Synthesis of Diphenyl Ether and Xanthone Derivatives via Smiles Rearrangement

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Thesis Title	Synthesis of Diphenyl Ether and Xanthone Derivatives via Smiles Rearrangement
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Major Program	Organic Chemistry

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Thesis Title	Synthesis of Diphenyl Ether and Xanthone Derivatives via Smiles Rearrangement
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Major Program	Organic Chemistry
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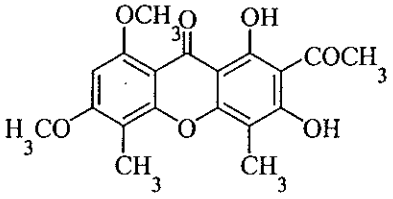
Abstract

The synthetic routes to diphenyl ether derivatives : 2-(4'-acetyl-3',5'-dihydroxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (125) and 2-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (68) and xanthone derivatives : 2-acetyl-1,3-dihydroxy-6,8-dimethoxy-4,5-dimethylxanthone (127) and 1,3-dihydroxy-2-methoxycarbonyl-6,8-dimethoxy-4,5-dimethylxanthone (131) have been described. These syntheses employed a Smiles rearrangement of precursor *para*-depsides (124) and (67) in key step.



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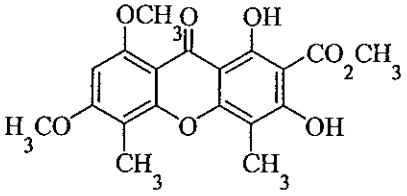

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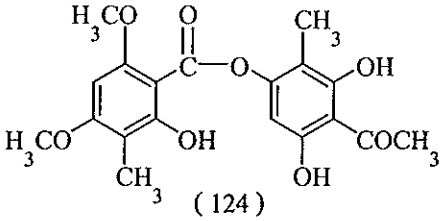

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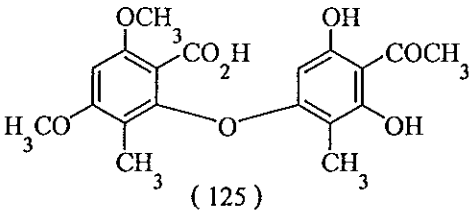
Smiles rearrangement



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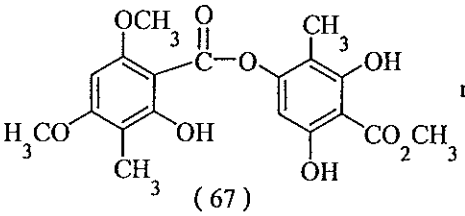
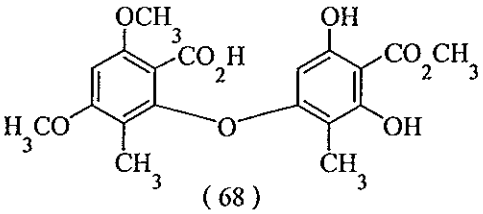


(67)

Smiles rearrangement



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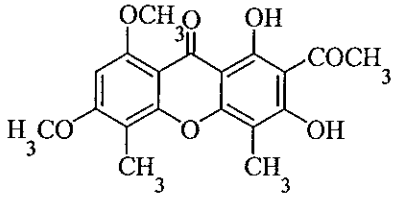
ชื่อวิทยานิพนธ์	การสังเคราะห์อนุพันธ์ไดฟีนิวอีเธอร์และอนุพันธ์แซนโทนโดยผ่านกระบวนการของสไมล์
ผู้เขียน	นางสาวนิสากร แซ่วัน
สาขาวิชา	เคมีอินทรีย์
ปีการศึกษา	2543

บทคัดย่อ

อธิบายแนวทางการสังเคราะห์อนุพันธ์สารประกอบไดฟีนิวอีเธอร์ : 2-(4'-acetyl-3',5'-dihydroxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (125) และ 2-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (68) และอนุพันธ์แซนโทน : 2-acetyl-1,3-dihydroxy-6,8-dimethoxy-4,5-dimethylxanthone (127) และ 1,3-dihydroxy-2-methoxycarbonyl-6,8-dimethoxy-4,5-dimethylxanthone (131) ขั้นตอนสำคัญในการสังเคราะห์ครั้งนี้คือ ปฏิกิริยาการจัดเรียงตัวใหม่ของ Smiles (Smiles Rearrangement) ของสารประกอบ *para*-depsides (124) และ (67) ตามลำดับ



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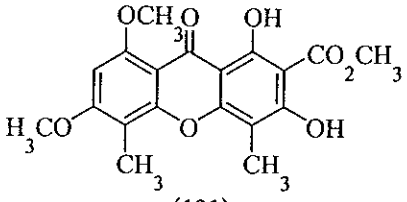

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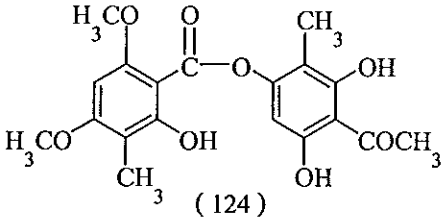

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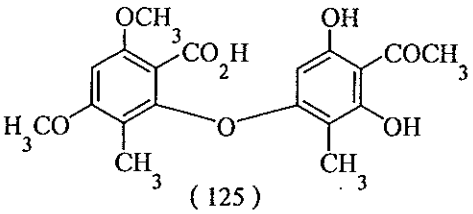
Smiles rearrangement



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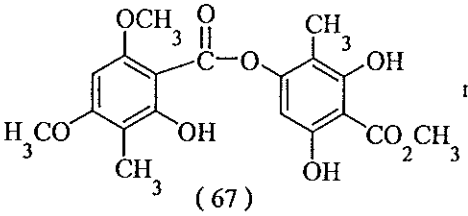

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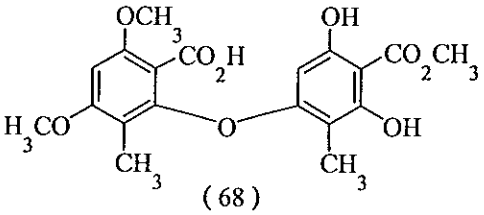
Smiles rearrangement



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20.	Mechanism of esterification using DCC as reagent	90

ABBREVIATIONS AND SYMBOLS

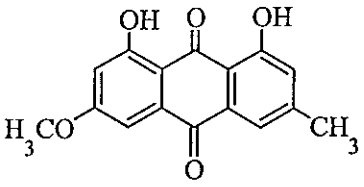
COSY	=	Correlation spectroscopy
DCC	=	*N,N'*-Dicyclohexylcarbodiimide
DEPT	=	Distortionless enhancement by polarization transfer
DMAP	=	4-Dimethylaminopyridine
DMF	=	*N,N'*-Dimethylformamide
DMSO	=	Dimethyl sulfoxide
FTIR	=	Fourier transform infrared
^{1}H NMR	=	Proton nuclear magnetic resonance
^{13}C NMR	=	Carbon nuclear magnetic resonance
NOE	=	Nuclear overhauser effect enhancement
HMBC	=	Heteronuclear multiple bond correlation
HMQC	=	Heteronuclear multiple quantum coherence
m.p.	=	Melting point
t.l.c.	=	Thin layer chromatography
TFAA	=	trifluoroacetic anhydride
THF	=	tetrahydrofuran

Chapter 1

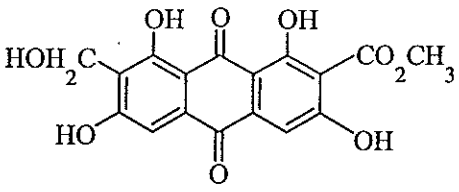
Introduction

Lichens are symbiotic associations of algae and fungi. Some of lichen substances (metabolic products of lichens) occur only in lichens, whereas others are also found in fungi and higher plants. Under certain conditions, some lichens fungi are able to synthesize the compounds present in the corresponding lichens by themselves. Parietin (1), rhodocladonic acid (2), pulvinic acid (3), usnic acid (4) and didymic acid (5) can be established in cultures of lichen fungi. However none of these substances could be isolated from cultures of lichen fungi which are capable of forming depsides and depsidones in symbiosis with algae (Hess, 1949). The mycelia of fungi generated only simple phenols, including oresellinic acid (6) and haematommic acid (7). Obviously, by symbiosis, (a). the simple phenols synthesized by 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.

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 substance. The two masters of lichens 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.



(1)



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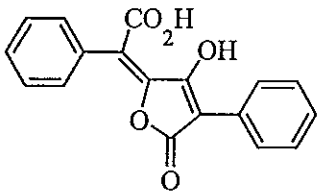

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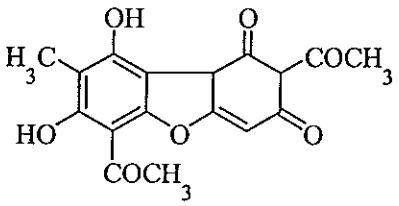

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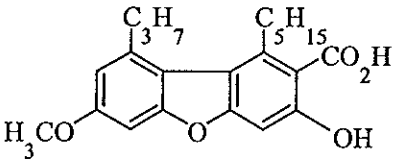
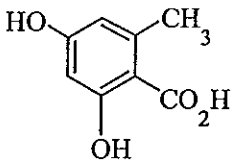
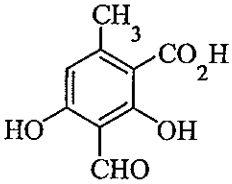


(5)



(6)



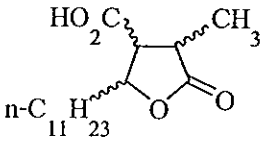
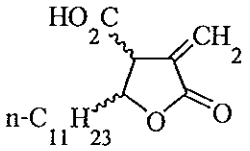
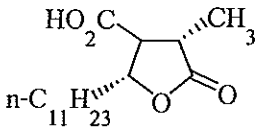
(7)

1. Classification of Lichen Substances.

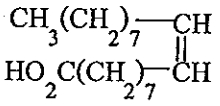
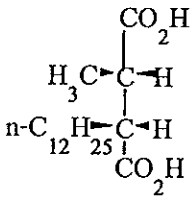
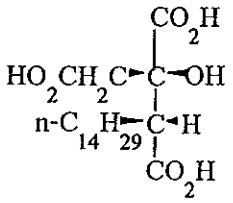
The known lichen substances may be grouped as shown in **Table 1** (Huneck, 1972).

Table 1 Classification of lichen substances

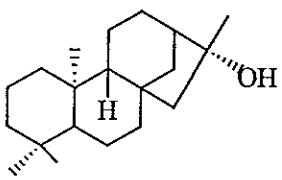
1. γ-Lactonic acid derivatives

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

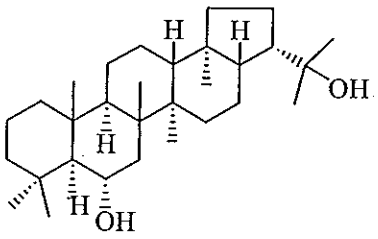
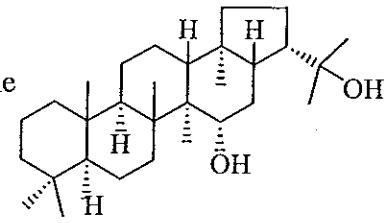
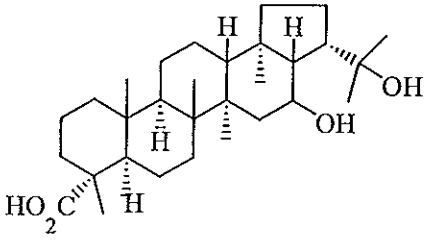
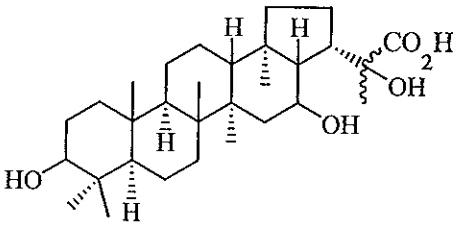
2. Mono-, di- and tribasic fatty acids

Compounds	Structures	References
Oleic acid		Klima, 1932
(+)-Roccellic acid		Akermark, 1962
(-)-Caperatic acid		Asahina and Shibata, 1954

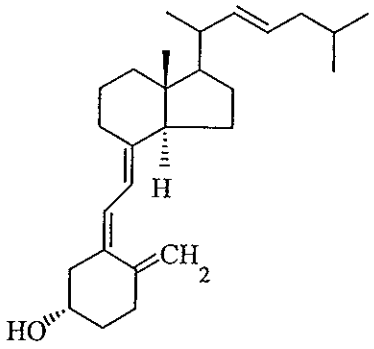
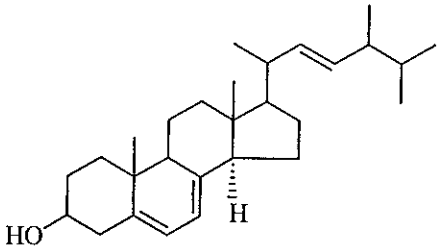
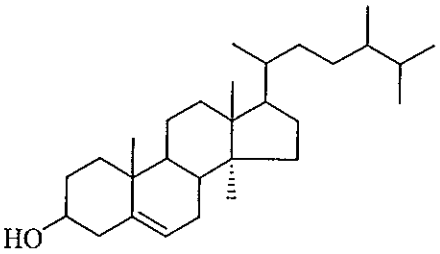
3. Diterpenes

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

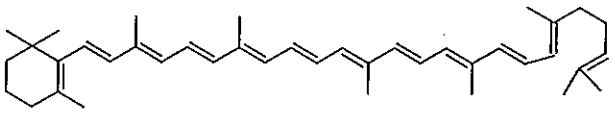
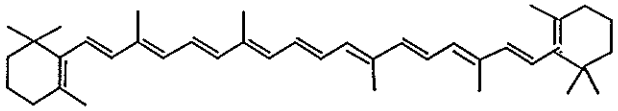
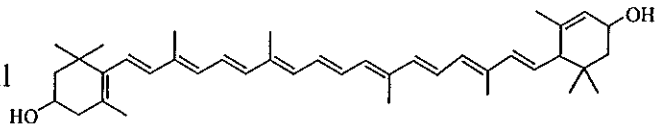
4. Triterpenes

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

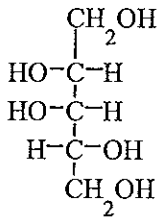
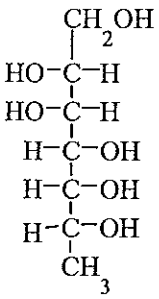
5. Steroids

Compounds	Structures	References
Vitamin D_2		Murty and Sankgra, 1959
Ergosterol		Alertsen, Brum and Hemmer, 1962
β-Sitosterol		Follmann and Huneck, 1995 Follmann and Huneck, 1996

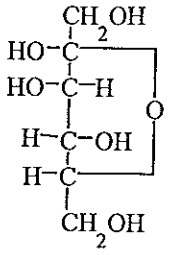
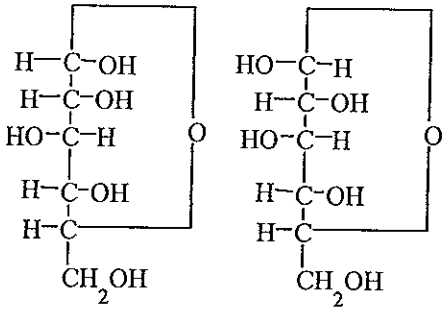
6. Carotenoids

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

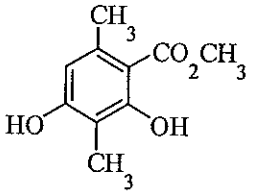
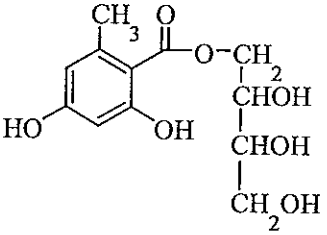
7. Polyhydric alcohols

Compounds	Structures	References
D-Arabitol		Lindberg, Misiorny and Washtmeister, 1953
D-Siphulitol		Lindberg and Meier, 1962

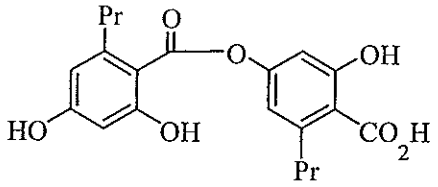
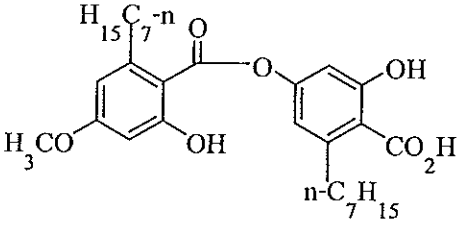
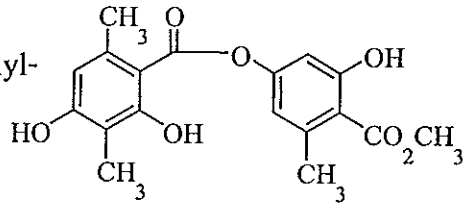
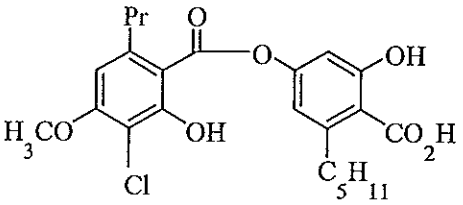
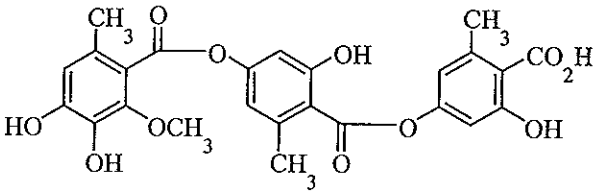
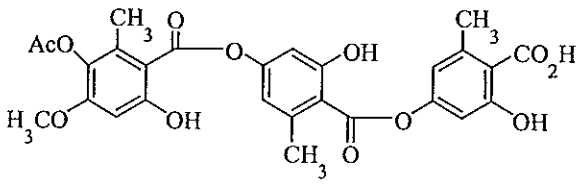
8. Carbohydrates

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

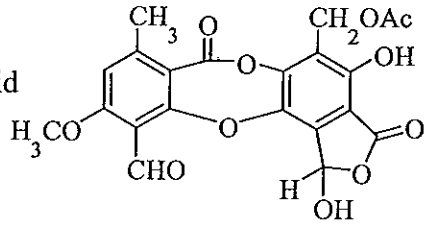
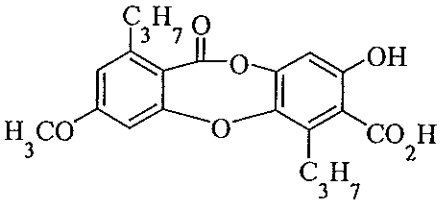
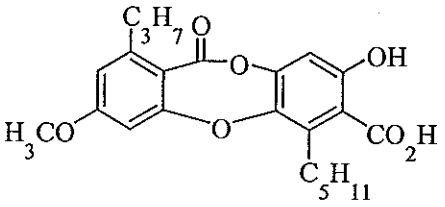
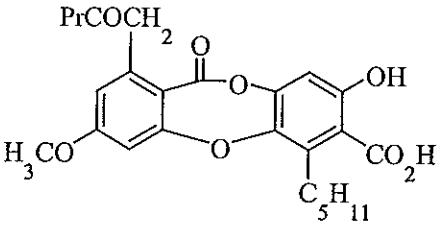
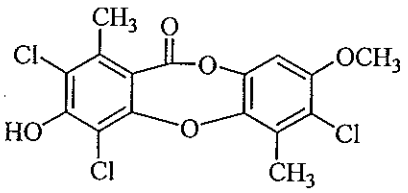
9. Orcinol derivatives

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

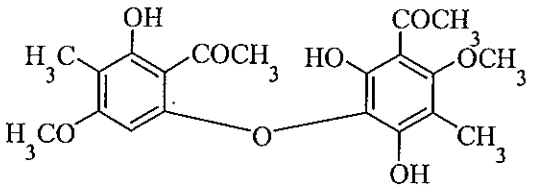
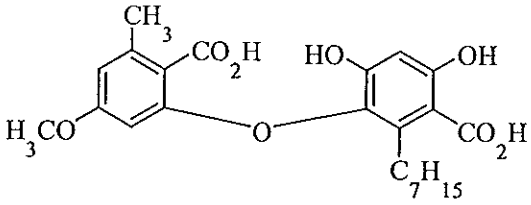
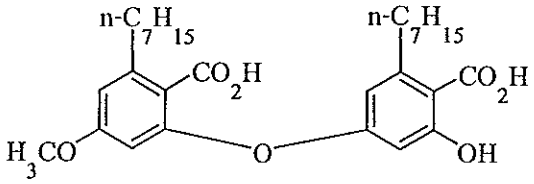
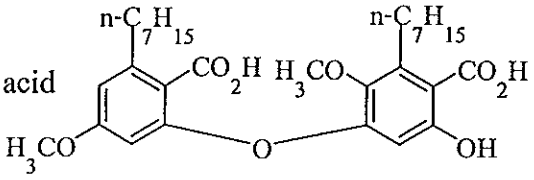
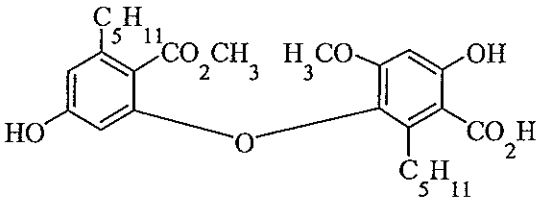
10. Depsides

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-umblicaric acid		Alder, Elix and Yu, 1989
5-o-Acetyl-4-o-methylhiascic acid		Elix, Tonsberg and Yu, 1990

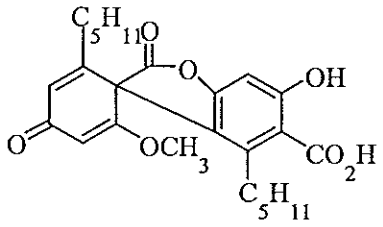
11. Depsidones

Compounds	Structures	References
O-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

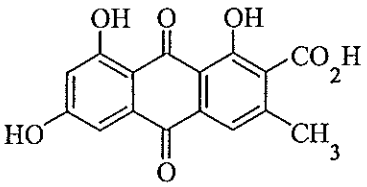
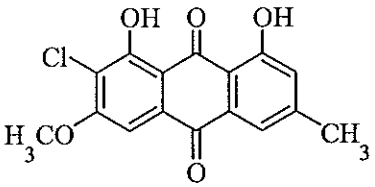
12. Diphenyl ethers

Compounds	Structures	References
Leopromin		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

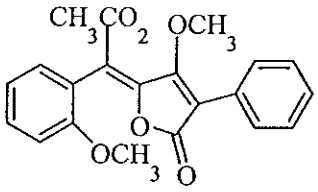
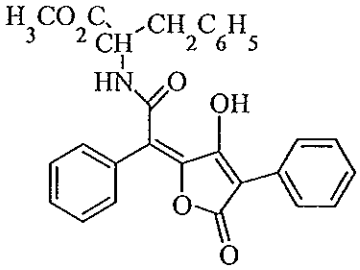
13. Depsones

Compounds	Structures	References
Picrolichenic Acid		Harper and Letcher, 1966

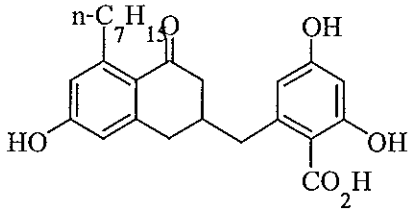
14. Quinones

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

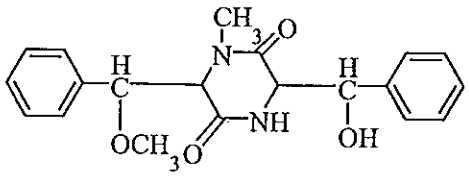
15. Pulvinic acid derivatives

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

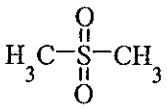
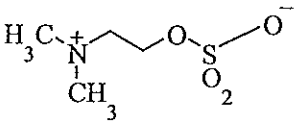
16. Chromanone derivatives

Compounds	Structures	References
Siphulin		Bruun, 1960

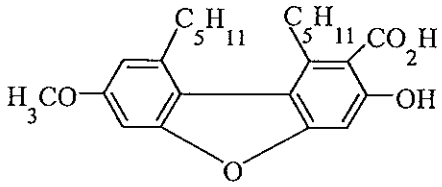
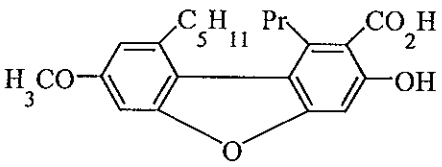
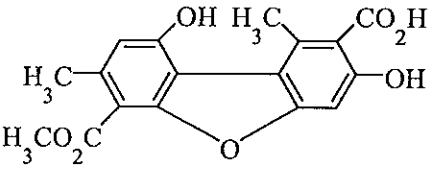
17. Nitrogen-containing compounds

Compounds	Structures	References
Picroroccellin		Asahina and Shibata, 1954

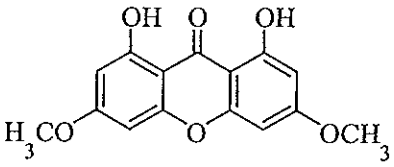
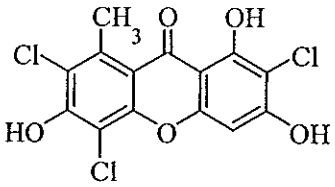
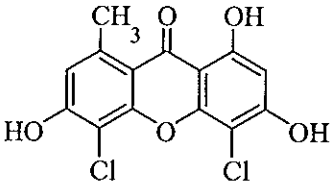
18. Sulphur-containing compounds

Compounds	Structures	References
Dimethyl sulphone		Bruun and Sörensen, 1954
Cholinesulphate ester		Harper and Letcher, 1966

19. Dibenzofuran derivatives

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

20. Xanthone derivatives

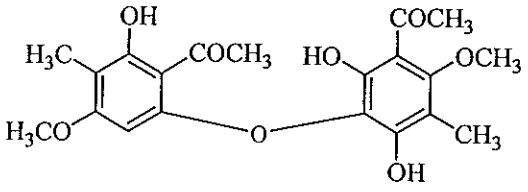
Compounds	Structures	References
1,8-Dihydroxy-3,6-dimethoxyxanthone		Elix, Gaul and Lumbsch, 1987
2,5,7-Trichloro-norlichexanthone		Elix, Jiang and Portelli, 1990
4,5-Dichloro-6-*O*-methylnorlichexanthone		Bennett, Elix and Jiang, 1991

2. Diphenyl Ethers

Diphenyl Ethers can be found in lichen substances and marine natural products. Some of diphenyl ethers occurred in marine natural products contain bromine atom.

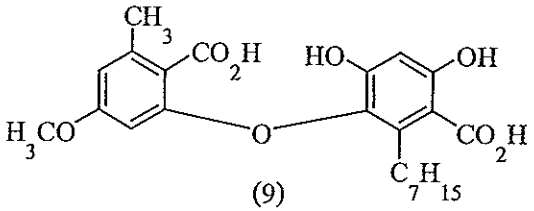
2.1 Diphenyl ethers occurred in lichens

A novel diphenyl ethers occurred in lichen *Psoroma leprolomum*. Leprolomin (8) [3-(2'-acetyl-3'-hydroxy-5'-methoxy-4'-methylphenoxy)-2,4-dihydro-xy-6-methoxy-5-methylacetophenone] was isolated and the structure was elucidated by spectroscopic and x-ray diffraction data (Elix *et al.*, 1978).



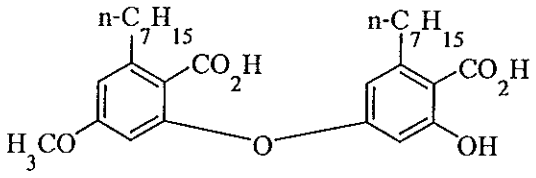
(8)

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



(9)

Two new diphenyl ethers, micareic acid (10) [4-(2'-carboxy-3'-heptyl-5'-methoxyphenoxy)-2-heptyl-6-hydroxybenzoic acid] and methoxymicareic acid (11) [4-(2'-carboxy-3'-heptyl-5'-methoxyphenoxy)-2-heptyl-6-hydroxy-3-methoxybenzoic acid] have been detected in chemical races of the lichen *Micarea prasina* Fr. (Coppin *et al.*, 1984). The structures of these compounds have been confirmed by total synthesis as shown in Scheme 1 and 2.



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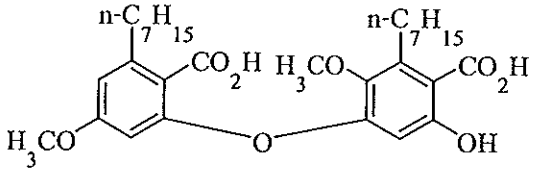
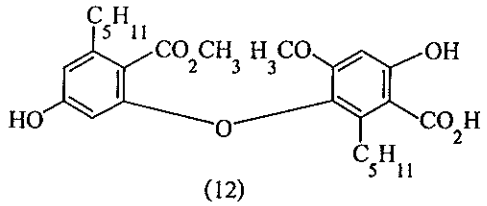
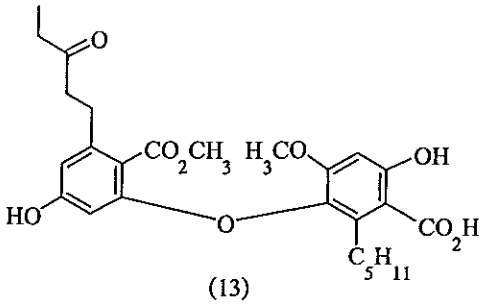


(11)

In 1986, the lichen diphenyl ether epiphorellic acid 1 (12) [6- hydroxy-3-(5'-hydroxy-2'-methoxycarbonyl-3'-pentylphenoxy)-4-methoxy-2-pentylbenzoic acid] and epiphorellic acid 2 (13) [6-hydroxy-3-(5'-hydroxy-2'-methoxycarbonyl-3'-pentanoyl-phenoxy)-4-methoxy-2-pentylbenzoic acid] was isolated from the Chilean lichen *Cornicularia epiphorella* (Nyl.) Du Rietz (Quilhot *et al.*, 1986). The diphenyl ether (12) was prepared by unambiguous synthesis (Elix and Jenie, 1989) as shown in Scheme 4.

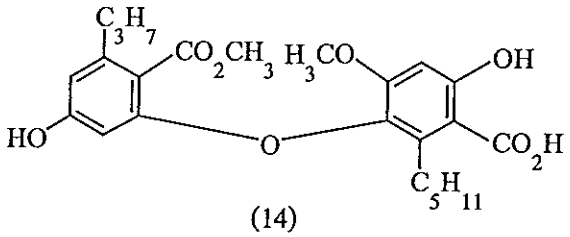


(12)



(13)

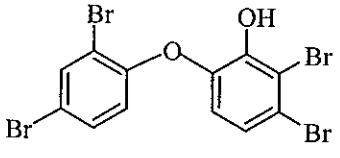
The diphenyl ether epiphollic acid 3 (14) [6-hydroxy-3-(5'-hydroxy-2'-methoxycarbonyl-3'-propylphenoxy)-4-methoxy-2-pentylbenzoic acid] has been detected in the lichen *Coelopogon abraxas* by chromatographic and spectroscopic comparisons (Elix and McCaffery, 1997).



(14)

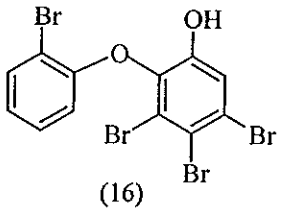
2.2 Diphenyl ethers occurred in marine natural products.

The structure of a new brominated diphenyl ether (15), isolated from an unidentified species of *Dysidea* sponge, has been solved by spectroscopic analysis. **^{13}C NMR** data of related diphenyl ether were also assigned by analysis of their **HMQC** and **HMBC** spectra (Fu *et al.*, 1996).

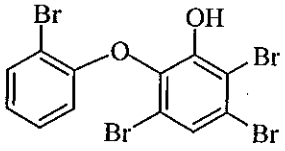


(15)

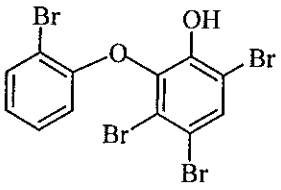
The marine sponge *Dysidea herbacea* collected from Indonesia yielded four new polybrominated diphenyl ether congeners (16-19). The structures of the new compounds were unambiguously established on the basis of **NMR** spectroscopic (^{1}**H**, ^{13}**C**, **COSY**, **HMQC**, **HMBC**) and mass spectrometric (**EIMS**) data. All of the compounds were active against the Gram-positive bacteria *Bacillus subtilis* and the phytopathogenic fungus *Cladosporium cucumerinum*. The isolated polybrominated compounds were also active in the brine shrimp lethality test (Dian Handayani *et al.*, 1997).



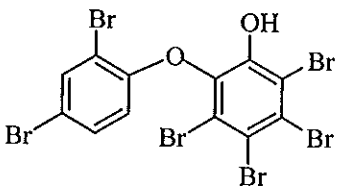
(16)



(17)

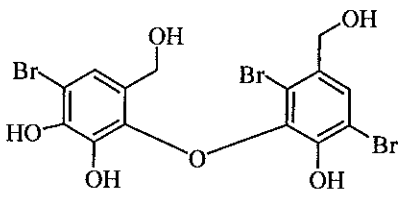


(18)



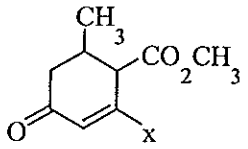
(19)

A novel polybrominated diphenyl ether (20) [2-(4'-bromo-2',3'-dihydroxy-6'-hydroxymethylphenoxy)-3,6-dibromo-4-hydroxymethylphenol] was isolated from an extract of a red alga *Odonthalia corymbifera*. The compound (20) was found to be inhibitors of α-glucosidase (Kurihara *et al.*, 1999).

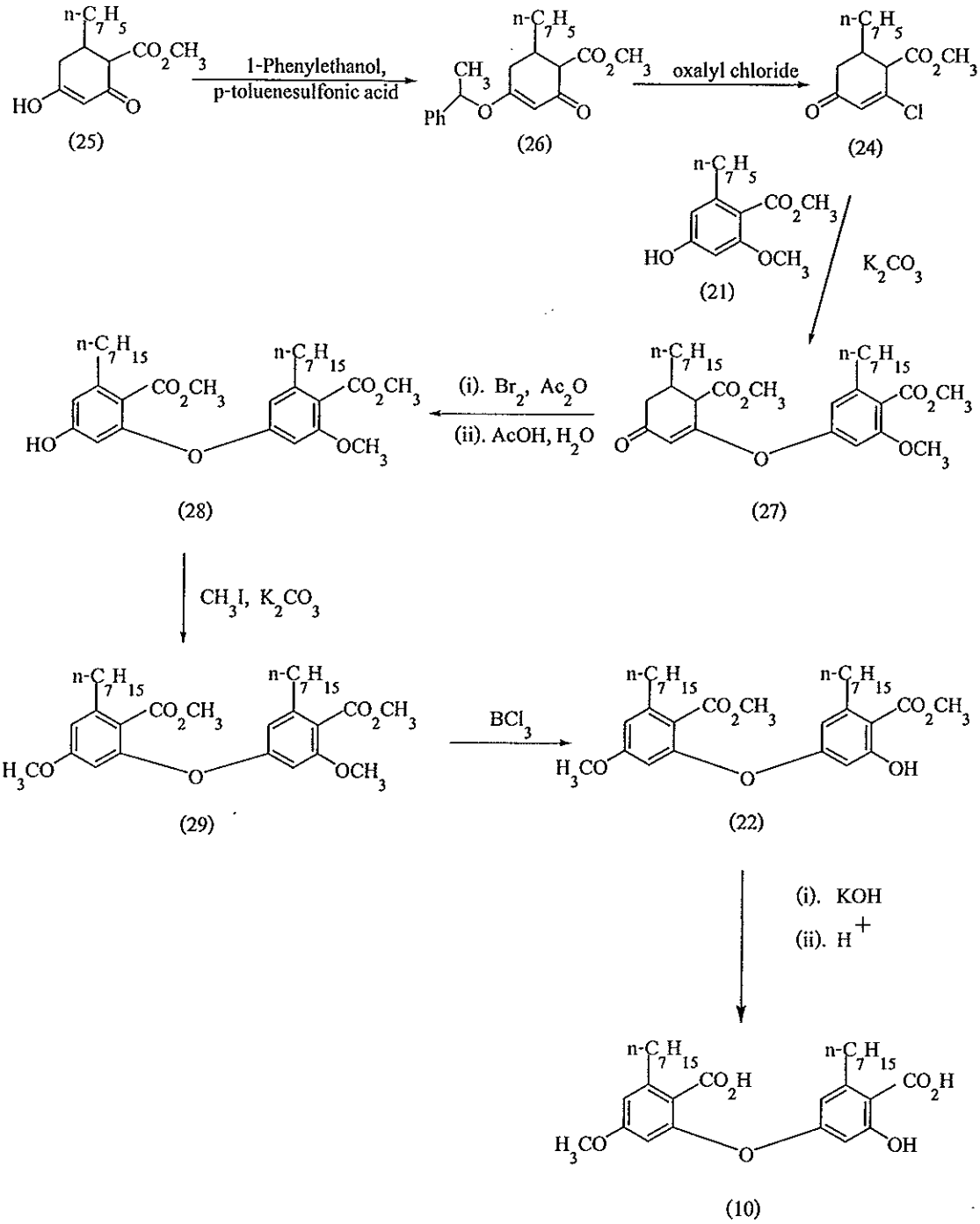


(20)

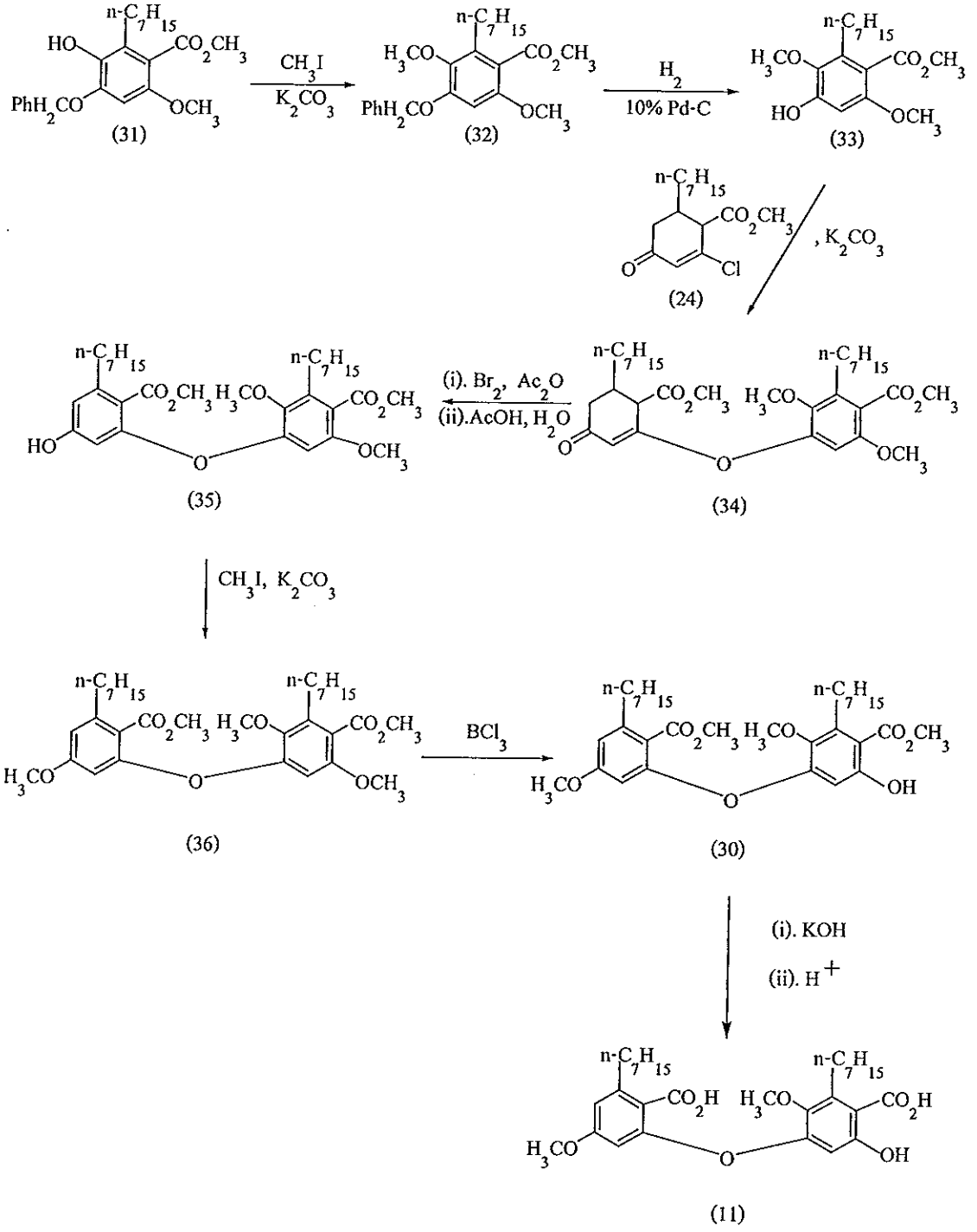
Diphenyl ethers have normally been prepared by the Ullmann ether synthesis (Moroz and Shvartsberg, 1974) involving the reaction between a phenol (or phenolate salt) and a halobenzene in the presence of a tertiary amine and catalysed by copper, cuprous or cupric salts. Such a synthetic approach to a highly substituted diphenyl ether such as (22) is feasible but the preparation of a suitably substituted halobenzene involves numerous steps (Djura and Sargent, 1976). Büchi and coworkers (Büchi and Wilard, 1978) have circumvented this difficulty by utilizing the more accessible methyl-2-halo-4-oxo-6-methylcyclohex-2-enecarboxylates (23; x = Br, Cl) in an Ullmann type reaction with the appropriate phenol. Elix and coworkers (Elix *et al.*, 1984) have now developed an efficient route to the corresponding heptyl derivative (24) and utilized the compound as a key intermediate in the synthesis of the diphenyl ethers (10) and (11).



(23)

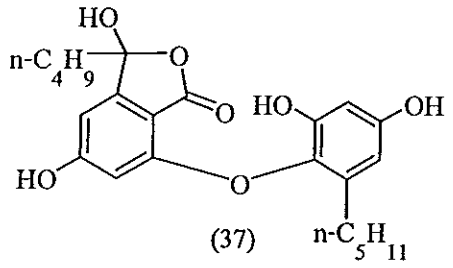


Scheme 1 Synthesis of micareic acid (10)

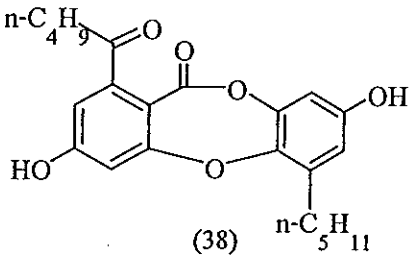


Scheme 2 Synthesis of methoxymicareic acid (11)

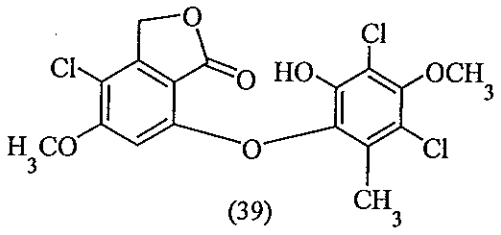
As mentioned previously, diphenyl ethers constitute a relatively rare group of lichens metabolites, which appear to be derived catabolically from co-occurring depsidones. For instance norlobariol (37) co-occurs with norlobaridone (38) and buellolide (39) with dichloro-O-methyldiploicin (40). Leprolomin (8) on the other hand appears to have a distinctly different biogenetic origin, apparently by direct oxidative coupling of two molecules of 2,4,6-trihydroxy-3-methylacetophenone.



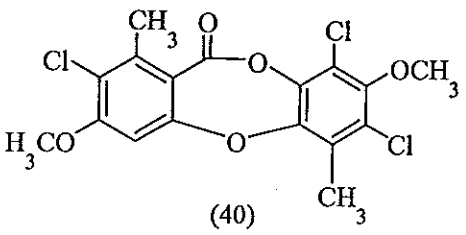
(37)



(38)



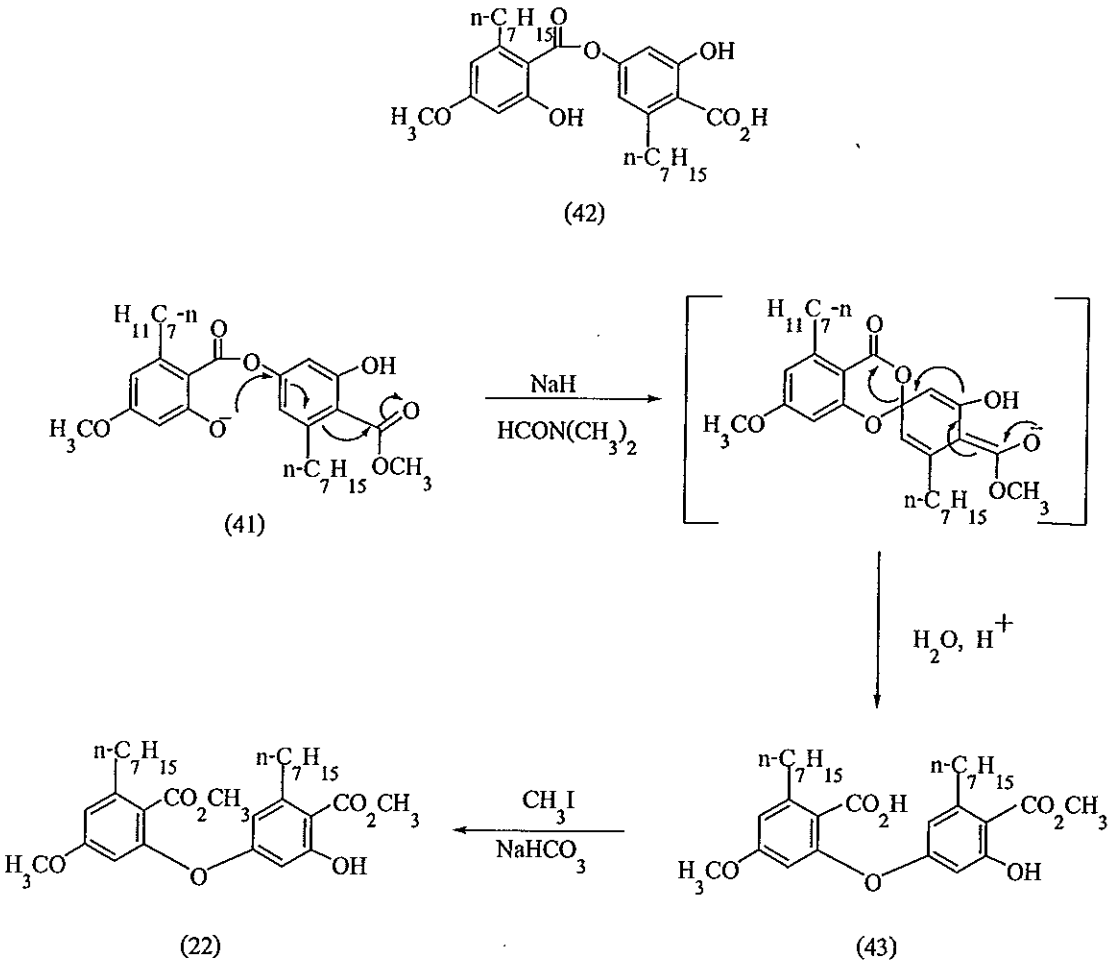
(39)



(40)

In contrast to all these compounds, micareic acid (10) and methoxymicareic acid (11) have distinctly different substitution patterns and presumably biogenetic origin. One intriguing possibility is that micareic acid (10) arises by an enzymatically induced Smiles rearrangement of the depside. It was found that pracinic acid (42) gave a diphenyl ether by treatment with sodium hydride in dimethylformamide (Ptister, 1982). When methyl prasinate (41) was made to react under analogous condition, methyl micareate (43) was obtained (Scheme 3). This rearrangement was also accompanied by a minor amount of depside cleavage. Subsequent methylation of acid

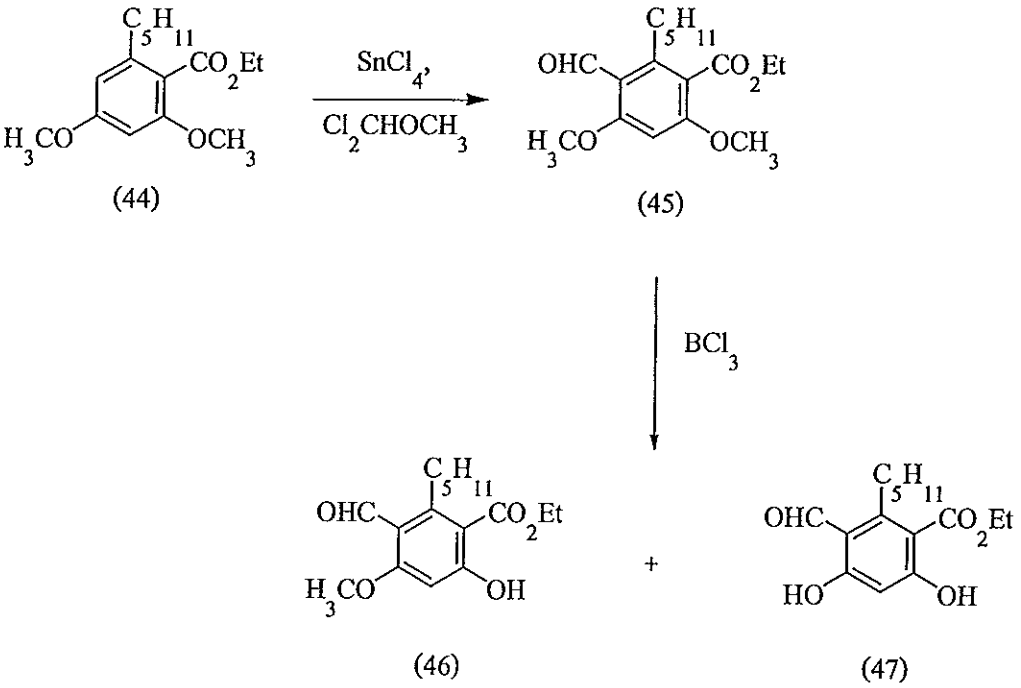
(43) gave dimethyl micareate (22), identical in all aspects with the authentic material. This synthesis gives credence to the proposal that Smiles rearrangement of the appropriate depside provides a viable biosynthetic pathway to these uniquely substituted diphenyl ethers.



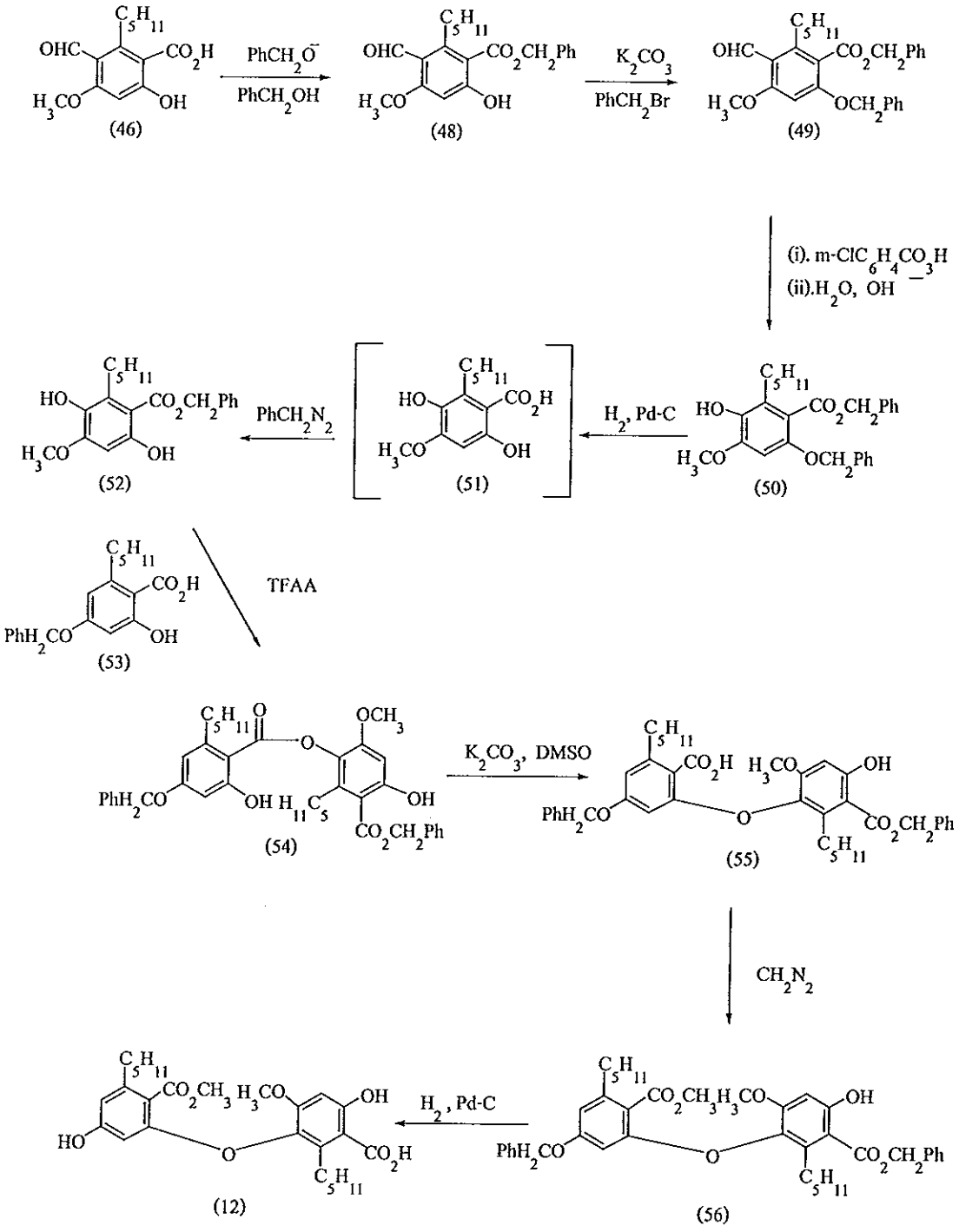
Scheme 3 Synthesis of dimethyl micarate (22) via Smiles rearrangement

The additional methoxy group present in methoxymicareic acid (11) is not inherent in the acetate-polymalonate pathway to this compound (Mosbach, 1969), but is apparently the result of nuclear hydroxylation followed by O-methylation. The actual sequence of these processes (i.e. before or after Smiles rearrangement of the depside precursor) remains a matter for conjecture.

