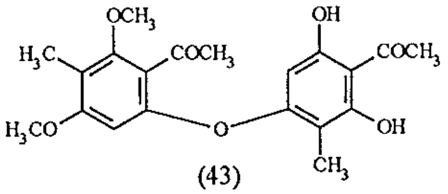
In 1986, the lichen diphenyl ether epiphorellic acid 1 (6-hydroxy-3-(5'-hydroxy-2'-methoxycarbonyl-3'-pentylphenoxy)-4-methoxy-2-pentylbenzoic acid) (29) was isolated from the Chilean lichen *Cornicularia epiphorella* (Nyl) Du Rietz (Quilhot, *et al.*, 1986). The diphenyl ether (29) was prepared by unambiguous synthesis (Elix and Jenie, 1989) as shown in **Scheme 4**. For the synthesis, 4-benzyloxy-2-hydroxy-6-pentylbenzoic acid (39) and ethyl 2,4-dimethoxy-6-pentylbenzoate (30) were used as starting materials and employed a Smiles rearrangement of precusor *meta*-depside (40) in the key step.





Scheme 4 Synthesis of epiphorellic acid 1 (29)

In 1979, Kan Chantrapromma and co-workers (Chantrapromma, Lertassawaphol and Mahandru, 1979) reported the isolation of a new diphenyl ether trivially named as crocynol (43) from the lichen *Crocynia spp.* (only the genus could be identified). The structural investigation of crocynol (43) was carried out on the basis of spectroscopic data.



(43)

The spectroscopic (^{1}H NMR and MS) properties of crocynol (43) obtained from *Crocynia spp.* were consistent with the structure (43). Unfortunately no synthetic sample of crocynol (43) was available for comparison. In an attempt to solve this problem, we have carried out the synthetic studies of crocynol derivatives as indicated in **Schemes 6** and 7.

Chapter 2

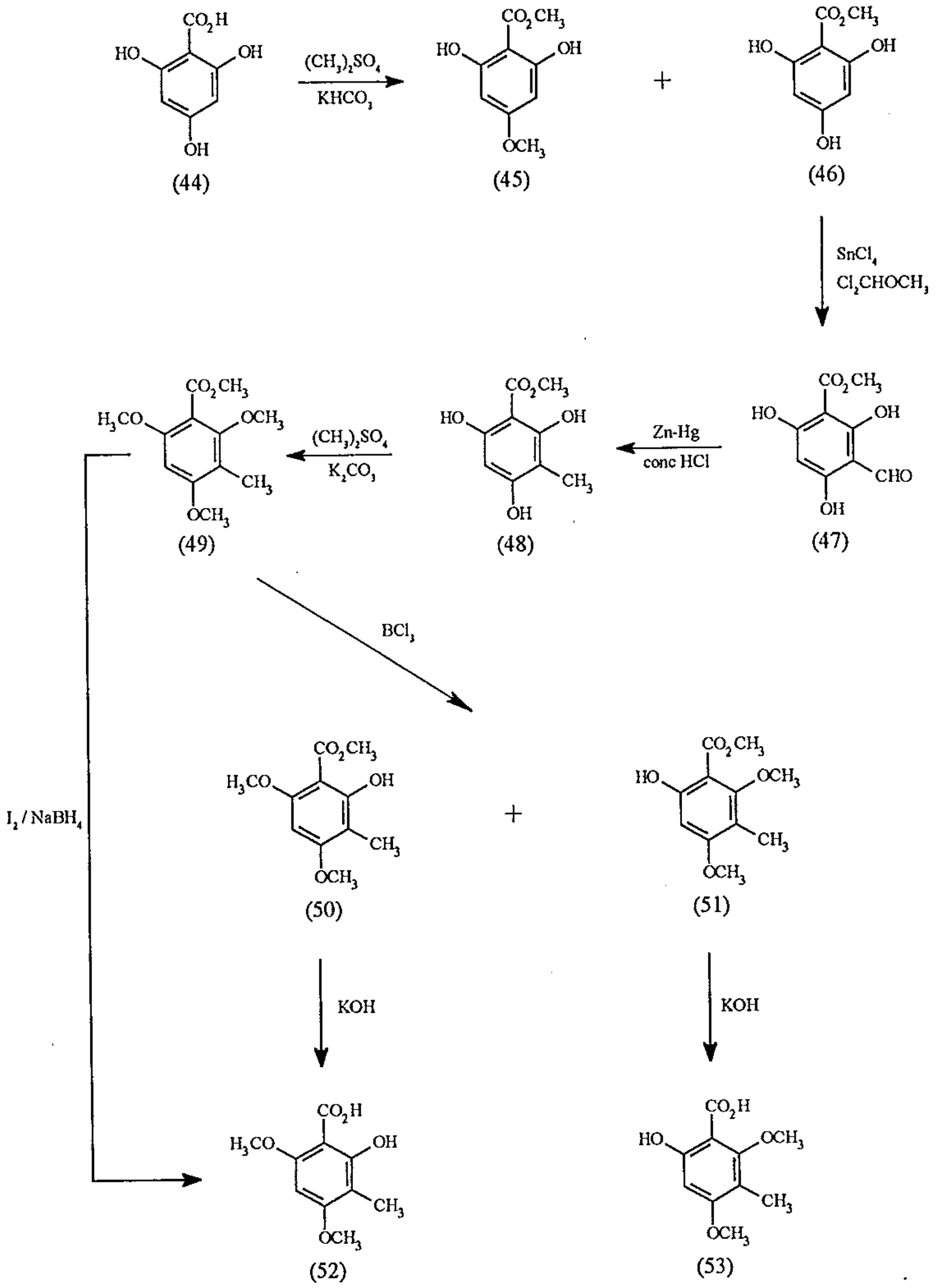
Result and Discussion

The synthetic route to 4-(2'-acetyl-3',5'-dimethoxy-6'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (57) and 4-(2'-acetyl-3',5'-dimethoxy-4'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (64) is outlined in **Schemes 6** and 7. These syntheses employed a novel Smiles rearrangement (Elix and Jenie, 1989) of precusor *para*-depsides (54) and (61) in the key step, to give the corresponding diphenyl ethers (55) and (62), respectively. For the syntheses, 4,6-dimethoxy-2-hydroxy-3-methylbenzoic acid (52), 2,4-dimethoxy-6-hydroxy-3-methylbenzoic acid (53) and methyl 3-methyl-2,4,6-trihydroxybenzoate (48) were used as starting materials (**Scheme 5**).

Synthesis of 4,6- Dimethoxy-2-hydroxy-3-methylbenzoic acid (52) and 2,4-Dimethoxy-6-hydroxy-3-methylbenzoic acid (53)

The selective methylation of 2,4,6- trihydroxybenzoic acid (44) with dimethyl sulfate and anhydrous potassium hydrogen carbonate afforded methyl 2,4,6- trihydroxy benzoate (46) (76 %) and methyl 2,6-dihydroxy-4-methoxybenzoate (45) (7 %) as the by-product (**Scheme 5**). Formylation of methyl 2,4,6-trihydroxy benzoate (46) by treatment with dichloromethyl methyl ether and stannic chloride gave methyl 3-formyl-2,4,6-trihydroxybenzoate (47) (83 %). The Clemmensen reduction of the aldehyde (47) afforded methyl 3-methyl-2,4,6-trihydroxybenzoate (48) (94 %) and subsequent methylation of the compound (48) with excess dimethyl sulfate in the presence of potassium carbonate gave methyl 3-methyl-2,4,6-trimethoxybenzoate (49) in high yield (93 %).

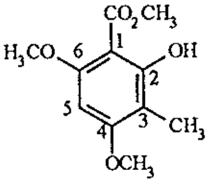
Demethylation of the ester (49) in three equivalents of boron trichloride at -15 °C afforded methyl 4,6-dimethoxy-2-hydroxy-3-methylbenzoate (50) (46 %) and methyl 2,4-dimethoxy-6-hydroxy-3-methylbenzoate (51) (47 %). The isomeric esters (50) and (51) were separated by column chromatography. The NOE difference spectrum is indeed

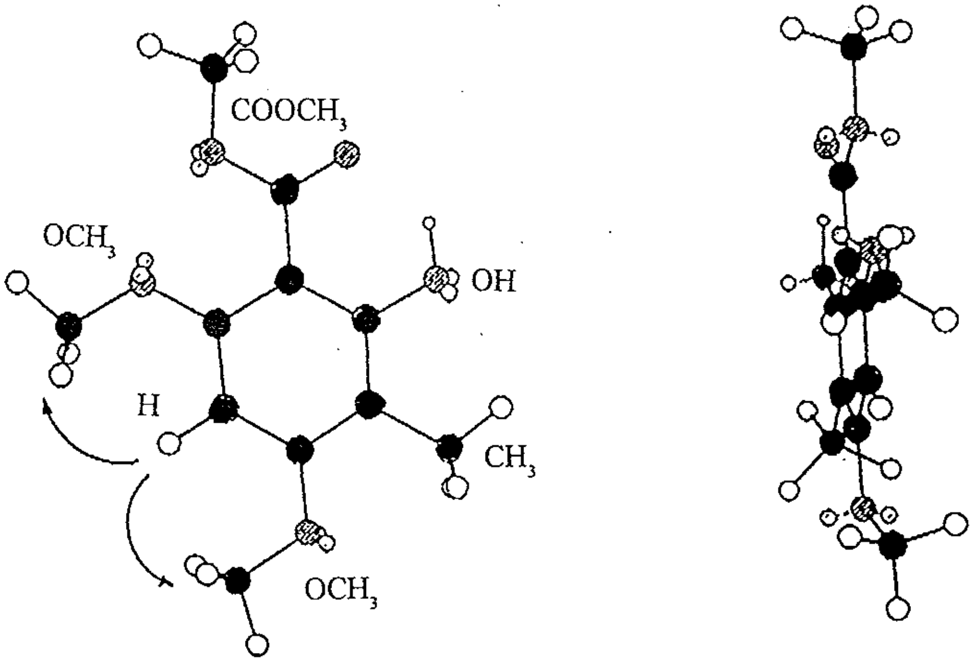


Scheme 5 Synthesis of 4,6-dimethoxy-2-hydroxy-3-methylbenzoic acid (52) and 2,4-dimethoxy-3-methylbenzoic acid (53)

a powerful tool for the identification of esters (50) and (51). Irradiation of the ester (50) at Ar-H showed enhancement of two methoxyl groups (2 x OCH_3). Thus, the ester (50) definitely has two methoxyl groups next to the Ar-H **(Figure 20)**. Similarly, irradiation of the ester (51) at Ar-H also showed the enhancement of one hydroxyl group (1 x OH) and one methoxyl group (1 x OCH_3) **(Figure 25)**. These results indicate that one hydroxyl group and one methoxyl group are next to the Aryl-H. Confirmation of this proposition was obtained by the ^{13}C NMR data. The ester (50) showed both OMe's in plane at 55 ppm **(Table 1)** while the ester (51) indicated 1 x OMe in plane and another out of plane (60 ppm) **(Table 2)**. The structures (50) and (51) are depicted in **Figures 1** and **2**.

Table 1 ^{13}C NMR assignments (δ) of methyl 4,6-dimethoxy-2-hydroxy-3-methyl benzoate (50)

Carbon	δ (ppm)	
C1	96.6	 (50)
C2	162.2	
C3	105.8	
C4	162.8	
C5	87.1	
C6	160.6	
1-CO_2CH_3	172.0	
1-CO_2CH_3	52.2	
3-CH_3	7.52	
4-OCH_3 6-OCH_3	55.47 / 56.23	

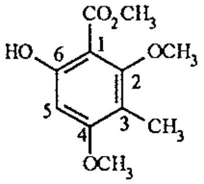


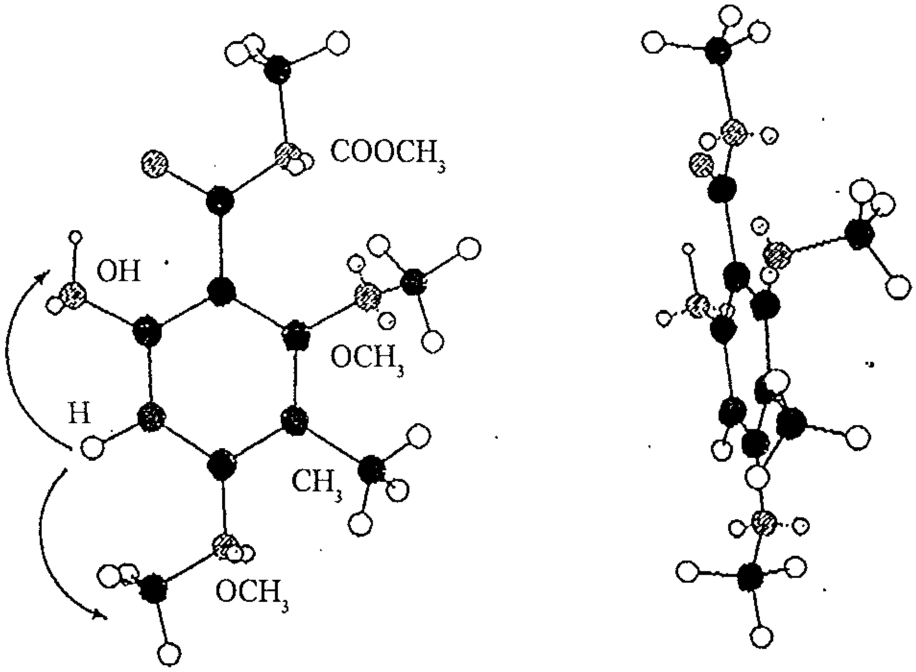
Expect NOE's to 2 x OCH_3

Side view : all atoms " in plane "

Figure 1 The structure of methyl 4,6-dimethoxy-2-hydroxy-3-methyl benzoate (50)

Table 2 ^{13}C NMR assignments (δ) of methyl 2,4-dimethoxy-6-hydroxy-3-methyl benzoate (51)

Carbon	δ (ppm)	
C1	99.9	 (51)
C2	159.6	
C3	112.5	
C4	163.9	
C5	95.6	
C6	163.1	
1-CO_2CH_3	171.2	
1-CO_2CH_3	52.4	
2-OCH_3	61.5	
3-CH_3	8.2	
4-OCH_3	55.7	



Expect NOE·s to 1 x OCH_3 (strong) and 1 x OH (weak) group.

Side view : one OCH_3 group " out of plane "

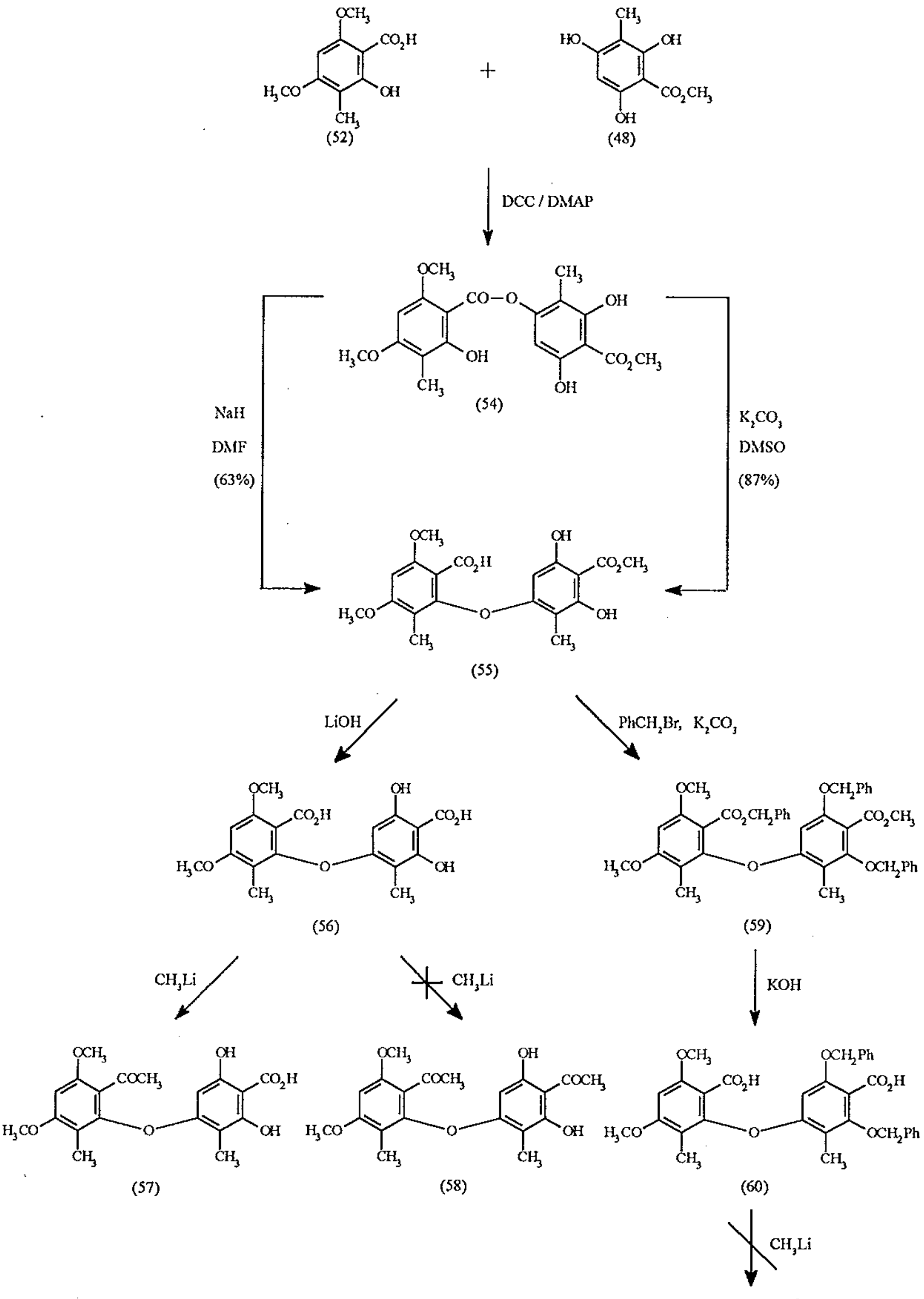
Figure 2 The structure of methyl 2,4-dimethoxy-6-hydroxy-3-methyl benzoate (51)

Hydrolysis of the ester groups of the compounds (50) and (51) with potassium hydroxide in aqueous dimethyl sulfoxide gave 4,6-dimethoxy-2-hydroxy-3-methylbenzoic acid (52) (87 %) and 2,4-dimethoxy-6-hydroxy-3-methylbenzoic acid (53) (89 %), respectively. However, the treatment of methyl 3-methyl-2,4,6-trimethoxybenzoate (49) with iodine and sodium borohydride at room temperature effected selective demethylation and concomitant decarboxylation to afford the acid (52) in moderate yield (71 %).

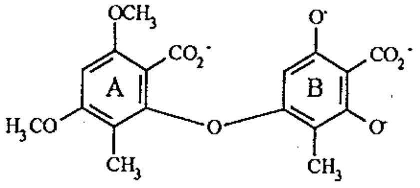
Synthesis of 4-(2'-acetyl-3',5'-dimethoxy-6'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (57)

The condensation between the acid (52) and the ester (48) in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) gave the depside (54) in high yield (96 %) (**Scheme 6**). Regioselective esterification of the phenolic ester (48) occurred at the less hindered, non-or weakly intramolecularly hydrogen-bonded hydroxyl group of each ester (Elix, *et al.*, 1990). Treatment of the depside (54) with anhydrous potassium carbonate in dimethyl sulfoxide at room temperature, effected the Smiles rearrangement and afforded the corresponding diphenyl ether (55) (87 %). Alternatively, treatment of the depside (54) with sodium hydride in N,N'-dimethylformamide (DMF) gave the diphenyl ether (55) in moderate yield (63 %). Attempted hydrolysis of the diphenyl ether (55) with potassium hydroxide in dimethylsulfoxide and water at 90-95 °C for 5 h gave the acid (56) (42 %), the acid (52) (16 %), unidentified products and the unchanged starting material. Furthermore, when this reaction was reacted at room temperature for 15 h, the acids (56) (53%) and (52) (9%) were obtained together with some unidentified products and the unchanged starting material. Fortunately, the acid (56) was obtained in high yield (94 %) when the reaction was carried out with lithium hydroxide in methanol and water at 60-65 °C for 10 h.

Stirring of the acid (56) with methyllithium in dry tetrahydrofuran at 0 °C, for 3 h afforded the acid (57) (7 %) together with some unidentified products and the unchanged starting material. The expected product (58) was not detected. It seems that the second carboxyl group (on ring B) of the acid (56) does not react with methyllithium because of the high density of negative charge (due to the phenoxy anions). This would severely deactivate the carboxyl group on the ring B as indicated in structure (65).



Scheme 6 Synthesis of 4-(2'-acetyl-3',5'-dimethoxy-6'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (57)

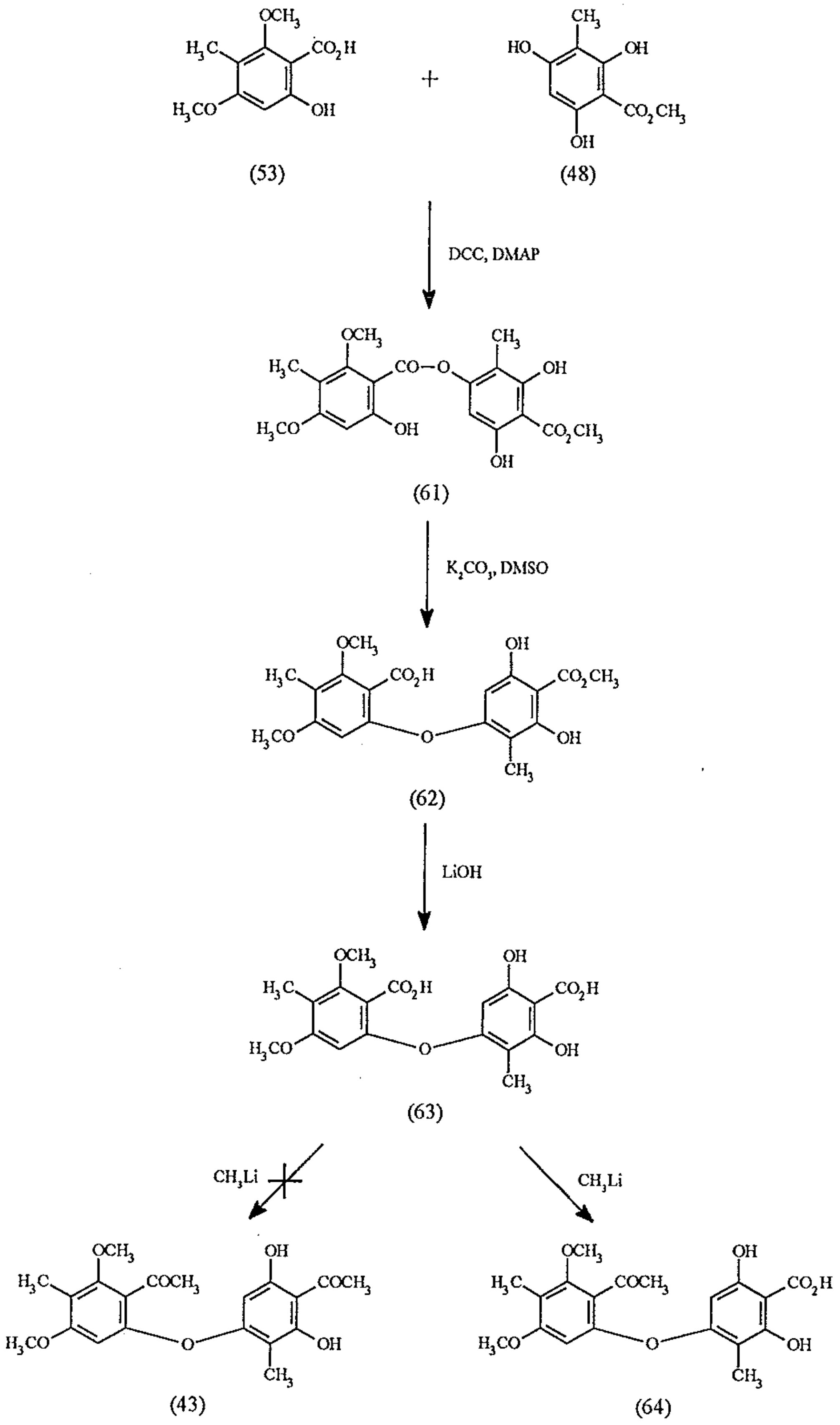


(65)

In an attempt to solve this problem, the hydroxy groups of the acid (55) were first protected. Benzylation of the diphenyl ether (55) with benzyl bromide and anhydrous potassium carbonate afforded the corresponding benzyl ester (59) (91 %). Treatment of the benzyl ester (59) with potassium hydroxide in aqueous dimethyl sulfoxide and water at 90-95 °C effected hydrolysis to afford the acid (60) (96 %). However, when the acid (60) was stirred with methyllithium either at 0 °C for 3 h or at room temperature for 18 h, only the unchanged starting material was recovered. It seems that the acid (59) did not react with methyllithium due to steric hindrance.

Synthesis of 4-(2'-acetyl-3',5'-dimethoxy-4'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (64)

The acid (64) was synthesized as indicated in **Scheme 7** via condensation of the acid (53) with the ester (48) in the presence of dicyclohexylcarbodiimide (DCC) and 4- dimethylaminopyridine (DMAP) in dry dichloromethane, the depside ester (61) was obtained in high yield (92 %). Subsequently, treatment of the depside (61) with anhydrous potassium carbonate in anhydrous dimethylsulfoxide afforded the corresponding diphenyl ether (62) (81 %). Hydrolysis of the diphenyl ether (62) by treatment with lithium hydroxide in methanol and water gave the acid (63) in high yield (96%). The acid (63) was stirred with methyllithium in dry tetrahydrofuran at 0 °C for 3 h to give the acid (64) (9%) together with unidentified products and the unchanged starting material. Again, the expected compound, crocynol (43) was not detected.



Scheme 7 Synthesis of 4-(2'-acetyl-3',5'-dimethoxy-4'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (64)

Chapter 3

Conclusion

In this studies, although we have developed an unambiguous synthetic approach to crocynol (43) but the final step using methyllithium as the reagent, converted only one carboxyl group of the diphenyl ether (63) in ring A to acetyl group. It seems that the second carboxyl group on ring B does not react with methyllithium because of the high density of negative charge of the phenoxy anions. However, when hydroxyls on ring B were protected with benzyl bromide, it was found that both carboxyls on ring A and B were unchanged. This is possibly due to the steric hindrance of bulky benzyl groups.

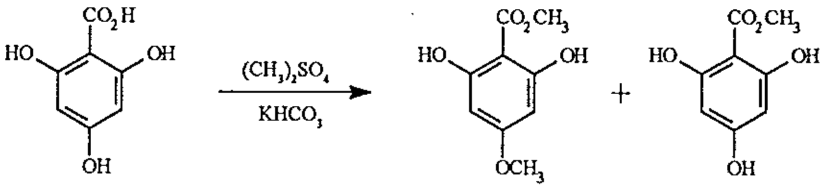
For future studies, alternative less bulky protecting reagents should be tried in order to overcome the final step.

Chapter 4

Experimental

Infrared spectra were determined on a Perkin-Elmer IR 783 and are recorded in cm^{-1}. Proton nuclear magnetic resonance spectra were recorded at 60 MHz on a JEOL-PM_X60 spectrometer, at 300 MHz on a Bruker AC - 300 spectrometer and at 500 MHz on a JEOL-JNM-A500 spectrometer with tetramethylsilane as internal standard. Chemical shifts were expressed in ppm (δ) ; multiplicity, s = singlet, d = doublet, t = triplet, q = guartet, m = multiplet. Mass spectra were recorded on a TRIO-2000 and AEIMS-902 spectrometer operating at 70 eV. Melting points were measured on electrothermal melting point apparatus and are uncorrected. All layer chromatograms were carried out on glass plates using silica gel 60 GF_{254} and PF_{254} (Merck) as adsorbent. Bands were detected by exposure to short wavelength ultraviolet light. Column chromatography utilized silica gel 60 (70-230 mesh ASTM, Merck). Dry column flash chromatography was obtained with silica gel 60 GF_{254} (Merck) and all organic extracts were dried over anhydrous sodium sulfate (Na_2SO_4).

Methyl 2,4,6-Trihydroxybenzoate (46)


(44) (45) (46)

Dimethyl sulfate (0.15 ml, 1.16 mmole) was added dropwise to the stirred mixture of 2,4,6-dihydroxybenzoic acid (44) (200 mg, 1.06 mmole) and anhydrous potassium hydrogen carbonate (210 mg, 2.13 mmole) in dry acetone (5 ml) in a nitrogen atmosphere at room temperature. The mixture was stirred at room temperature for 4 h, followed by addition of 6 N ammonium hydroxide (5 ml) and stirring for 0.5 h. Then the mixture was poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with 5% sodium hydrogen carbonate, saturated brine, dried and the solvent removed. The residue was purified by preparative t.l.c. with 10 % ethyl acetate \ chloroform as eluent. The first band yielded methyl 2,6-dihydroxy-4-methoxybenzoate (45) (15 mg, 7 %) which was recrystallized from chloroform as colourless crystals, m.p. 123-124 °. The second band was concentrated to give methyl 2,4,6-trihydroxybenzoate (46) (150 mg, 76 %) and recrystallized from chloroform as colourless crystals, m.p. 178-180 °.

Methyl 2,6-dimethoxy-4-methoxybenzoate (45)

IR (KBr, cm^{-1}) : 1040, 1660, 2860, 2960, 3120, 3440

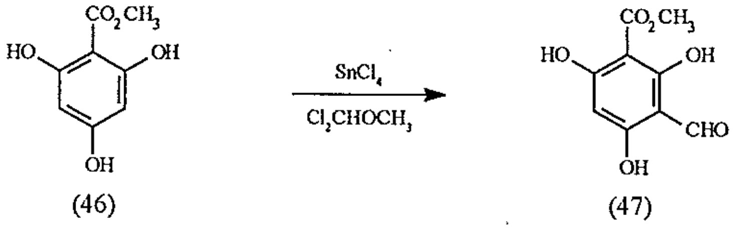
NMR ($CDCl_3$) δ : 3.75, 4.00 (s, OCH_3)
: 5.96 (s, 2 x ArH)
: 9.72 (s, 2 x OH)

Methyl 2,4,6-trihydroxybenzoate (46)

IR (KBr, cm^{-1}) : 1375, 1650, 2970, 3190, 3440

NMR ($CDCl_3$ + CD_3COCD_3) δ : 4.03 (s, OCH_3)
: 5.97 (s, 2 x ArH)
: 8.80 (s, OH)
: 9.80 (s, 2 x OH)

Methyl 3-formyl-2,4,6-trihydroxybenzoate (47)

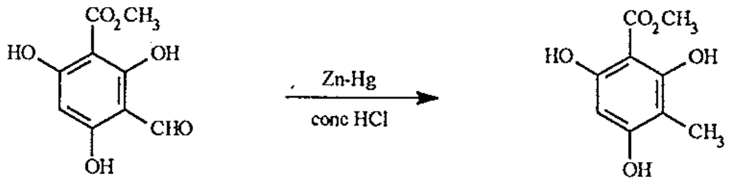


A solution of methyl 2,4,6-trihydroxybenzoate (46) (3.00 g, 16.30 mmole) and stannic chloride (5.75 ml, 48.90 mmole) in dry dichloromethane (100 ml) was stirred in an atmosphere of nitrogen at 0 °C while dichloromethyl methyl ether (5.50 ml, 48.90 mmole) was added dropwise over 0.5 h. The cooling bath was removed and the mixture was stirred at room temperature for 4 h and then poured into cold dilute hydrochloric acid and extracted with ether. The organic layer was washed with water, saturated brine, dried and the solvent removed. The residue was purified by dry-column flash chromatography with 50 % hexane\ dichloromethane as eluent to give methyl 3-formyl-2,4,6,-trihydroxybenzoate (47) (2.87 g, 83 %) and recrytallized from dichloromethane as colourless crystals, m.p. 160-162 °(d).

IR (KBr, cm^{-1}) : 1650, 1690, 3080, 3360

NMR ($CDCl_3$) δ : 4.05 (s, OCH_3)
: 5.93 (s, ArH)
: 10.00, 11.03 (b, 2 x OH)
: 10.13 (s, CHO)
: 12.63 (s, OH)

Methyl 3-methyl-2,4,6-trihydroxybenzoate (48)



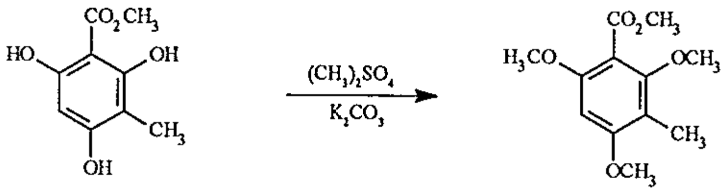
(47) (48)

A mixture of zinc powder (34.62 g, 530.66 mmole), mercury (II) chloride (1.92 g, 7.10 mmole), concentrated hydrochloric acid (17 ml) and water (23 ml) was stirred for 5 minutes. The aqueous solution was decanted and replaced by concentrated hydrochloric acid (56 ml) and water (45 ml). The mixture was then heated to reflux and a solution of methyl 3-formyl-2,4,6-trihydroxybenzoate (47) (7.50 g, 35.38 mmole) in hot ethanol (150 ml) was added at such a rate as to prevent crystallization in the funnel. The reaction mixture was then boiled under reflux for 1 h, cooled, diluted with water and extracted with ether. The organic layer was washed with water, saturated brine, dried and the solvent removed. The residue was recrystallized from chloroform to give methyl 3-methyl-2,4,6-trihydroxybenzoate (48) (6.56 g, 94 %) as colourless crystals, m.p. 140-142°.

IR (KBr, cm^{-1}) : 1375, 1650, 2880, 2940, 3000, 3410

NMR ($CDCl_3$ + CD_3COCD_3) δ : 2.02 (s, CH_3)
: 4.00 (s, OCH_3)
: 5.97 (s, ArH)
: 8.37, 9.42, 10.13 (s, 3 x OH)

Methyl 3-methyl-2,4,6-trimethoxybenzoate (49)



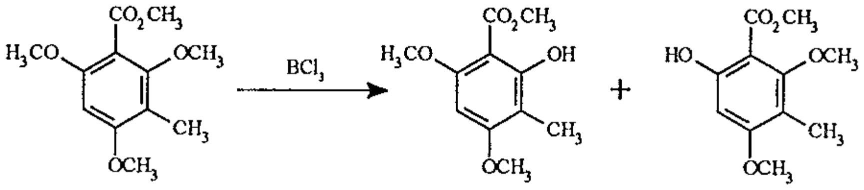
(48) (49)

A mixture of methyl 2,4,6-trihydroxybenzoate (48) (5.00 g, 25.25 mmole), anhydrous potassium carbonate (42.00 g, 303.00 mmole) and dimethyl sulfate (17.00 ml,176.76 mmole) was stirred and heated under reflux in dry acetone (150 ml) in an atmosphere of nitrogen for 24 h. The mixture was cooled to room temperature, added 6 N ammonium hydroxide (20 ml) and stirred for a further 0.5 h. The mixture was poured into cold dilute hydrochloric acid and extracted with ether. The organic layer was washed with 5% sodium hydroxide, water, saturated brine, dried and the solvent removed. The residue was purified by column chromatography with dichloromethane as eluent to give methyl 3- methyl-2,4,6-trimethoxy- benzoate (49) (5.68 g, 93 %) and recrystallized from hexane in dichromethane as colourless crystals, m.p. 77-78°.

IR (KBr, cm^{-1}) : 1370, 1740, 2860, 2960, 3000

NMR ($CDCl_3$) δ : 2.07 (s, CH_3)
: 3.73, 3.80, 3.83, 3.90 (s, 4 x OCH_3)
: 6.02 (s, ArH)

Methyl 4,6-dimethoxy-2-hydroxy-3-methylbenzoate (50) and Methyl 2,4-dimethoxy-6-hydroxy-3-methylbenzoate (51)



(49) (50) (51)

A solution of boron trichloride (3.91 g, 33.33 mmole) in hexane (33 ml) was added dropwise to a stirred solution of methyl 3-methyl-2,4,6-trimethoxybenzoate (49) (2.00 g, 8.33 mmole) in dry dichloromethane (40 ml) in an atmosphere of nitrogen at -15 °C. The mixture was stirred at -15 °C for a further 1.30 h, then poured into ice-water and extracted with ethyl acetate. The organic layer was washed with water, saturated brine, dried and the solvent removed. The residue was purified by column chromatography with 20 % ethyl acetate \ hexane as eluent. The first fraction yielded methyl 2,4-dimethoxy-6-hydroxy-3-methylbenzoate (51) (0.94 g, 47 %) which was recrystallized from petroleum ether \ dichloromethane as colourless crystals, m.p. 103-104°. The second fraction yielded methyl 4,6-dimethoxy-2-hydroxy-3-methylbenzoate (50) (0.91 g, 46 %) which was recrystallized from hexane \ dichloromethane as colourless crystals, m.p. 146-148°.