In 1986, the lichen diphenyl ether epiphorellic acid (12) [6-hydroxy-3-(5'-hydroxy-2'-methoxycarbonyl-3'-pentylphenoxy)-4-methoxy-2-pentylbenzoic acid] was prepared by unambiguous synthesis (Elix and Jenie, 1989) as shown in Scheme 4. For the synthesis, 4-benzyloxy-2-hydroxy-6-pentylbenzoic acid (53) and ethyl 2,4-dimethoxy-6-pentylbenzoate (44) were used as starting materials and employed a Smiles rearrangement of a precursor mata-depside (54) in the key step.

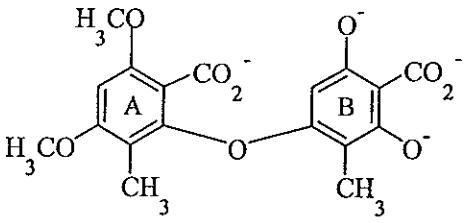


(44) (45) (46) (47)

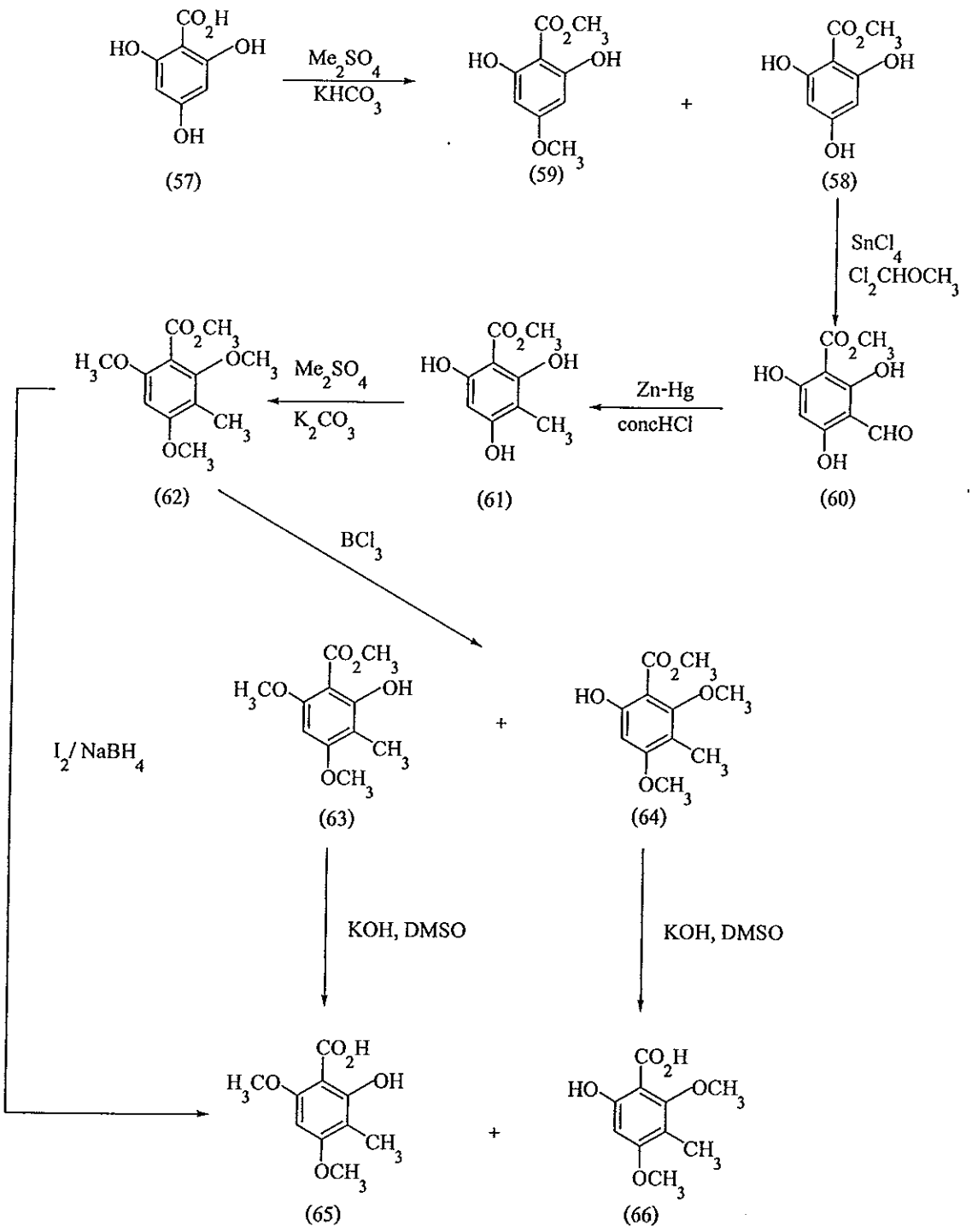


Scheme 4 Synthesis of epiphollic acid 1 (12)

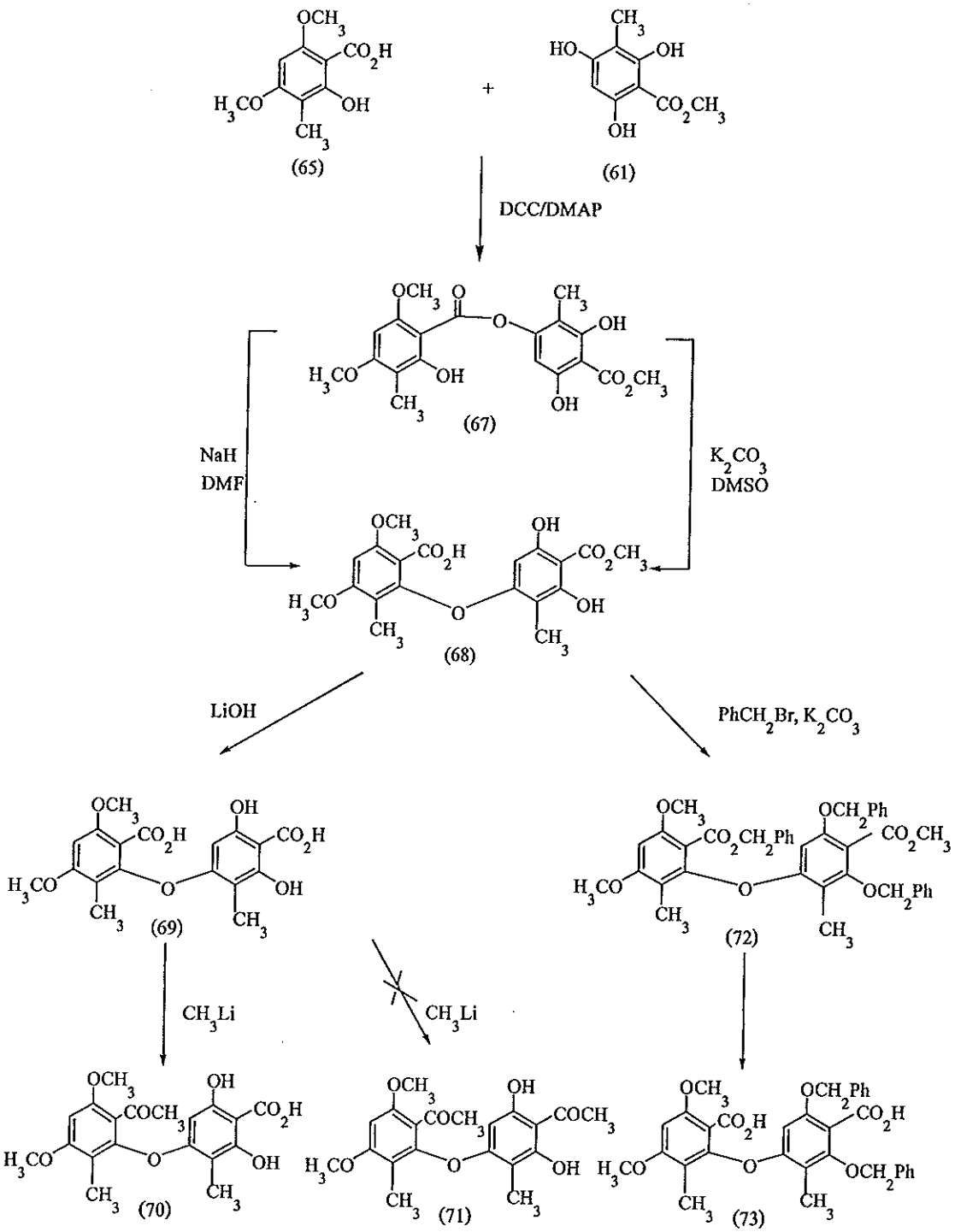
In 1995, Suttirak (Suttirak, 1995) described the synthetic route to diphenyl ether derivatives ; 4-(2'-acetyl-3',5'-dimethoxy-6'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (70) and 4-(2'-acetyl-3',5'-dimethoxy-4'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (77) (Scheme 7). The syntheses employed a novel Smiles rearrangement of precursor *para*-depside (67) and (74) in the key step, to give the corresponding diphenyl ethers (68) and (75), respectively. Then hydrolysis of two diphenyl ethers gave the corresponding diacid derivatives. In an attempt to C-methylation of two diacids to (70) and (77) with methyl lithium, the expected products (71) and (78) were not detected (Schemes 5,6,7). It seems that the second carboxyl groups (on ring B) of the acid (70), (77) do not react with methyl lithium because of the high density of negative charges (due to the phenoxy anions). This would severely deactivate the carboxyl group on the ring B as indicated in structure (79). These thesis has renewed efforts in the development of versatile methodology for its construction as indicated in Schemes 13,16, 17.



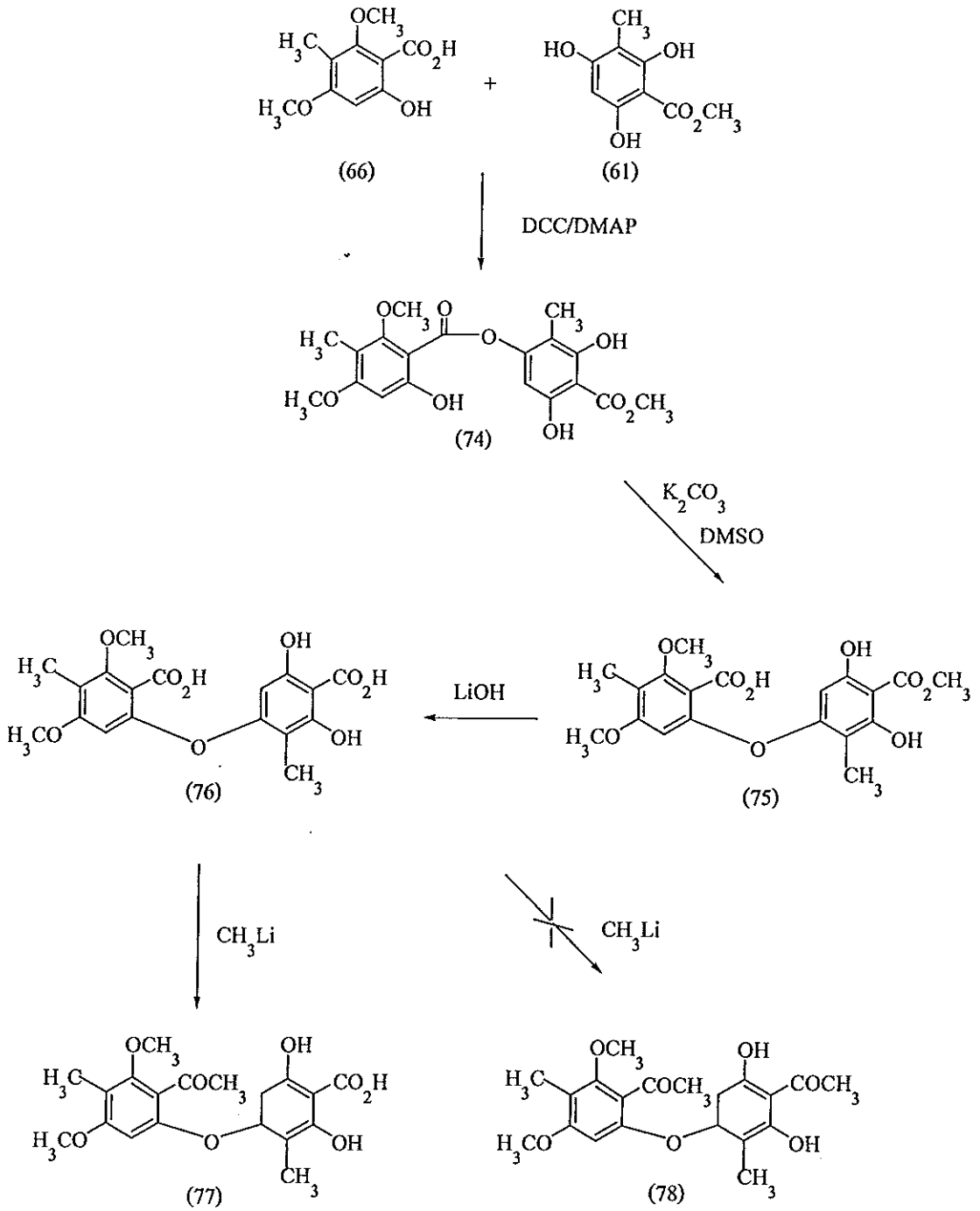
(79)



Scheme 5 Synthesis of 4,6-dimethoxy-2-hydroxy-3-methylbenzoic acid (65) and 2,4-dimethoxy-6-hydroxy-3-methylbenzoic acid (66)



Scheme 6 Synthesis of 4-(2'-acetyl–3',5'-dimethoxy-6'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (70)



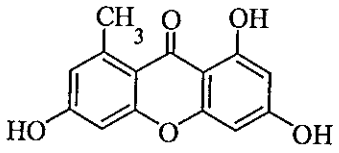
Scheme 7 Synthesis of 4-(2'-acetyl-3',5'-dimethoxy-4'-methylphenoxy)-2,6-dihydroxy-3-methylbenzoic acid (77)

3. Xanthones

Xanthones can be found in lichen substances, which may contain chlorine atom, and secondary metabolites of other plants.

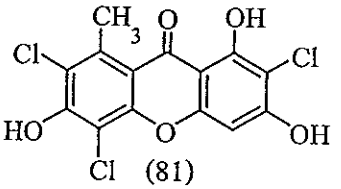
3.1 Xanthones occurred in lichens

Derivatives of norlichexanthone (80) (1,3,6-trihydroxy-8-methylxanthone) are well known and very common in lichens.



(80)

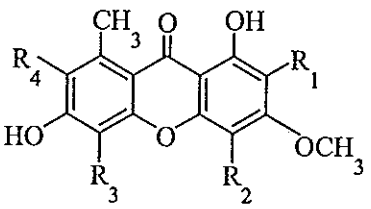
Isoarthothelin (81) (2,5,7-trichloro-1,3,6-trihydroxy-8-methylxanthone or 2,5,7-trichloronorlichexanthone) has been reported as occurring in the lichens *Lecanora sulphurata* (Ach.) Nyl., L. *flavo-pallescens* Nyl. (Santesson, 1969) and L. *broccha* (Elix *et al.*, 1990). The structure of compound (81) was confirmed by total synthesis as shown in Scheme 9.



(81)

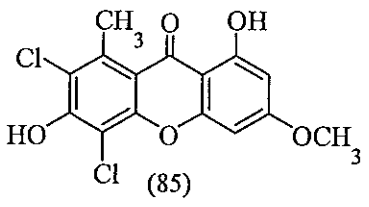
Three such isomers of lichen xanthone, which had a molecular formula $C_{15}H_9Cl_3O_5$ as established by high-resolution mass spectrometric data, have been reported previously as occurring in lichens. Thuringione (82) (2,4,5-trichloro-3-O-

methylnorlichexanthone) is a well known lichen metabolite (Elix *et al.*, 1984), the structure of which has been confirmed independently by several workers (Fitzpatrict *et al.*, 1980). O-Methylasemone (83) (4,5,7-trichloro-3-O-methylnorlichexanthone), a compound previously prepared by several independent synthesis (Sundholm, 1979), has been reported to occur in the lichen *Lecidella buelliastum* (Müll.Arg.) Knoph & Rambold (Knoph, 1989). A third isomer, 2,5,7-trichloro-3-O-methylnorlichexanthone (84), has been reported as occurring in the lichen *Lecanora capistrata* (Darb.) Zahlbr and the structure established by unambiguous synthesis (Sundholm *et al.*, 1979).



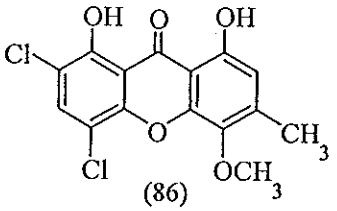
	R_1	R_2	R_3	R_4
(82)	Cl	Cl	Cl	H
(83)	H	Cl	Cl	Cl
(84)	Cl	H	Cl	Cl

5,7- Dichloro-3-O-methylnorlichexanthone (85) (5,7-Dichloro-1,6-dihydroxy-3-methoxy-8-methylxanthone) has been synthesized and shown to occur in the lichen *Lecanora broccha* (Elix *et al.*, 1990).



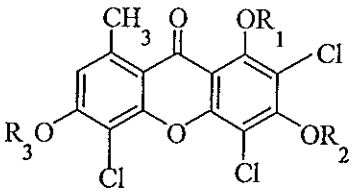
(85)

The lichen xanthone thiomelin (86) (2,4-dichloro-1,8-dihydroxy-5-methoxy-6-methylxanthone) and its congenors were first isolated by Leuckert and Mayrhofer in 1984 (Leuckert and Mayrhofer, 1984) from the lichens *Rinodina thiomela* (Nyl.) Müll.Arg. and R.*lepida* (Nyl.) Müll.Arg. This compound has been synthesized by John A. Elix as shown in Schem 10 (Elix and Porteli, 1990).



(86)

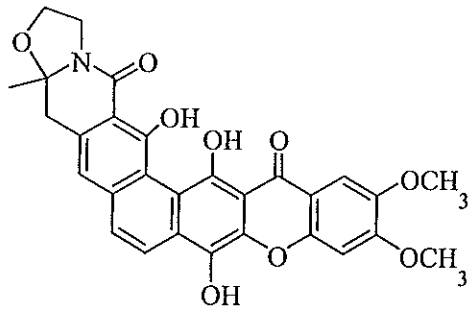
6-O-Methylarthothelin (87) (2,4,5-trichloro-1,3-dihydroxy-6-methoxy-8-methylxanthone) and 1,3,6-tri-O-methylarthothelin (88) (2,4,5-trichloro-1,3,6-trimethoxy-8-methylxanthone) have been synthesized and shown to occur in a *Dimelaena* lichen (Elix and Bennett, 1990).



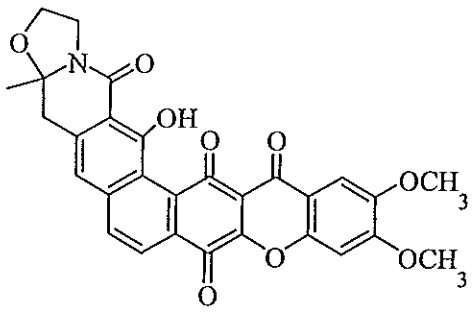
	R_1	R_2	R_3
(87)	H	H	CH_3
(88)	CH_3	CH_3	CH_3

3.2 Xanthone occurred in other plants

A new species *Streptomycis cervinus* sp. Nov. in was discovered and a collaborative effort led to the isolation and structural determination of novel antibiotic substances cervinomycins A_1 (89) and A_2 (90) in 1986 (Omura *et al.*, 1994). These xanthones were prepared by unambiguous synthesis (Mehta et al., 1994).

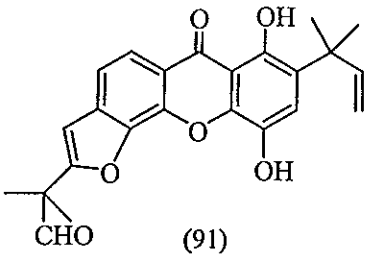


(89)

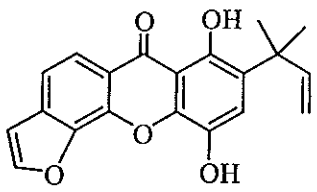


(90)

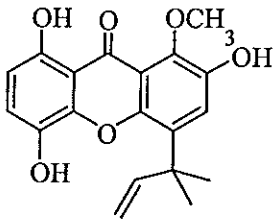
In 1996, three new prenylated xanthones, garcinia xanthones F (91), G(92) and H(93) have been isolated as antioxidative substances from the wood of *Garcinia subelliptica* (Guttiferae). Their structures have been elucidated on the basis of spectroscopic data involving comparison of their **^{13}C-NMR** data with those of previously known xanthones. The antioxidant properties of the new compounds have been evaluated by three assay systems : antilipid peroxidation, α,α-diphenyl-β-picrylhydrazyl radical scavenging activity and superoxide radical scavenging activity (Minami *et al.*, 1996).



(91)

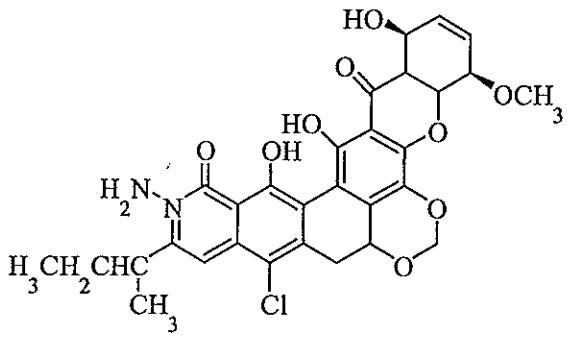


(92)



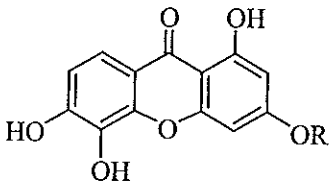
(93)

An antifungal agent, Sch 54445 (94), was isolated from the fermentation broth of an Actinoplanes species. Sch54445 (94) was identified to be a polycyclic xanthone related to the albofungin family on the basis of spectroscopic data. As a broad spectrum antifungal agent, Sch 54445 (94) exhibits highly potent activities against various yeasts and dermatophytes with MIC values~0.00038 ug/mL (Min Chu *et al.*, 1997).



(94)

Two xanthone glycosides, patuloside A (95) (3-β-D-glucopyranosyloxy-1,5,6-trihy-droxyxanthone) and patuloside B (96) [3-(2-O-α-L-rhamnopyranosyl-β-D-glucopyranosyl)oxy-1,5,6-trihydroxyxanthone], have been isolated from cell suspension cultures of *Hypericum patulum*. Their structures were elucidated by spectroscopic techniques (Ishiguro *et al.*, 1999).



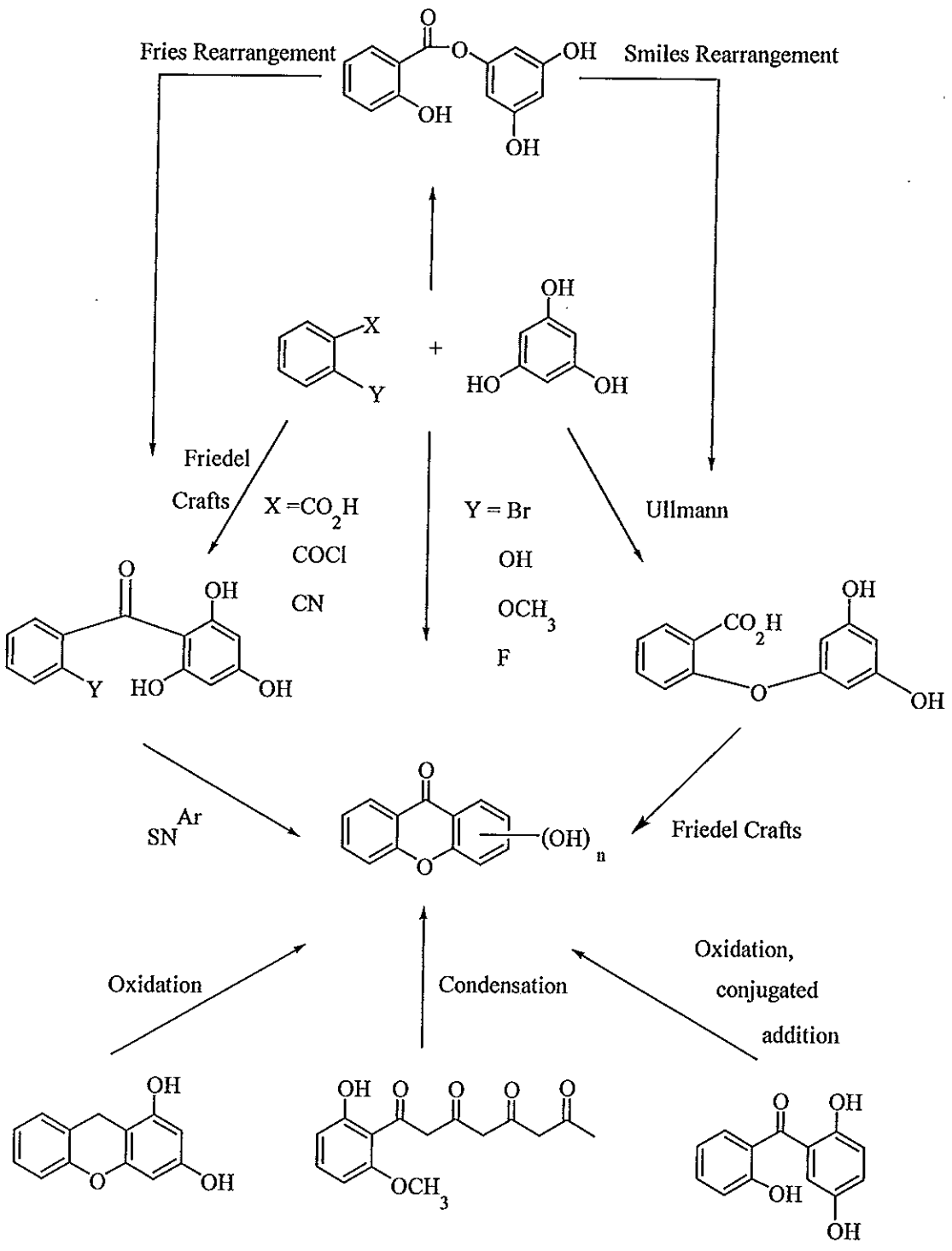
(95) R = Glc

(96) R = GLc-Rha

Traditional xanthone synthesis involves the connection of two aryl fragments to form the internal pyranone ring. The carbonyl connection can be formed by three reaction types.

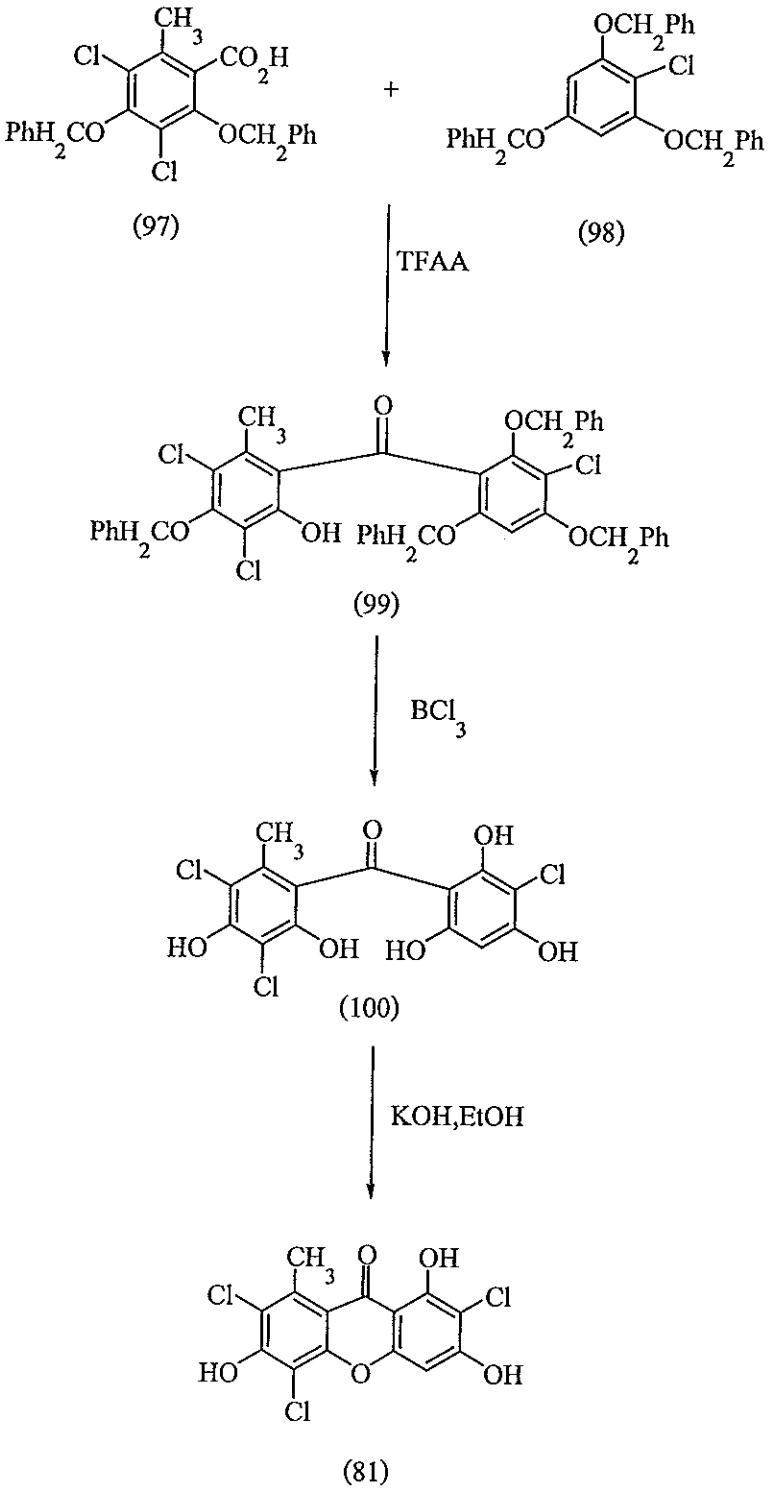
1. Friedel-Craft acylation and variants.
2. Biaryl ester migration, such as the Fries rearrangement.
3. Aryl anion addition to a benzoyl chloride.

The ether lingkage can be formed intermolecularly by Ullmann method or intramoleculary by an SN^{Ar} mechanism or Smiles rearrangement (Linda *et al.*, 1999).

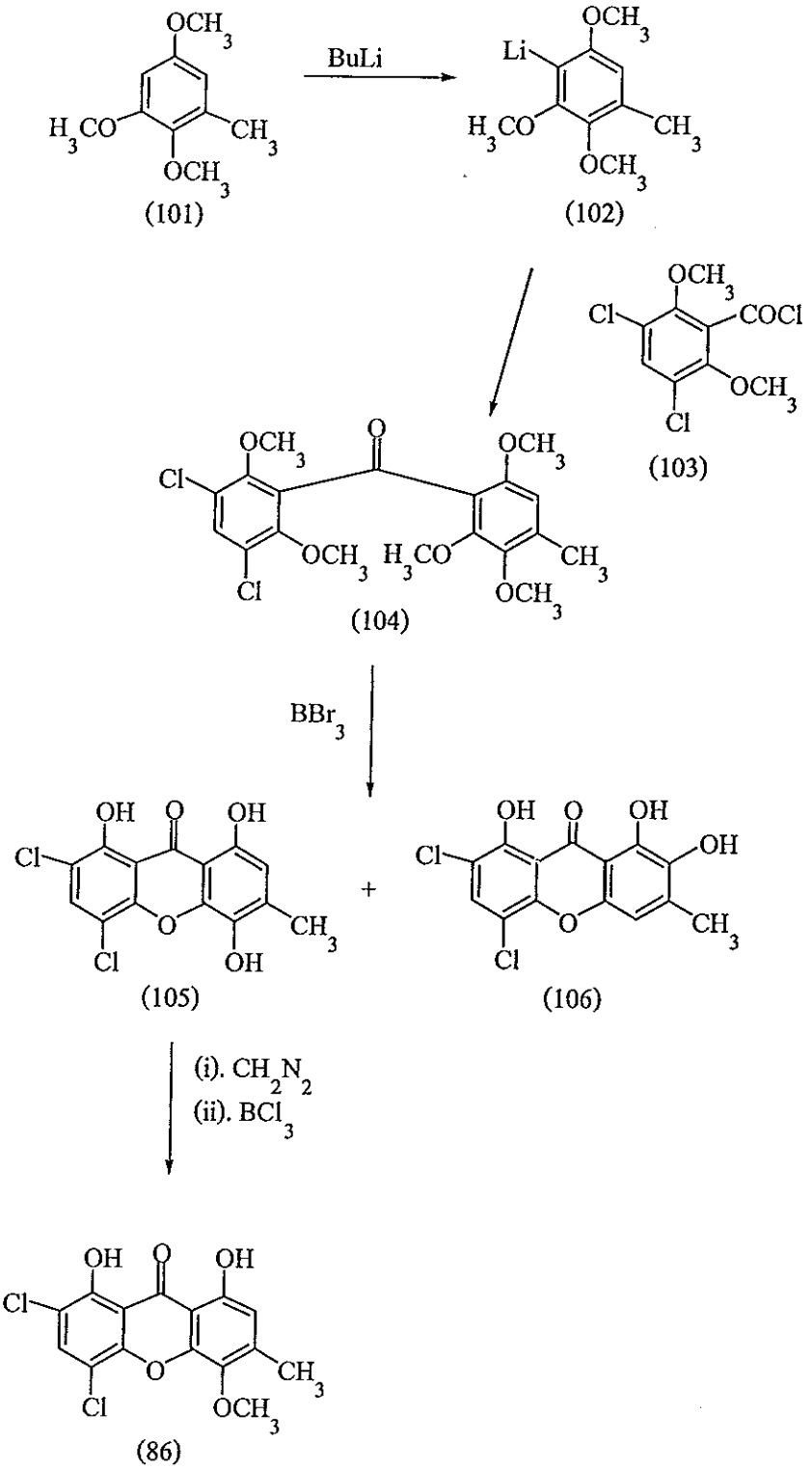


Scheme 8 The standard methods of xanthone synthesis.

For isoarthothelin (81) and thiomelin (86), the synthesis can be achieved by acylation followed by cyclization to form the biaryl ether.

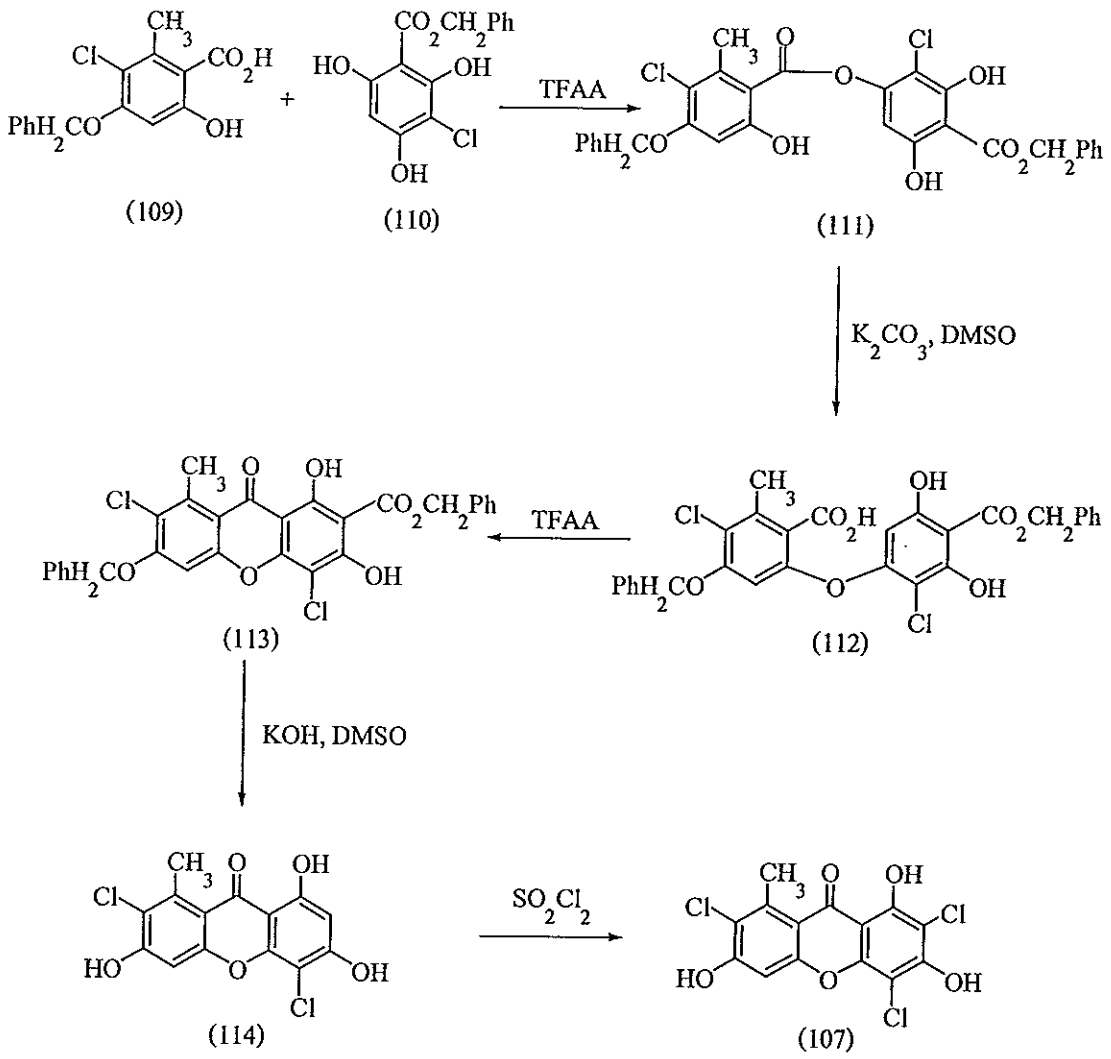


Scheme 9 Synthesis of isoarthothelin (81)

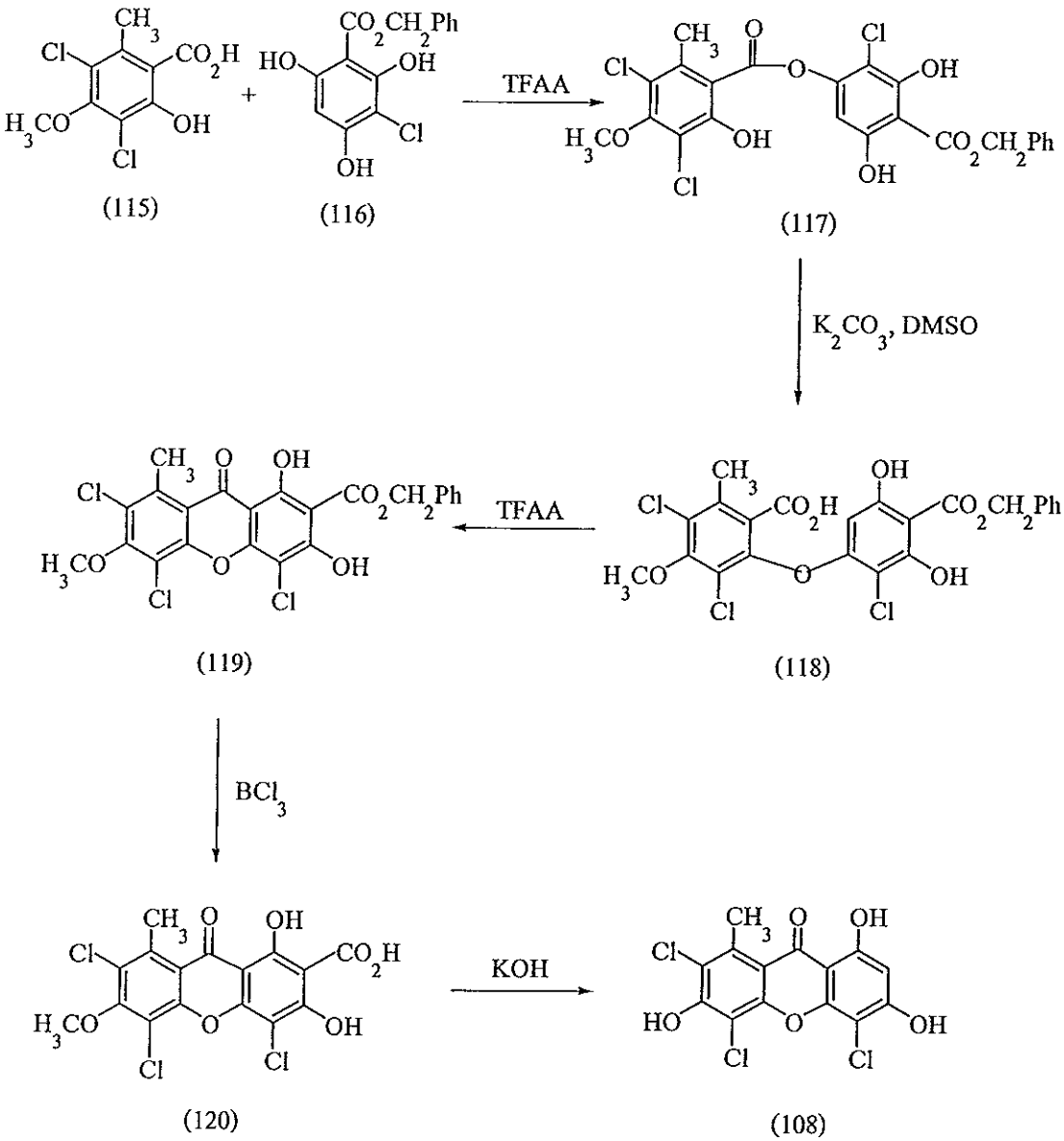


Scheme 10 Synthesis of thiomelin (86)

In 1990, A new synthetic route to norlichexanthone (1,3,6-trimethoxy-8-methylxanthone) derivatives has been developed using Smiles rearrangement of an appropriate substituted depside in the key step. 2,4,7-Trichloronorlichexanthone (107) and 4,5,7-trichloronorlichexanthone (108) have been prepared by this method (Schemes 11 and 12). The former xanthone (107) was shown to be a constituent of the lichens *Lecanora sulphurata* and L. *flavo-pallescents* and the latter (108) a constituent of *Micarea austroternaria* var. *isabellina.*



Scheme 11 Synthesis of 2,4,7-trichloronorlichexanthone (107)



Scheme 14 Synthesis of 4,5,7-trichloronorlichexanthone (108)

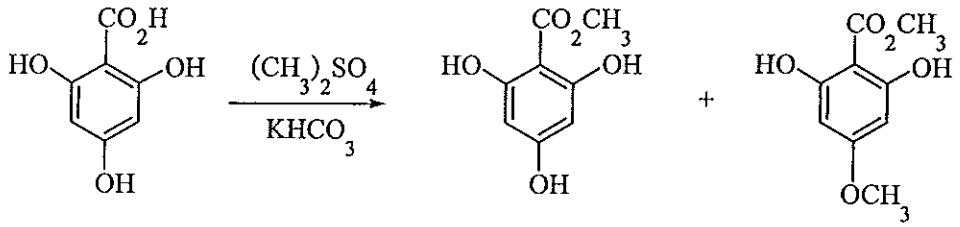
This strategy should prove useful in future syntheses of complex xanthone-based natural products which are of broader importance for their demonstrated biological and pharmacological properties e.g., antileukemic, antiinflammatory, antimicrobial and tuberculostatic. We have carried out the synthetic studies in the corresponding xanthones as indicated in Schemes 16 and 17.

Chapter 2

Experiment

Infrared spectra were determined on a Perkin-Elmer FT-IR spectrophotometer GX and recorded in cm^{-1}. Proton nuclear magnetic resonance spectra were recorded at 60 MHz on a JEOL-PM_X60 spectrometer, and 500 MHz on Varian UNITY INOVA with tetramethylsilane as internal standard. Chemical shifts were expressed in ppm (δ); multiplicity, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were recorded on a Micro mass LCT 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} as absorbent. Bands were detected by exposure to short wave length ultraviolet light. Column chromatography utilized silica gel 60 (70-230 mesh ASTM, Merck) and all organic extracts were dried over anhydrous sodium sulfate (Na_2SO_4). Intensity data for x-ray analysis were collected on a SMART and SAINT diffractometer and computations were carried out on a SHELXTL computer.

1. Methyl 2,4,6-trihydroxybenzoate (58)

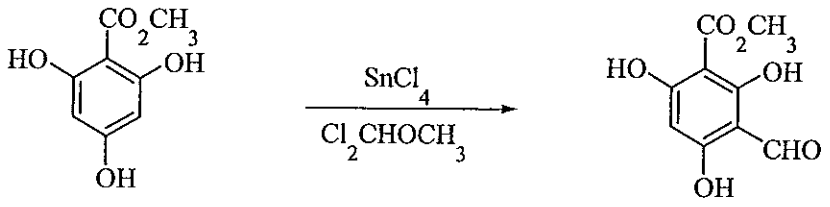


(57) (58) (59)

Dimethyl sulfate (0.70 ml, 1.16 mmol) was added to the stirred mixture of 2,4,6-trihydroxybenzoic acid (57) (1.08 g, 5.75 mmol) and anhydrous potassium hydrogen carbonate (1.09 g, 2.13 mmol) in dry acetone (50 ml) under nitrogen atmosphere at room temperature over 4 hr, followed by addition of 6 N ammonium hydroxide (5 ml) and the stirring was continued for 0.5 hr. Then the mixture was poured into cold dilute hydrochloric acid and extracted with hexane and ethyl acetate respectively. Each organic layer was washed with 5% sodium hydrogen carbonate, saturated brine, dried and the solvent removed. The hexane extract was evaporated to give a solid and then recrystallized from chloroform to give methyl 2,6-dihydroxy-4-methoxybenzoate (59) (0.05 g, 4.83 %) as colourless crystals, m.p. 123-124 $^{\circ}$C. **IR** (KBr) ν_{max} 3418, 3100, 2961, 2852, 1648, 1578, 1254, 1153 cm^{-1}; ^{1}**H NMR** ($CDCl_3$, 60 MHz) δ 3.75 (3H, *s*, OCH_3), 3.96 (3H, *s*, OCH_3), 5.90 (2H, *s*, H-3, H-5), 9.70 (2H, *s*, 2 x OH).

The ethyl acetate extract was evaporated to dryness to give the solid which was recrystallized from chloroform to give methyl 2,4,6-trihydroxybenzoate (58) (0.82 g, 78.06 %) as colourless crystals, m.p.178-180 ^{o}C. **IR** (KBr) ν_{max} 3413, 3131, 2940, 2837, 1679, 1641, 1613, 1594, 1288, 1266, 1149, 1135 cm^{-1}; ^{1}**H NMR** ($CDCl_3$, 60 MHz) δ 4.00 (3H, *s*, OCH_3), 5.90 (2H, *s*, H-3, H-5), 9.75 (2H, *s*, 2 x OH).

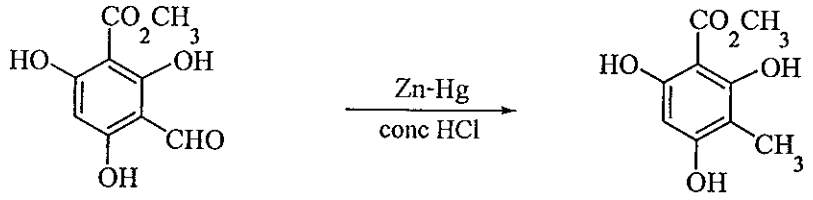
2. Methyl 3-formyl-2,4,6-trihydroxybenzoate (60)



(58) (60)

A solution of methyl 2,4,6-trihydroxybenzoate (58) (0.30 g, 1.65 mmol) and stannic chloride (0.57 mg, 4.89 mmol) in dry dichloromethane (15 ml) was stirred in an atmosphere of nitrogen at 0 °C while dichloromethyl methyl ether (0.55 ml, 4.89 mmol) was added dropwise over 30 min. The cooling bath was removed and the mixture was stirred at room temperature for 4 hr and then poured into cold dilute hydrochloric acid and extracted with ether. The organic layer was washed with water, saturated brine, dried and concentrated. The residue was purified by column chromatography with a mixture of hexane and dichloromethane (1:1) as eluent to give methyl 3-formyl-2,4,6-trihydroxybenzoate (60) (0.29 g, 85.29 %) which was further purified by recrystallization from dichloromethane as colourless crystals, m.p.160-162 ^{o}C. **IR** (KBr) ν_{max} 3333, 3074, 2955, 2865, 1669, 1655, 1204, 1162 cm^{-1}; ^{1}**H NMR** ($CDCl_3$, 60 MHz) δ 4.03 (3H, *s*, OCH_3), 5.90 (1H, *s*, H-5), 10.06 (1H, *s*, CHO), 10.90 (1H, *b*, OH chelated), 12.50 (1H, *b*, OH chelated).

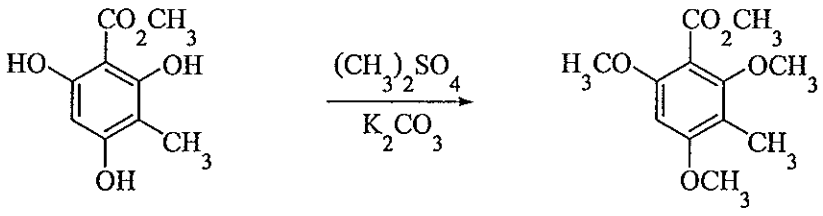
3. Methyl 2,4,6-trihydroxy-3-methylbenzoate (61)



(60) (61)

A mixture of zinc powder (3.46 g, 53.06 mmol), mercury (II) chloride (0.19 g, 0.71 mmol), concentrated hydrochloric acid (1.70 ml) and water (3 ml) was stirred for 5 minutes. The aqueous solution was decanted and replaced by concentrated hydrochloric acid (6 ml) and water (4.50 ml). The mixture was then heated to reflux and a solution of methyl 3-formyl-2,4,6-trihydroxybenzoate (60) (0.75 mg, 3.53 mmol) in hot ethanol (15 ml) was added at such a rate as to prevent crystallization in the funnel. The reaction mixture was then boiled under reflux for 1 hr, cooled, diluted with water. The resulting mixture was extracted which ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was recrystallized from chloroform to give methyl 2,4,6-trihydroxy-3-methylbenzoate (61) (0.63 g, 90.13 %) a colourless crystals, m.p.140-142 °C. **IR** (KBr) ν_{max} 3400, 3328, 3022, 2962, 2925, 1676, 1637, 1611, 1289, 1163 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 60 MHz) δ 2.02 (3H, *s*, CH_3), 4.00 (3H, *s*, OCH_3), 5.90 (3H, *s*, H-5), 9.42 (1H, *s*, OH), 10.13 (1H, *s*, OH chelated).

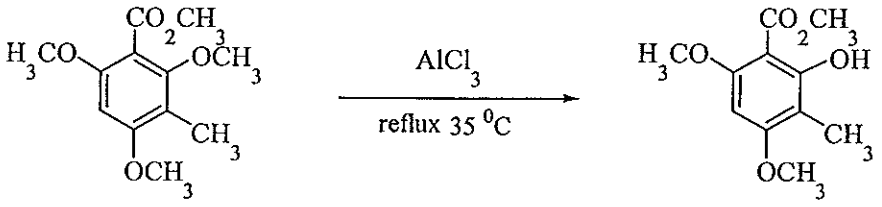
4. Methyl 2,4,6-trimethoxy-3-methylbenzoate (62)



(61) (62)

A mixture of methyl 3-methyl-2,4,6-trihydroxybenzoate (61)(0.20 g, 1.01 mmol), anhydrous potassium carbonate (1.39 g, 10.02 mmol) and dimethyl sulfate (0.34 ml, 3.53 mmol) was stirred and heated under reflux in dry acetone (5 ml) in an atmosphere of nitrogen for 24 hr. The mixture was cooled to room temperature, added 6 N ammonium hydroxide (5 ml) and stirred for a further 0.5 hr. 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 2,4,6-trimethoxy-3-methylbenzoate (62) (0.23 g, 94.90 %) and recrystallized from hexane as colourless crystals, m.p. 77-78 °C. **IR** (KBr) ν_{max} 2992, 2945, 2843, 1732, 1607, 1277, 1157, 1107 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 2.03 (3H, *s*, CH_3), 3.73 (3H, *s*, OCH_3), 3.80 (3H, *s*, OCH_3), 3.82 (3H, *s*, OCH_3), 3.87 (3H, *s*, OCH_3), 6.23 (1H, *s*, H-5); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 7.89, 52.05, 55.49, 55.92, 61.65, 91.25, 110.62, 112.10, 156.37, 157.37, 160.67, 167.60.