Methyl 4,6-dimethoxy-2-hydroxy-3-methylbenzoate (50)

IR (KBr, cm^{-1}) : 1370, 1660, 3280, 3000

NMR ($CDCl_3$) δ : 2.13 (s, CH_3)
: 3.86, 3.87, 3.92 (s, 3 x OCH_3)
: 6.00 (s, ArH)
: 12.20 (s, OH)

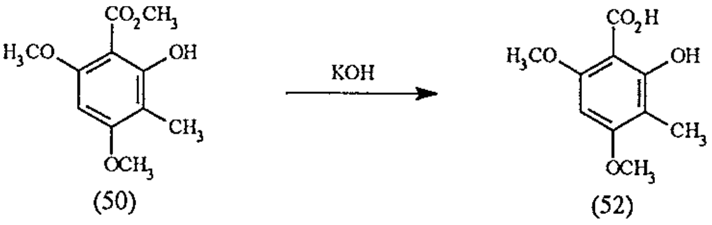
Methyl 2,4-dimethoxy-6-hydroxy-3-methylbenzoate (51)

IR (KBr, cm^{-1}) : 1650, 2870, 3000, 3300-3600

NMR ($CDCl_3$) δ : 2.05 (s, CH_3)
: 3.72, 3.79, 3.97 (s, 3 x OCH_3)
: 6.29 (s, ArH)
: 11.59 (s, OH)

4,6-Dimethoxy-2-hydroxy-3-methylbenzoic acid (52)

Method A

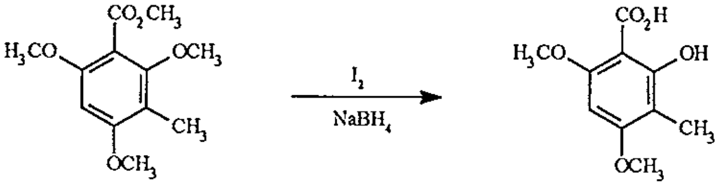


A mixture of methyl 4,6-dimethoxy-2-hydroxy-3-methylbenzoate (50) (1.70 g, 7.52 mmole), potassium hydroxide (1.69 g, 30.10 mmole),water (15 ml) and dimethyl sulfoxide (50 ml) was stirred and heated at 90 °C for 3 h. The mixture was then cooled and poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water, saturated brine and dried and the solvent removed. The residue was recrystallized from ethyl acetate to give 4,6-dimethoxy-2-hydroxy-3-methylbenzoic acid (52) (1.38 g, 87%) as colourless crystals, m.p. 180-181°.

IR (KBr, cm^{-1}) : 1670, 3000, 2600-3400

NMR (CDCl$_3$) δ : 2.03 (s, CH$_3$)
: 3.87, 4.00 (s, 2 x OCH$_3$)
: 6.00 (s, ArH)
: 11.13, 12.50 (s, 2 x OH)

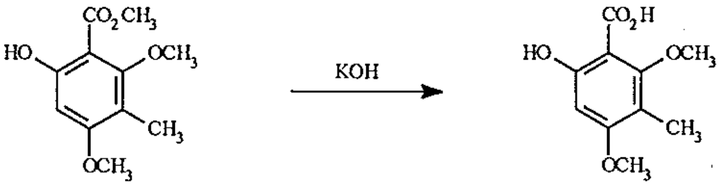
Method B



(49) (52)

A mixture of methyl 3-methyl-2,4,6-trimethoxybenzoate (49) (200 mg, 0.93 mmole), iodine (300 mg, 1.16 mmole) and sodium borohydride (130 mg, 3.33 mmole) in dry chloroform was stirred in a nitrogen atmosphere at 0-5 °C for 3 h. The mixture was then stirred at room temperature for a further 31 h, poured into aqueous sodium hydroxide (0.1 N, 20 ml) and extracted with ether. Upon acidification of the aqueous basic solution with dilute hydrochloric acid and crystallization of the precipitate from ethyl acetate, 4,6-dimethoxy-2-hydroxy-3-methylbenzoic acid (52) (130 mg, 71 %) was obtained as colourless crystals, m.p. 180-181°.

2,4-Dimethoxy-6-hydroxy-3-methylbenzoic acid (53)



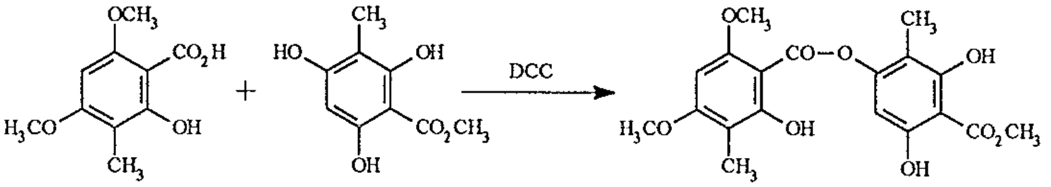
(51) (53)

A mixture of methyl 2,4-dimethoxy-6-hydroxy-3-methylbenzoate (51) (1.70 g, 7.52 mmole), potassium hydroxide (1.69 g, 30.10 mmole), water (15 ml) and dimethyl sulfoxide (50 ml) was stirred and heated at 90 °C for 3 h. The mixture was then cooled and poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water, saturated brine and dried and the solvent removed. The residue was recrystallized from ethyl acetate to give 2,4-dimethoxy-2-hydroxy-3-methylbenzoic acid (53) (1.42 g, 90%) as colourless crystals, m.p. 145-146°.

IR (KBr, cm^{-1}) : 1700, 2300-3300, 3000

NMR ($CDCl_3$) δ : 2.03 (s, CH_3)
: 3.80, 3.83 (s, 2 x OCH_3)
: 6.27 (s, ArH)
: 11.77, 12.00 (s, 2 x OH)

Methyl 2,6-dihydroxy-4-(4',6'-dimethoxy-2'-hydroxy-3'-methylbenzoyloxy)-3-methylbenzoate (54)



(52) (48) (54)

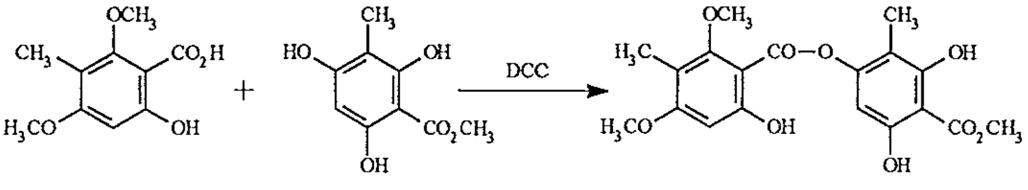
To a stirred solution of 4,6-dimethoxy-2-hydroxy-3-methylbenzoic acid (52) (186 mg, 0.87 mmole) in dry dichloromethane (20 ml) was added methyl 3-methyl-2,4,6-trihydroxybenzoate (48) (174 mg, 0.87 mmole), 4-dimethylaminopyridine (DMAP) (10 mg, 0.09 mmole) and cooled to 0-5°C in an atmosphere of nitrogen. N,N'-Dicyclohexylcarbodiimide (DCC) (0.54 g, 2.63 mmole) was added to the reaction mixture which was then stirred for 30 min at 0-5°C and 3 h at room temperature. Precipitated urea was then filtered off and the filtrate evaporated. The residue was purified by preparative t.l.c. using dichloromethane as eluent to give the depside (54) (328 mg, 96 %) which was recrystallized from petroleum ether \ dichloromethane as colourless crystals, m.p. 173-174° (d).

IR (KBr, cm^{-1}) : 1650, 1690, 2860, 2880, 2940, 3100, 3400

NMR ($CDCl_3$) δ : 2.00, 2.03 (s, 2 x CH_3)
: 3.90 (s, 2 x OCH_3)
: 4.06 (s, OCH_3)
: 6.03, 6.33 (s, 2 x ArH)
: 9.37, 10.30, 11.48 (s, 3 x OH)

MS (m/e, 392) : M^+, (20 %)
: 360, (18 %)
: 212, (1.2 %)
: 195, (81 %)
: 194, (56 %)
: 181, (5 %)
: 167, (25 %)
: 166, (57 %)

Methyl 2,6-dihydroxy-4-(2',4'-dimethoxy-6'-hydroxy-3'-methylbenzoyloxy)-3-methylbenzoate (61)



(53) (48) (61)

To a stirred solution of 2,6-dimethoxy-6-hydroxy-3-methylbenzoic acid (53) (30 mg, 0.15 mmole) in dry dichloromethane (10 ml) was added methyl 3-methyl-2,4,6-trihydroxybenzoate (48) (28 mg, 0.15 mmole), 4-dimethylaminopyridine (DMAP) (1 mg, 0.02 mmole) and cooled to 0-5 °C in an atmosphere of nitrogen. N,N'-Dicyclohexylcarbodiimide (DCC) (44 mg, 0.21 mmole) was added to the reaction mixture which was then stirred for 30 min at 0-5 °C and 3 h at room temperature. Precipitated urea was then filtered off and the filtrate evaporated. The residue was purified by preparative t.l.c. using 50% hexane \ dichloromethane as eluent to give the depside (61) (51 mg, 92 %) which was recrystallized from petroleum ether \ dichloromethane as colourless crystals, m.p. 143-144°.

IR (KBr, cm^{-1}) : 1630, 1670, 2860, 3000, 3200-3600

NMR ($CDCl_3$) δ : 2.00, 2.06 (s, 2 x CH_3)

: 3.77, 3.81, 4.03 (s, 3 x OCH_3)

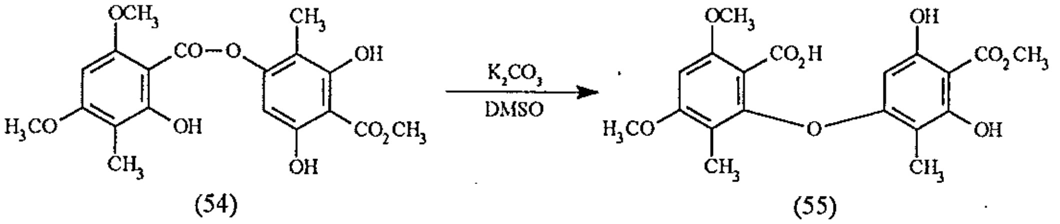
: 6.22 (s, 2 x ArH)

: 9.27, 10.17, 11.03 (s, 3 x OH)

MS (m/e, 392) : M^+, (3 %)
: 360, (1 %)
: 212, (1.2 %)
: 195, (100 %)
: 194, (26 %)
: 181, (1 %)
: 167, (13 %)
: 166, (60 %)

2-(3',5'-Dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (55)

Method A

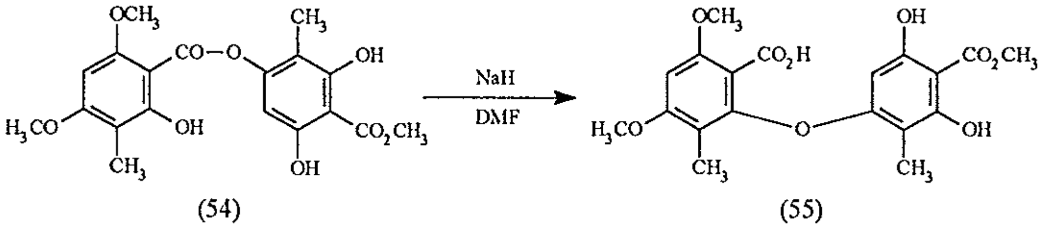


A mixture of methyl 2,6-dihydroxy-4-(4',6'-dimethoxy-2'-hydroxy-3'-methylbenzoyloxy)-3-methylbenzoate (54) (382 mg, 0.98 mmole) and anhydrous potassium carbonate (200 mg, 1.46 mmole) in anhydrous dimethyl sulfoxide (15 ml) was stirred in an atmosphere of nitrogen at room temperature for 12 h. The reaction mixture was then acidified with cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with several portions of water, saturated brine and then dried. After evaporation of the solvent the crude product was purified by preparative t.l.c. with 1 % acetic acid \ 40 % hexane \ 59 % ethyl acetate as eluent. The major band yielded the diphenyl ether (55) (332 mg, 87 %) which was recrystallized from hexane \ ethyl acetate as colourless crystals, m.p. 204-206° (d).

IR (KBr, cm^{-1})	: 1140, 1270, 1300, 1650-1700, 2400-3500, 3000
NMR ($CDCl_3 + CD_3COCD_3$) δ	: 1.87, 2.12 (s, 2 x CH_3)
	: 3.90 (s, 2 x OCH_3)
	: 4.03 (s, OCH_3)
	: 5.15, 6.48 (s, 2 x ArH)
	: 4.50 (b, OH)
	: 9.39, 10.27 (s, 2 x OH)

MS (m/e, 392) : M^+, (80 %)
: 347, (2.4 %)
: 212, (2 %)
: 195, (100 %)
: 194, (26 %)
: 166, (2 %)

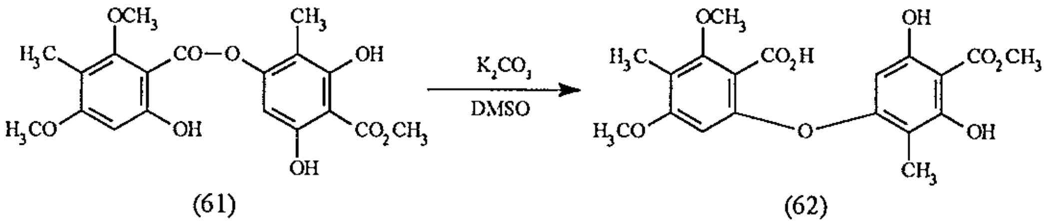
Method B



(54) (55)

Sodium hydride (24 mg, 1.02 mmole, 50 % dispersion in oil) was added to a solution of the depside (54) (78 mg, 0.19 mmole) in dry N,N-dimethylformamide (7 ml) and stirred in an atmosphere of nitrogen at room temperature for 12 h. The reaction mixture was then poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed repeatedly with water, saturated brine and dried. The solvent was evaporated and the residue purified by preparative t.l.c. with 1 % acetic acid / 40 % hexane / 59 % ethyl acetate as eluent. The major band afforded the diphenyl ether (55) (49 mg, 63 %).

6-(3',5'-Dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-2,4- dimethoxy-3-methylbenzoic acid (62)



A mixture of methyl 2,6-dihydroxy-4-(2',4'-dimethoxy-6'-hydroxy-3'-methylbenzoyloxy)-3-methylbenzoate (61) (74 mg, 0.02 mmole) and anhydrous potassium carbonate (40 mg, 0.28 mmole) in anhydrous dimethyl sulfoxide (10 ml) was stirred in an atmosphere of nitrogen at room temperature for 12 h. The reaction mixture was then acidified with cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with several portions of water, saturated brine and then dried. After evaporation of the solvent the crude product was purified by preparative t.l.c. with 1 % acetic acid / 40 % hexane / 59 % ethyl acetate as eluent. The major band yielded the diphenyl ether (62) (60 mg, 81 %) which was recrystallized from hexane / ethyl acetate as colourless crystals, m.p. 174-176°(d).

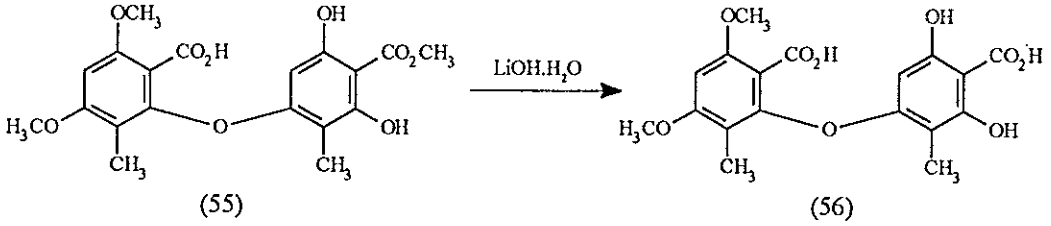
IR (KBr, cm^{-1}) : 1120, 1150, 1300, 1650-1700, 2400-3500, 3000

NMR ($CDCl_3 + CD_3COCD_3$) δ : 2.10, 2.13 (s, 2 x CH_3)
: 3.77, 3.83, 4.00 (s, 3 x OCH_3)
: 5.80, 6.27 (s, 2 x ArH)
: 5.93, 9.43 (b, 2 x OH)
: 10.23 (s, OH)

MS (m/e, 392) : M^+, (90 %)
: 347, (7 %)
: 212, (2 %)
: 195, (100 %)
: 194, (48 %)
: 166, (15 %)

2-(3',5'-dihydroxy-4'-carboxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (56)

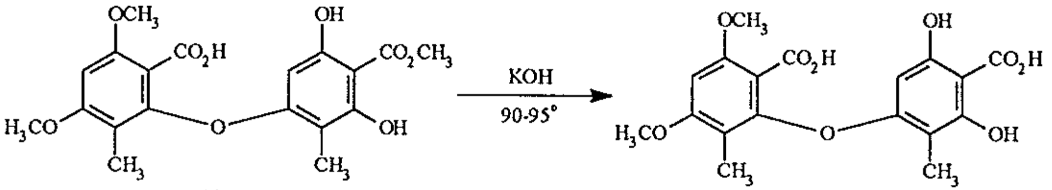
Method A



A mixture of 2-(3',5'-dihydroxy-4'-methoxycarbonyl-2'- methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (55) (200 mg, 0.51 mmole), lithium hydroxide hydrate (128 mg, 3.06 mmole), water (7 ml) and methanol (15 ml) was stirred and refluxed for 10 h. The mixture was then cooled and poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried. The solvent was then removed to give the crude diacid (56) (181 mg, 94 %).

IR (KBr, cm^{-1})	: 1400, 1600, 1700, 2400-3500
NMR ($CDCl_3$ + CD_3OD) δ	: 1.87, 2.12 (s, 2 x CH_3)
	: 3.87 (s, 2 x OCH_3)
	: 5.45, 6.30 (s, 2 x ArH)

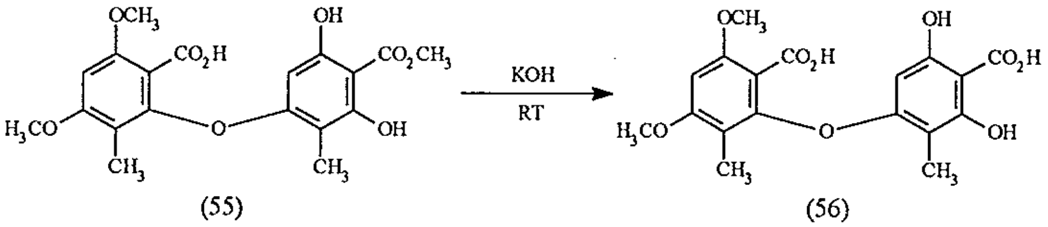
Method B



(55) (56)

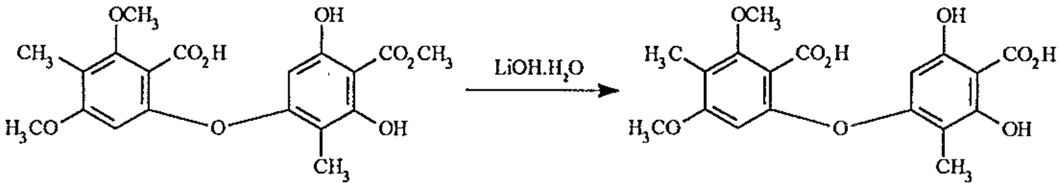
A mixture of the acid (55) (200 mg, 0.51 mmole), potassium hydroxide (114 mg, 2.04 mmole), water (1 ml) and dimethyl sulfoxide (10 ml) was stirred and heated at 90-95 °C for 5 h. The mixture was then cooled and poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with several portions of water, saturated brine, dried and the solvent removed. The residue was purified by preparative t.l.c. with 2 % acetic acid / 18 % methanol / 80 % chloroform as eluent. The first band yielded the acid (53) (17 mg, 16 %) and the second band yielded the acid (56) (82 mg, 42 %).

Method C



A mixture of the acid (55) (100 mg, 0.25 mmole), potassium hydroxide (57 mg, 1.02 mmole), water (1 ml) and dimethyl sulfoxide (6 ml) was stirred at room temperature for 10 h. The mixture was poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with several portions of water, saturated brine, dried and the solvent removed. The residue was purified by preparative t.l.c. with 2 % acetic acid / 18 % methanol / 80 % chloroform as eluent. The first band yielded the acid (53) (4 mg, 9 %) and the second band yielded the acid (56) (51 mg, 53 %).

6-(3',5'-Dihydroxy-4'-carboxy-2'-methylphenoxy)-2,4-dimethoxy-3-methylbenzoic acid (63)



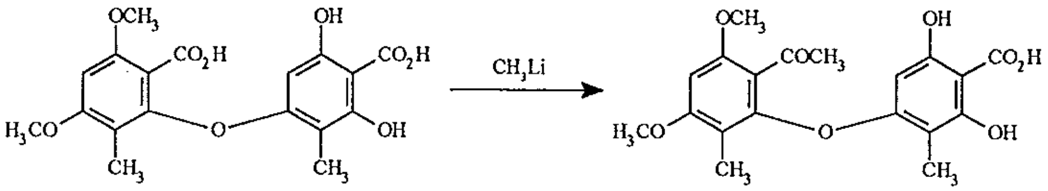
(62) (63)

A mixture of 6-(3',5'-dihydroxy-4'-methoxycarbonyl-2'- methylphenoxy)-2,4-dimethoxy-3-methylbenzoic acid (62) (200 mg, 0.51 mmole), lithium hydroxide hydrate (128 mg, 3.06 mmole), water (7 ml) and methanol (15 ml) was stirred and refluxed for 10 h. The mixture was then cooled and poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried. The solvent was then removed to give the crude diacid (63) (184 mg, 96 %).

IR (KBr, cm^{-1}) : 1700, 2500-3600, 3000

NMR ($CDCl_3$ + CD_3OD) δ : 2.00, 2.02 (s, 2 x CH_3)
: 3.65, 3.75 (s, 2 x OCH_3)
: 5.73, 6.18 (s, 2 x ArH)

4-(2'-acetyl-3',5'-dimethoxy-6'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (57)



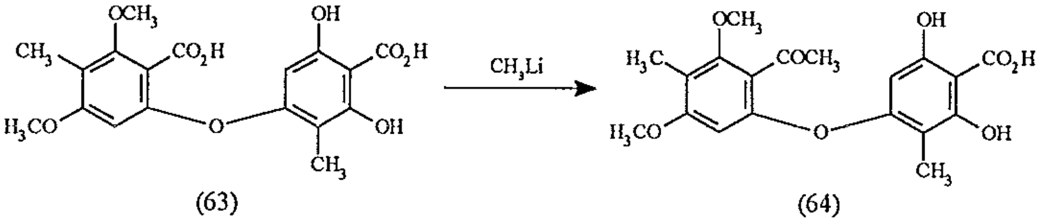
(56) (57)

A stirred solution of the acid (56) (50 mg, 0.13 mmole) in dry tetrahydrofuran (THF) (5 ml) in an atmosphere of nitrogen was cooled to 0 °C and then methyllithium was added repidly (2.6 ml, 2.64 mmole). After 3 h at 0 °C, the ice bath was then removed and the reaction mixture was stirred at room temperature for 24 h. Saturated ammonium chloride (20 ml) was rapidly added while stirring continued and the mixture was extracted with ether. The organic layer was dried and the solvent removed. The residue was purified by preparative t.l.c. with 20 % methanol / chloroform as eluent to give the acid (57) (3 mg, 7 %).

NMR ($CDCl_3$ + CD_3OD) δ : 1.91, 2.20 (s, 2 x CH_3)
: 2.65 (s, $COCH_3$)
: 3.94 (s, 2 x OCH_3)
: 5.42, 6.42 (s, 2 x ArH)

MS (m/e, 376) : M^+, (10 %)
: 358, (20 %)
: 195, (87 %)
: 193, (8 %)
: 178, (27 %)
: 167, (83 %)
: 150, (8 %)
: 149, (36 %)
: 121, (14 %)

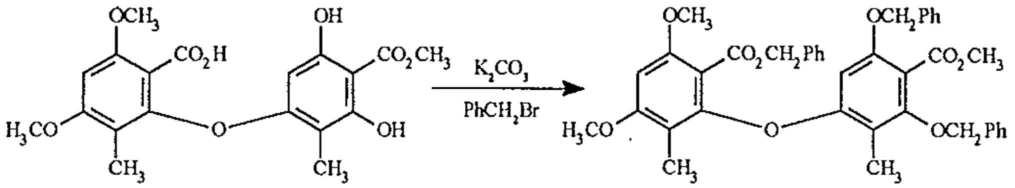
4-(2'-acetyl-3',5'-dimethoxy-4'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (64)



A stirred solution of the acid (63) (100 mg, 0.26 mmole) in dry tetrahydrofuran (THF) (5 ml) in an atmosphere of nitrogen was cooled to 0 °C and then methyllithium was added rapidly (5.2 ml, 5.29 mmole). After 3 h at 0 °C, the ice bath was then removed and the reaction mixture stirred at room temperature for 24 h. Saturated ammonium chloride (30 ml) was rapidly added while stirring continued and the mixture was extracted with ether. The organic layer was dried and the solvent removed. The residue was purified by preparative t.l.c. with 20% methanol in chloroform as eluent to give the acid (64) (9 mg, 9 %).

NMR ($CDCl_3$ + CD_3OD) δ	: 2.08, 2.09 (s, 2 x CH_3)
	: 2.67 (s, $COCH_3$)
	: 3.76, 3.82 (s, OCH_3)
	: 5.73, 6.27 (s, 2 x ArH)
MS (m/e, 376)	: M^+, (2 %)
	: 358, (5 %)
	: 195, (10 %)
	: 193, (8 %)
	: 178, (2 %)
	: 167, (12 %)
	: 150, (4 %)
	: 149, (2 %)
	: 121, (11 %)

Benzyl 2-(4'-benzyloxycarbonyl-3',5'-dibenzyloxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoate (59)



(55) (59)

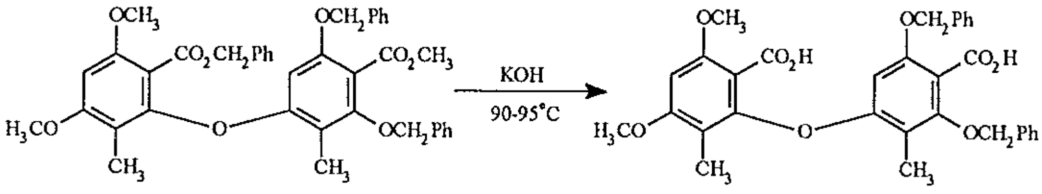
A mixture of the acid (55) (200 mg, 0.51 mmole), benzyl bromide (0.24 ml, 2.04 mmole) and potassium carbonate (64 mg, 4.59 mmole) in dry dimethyl sulfoxide (10 ml) was stirred in an atmosphere of nitrogen at room temperature for 24 h. The mixture was then poured into cold dilute hydrochloric acid and extracted with ether. The organic layer was washed with water, saturated brine, dried and the solvent evaporated. The residue was purified by preparative t.l.c. using 30 % hexane / dichloromethane as eluent to give the ester (59) (308 mg, 91 %).

IR (KBr, cm^{-1}) : 1160, 1130, 1275, 1730, 3000

NMR ($CDCl_3$) δ : 1.67, 2.06 (s, 2 x CH_3)
: 3.77 (s, OCH_3)
: 3.83 (s, 2 x OCH_3)
: 4.67, 4.87, 5.03 (s, 3 x OCH_2)
: 5.83, 6.33 (s, 2 x ArH)
: 7.15 (m, 3 x Ph)

MS (m/e, 662) : M^+, (8 %)
: 377, (1 %)
: 286, (1 %)
: 91, (100 %)
: 65, (7 %)

2-(4'-carboxy-3',5'-dibenzyloxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (60)



(59) (60)

A mixture of the ester (59) (259 mg, 0.39 mmole), potassium hydroxide (175 mg, 3.12 mmole), water (6 ml) and dimethyl sufoxide (18 ml) was stirred and heated at 90-95 °C for 10 h. The solution was then cooled and poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water, saturated brine and dried. The solvent was evaporated to give the crude diacid (60) (210 mg, 96 %).

IR (KBr, cm^{-1}) : 1450, 1600, 1700, 2400-3400, 3000

NMR ($CDCl_3$ + CD_3COCD_3) δ : 1.66, 2.21 (s, 2 x CH_3)
: 3.93 (s, 2 x OCH_3)
: 4.78, 4.87 (s, 2 x OCH_2)
: 5.84, 6.42 (s, 2 x ArH)
: 7.24 (m, 2 x Ph)

Preparation of methyllithium (Baumgarten (ed.), 1973 and Semmelhack (ed.), 1984)

Methyl iodide (40.00 g, 281.8 mmole) was added with stirring to lithium (4.50 g, 648.5 mmole) in dry ether (240 ml) under nitrogen at a rate adequate to maintain gentle reflux of the ether. After the addition of methyl iodide was completed, the reaction mixture was stirred at room temperature for 24 h and then allowed to stand overnight or longer, whereupon the precipitated lithium chloride settles to the bottom of the flask. The supernatant methyllithium solution was transferred by forced siphon using a large-guage cannula through a glass wool pad into a receiving flask previously flushed with nitrogen gas. The concentration was estimated in the usual way by hydrolysis of an aliquot and titration with 0.1038 M hydrochloric acid. The solution contained 1.0224 M methyllithium.

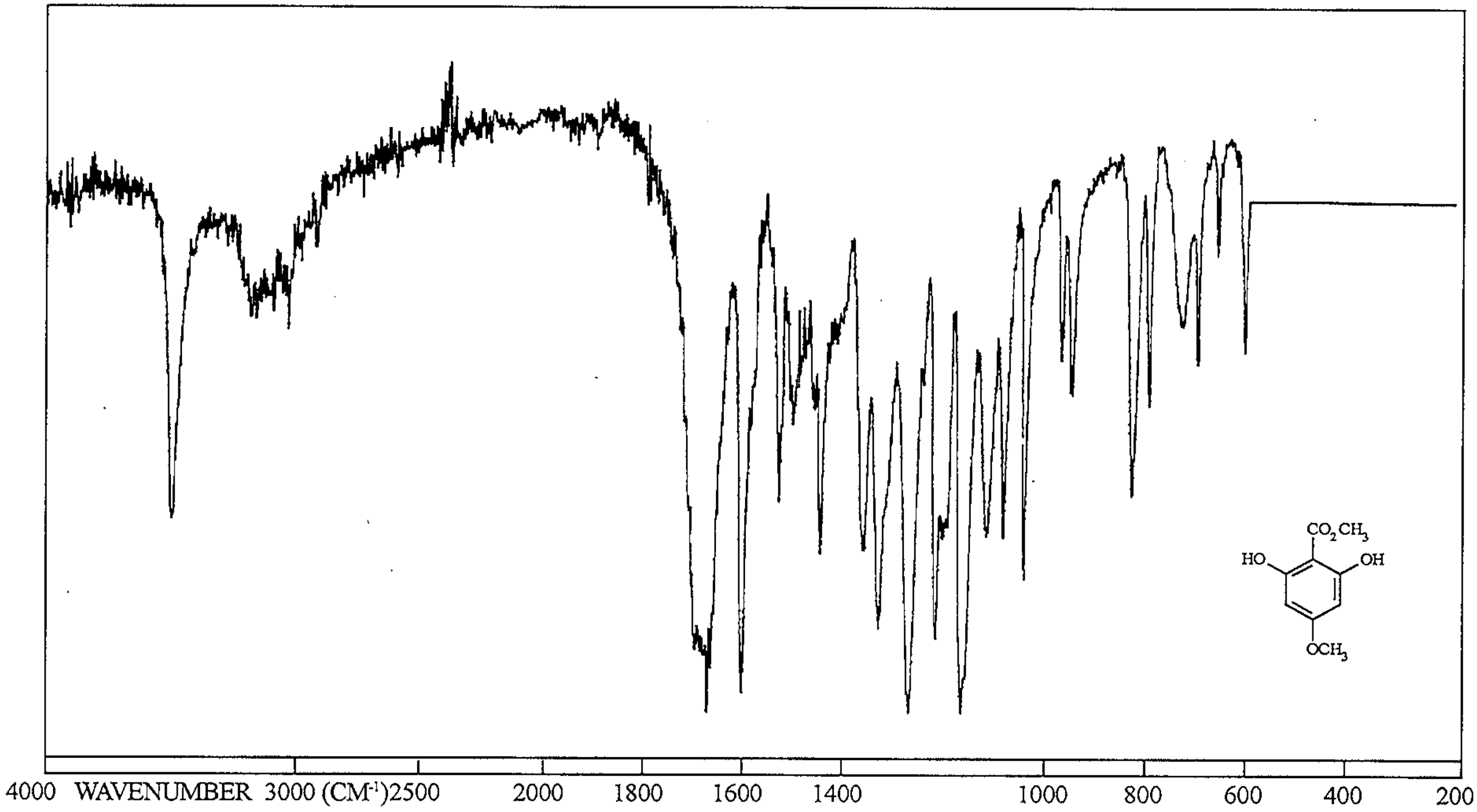


Figure 3 IR spectrum of methyl 2,6-dihydroxy-4-methoxybenzoate (45)

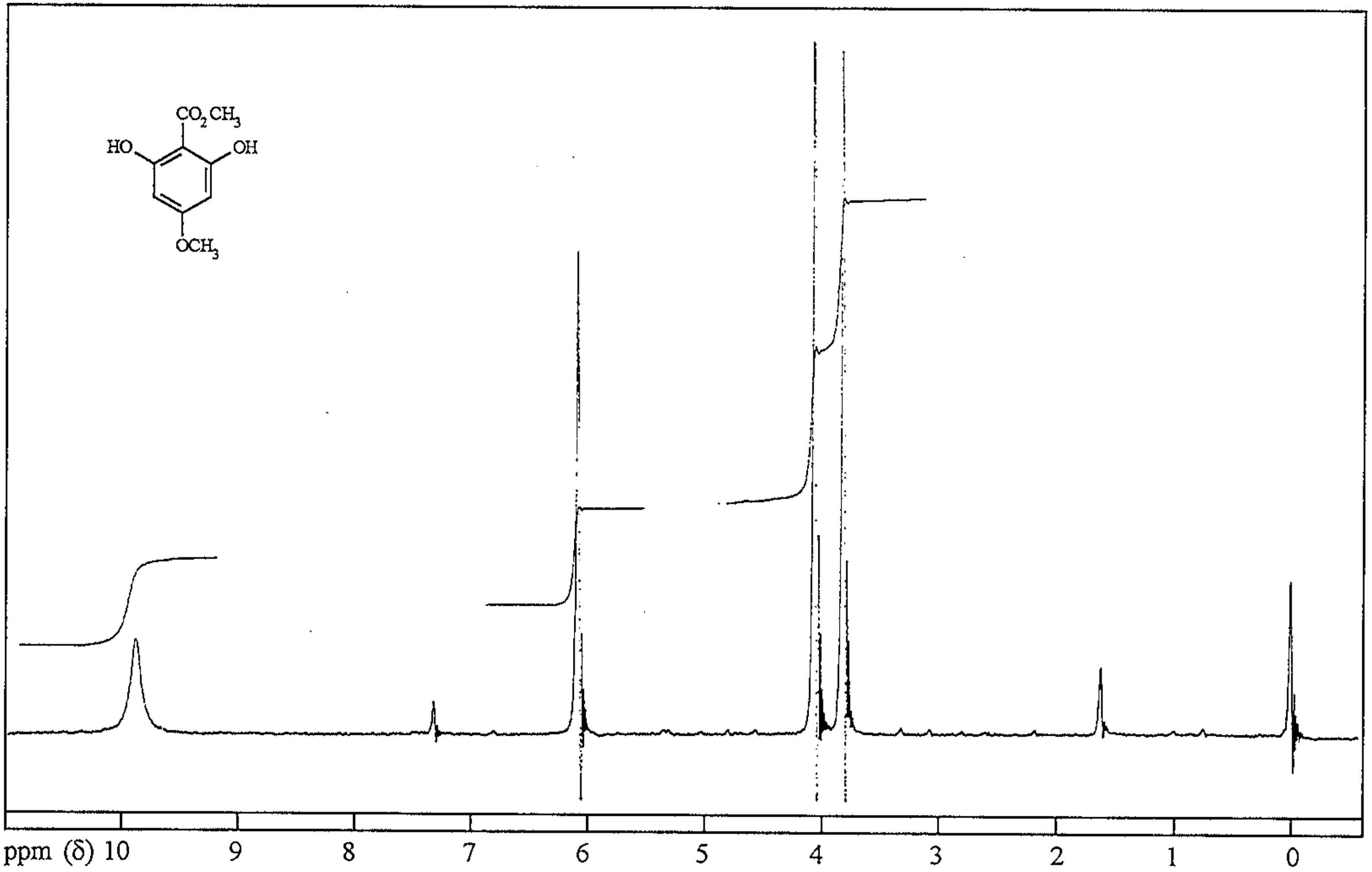


Figure 4 ^{1}H NMR spectrum of methyl 2,6-dihydroxy-4-methoxybenzoate (45)