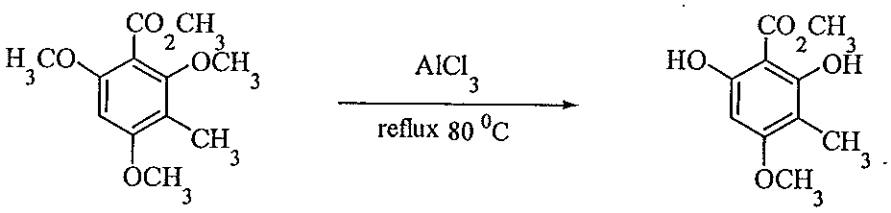
5. Methyl 2-hydroxy-4,6-dimethoxy-3-methylbenzoate (63)



(62) (63)

To a stirred solution of methyl 2,4,6-trimethoxy-3-methylbenzoate (62) (0.24 g, 1.00 mmol) in dry acetonitrile (5 ml) was added anhydrous aluminium chloride (0.26 g, 2.00 mmol) at 0 °C for 30 min and set aside for 40 min at room temperature. Then the mixture was warmed at 35 °C for 1 hr and the solvent was evaporated in vacuo. The residue was partitioned between ethyl acetate and water. The organic layer was washed with 5% sodium hydrogen carbonate, saturated brine, dried and evaporated. The residue was purified by column chromatography with a mixture of ethyl acetate and hexane (8:2) as eluent to give methyl 2-hydroxy-4,6-dimethoxy-3-methylbenzoate (63) (175.90 g, 77.78 %) as colourless crystals, m.p.146-148 °C. **IR** (KBr) ν_{max} 3015, 2945, 1648, 1211 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 60 MHz) δ 2.00 (3H, *s*, CH_3), 3.80 (3H, *s*, OCH_3), 3.86 (6H, *s*, 2 x OCH_3), 5.90 (1H, *s*, H-5), 11.90 (1H, *s*, OH chelated).

6. Methyl 2,6-dihydroxy-4-methoxy-3-methylbenzoate (121)

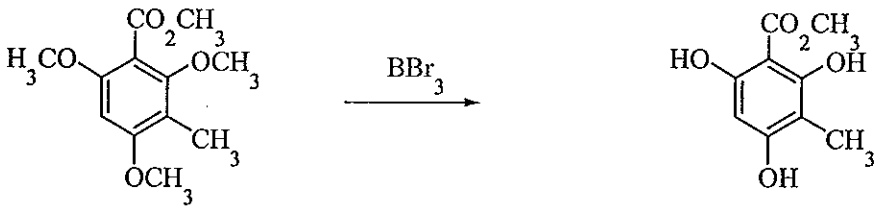


(62)

(121)

To a stirred solution of methyl 3-methyl-2,4,6-trimethoxybenzoate (62)(0.12 g, 0.50 mmol) in dry acetonitrile (1 ml) was added anhydrous aluminium chloride (0.13 g, 1.00 mmol) at 0 °C and set aside for 40 min at room temperature. Then the mixture was refluxed at 80 °C for 1 hr and the solvent was evaporated in vacuo. The organic layer was washed with 5% sodium hydrogen carbonate, saturated brine, dried and the solvent removed. The residue was purified by column chromatography with a mixture of ethyl acetate and hexane (8:2) as eluent to give methyl 2,6-dihydroxy-4-methoxy-3-methylbenzoate (121) (109.90 g, 6.46 %) as colourless crystals, m.p.110-113 °C. **IR** (KBr) ν_{max} 3413, 3044, 2955, 2858, 1659, 1639, 1316, 1253, 1158, 1084 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 60 MHz) δ 2.00 (3H, *s*, CH_3), 3.80 (3H, *s*, OCH_3), 4.00 (3H, *s*, OCH_3), 6.00 (1H, *s*, H-5), 9.60 (1H, *s*, OH), 9.93 (1H, *s*, OH).

7. Methyl 2,4,6-trihydroxy-3-methylbenzoate (61)

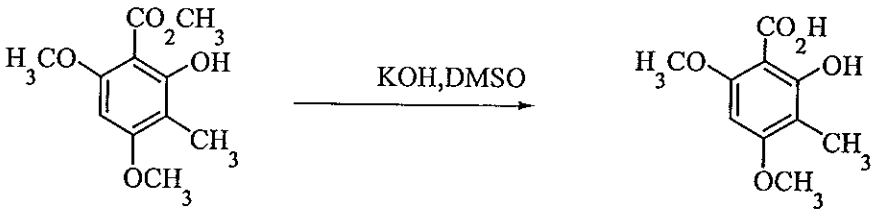


(62) (61)

A solution of boron tribromide (1.72 ml, 17.85 mmol) in hexane (18 ml) was added dropwise to a stirring solution of methyl 2,4,6-trihydroxy-3-methylbenzoate (62) (0.65 mg, 2.97 mmol) in dry dichloromethane (5 ml) in an atmosphere of nitrogen at 0 ^{o}C. After 15 min the cooling bath was removed and the mixture was stirred at room temperature for 3 hr, then poured into ice water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and then the solvent was removed. The residue was purified by column chromatography with a mixture of ethyl acetate and chloroform (2:8) as eluent to give methyl 2,4,6-trihydroxy-3-methylbenzoate (61) (0.49 mg, 84.52 %) which was recrystallized from chloroform as colourless crystals, m.p. 140-142 ^{o}C.

8. 2-Hydroxy-4,6-dimethoxy-3-methylbenzoic acid (65)

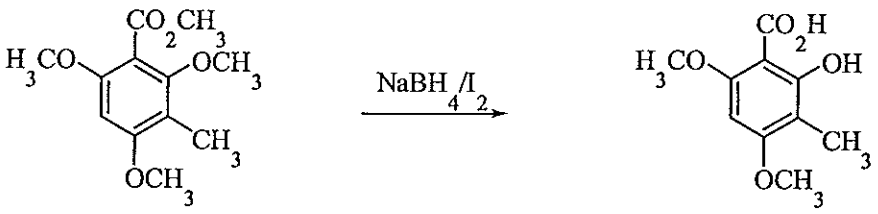
Method A



(63) (65)

A mixture of methyl 2-hydroxy-4,6-dimethoxy-3-methylbenzoate (63) (1.70 g, 7.52 mmol), potassium hydroxide (1.69 g, 30.10 mmol), water (15 ml) and dimethyl sulfoxide (50 ml) was stirred and heated at 90 °C for 3 hr. 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, dried and the solvent removed. The residue was recrystallized from ethyl acetate to give 2-hydroxy-4,6-dimethoxy-3-methyl-benzoic acid (65) (1.38 g, 87 %) as colourless crystals, m.p. 180-181 °C. **IR** (KBr) ν_{max} 3462 (b), 3216, 2950, 2865, 1672, 1633, 1595, 1307, 1177 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 60 MHz) δ 2.00 (3H, *s*, CH_3), 3.87 (3H, *s*, OCH_3), 4.00 (3H, *s*, OCH_3), 6.00 (1H, *s*, H-5), 12.50 (1H, *s*, OH chelated).

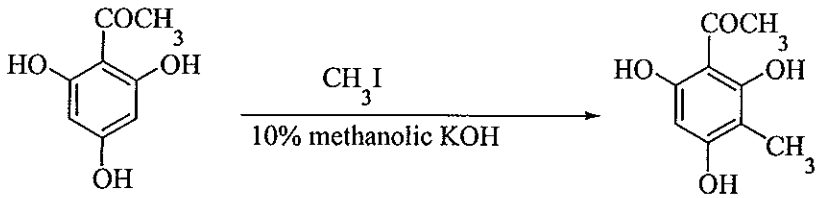
Method B



(62) (65)

A mixture of methyl 2,4,6-trimethoxy-3-methylbenzoate (62) (0.53 g, 2.21 mmol), iodine (0.35 g, 1.37 mmol) and sodium borohydride (0.71 g, 32.56 mmol) in dry chloroform was stirred in a nitrogen atmosphere at 0-5 ^{o}C for 3 hr. The mixture was then stirred at room temperature for a further 24 hr, 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, 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid (65) (0.36 g, 77.18 %) was obtained as colourless crystals, m.p.180-181 ^{o}C.

9. 2,4,6-Trihydroxy-3-methylacetophenone (123)

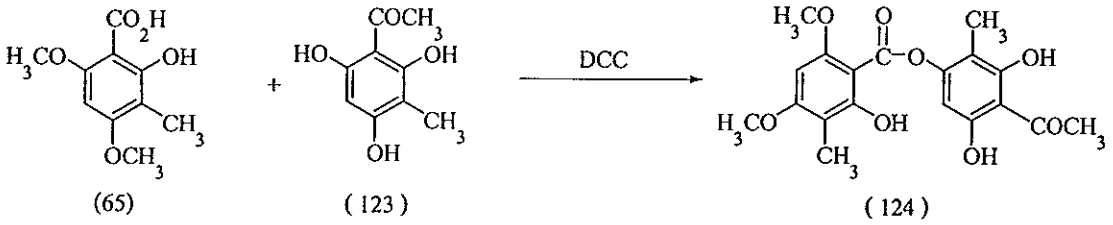


(122) (123)

To a refluxing solution of 2,4,6-trihydroxyacetophenone (122) (3.00 g, 17.85 mmol), absolute methanol (5 ml) and methyl iodide (6.00 ml, 95.91 mmol) was added 10 % methanolic potassium hydroxide (0.60 ml, 1.02 mmol) in 6 portions over 3 hr. During this period more methyl iodide (3.00 ml, 47.95 mmol) was added. After evaporation of the solvent the residue was treated with dilute hydrochloric acid and extracted with ether. The ether layer was washed with several portions of water, saturated brine, dried and the solvent removed. The residue was purified by praparative t.l.c. with a mixture of toluene, ethyl formate and formic acid (5:4:1) as eluent to afford 2,4,6-trihydroxy-3-methylacetophenone (123) (0.47 g, 48.45 %) which was finally recrystallized from methanol giving colouress crystals, m.p.205-206 ^{o}C. **IR** (KBr) ν_{max} 3446 (b), 3008, 2925, 2850, 1627, 1595, 1294, 1277, 1143 cm^{-1}; **^{1}H NMR** ($CDCl_3$ + CD_3OD, 60 MHz) δ 1.93 (3H, *s*, CH_3), 2.56 (3H, *s*, $COCH_3$), 5.73 (1H, *s*, H-5).

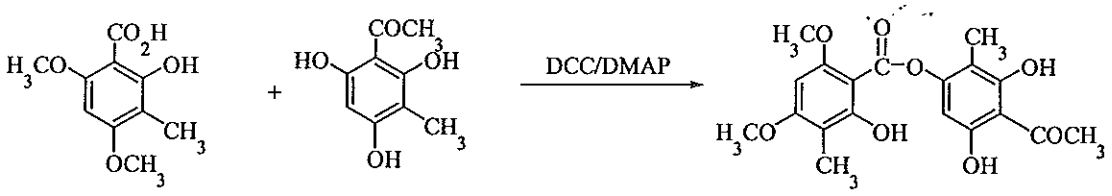
10. 2,6-Dihydroxy-4-(2'-hydroxy-4',6'-dimethoxy-3'-methylbenzoyloxy)-3-methyl-acetophenone (124)

Method A



To a stirred solution of 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid (65) (15.3 mg, 0.07 mmol) in dry dichloromethane (2 ml) was added 2,4,6-trihydroxy-3-methylacetophenone (123) (0.14 g, 0.80 mmol) and cooled to 0-5 °C in an atmosphere of nitrogen. *N,N'*-dicyclohexylcarbodiimide (DCC) (19.1 mg, 0.09 mmol) was added to the reaction mixture which was then stirred for 30 min at 0-5 °C and 3 hr at room temperature. Precipitate urea was then filtered off and the filtrate evaporated. The residue was purified by preparative t.l.c. with a mixture of ethyl acetate and chloroform (2:8) as eluent to give depside (124) (12.00 mg, 45.59 %) which was recrystallized from methanol as yellow crystals, m.p. 174-176 °C. **IR** (KBr) ν_{max} 3338 (b), 3007, 2925, 2843, 1655, 1612, 1298, 1269, 1176, 1142, 1113 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 60 MHz) δ 1.96 (3H, *s*, CH_3), 2.00 (3H, *s*, CH_3), 2.66 (3H, *s*, $COCH_3$), 3.86 (6H, *s*, 2 x OCH_3), 6.00 (1H, *s*, H-5), 6.13 (1H, *s*, H-5'); **EI MS** *m/z* 376 $[M]^+$.

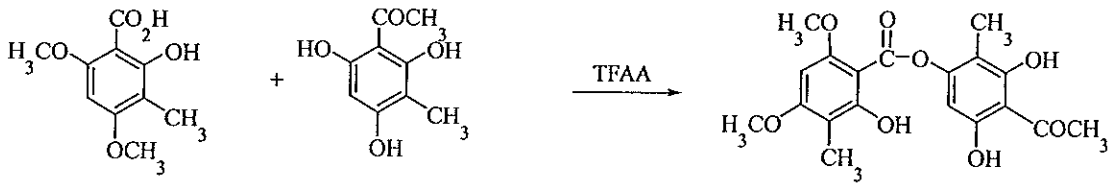
METHOD B



(65) (123) (124)

To a stirred solution of 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid (65) (0.18 g, 0.80 mmol) in dry dichloromethane (25 ml) was added 2,4,6-trihydroxy-3-methylacetophenone (123) (0.14 g, 0.80 mmol), 4-dimethylaminopyridine (DMAP) (0.10 g, 0.80 mmol) and cooled to 0-5°C in an atmosphere of nitrogen. *N,N'*-dicyclohexylcarbodiimide (DCC) (0.26 g, 1.27 mmol) was added to the reaction mixture which was then stirred for 30 min at 0-5 $^{\circ}$C and 3 hr at room temperature. Precipitated urea was then filtered off and the filtrate evaporated. The residue was purified by column chromatography with a mixture of ethyl acetate and chloroform (1:9) as eluent to give the depside (124) (0.20 g, 66.69 %).

Method C

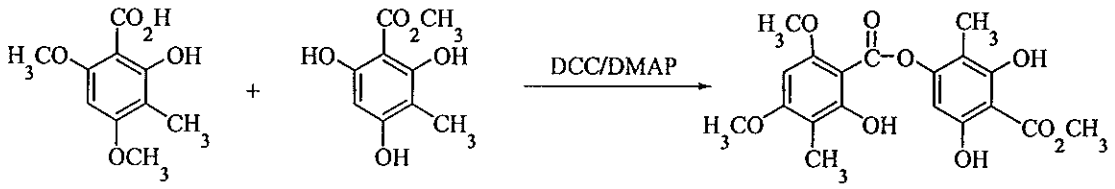


(65) (123) (124)

To a solution mixture of 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid (65) (15.00 mg, 0.07 mmol) and 2,4,6-trihydroxy-3-methylacetophenone (123) (15.40 mg, 0.08 mmol) in anhydrous toluene (1 ml) was added trifluoroacetic anhydride (0.07 ml, 0.52 mmol) in an atmosphere of nitrogen at 0 °C. The stirring was continued at 0 °C for 3 hr. The cooling bath was removed and the mixture was stirred at room temperature for 3 hr and then the solvent was removed. The residue was purified by preparative t.l.c. with a mixture of ethyl acetate and chloroform (2 : 8) as eluent to give the depside (124) (12.30 mg, 47.30 %).

11. Methyl 2,6-dihydroxy-4-(2'-hydroxy-4',6'-dimethoxy-3'-methylbenzoyloxy)-3-methylbenzoate (67)

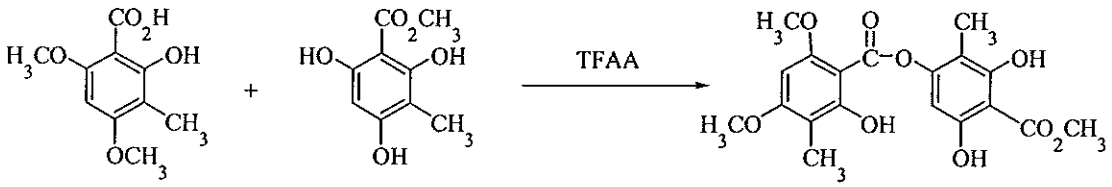
Method A



(65) (61) (67)

To a stirred solution of 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid (65) (0.18 g, 0.87 mmol) in dry dichloromethane (30 ml) was added methyl 2,4,6-trihydroxy-3-methylbenzoate (61) (0.17 g, 0.87 mmol), 4-dimethylaminopyridine (DMAP) (0.01 g, 0.09 mmol) and cooled to 0-5 $^{\circ}$C in an atmosphere of nitrogen. *N,N'*-dicyclohexylcarbodiimide (DCC) (0.54 g, 2.63 mmol) was added to the reaction mixture which was then stirred for 30 min at 0-5 $^{\circ}$C and 3 hr at room temperature. Precipitate urea was then filtered off and the filtrate evaporated. The solid was washed with ethyl acetate to give the depside (67) (0.25 g, 74.47 %) which was recrystallized from a mixture of petroleum ether and dichloromethane as colourless crystals, m.p.143-144°C. **IR** (KBr) ν_{max} 3388, 3082, 2950, 2873, 1680, 1651, 1621, 1599, 1273, 1257, 1153, 1132 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 60 MHz) δ 2.06 (6H, *s*, 2 x CH_3), 3.93 (6H, *s*, 2 x OCH_3), 4.03 (3H, *s*, OCH_3, 6.03 (1H, *s*, H-5), 6.36 (1H, *s*, H-5'), 9.45 (1H, *s*, OH), 10.36 (1H, *s*, OH chelated), 11.53 (1H, *s*, OH chelated); **ES MS** *m/z* 415 $[M+Na]^+$.

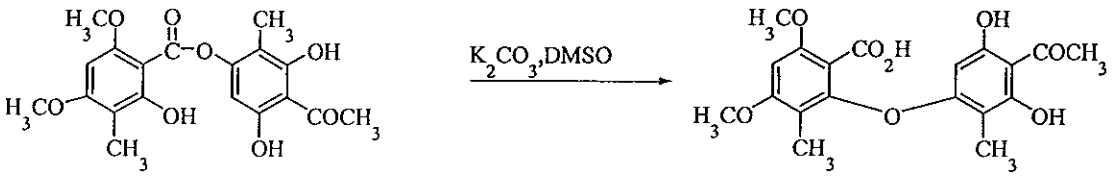
Method B



(65) (61) (67)

To a stirred solution mixture of 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid (65) (100.00 mg, 0.47 mmol) and methyl 2,4,6-trihydroxy-3-methylbenzoate (61) (93.40 mg, 0.08 mmol) in anhydrous toluene (1 ml) was added trifluoroacetic anhydride (0.53 ml, 3.77 mmol) in an atmosphere of nitrogen at 0 ^{o}C. The stirring was continued at 0 ^{o}C for 3 hr. The cooling bath was removed and the mixture was stirred at room temperature for 3 hr and then the solvent was removed. The residue was purified by preparative t.l.c. with a mixture of ethyl acetate and chloroform (2 : 8) as eluent to give the depside (67) (118.30 mg, 67.30 %).

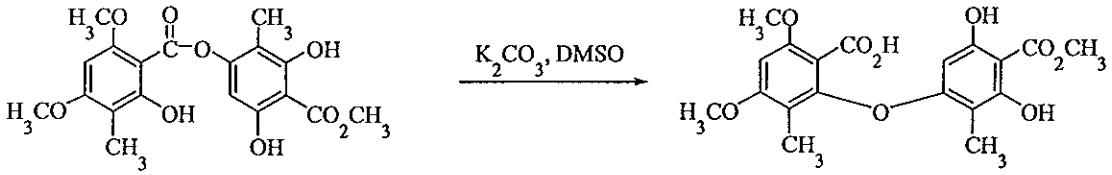
12. 2-(4'-Acetyl-3',5'-dihydroxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (125)



124) (125)

A mixture of 2,6-dihydroxy-4-(2'-hydroxy-4',6'-dimethoxy-3'-methylbenzoyl-oxy)-3-methylacetophenone (124) (0.33 g, 0.89 mmol), anhydrous potassium carbonate (0.17 g, 1.25 mmol) and anhydrous dimethyl sulfoxide (5 ml) was stirred in an atmosphere of nitrogen at room temperature for 16 hr. 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 recrystallized from methanol to give 2-(4'-acetyl-3',5'-dihydroxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (125) (0.23 mg, 70.80 %) as colourless crystals, m.p. 174-176 ^{o}C. **IR** (KBr) ν_{max} 3396, 3119, 2925, 2850, 1663, 1617, 1607, 1283, 1130, 1116 cm^{-1}; **^{1}H NMR** ($CDCl_3$ + CD_3OD, 60 MHz) δ 1.80 (3H, *s*, CH_3), 2.06 (3H, *s*, CH_3), 2.53 (3H, *s*, $COCH_3$), 3.80 (6H, *s*, 2 x OCH_3), 5.36 (1H, *s*, H-5'), 6.30 (1H, *s*, H-5); **^{13}C NMR** ($CDCl_3$+CD_3OD, 125 MHz) δ 7.47, 8.75, 33.01, 59.51, 56.79, 93.79, 94.06, 104.97, 106.68, 112.29, 113.17, 151.64, 158.16, 161.59, 161.92, 163.43, 164.39, 168.95, 203.50; **EI MS** m/z 376 $[M]^+$.

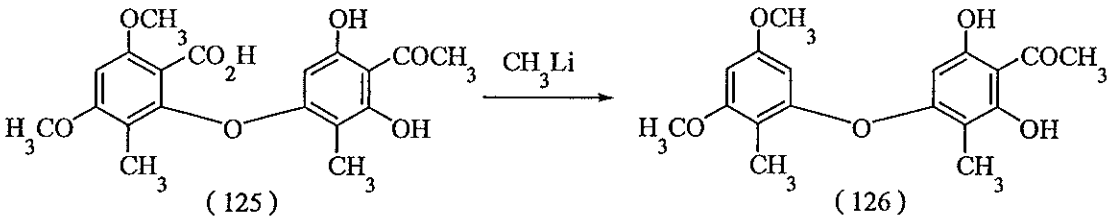
13. 2-(3',5'-Dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (68)



(67) (68)

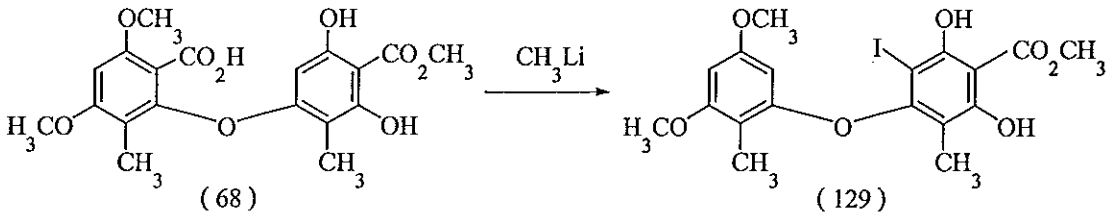
A mixture of methyl 2,6-dihydroxy-4-(2'-hydroxy-4',6'-dimethoxy-3'-methylbenzoyloxy)-3-methylbenzoate (67) (0.13 g, 0.32 mmol), anhydrous potassium carbonate (0.06 g, 0.48 mmol) and anhydrous dimethyl sulfoxide (5 ml) was stirred in an atmosphere of nitrogen at room temperature for 12 hr. The reaction 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 recrystallized from a mixture of ethyl acetate and hexane to give 2-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (68) (101.54 mg, 81.88 %) as colourless crystals m.p. 174-176 $^{\circ}$C. **IR** (KBr) ν_{max} 3410, 3139, 2930, 2837, 1679, 1640, 1609, 1594, 1288, 1265, 1149, 1134 cm^{-1}; **^{1}H NMR** (CD_3OD, 60 MHz) δ 1.87 (3H, *s*, CH_3), 2.17 (3H, *s*, CH_3), 3.77 (6H, *s*, 2 x OCH_3), 3.90 (3H, *s*, OCH_3), 5.47 (1H, *s*, H-5'), 6.27 (1H, *s*, H-5) ; **^{13}C NMR** (CD_3OD, 125 MHz) δ 7.81, 8.70, 52.95, 56.50, 56.75, 94.13, 94.94, 95.86, 105.70, 112.45, 112.99, 151.54, 158.09, 160.97, 161.25, 161.85, 163.62, 169.07, 171.79; **ES MS** *m/z* 415 $[M+Na]^+$.

14. 2,6-Dihydroxy-4-(3',5'-dimethoxy-2'-methylphenoxy)-3-methylacetophenone (126)



A stirred solution of the acid (125) (61.00 mg, 0.16 mmol) in dry tetrahydrofuran (THF) (5 ml) in an atmosphere of nitrogen was cooled to 0°C and then methyl lithium was added rapidly (2.40 ml, 1.95 mmol). After 3 hr at 0°C, the ice bath was then removed and the stirring was continued at room temperature for 6 hr. Saturated ammonium chloride (30 ml) was rapidly added while stirring continued and the mixture was extracted with ether. The residue was purified by preparative t.l.c. with a mixture of hexane chloroform (2:8) as eluent to give the ketone (126) (3.7 mg, 6.90 %). **IR** (KBr) ν_{max} 3386 (b), 3092, 2924, 2850, 1618, 1585, 1439, 1420, 1149, 1122 ; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 1.92 (3H, *s*, CH_3), 2.17 (3H, *s*, CH_3), 3.75 (3H, *s*, OCH_3), 3.83 (3H, *s*, OCH_3), 5.53 (1H, *s*, H-3), 6.15 (1H, d, H-6', J = 2.0 Hz), 6.34 (1H, *d*, H-4' , J = 2.0 Hz) ; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 7.68, 8.55, 33.16, 55.75, 55.97, 94.48, 95.88, 98.38, 105.87, 111.89, 153.81, 159.32, 159.87, 162.50, 203.81; **ES MS** *m/z* 333 $[M+H]^+$.

15. Methyl 2,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy)-5-methyl-benzoate (129)

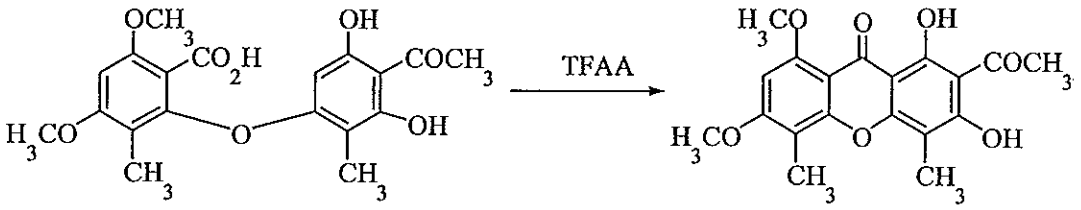


A stirred solution of the acid (68) (39.00 mg, 0.01 mmol) in dry tetrahydrofuran (THF) (5 ml) in an atmosphere of nitrogen was cooled to 0 ^{o}C and then methyl lithium was added rapidly (1.10 ml, 0.99 mmol). After 3 hr at 0 ^{o}C , the ice bath was then removed and the stirring was continued at room temperature for 6 hr. Saturated ammonium chloride (30 ml) was rapidly added while stirring continued and the mixture was extracted with ether. The residue was purified by preparative t.l.c. with 20% hexane/chloroform as eluent to give methyl 2,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy)-5-methylbenzoate (129) (2.80 mg, 0.72 %) m.p. 140-142 ^{o}C. **IR** (KBr) ν_{max} 3423 (b), 3003, 2956, 2924, 1734, 1670, 1591, 1413, 1126 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 1.98 (3H, *s*, CH_3), 2.23 (3H, *s*, CH_3), 3.62 (3H, *s*, OCH_3), 3.84 (3H, *s*, OCH_3), 4.12 (3H, *s*, OCH_3), 5.54 (1H, *d*, 2 x ArH ; J = 2.5 Hz), 6.18 (1H, *d*, 2 x ArH ; J = 2.5 Hz), 10.18 (1H, *b*, OH chelated), 10.50 (1H, *b*, OH chelated); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 7.80, 9.25, 53.17, 55.21, 55.54, 91.93, 92.27, 97.61, 107.30, 112.91, 155.84, 159.23, 159.78, 160.12, 169.97 ; **ES MS** *m/z* 497 $[M+Na]^+$.

16. Preparation of methyl lithium (Baumgarten (ed.), 1973 and Semmelhack(ed.), 1984)

Methyl iodide (20.00 g, 140.90 mmol) was added with stirring to lithium (2.25 g, 324.25 mmol) in anhydrous ether (120.00 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 hr and then set aside for 6 hr, whereupon the precipitated lithium chloride settled to the bottom of the flask. The concentration was estimated in the usual way by hydrolysis of an aliquot and titration with 0.10 M hydrochloric acid. The solution contained 0.98 M methyl lithium.

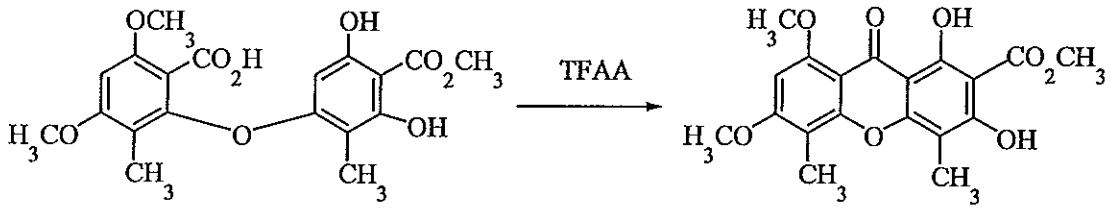
17. 2-Acetyl-1,3-dihydroxy-6,8-dimethoxy-4,5-dimethylxanthone (127)



(125) (127)

To a stirred solution of 6-(4'-acetyl-3',5'-dihydroxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (125) (5.00 mg, 0.01 mmol) in anhydrous toluene (1 ml) was added trifluoroacetic anhydride (0.15 mg, 1.07 mmol) in an atmosphere of nitrogen at 0 °C. The stirring was continued at 0 °C for 10 min. The cooling bath was removed and the mixture was stirred at room temperature for 20 hr and then the solvent was removed. Washing the residue with ethyl acetate gave 1,3-dihydroxy-2-acetyl-6,8-dimethoxy-4,5-dimethylxanthone (127) (4.30 mg, 93.4 %) m.p. 228-229 °C. **IR** (KBr) ν_{max} 3432 (b), 3000, 2936, 2835, 1639, 1626, 1595, 1573, 1318, 1196, 1147 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 2.23 (3H, *s*, CH_3), 2.28 (3H, *s*, CH_3), 2.79 (3H, *s*, $COCH_3$), 3.98 (3H, *s*, OCH_3), 4.04 (3H, *s*, OCH_3), 6.31 (1H, *s*, H-7), 14.64 (1H, *s*, OH chelated); **EI MS** *m/z* 358 $[M]^+$.

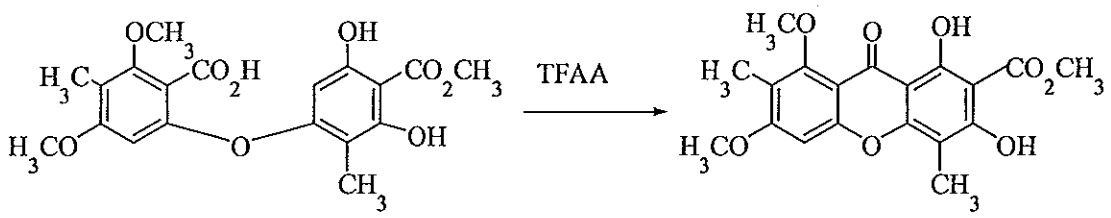
18. 1,3-Dihydroxy-6,8-dimethoxy-2-methoxycarbonyl-4,5-dimethylxanthone (131)



(68) (131)

To a stirred solution of 2-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (68) (4.30 mg, 0.01 mmol) in anhydrous toluene (0.30 ml) was added trifluoroacetic anhydride (0.12 ml, 0.89 mmol) in an atmosphere of nitrogen at 0 °C. The stirring was continued at 0 °C for 10 min. The cooling bath was removed and the mixture was stirred at room temperature for 20 hr and then the solvent was removed. Washing the residue with ethyl acetate gave 1,3-dihydroxy-6,8-dimethoxy-2-methoxycarbonyl-4,5-dimethylxanthone (131) (4.0 mg, 97.56 %) m.p. 228-229°C. **IR** (KBr) ν_{max} 3444 (b), 2993, 2933, 2837, 1652, 1594, 1574, 1222, 1158 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ : 2.30 (3H, *s*, CH_3), 2.31 (3H, *s*, CH_3), 4.01 (3H, *s*, OCH_3), 4.06 (3H, *s*, OCH_3), 4.07 (3H, *s*, OCH_3), 6.42 (1H, *s*, H-7), 12.93 (1H, *s*, OH chelated); **EI MS** *m/z* 374 $[M]^+$.

19. 1,3-Dihydroxy-6,8-dimethoxy-2-methoxycarbonyl-4,7-dimethylxanthone (133)



(75)

(133)

To a stirred solution of 2-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (75) (20.50 mg, 0.052 mmol) in anhydrous toluene (0.30 ml) was added trifluoroacetic anhydride (0.58 ml, 4.18 mmol) in an atmosphere of nitrogen at 0 °C. The stirring was continued at 0 °C for 10 min. The cooling bath was removed and the mixture was stirred at room temperature for 20 hr and then the solvent was removed. Washing the residue with ethyl acetate gave 1,3-dihydroxy-6,8-dimethoxy-2-methoxycarbonyl-4,7-dimethylxanthone (133) (18.2 mg, 93.81 %) m.p. 228-229°C. **IR** (KBr) ν_{max} 3451 (b), 2936, 2843, 1664, 1643, 1613, 1592, 1252, 1223, 1127 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 60 MHz) δ 2.13 (3H, *s*, CH_3), 2.20 (3H, *s*, CH_3), 3.80 (3H, *s*, OCH_3), 3.90 (3H, *s*, OCH_3), 3.96 (3H, *s*, OCH_3), 6.60 (1H, *s*, H-5), 12.80 (1H, *s*, OH chelated); **^{13}C NMR** δ ($CDCl_3$, 125 MHz) 7.28, 8.14, 52.65, 56.14, 61.60, 94.91, 97.05, 102.01, 102.24, 107.95, 118.33, 156.91, 157.11, 158.63, 164.13, 165.58, 166.43, 171.92, 180.56; **EI MS** *m/z* 374 $[M]^+$.

Chapter 3

Results and Discussion

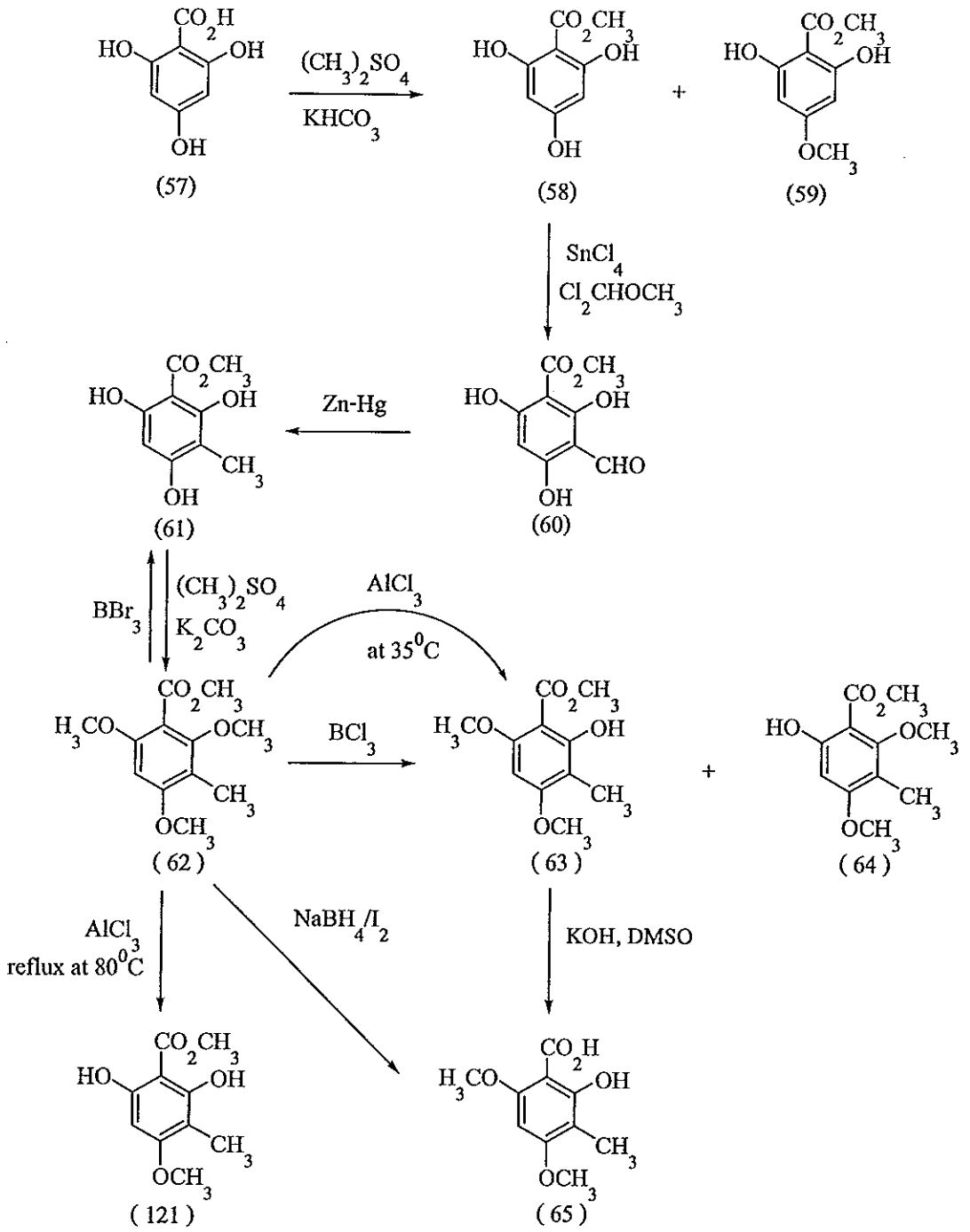
The synthetic route to 2-(4'-acetyl-3',5'-dihydroxy-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (125) and 2-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (68) is outline in Schemes 16 and 17. These syntheses employed a novel Smiles rearrangement (Elix and Jenie, 1989) of precusor para depsides (124) and (67) in key step, to give the corresponding diphenyl ethers (125) and (68), respectively. Intramolecular cyclization of diphenyl ethers (125), (68) and (75) afforded xanthones (127), (131) and (134) ,respectively (Schemes 16 and 17). For these syntheses, methyl 2,4,6-trihydroxy-3-methylbenzoate (61), methyl 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid (65) and 2,4,6-trihydroxy-3-methyl-acetophenone (123) were used as starting materials (Scheme 13).

1. Synthesis of methyl 2,4,6-trihydroxy-3-methylbenzoate (61) and 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid (65)

The selective methylation of 2,4,6-trihydroxybenzoic acid (57) with dimethyl sulfate and anhydrous potassium hydrogen carbonate gave methyl 2,4,6-trihydroxybenzoate (58) (78%) and methyl 2,6-dihydroxy-4-methoxybenzoate (59) (4%) as by product (Scheme 13). Formylation of methyl 2,4,6-trihydroxybenzoate (58) with dichloromethyl methyl ether and stannic chloride afforded methyl 3-formyl-2,4,6-trihydroxybenzoate (60) (85%). The Clemmensen reduction of aldehyde (60) afforded

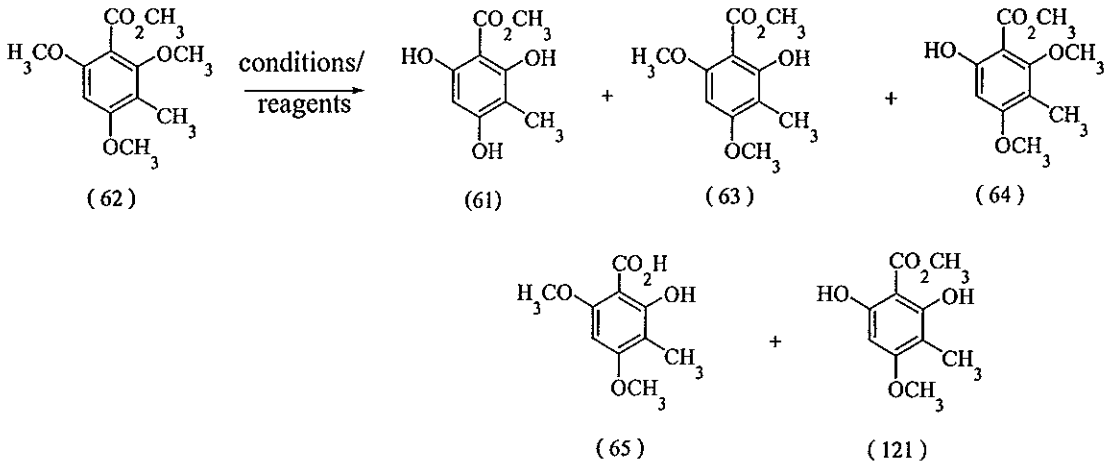
methyl 2,4,6-trihydroxy-3-methylbenzoate (61) (90%). Full methylation of compound (61) with excess dimethyl sulfate in the presence of potassium carbonate afforded methyl 2,4,6-trimethoxy-3-methylbenzoate (62) (95%).

The synthetic route to 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid (65) (Scheme 13) can be employed by two reaction types : 1. treatment of methyl 2,4,6-trimethoxy-3-methylbenzoate (62) with iodine and sodium borohydride at room temperature resulted in the selective demethylation of methoxy group at position 2 and concomitant with reductive cleavage of ester (ester hydrolysis) to afford the acid (65) in moderate yield (77%) ; 2. hydrolysis of the ester group of the compound (63) with potassium hydroxide in dimethyl sulfoxide gave the acid (65) (87%).



Scheme 13 Synthesis of methyl 2,4,6-trihydroxy-3-methylbenzoate (61) and 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid (65)

The results of demethylation of methyl 2,4,6-trimethoxy-3-methylbenzoate (62) (Scheme 14) using various reagents and conditions are shown in Table 2. The order of reactivity of demethylating reagents was arranged as follow $BBr_3 > BCl_3 > AlCl_3$. Boron tribromide demethylated all three methoxy groups at positions 2,4 and 6 to give methyl 2,4,6-trihydroxy-3-methylbenzoate (61) (84 %) (entry 2). Boron trichloride demethylated only one methoxy group at position 2 or 6 to give methyl 2-hydroxy-4,6-dimethoxy-3-methylbenzoate (63) and methyl 6-hydroxy-2,4-dimethoxy-3-methylbenzoate (64) (entry 3). Hence, boron tribromide is more reactive but less selective than boron trichloride, perhaps because bromide ion is more strongly nucleophilic than chloride ion. Treatment of (62) with aluminium chloride at 35°C resulted in selective demethylation of out of plane methoxy group (ortho methoxy group at position 2) to give methyl 2-hydroxy-4,6-dimethoxy-3-methylbenzoate (63) (entry 4). Furthermore, the reaction conducted at 80 °C afforded the product which both ortho methoxy groups were demethylated (121)(entry 5). The selectivity of demethylation depends upon co-ordination of the lewis acid with two oxygen atoms to form six-membered ring as indicated in scheme 15.

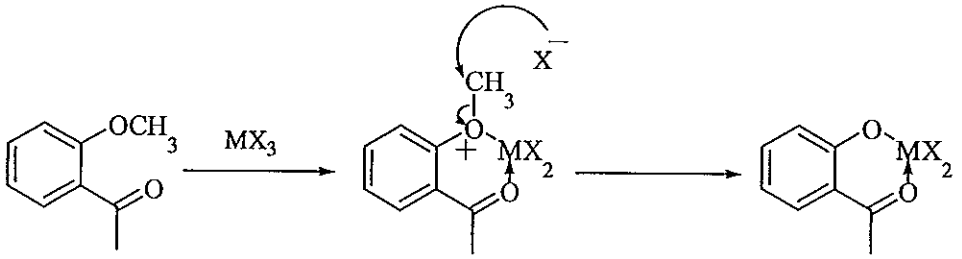


Scheme 14 Demethylation of methyl 2,4,6-trimethoxy-3-methylbenzoate (62)

Table 2 Demethylation of methyl 2,4,6-trimethoxy-3-methylbenzoate (62) with various reagents.

Entry	Reagents / Conditions	% Products				
		61	63	64	65	121
1	$NaBH_4/I_2$ in $CHCl_3$, $0^{\circ}C$ 30 min, RT 24 hr	-	-	-	77	-
2	BBr_3 in CH_2Cl_2, $0^{\circ}C$ 15 min, RT 24 hr	84	-	-	-	-
3	*BCl_3 in CH_2Cl_2, $0^{\circ}C$ 15 min, RT 24 hr	-	49	48	-	-
4	$AlCl_3$ in CH_3CN, $0^{\circ}C$ 30 min and $35^{0}C$ 1 hr.	-	77	-	-	-
5	$AlCl_3$ in CH_3CN, 30 min, reflux $80^{0}C$ 1 hr.	-	-	-	-	96

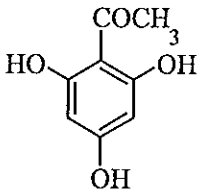
* Data cited from Suttirak (Suttirak, 1995)



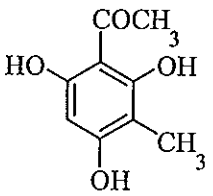
Scheme 15 Co-ordination of the lewis acid with two oxygen atoms to form six-membered ring (Dean *et al.*, 1966).

2. Synthesis of 2,4,6-trihydroxy-3-methylacetophenone (123).

C-Methylation of 2,4,6-trihydroxyacetophenone (122) with methyl iodide in 10% methanolic potassium hydroxide afforded 2,4,6-trihydroxy-3-methylacetophenone (123) (48 %).



(122)



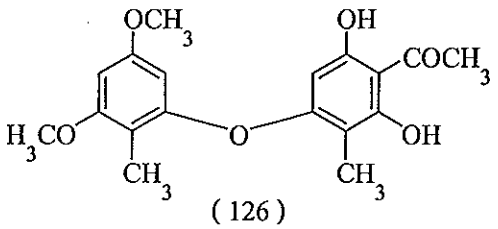
(123)

3. Synthesis of 2,6-dihydroxy-4-(3',5'-dimethoxy-2'-methylphenoxy)-3-methylacetophenone (126) and 2-acetyl-1,3-dihydroxy-6,8-dimethoxy-4,5-methylxanthone (127).

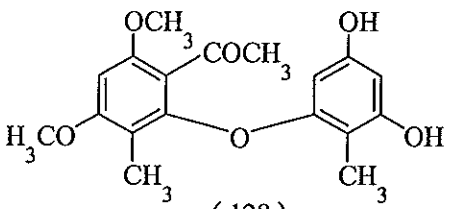
The condensation between the acid (65) and the ketone (123) in the presence of *N, N'*-dicyclohexylcarbodiimide (DCC) gave the depside (124) in moderate yield (45%) (Scheme 16). Futhermore, when this reaction was added 4-dimethylaminopyridine (DMAP), the depside(124) was obtained in higher yield (66%). Reaction with trifluoroacetic anhydride in anhydrous toluene at $0^{\circ}C$ for 16 hr afforded the depside (124) (47%). Regioselective esterification of the phenolic ketone (123) occurred at the less hindered, non-or weakly intramolecularly hydrogen-bonded hydroxy group of each ester (Elix *et al.*, 1990). Treatment of the depside (124) with anhydrous potassium carbonate in dimethyl sulfoxide at room temperature effected the Smiles rearrangement and afforded the corresponding diphenyl ether (125) (69 %). Subsequently, intramolecular Friedel Craft acylation of the diphenyl ether (125) by treatment with trifluoroacetic anhydride in anhydrous toluene yielded the corresponding xanthone (127) (93 %).

The next step is a conversion of carboxyl group of compound (125) to the corresponding methyl ketone (71) by a standard method (Rubottom and Kim, 1958). Inspection of NMR signal of the expected product (71) did not show the increase in the number of acetyl signals so (71) was not formed. The **^{1}H NMR** spectral data of the product showed similarities to that of the starting material (125), except an additional two doublet aromatic protons at δ_H 6.15 and 6.34 (J = 2.0 Hz) and one singlet aromatic proton at δ_H 6.34. The **^{13}C NMR** spectrum of the product showed 15 signals attributable to (as determined by the **DEPT** spectra) five methyl, three methine and seven quaternary carbons. The **HMQC** spectral data of the product was employed for the assignment of

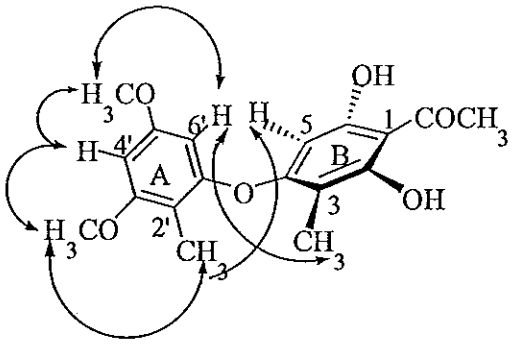
the structure to be limited to two possibilities. The **NOE** spectrum is indeed a powerful tool for the identification of possible structures (126) and (128). Irradiation at 3.75 ppm (OCH_3-5') showed enhancement of two aromatic protons (6.15 and 6.34 ppm). Irradiation at 3.83 ppm (OCH_3-3') showed enhancement of one aromatic proton (6.34 ppm). The methoxy group at 3.75 ppm must be situated between two aromatic protons. Thus, the product definitely has two aromatic protons on ring A and the **HMBC** spectrum of diphenyl ether (126) clearly demonstrated the presence of the aromatic protons attached to aromatic carbon atom at C-6' (cross peaks observed from H-6' to C-1', C-2', C-4' and C-5' and H-4' to C-2', C-5' and C-6'). Confirmation of this proposition was obtained by **NOE, DEPT, HMQC** and **HMBC** data (Table 3) and mass spectral data. Finally the crystal structure of the product (126) was determined by x-ray diffraction (Karalai *et al.*, 2001).



(126)

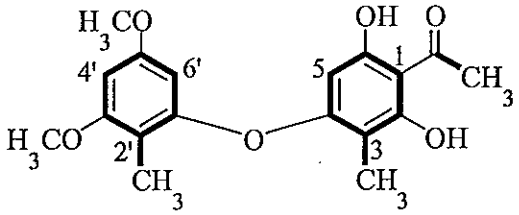


(128)



(126)

Figure 1 Represent enhancement from the **NOE** experiment on 2,6-dihydroxy-4-(3',5'-dimethoxy-2'-methylphenoxy)-3-methylacetophenone (126).



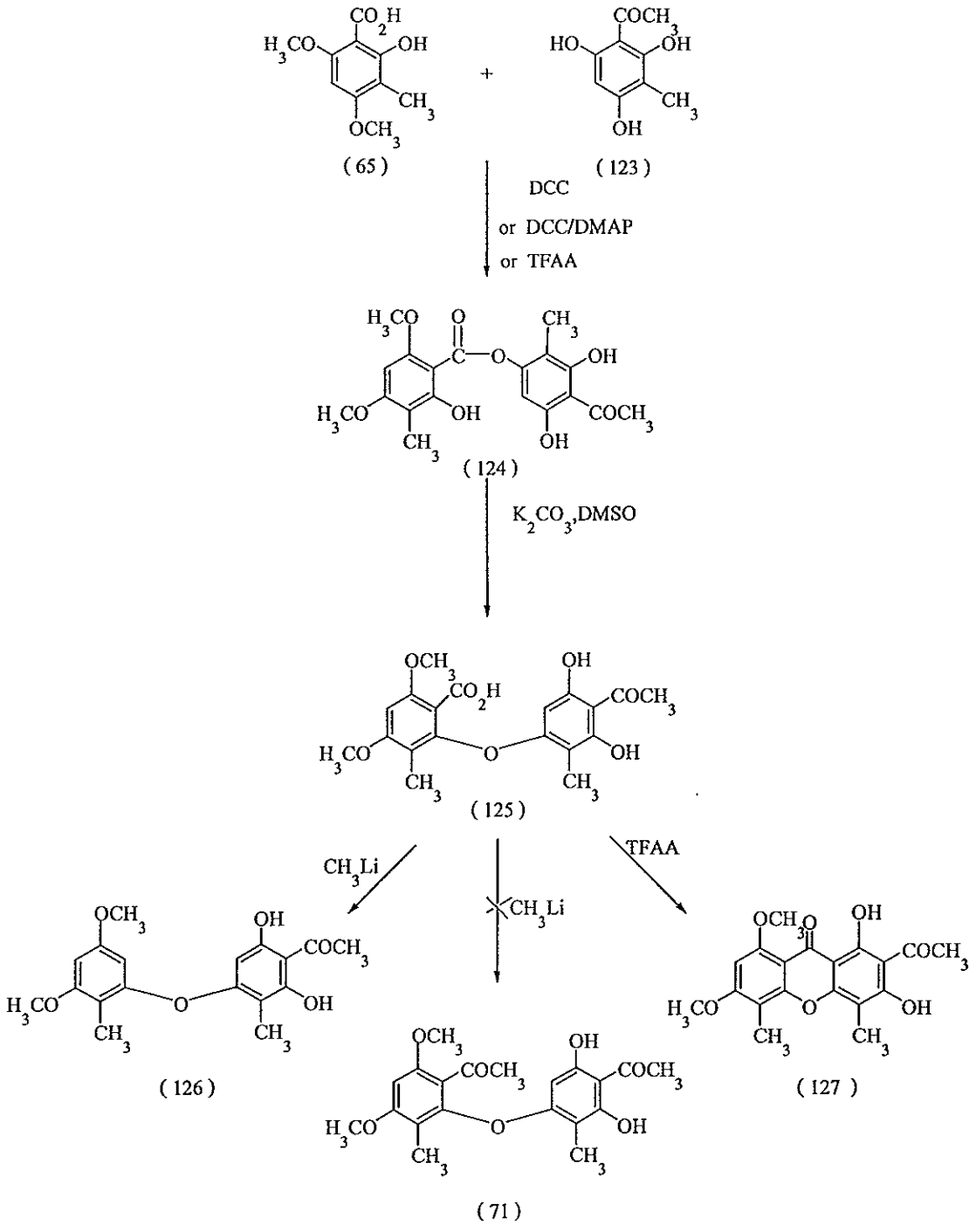
(126)

Figure 2 Structures of 2,6-dihydroxy-4-(3',5'-dimethoxy-2'-methylphenoxy)-3-methyl-acetophenone (126). Thick line represent connectivity disclosed from the **HMBC** experiment.

Table 3 NMR data for 2,6-dihydroxy-4-(3',5'-dimethoxy-2'-methylphenoxy)-3-methylacetophenone (126).

Position	$\delta^{1}H$	$\delta^{13}C$	NOE	HMQC $^{1}J_{CH}$	HMBC $^{n}J_{CH}$
1	-	105.86	-	-	-
2	-	162.15	-	-	-
3	-	105.86	-	-	-
4	-	162.15	-	-	-
5	5.53	94.47	-	94.47	162.15(C-4), 159.32(C-6), 105.86(C-3)
6	-	159.32	-	-	-
H_3CCO-1	2.66	32.91	-	32.91	203.80(C=O)
CO-1	-	203.80	-	-	-
HO-2	-	-	-	-	-
H_3C-3	2.17	7.67	6.15	7.67	162.15(C-4), 105.86(C-3)
HO-6	-	-	-	-	-
1'	-	153.81	-	-	-
2'	-	111.88	-	-	-
3'	-	159.86	-	-	-
4'	6.34 (d,J=2.0Hz)	95.87	-	95.87	159.32(C-5'), 111.88(C-2'), 98.38(C-6')
5'	-	159.32	-	-	-
6'	6.15 (d,J=2.0Hz)	98.38	-	98.38	153.81(C-1'), 111.88(C-2'), 95.38(C-4')
H_3C-2'	1.92	8.55	3.83, 5.53	8.55	159.86(C-3'), 153.88(C-1'), 111.88(C-2'), 98.38(C-6')

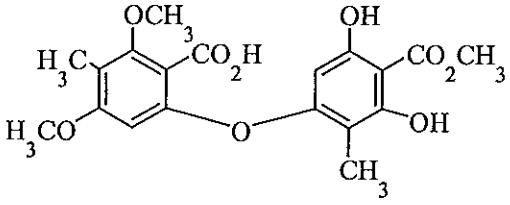
Position	$\delta^{1}H$	$\delta^{13}C$	NOE	HMQC $^{1}J_{CH}$	HMBC $^{n}J_{CH}$
H_3CO-3'	3.83	55.96	6.34	55.96	159.86(C-3')
H_3CO-5'	3.75	55.75	6.15, 6.34	55.75	159.32(C-5')



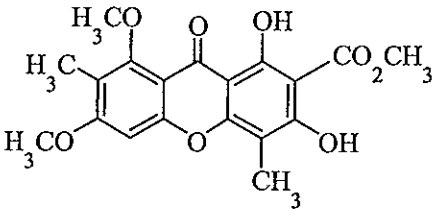
Scheme 16 Synthesis of the diphenyl ether (126) and the xanthone (127).

4. Synthesis of methyl 4,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy)-5-methylbenzoate (129) and 1,3-dihydroxy-2-methoxycarbonyl-6,8-dimethoxy-4,5-dimethylxanthone (131).

The treatment of the acid (65) and the ester (61) with dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) gave the depside (67) and subsequent Smiles rearrangement of the compound (67) with anhydrous potassium carbonate in anhydrous dimethyl sulfoxide afforded the corresponding diphenyl ether (68) (82 %). Intramolecular cyclization of the diphenyl ether (68) with trifluoroacetic anhydride afforded the corresponding xanthone (131) (Scheme 17). Similarly, treatment of the diphenyl ether (75)(isomeric diphenyl ether from authentic sample) with trifluoroacetic anhydride afforded the corresponding xanthone (133).



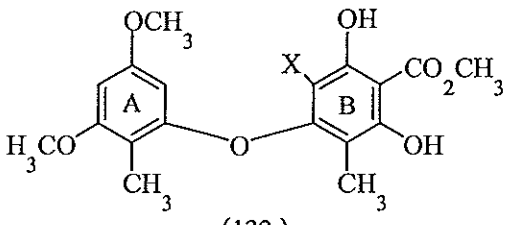
(75)



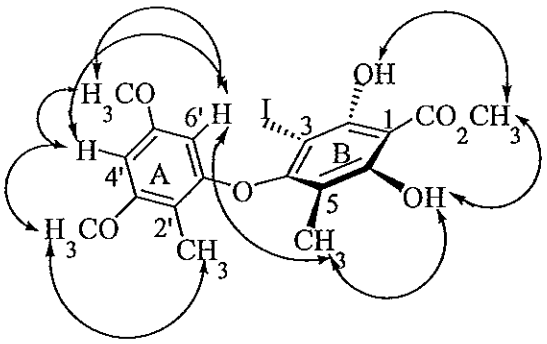
(133)

2-(3',5'-Dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (68) was reacted with methyl lithium in anhydrous tetrahydrofuran (THF) at 0°C for 3 hr and room temperature for 6 hr. The **^{1}H NMR** spectra of the purified product did not show the acetyl signal (about 2.7 ppm) which implied absence of acetyl group. The **^{1}H NMR** spectral data indicated no detection of the expected product (130). The **^{13}C NMR** spectrum of the product showed 15 signals attributable to (as determined

by the **DEPT** spectra) five methyl, two methine and eight quaternary carbons. The **HMQC** spectral data of the compound was employed for the assignment of protons connected to their respective carbons. The **^{1}H NMR** spectrum of the product was similar to that of starting material (68), except that two singlet aromatic protons from individual ring (δ_H 5.54 and 6.18 ppm) in (68) were replaced by two meta aromatic protons (δ_H 5.54 and 6.18, J = 2.5 Hz). From the **NOE** experiment, irradiation at 3.62 ppm (CH_3O-5') showed enhancement of two aromatic protons (δ_H 5.54 and 6.18 ppm). Irradiation at 3.84 ppm (OCH_3-3') showed enhancement of one aromatic proton signal (at 6.18 ppm). The **NOE** experiment confirmed that one methoxy group at 3.62 ppm must be ortho to two aromatic protons. From **HMBC** spectrum of the product, there were correlations from H-4' to C-2', C-5' and C-6' and H-6' to C-1', C-2', C-4' and C-6'. Thus, the product definitely has two aromatic protons on ring A. The absence of aromatic proton signal in ring B suggested full substitution on ring B. The possible structure from the above information data could be assigned as structure (132) when x is a substituent group. Furthermore, the product had a molecular weight plus sodium as 947. So that, a substituent group (x) must be iodine atom. Finally, the structure has been proved by x-ray. The plausible mechanism metal-halogen exchange was shown in scheme 18. The more detail inference such as **DEPT, COSY, HMQC** and **HMBC** data was shown in Table 4.

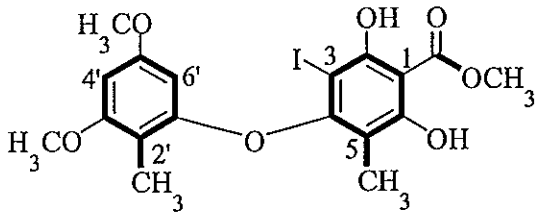


(132)



(129)

Figure 3 Represent enhancement from the **NOE** experiment on methyl 4,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy)-5-methylbenzoate (129).



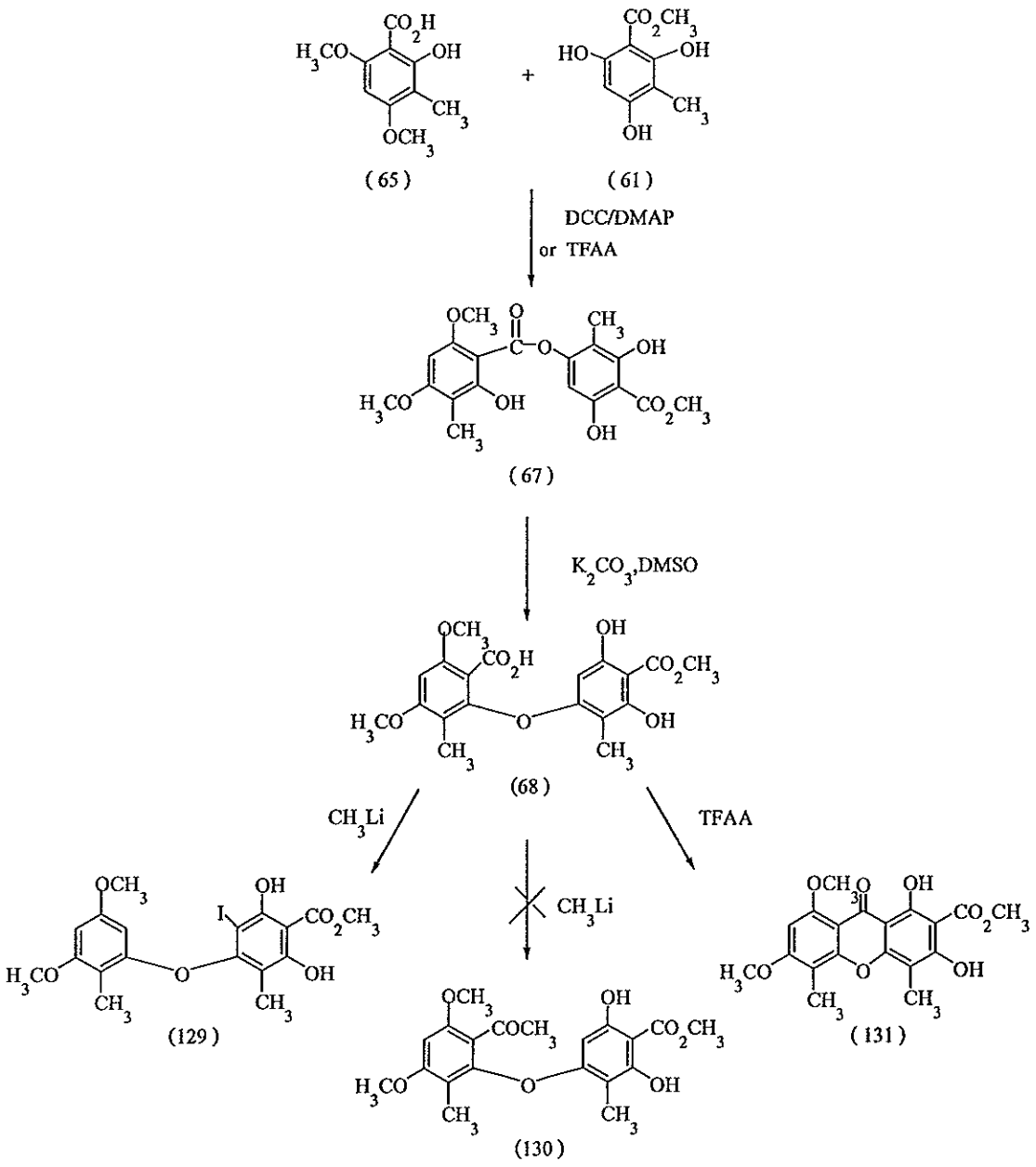
(132)

Figure 4 Structures of methyl 4,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy)-5-methylbenzoate (132). Thick line represent connectivities disclosed from the **HMBC** experiment.

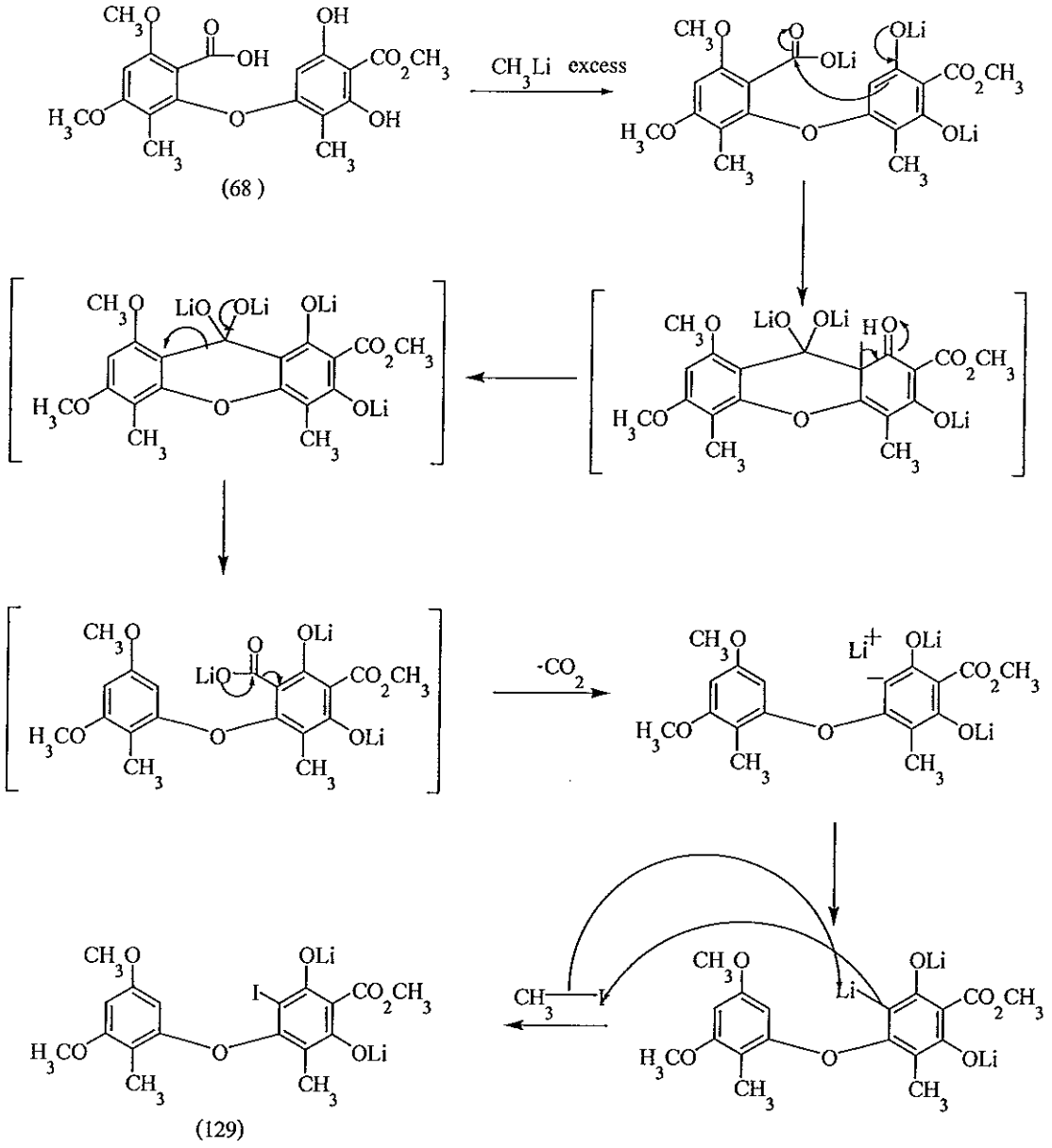
Table 4 NMR data for methyl 4,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy)-5-methylbenzoate (129).

Position	δ^1H	$\delta^{13}C$	NOE	HMQC $^1J_{CH}$	HMBC $^nJ_{CH}$
1	-	112.91	-	-	-
2	-	160.12	-	-	-
3	-	97.61	-	-	-
4	-	160.12	-	-	-
5	-	112.91	-	-	-
6	-	160.12	-	-	-
H_3CO_2C-1	4.12	53.17	-	53.17	169.97(C=O)
CO-1	-	169.97	-	-	-
HO-2	10.50	-	4.12	-	-
H_3C-5	1.98	9.25	5.54	-	160.12(C-2,C-4,C-6), 112.91 (C-1,C-5), 97.61(C-3)
HO-6	10.18	-	1.98, 4.12	-	-
1'	-	155.84	-	-	-
2'	-	107.30	-	-	-
3'	-	159.78	-	-	-
4'	6.18 (d, J= 2.5 Hz)	91.93	3.62, 3.84, 5.54	91.93	159.23(C-5'), 107.30(C-2'), 92.27(C-6')

Position	$\delta^{1}H$	$\delta^{13}C$	NOE	HMQC $^{1}J_{CH}$	HMBC $^{n}J_{CH}$
5'	-	159.23	-	-	-
6'	5.54 (d,J=2.5 Hz)	92.27	-	92.27	159.23(C-5'), 155.84(C-1'), 107.30(C-2'), 91.93(C-4')
H_3C-2'	2.23	7.80	3.84	-	159.78(C-3'), 155.84(C-1'), 107.30(C-2')
H_3CO-3'	3.84	55.54	6.18	55.54	159.78(C-3')
H_3CO-5'	3.62	55.21	5.54, 6.18	55.21	159.23(C-5')



Scheme 17 Synthesis of the diphenyl ether (129) and the xanthone (131).

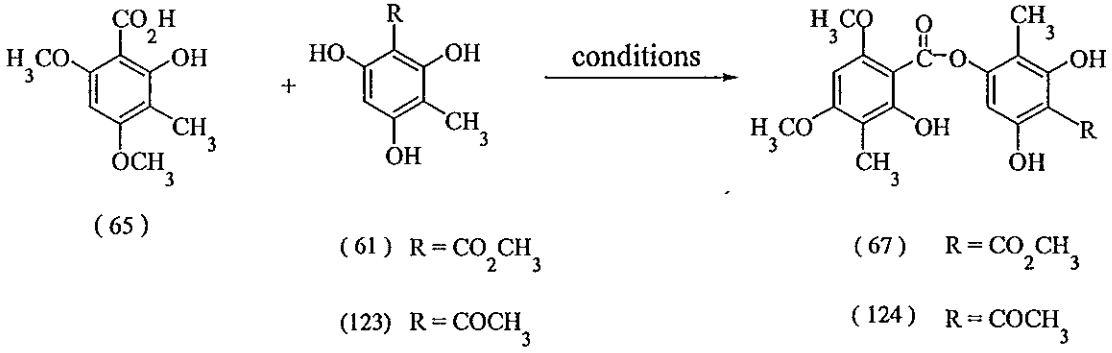


(68)

(129)

Scheme 18 The plausible mechanism of the metal-halogen exchange.

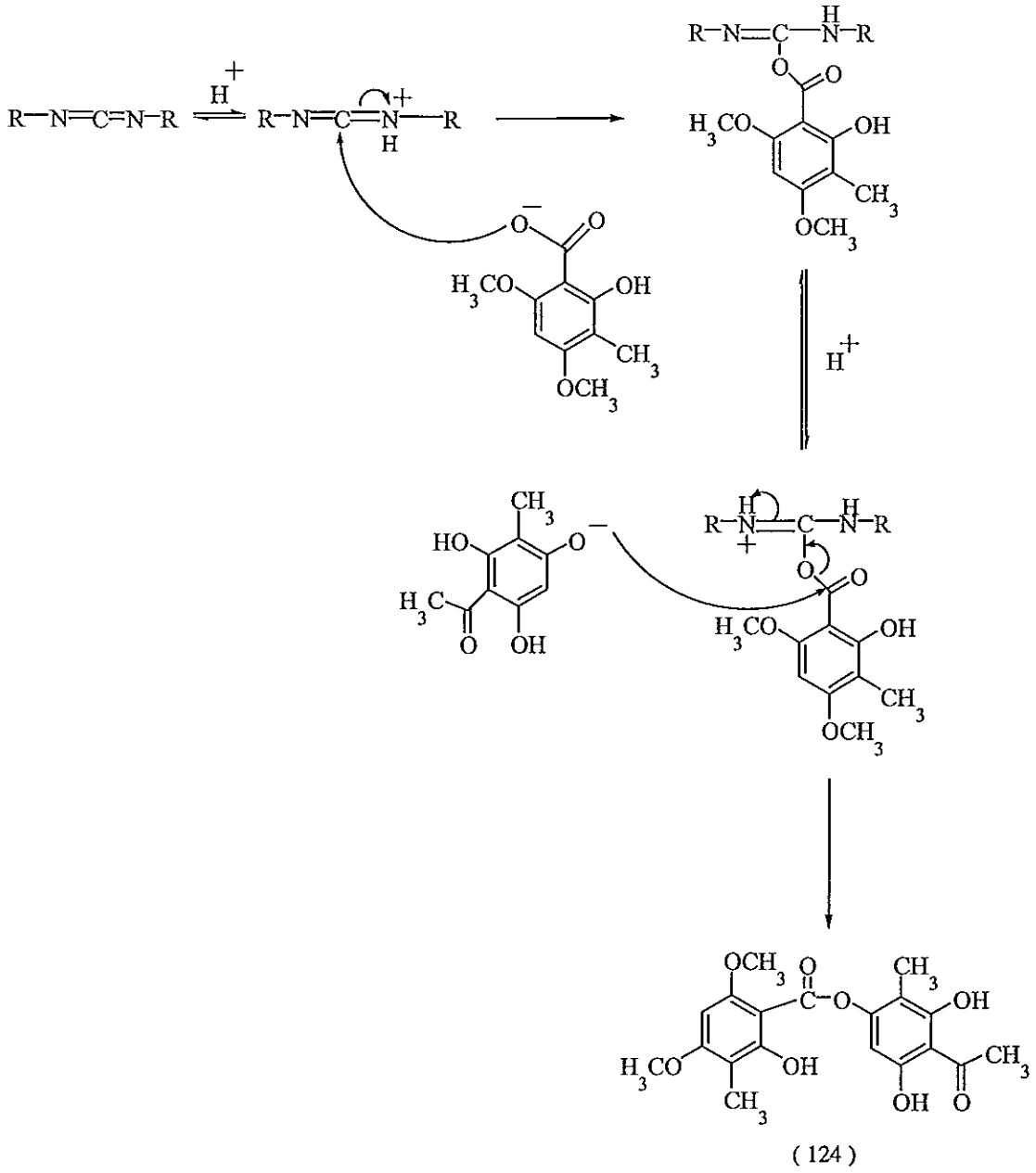
Table 5 represents synthesis of the depside (124) in different conditions. Esterification of the acid (65) with the ketone (123) gave the corresponding depside (124) (Scheme 19). Entry 1, using DCC as reagent, the four steps mechanism, has been suggested by Khorana and coworkers (Scheme 20). Entry 2 gave higher yield because DMAP increased rate of generated carboxylate unit.



Scheme 19 Synthesis of the depside (124) and (67) in different conditions.

Table 5 Synthesis of the depsides (124) and (67) in different conditions

entry	R groups	conditions	% yield
1.	$-COCH_3$	DCC	45
2.	$-COCH_3$	DCC / DMAP	66
3.	$-COCH_3$	TFAA	47
4.	$-CO_2CH_3$	DCC / DMAP	87
5.	$-CO_2CH_3$	TFAA	64



(124)

Scheme 20 Mechanism of esterification using DCC as reagent.

Higher yield of depside was obtained with R being a phenolate ester (entry 4 and 5). The results can be explained in term of nucleophilicity. Nucleophilicity of para- hydroxy group with R being an ester (61) is more than that with R being a ketone (123) because of electronic effect. Ketone group are stronger electron-withdrawing than ester group so that electron density at para-hydroxy of phenolate ketone (123) is less than phenolate ester (61)

The diphenyl ether (125) exhibited weak activity against the microbial S. *aereus* ATCC 25923 (minimum inhibited concentrations (MIC) of more than 200 μg/mL), the corresponding xanthone (127) was found to be inactive against *S .aereus* ATCC 25923 and *E. coli* ATCC 25922). Compounds (127), (131) and (133) were inactive against *Mycobacterium tuberculosis* H37Ra (at 200 μg/mL), KB and BC.

Table 6 Biological activities of xanthones (127), (131) and (133) the diphenyl ether (125)

Compound	Antimicrobial (MIC, μg/mL)		Anti Malarial (EC_{50}, μg/mL)	Anti Fungal (IC_{50}, μg/mL)	Cytotoxicity (IC_{50}, μg/mL)		Anti Tuberculous (MIC, μg/mL)
	S. aureus ATCC 25923	E. coli ATCC 25922			KB[a]	BC[b]	TB[c]
125	> 200	inactive	-	-	-	-	-
127	-	-	inactive	> 50	inactive	inactive	inactive
131	-	-	inactive	> 50	inactive	inactive	inactive
133	-	-	inactive	> 50	inactive	inactive	inactive

[a]Oral human epidermoid carcinoma

[b]Human breast cancer cells

[c]In vitro anti tuberculous activity against *Mycrobacterium tuberculosis* H37Ra

Chapter 4

Conclusion

In this studies, diphenyl ethers (68) and (125) have been prepared by Smiles rearrangement of precursor para-depsides (67) and (124), respectively. The depsides (67) and (124), which have been prepared by condensation between phenols (61) or (123) with activated benzoic acid (65). Intramolecular Friedel Crafts cyclization of diphenyl ether (68) and (125) gave the corresponding xanthones (127) and (131), respectively, when treated with trifluoroacetic anhydride.

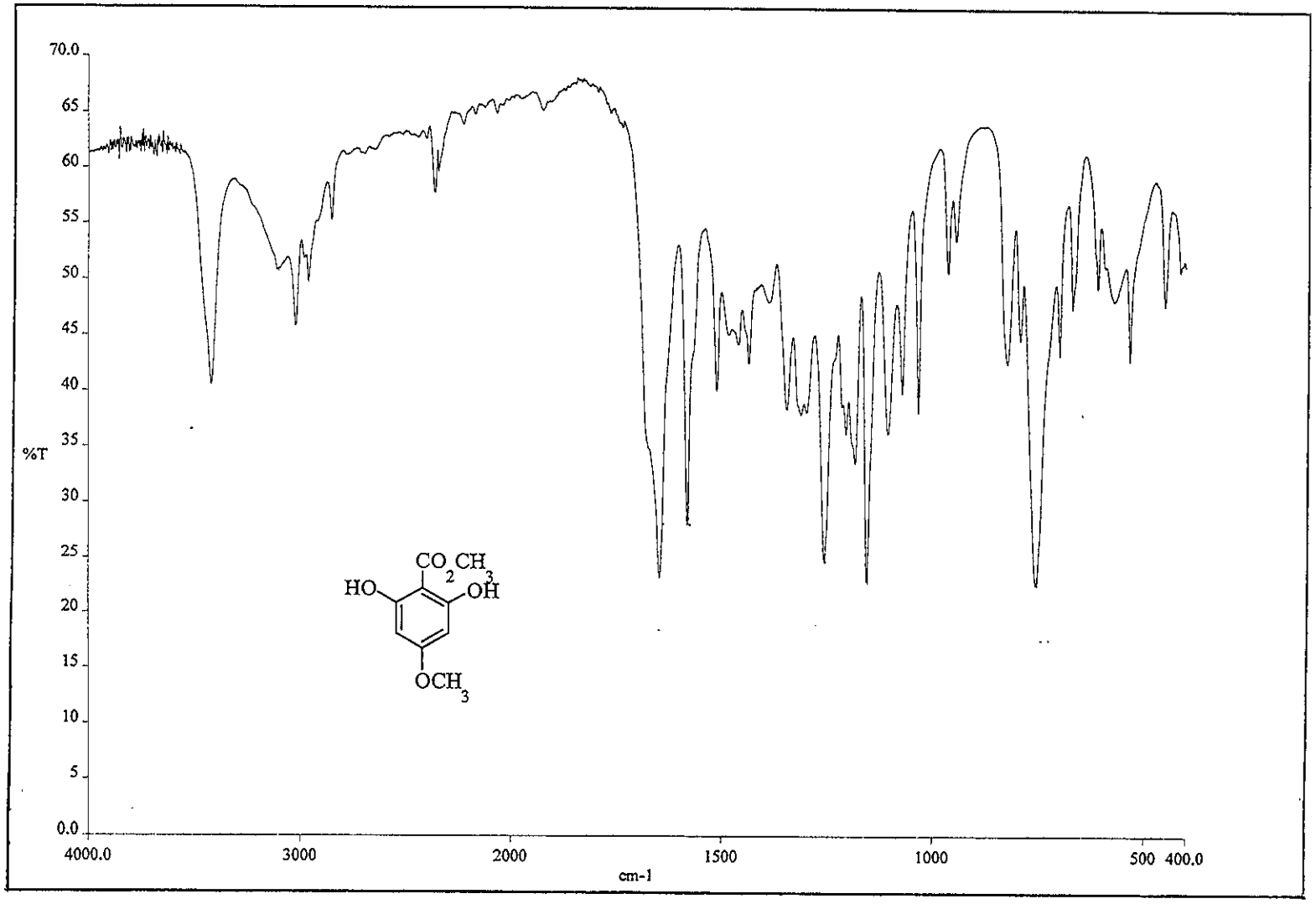


Figure 5. FTIR spectrum of methyl 2,6-dihydroxy-4-methoxybenzoate (59)

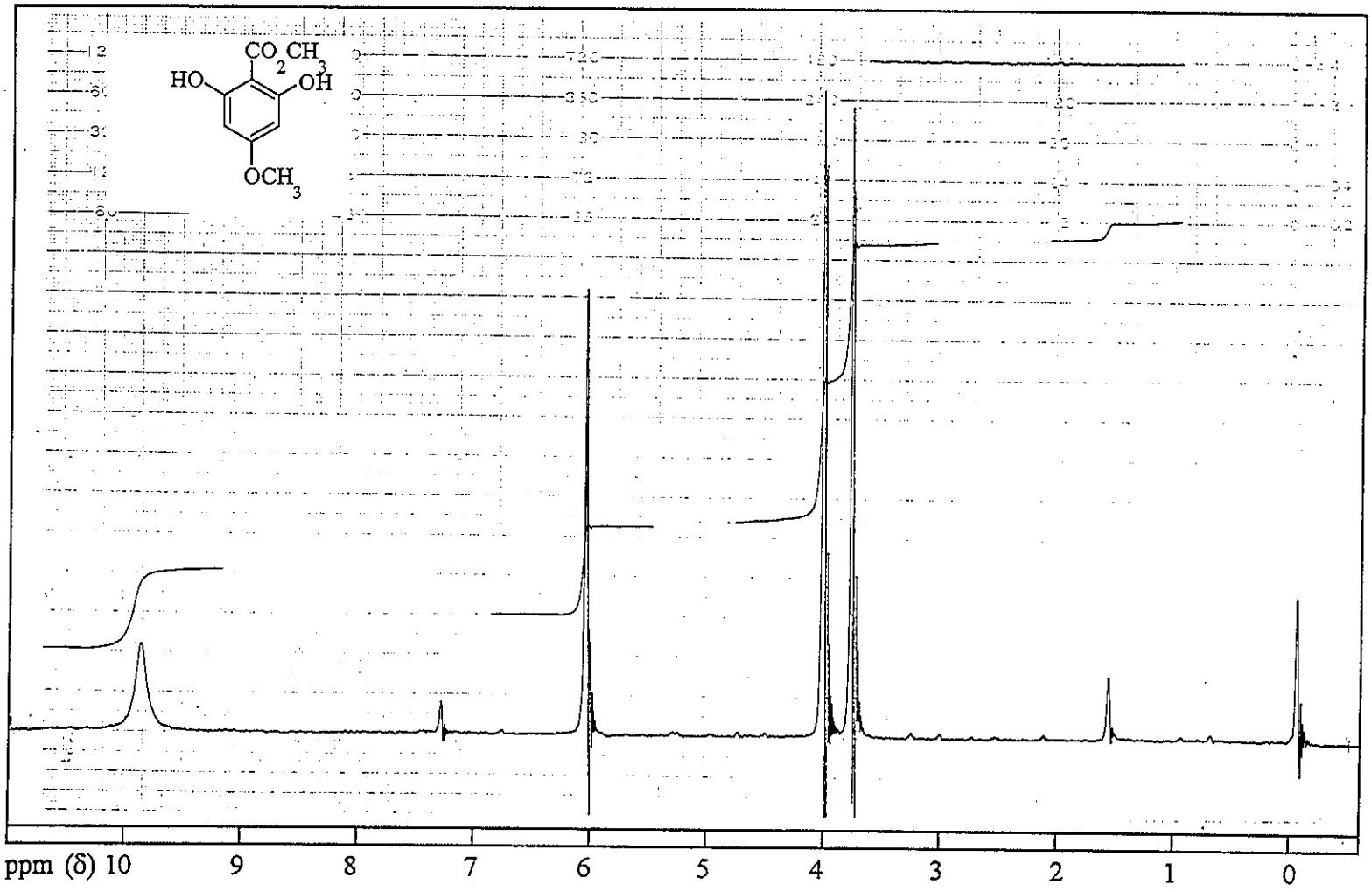


Figure 6. ^{1}H NMR spectrum of methyl 2,6-dihydroxy-4-methoxybenzoate (59)

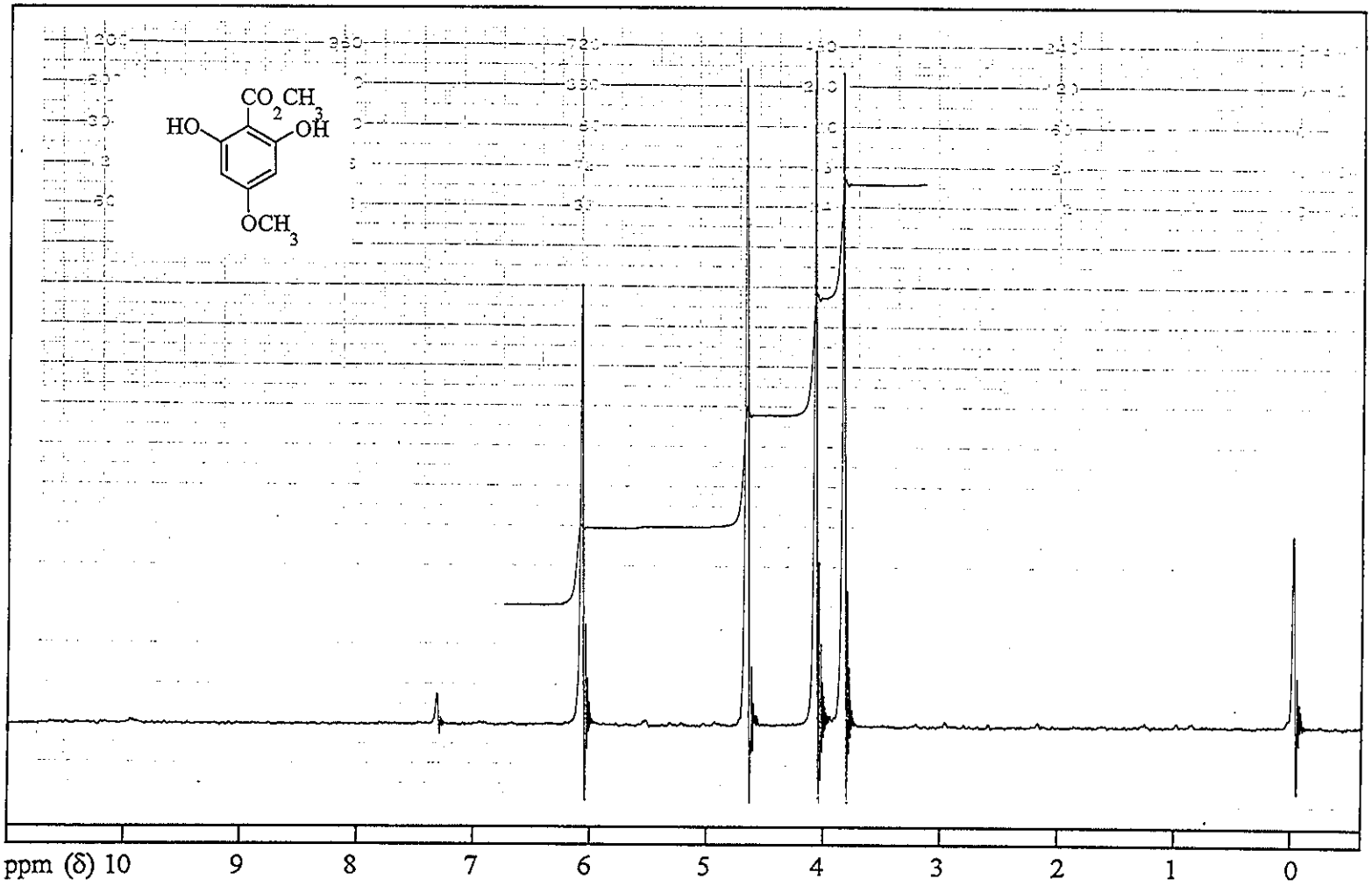


Figure 7. ^{1}H NMR spectrum of methyl 2,6-dihydroxy-4-methoxybenzoate (59) (D_2O)

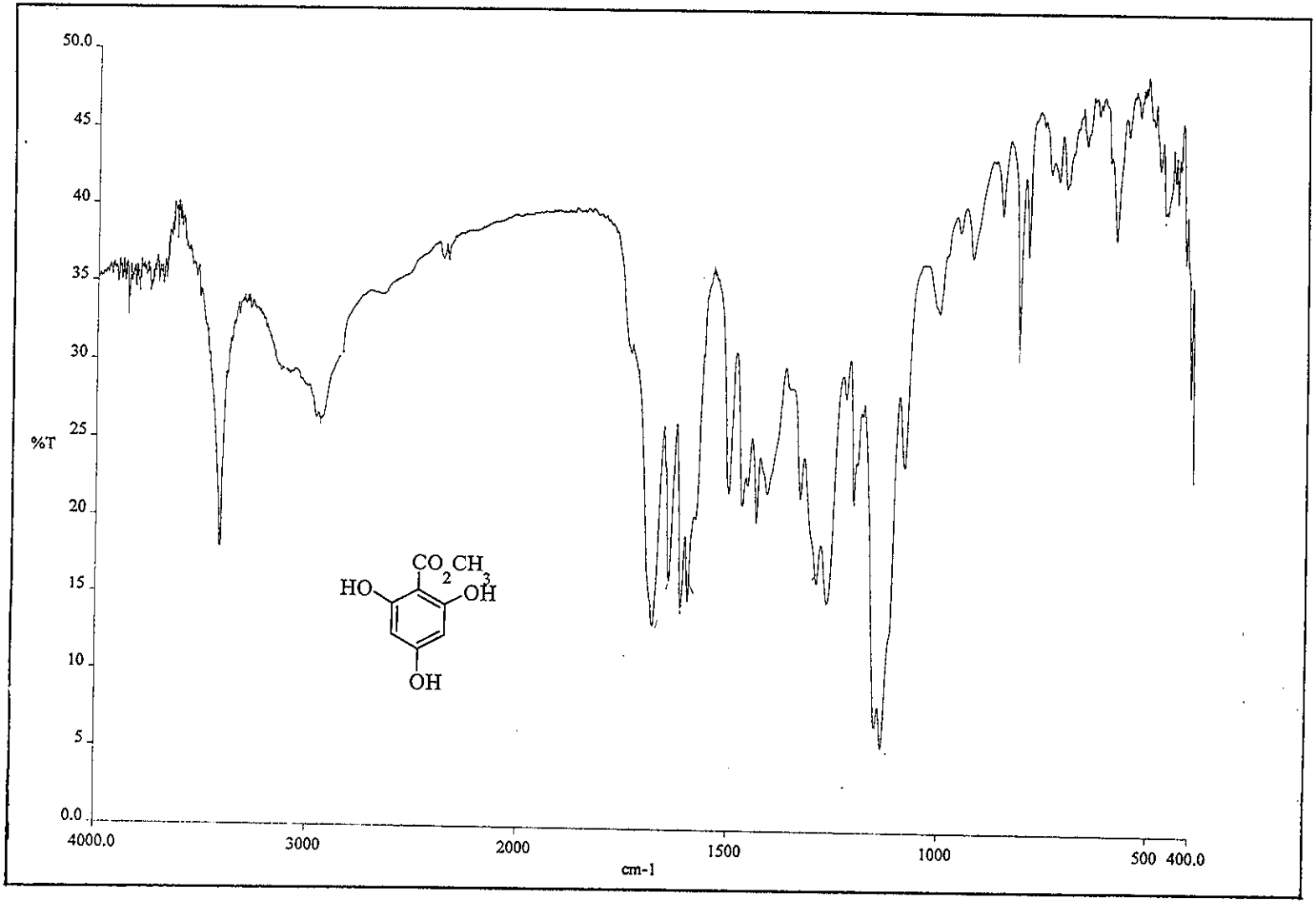


Figure 8. FTIR spectrum of methyl 2,4,6-trihydroxybenzoate (58)

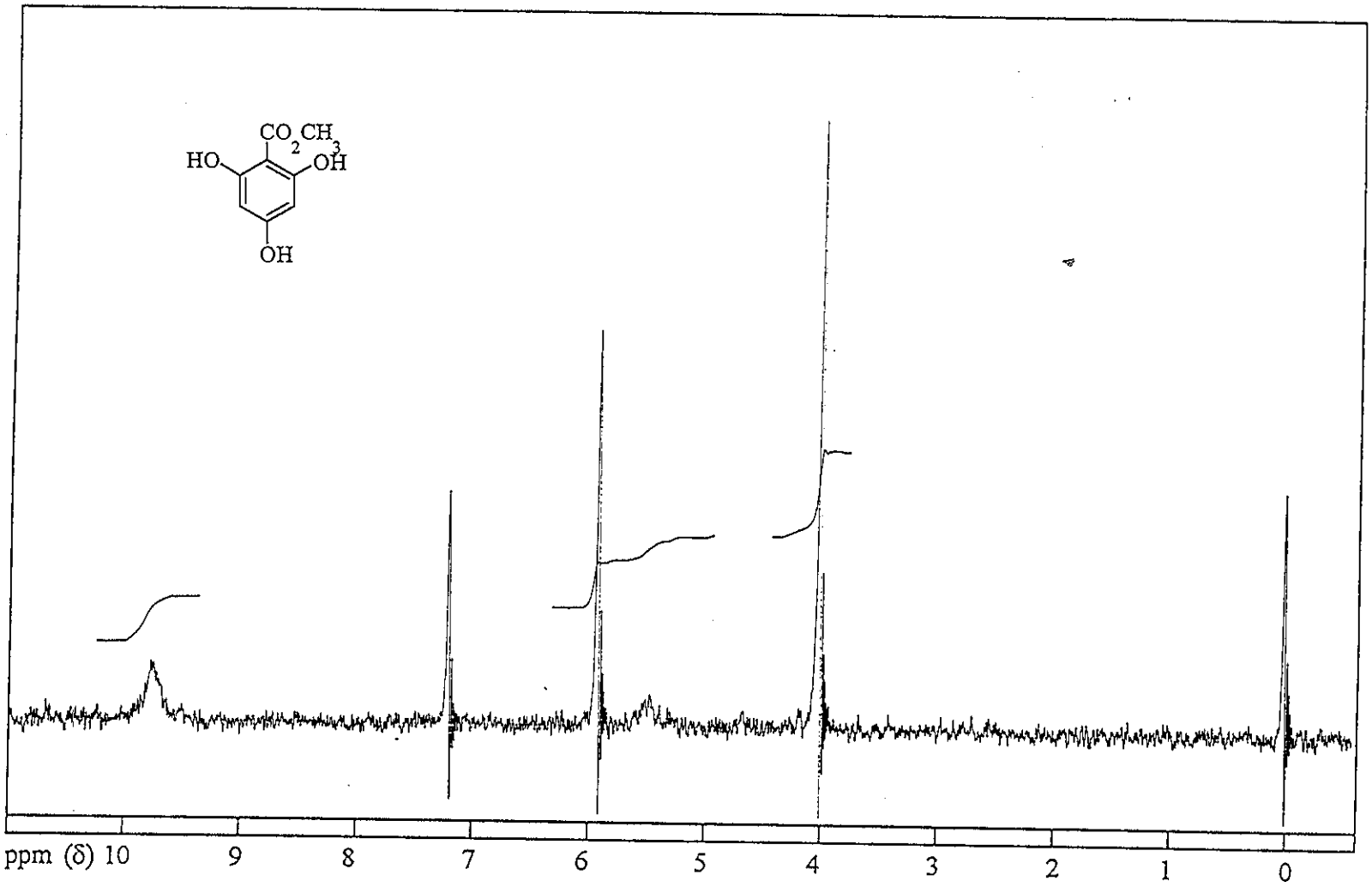


Figure 9. ^{1}H NMR spectrum of methyl 2,4,6-trihydroxybenzoate (58)

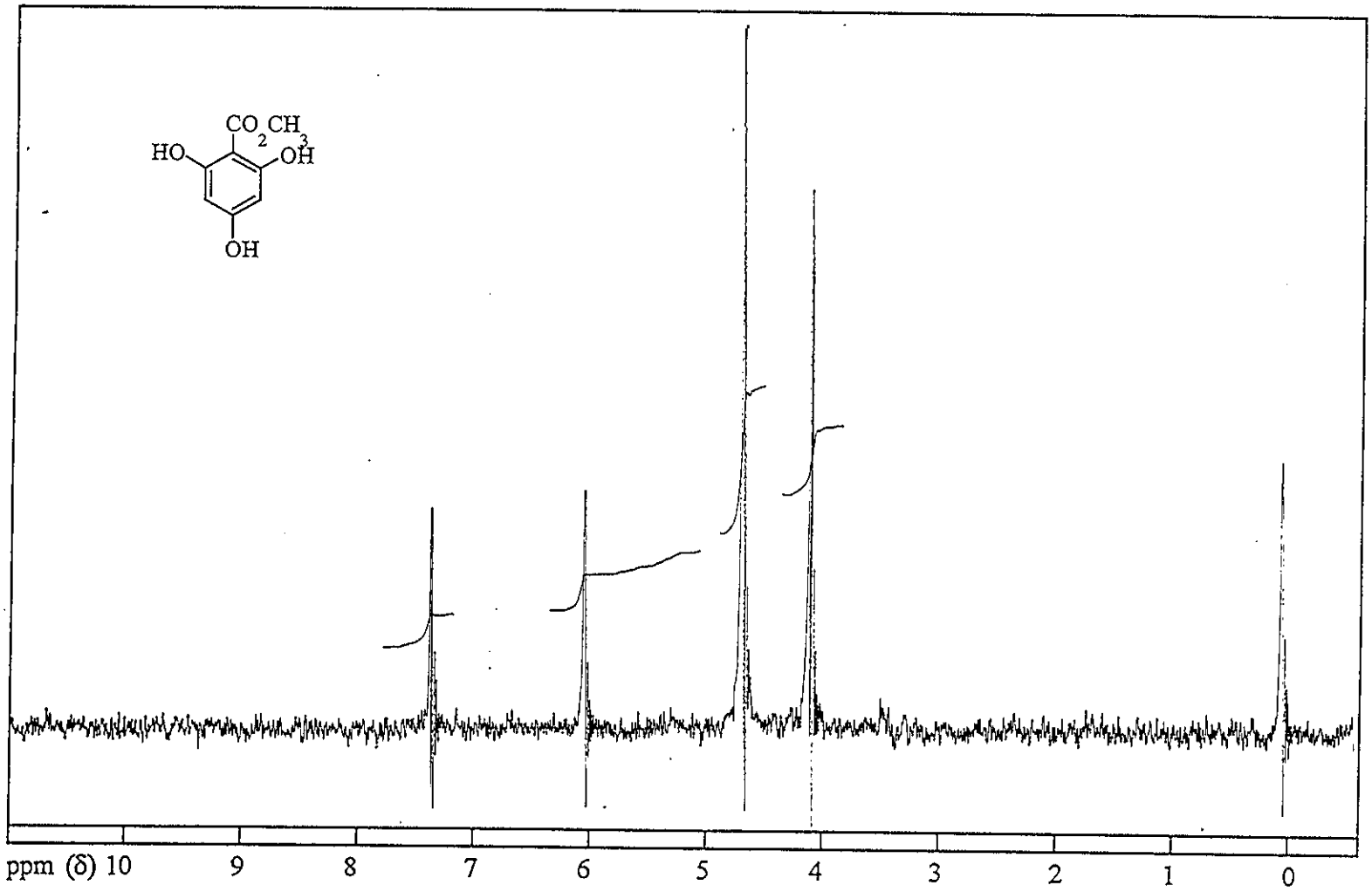


Figure 10. ^{1}H NMR spectrum of methyl 2,4,6-trihydroxybenzoate (58) (D_2O)

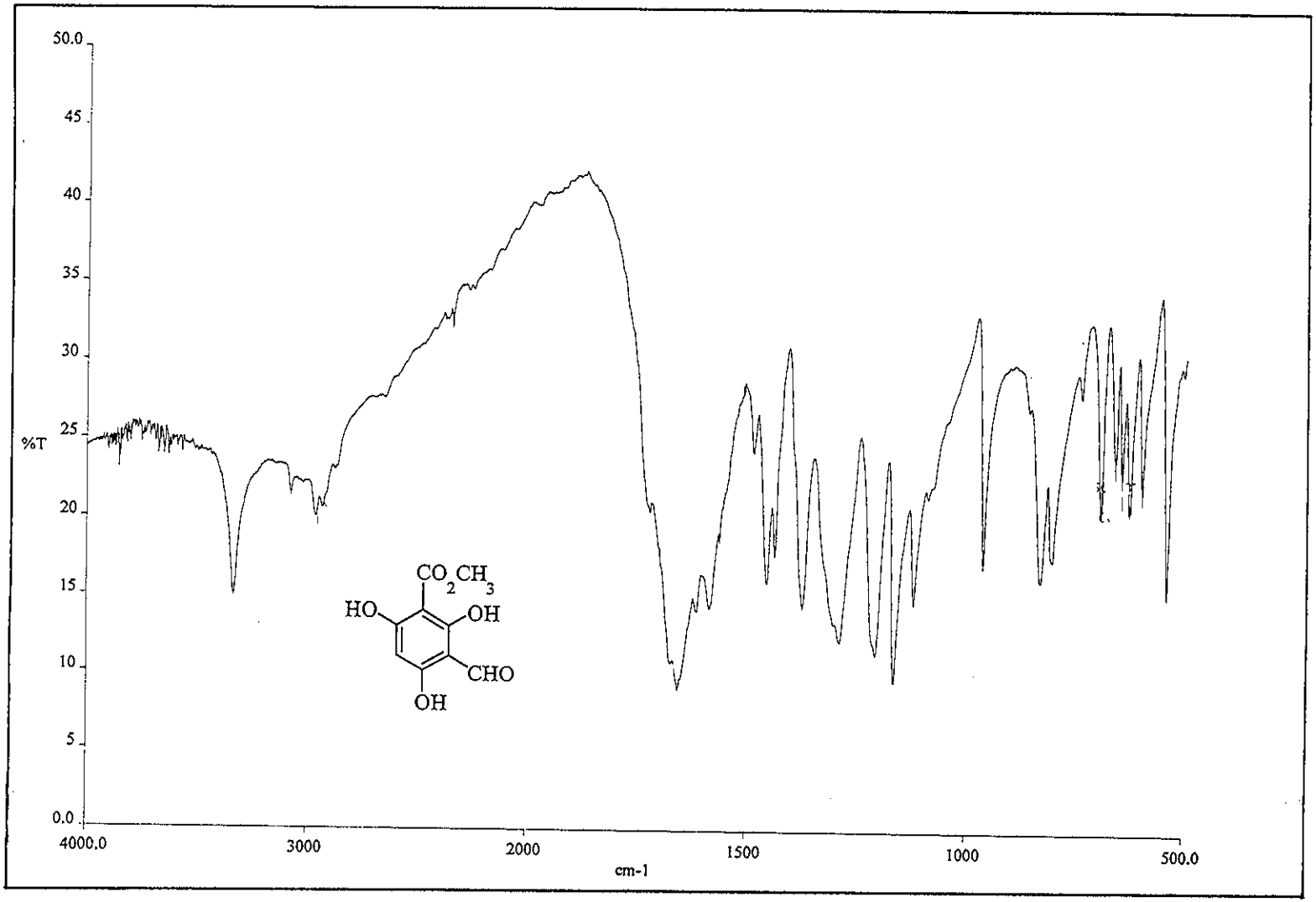


Figure 11. FTIR spectrum of methyl 3-formyl-2,4,6-trihydroxybenzoate (60)