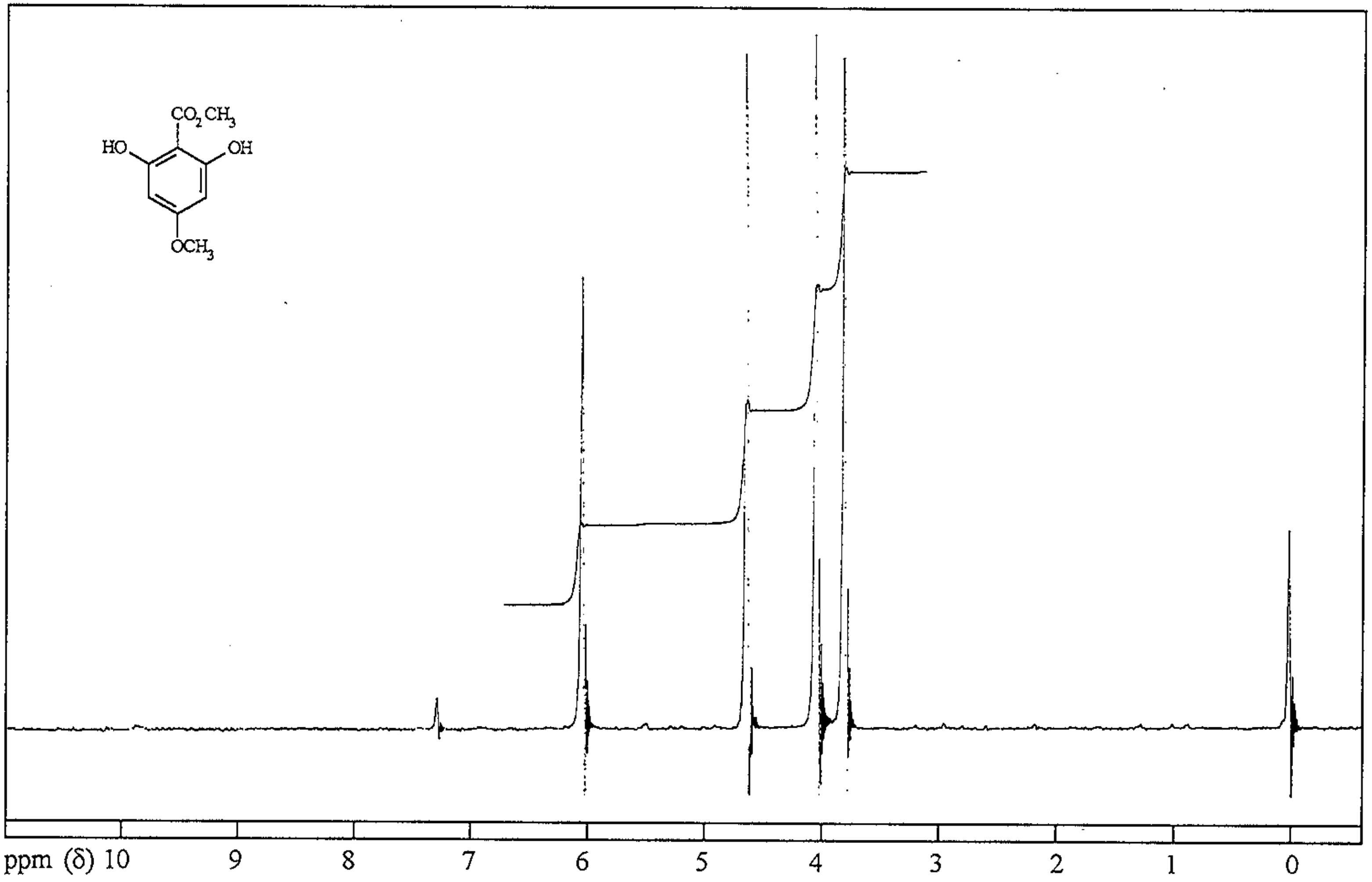


Figure 5 ^1H NMR spectrum of methyl 2,6-dihydroxy-4-methoxybenzoate (45) (D_2O)

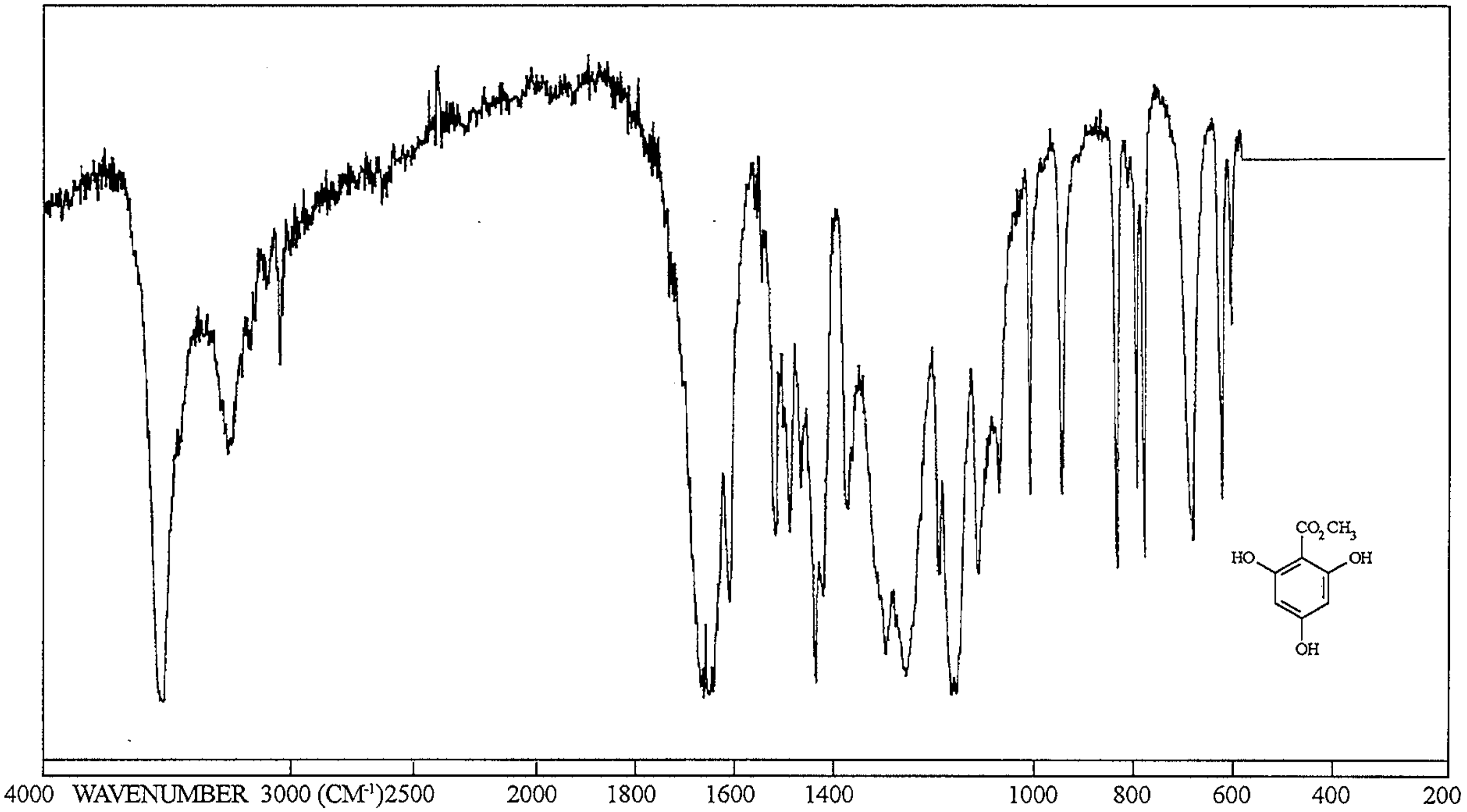


Figure 6 IR spectrum of methyl 2,4,6-trihydroxybenzoate (46)

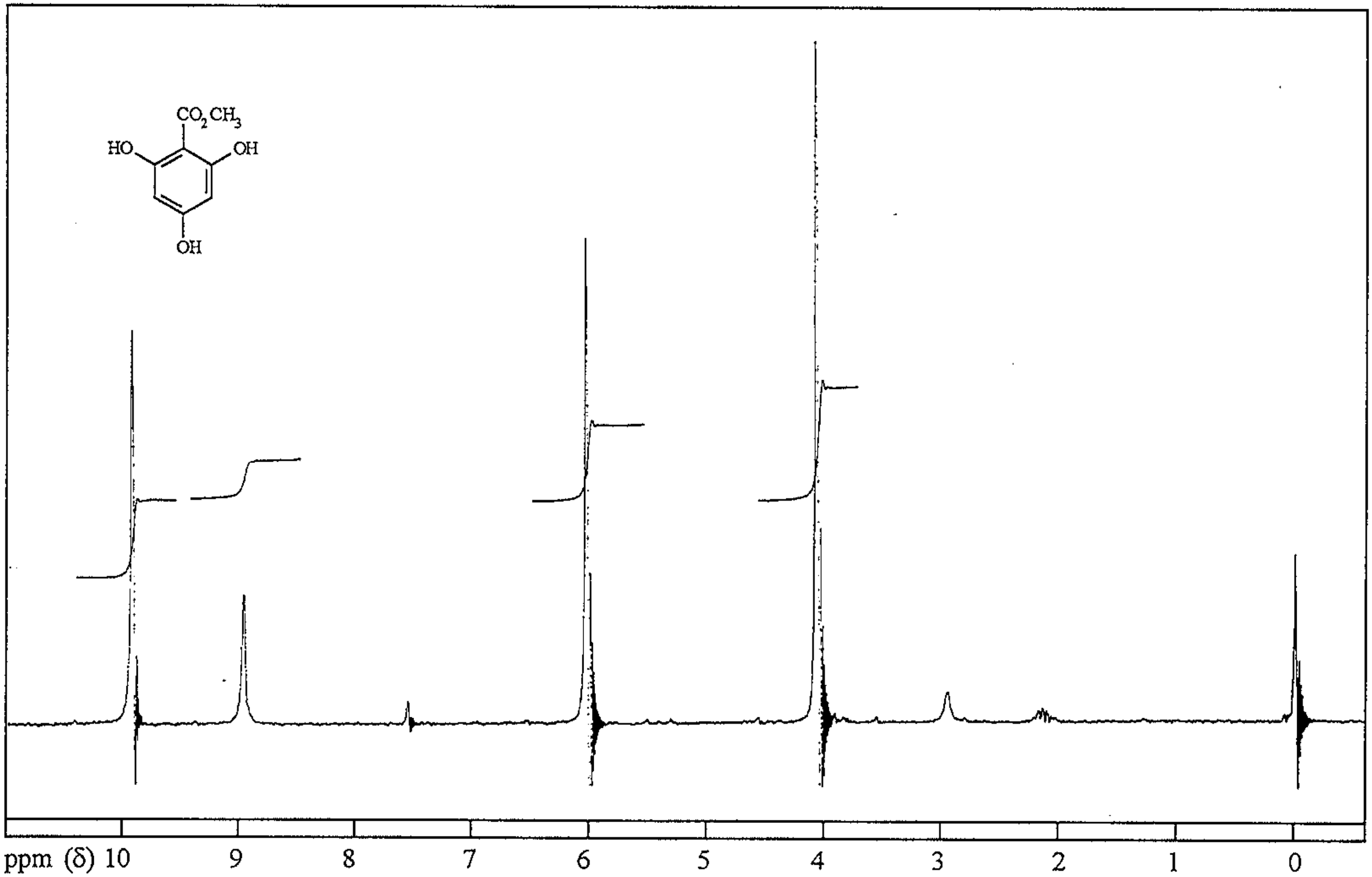


Figure 7 ^{1}H NMR spectrum of methyl 2,4,6-trihydroxybenzoate (46)

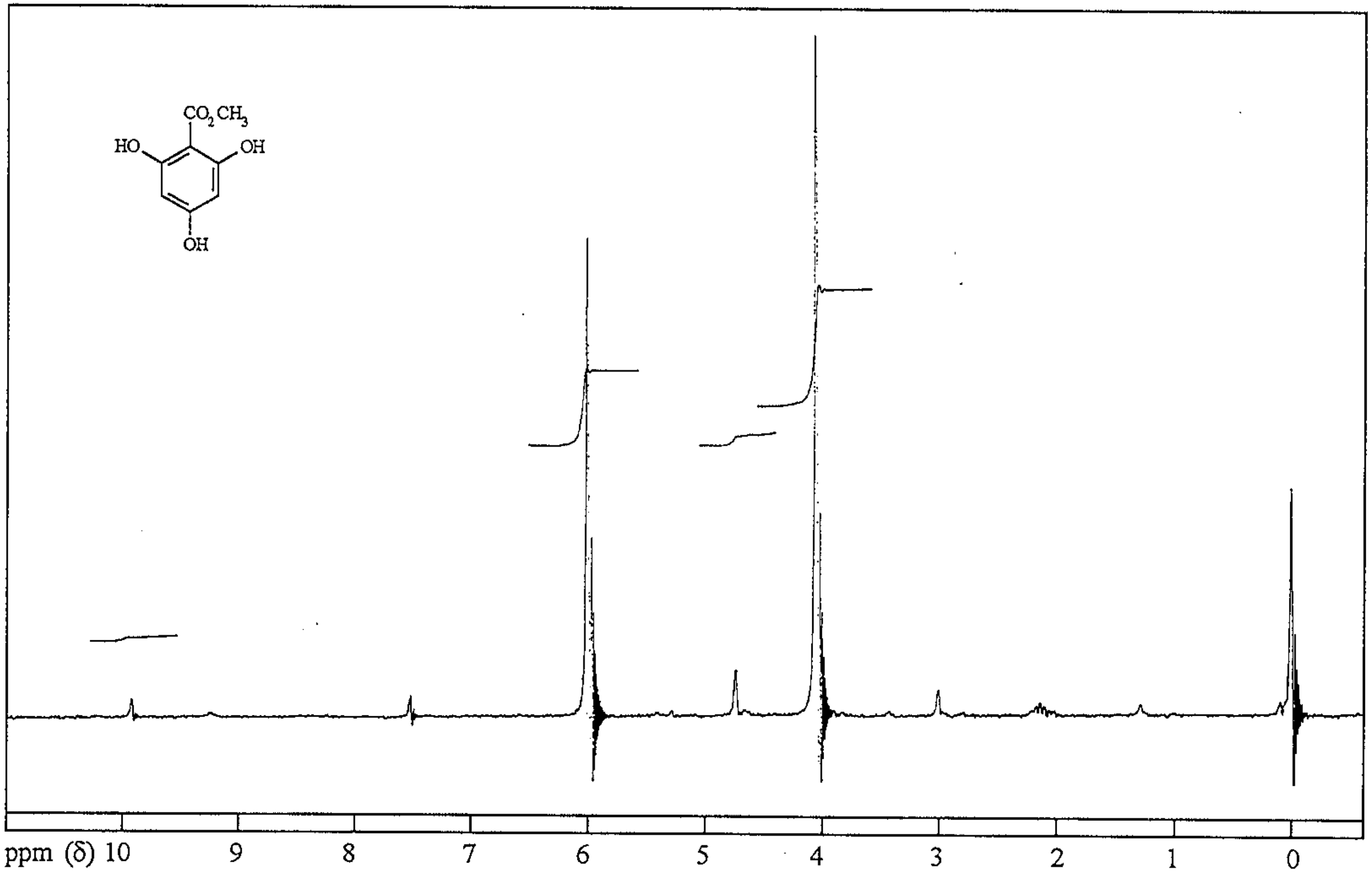


Figure 8 ^{1}H NMR spectrum of methyl 2,4,6-trihydroxybenzoate (46) (D_2O)

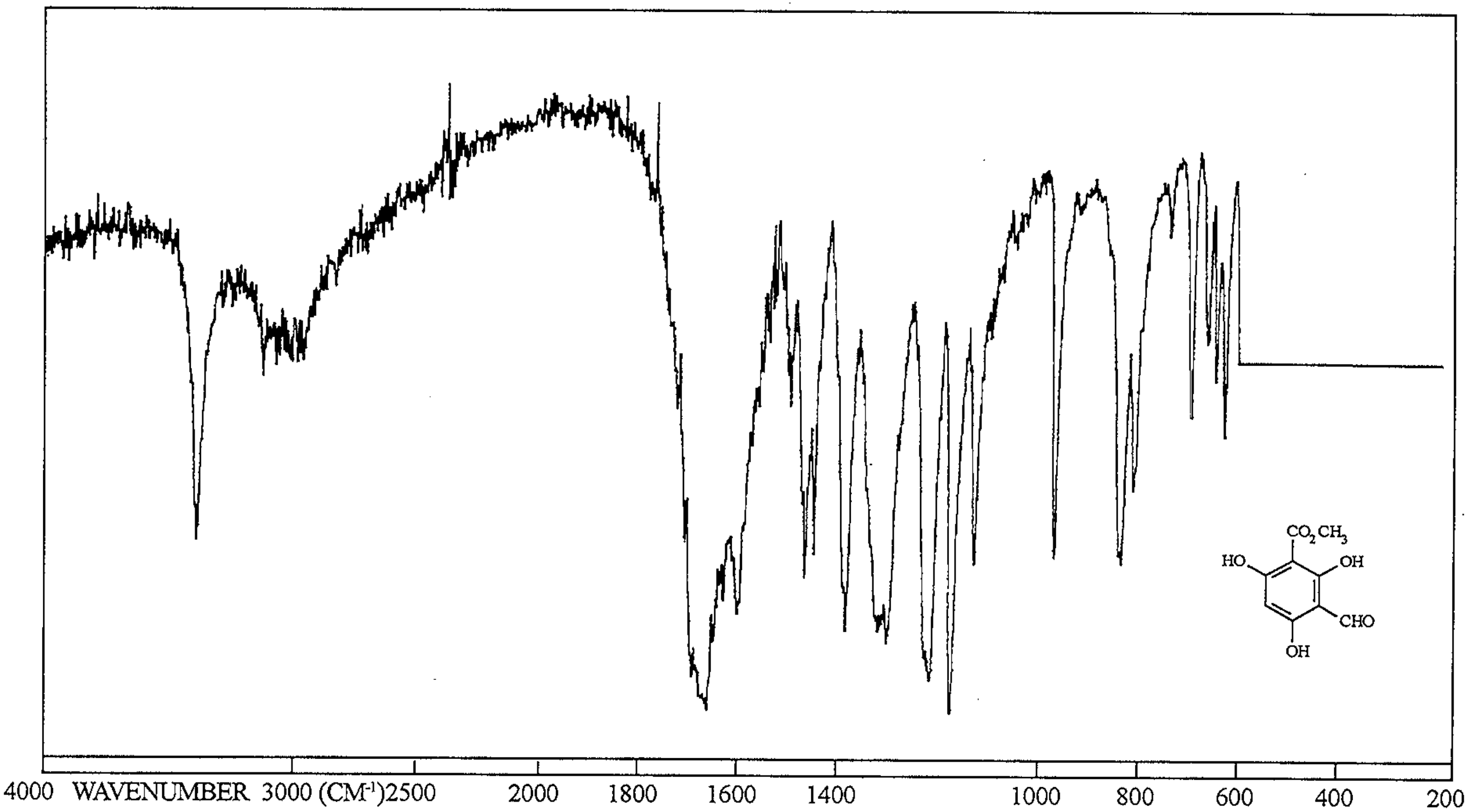


Figure 9 IR spectrum of methyl 3-formyl-2,4,6-trihydroxybenzoate (47)

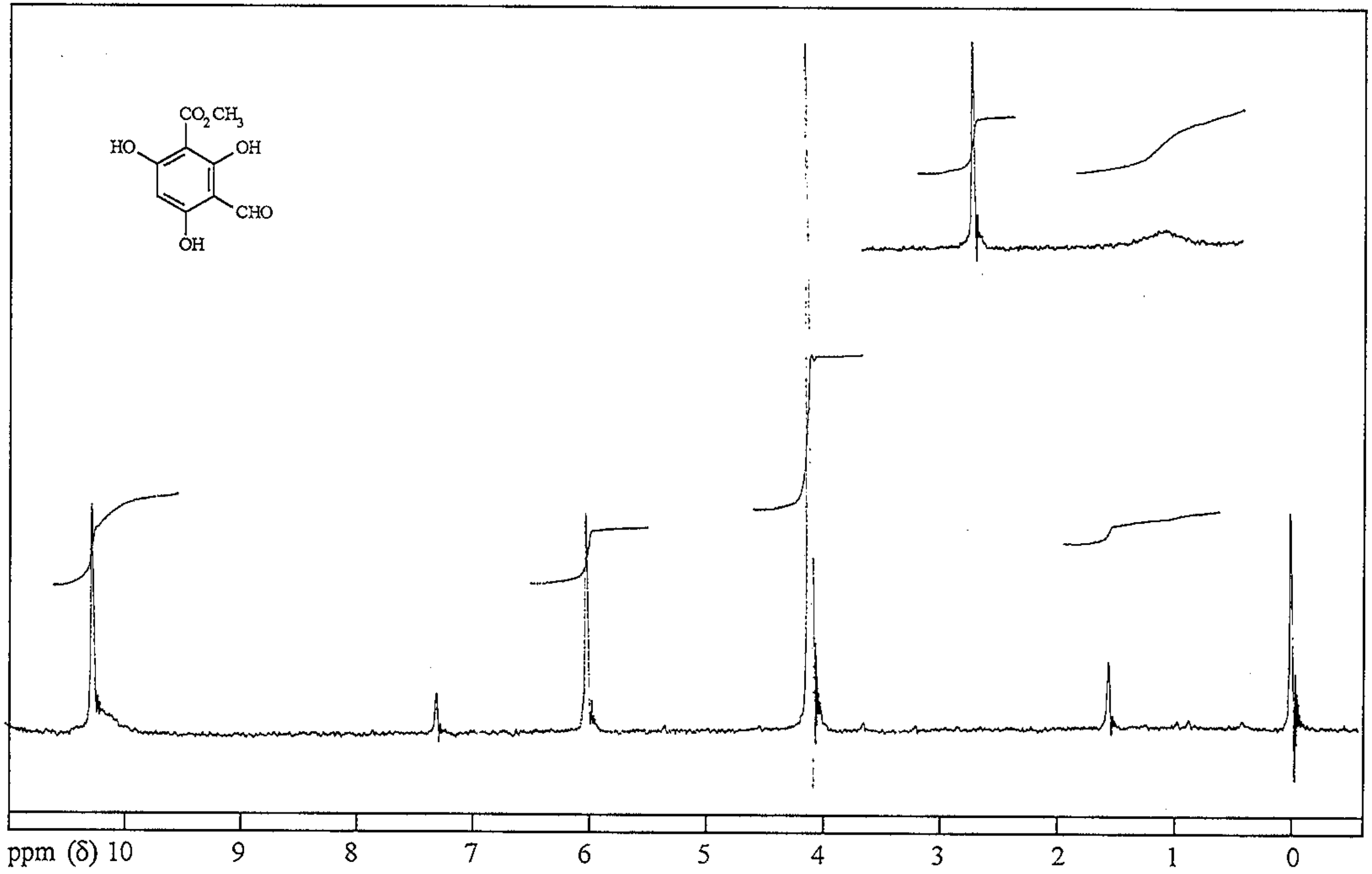


Figure 10 ^{1}H NMR spectrum of methyl 3-formyl-2,4,6-trihydroxybenzoate (47)

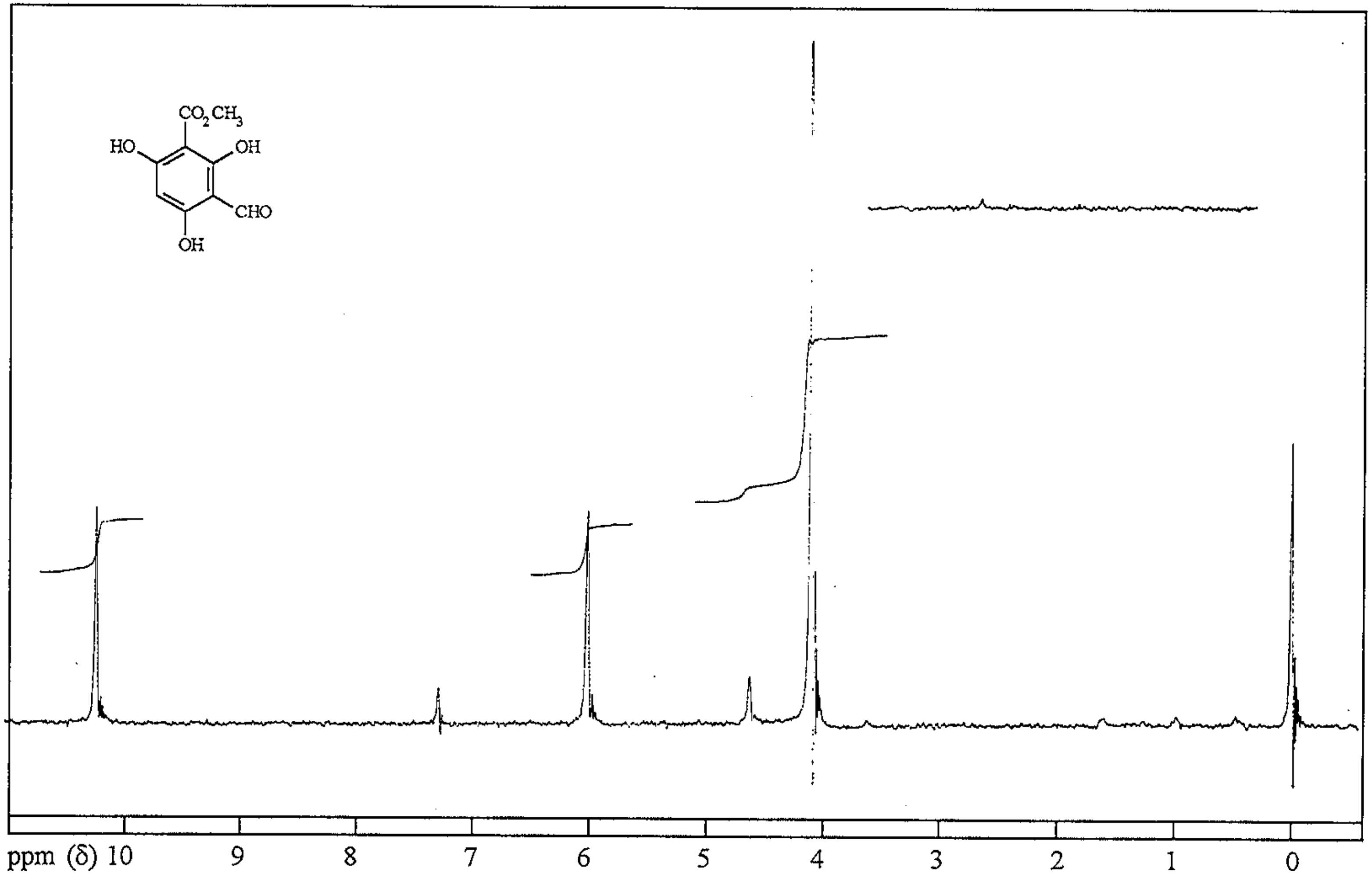


Figure 11 ^{1}H NMR spectrum of methyl 3-formyl-2,4,6-trihydroxybenzoate (47) (D_2O)

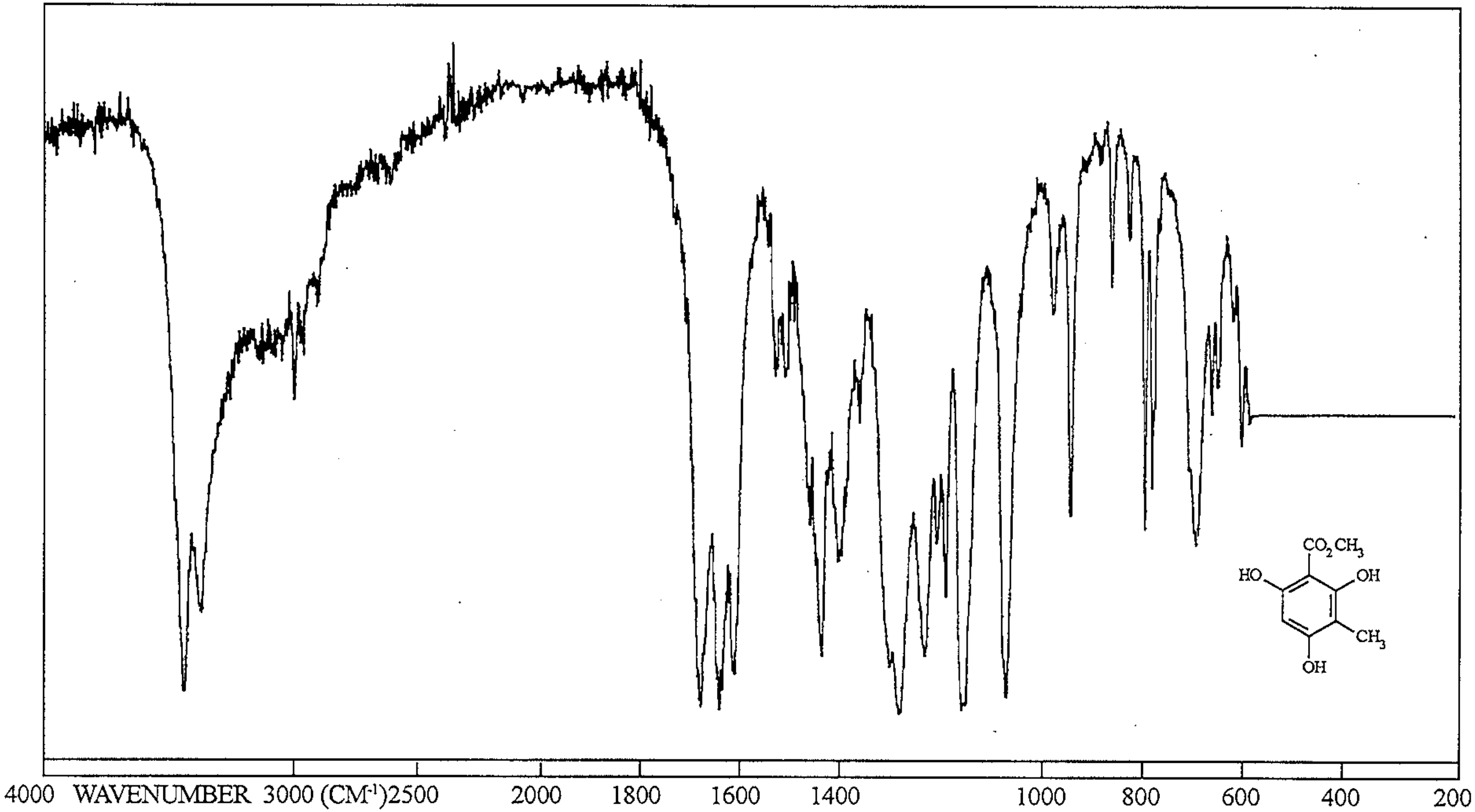


Figure 12 IR spectrum of methyl 3-methyl-2,4,6-trihydroxybenzoate (48)

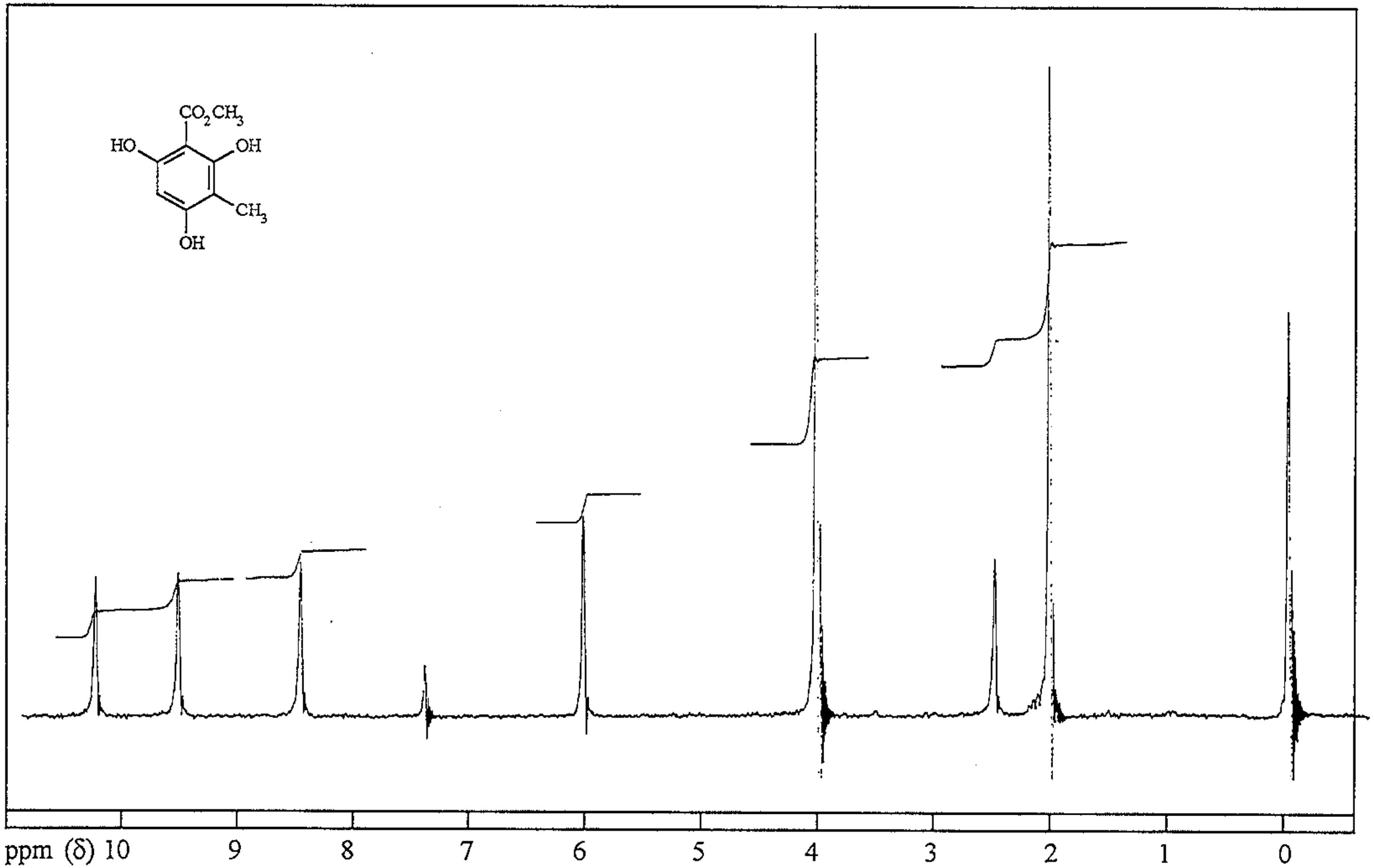


Figure 13 ^{1}H NMR spectrum of methyl 3-methyl-2,4,6-trihydroxybenzoate (48)

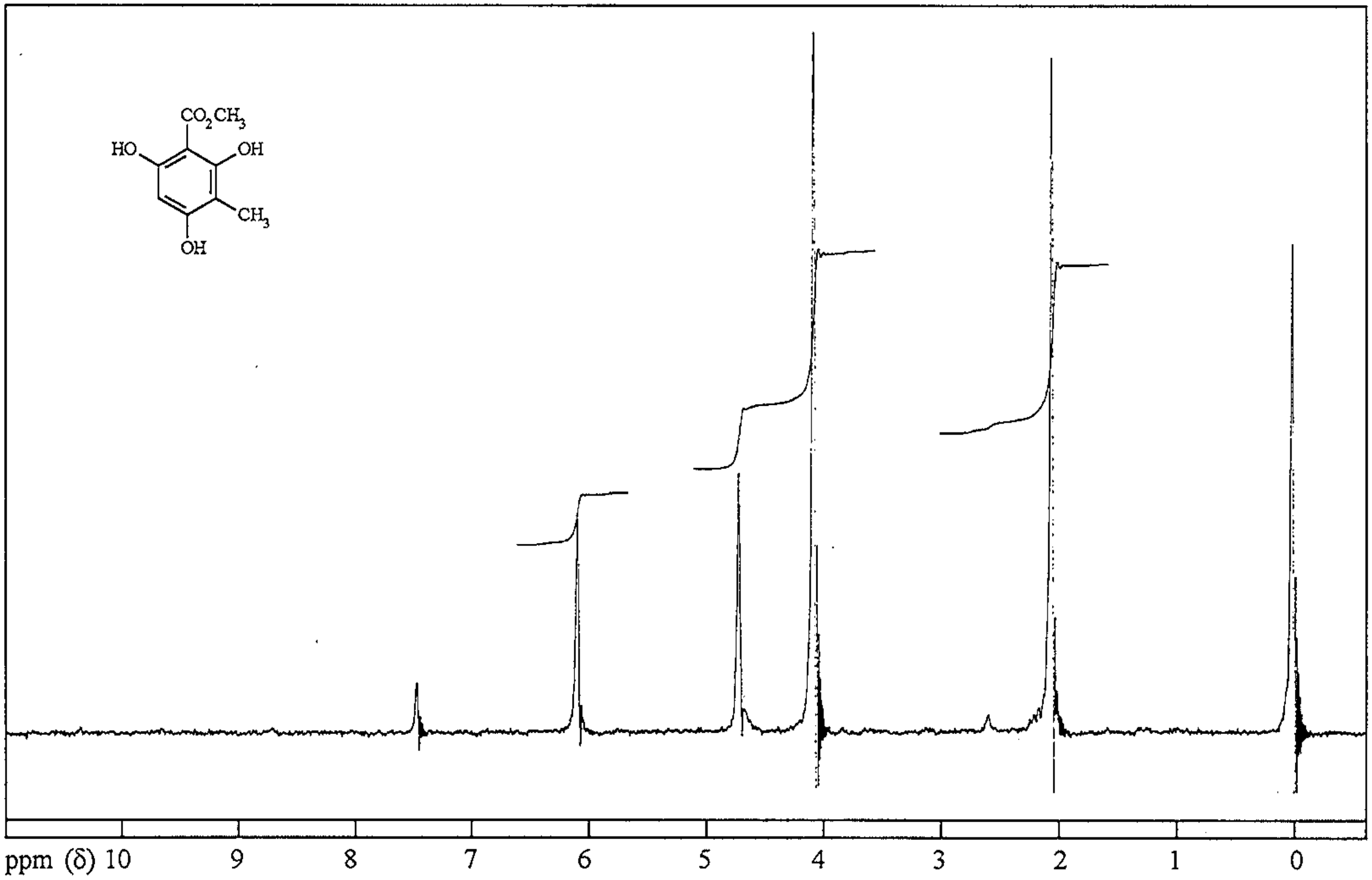


Figure 14 ^{1}H NMR spectrum of methyl 3-methyl-2,4,6-trihydroxybenzoate (48) (D_2O)