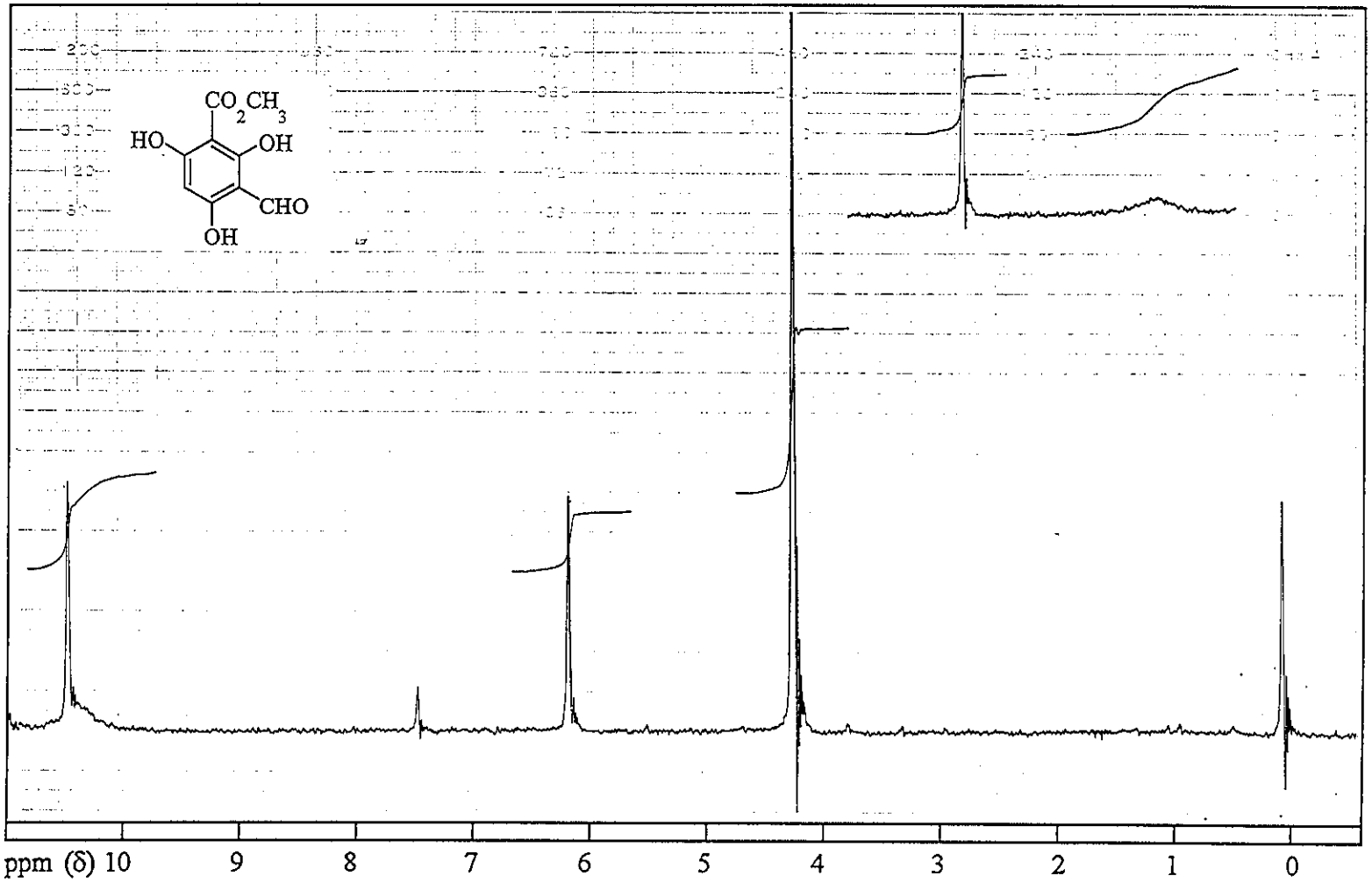


Figure 12. ^{1}H NMR spectrum of methyl 3-formyl-2,4,6-trihydroxybenzoate (60)

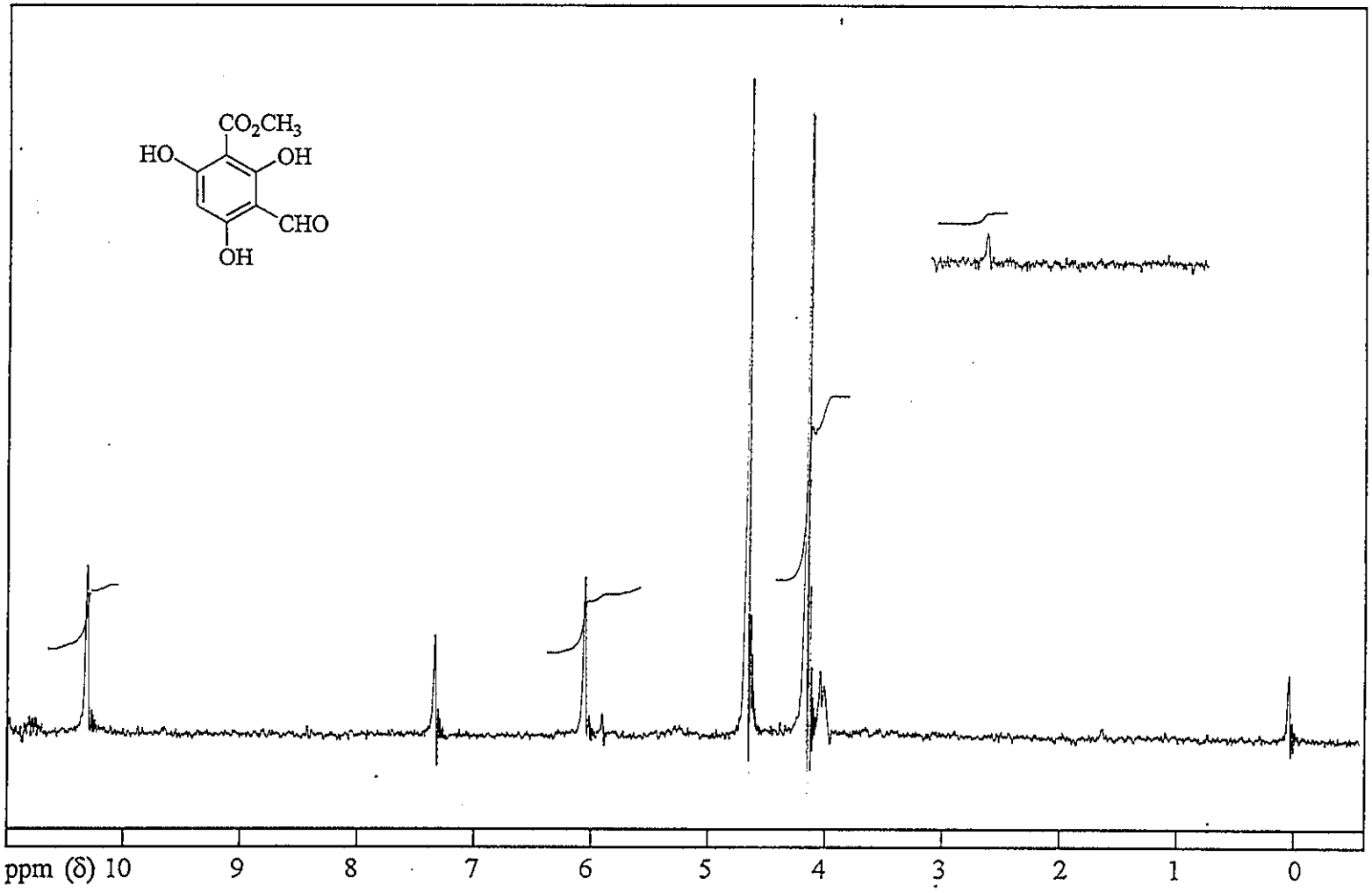


Figure 13. ^{1}H NMR spectrum of methyl 3-formyl-2,4,6-trihydroxybenzoate (60) (D_2O)

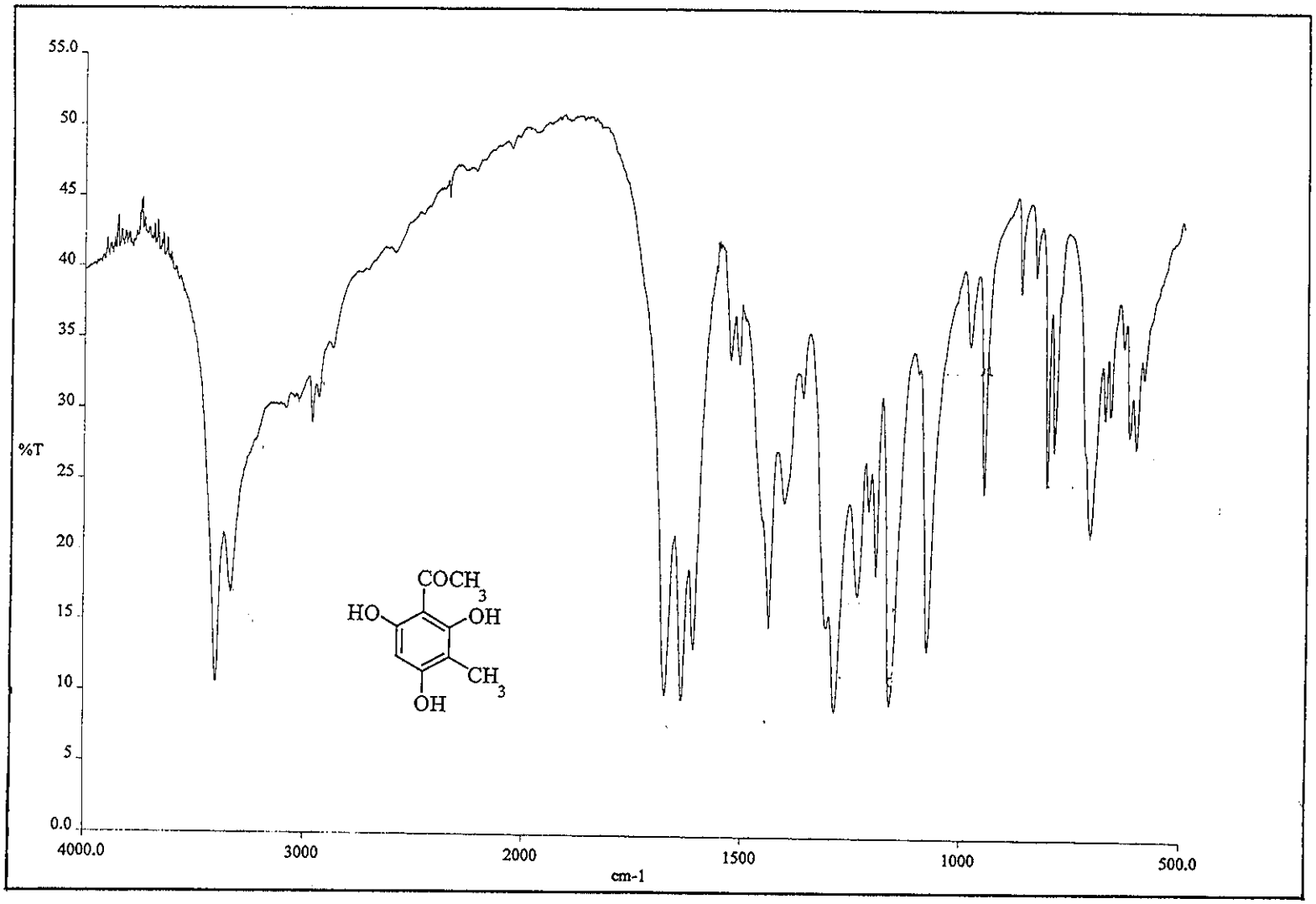


Figure 14. FTIR spectrum of methyl 2,4,6-trihydroxy-3-methylbenzoate (61)

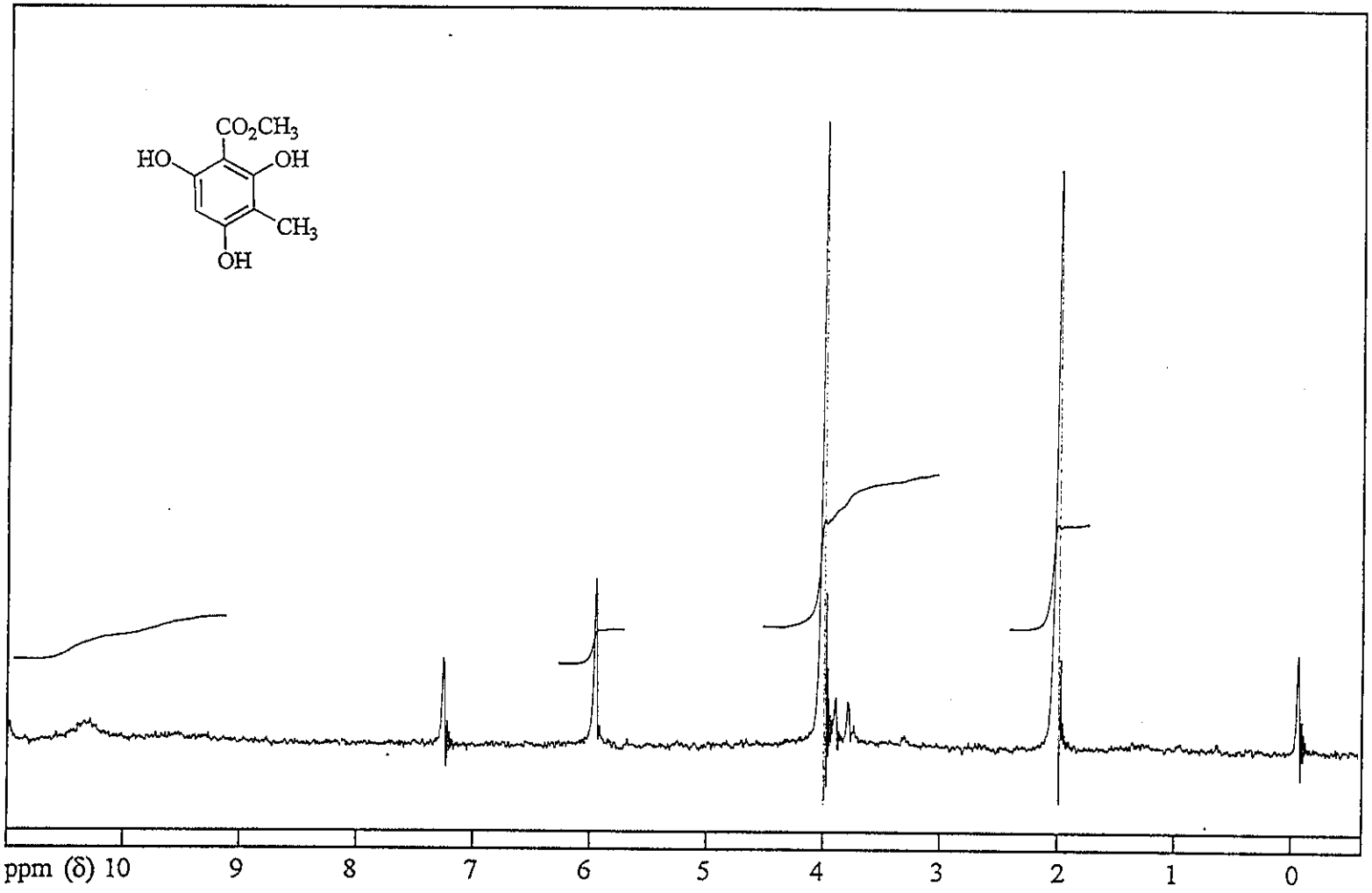


Figure 15. ^{1}H NMR spectrum of methyl 2,4,6-trihydroxy-3-methylbenzoate (61)

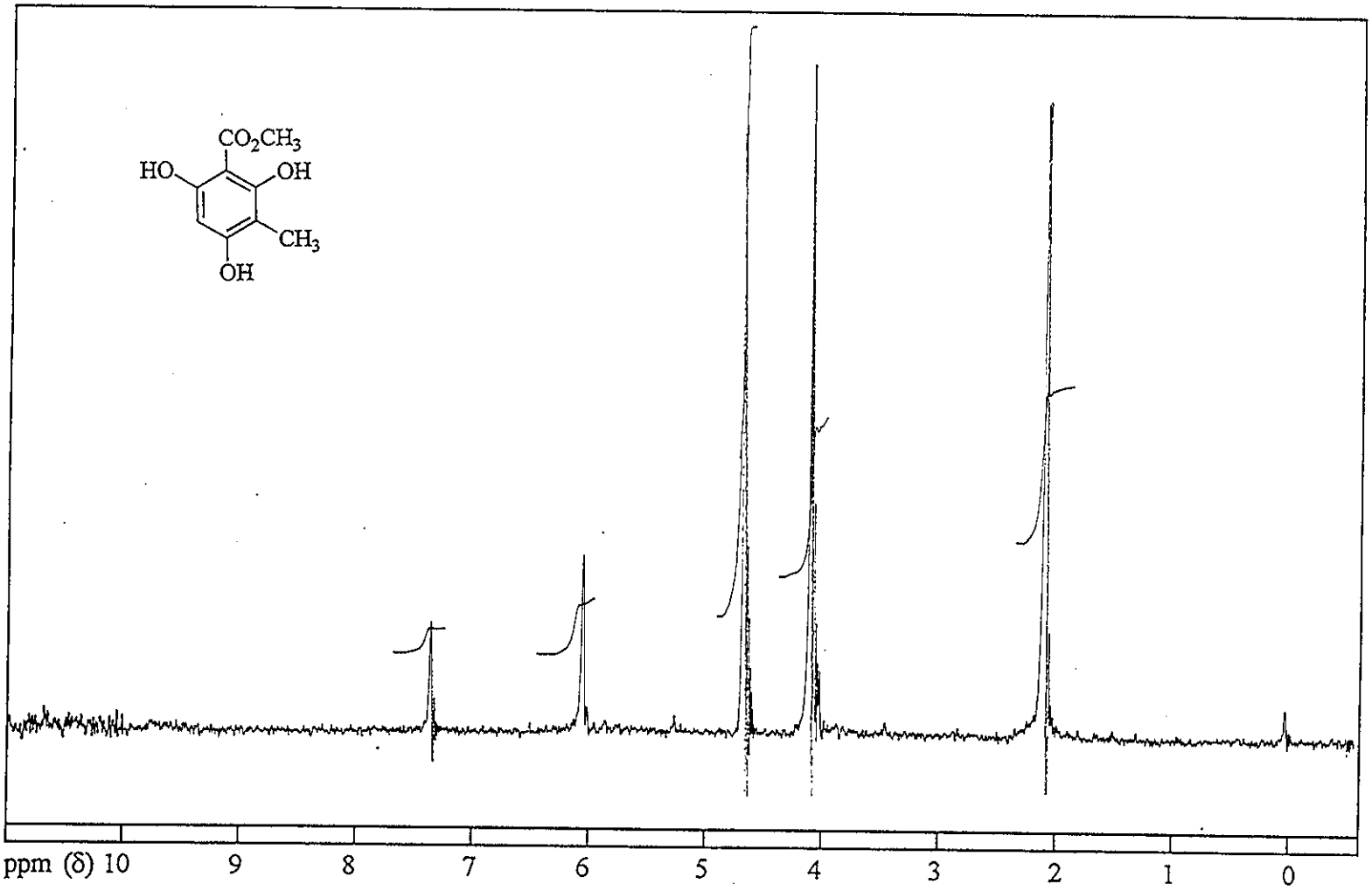


Figure 16. ^{1}H NMR spectrum of methyl 2,4,6-trihydroxy-3-methylbenzoate (61) (D_2O)

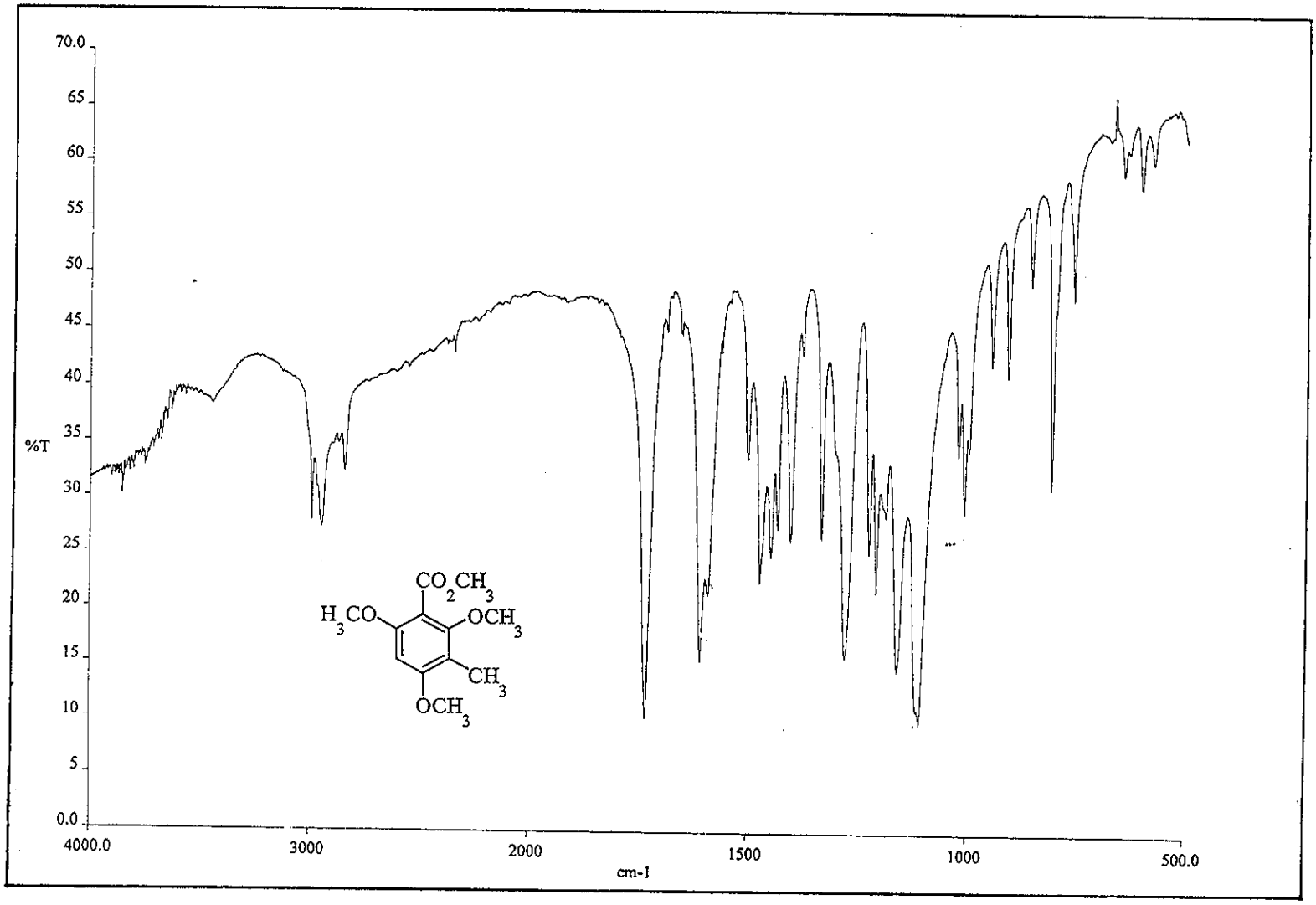


Figure 17. FTIR spectrum of methyl 2,4,6-trimethoxy-3-methylbenzoate (62)

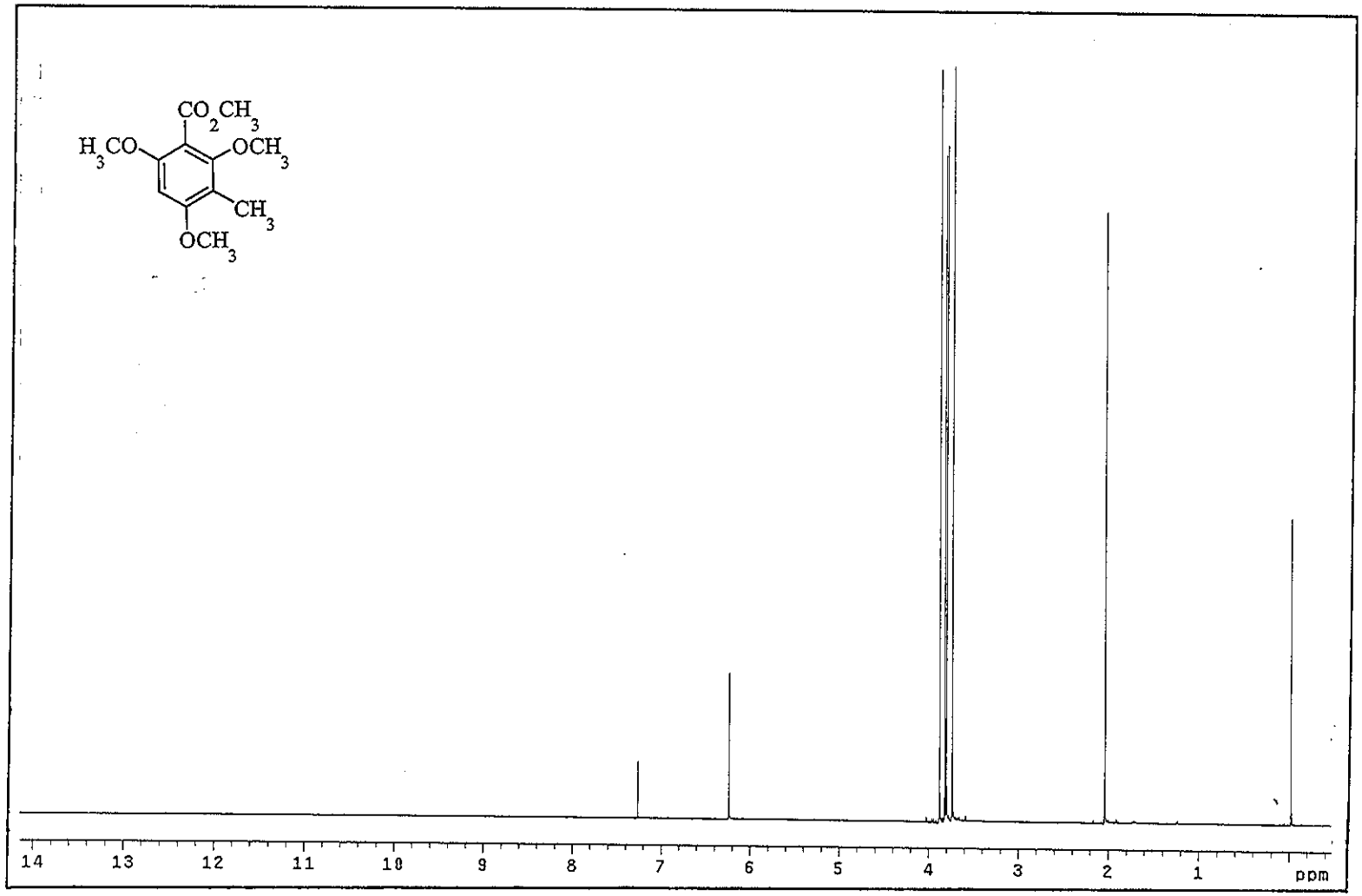


Figure 18. ^{1}H NMR spectrum of methyl 2,4,6-trimethoxy-3-methylbenzoate (62)

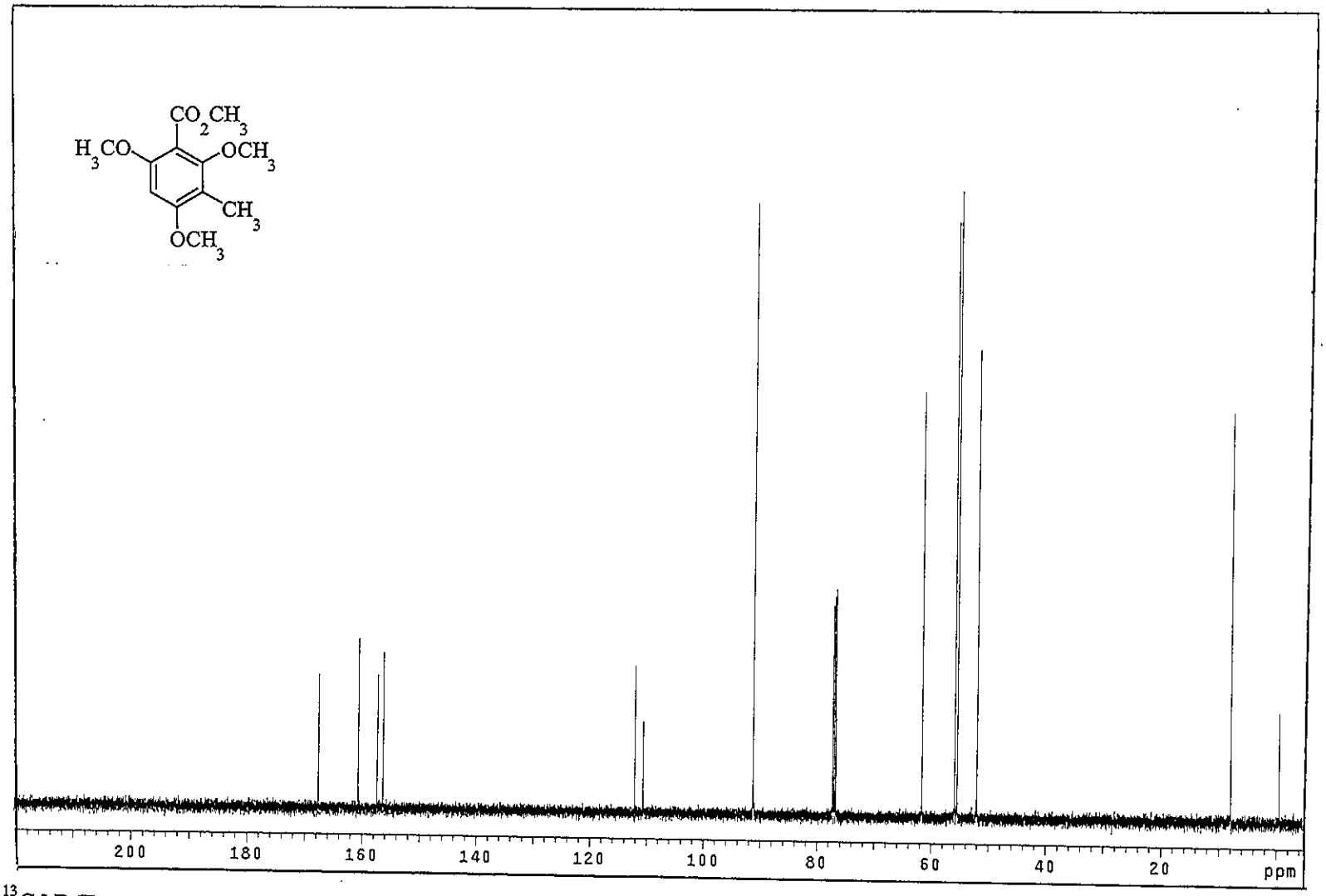


Figure 19. ^{13}C NMR spectrum of methyl 2,4,6-trimethoxy-3-methylbenzoate (62)

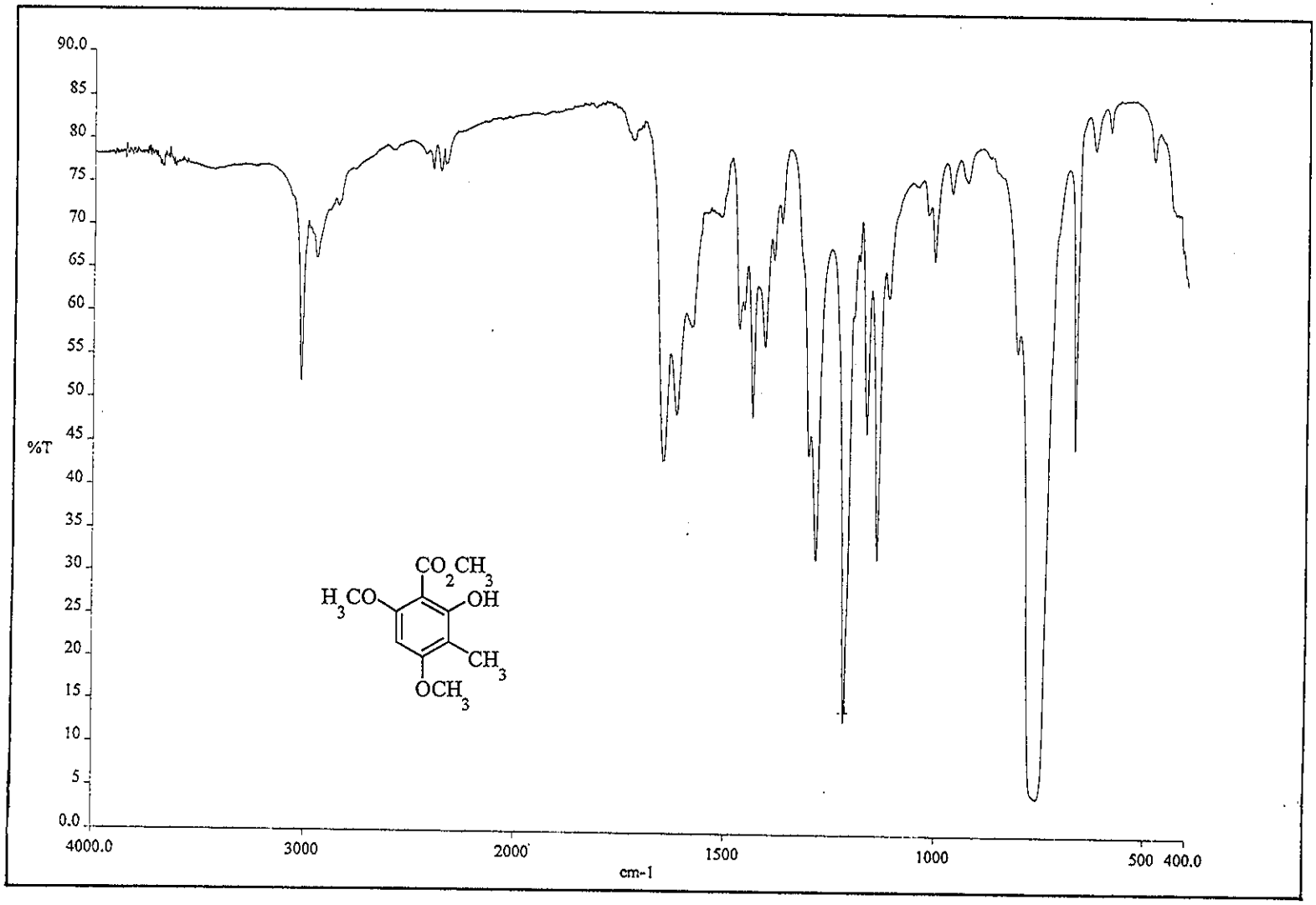


Figure 20. FTIR spectrum of methyl 2-hydroxy-4,6-dimethoxy-3-methylbenzoate (63)

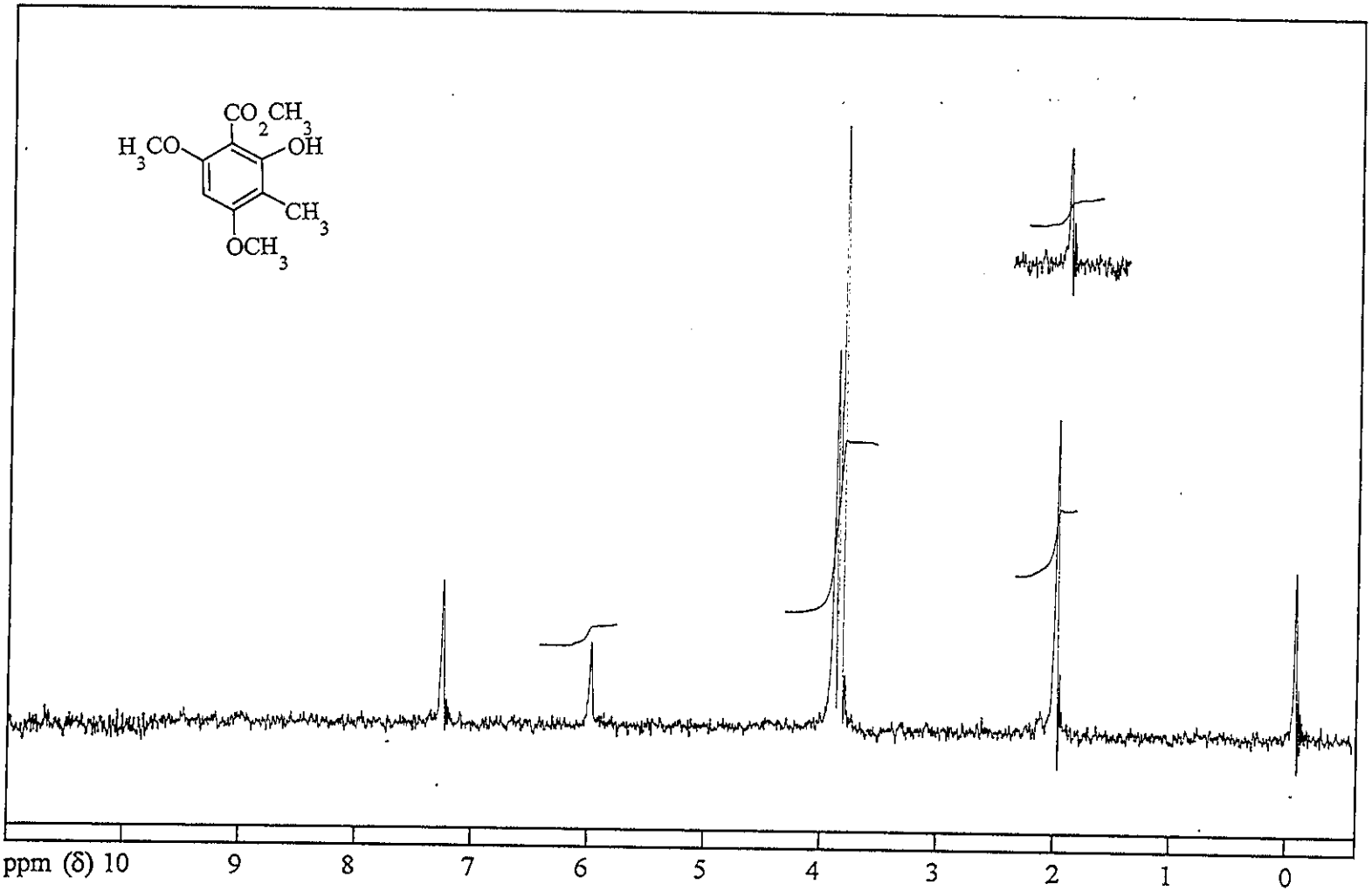


Figure 21. ^{1}H NMR spectrum of methyl 2-hydroxy-4,6-dimethoxy-3-methylbenzoate (63)

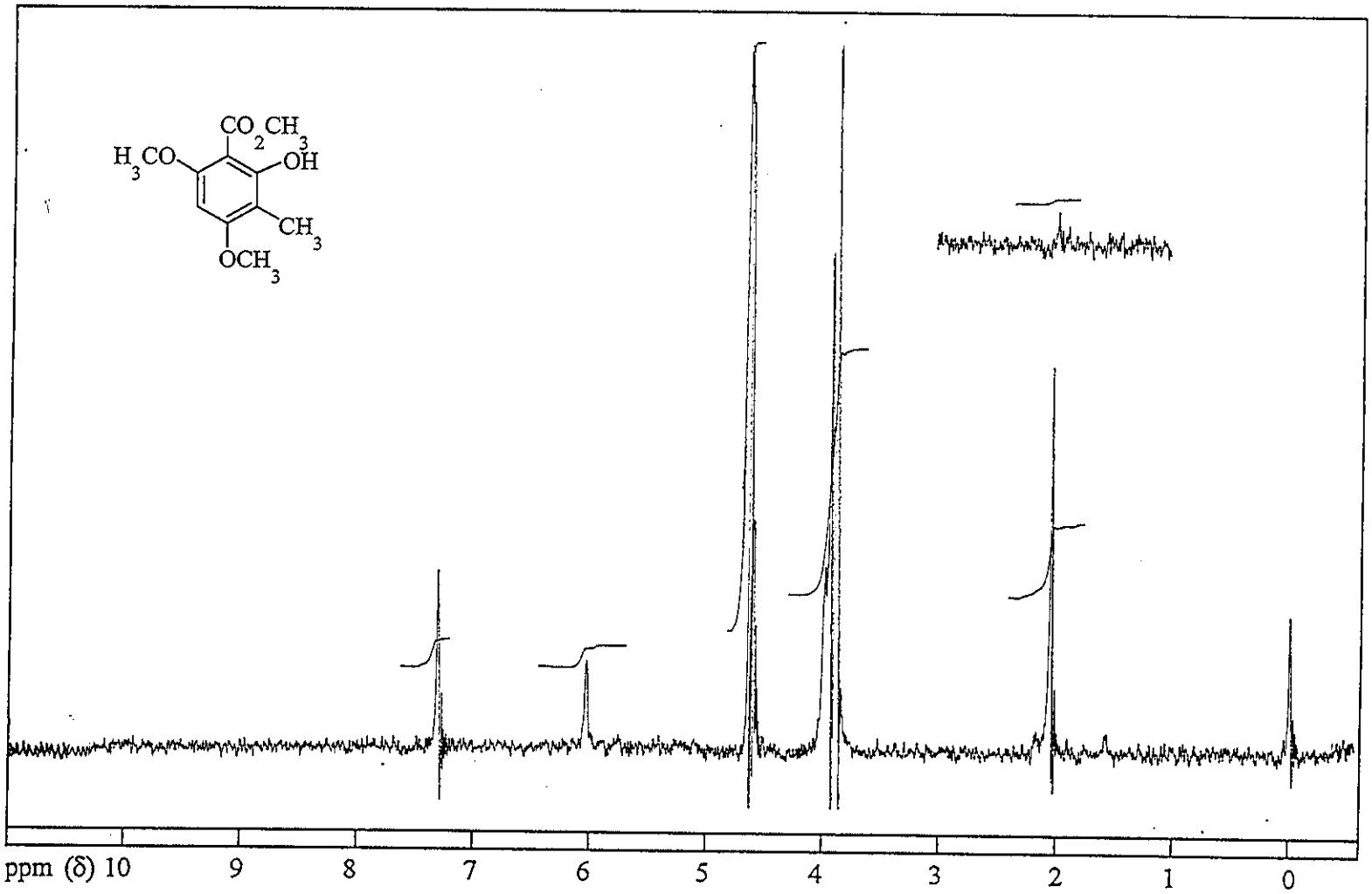


Figure 22. ^{1}H NMR spectrum of methyl 2-hydroxy-4,6-dimethoxy-3-methylbenzoate (63) (D_2O)

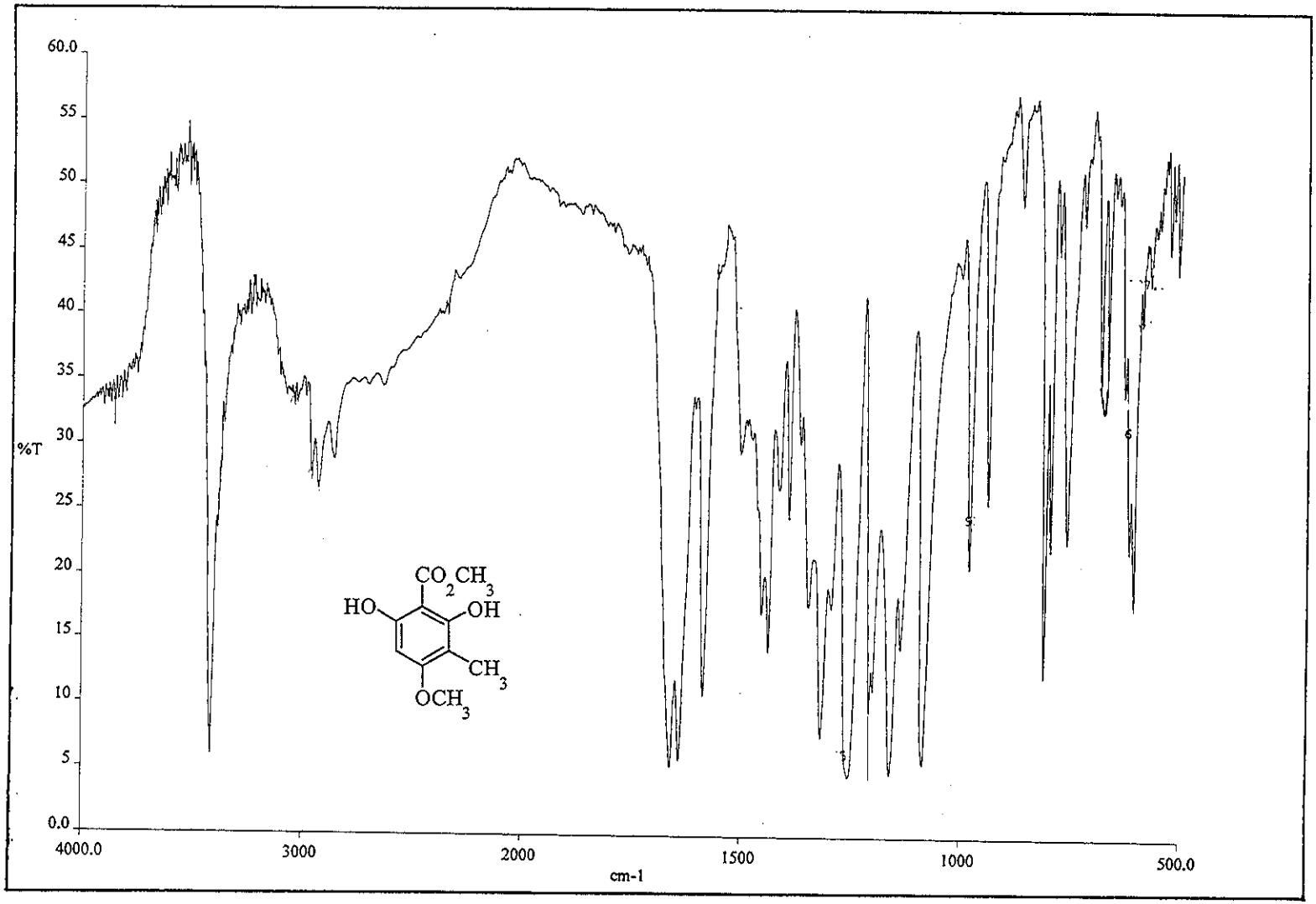


Figure 23. FTIR spectrum of methyl 2,6-dihydroxy-4-methoxy-3-methylbenzoate (121)

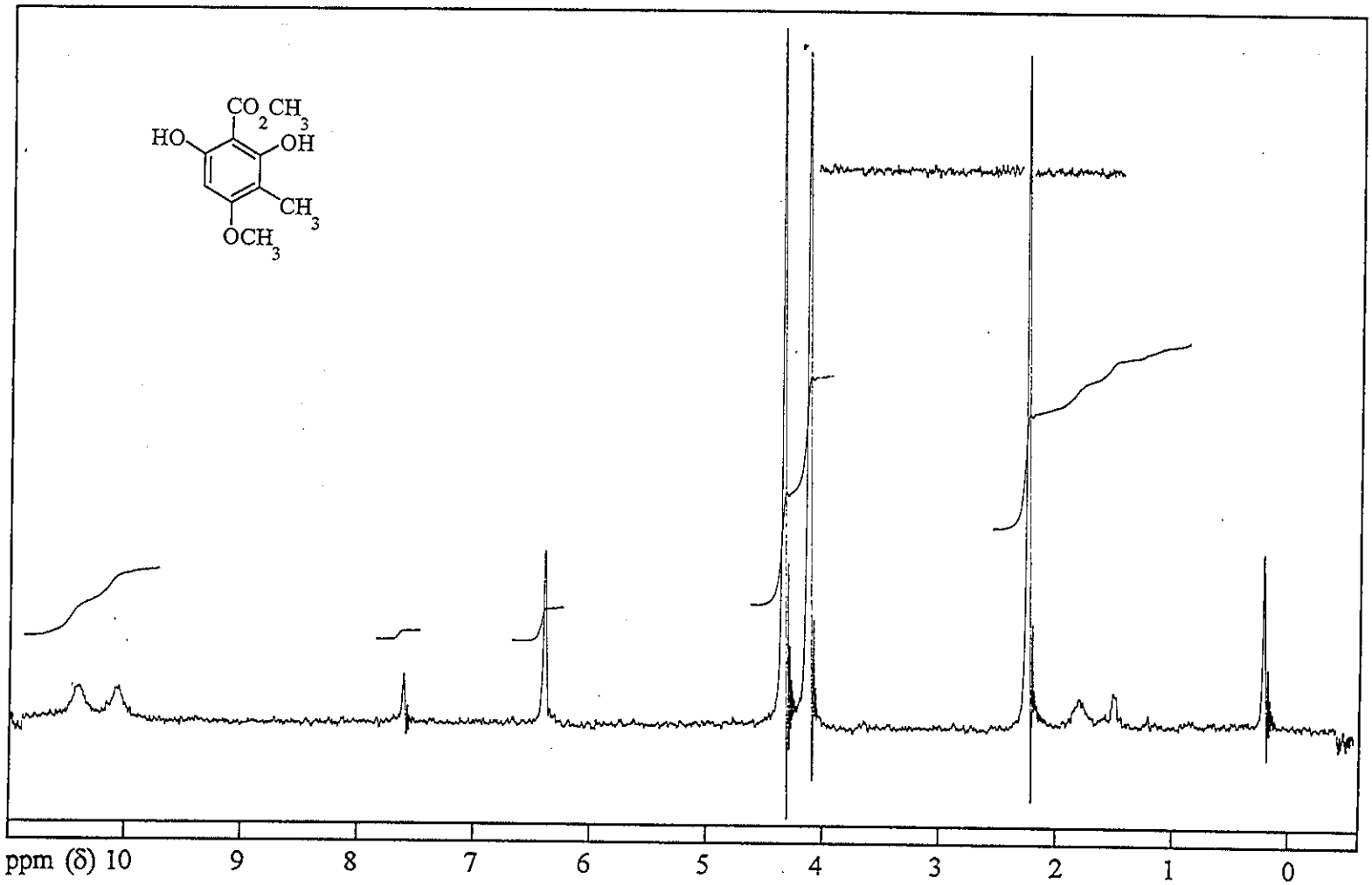


Figure 24. ^{1}H NMR spectrum of methyl 2,6-dihydroxy-4-methoxy-3-methylbenzoate (121)

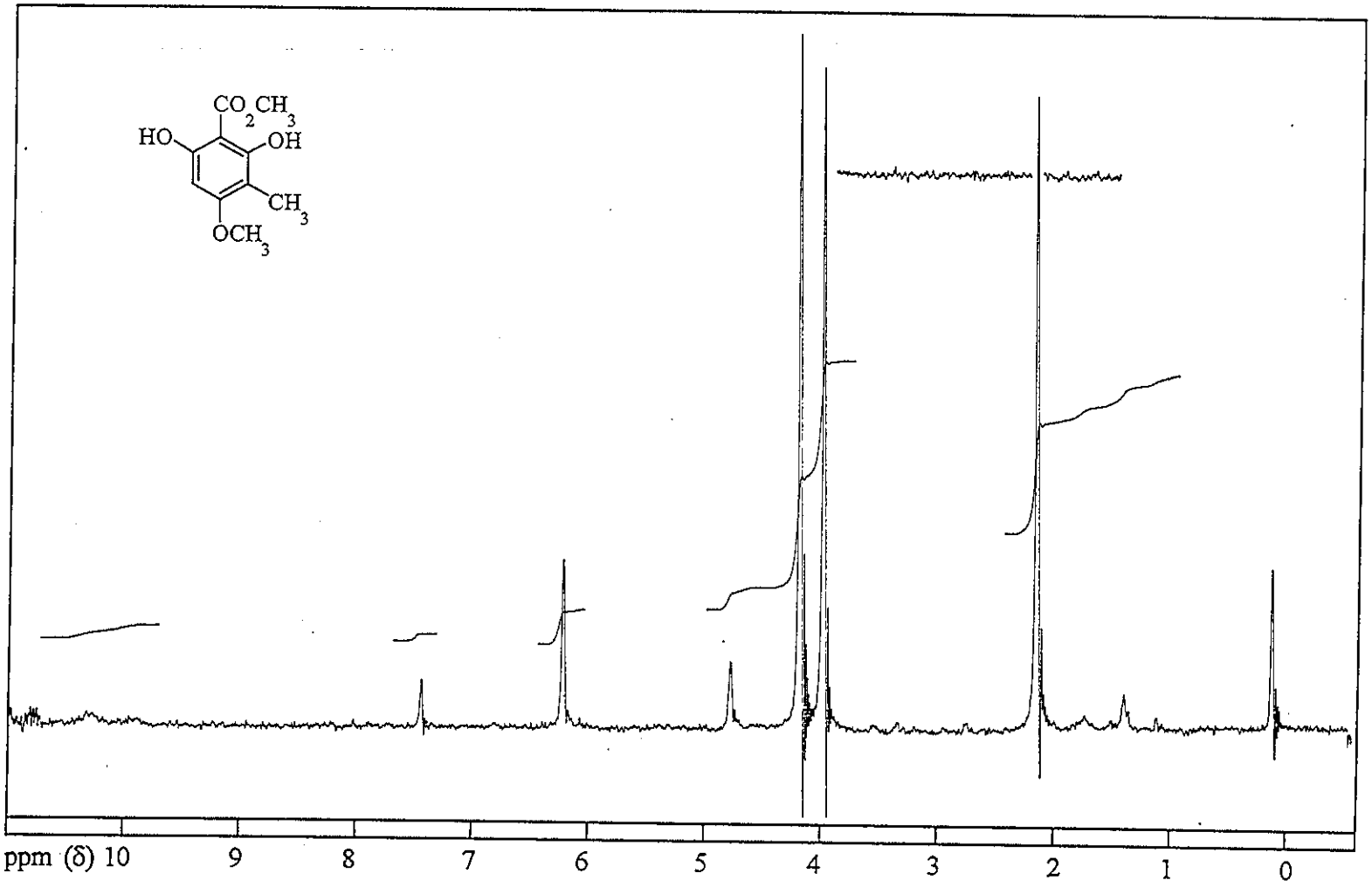


Figure 25. ^{1}H NMR spectrum of methyl 2,6-dihydroxy-4-methoxy-3-methylbenzoate (121) (D_2O)