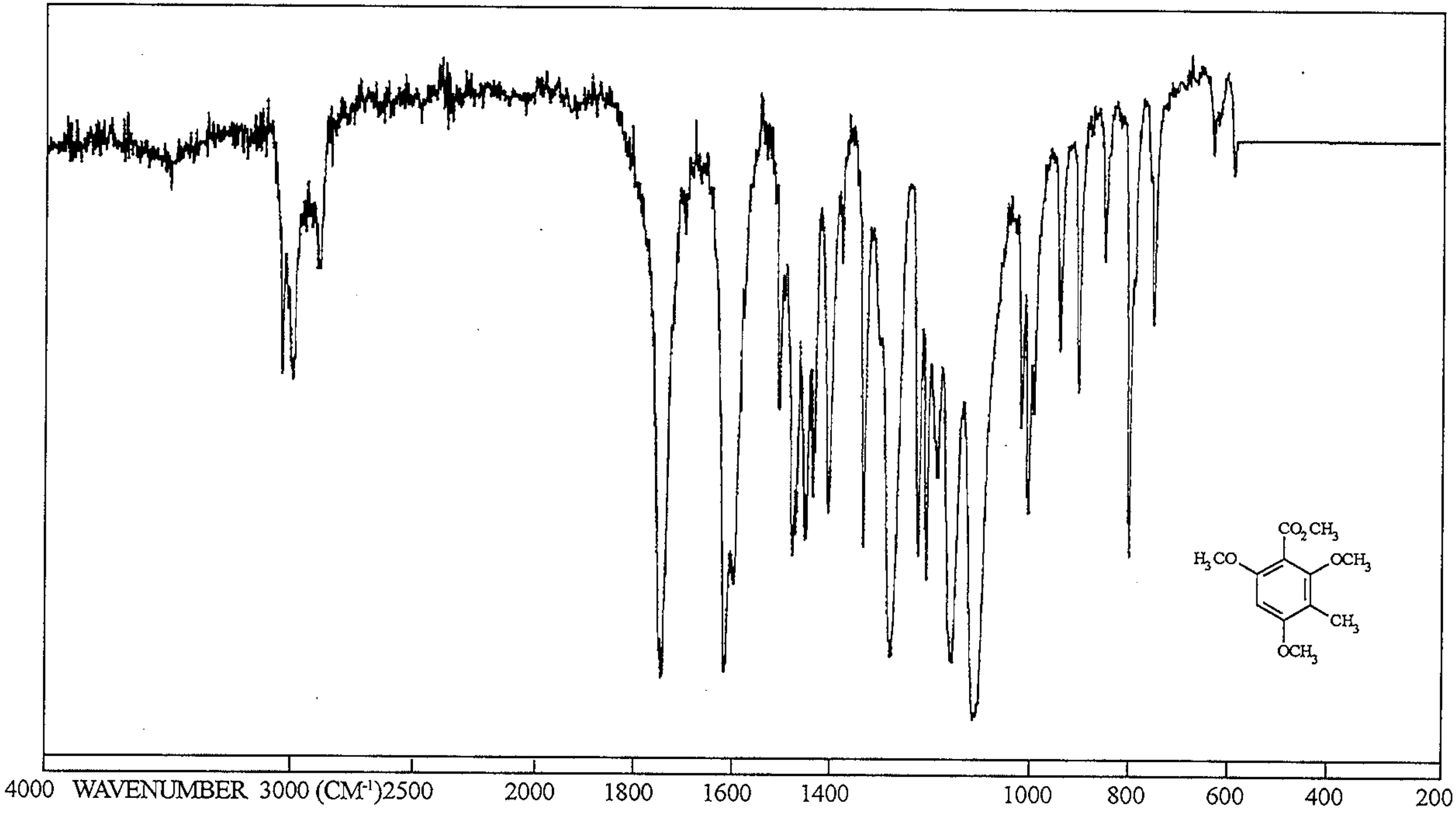


Figure 15 IR spectrum of methyl 3-methyl-2,4,6-trimethoxybenzoate (49)

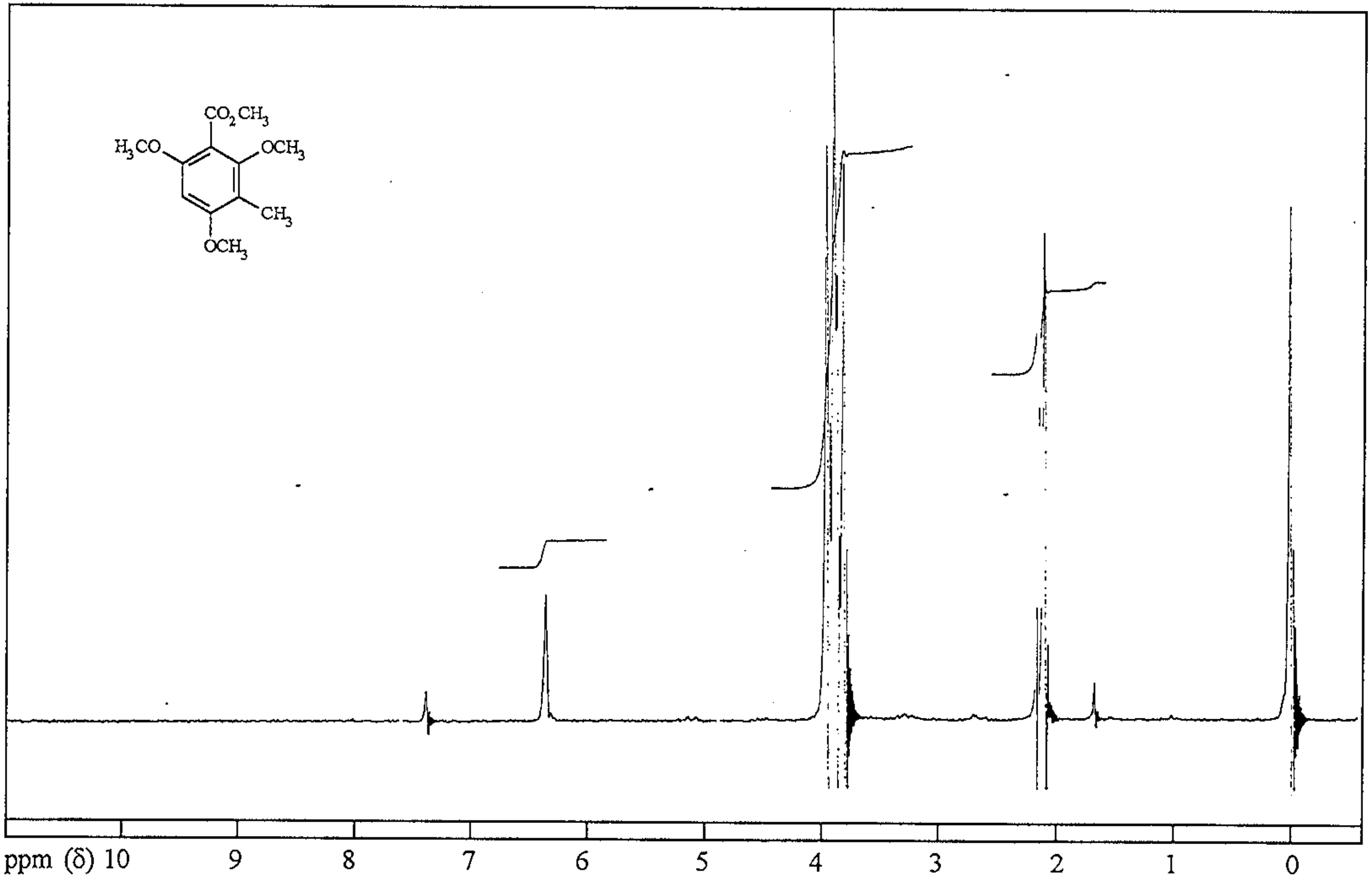


Figure 16 ^{1}H NMR spectrum of methyl 3-methyl-2,4,6-trimethoxybenzoate (49)

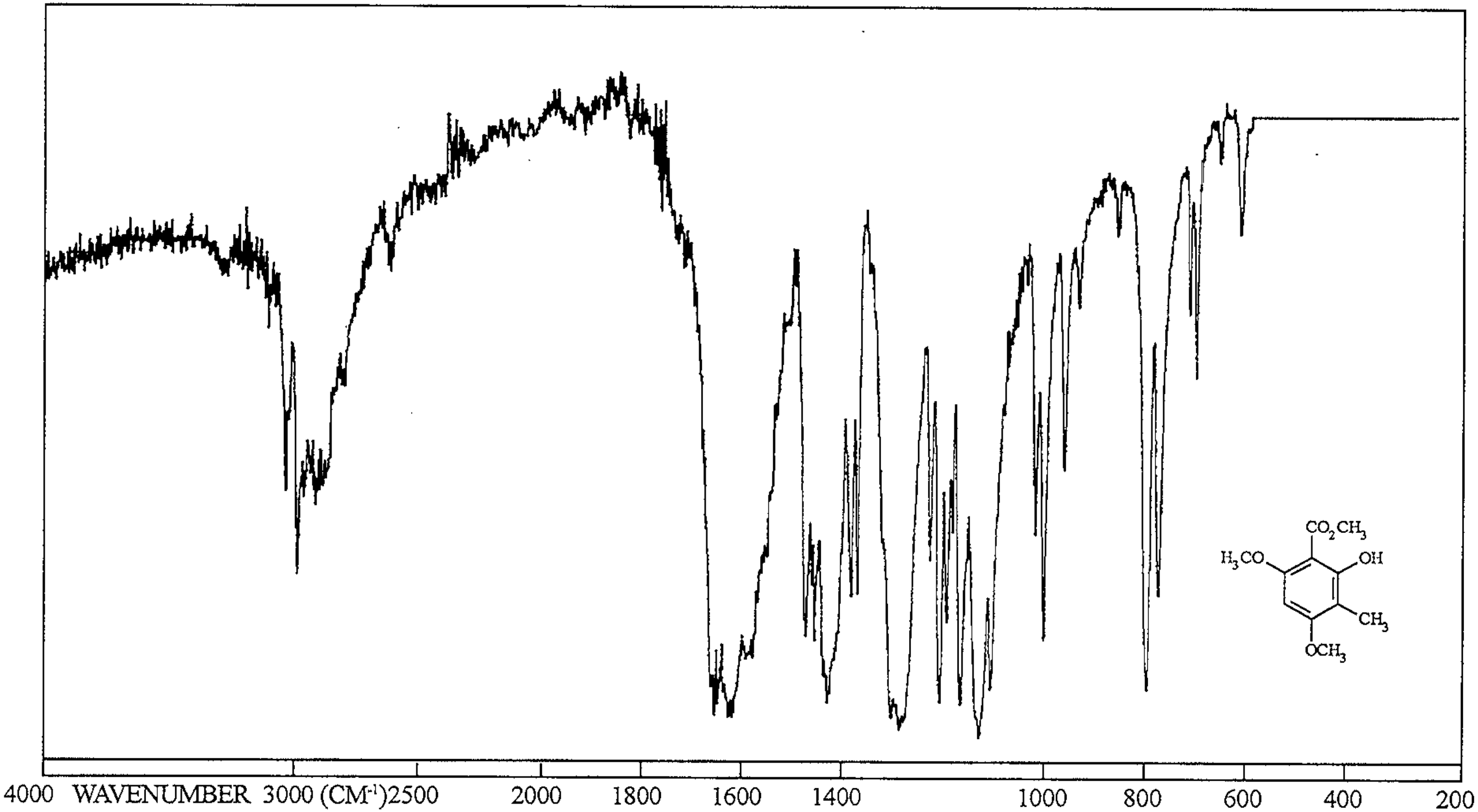


Figure 17 IR spectrum of methyl 4,6-dimethoxy-2-hydroxy-3-methyl benzoate (50)

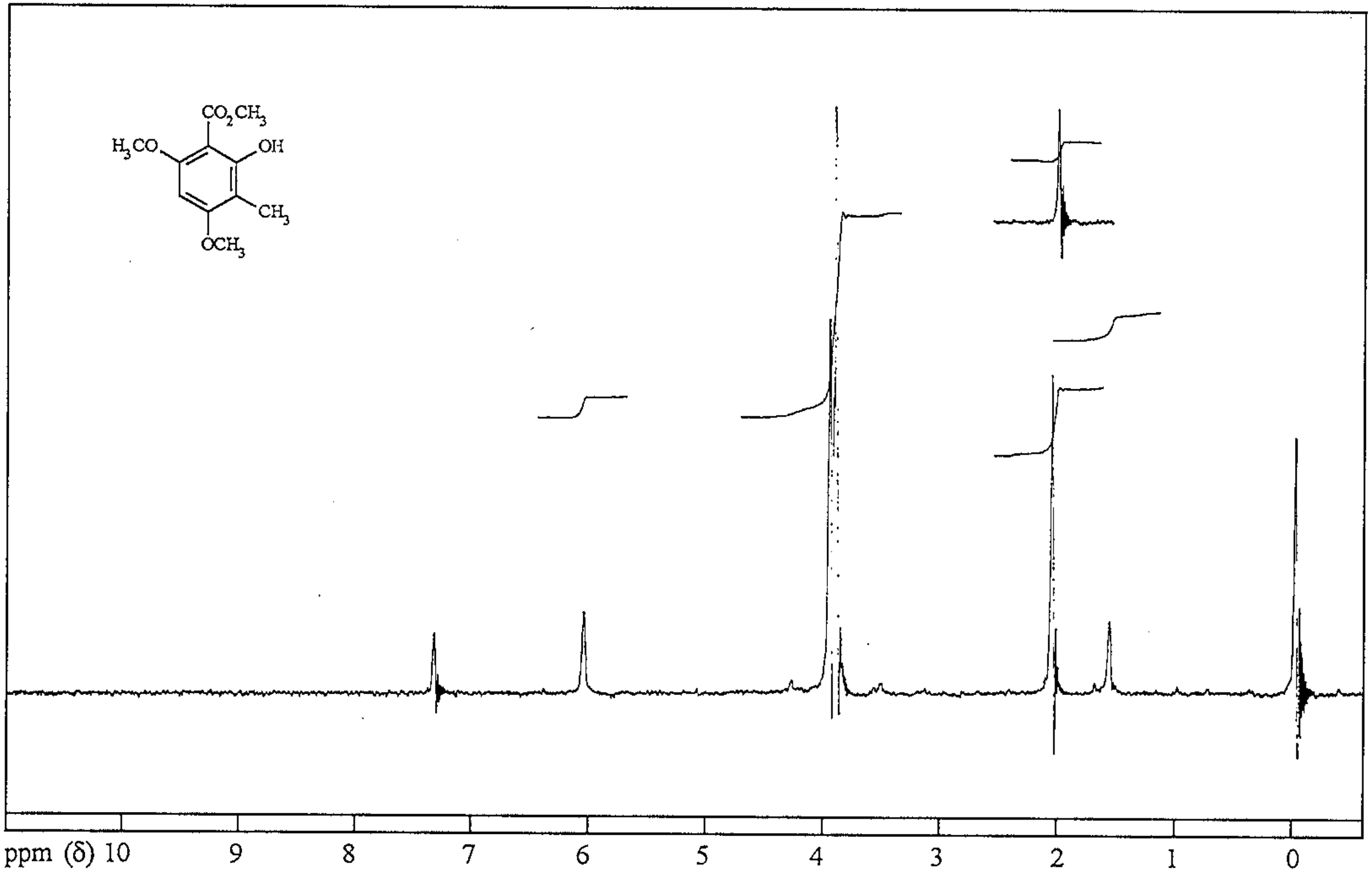


Figure 18 ^{1}H NMR spectrum of methyl 4,6-dimethoxy-2-hydroxy-3-methyl benzoate (50)

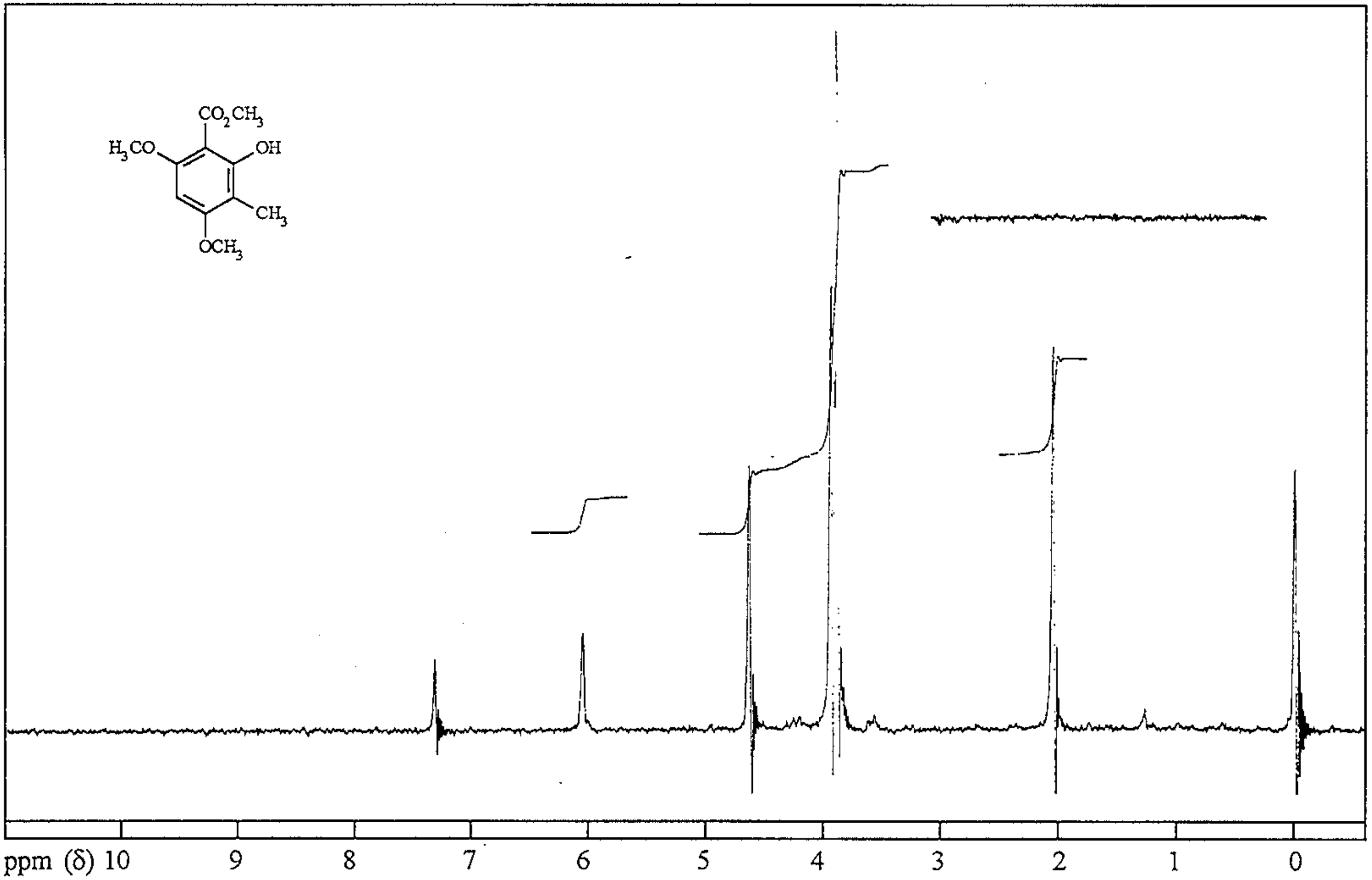


Figure 19 ^{1}H NMR spectrum of methyl 4,6-dimethoxy-2-hydroxy-3-methyl benzoate (50) (D_2O)

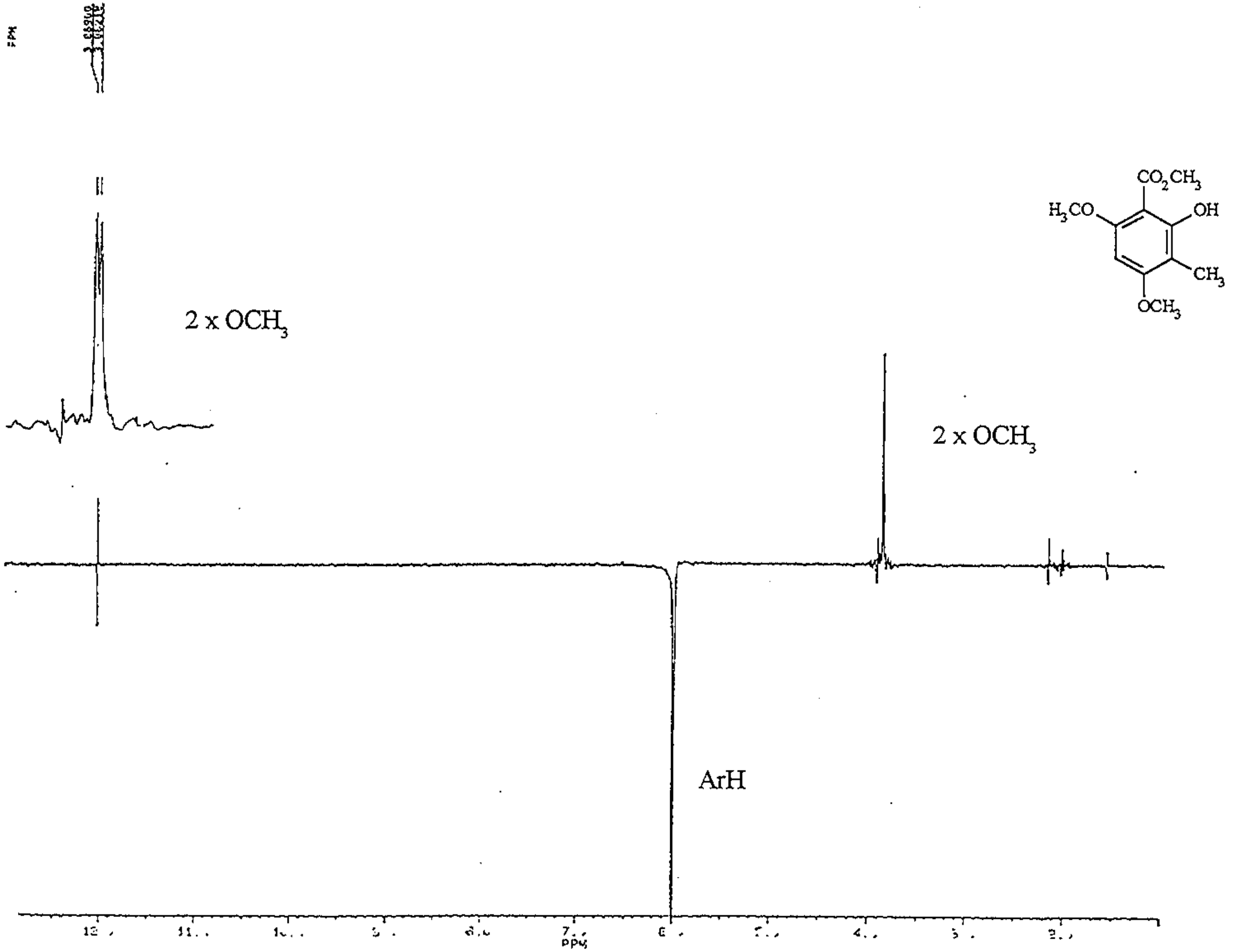


Figure 20 NOE spectrum of methyl 4,6-dimethoxy-2-hydroxy-3-methyl benzoate (50)

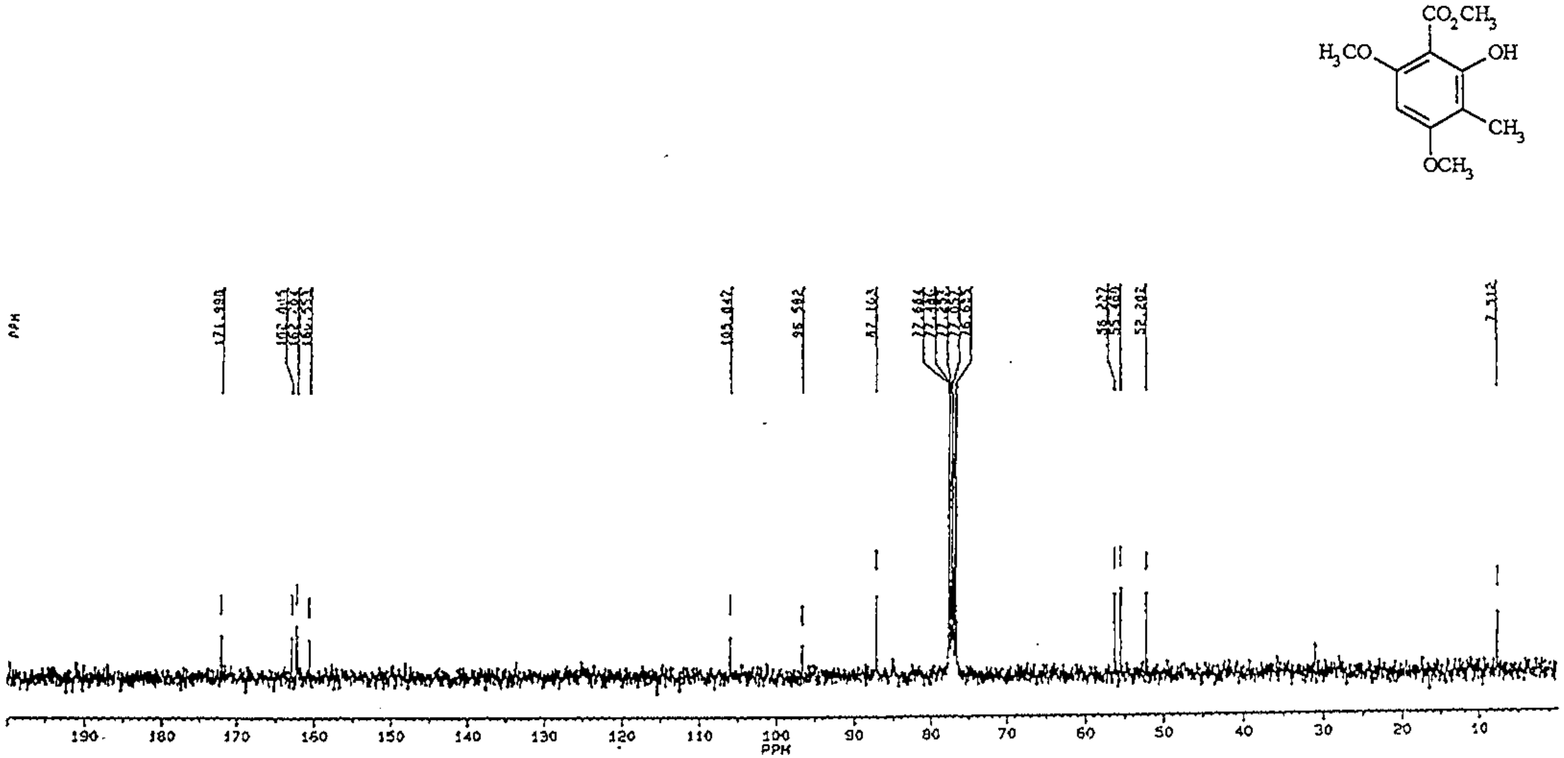


Figure 21 ^{13}C NMR spectrum of methyl 4,6-dimethoxy-2-hydroxy-3-methyl benzoate (50)

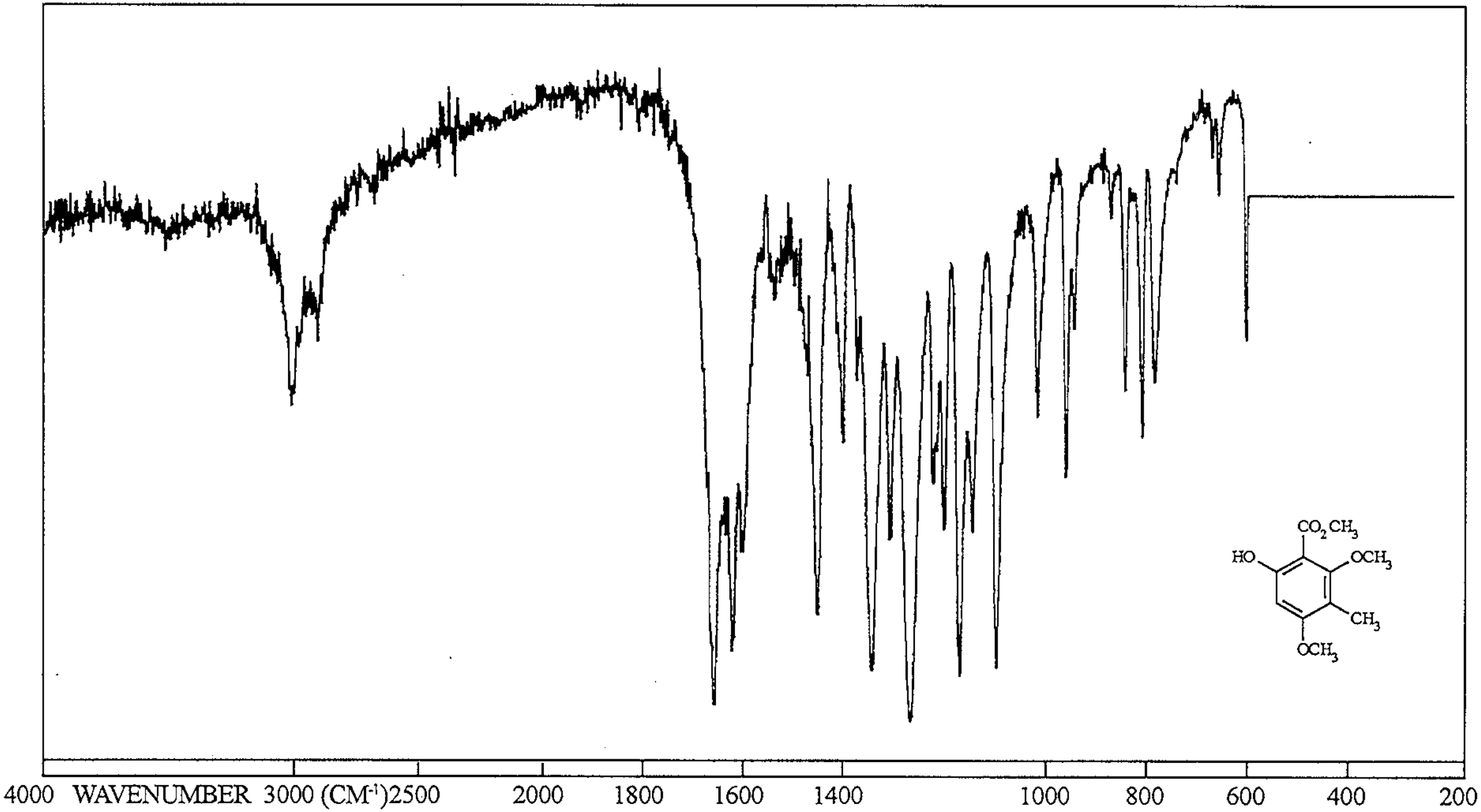


Figure 22 IR spectrum of methyl 2,4-dimethoxy-6-hydroxy-3-methyl benzoate (51)

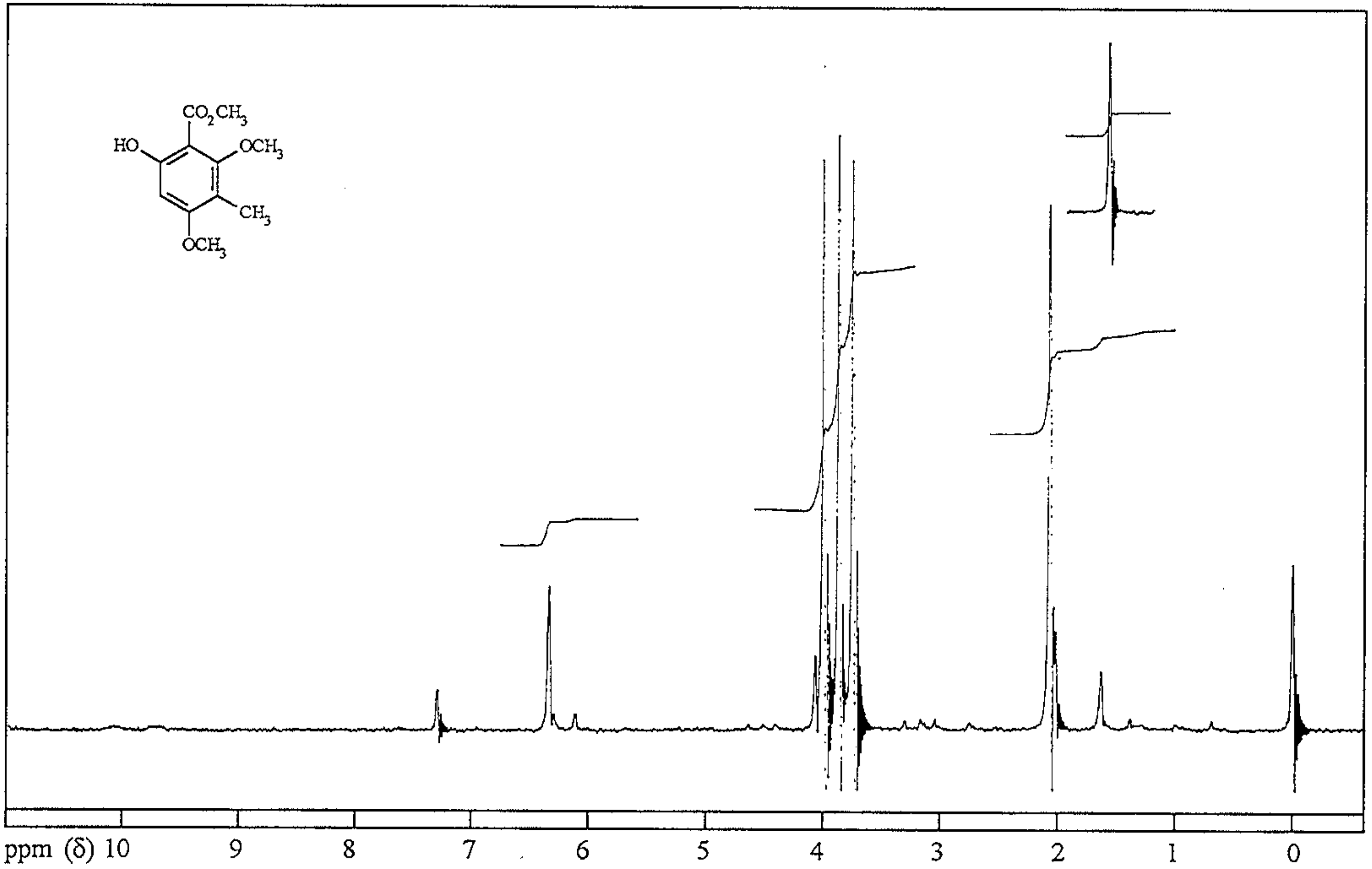


Figure 23 ^{1}H NMR spectrum of methyl 2,4-dimethoxy-6-hydroxy-3-methyl benzoate (51)