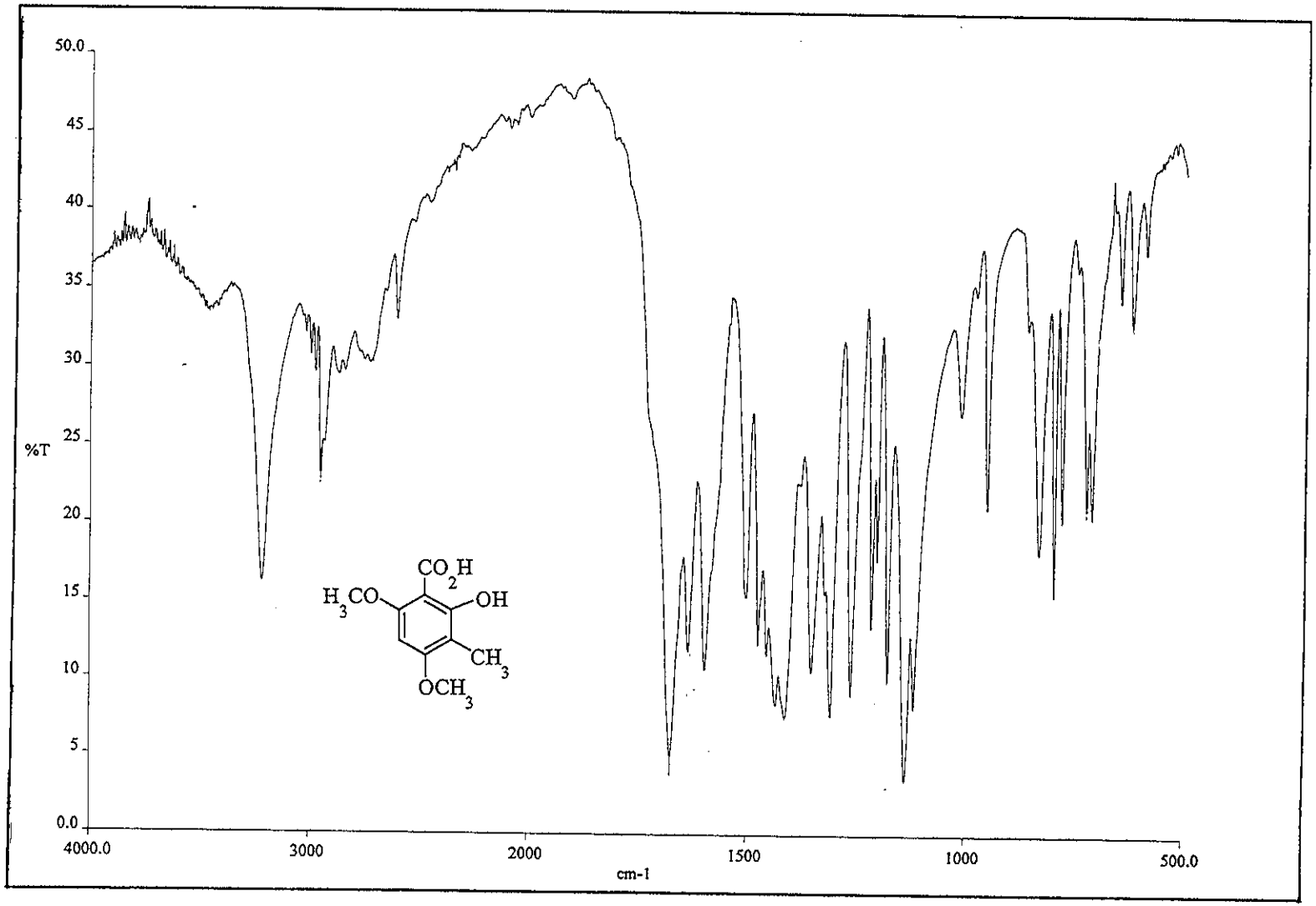


Figure 26. FTIR spectrum of 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid (65)

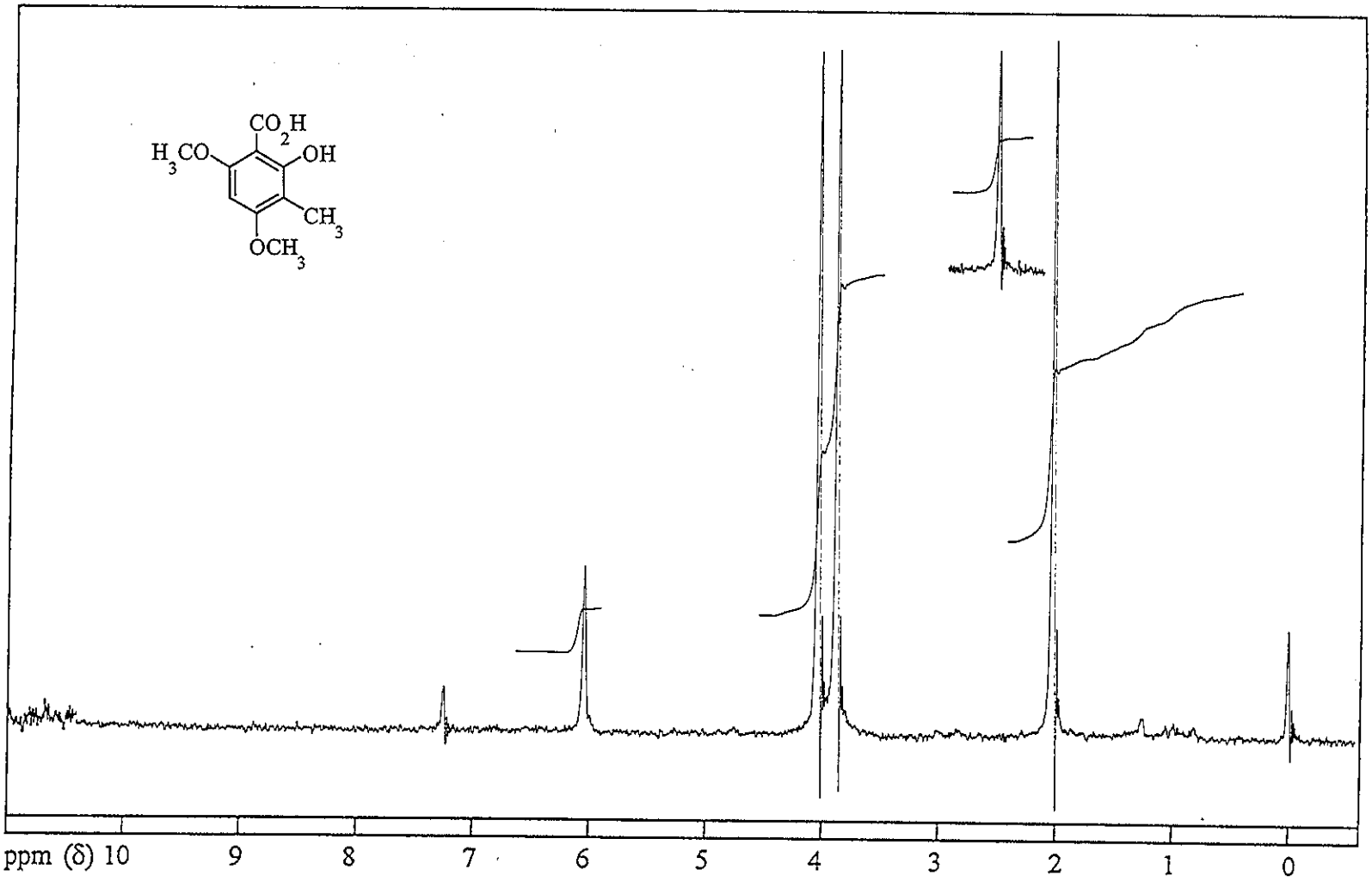


Figure 27. ^{1}H NMR spectrum of 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid (65)

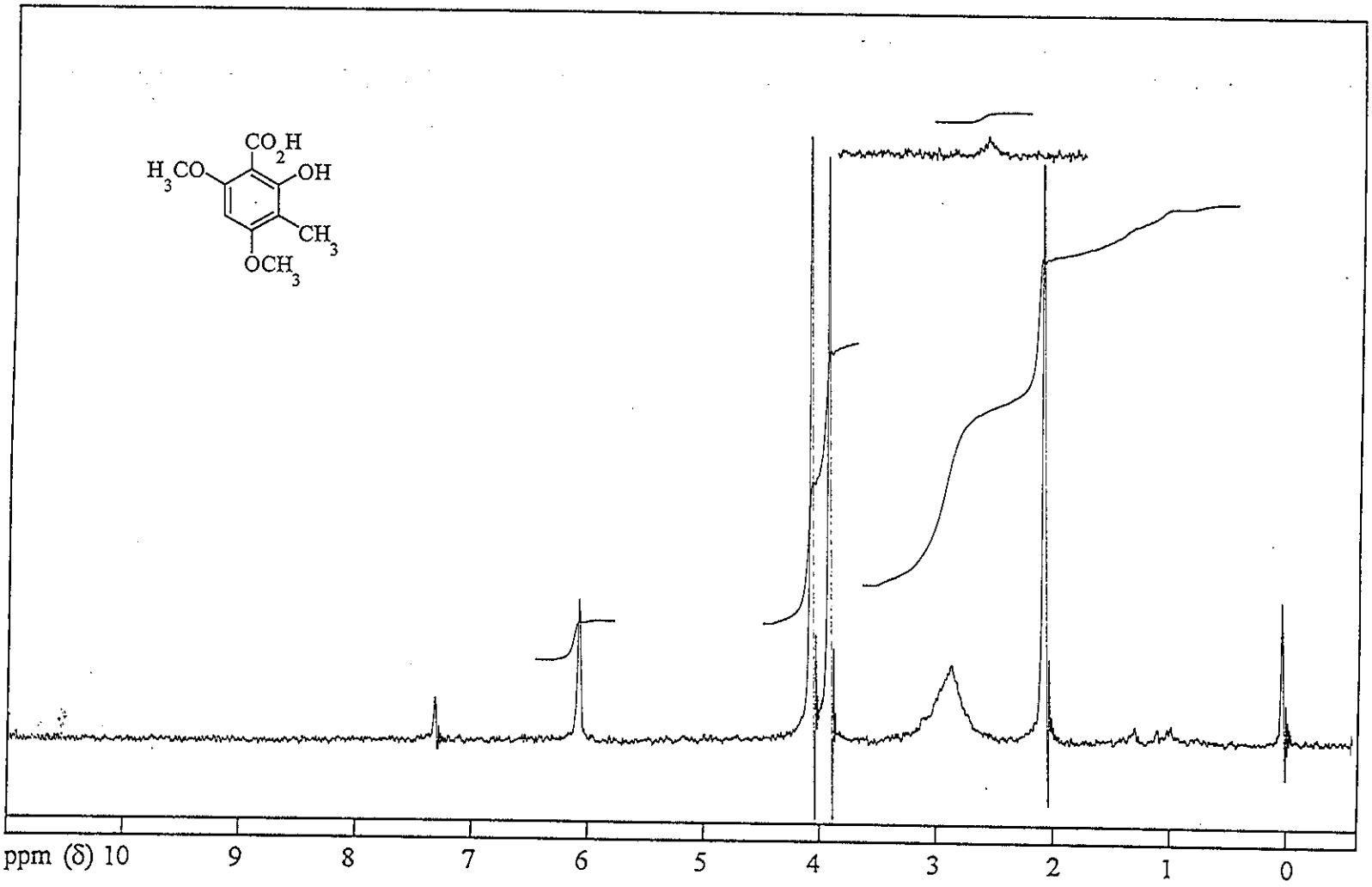


Figure 28. ^{1}H NMR spectrum of 2-hydroxy-4,6-dimethoxy-3-methylbenzoic acid (65) (D_2O)

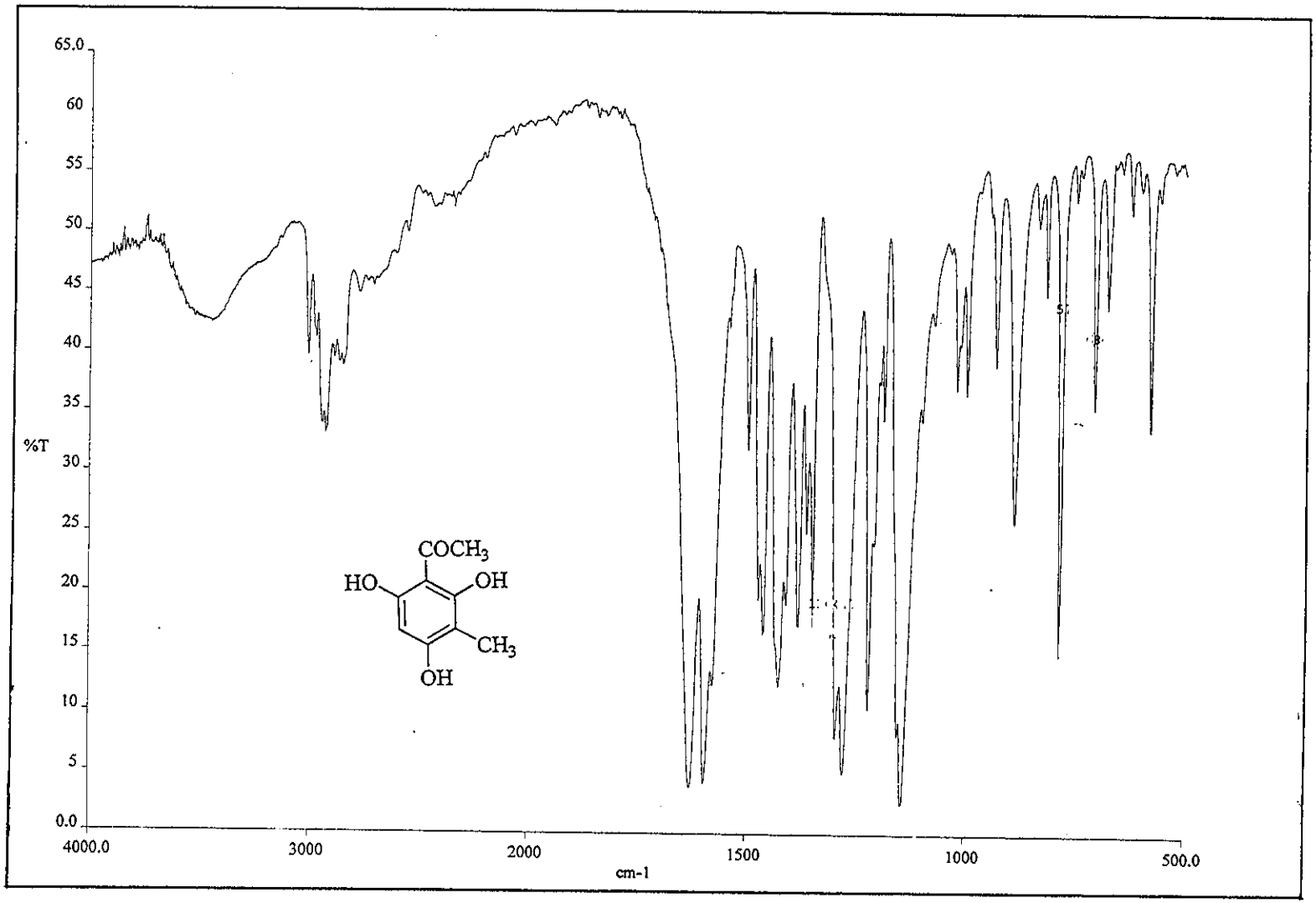


Figure 29. FTIR spectrum of 2,4,6-trihydroxy-3-methylacetophenone (123)

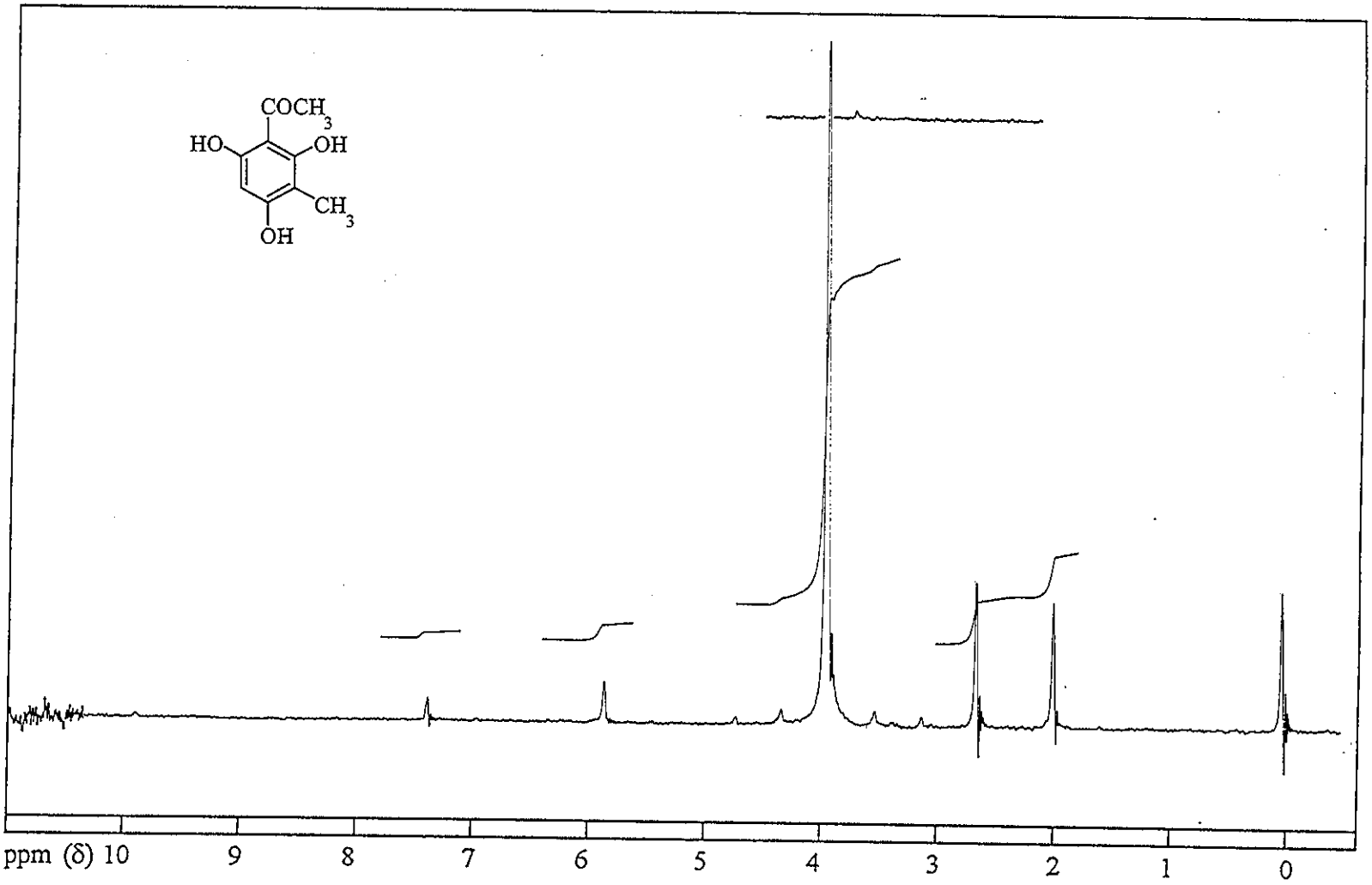


Figure 30. ^{1}H NMR spectrum of 2,4,6-trihydroxy-3-methylacetophenone (123)

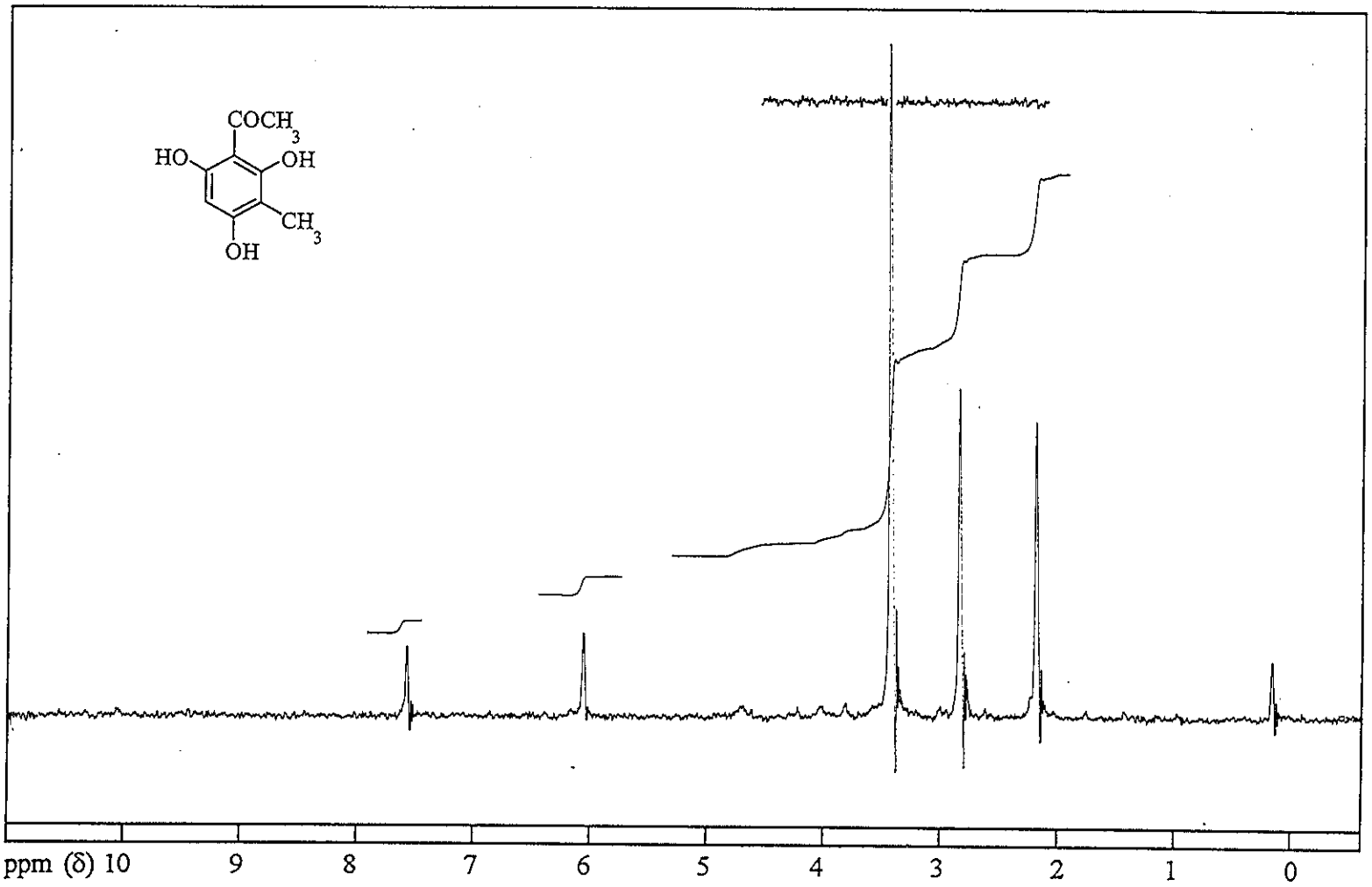


Figure 31. ^{1}H NMR spectrum of 2,4,6-trihydroxy-3-methylacetophenone (123)(D_2O)

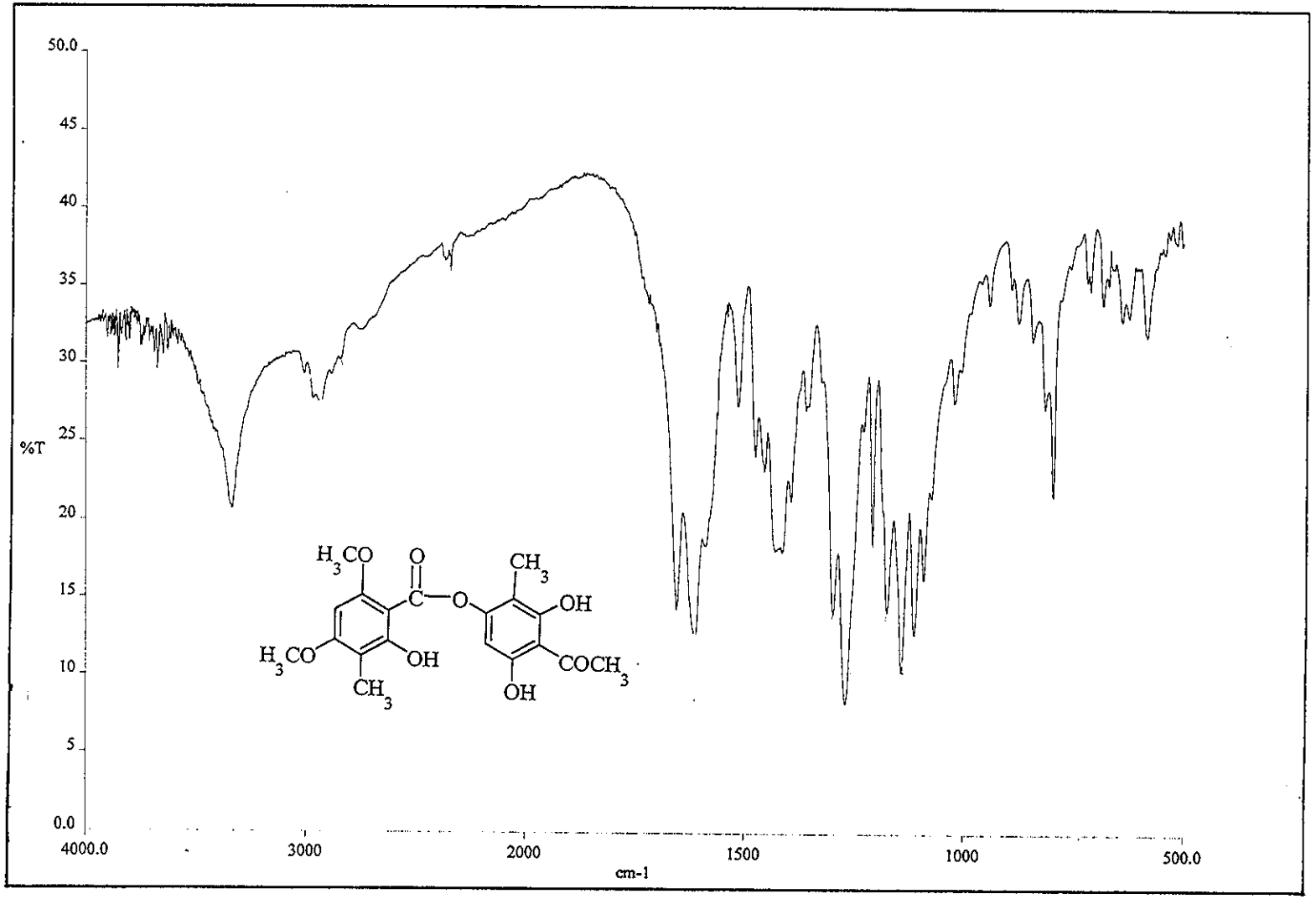


Figure 32. FTIR spectrum of 2,6-dihydroxy-4-(2'-hydroxy-4',6'-dimethoxy-3'-methylbenzoyloxy)-3-methylacetophenone (124)

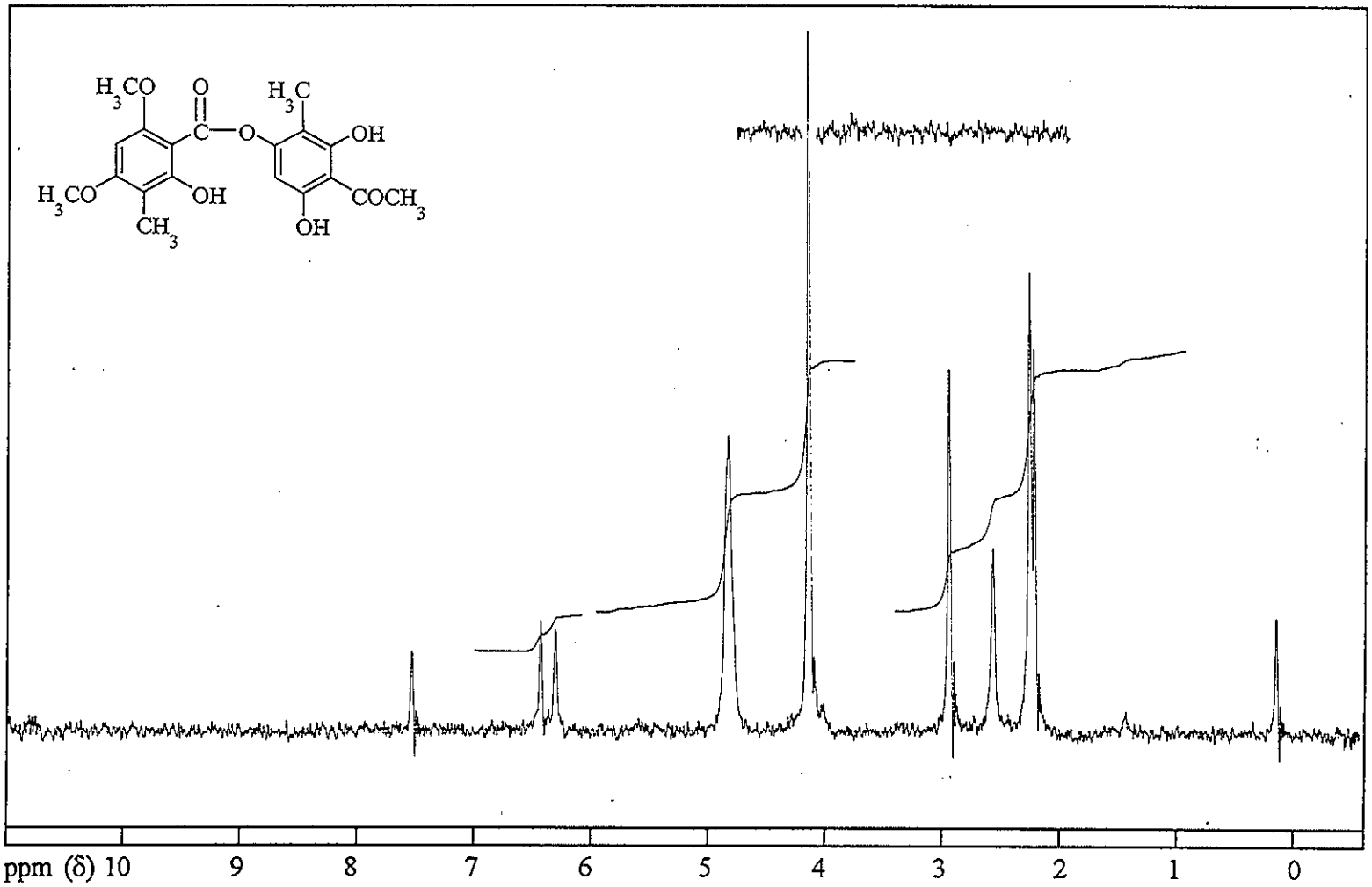


Figure 33. ^{1}H NMR spectrum of 2,6-dihydroxy-4-(2'-hydroxy-4',6'-dimethoxy-3'-methylbenzoyloxy)-3-methylacetophenone (124)

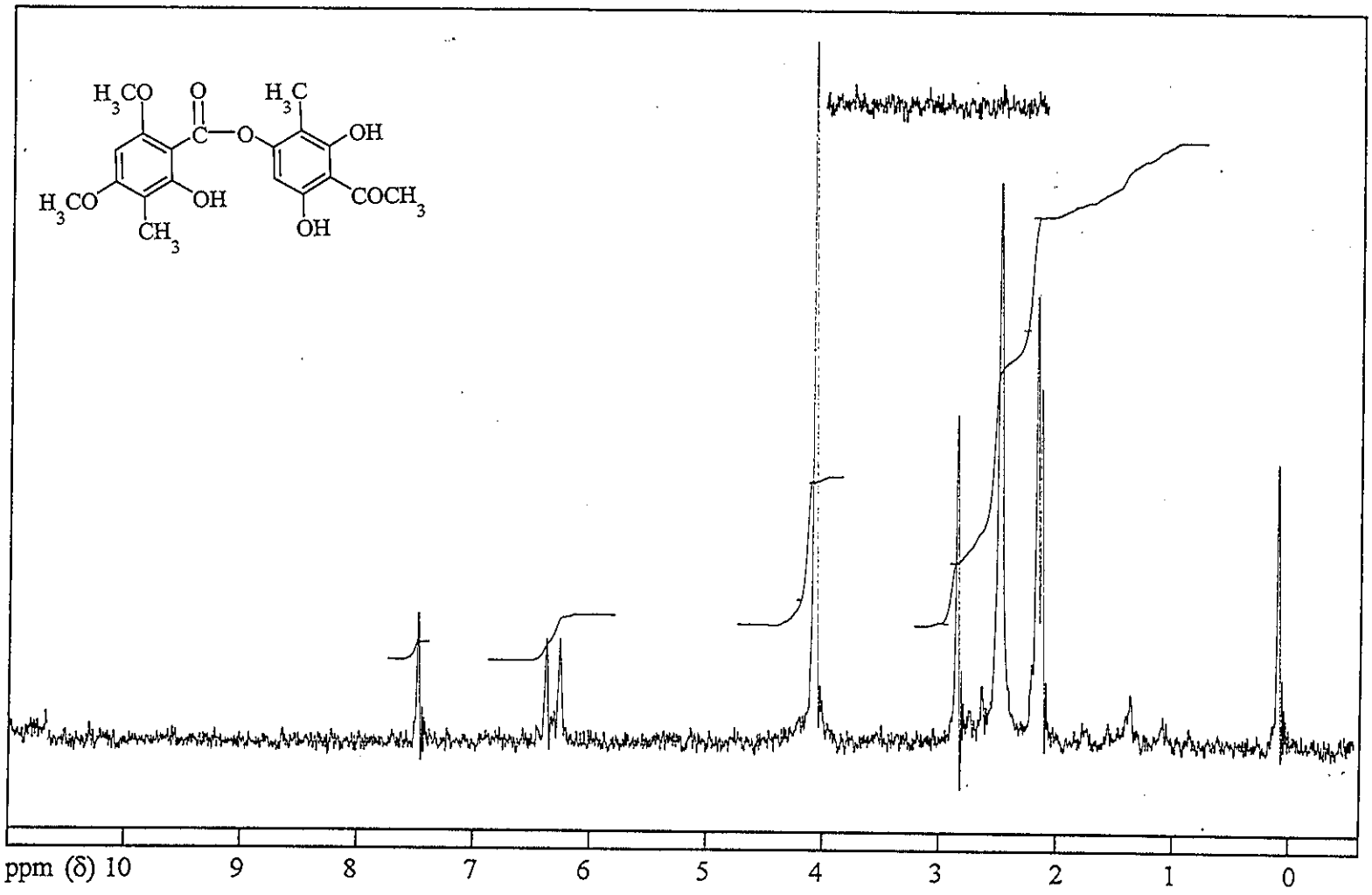


Figure 34. ^{1}H NMR spectrum of 2,6-dihydroxy-4-(2'-hydroxy-4',6'-dimethoxy-3'-methylbenzoyloxy)-3-methylacetophenone(124) (D_2O)

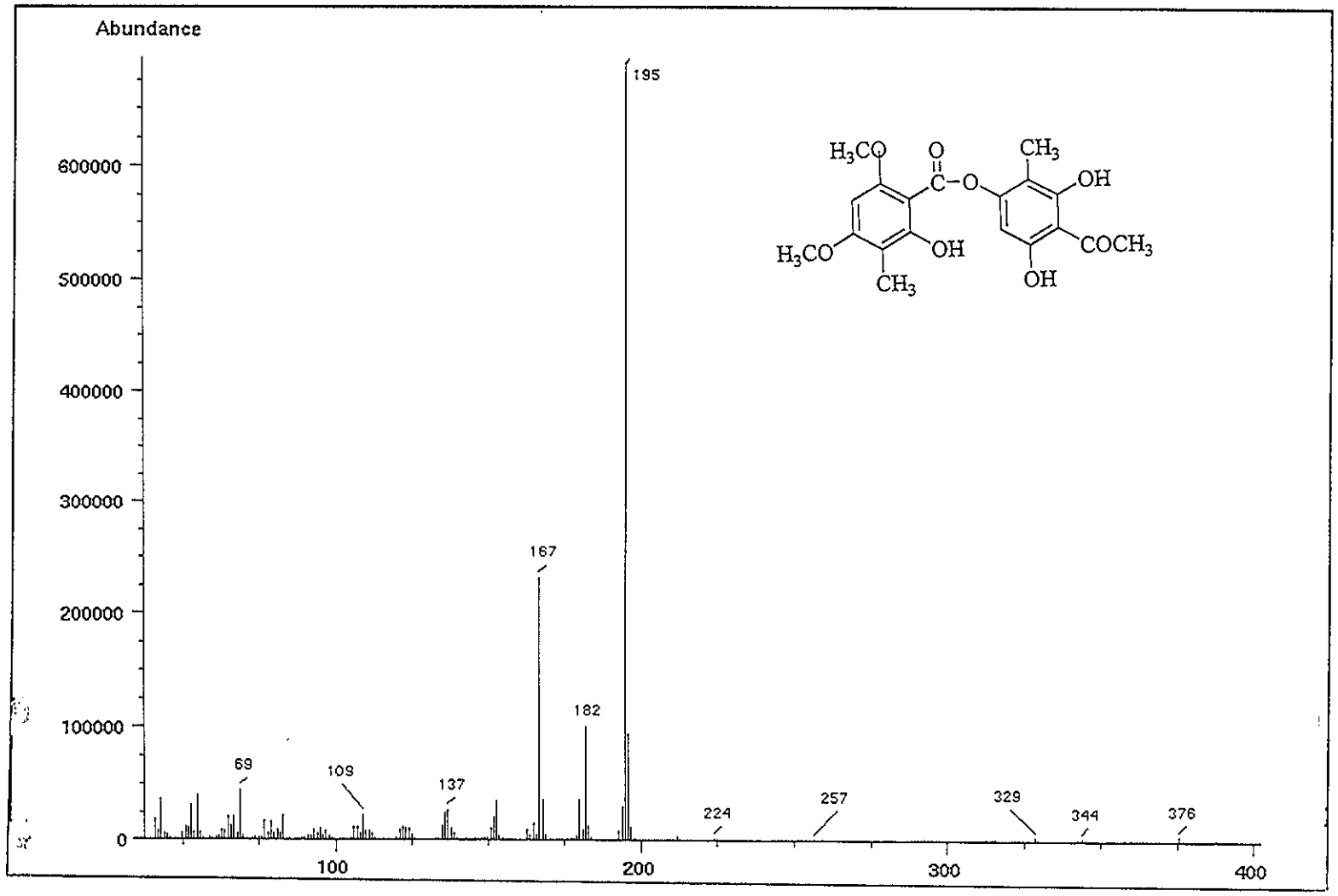


Figure 35. Mass spectrum (EIMS) of 2,6-dihydroxy-4-(2'-hydroxy-4',6'-dimethoxy-3'-methylbenzoyloxy)-3-methylacetophenone (124)

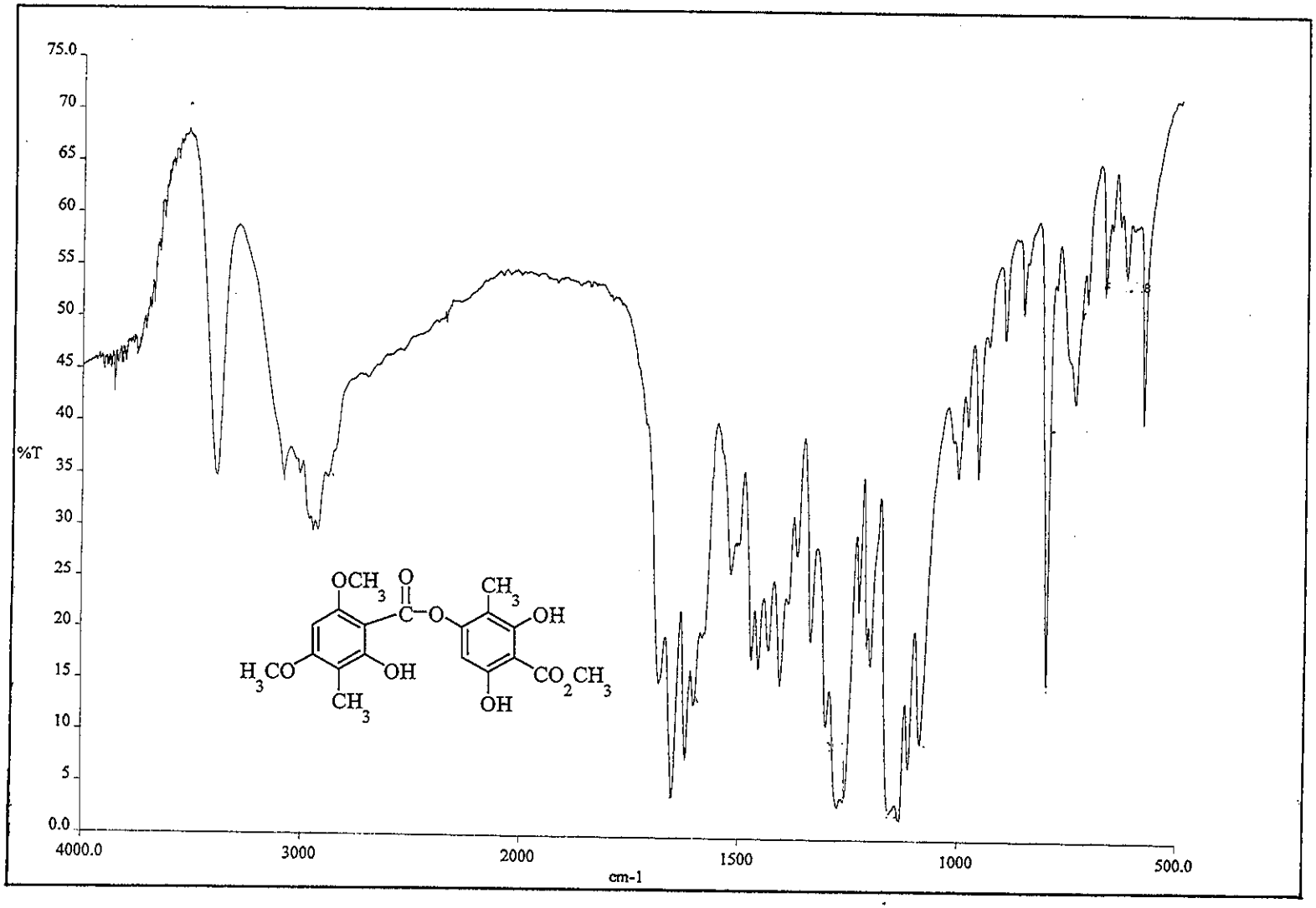


Figure 36. FTIR spectrum of methyl-2,6-dihydroxy-4-(2'-hydroxy-4',6'- dimethoxy-3'-methylbenzoyloxy)-3-methylbenzoate (67)

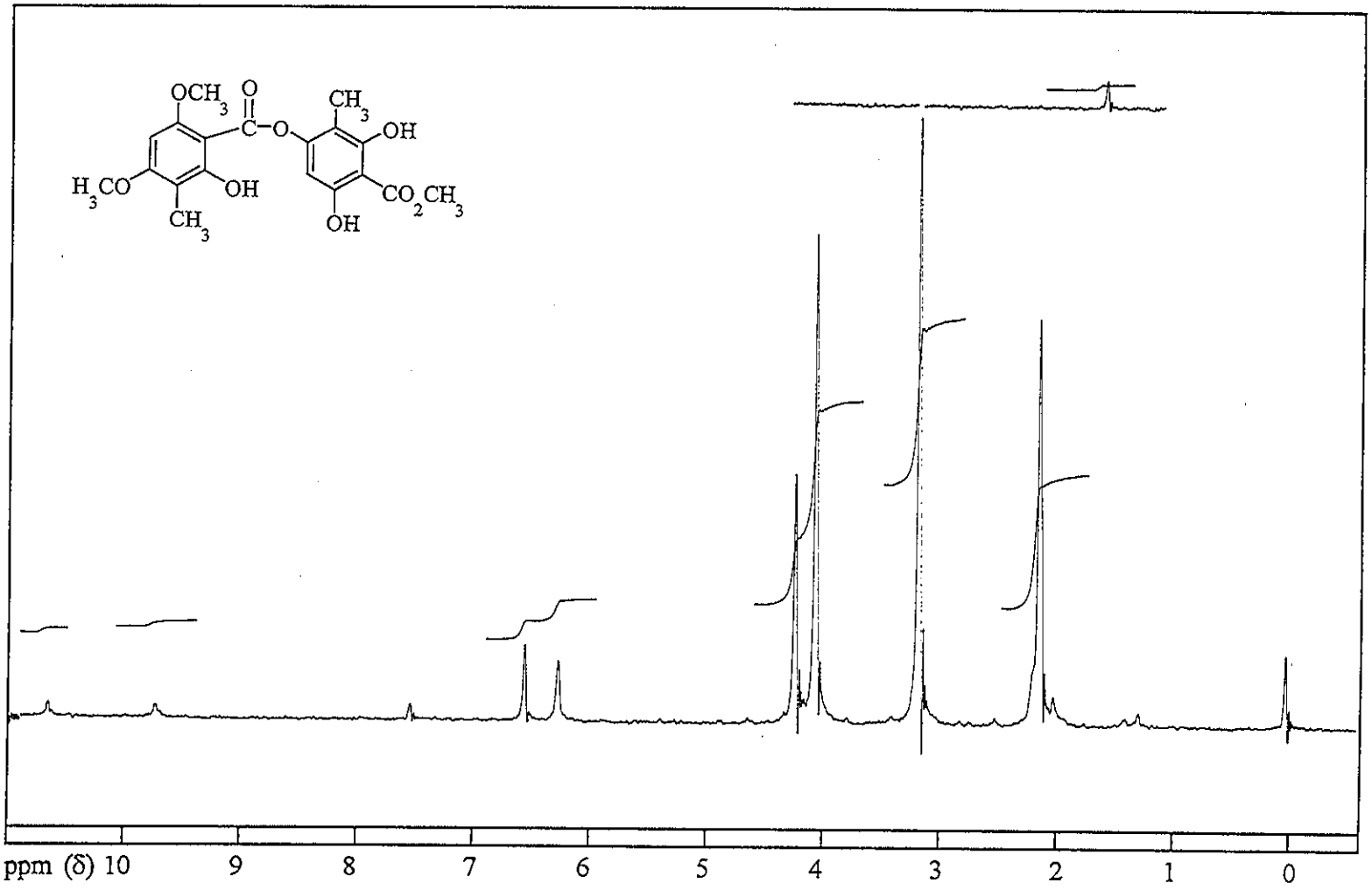


Figure 37. ^{1}H NMR spectrum of methyl-2,6-dihydroxy-4-(2'-hydroxy-4',6'- dimethoxy-3'-methylbenzoyloxy)-3-methylbenzoate (67)

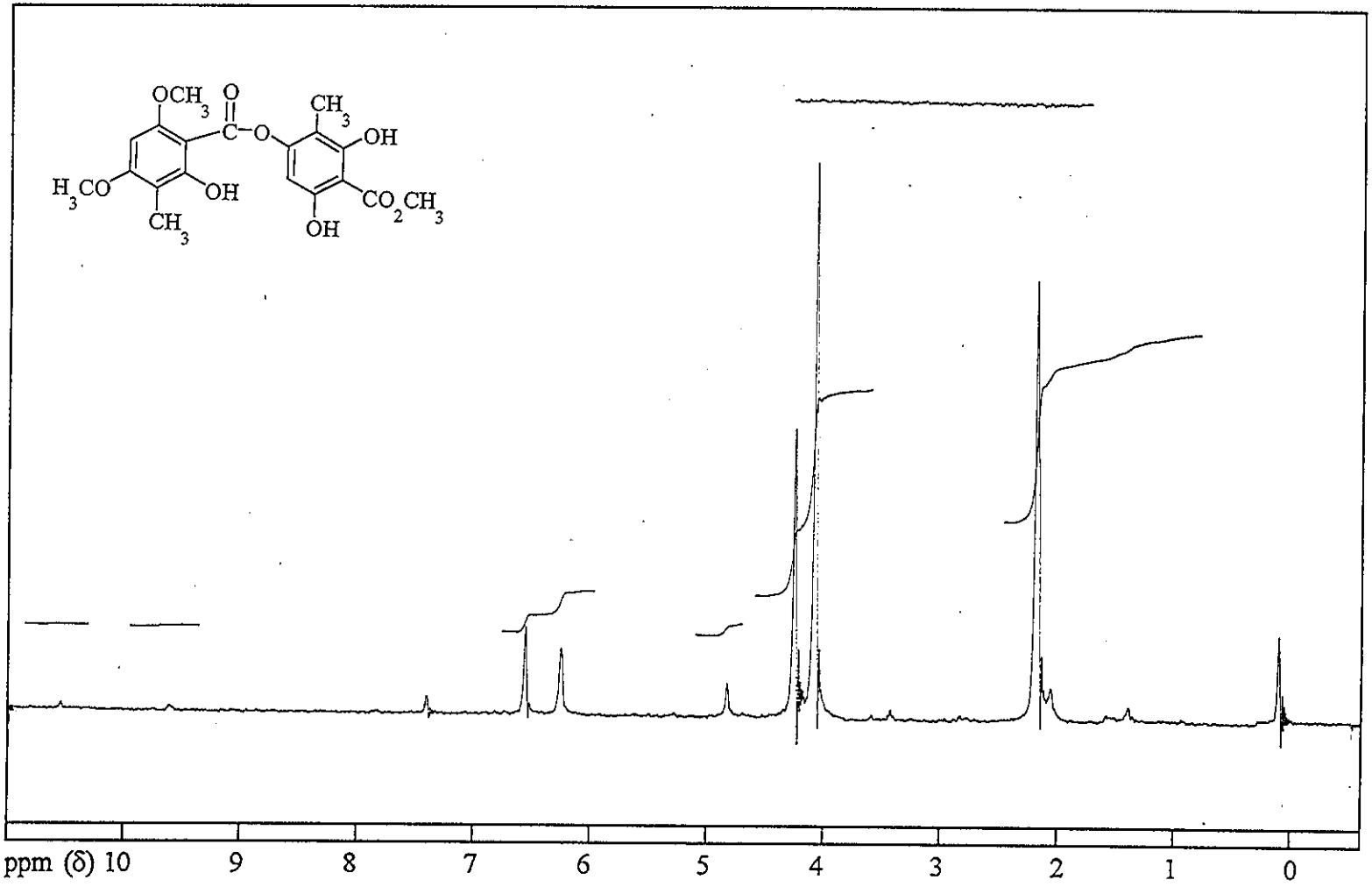


Figure 38. ^{1}H NMR spectrum of methyl 2,6-dihydroxy-4-(2'- hydroxy-4',6'-dimethoxy -3'-methylbenzoyloxy)-3-methylbenzoate (67) (D_2O)

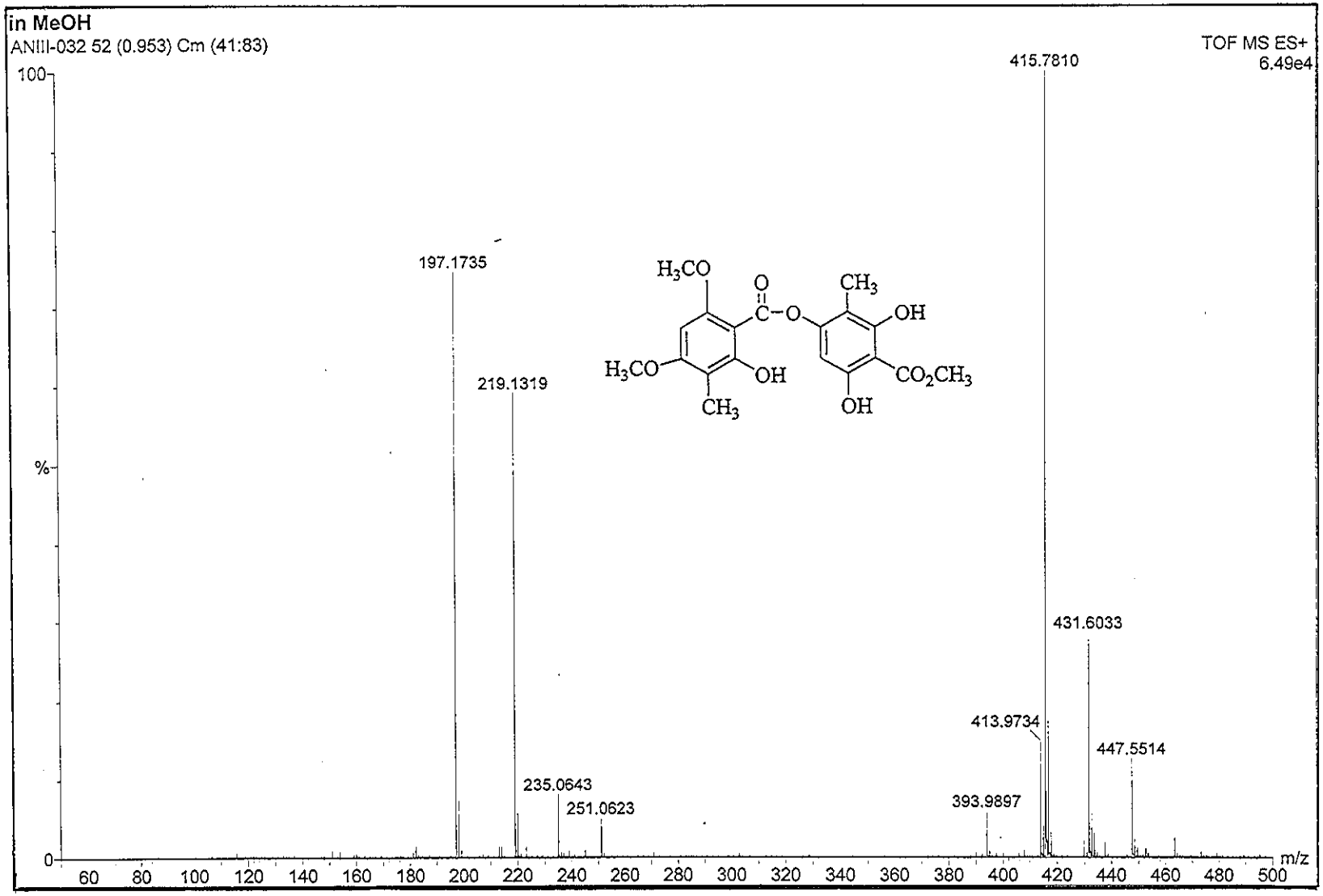


Figure 39. Mass spectrum (ES MS) of methyl-2,6-dihydroxy-4-(2'-hydroxy-4',6'-dimethoxy-3'-methylbenzoyloxy)-3-methylbenzoate (67)

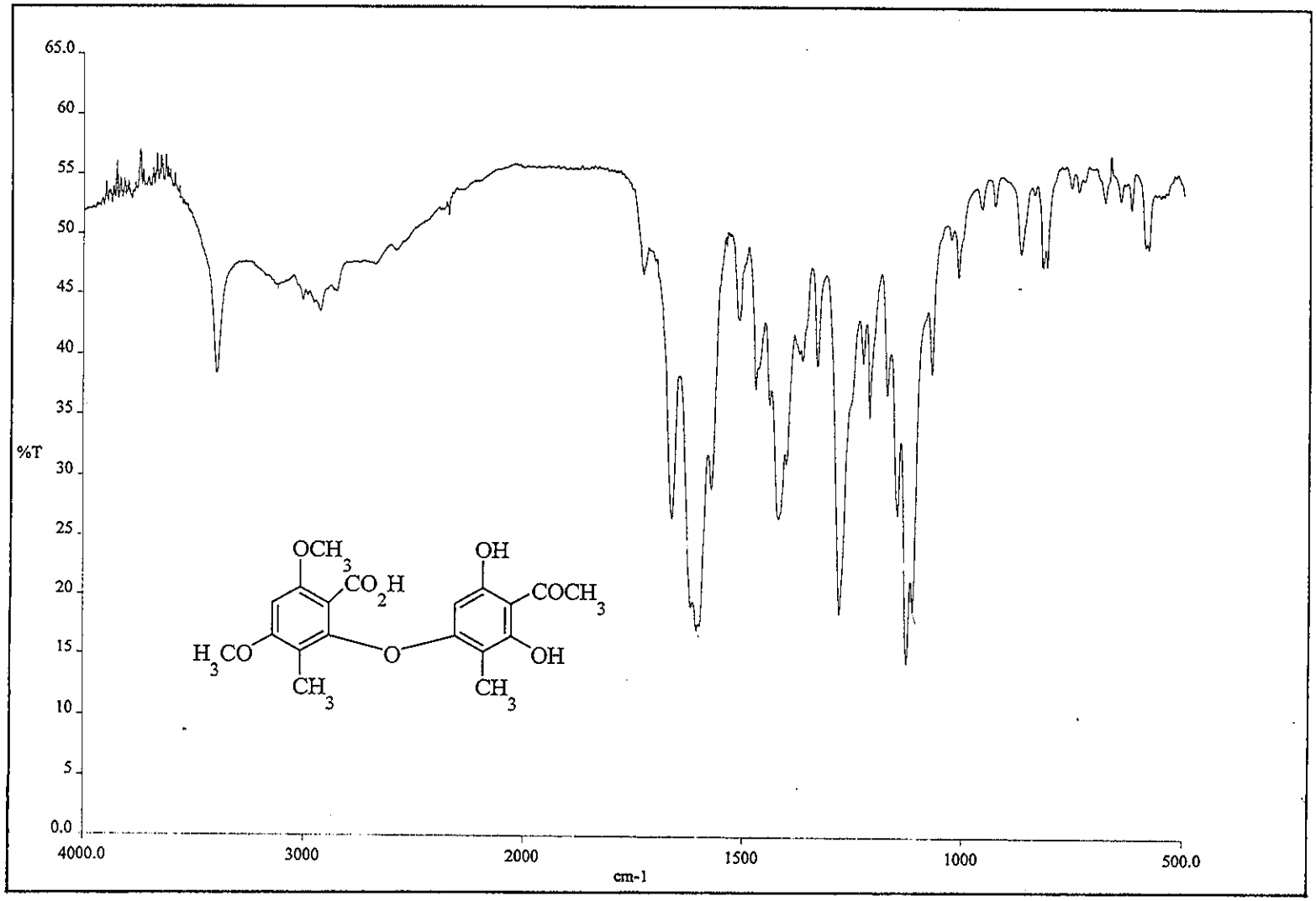


Figure 40. FTIR spectrum of 2-(4'-acetyl-3',5'-dihydroxy-2'-methylphenoxy)-4,6-dimethyl-3-methylbenzoic acid (125)

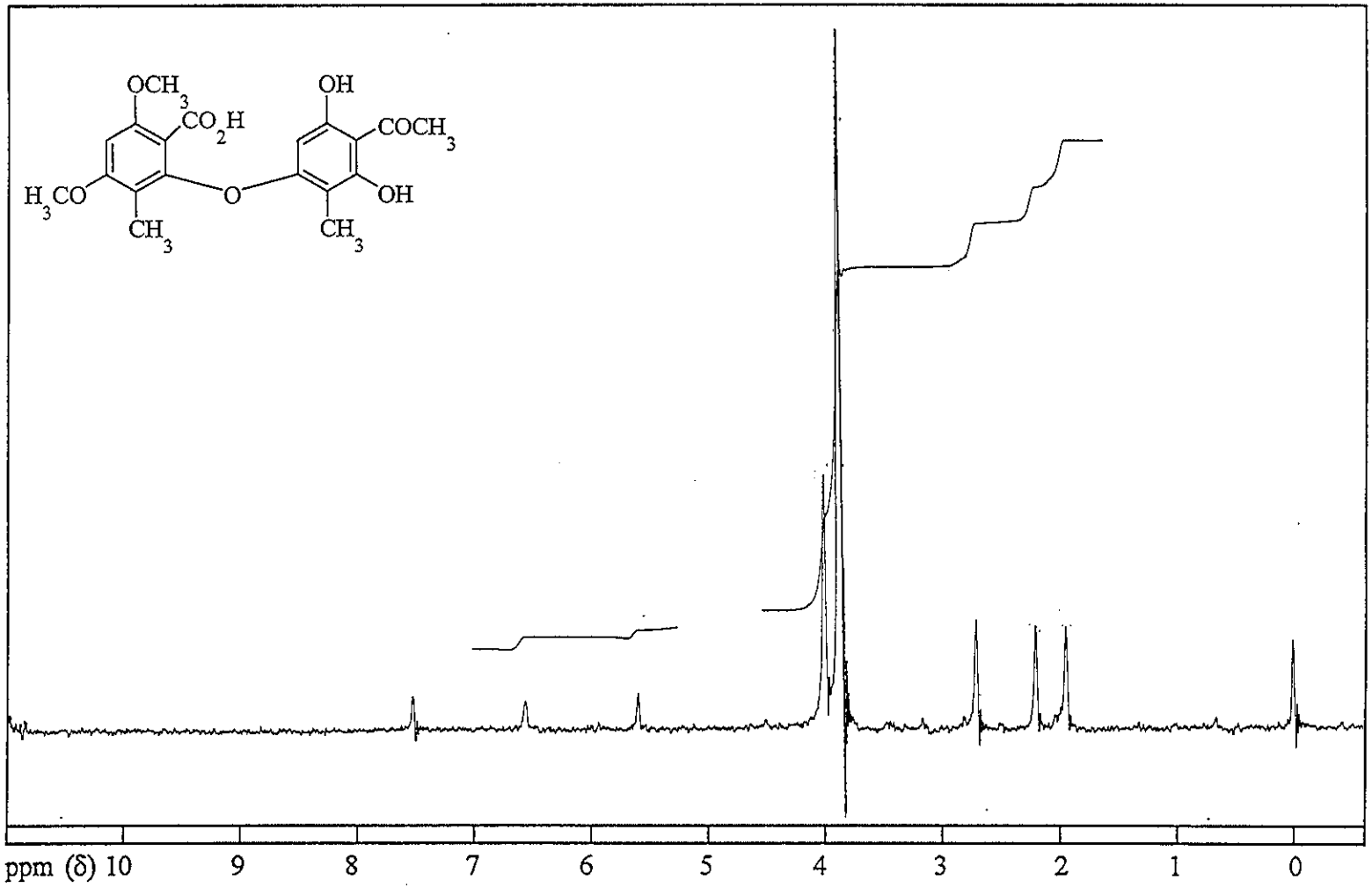


Figure 41. ^{1}H NMR spectrum of 2-(4'-acetyl-3',5'-dihydroxy-2'-methylphenoxy)-4,6-dimethyl-3-methylbenzoic acid (125)

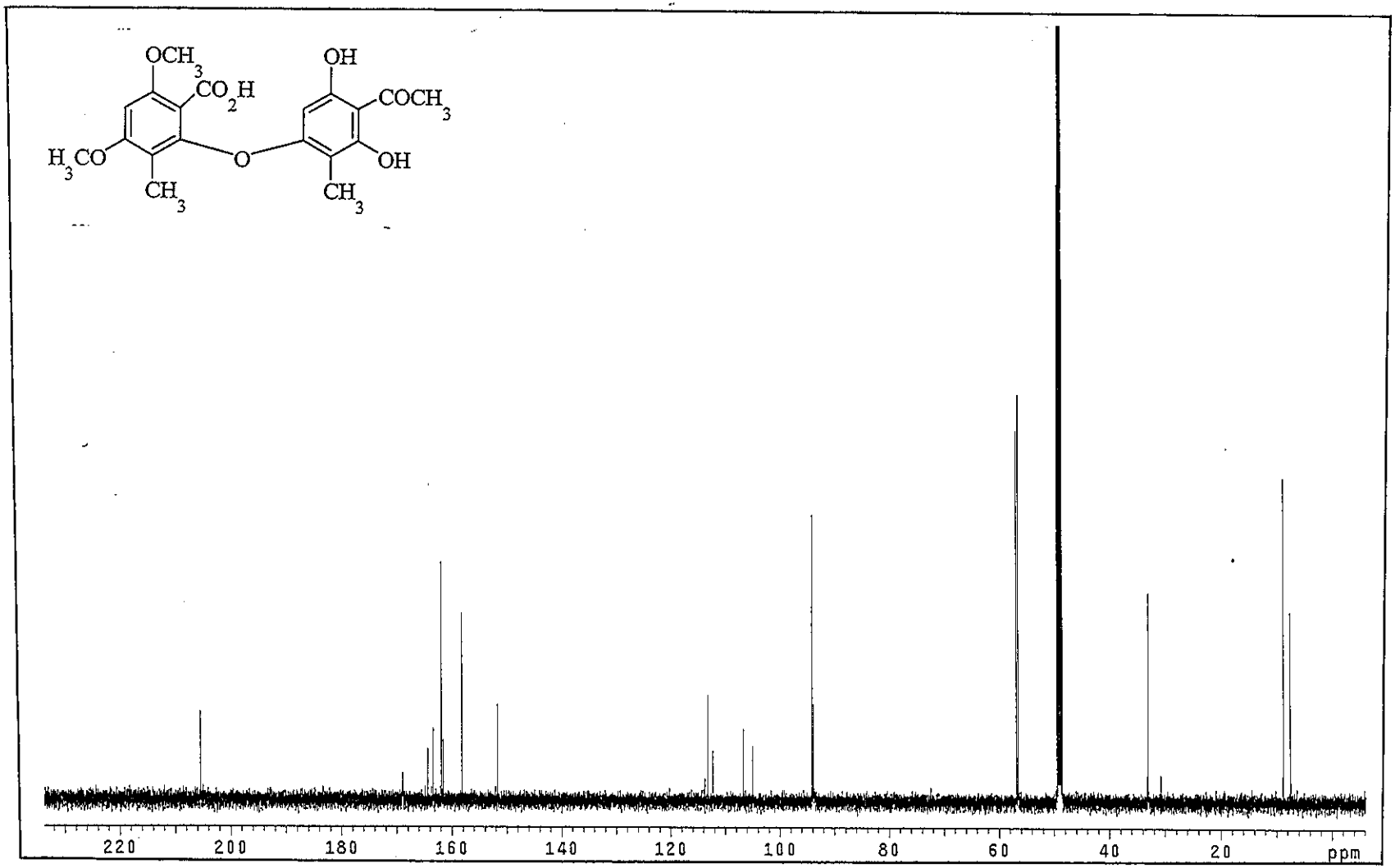


Figure 42. ^{13}C NMR spectrum of 2-(4'-acetyl-3',5'-dihydroxy-2'-methylphenoxy)-4,6-dimethyl-3-methylbenzoic acid (125)

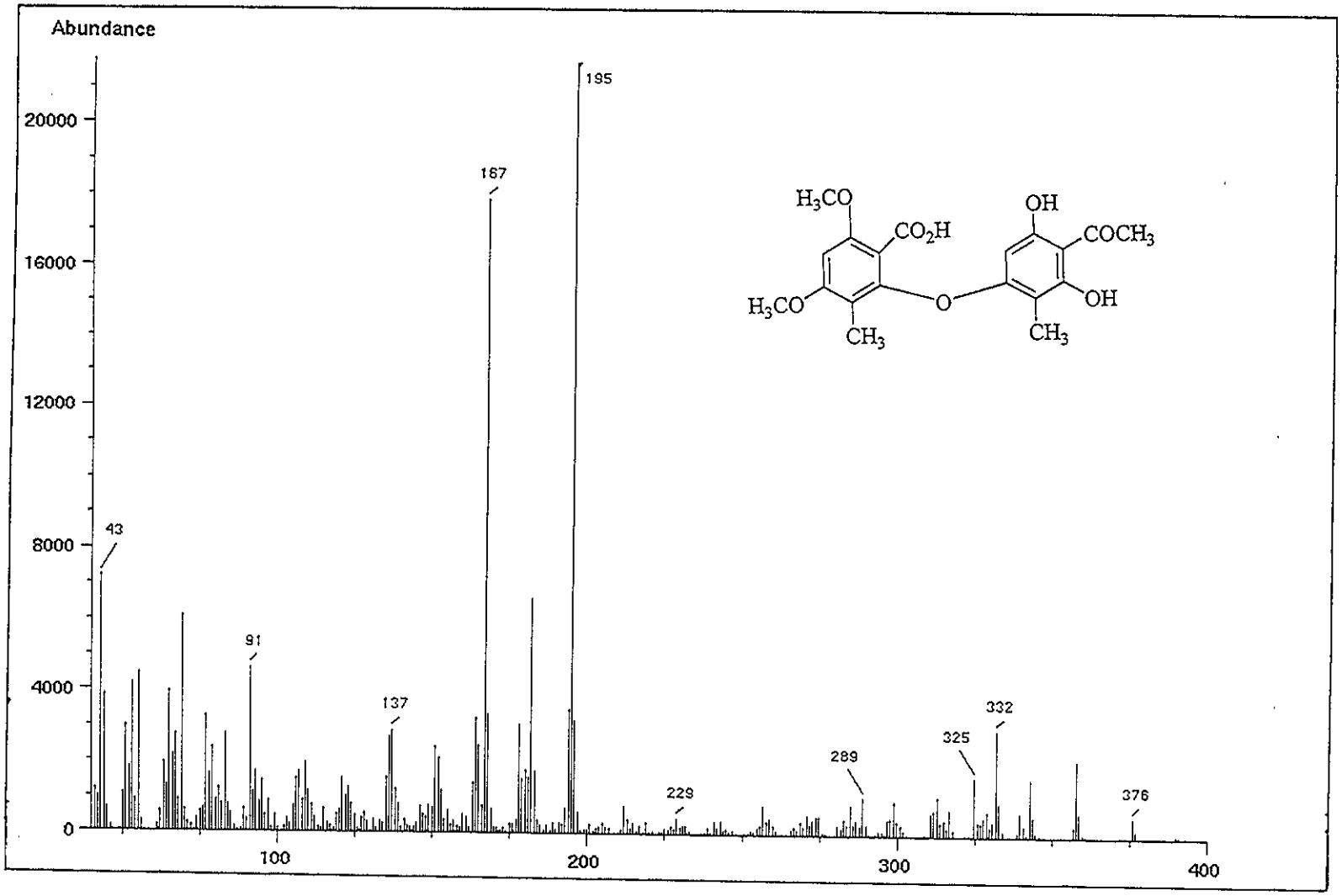


Figure 43.. Mass spectrum (EIMS) of 2-(4'-acetyl-3',5'-dihydroxy-2'-methylphenoxy)-4,6-dimethyl-3-methylbenzoic acid (125)

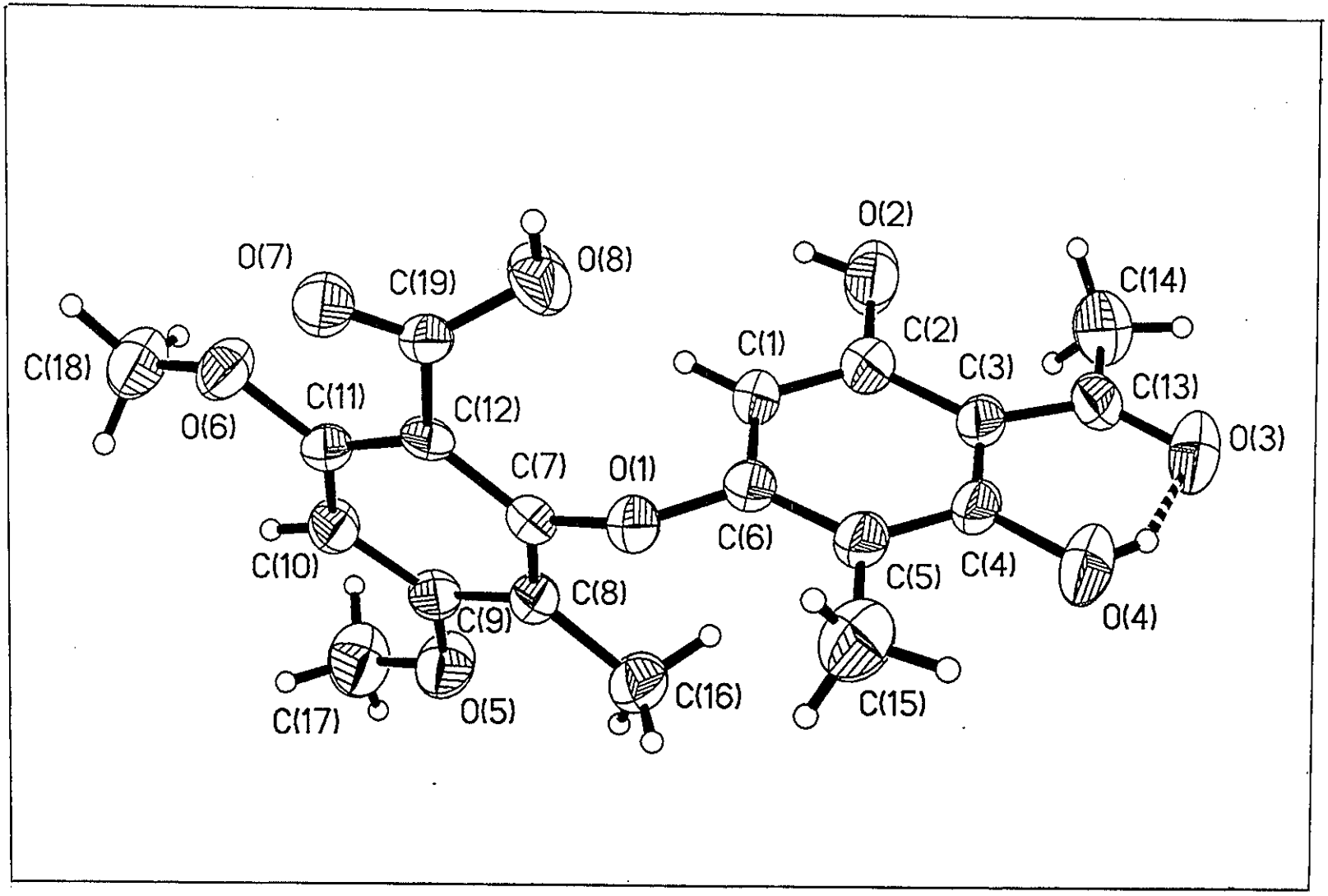


Figure 44. ORTEP drawing of 2-(4'-acetyl-3',5'-dihydroxy-2'-methylphenoxy)-4,6-dimethyl-3-methylbenzoic acid (125)

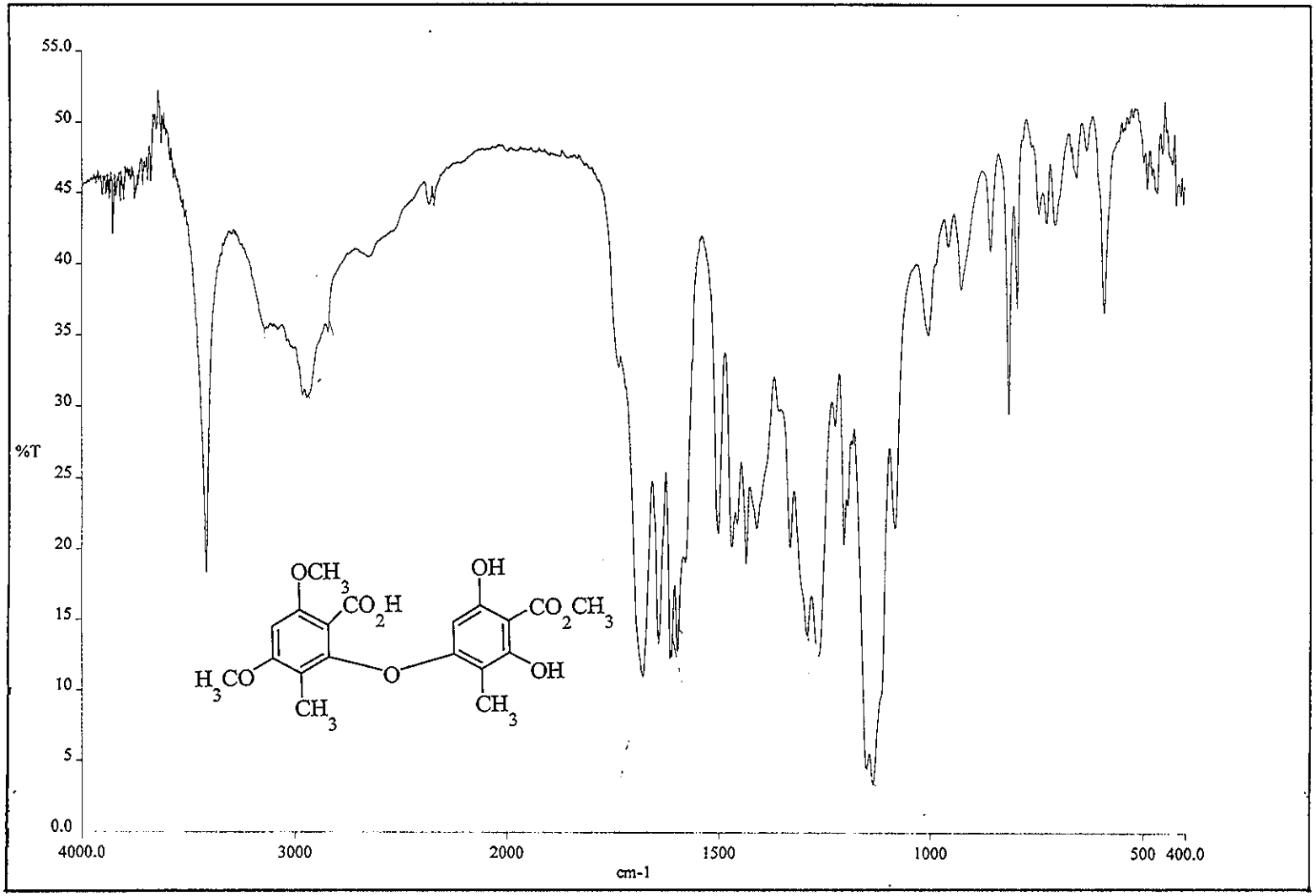


Figure 45. FTIR spectrum of 2-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethyl-3-methylbenzoic acid (68)

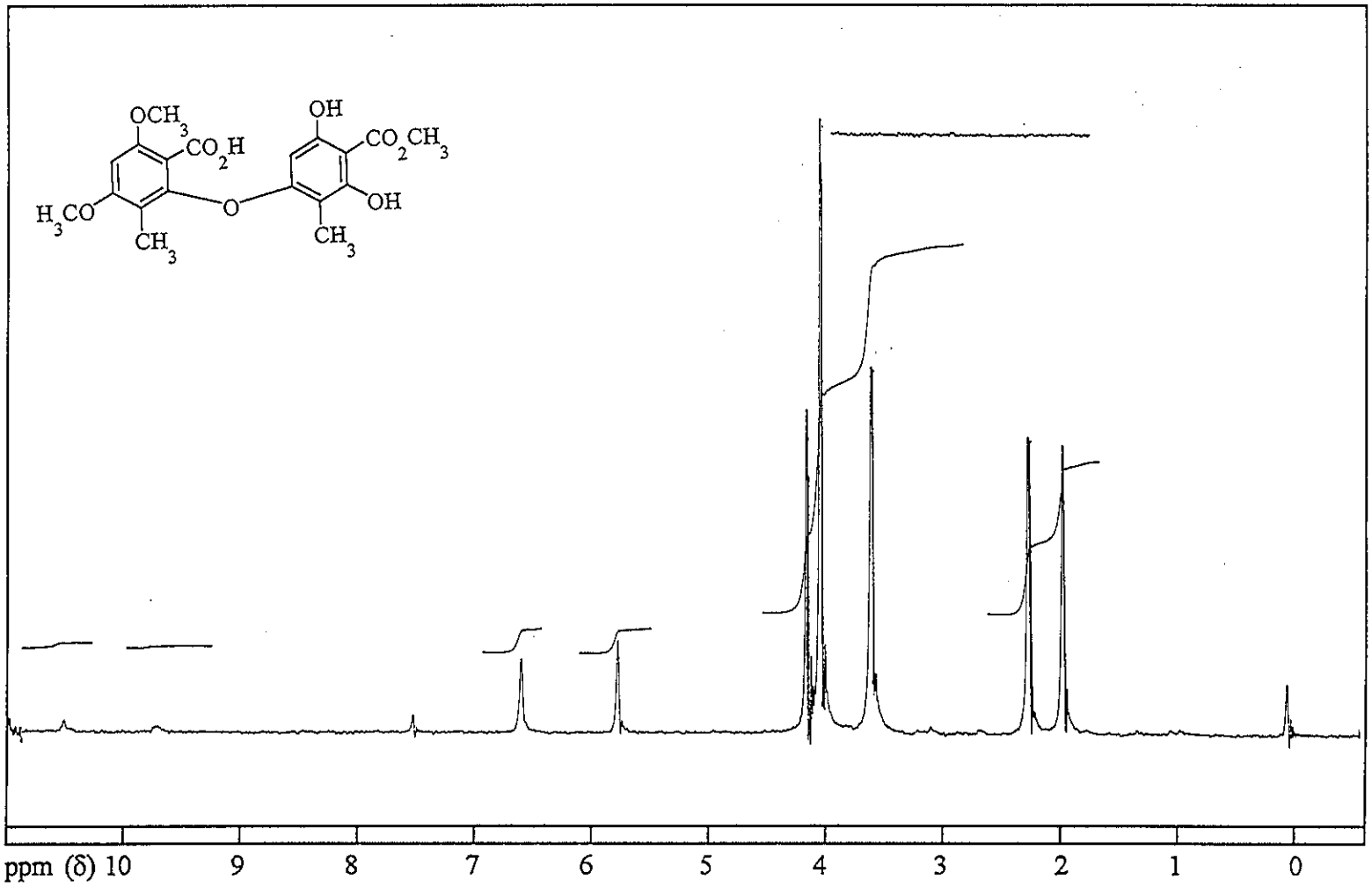


Figure 46. ^{1}H NMR spectrum of 2-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (68)

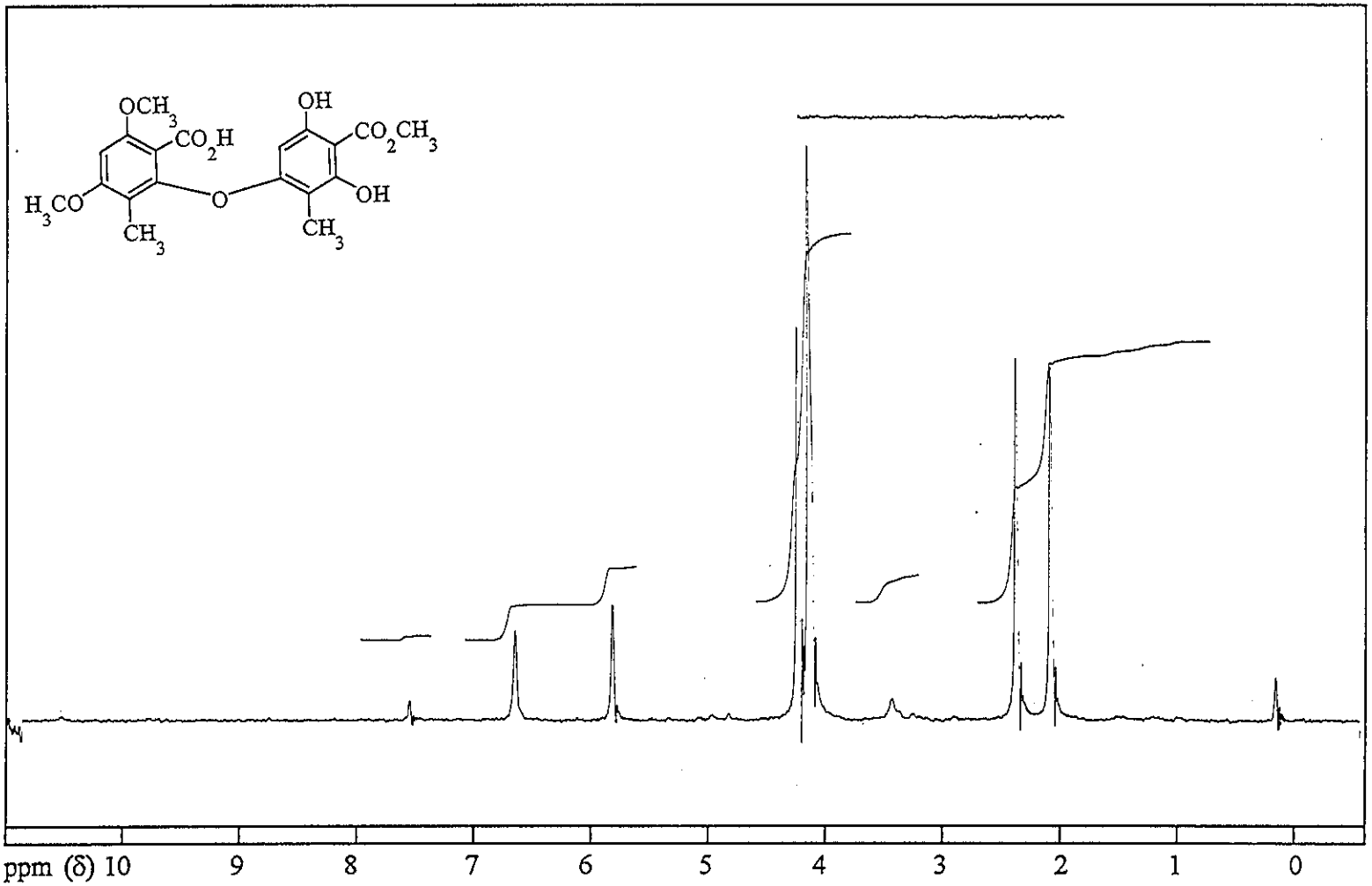


Figure 47. ^{1}H NMR spectrum of 2-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (68) (D_2O)

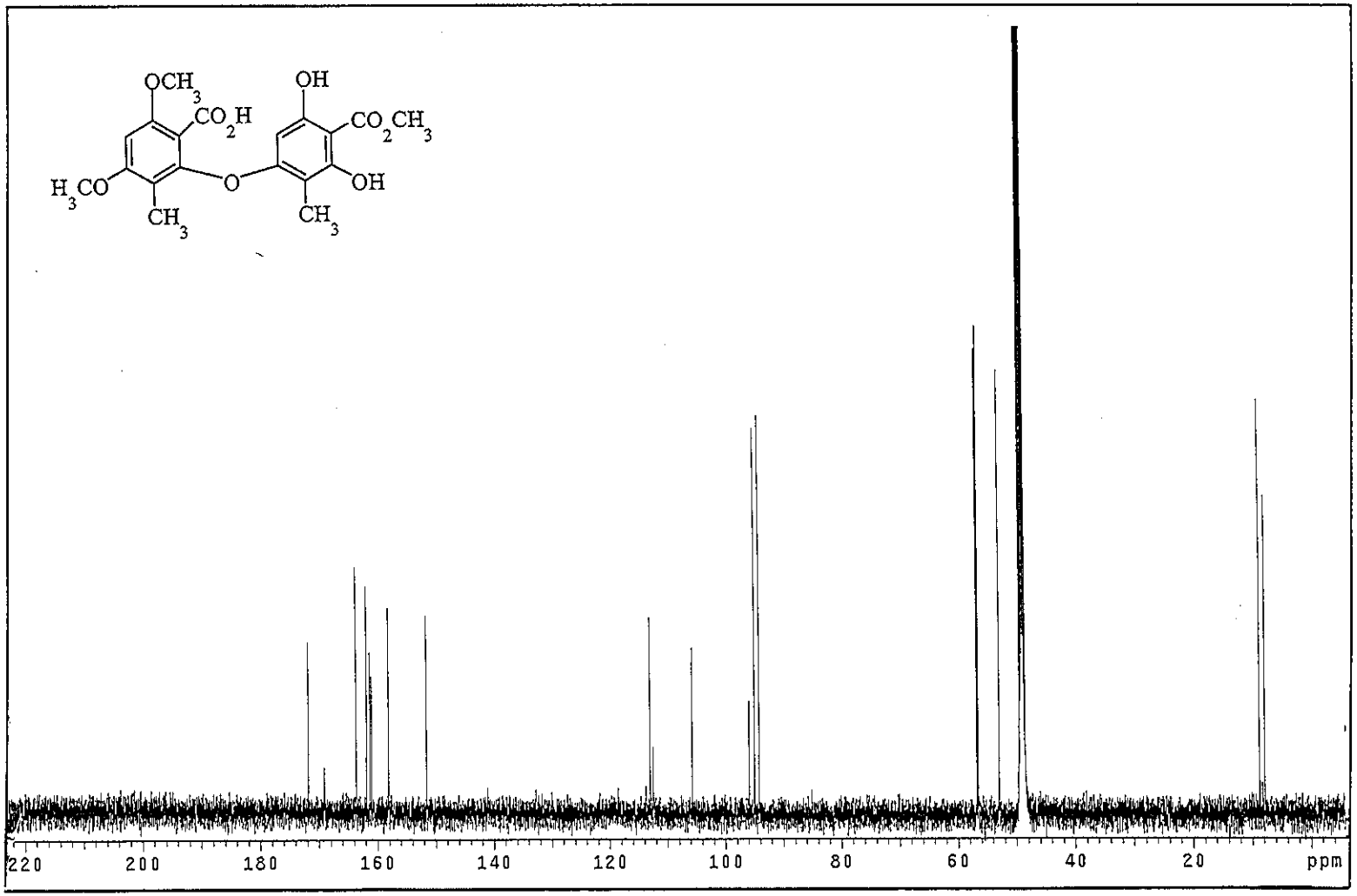


Figure 48. ^{13}C NMR spectrum of 2-(3',5'-dihydroxy-4'-methoxycarbonyl-2'-methylphenoxy)-4,6-dimethoxy-3-methylbenzoic acid (68)

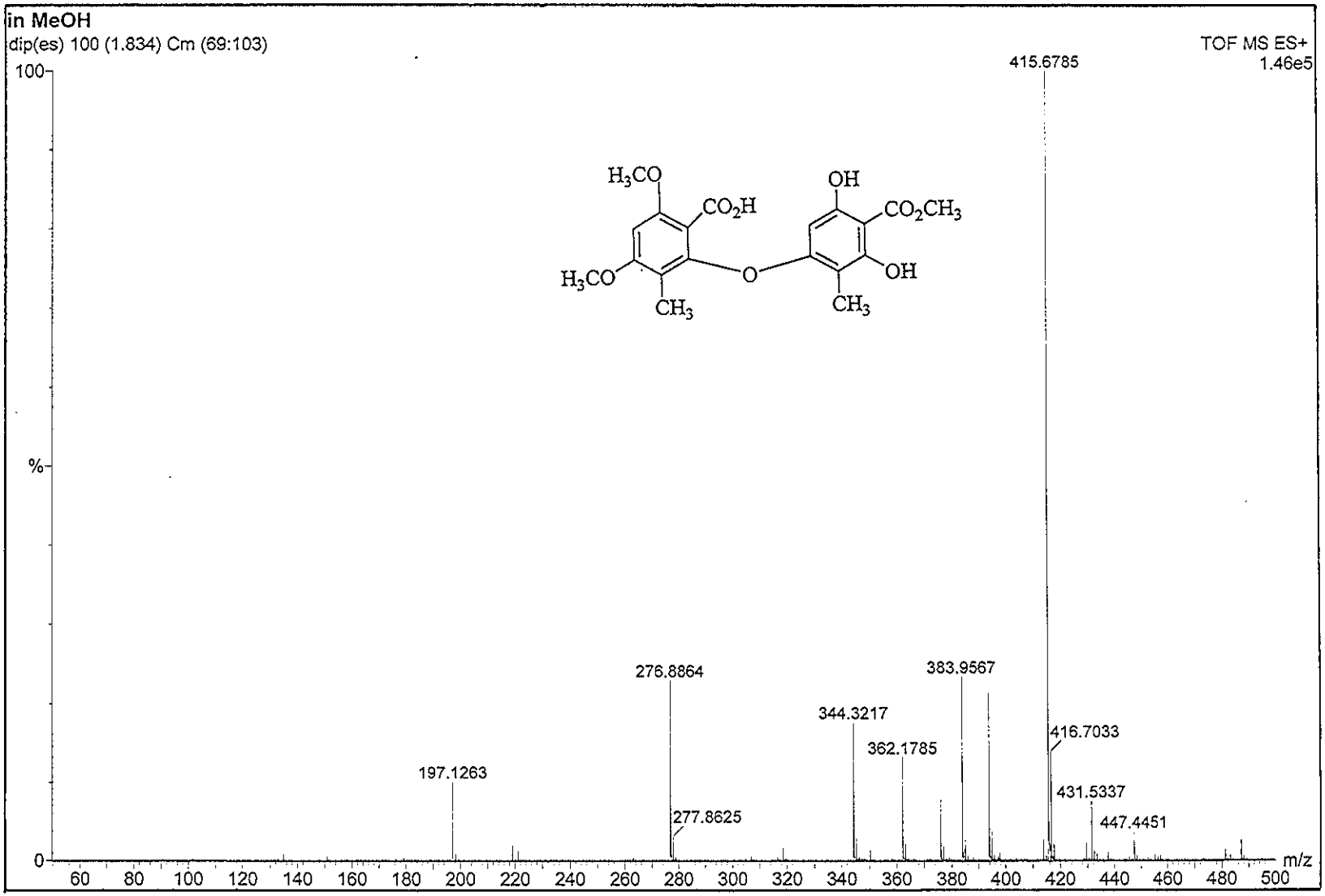


Figure 49. Mass spectrum (ESMS) of 2-(3',5'-dihydroxy-4'-methoxycarbonyl -2'-methylphenoxy)-4,6-dimethyl-3-methylbenzoic acid (68)

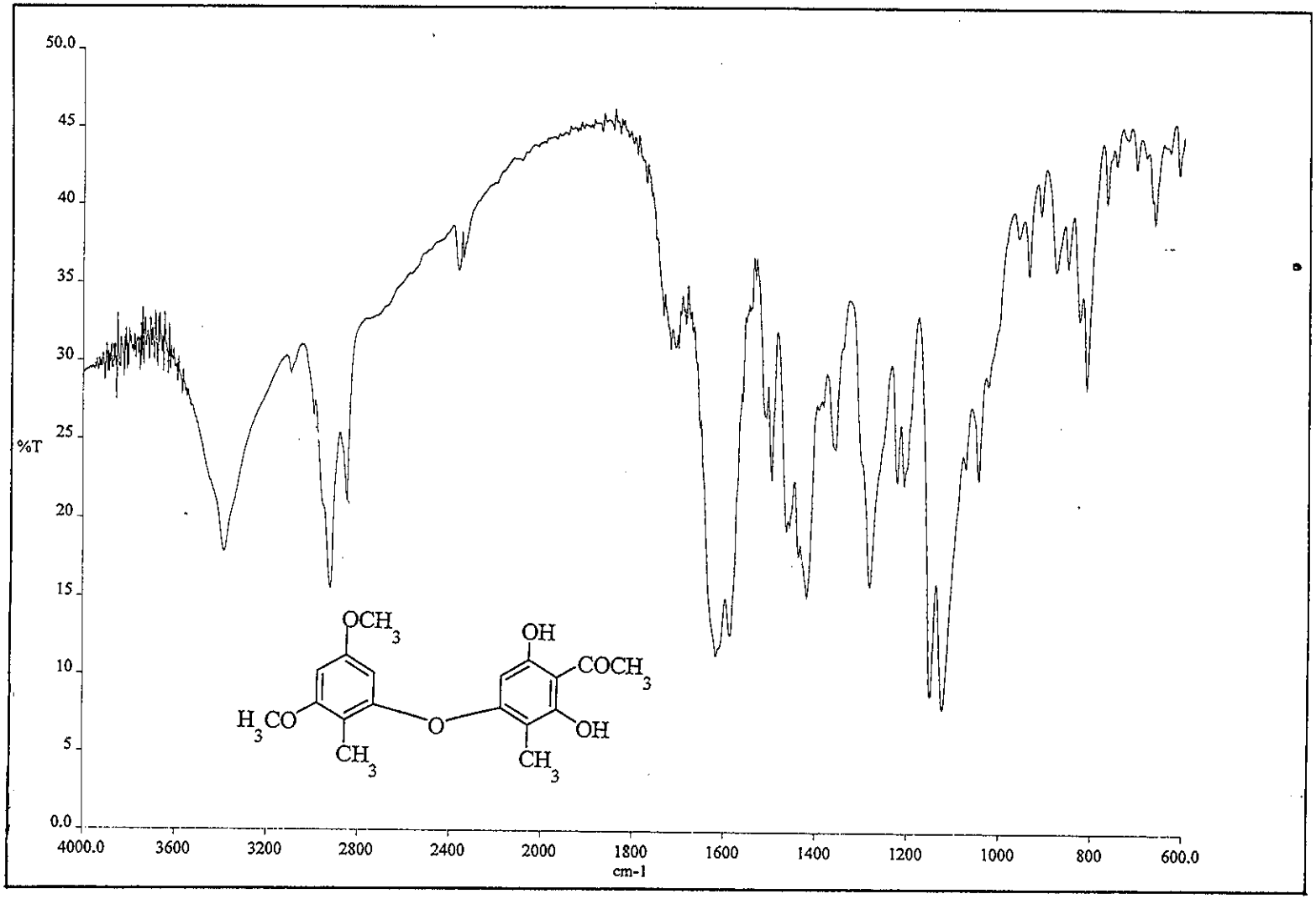


Figure 50. FTIR spectrum of 2,6-dihydroxy-4-(3',5'-dimethoxy-2'-methylphenoxy)-3-methylacetophenone (126)

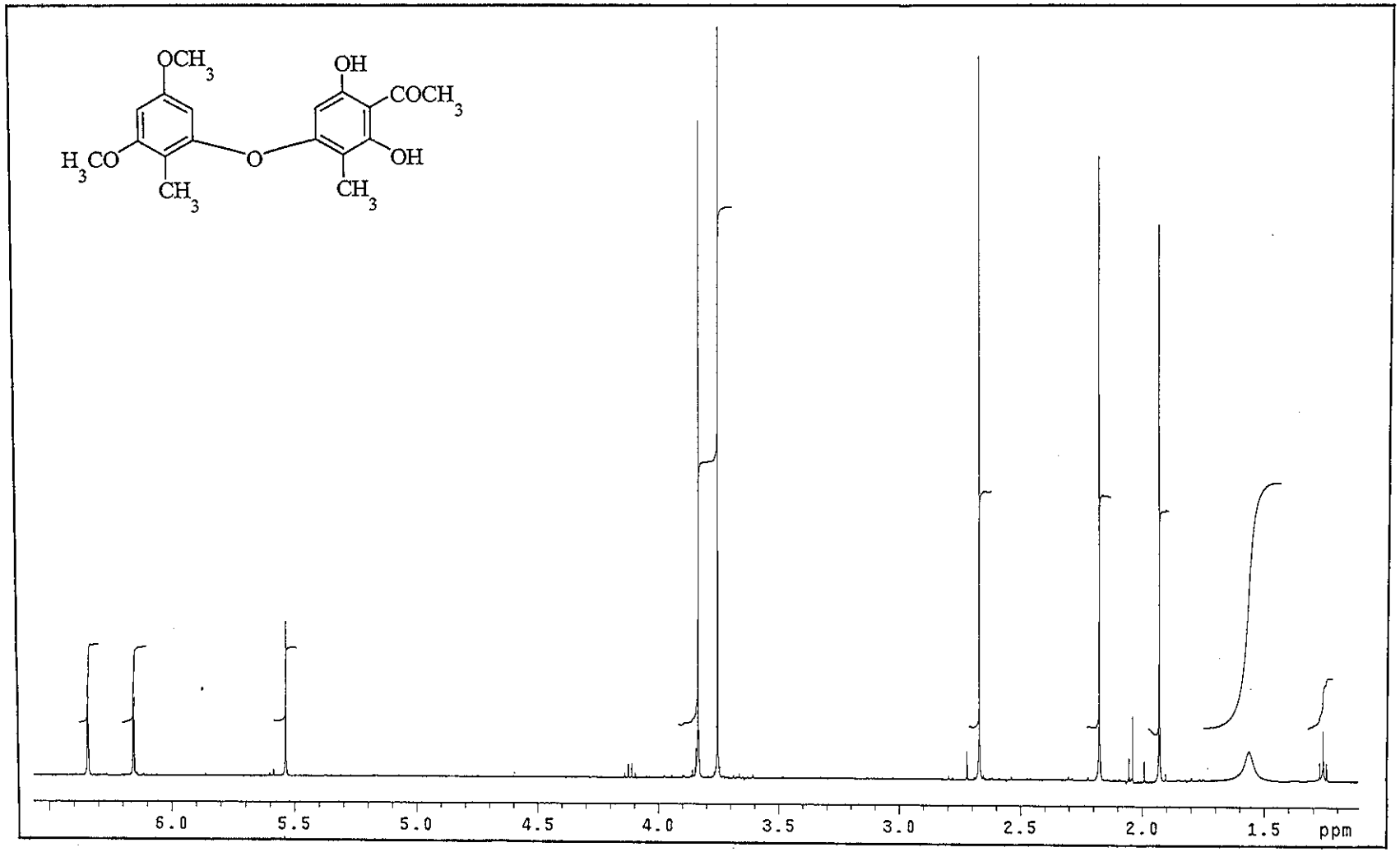


Figure 51. ^{1}H NMR. spectrum of 2,6-dihydroxy-4-(3',5'-dimethoxy-2'-methylphenoxy)-3-methylacetophenone (126)

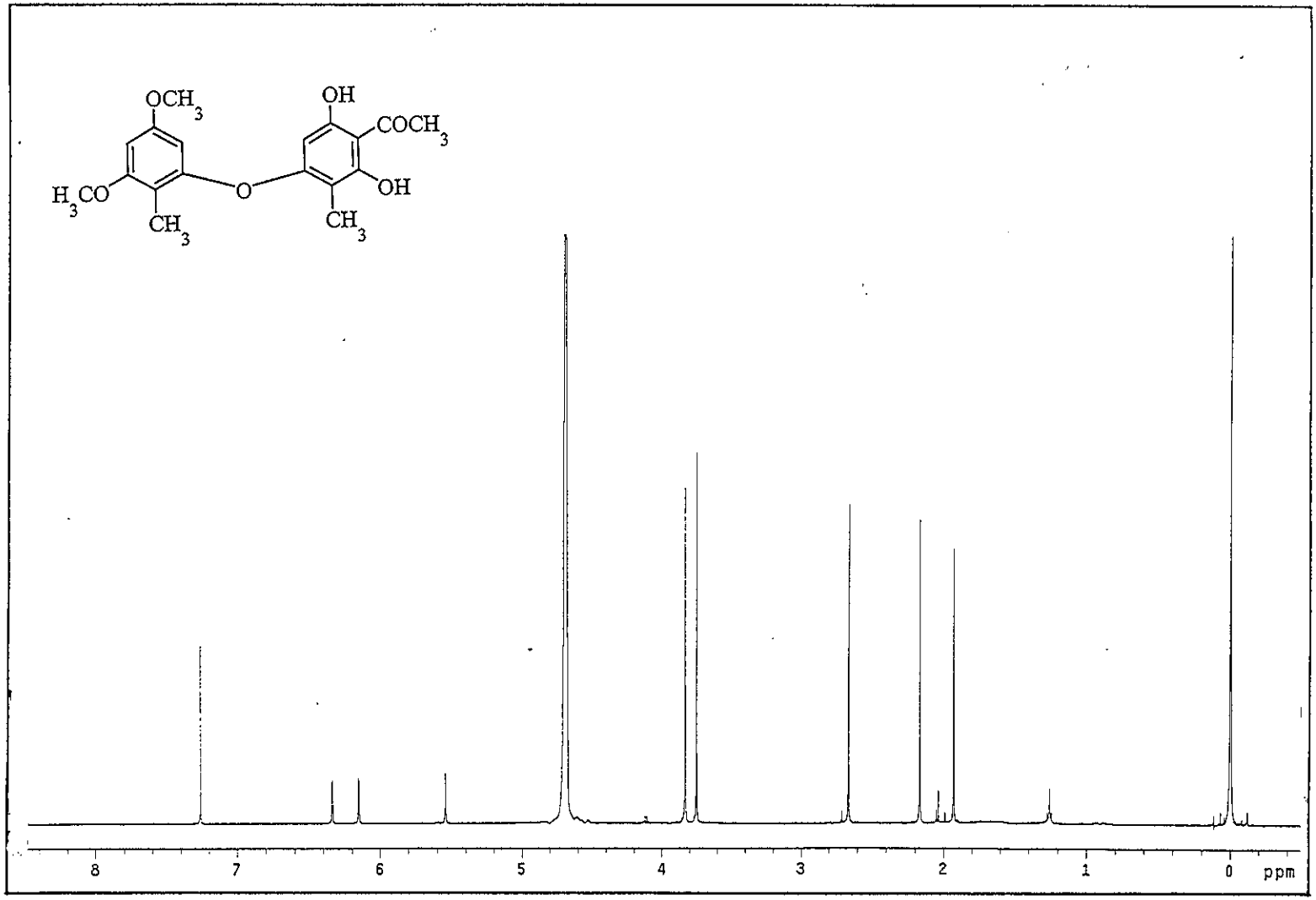


Figure 52. ^{1}H NMR spectrum of 2,6-dihydroxy-4-(3',5'-dimethoxy-2'-methylphenoxy)-3-methylacetophenone (126) (D_2O)