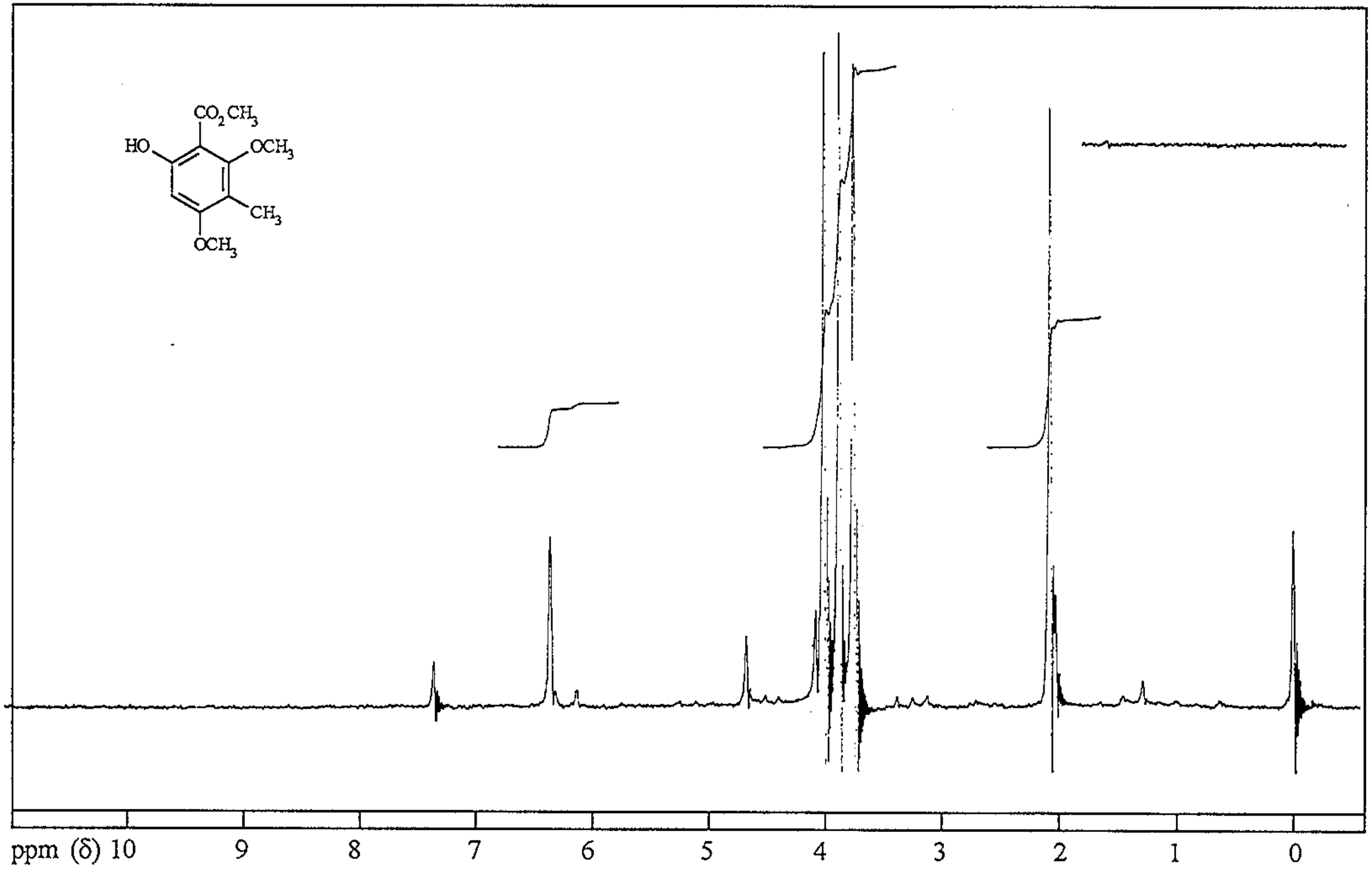


Figure 24 ^{1}H NMR spectrum of methyl 2,4-dimethoxy-6-hydroxy-3-methyl benzoate (51) (D_2O)

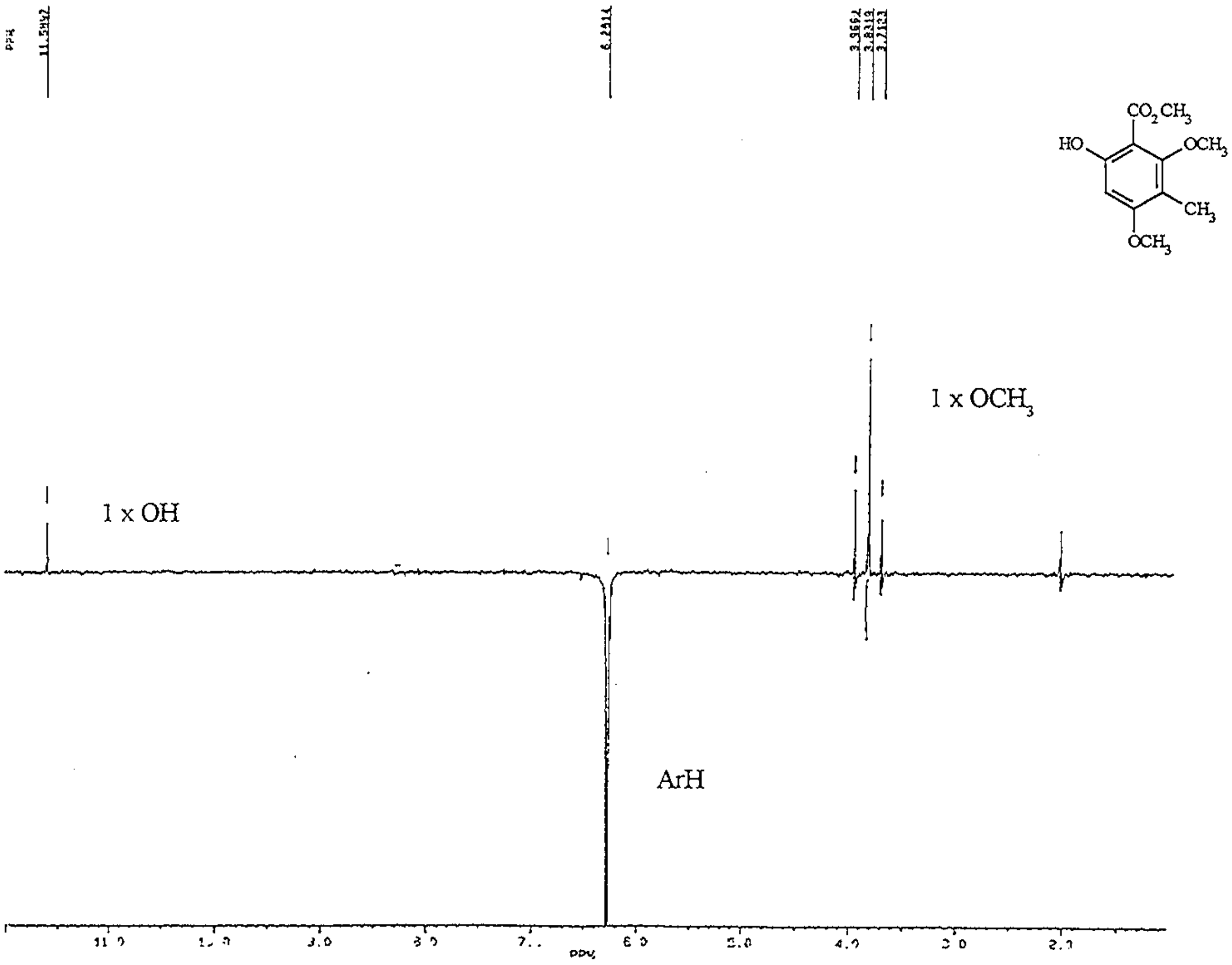


Figure 25 NOE spectrum of methyl 2,4-dimethoxy-6-hydroxy-3-methyl benzoate (51)

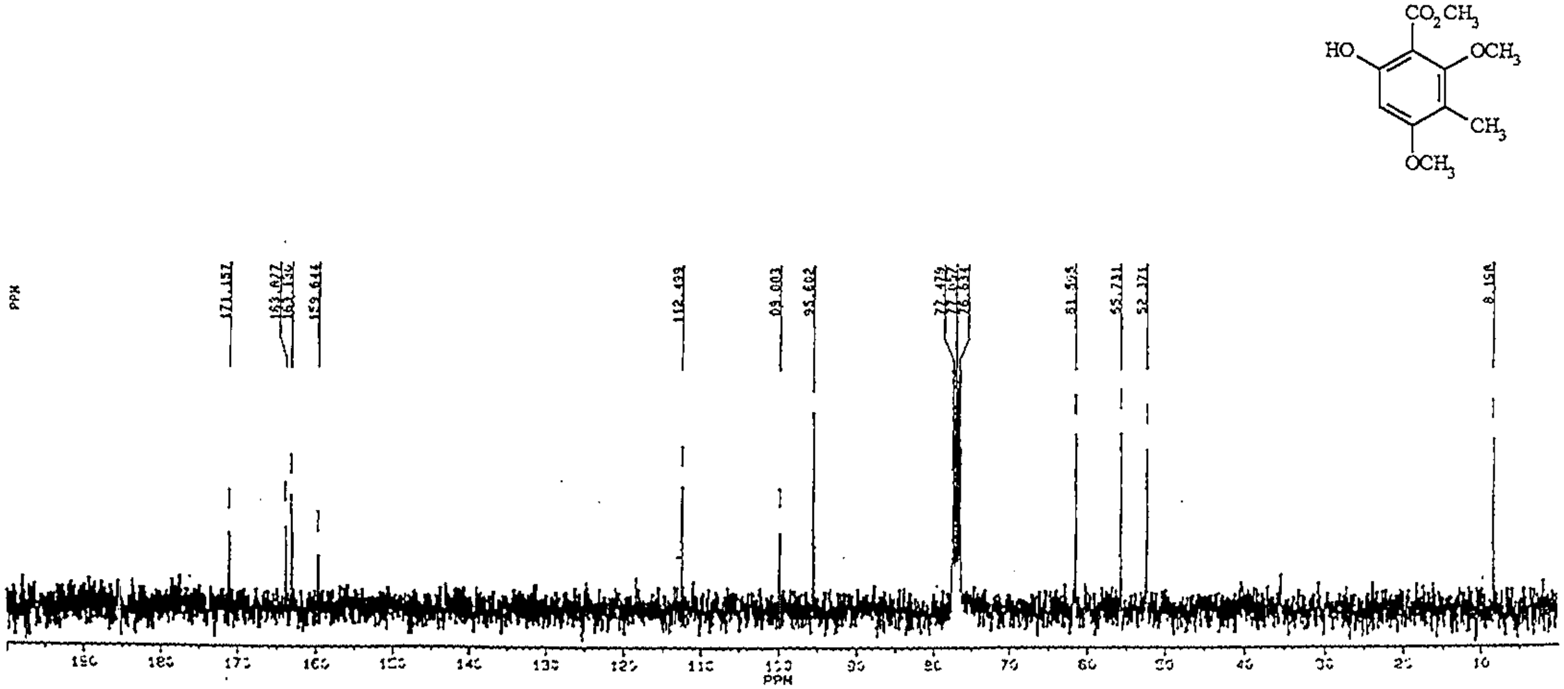


Figure 26 ^{13}C NMR spectrum of methyl 2,4-dimethoxy-6-hydroxy-3-methyl benzoate (51)

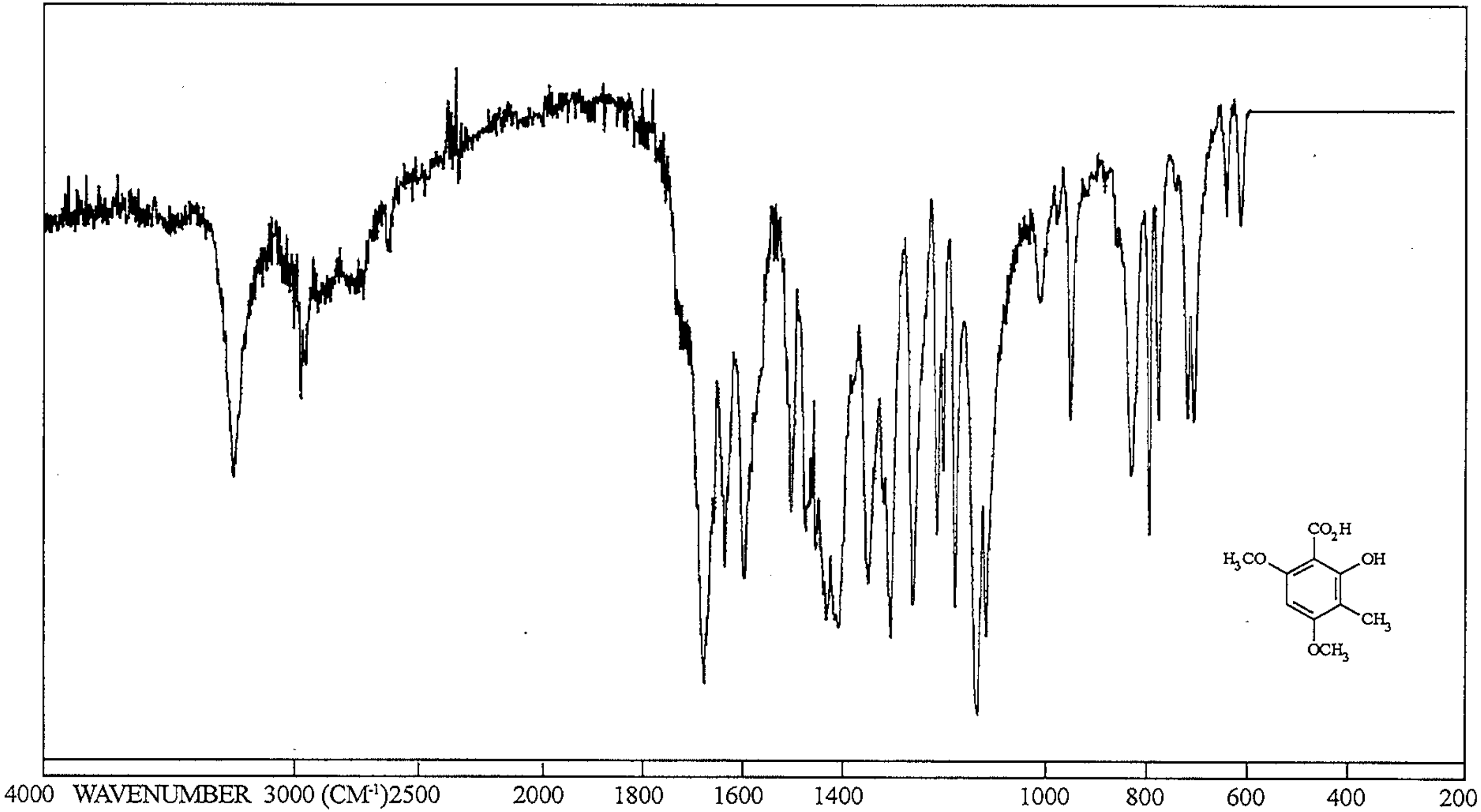


Figure 27 IR spectrum of 4,6-dimethoxy-2-hydroxy-3-methylbenzoic acid (52)

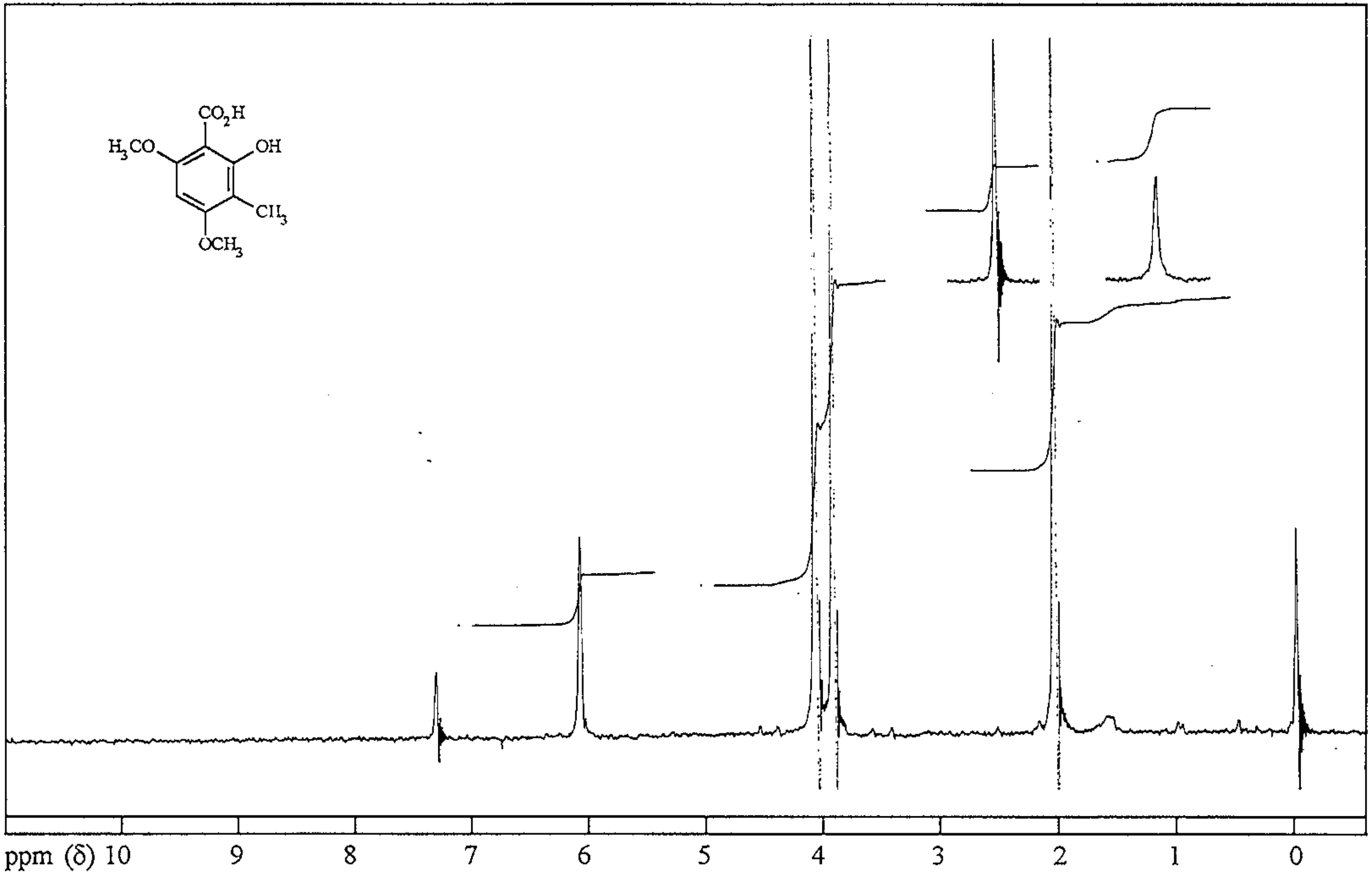


Figure 28 ¹H NMR spectrum of 4,6-dimethoxy-2-hydroxy-3-methylbenzoic acid (52)

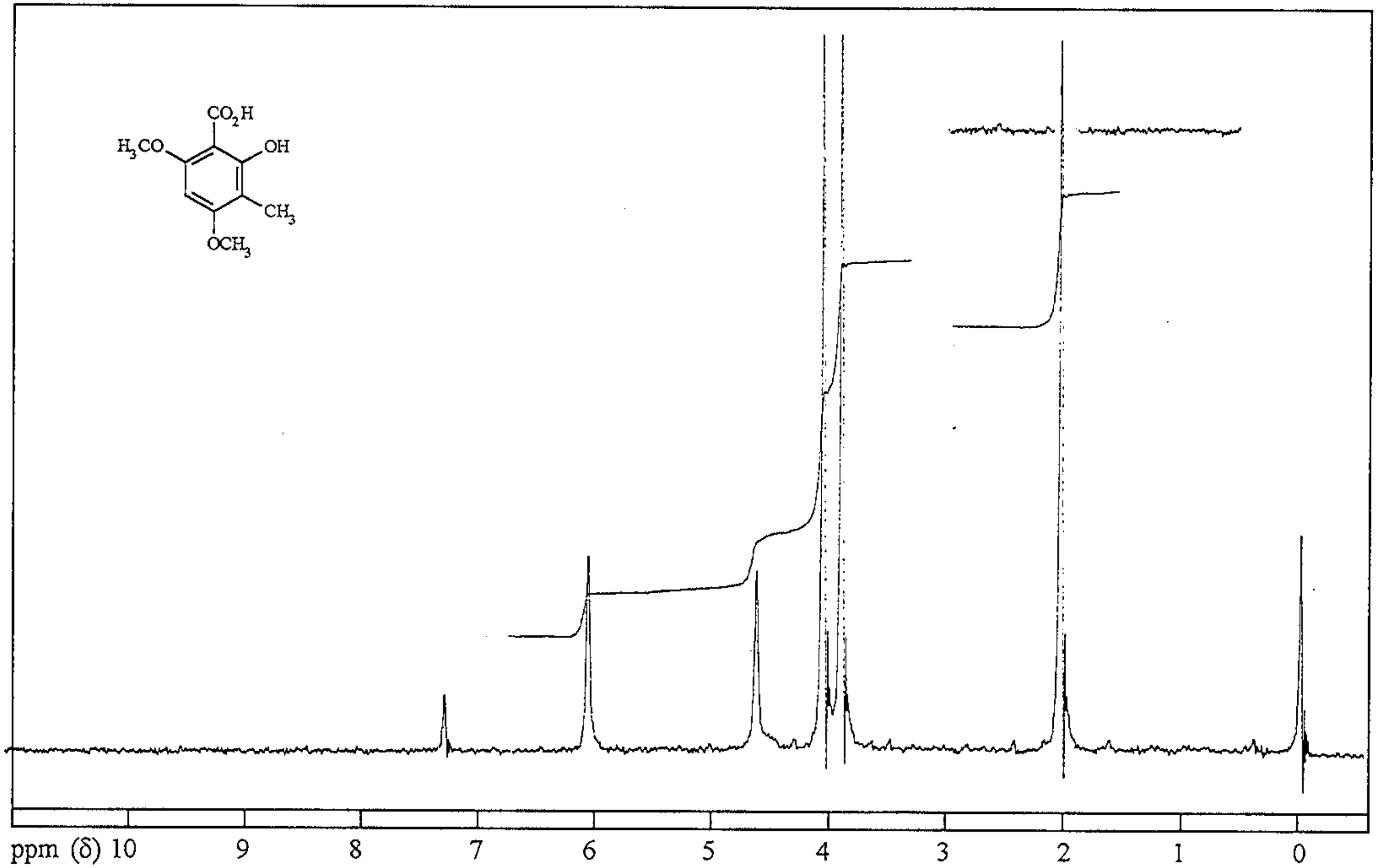


Figure 29 ^{1}H NMR spectrum of 4,6-dimethoxy-2-hydroxy-3-methylbenzoic acid (52) (D_2O)

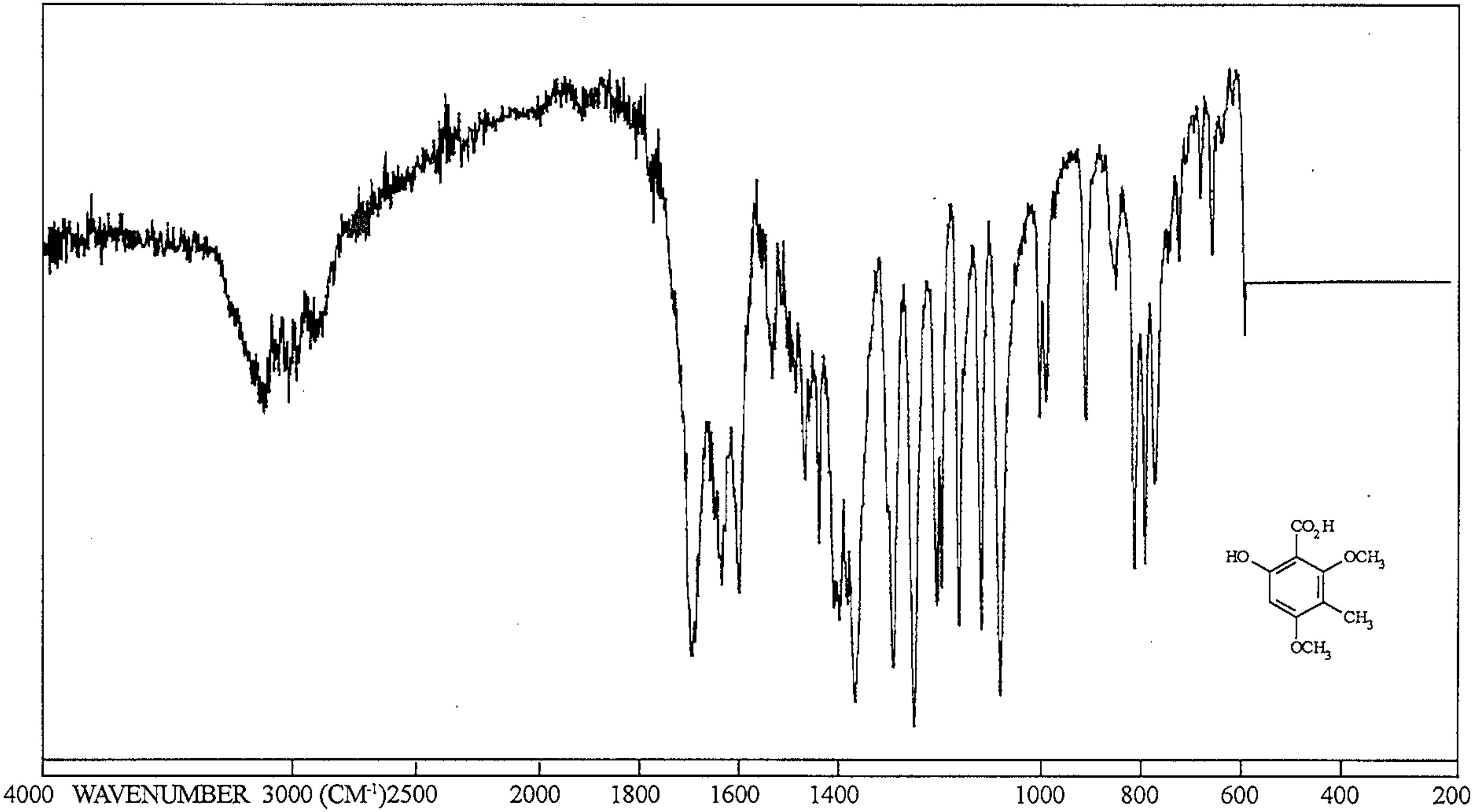


Figure 30 IR spectrum of 2,4-dimethoxy-6-hydroxy-3-methylbenzoic acid (53)

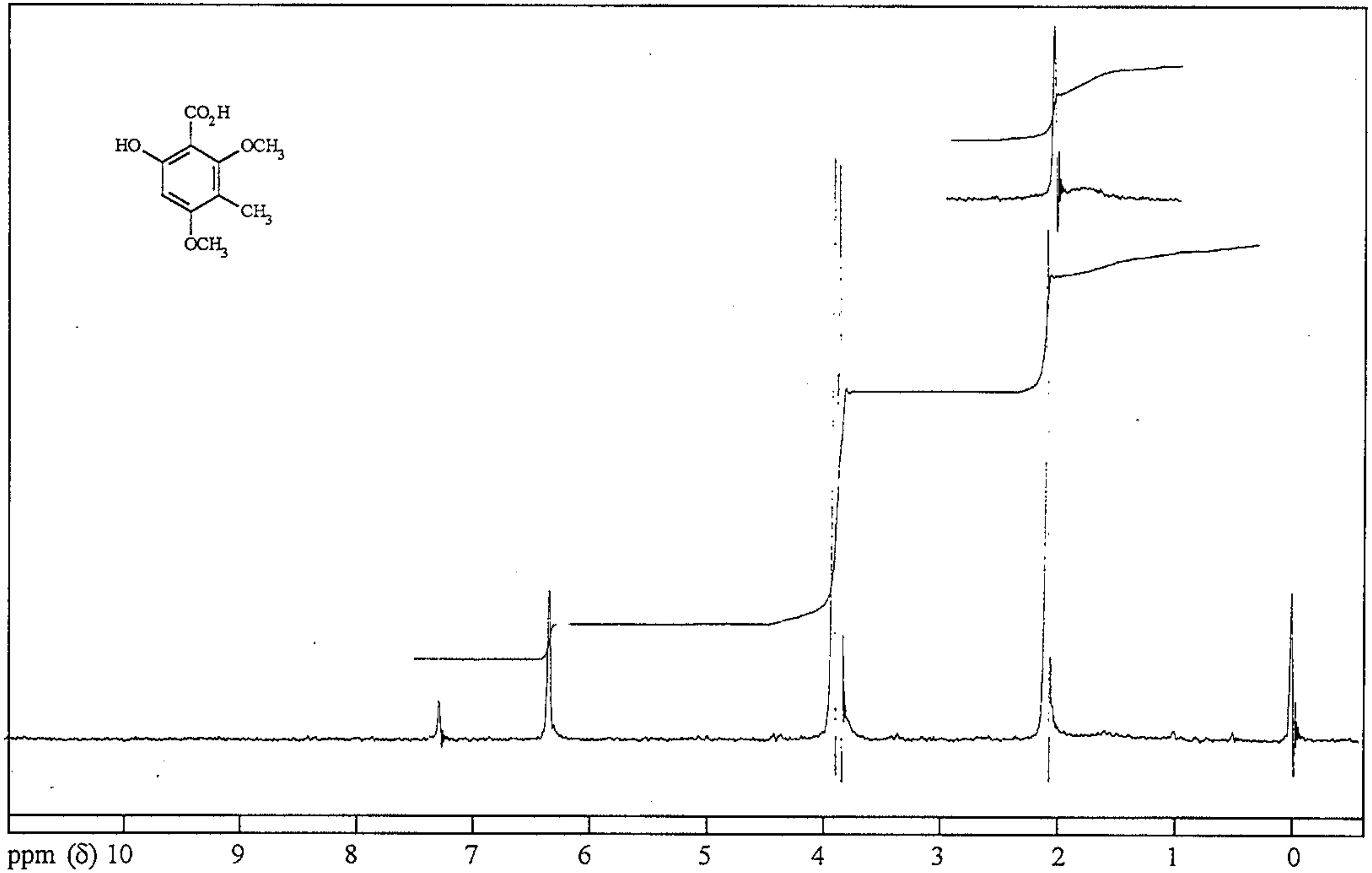


Figure 31 ^{1}H NMR spectrum of 2,4-dimethoxy-6-hydroxy-3-methylbenzoic acid (53)

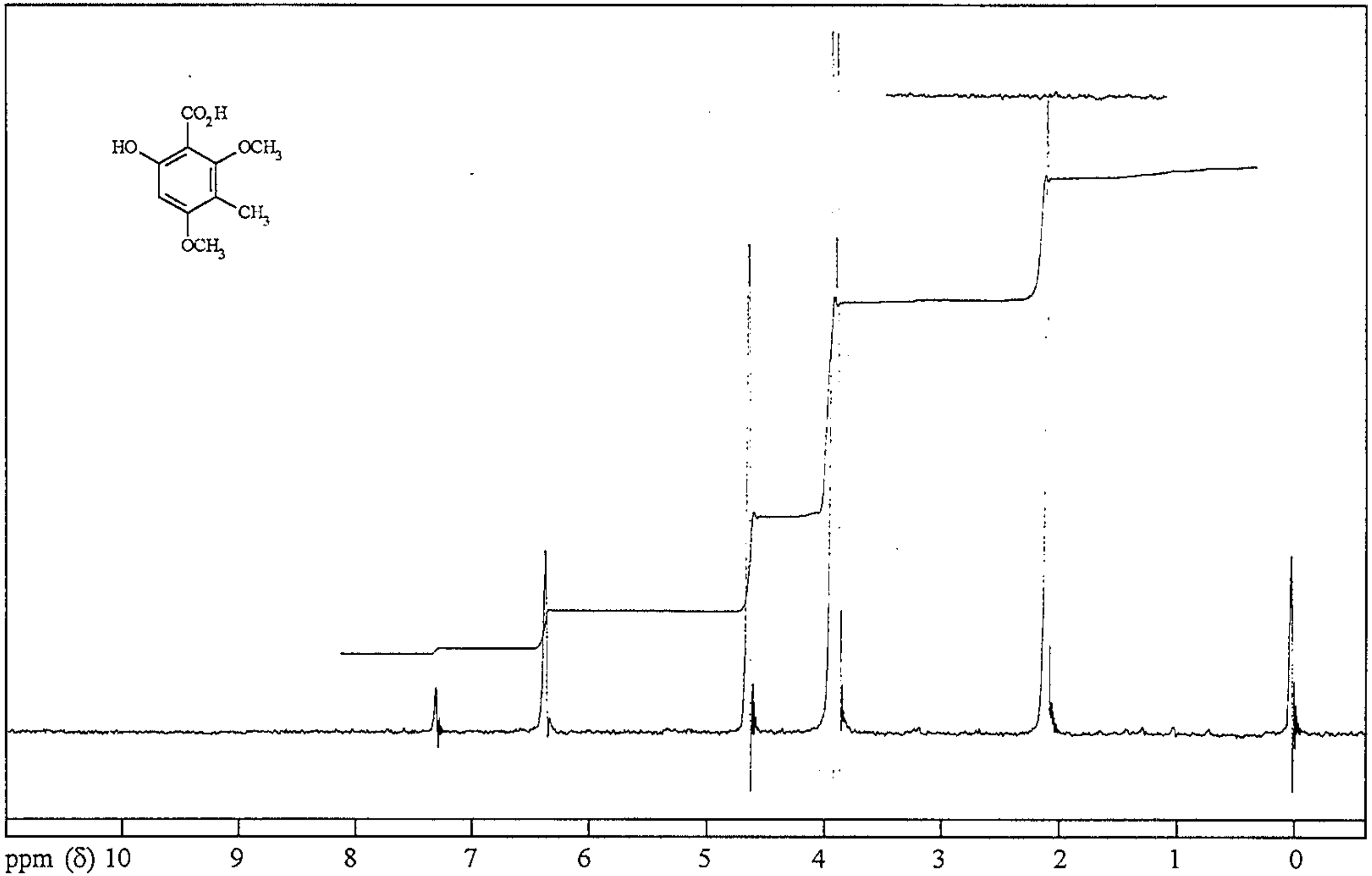


Figure 32 ^{1}H NMR spectrum of 2,4-dimethoxy-6-hydroxy-3-methylbenzoic acid (53) (D_2O)

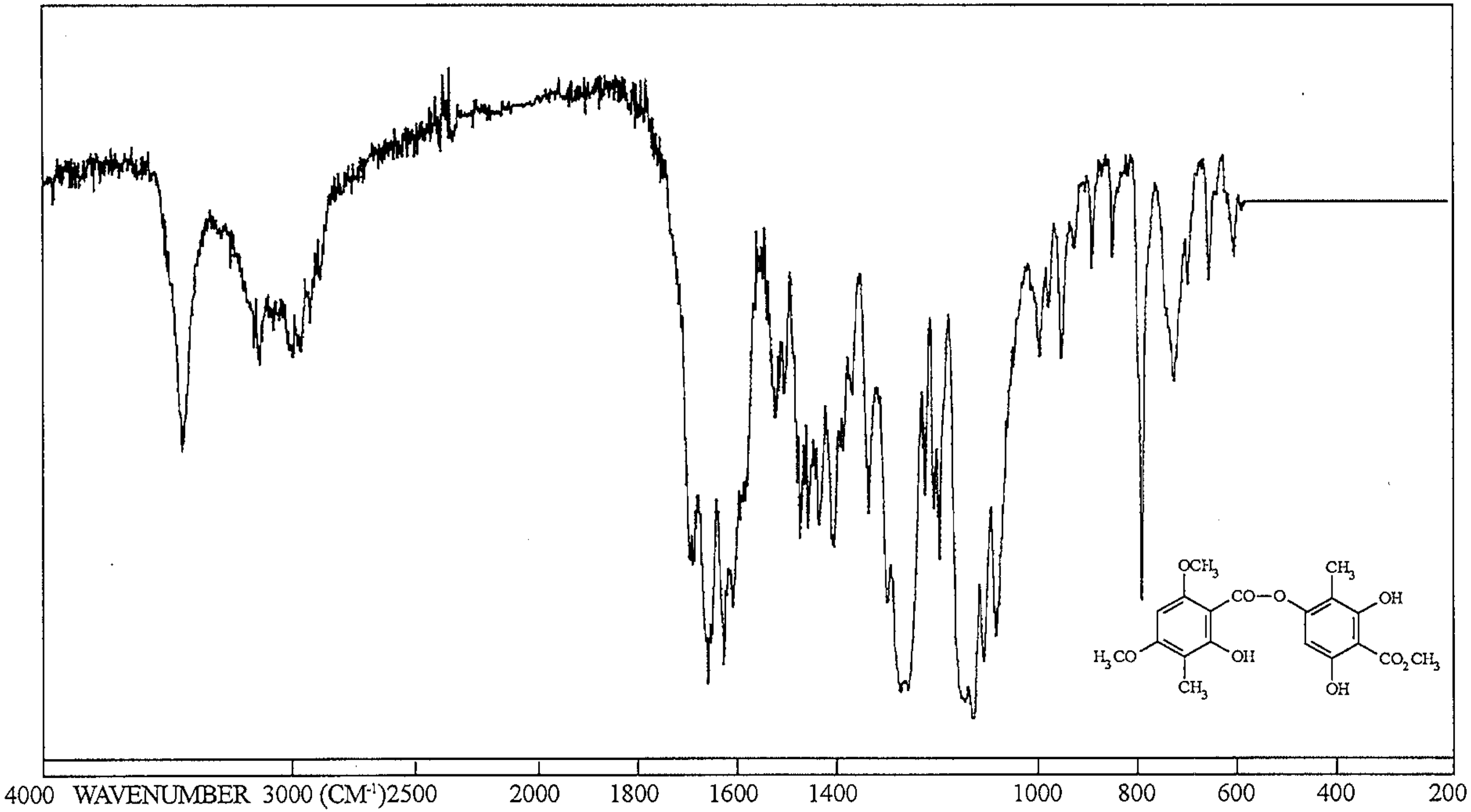


Figure 31 IR spectrum of methyl 2,6-dihydroxy-4-(4',6'-dimethoxy-2'-hydroxy-3'-methylbenzoyloxy)-3-methylbenzoate (54)

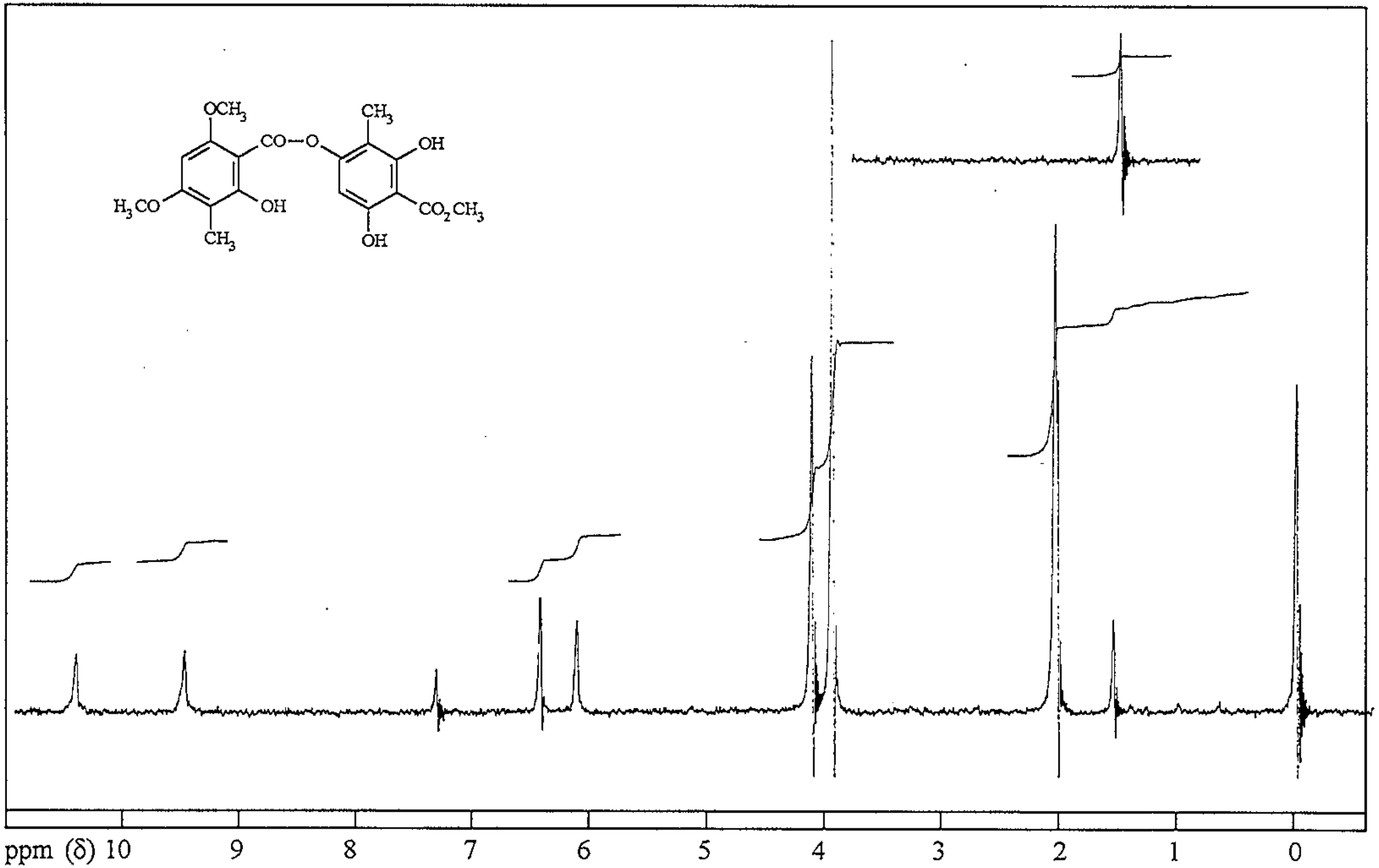


Figure 34 ^{1}H NMR spectrum of methyl 2,6-dihydroxy-4-(4',6'-dimethoxy-2'-hydroxy-3'-methylbenzoyloxy)-3-methylbenzoate (54)

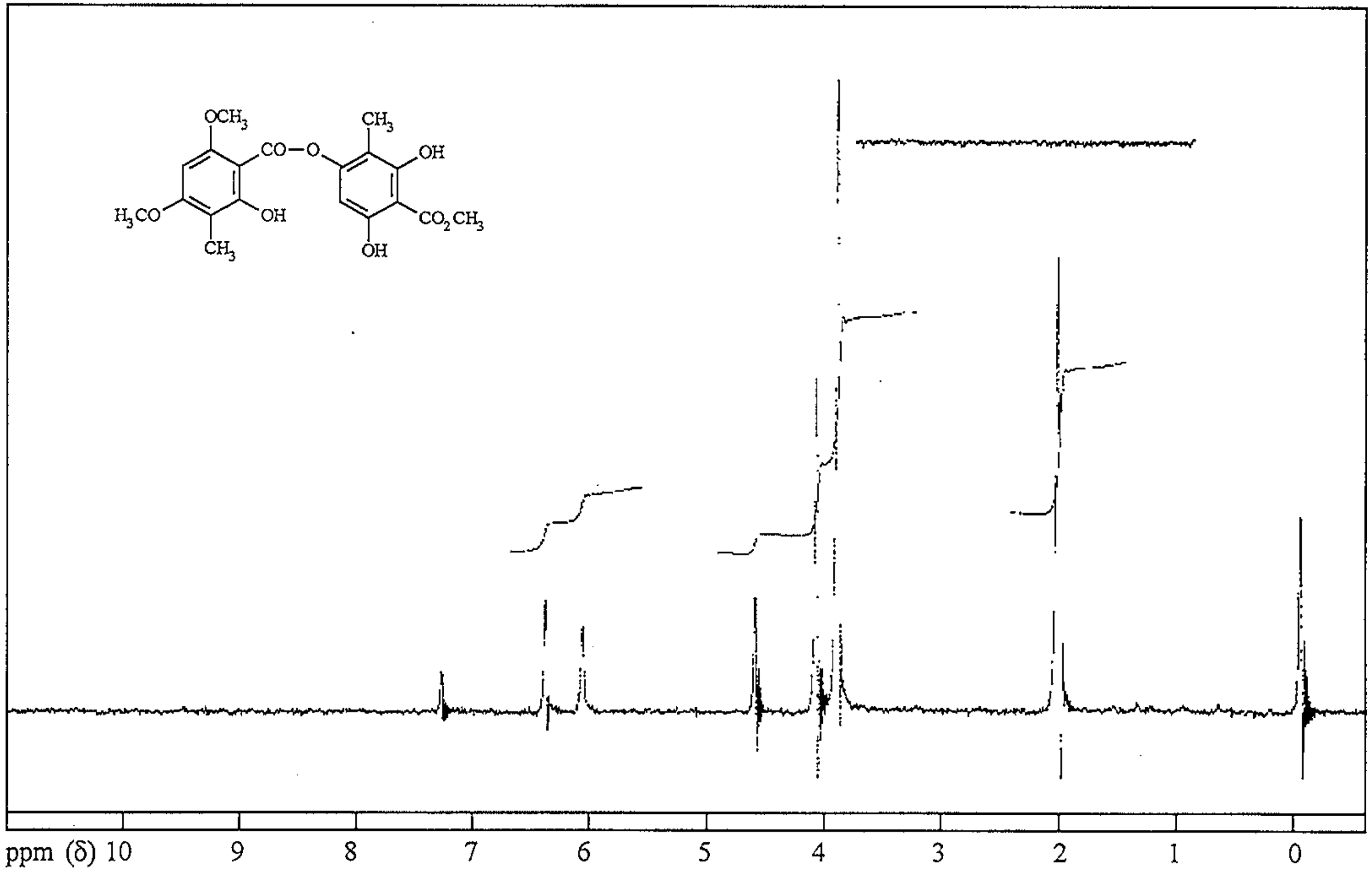


Figure 35 ¹H NMR spectrum of methyl 2,6-dihydroxy-4-(4',6'-dimethoxy-2'-hydroxy-3'-methylbenzoyloxy)-3-methylbenzoate (54) (D_2O)

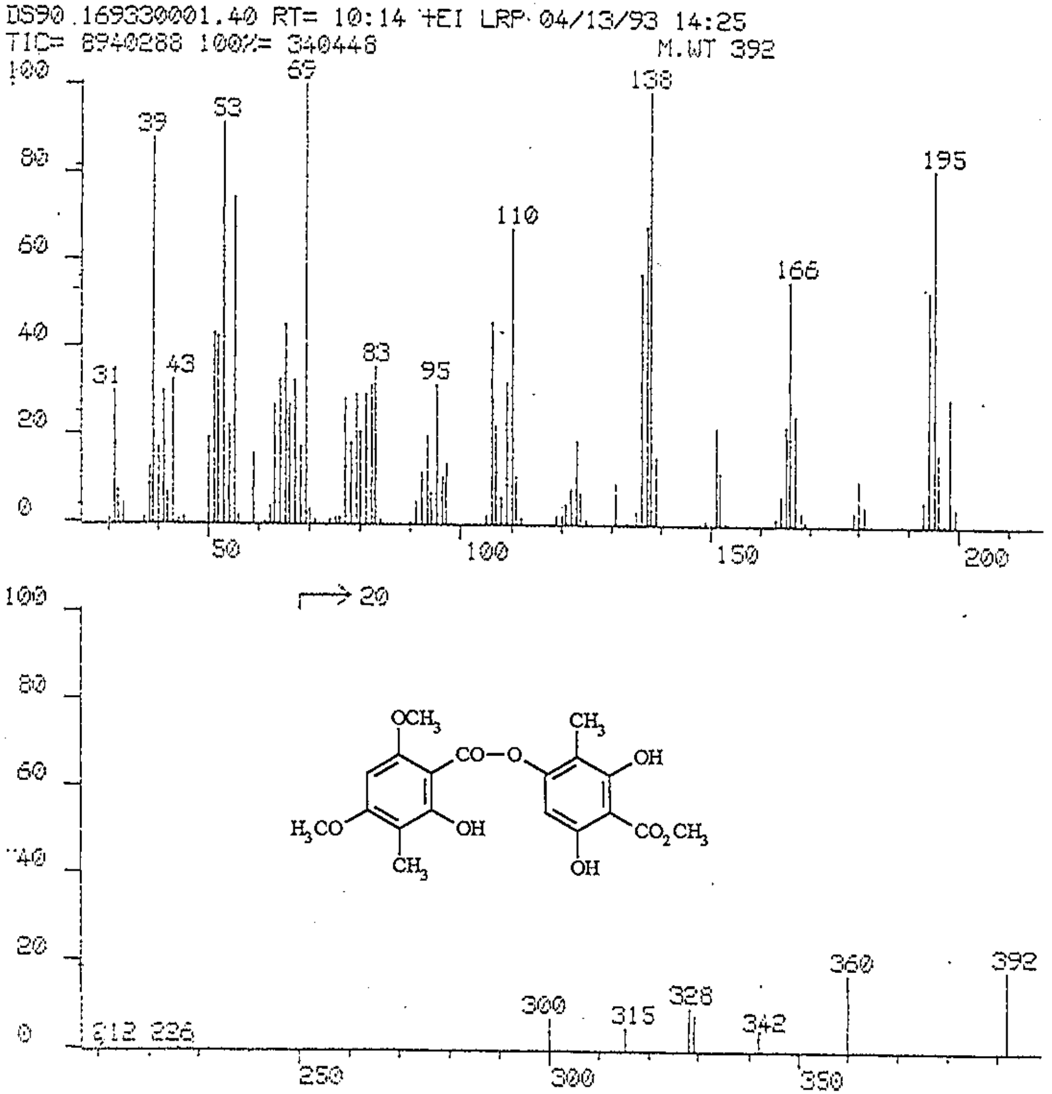


Figure 36 Mass spectrum of methyl 2,6-dihydroxy-4-(4',6'-dimethoxy-2'-hydroxy-3'-methylbenzoyloxy)-3-methylbenzoate (54)

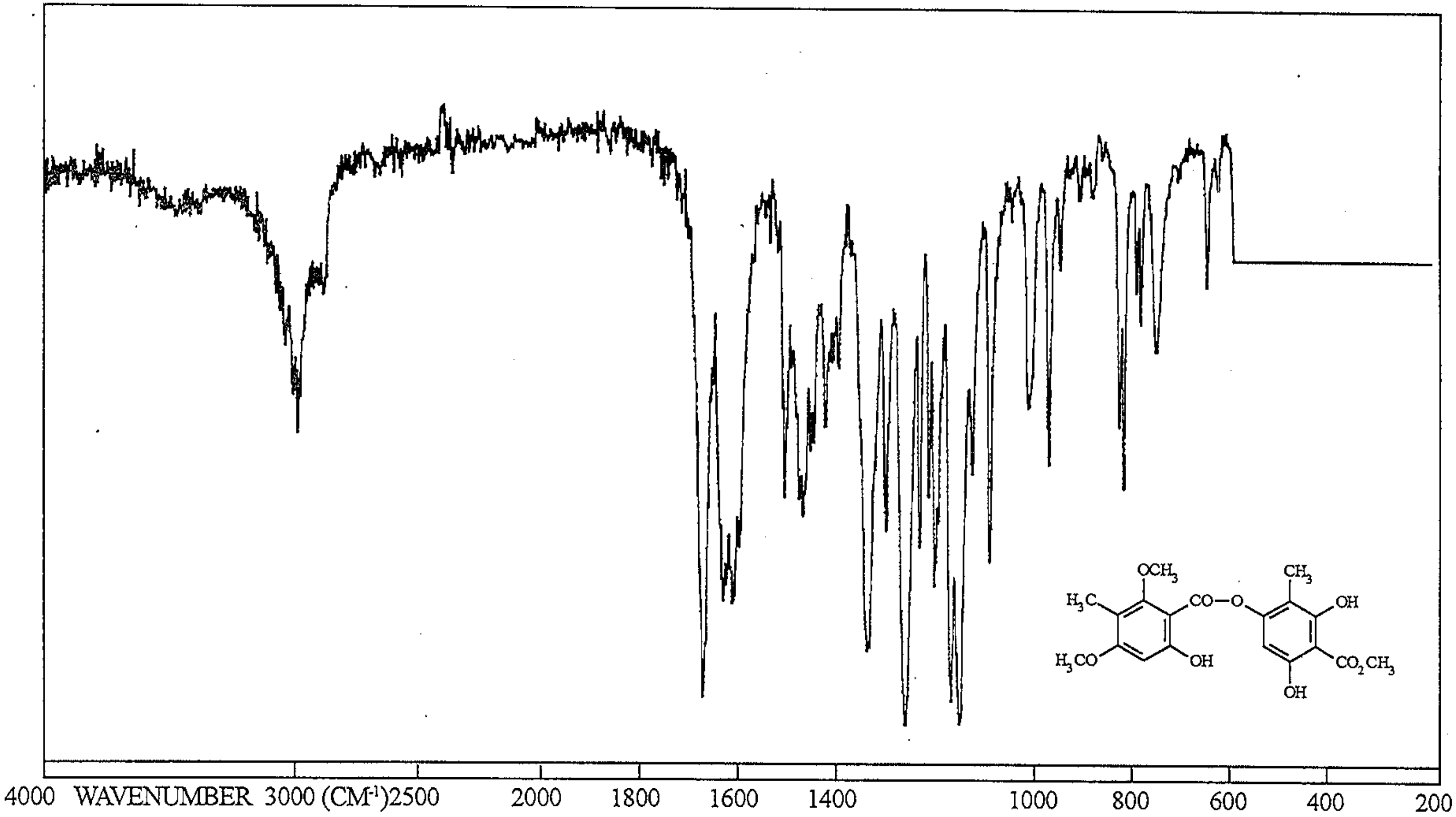


Figure 37 IR spectrum of methyl 2,6-dihydroxy-4-(2',4'-dimethoxy-6'-hydroxy-3'-methylbenzoyloxy)-3-methylbenzoate (61)

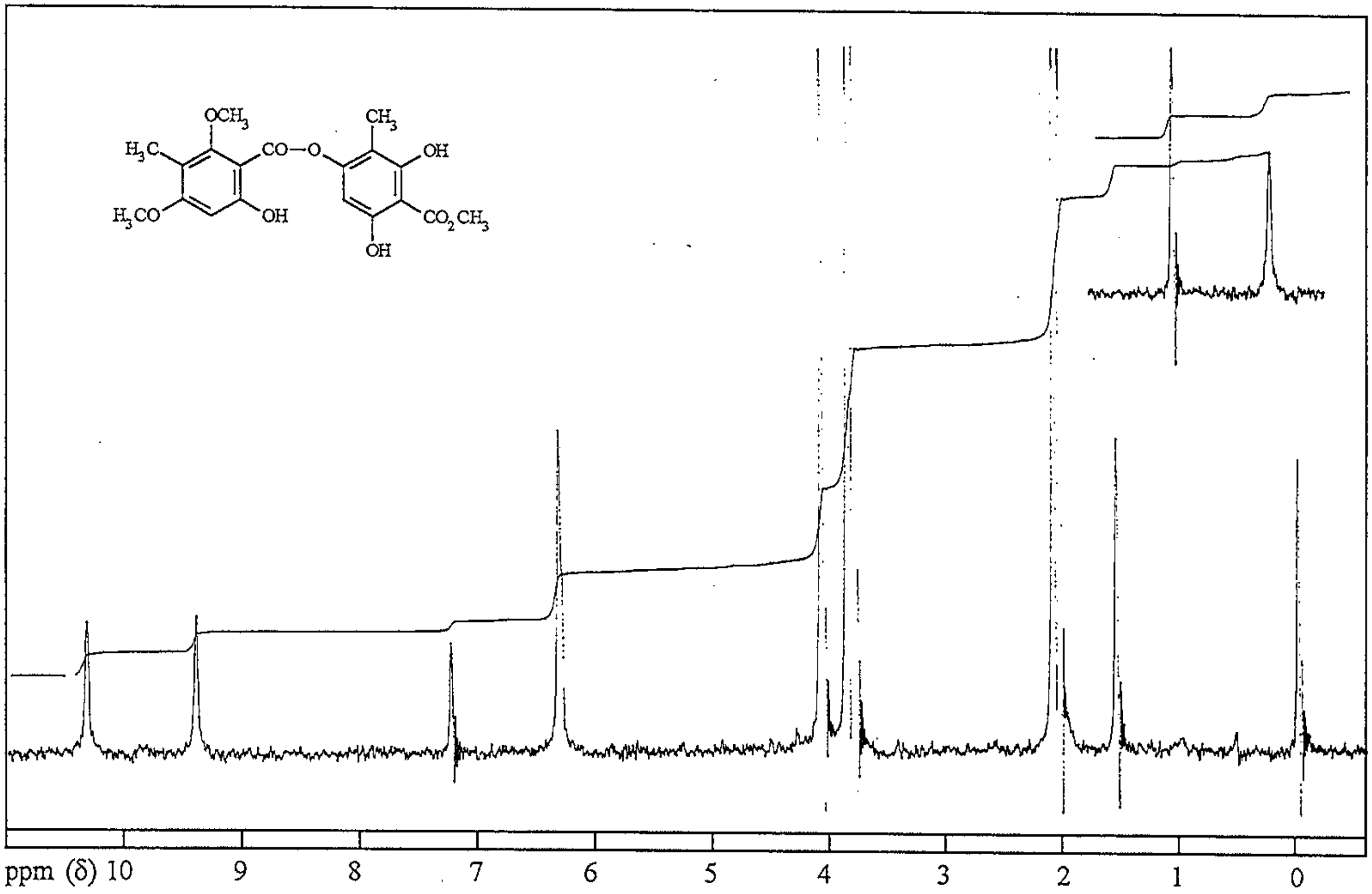


Figure 38 ^{1}H NMR spectrum of methyl 2,6-dihydroxy-4-(2',4'-dimethoxy-6'-hydroxy-3'-methylbenzoyloxy)-3-methylbenzoate (61)

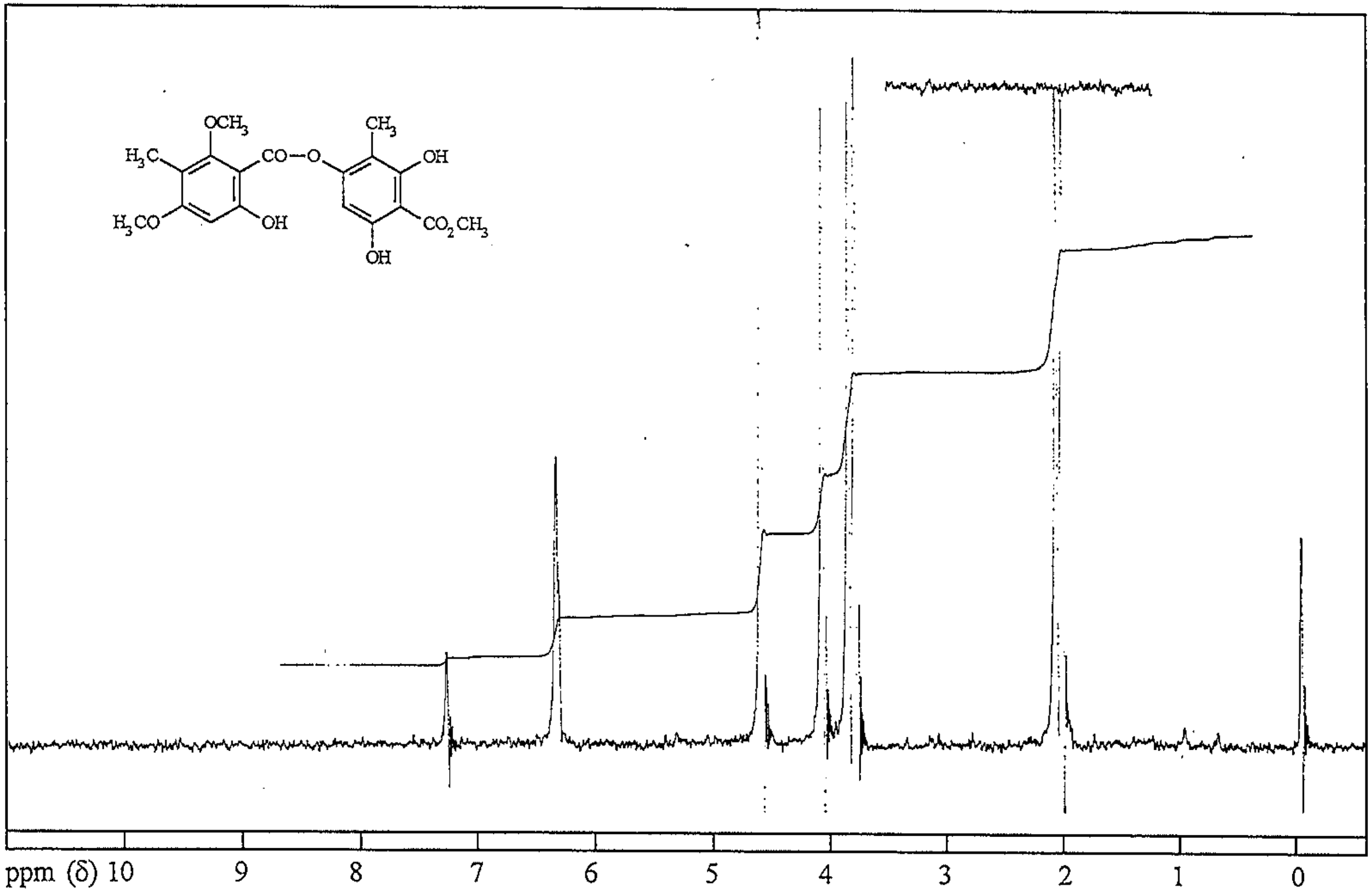


Figure 39 ^{1}H NMR spectrum of methyl 2,6-dihydroxy-4-(2',4'-dimethoxy-6'-hydroxy-3'-methylbenzoyloxy)-3-methylbenzoate (61) (D_2O)

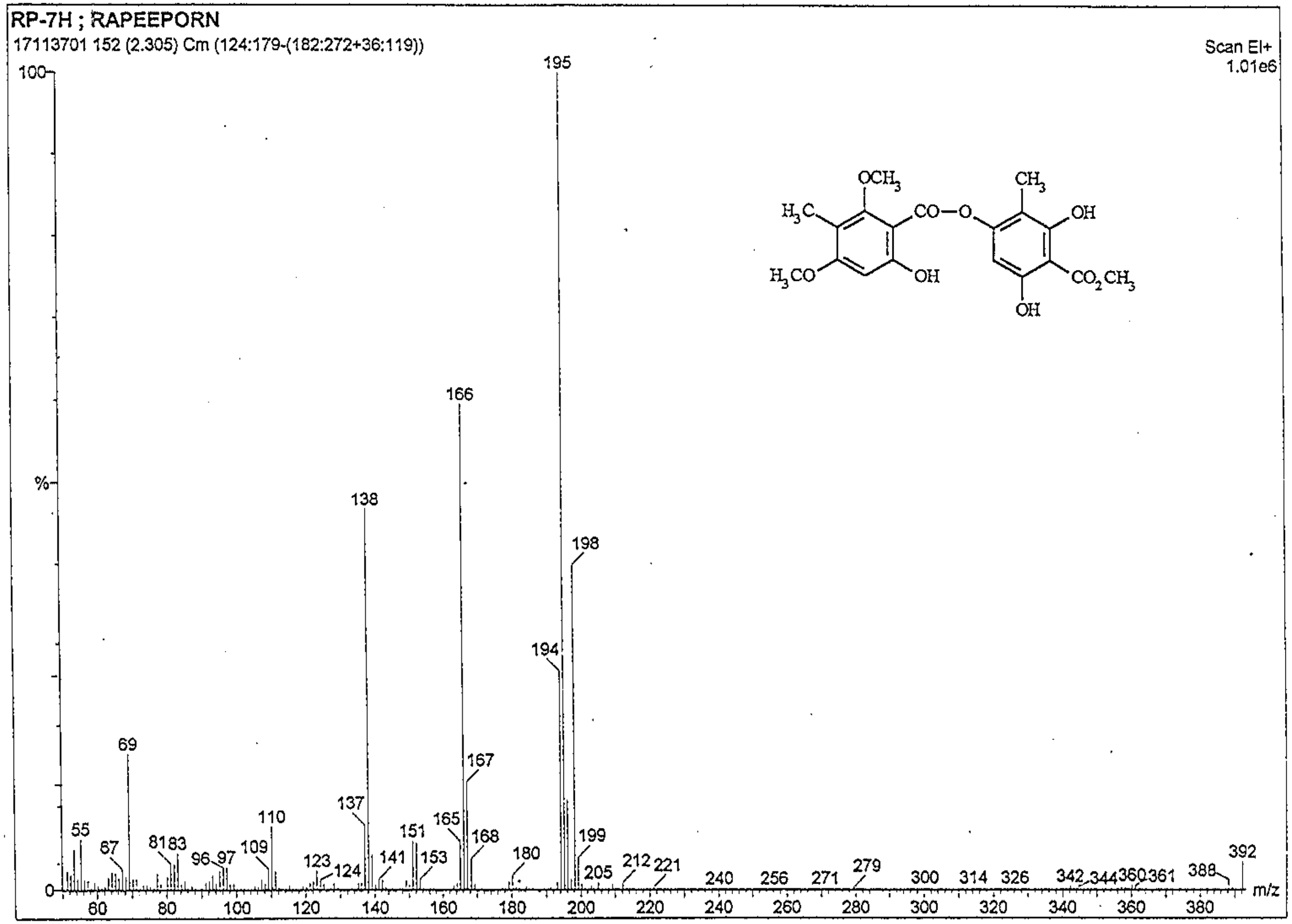


Figure 40 Mass spectrum of methyl 2,6-dihydroxy-4-(2',4'-dimethoxy-6'-hydroxy-3'-methylbenzoyloxy)-3-methylbenzoate (61)

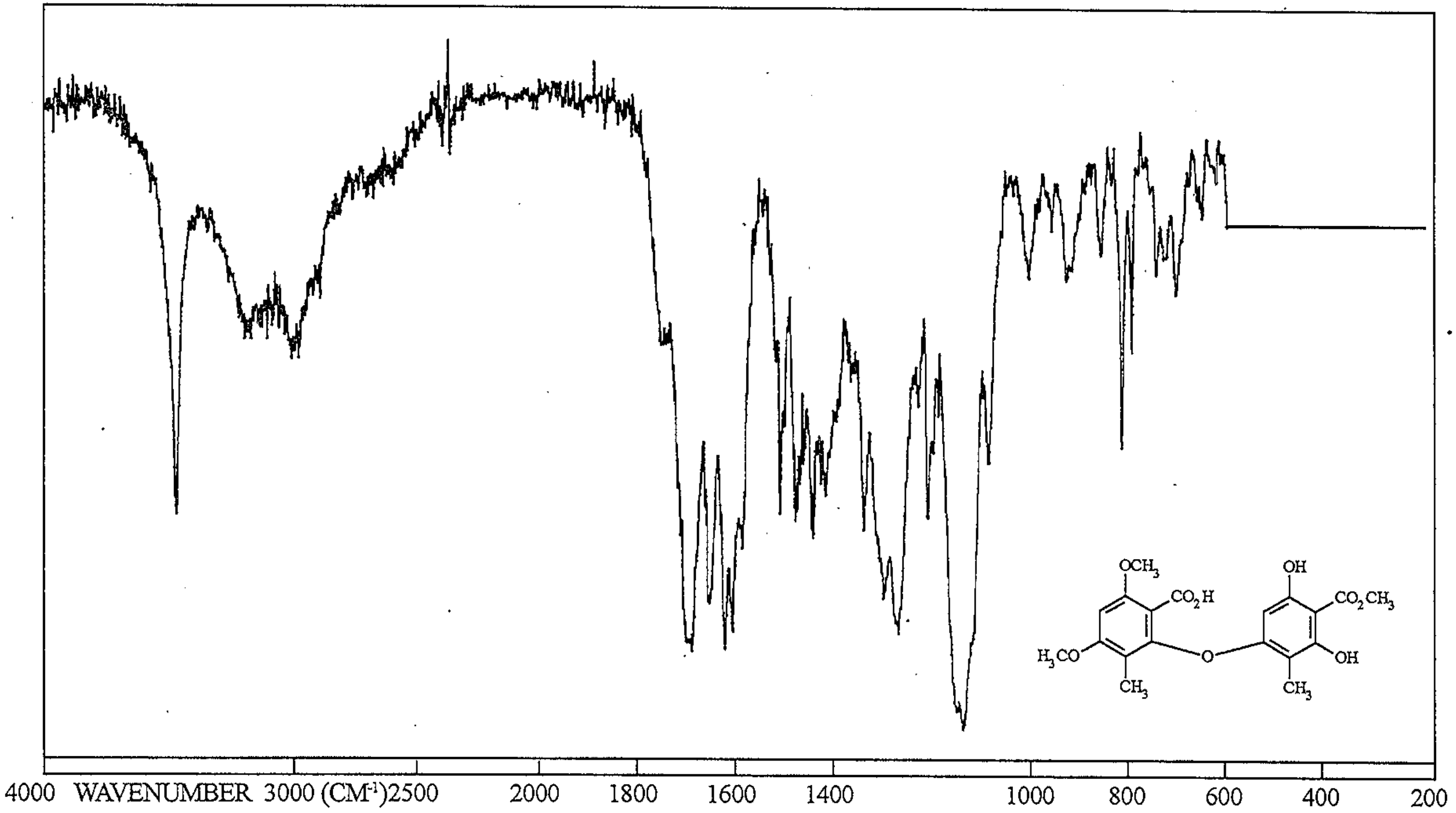


Figure 41 IR spectrum of 2-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (55)

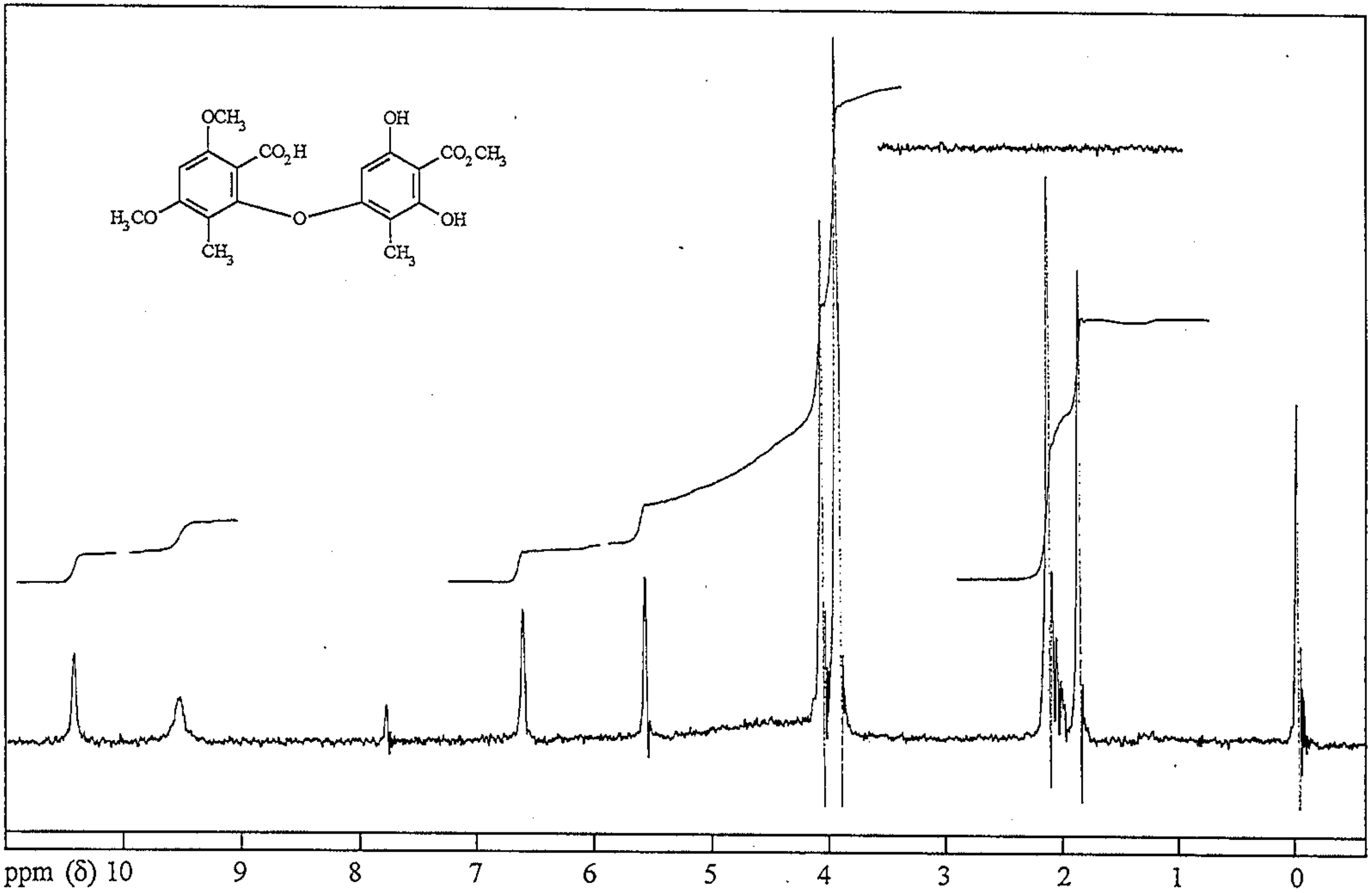


Figure 42 ^{1}H NMR spectrum of 2-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (55)

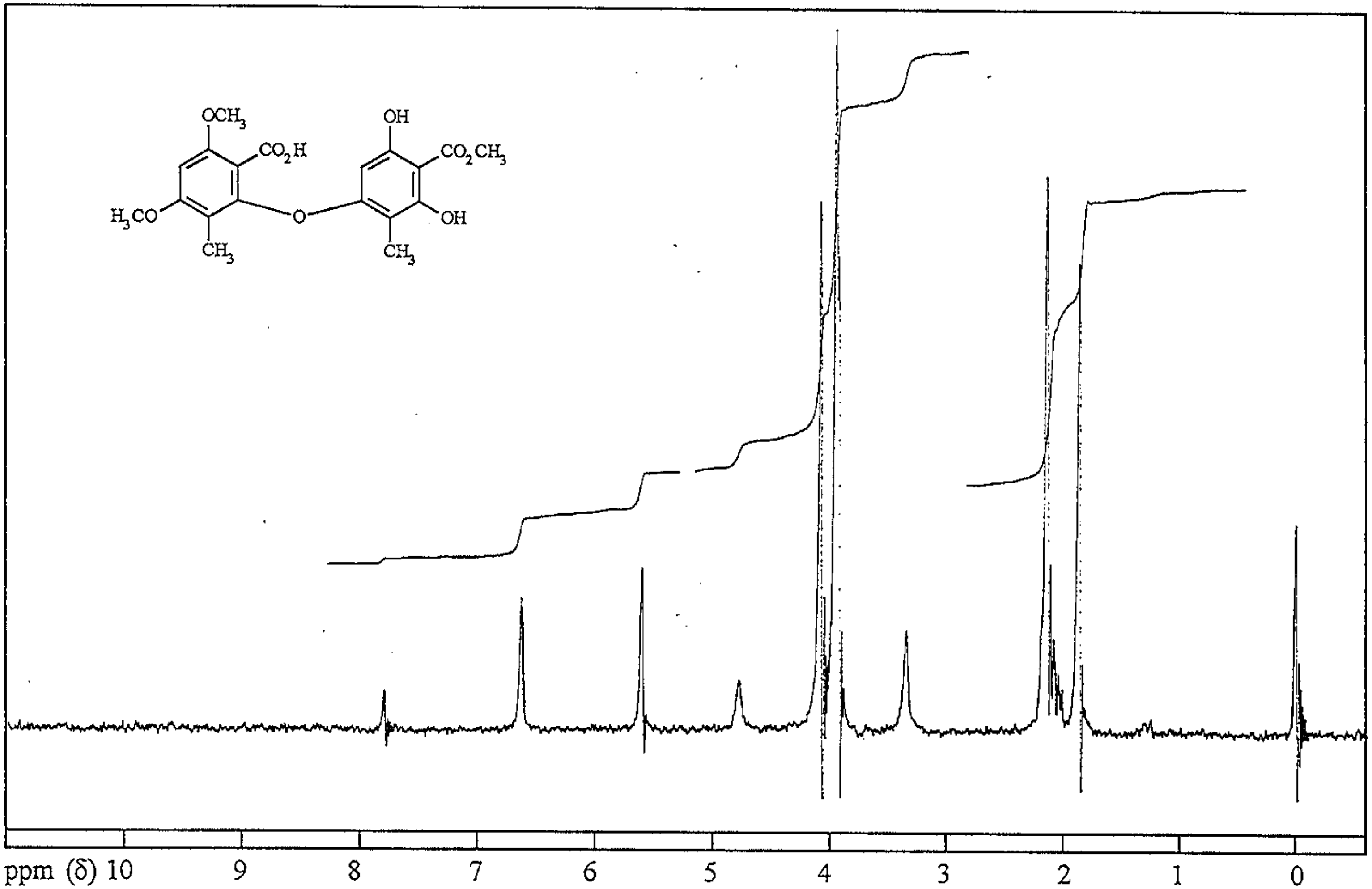


Figure 43 ^{1}H NMR spectrum of 2-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (55) (D_2O)

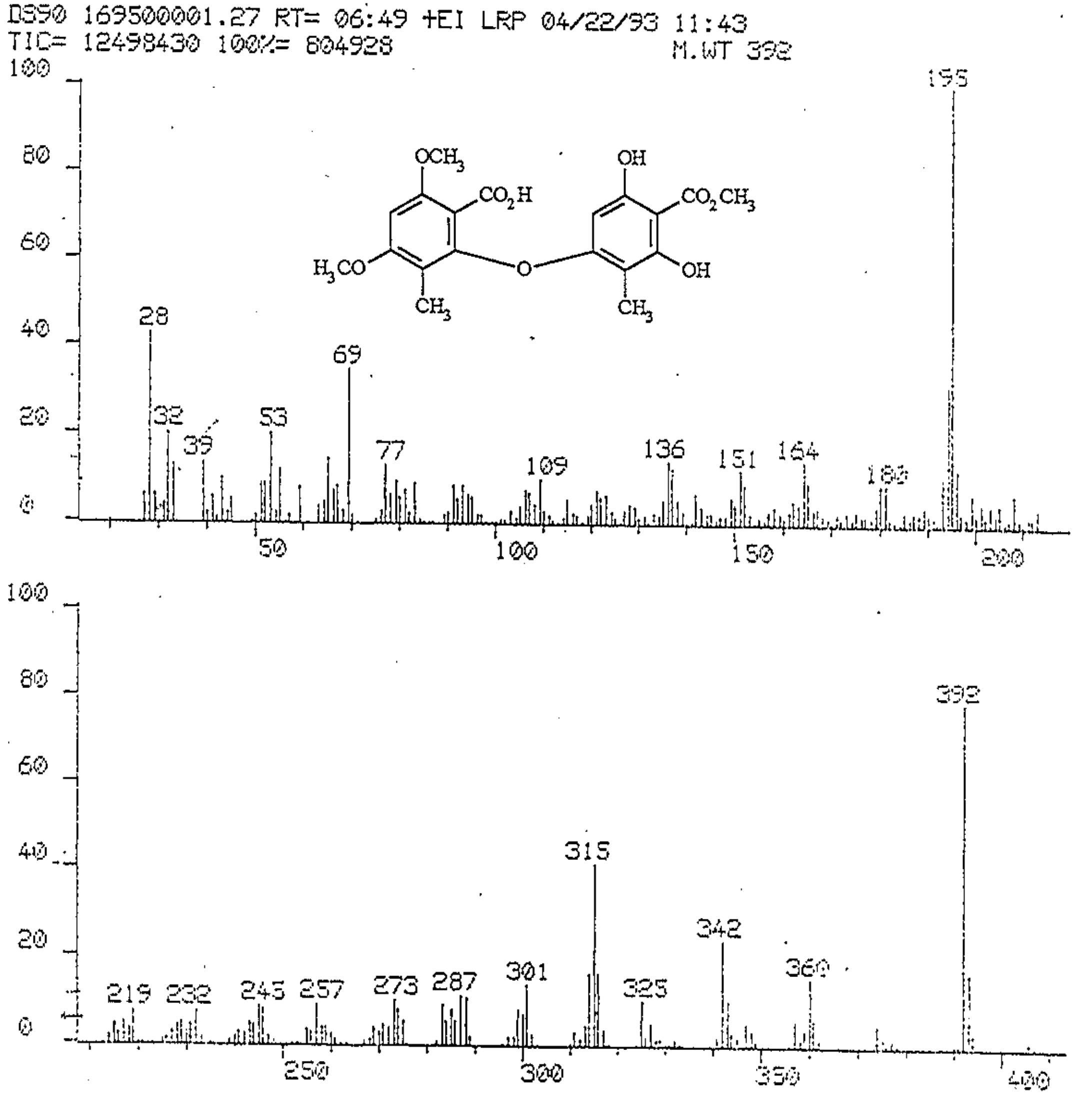


Figure 44 Mass spectrum of 2-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (55)

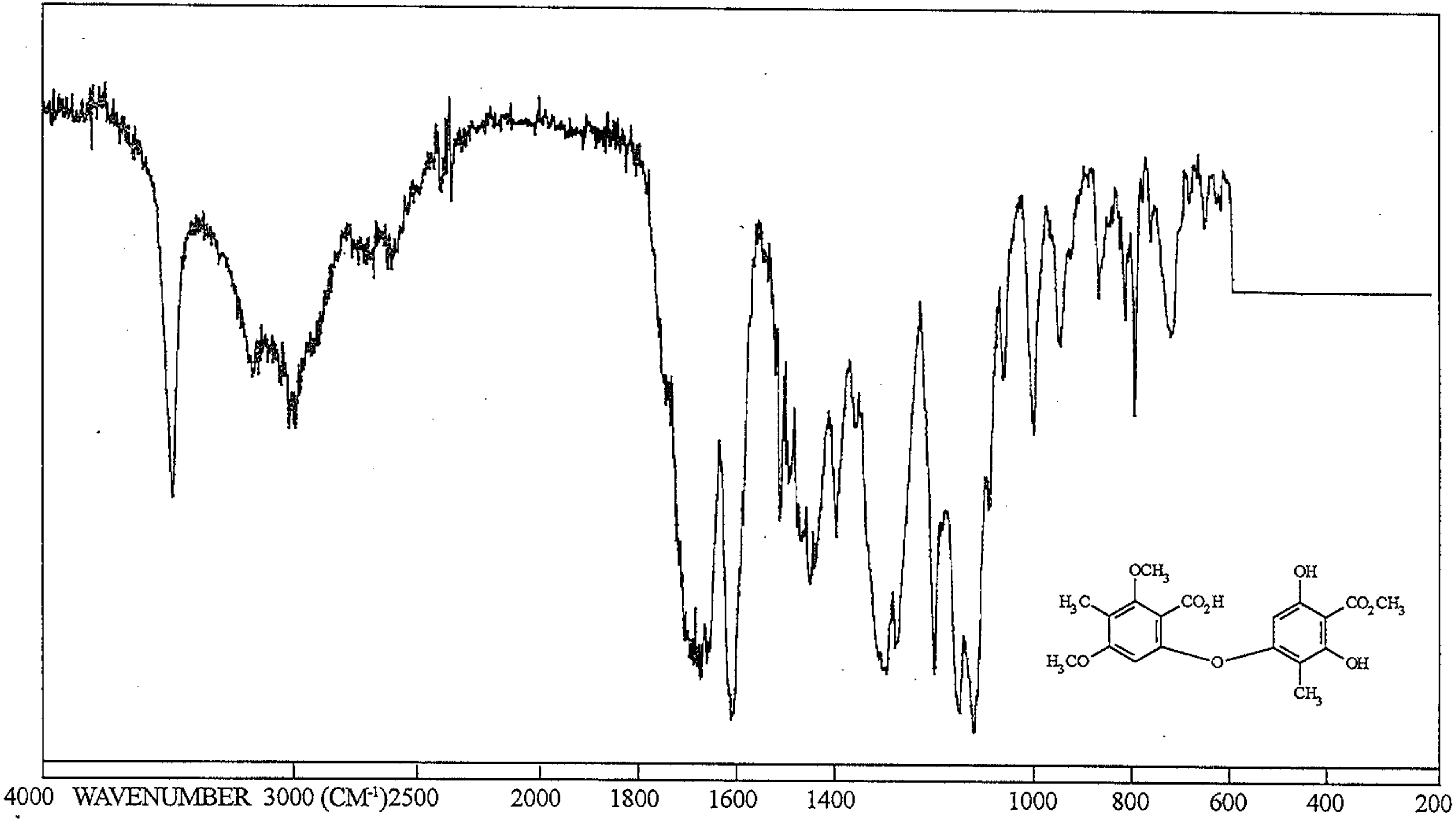


Figure 45 IR spectrum of 6-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-2,4-dimethoxy-3-methylbenzoic acid (62)

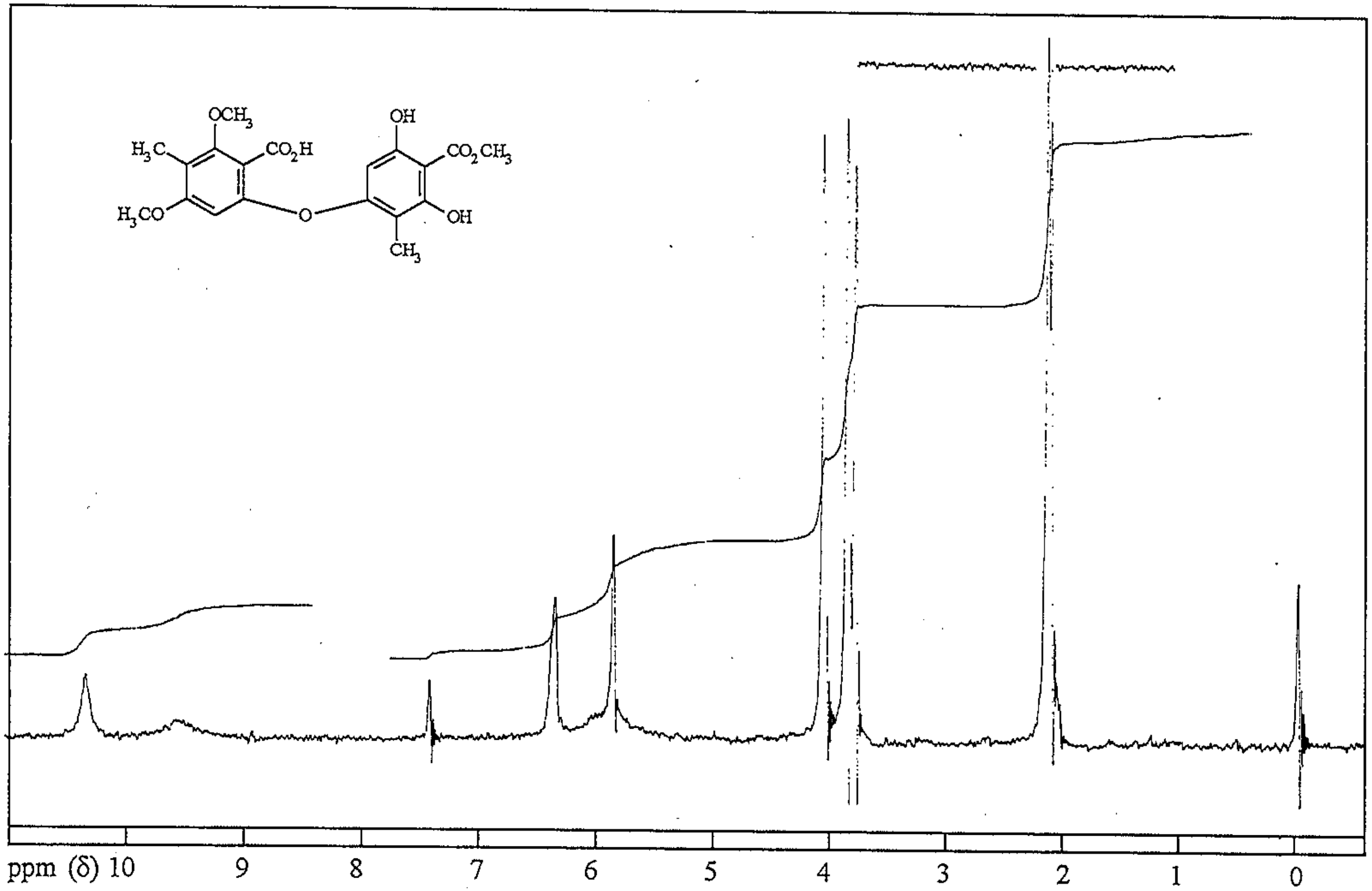


Figure 46 ^{1}H NMR spectrum of 6-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-2,4-dimethoxy-3-methylbenzoic acid (62)

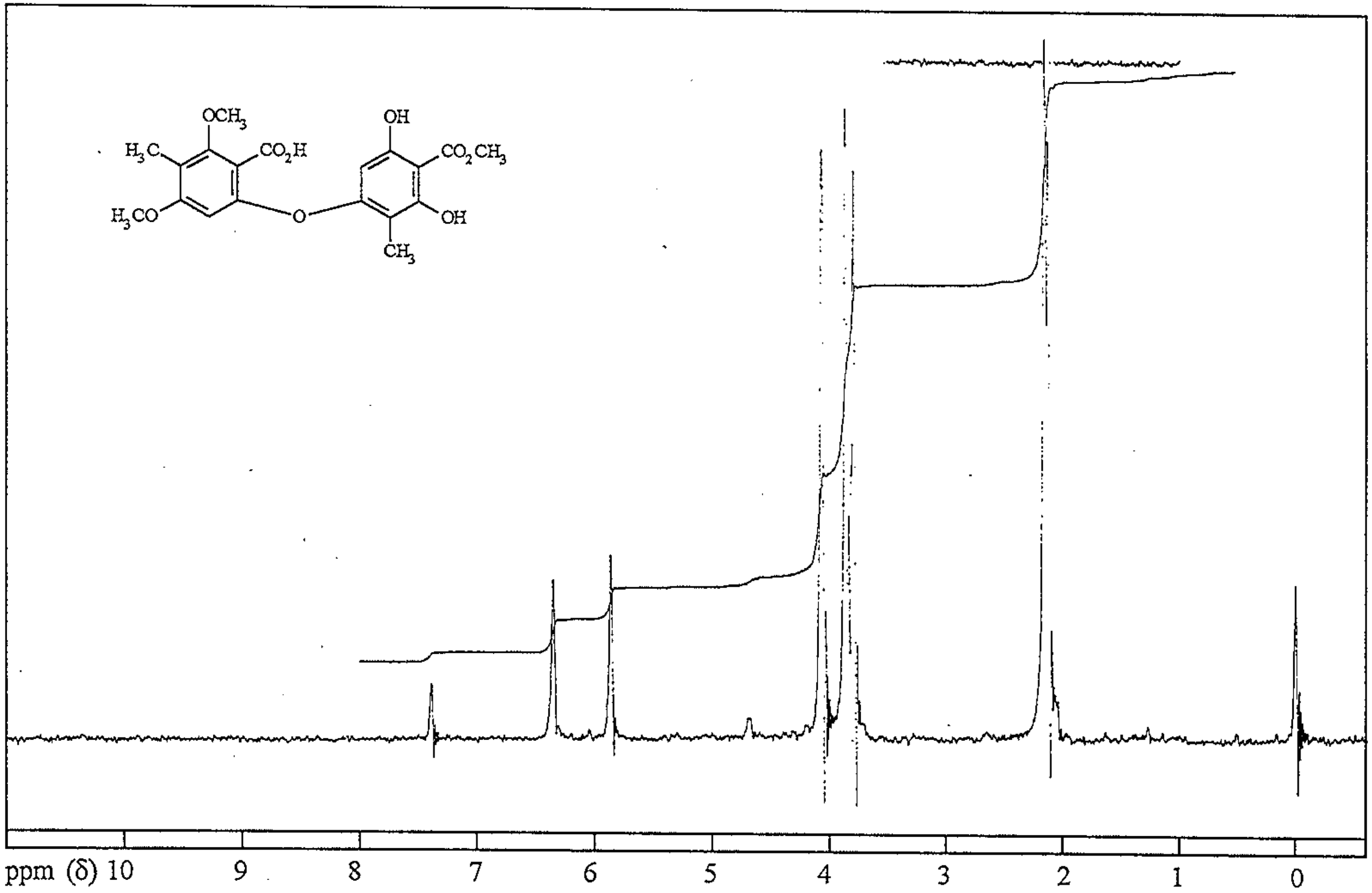


Figure 47 ^{1}H NMR spectrum of 6-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-2,4-dimethoxy-3-methylbenzoic acid (62) (D_2O)

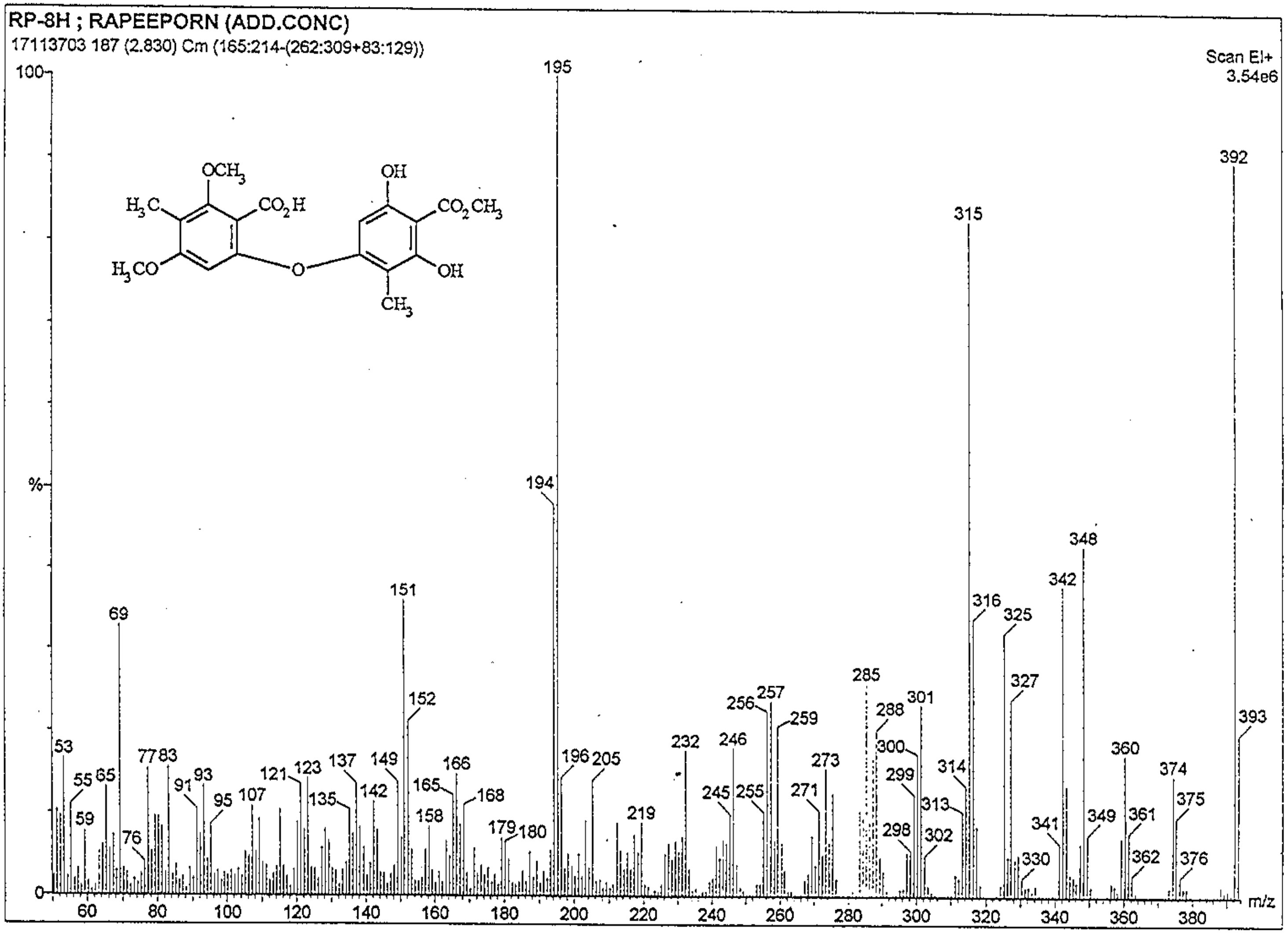


Figure 48 Mass spectrum of 6-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-2,4-dimethoxy-3-methylbenzoic acid (62)

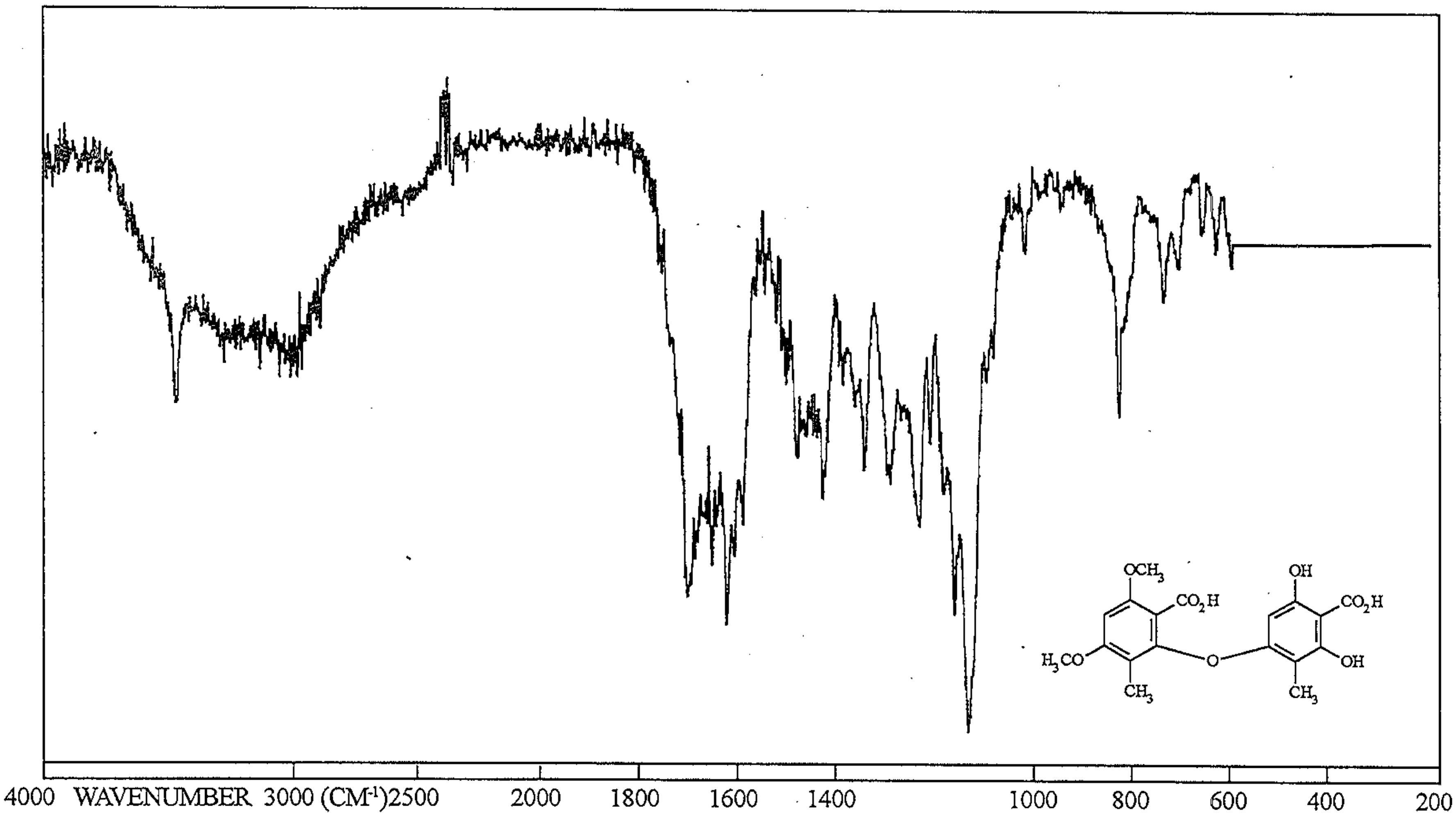


Figure 49 IR spectrum of 2-(3',5'-dihydroxy-4'-carboxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (56)

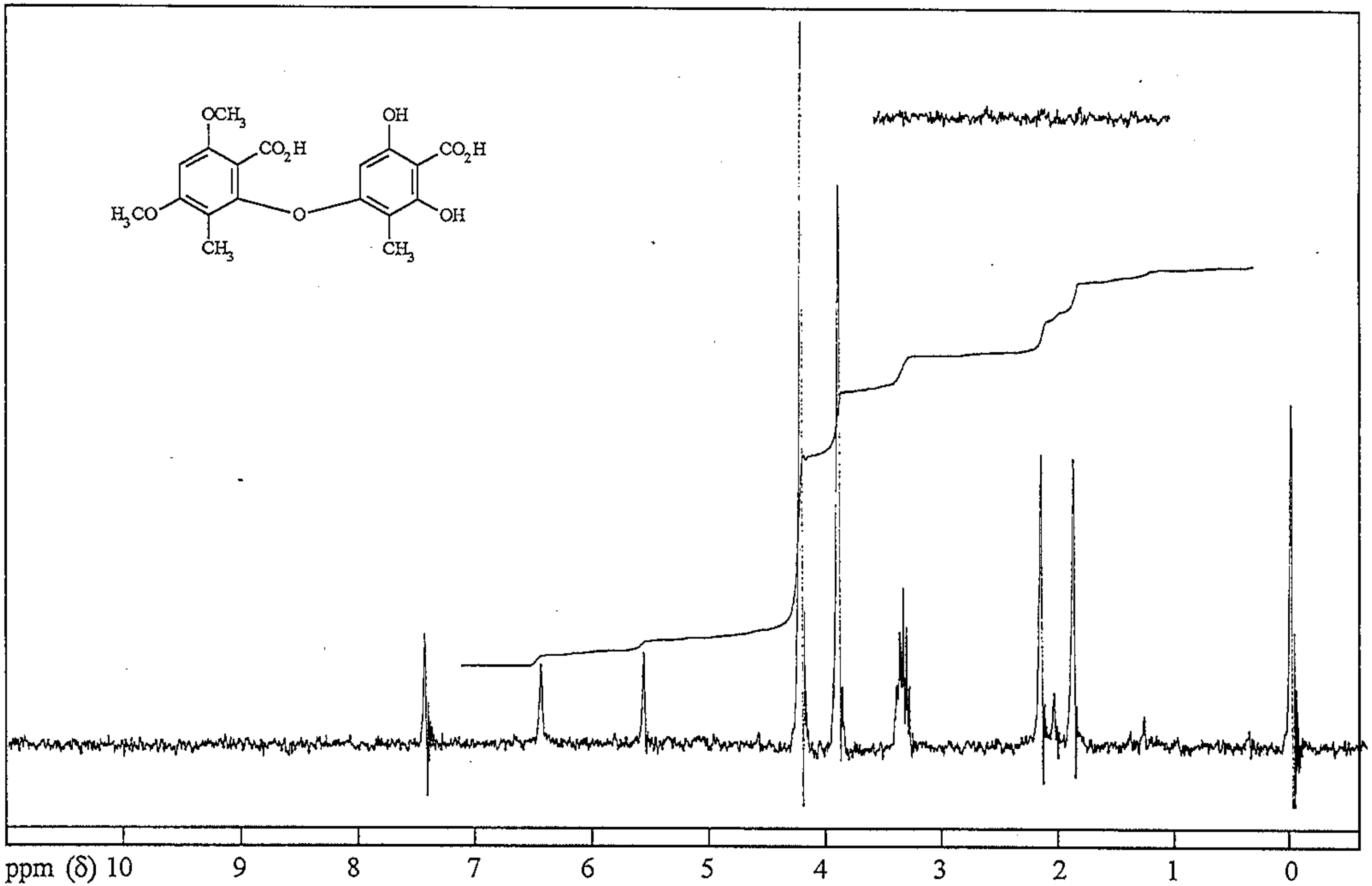


Figure 50 ¹H NMR spectrum of 2-(3',5'-dihydroxy-4'-carboxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (56)

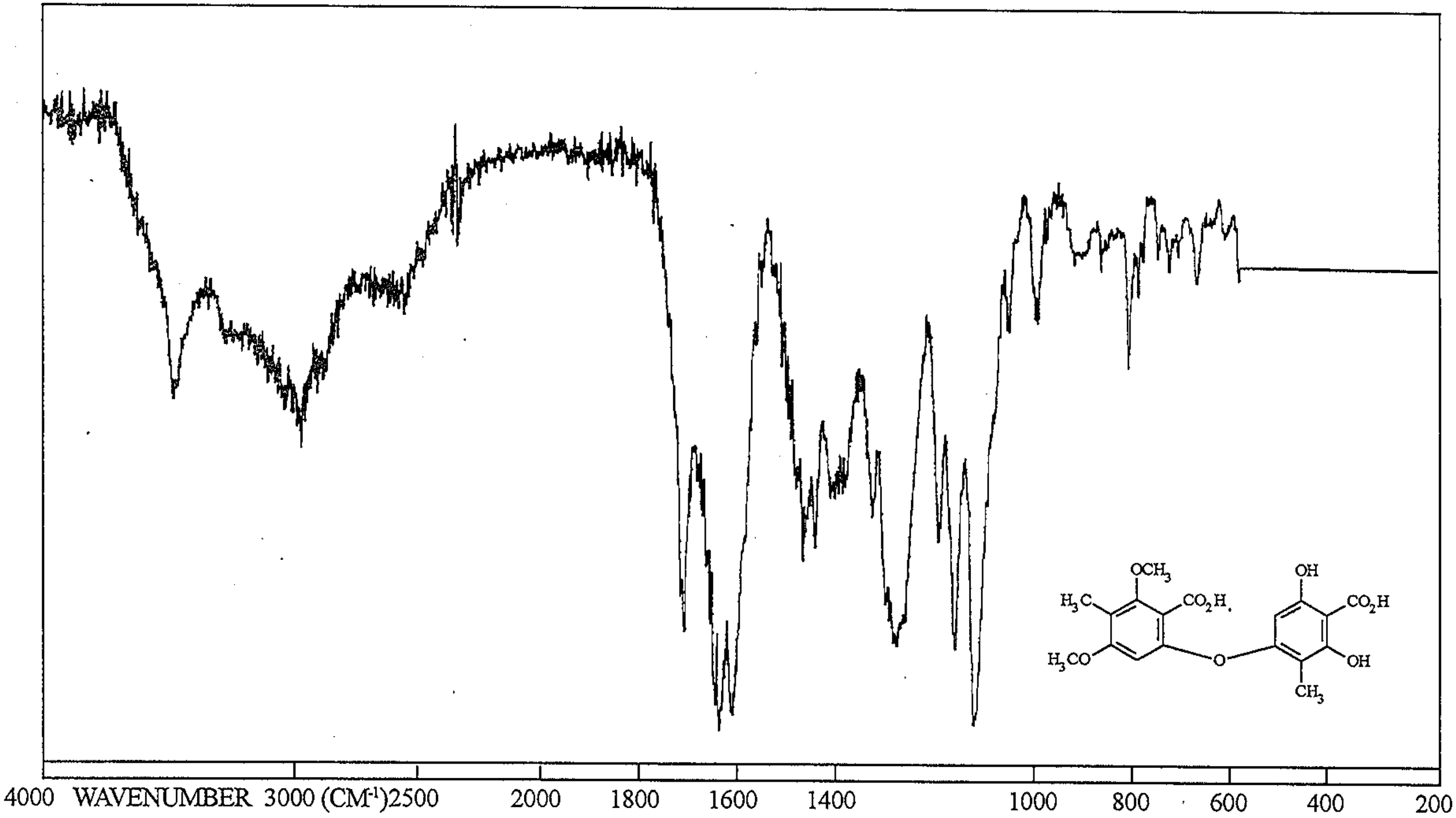


Figure 51 IR spectrum of 6-(3',5'-dihydroxy-4'-carboxy-2'-methylphenoxy)-2,4-dimethoxy-3-methylbenzoic acid (63)

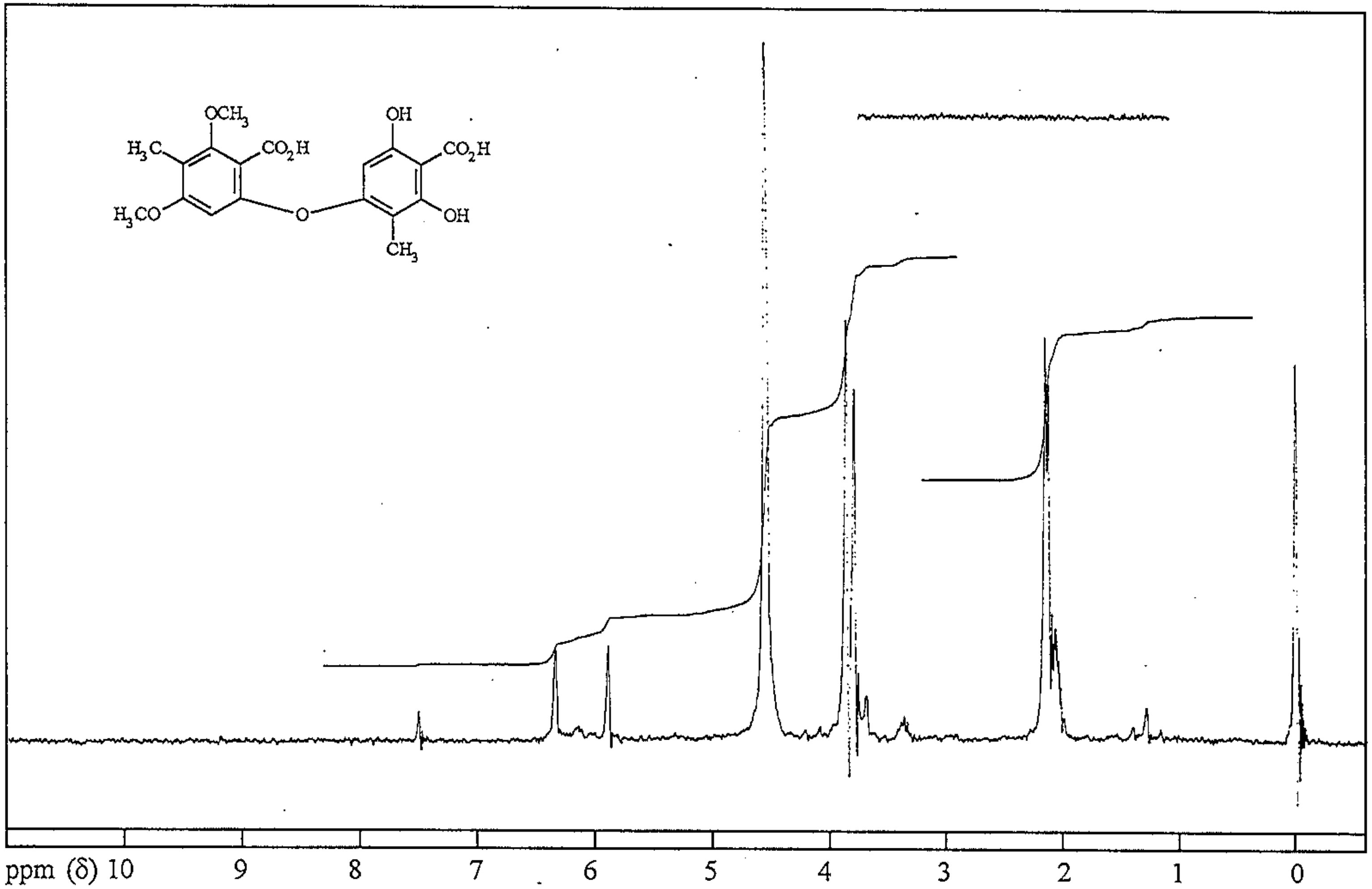


Figure 52 ^{1}H NMR spectrum of 6-(3',5'-dihydroxy-4'-carboxy-2'-methylphenoxy)-2,4-dimethoxy-3-methylbenzoic acid (63)

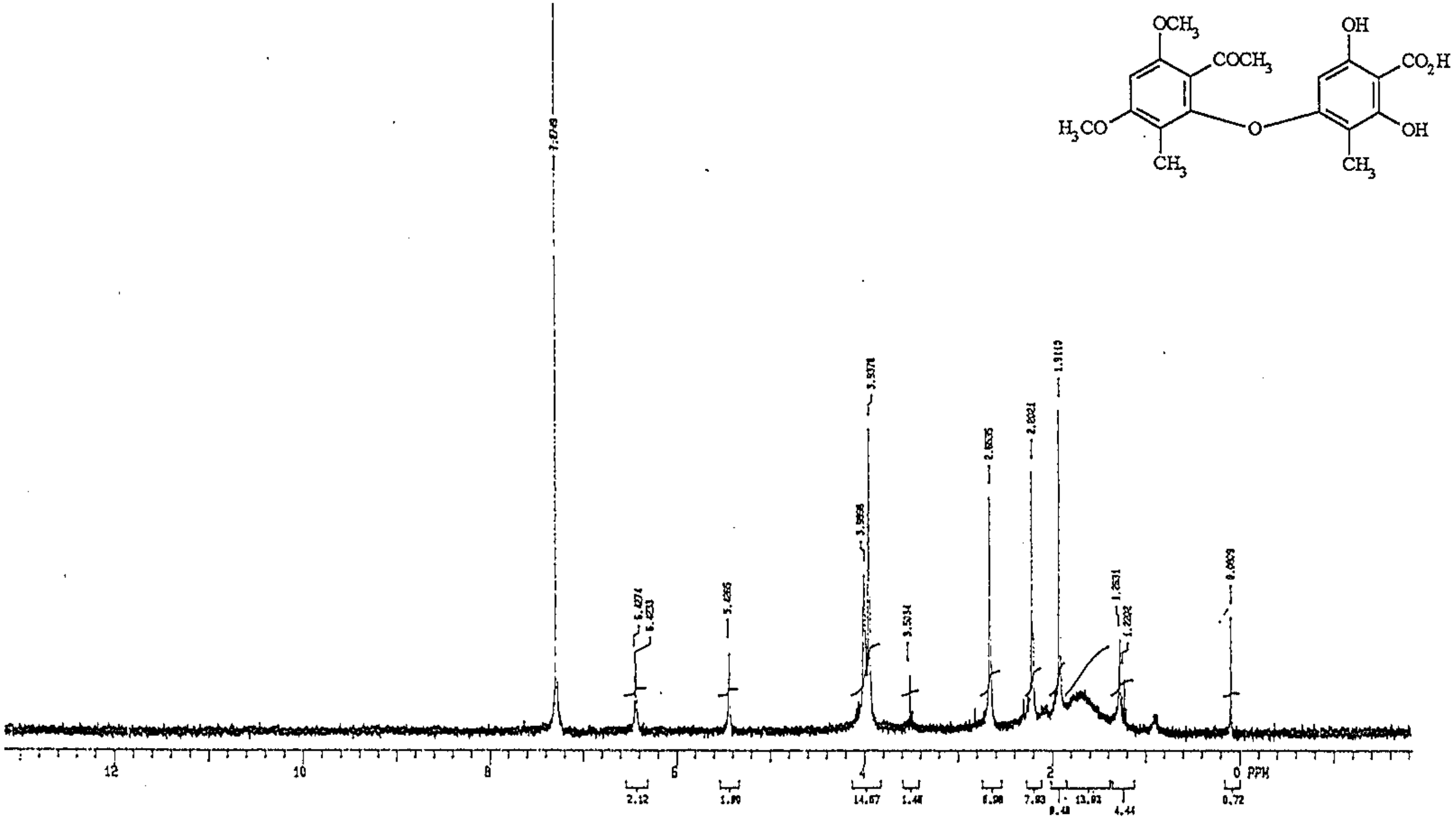


Figure 53 ^1H NMR spectrum of 4-(2'-acetyl-3',5'-dimethoxy-6'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (57)

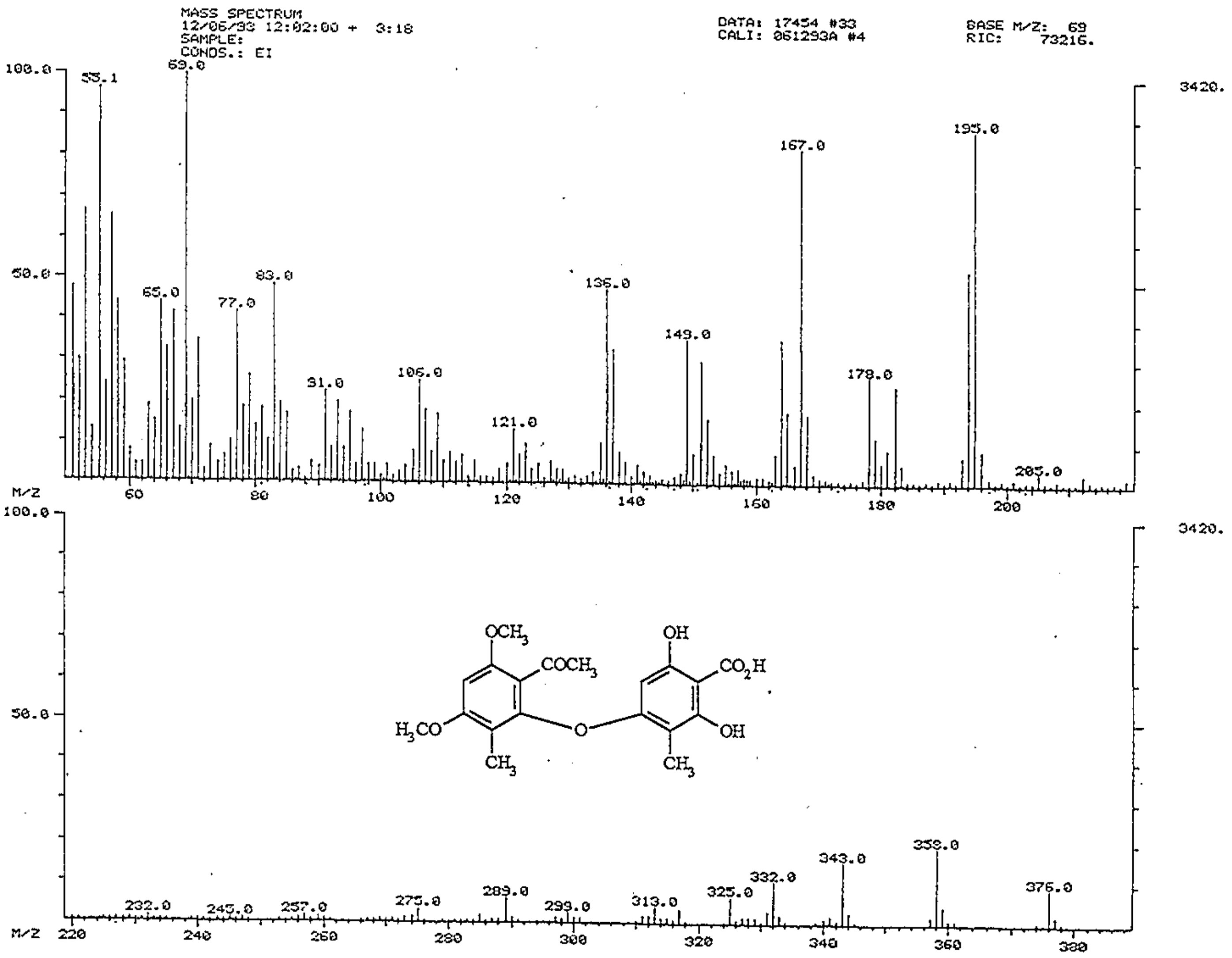
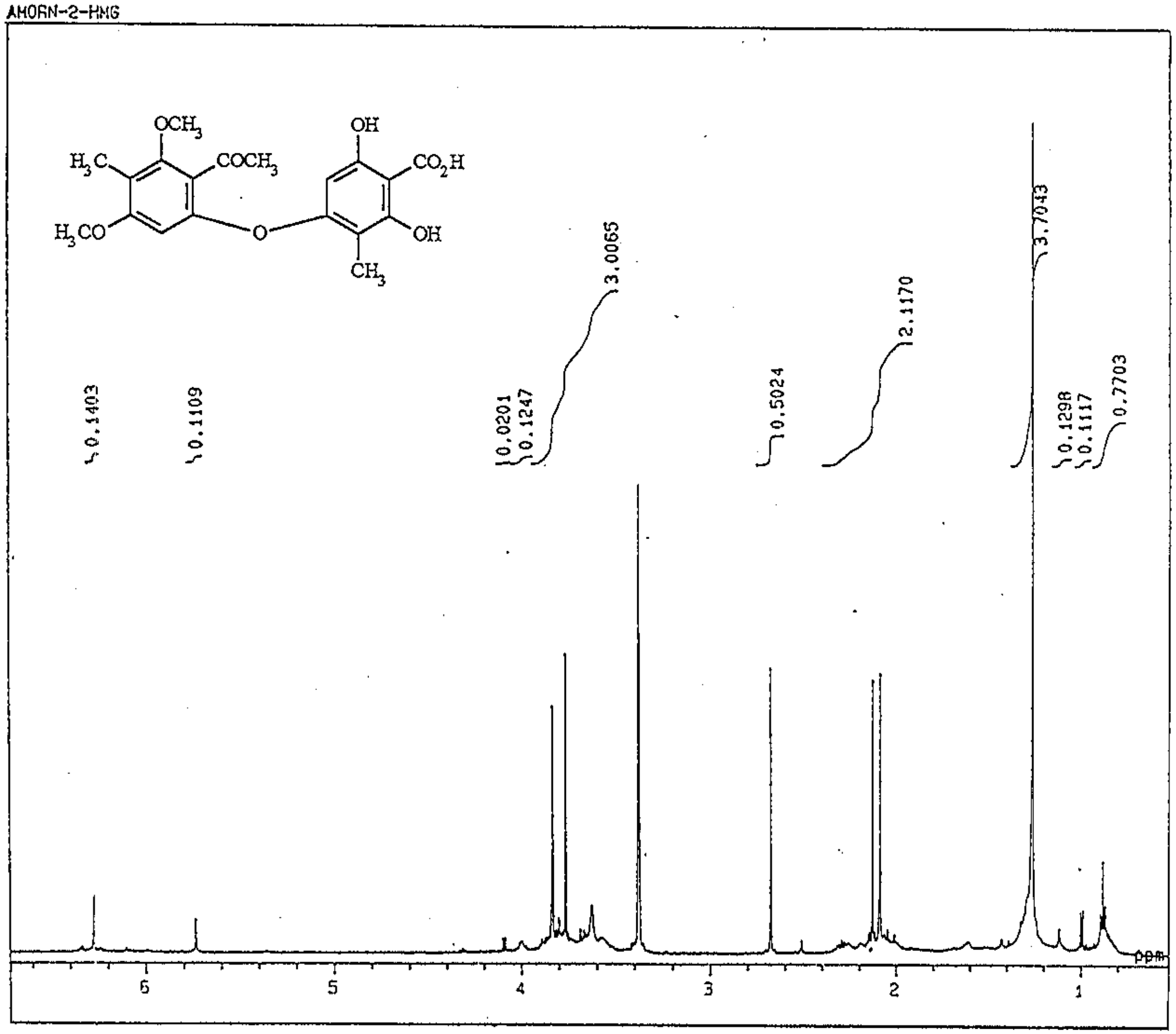


Figure 54 Mass spectrum of 4-(2'-acetyl-3',5'-dimethoxy-6'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (57)



NO	IGVAL	INI PPM	FIN PPM	IG
1	0.1403	6.31	6.25	0.05
2	0.1109	5.77	5.70	0.05
3	0.0201	4.12	4.06	0.05
4	0.1247	4.05	3.94	0.05
5	3.0065	3.94	3.48	0.05
6	0.5024	2.74	2.60	0.05
7	2.1170	2.39	1.91	0.05
8	3.7043	1.37	1.19	0.05
9	0.1298	1.15	1.06	0.05
10	0.1117	1.03	0.95	0.05
11	0.7703	0.94	0.77	0.05

Figure 55 ^{1}H NMR spectrum of 4-(2'-acetyl-3',5'-dimethoxy-4'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (64)

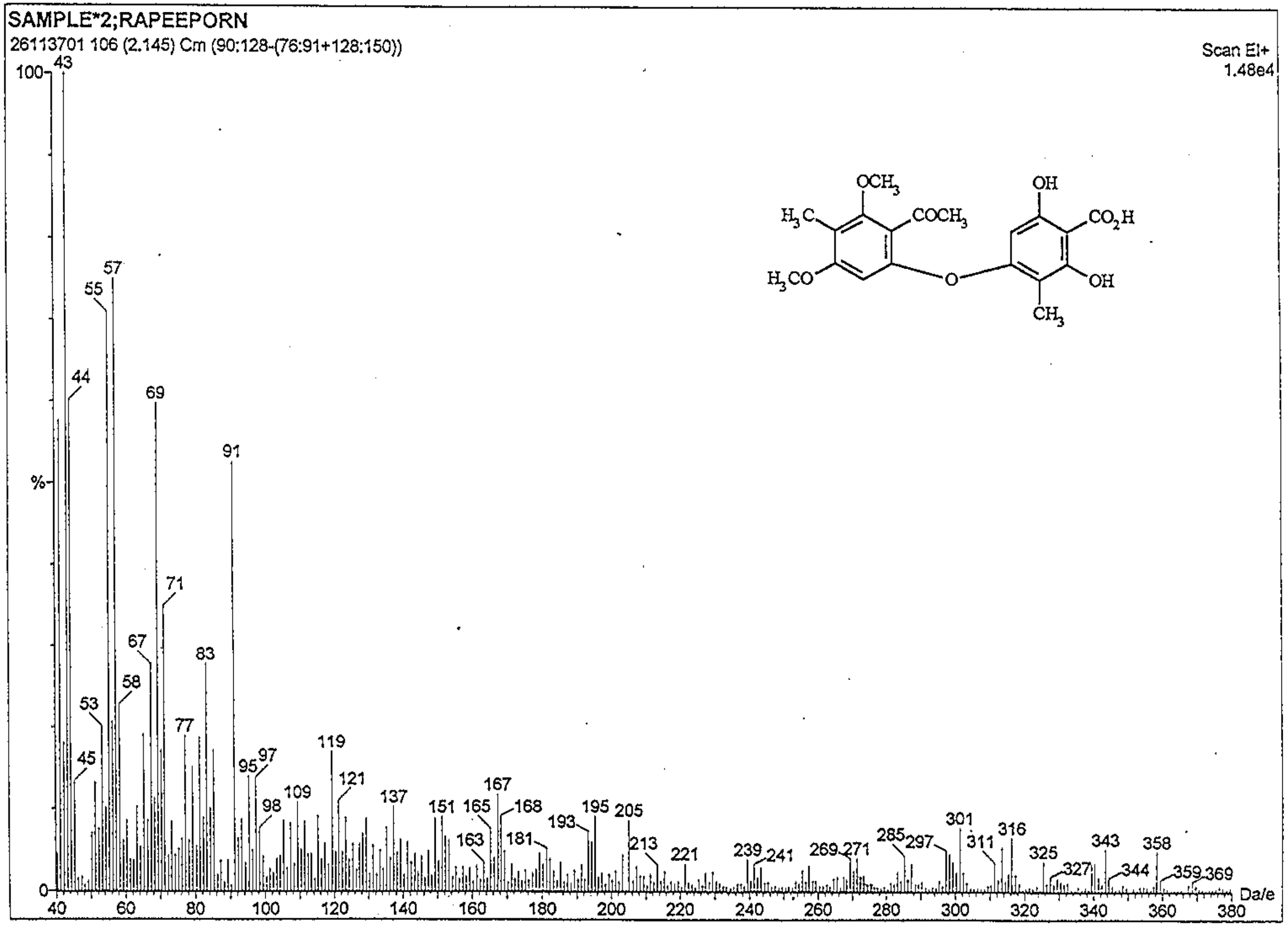


Figure 56 Mass spectrum of 4-(2'-acetyl-3',5'-dimethoxy-4'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (64)

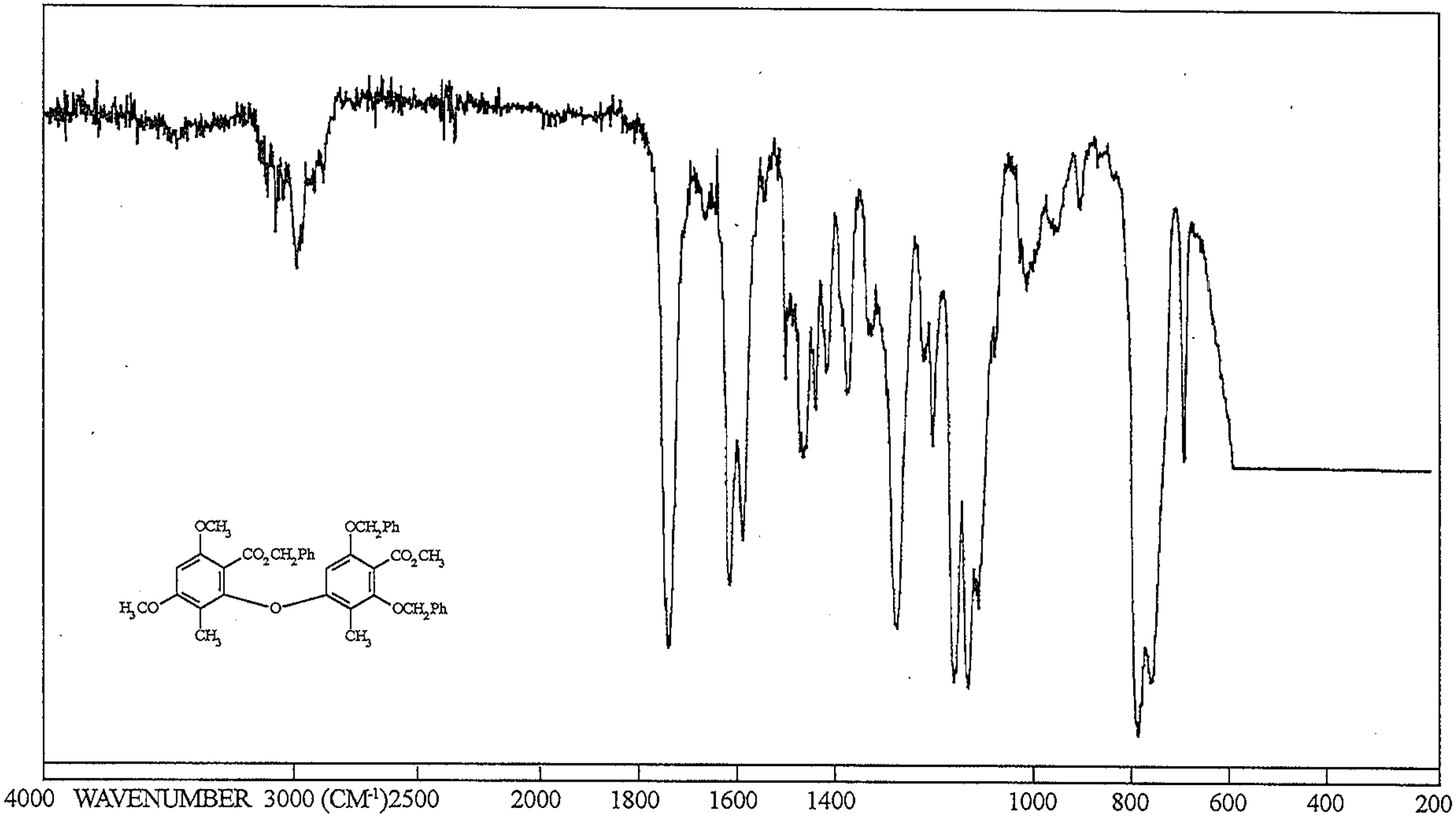


Figure 57 IR spectrum of benzyl 2-(4'-benzyloxycarbonyl-3',5'-dibenzyloxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoate (59)

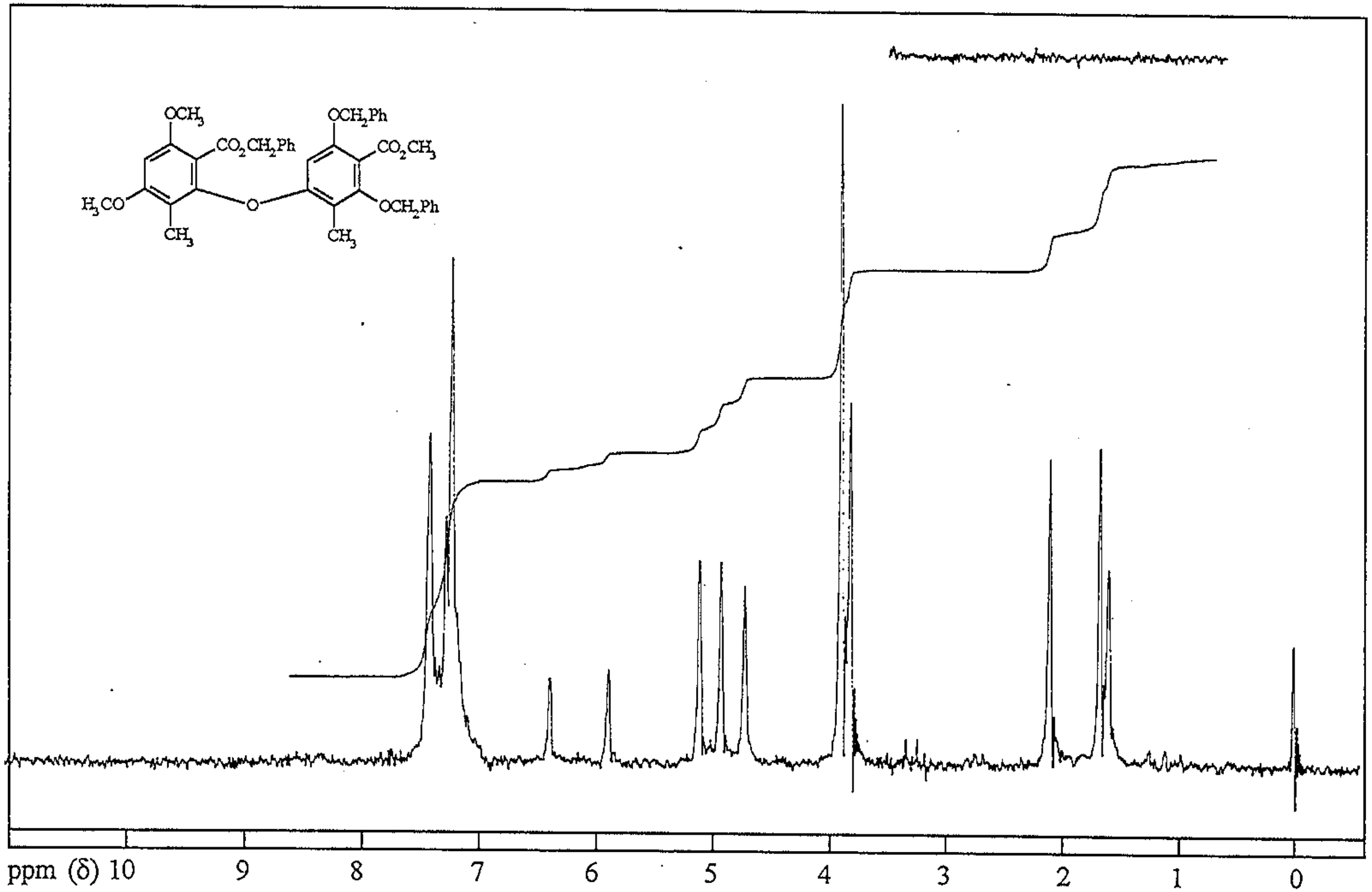


Figure 58 ^{1}H NMR spectrum of benzyl 2-(4'-benzyloxycarbonyl-3',5'-dibenzyloxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoate (59)

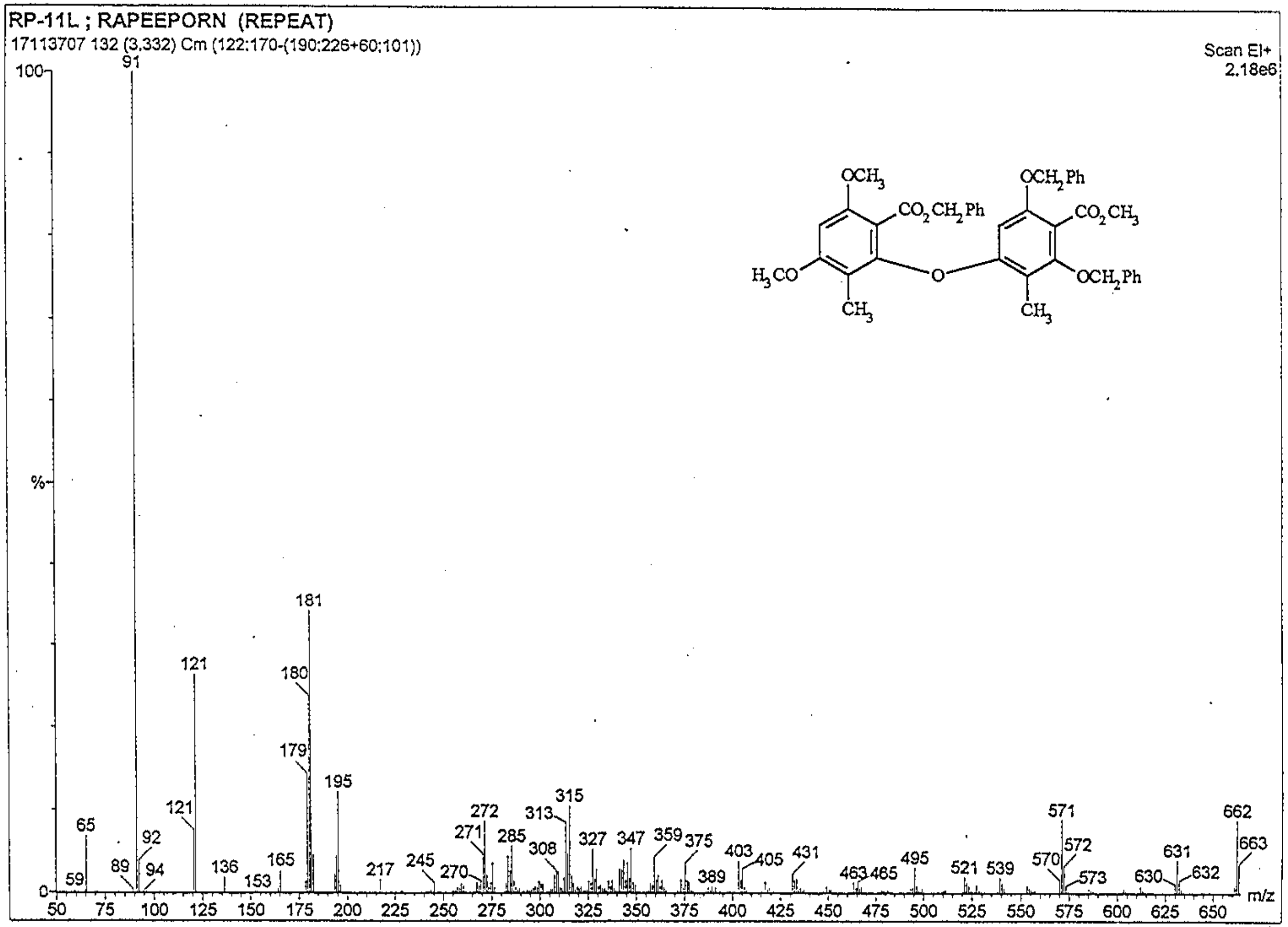


Figure 59 Mass spectrum of benzyl 2-(4'-benzyloxycarbonyl-3',5'-dibenzyloxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoate (59)

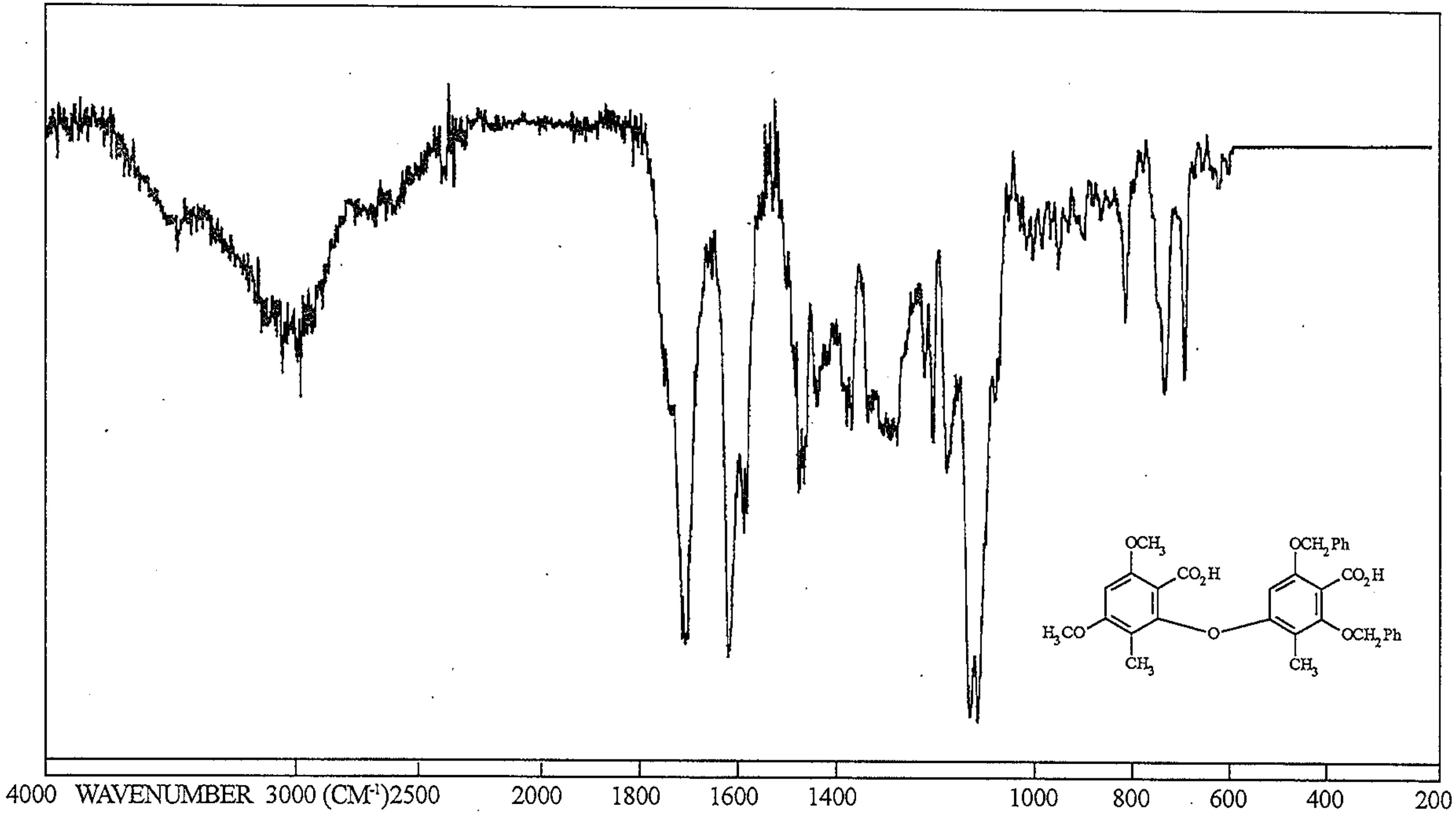


Figure 60 IR spectrum of 2-(4'-carboxy-3',5'-dibenzyloxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (60)

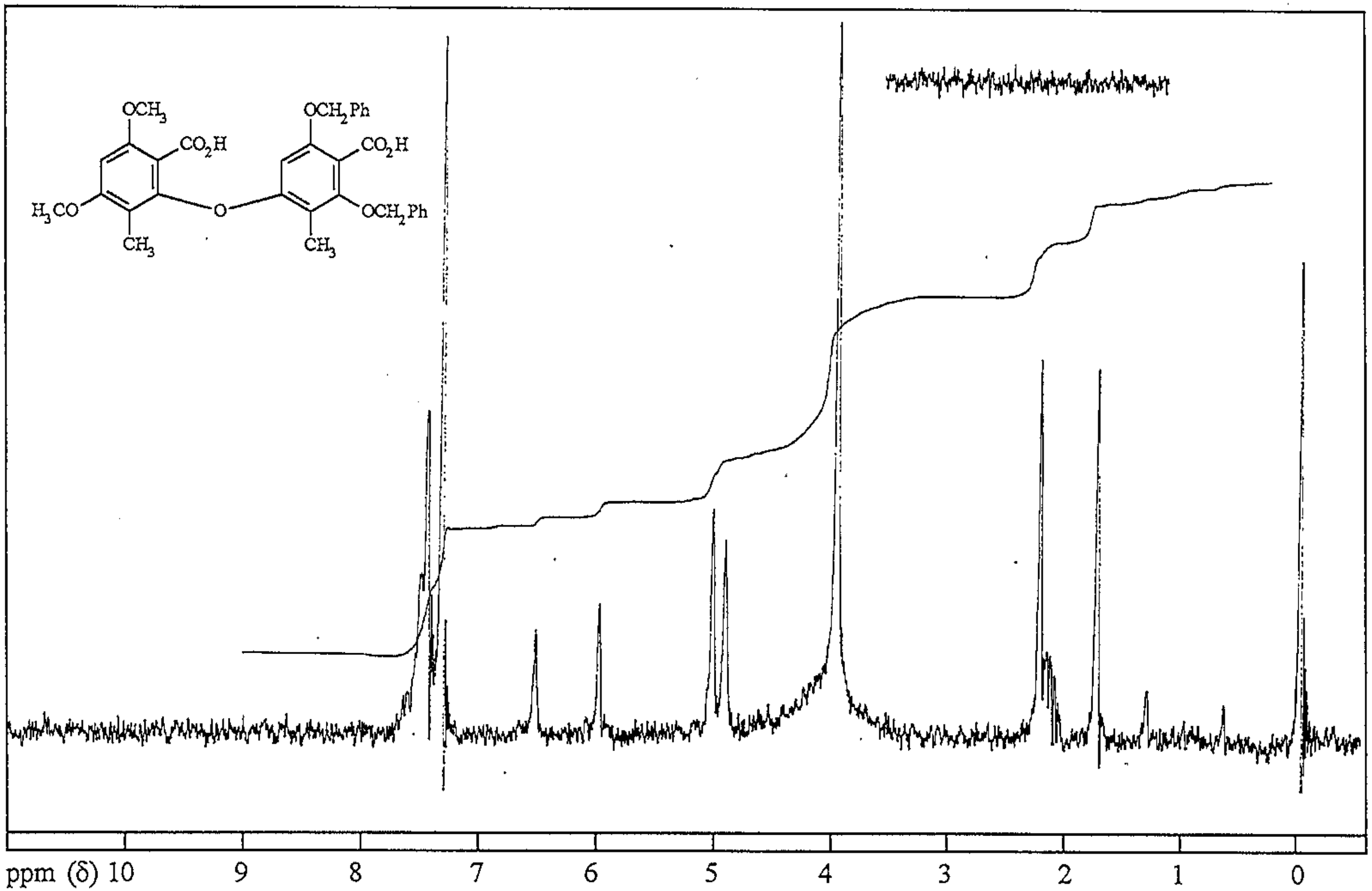


Figure 61 ^{1}H NMR spectrum of 2-(4'-carboxy-3',5'-dibenzyloxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (60)

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