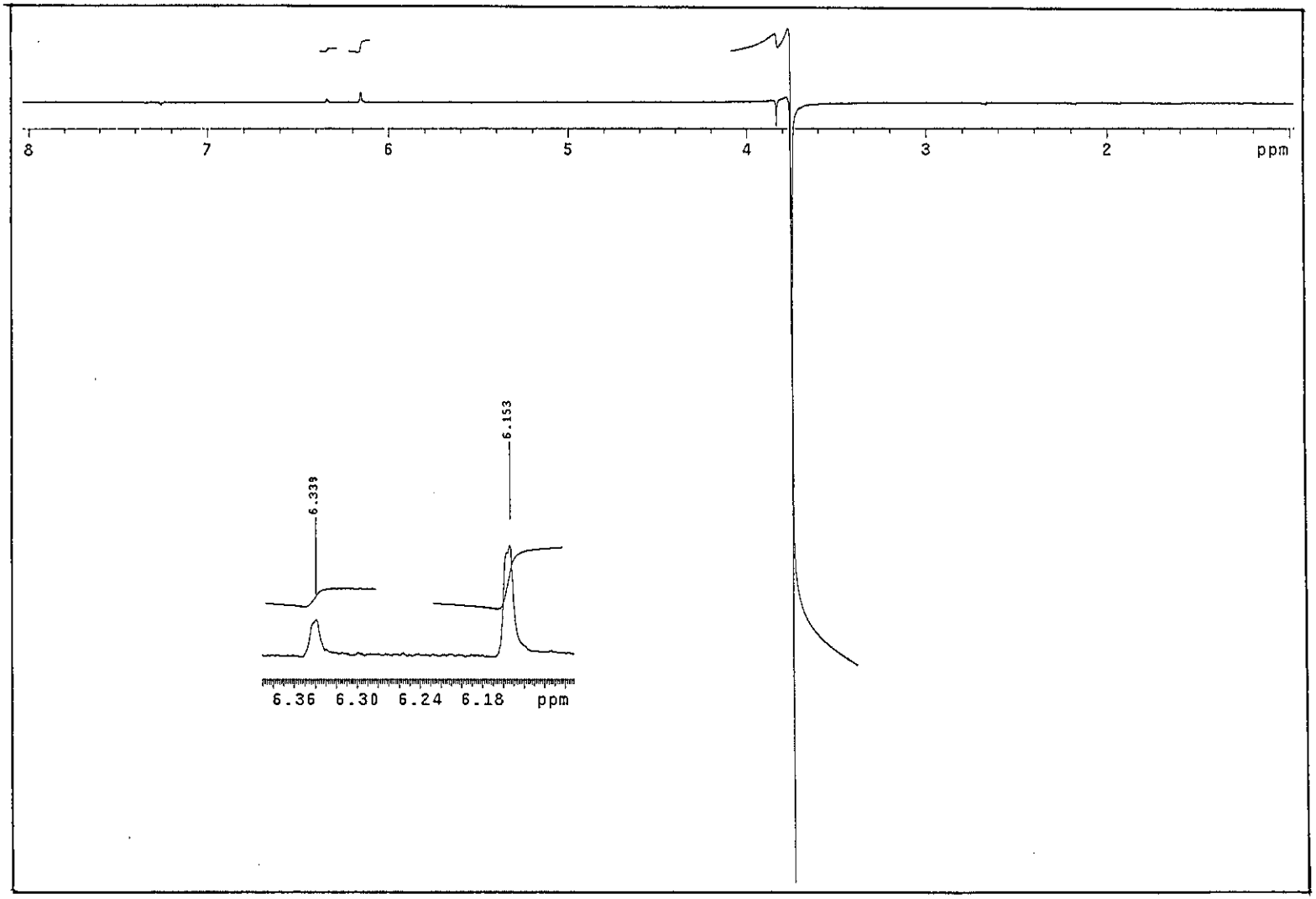


Figure 53. NOE difference spectrum of 2,6-dihydroxy-4-(3',5'-dimethoxy-2'- methylphenoxy)-3-methylacetophenone (126) irradiated at 3.75 ppm

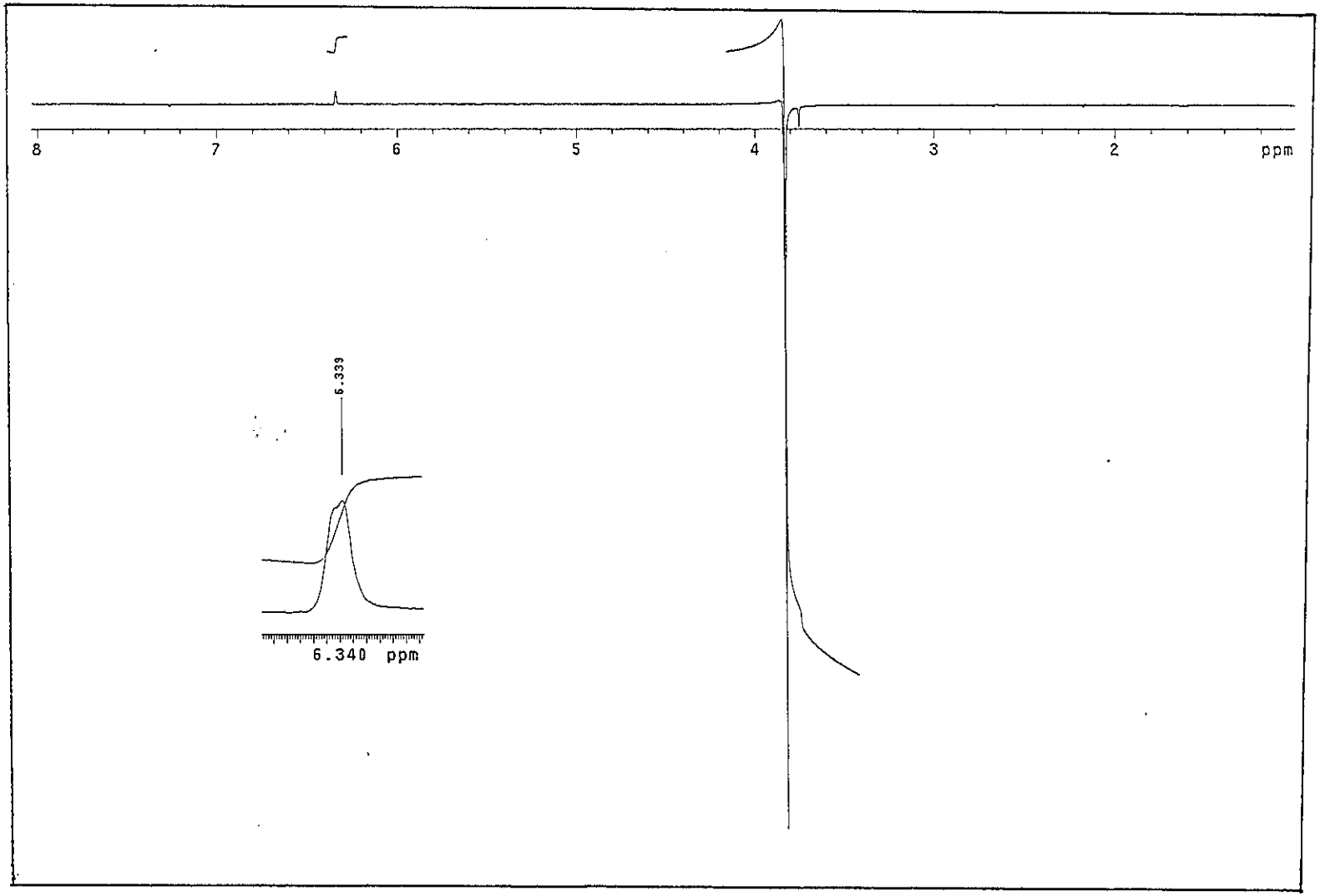


Figure 54. NOE difference spectrum of 2,6-dihydroxy-4-(3',5'-dimethoxy-2'-methylphenoxy)-3-methylacetophenone (126) irradiated at 3.83 ppm

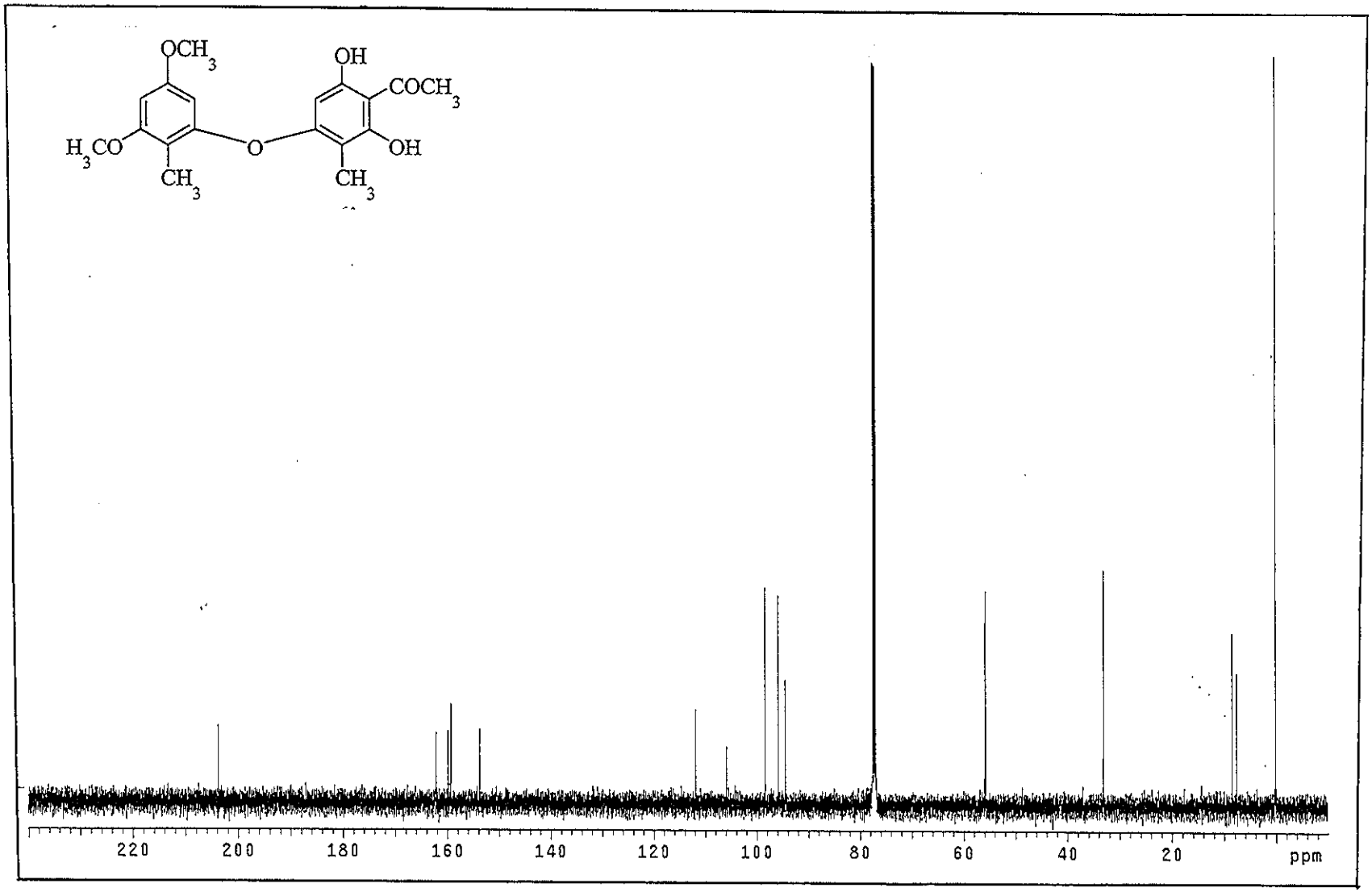


Figure 55. ^{13}C NMR spectrum of 2,6-dihydroxy-4-(3',5'-dimethoxy-2'-methyl- phenoxy)-3-methylacetophenone (126)

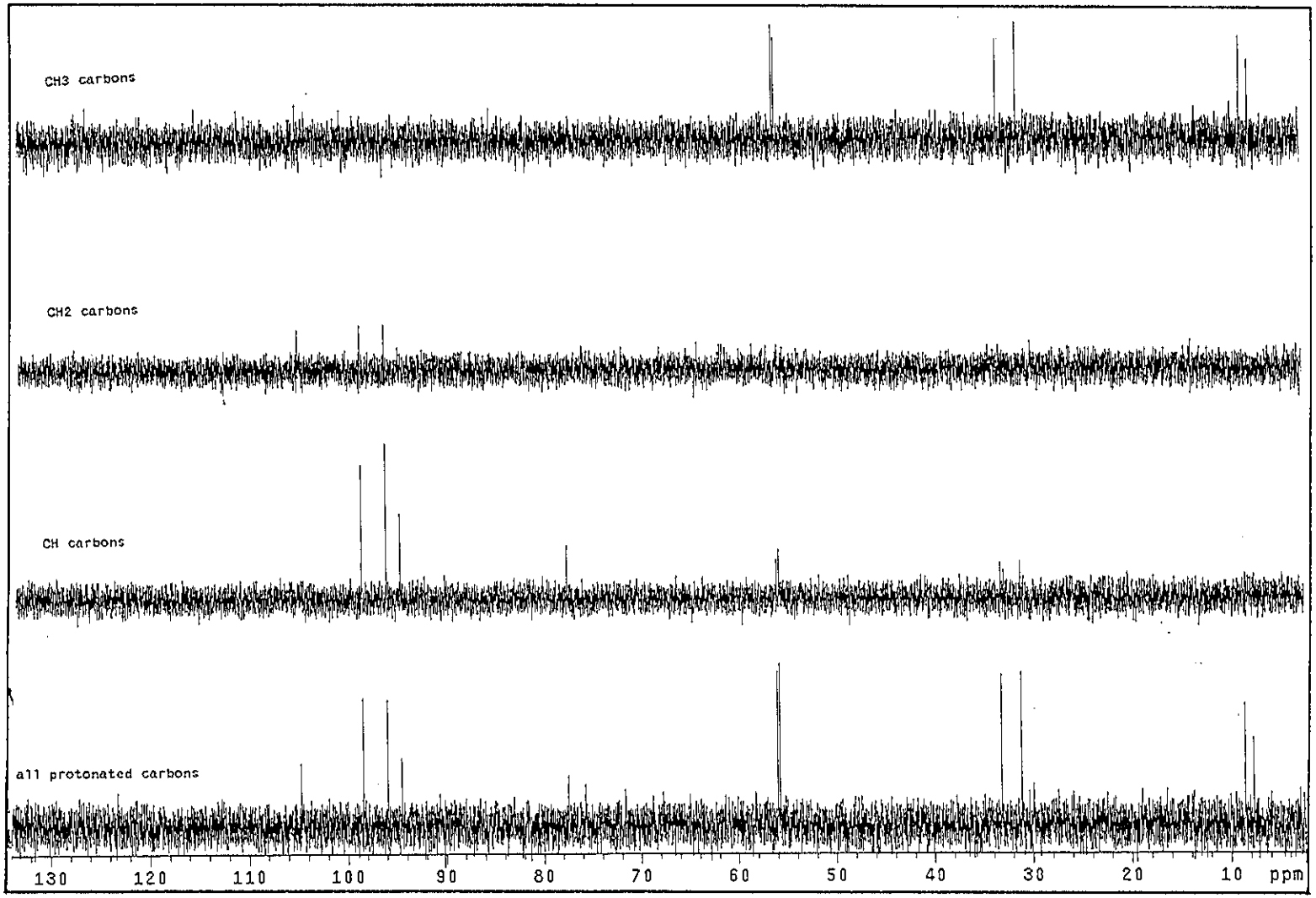


Figure 56. DEPT spectrum of 2,6-dihydroxy-4-(3',5'-dimethoxy-2'-methylphenoxy)-3-methylacetophenone (126)

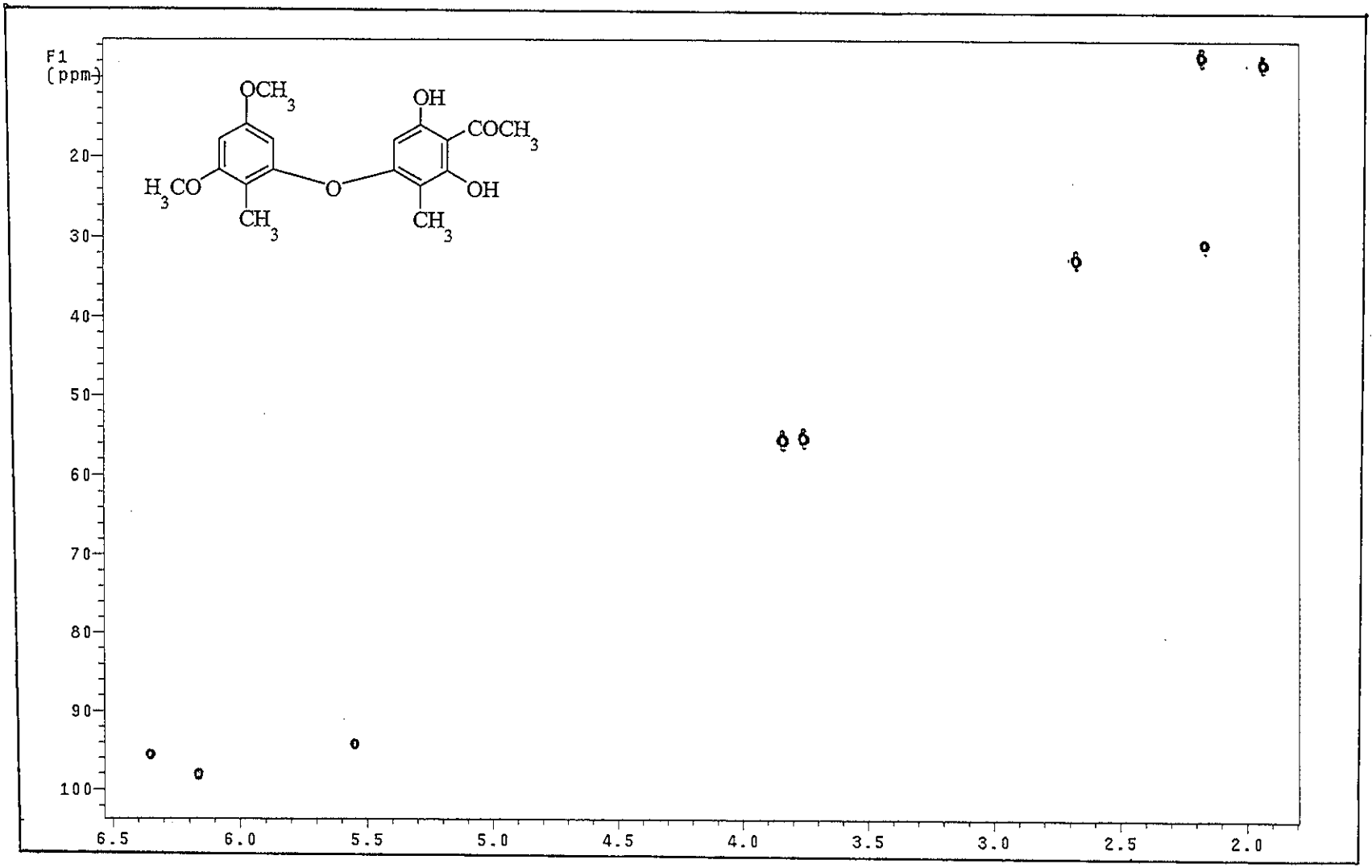


Figure 57. HMQC spectrum of 2,6-dihydroxy-4-(3',5'-dimethoxy-2'-methylphenoxy)-3-methylacetophenone (126)

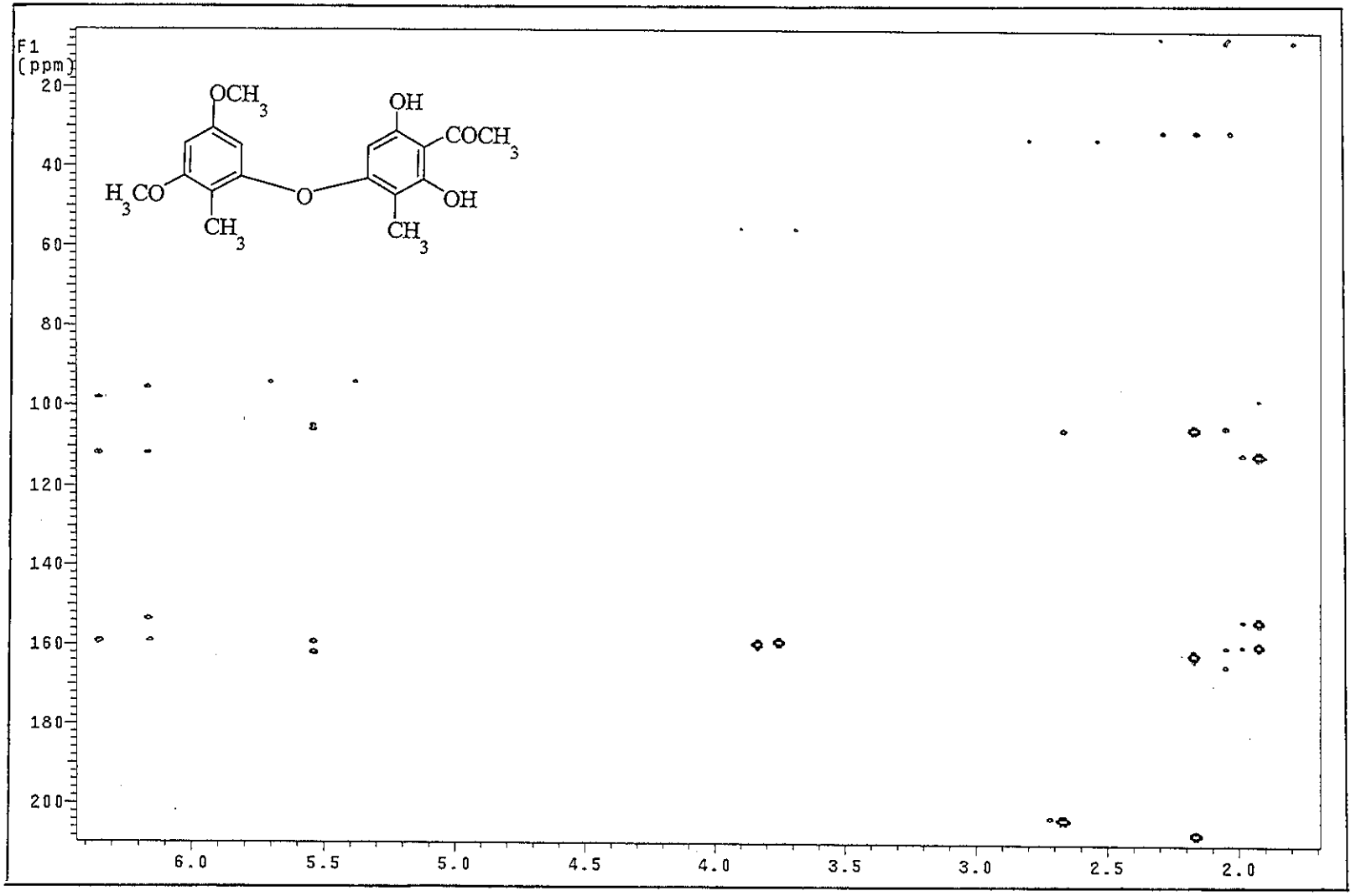


Figure 58. HMBC spectrum of 2,6-dihydroxy-4-(3',5'-dimethoxy-2'-methylphenoxy)3-methylacetophenone (126)

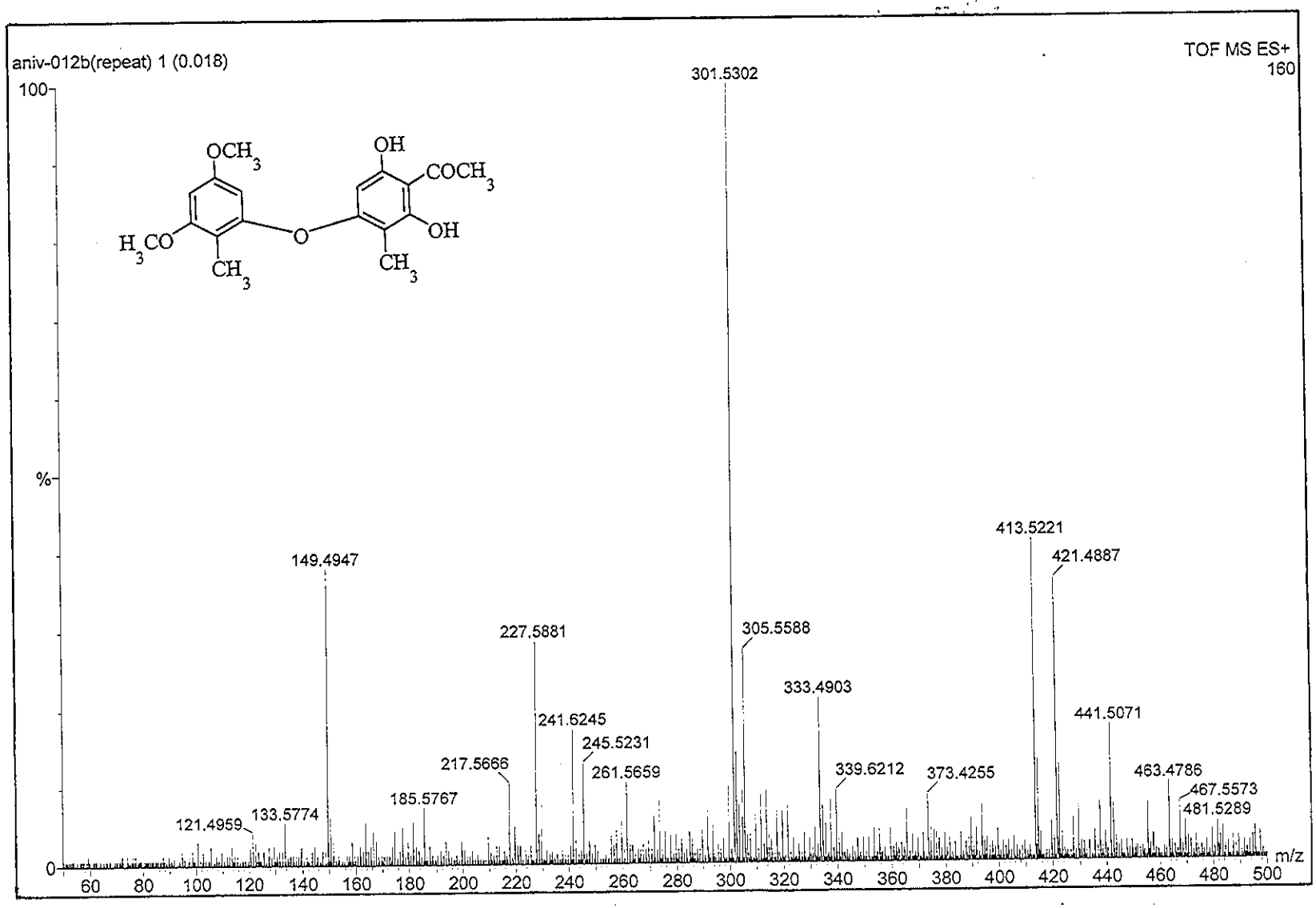


Figure 59. Mass spectrum (ESMS) of 2,6-dihydroxy-4-(3',5'-dimethoxy-2'-methylphenoxy)-3-methylacetophenone (126)

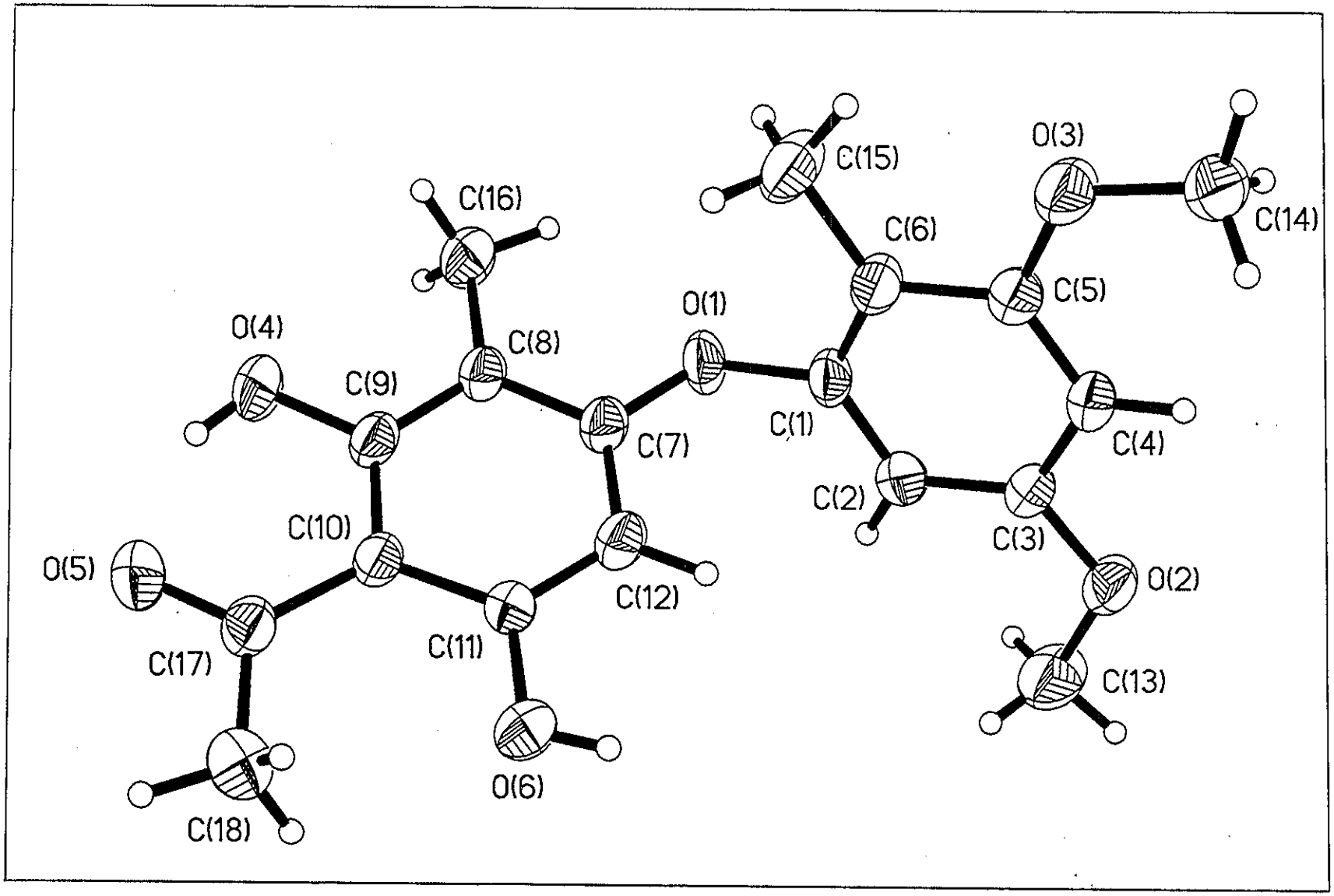


Figure 60. ORTEP drawing of 2,6-dihydroxy-4-(3',5'-dimethoxy-2'-methylphenoxy)-3-methylacetophenone (126)

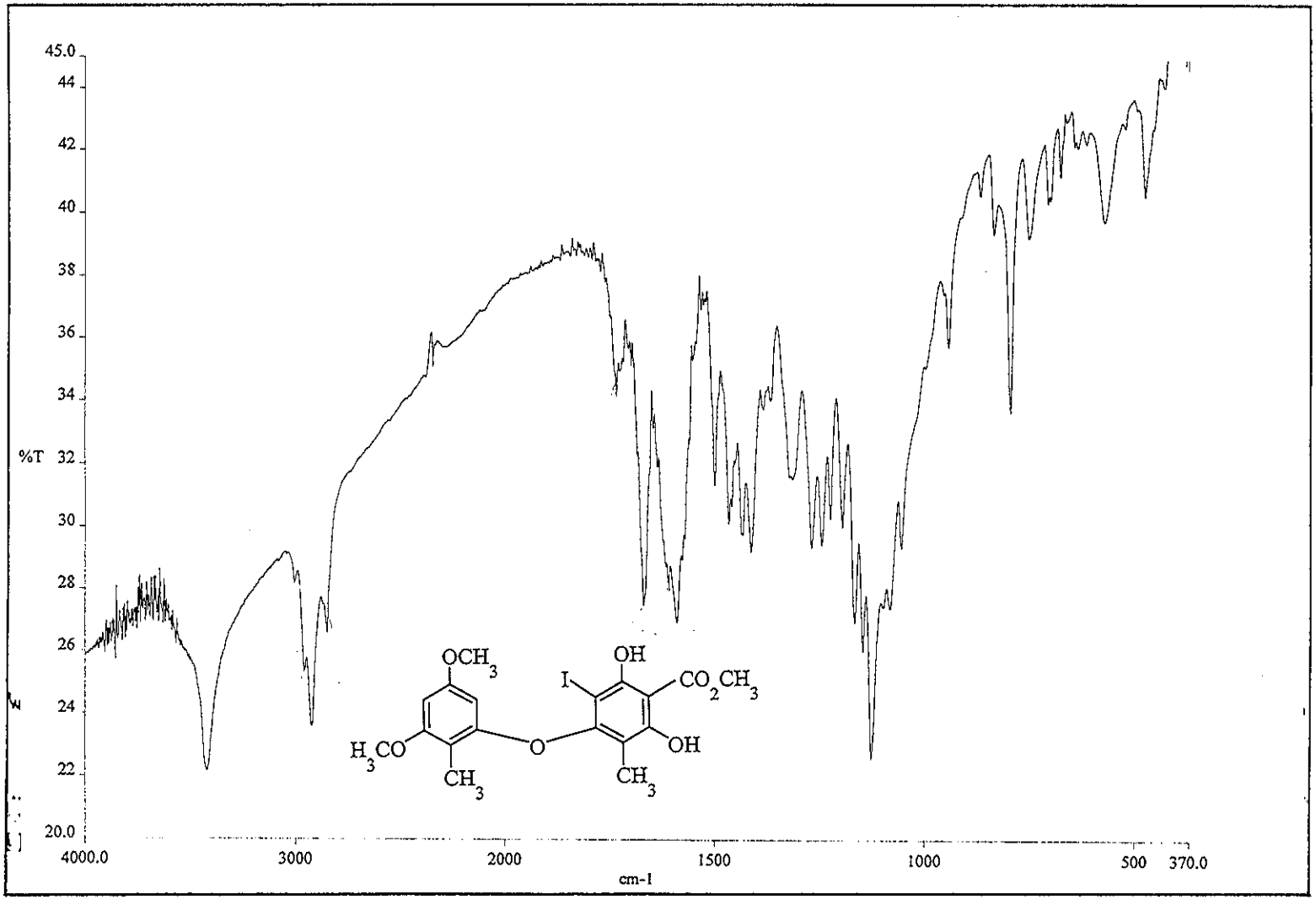


Figure 61. FTIR spectrum of methyl 2,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy)-5-methylbenzoate (129)

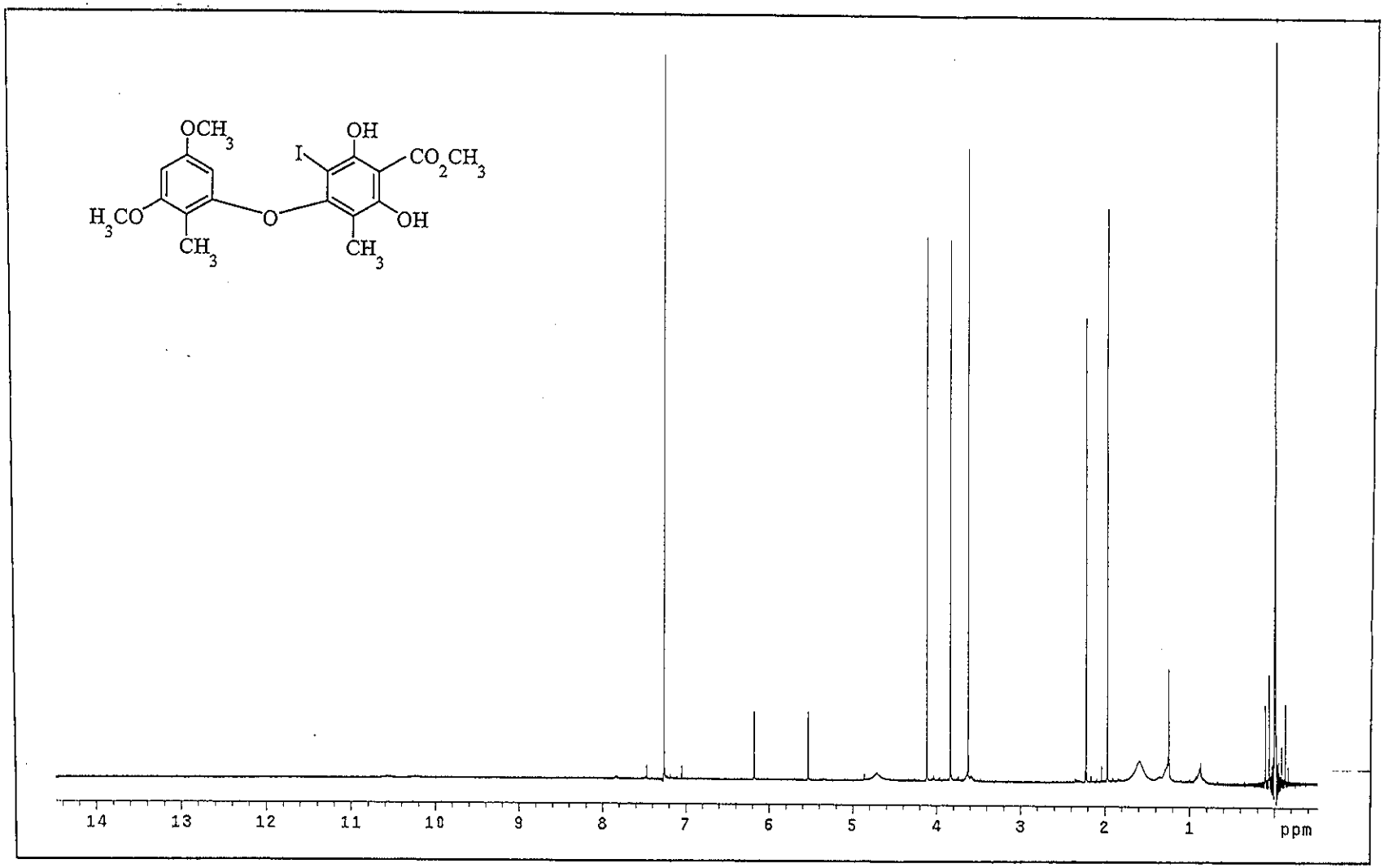


Figure 62. ^{1}H NMR spectrum of methyl 2,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy-5-methylbenzoate (129)

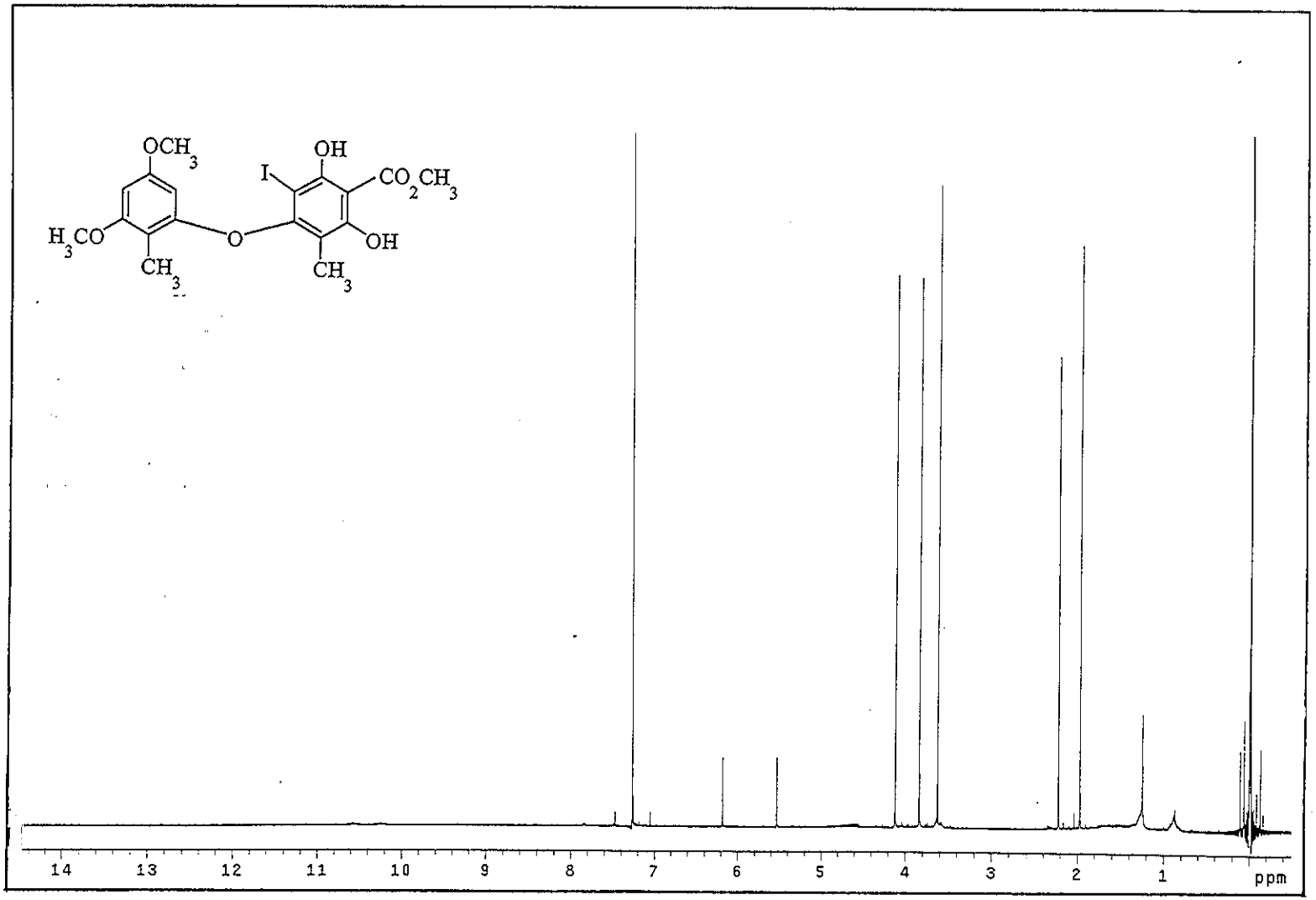


Figure 63. ^{1}H NMR spectrum of methyl 2,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy)-5-methylbenzoate (129) (D_2O)

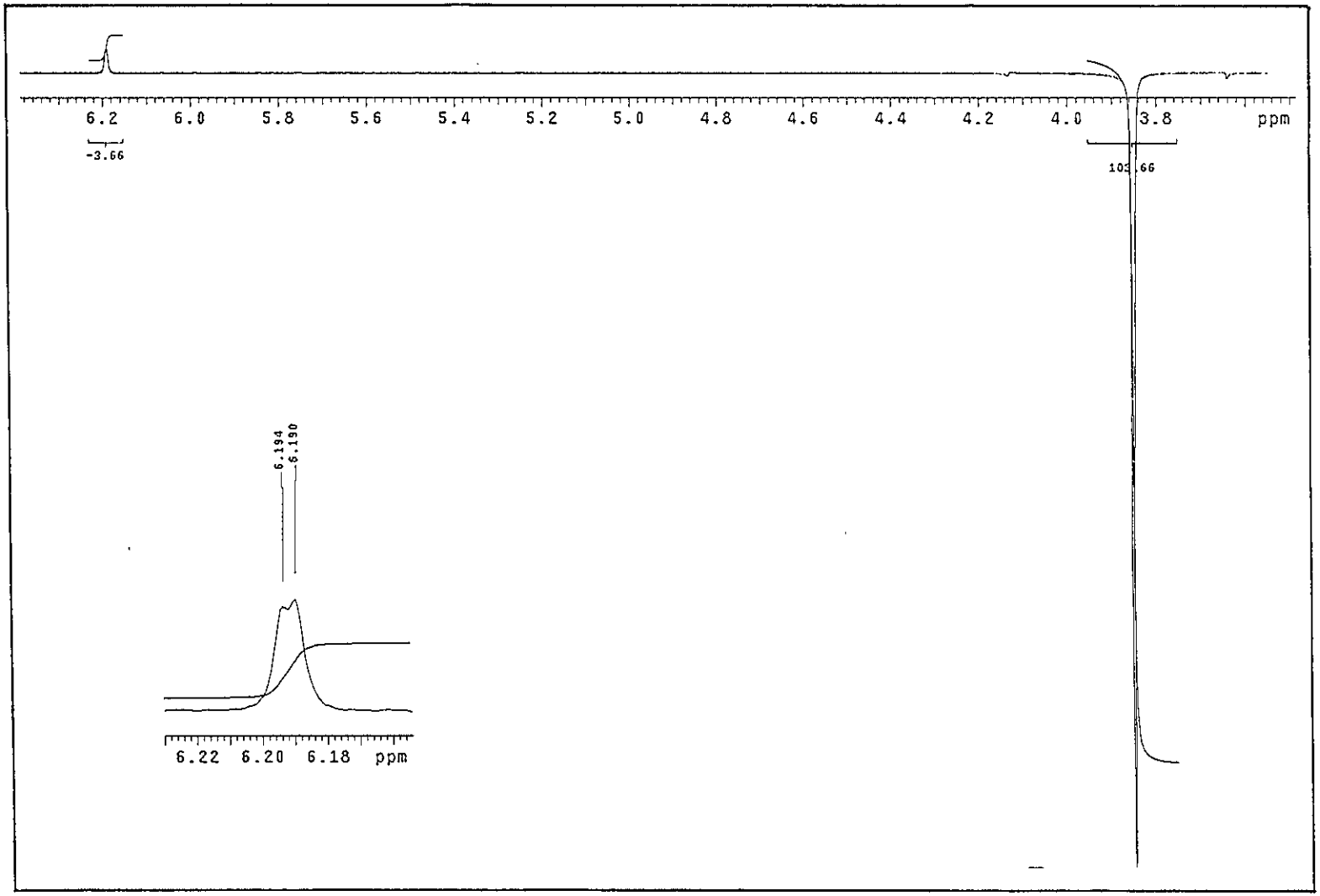


Figure 64. NOE difference spectrum of methyl 2,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy)-5-methylbenzoate (129) irradiated at 3.85 ppm

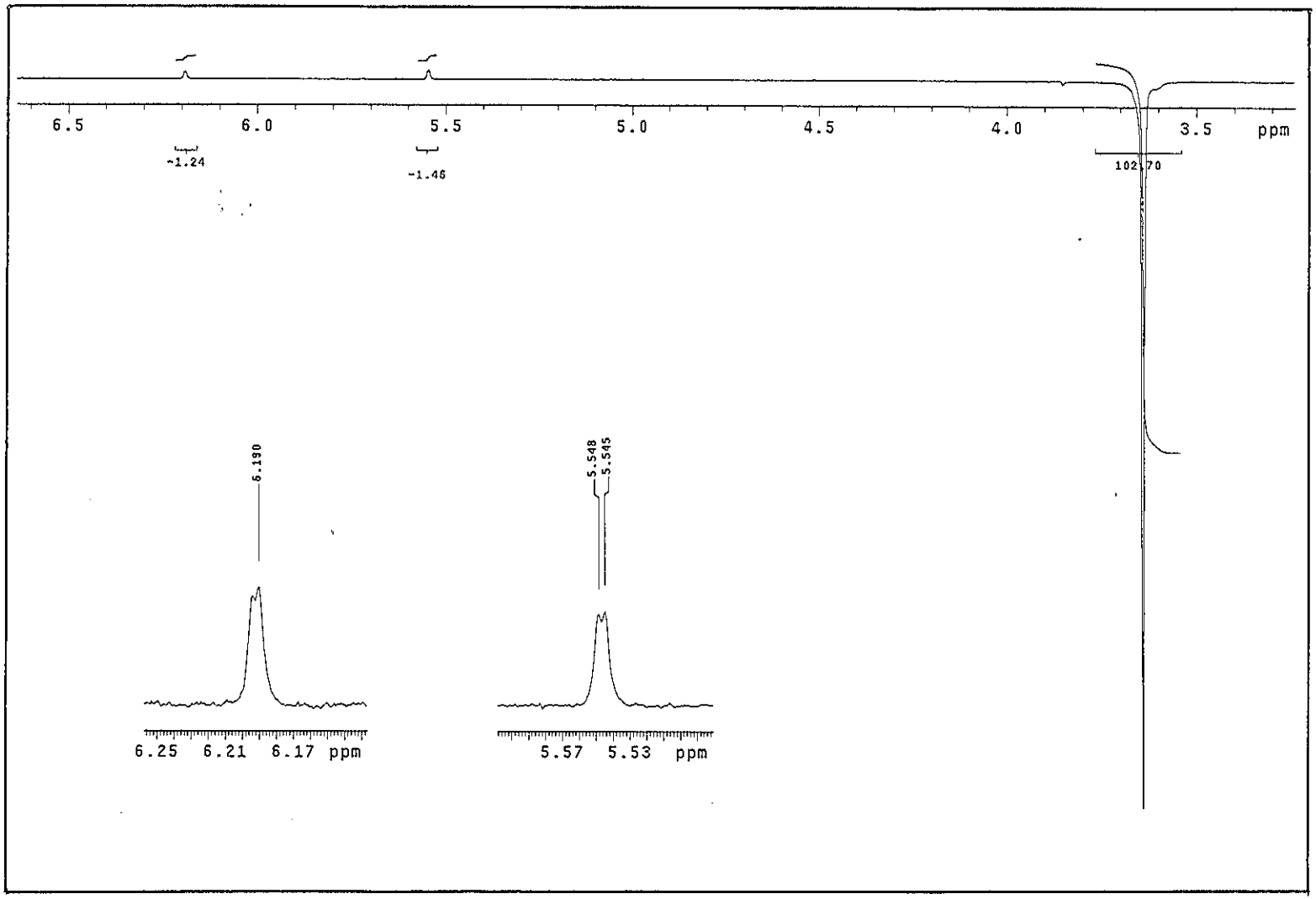


Figure 65. NOE difference spectrum of methyl 2,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy)-5-methylbenzoate (129) irradiated at 3.62 ppm

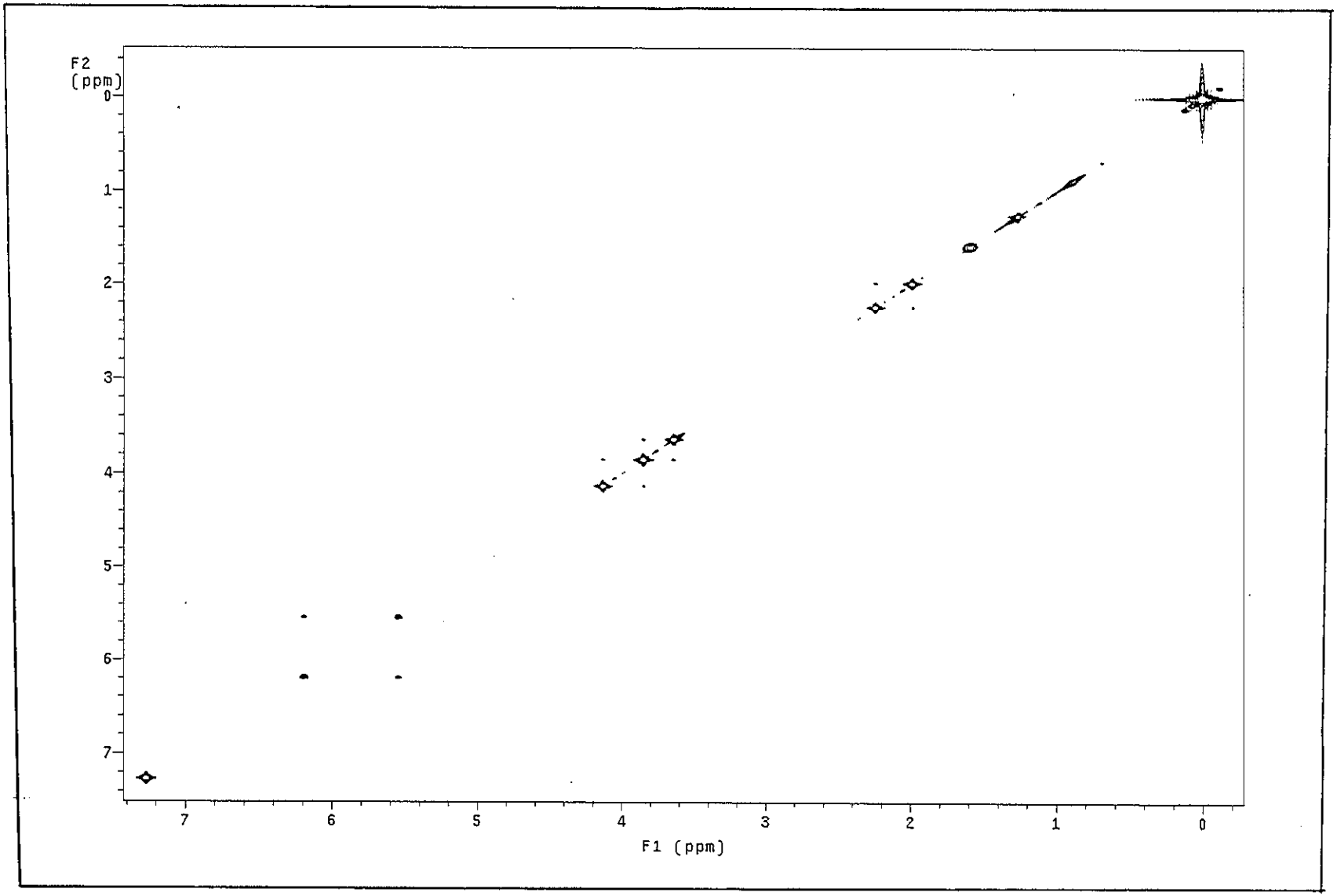


Figure 66. COSY spectrum of methyl 2,6-dihydroxy-3-iodo-4-(3',5'- dimethoxy-2'-methylphenoxy)-5-methylbenzoate (129)

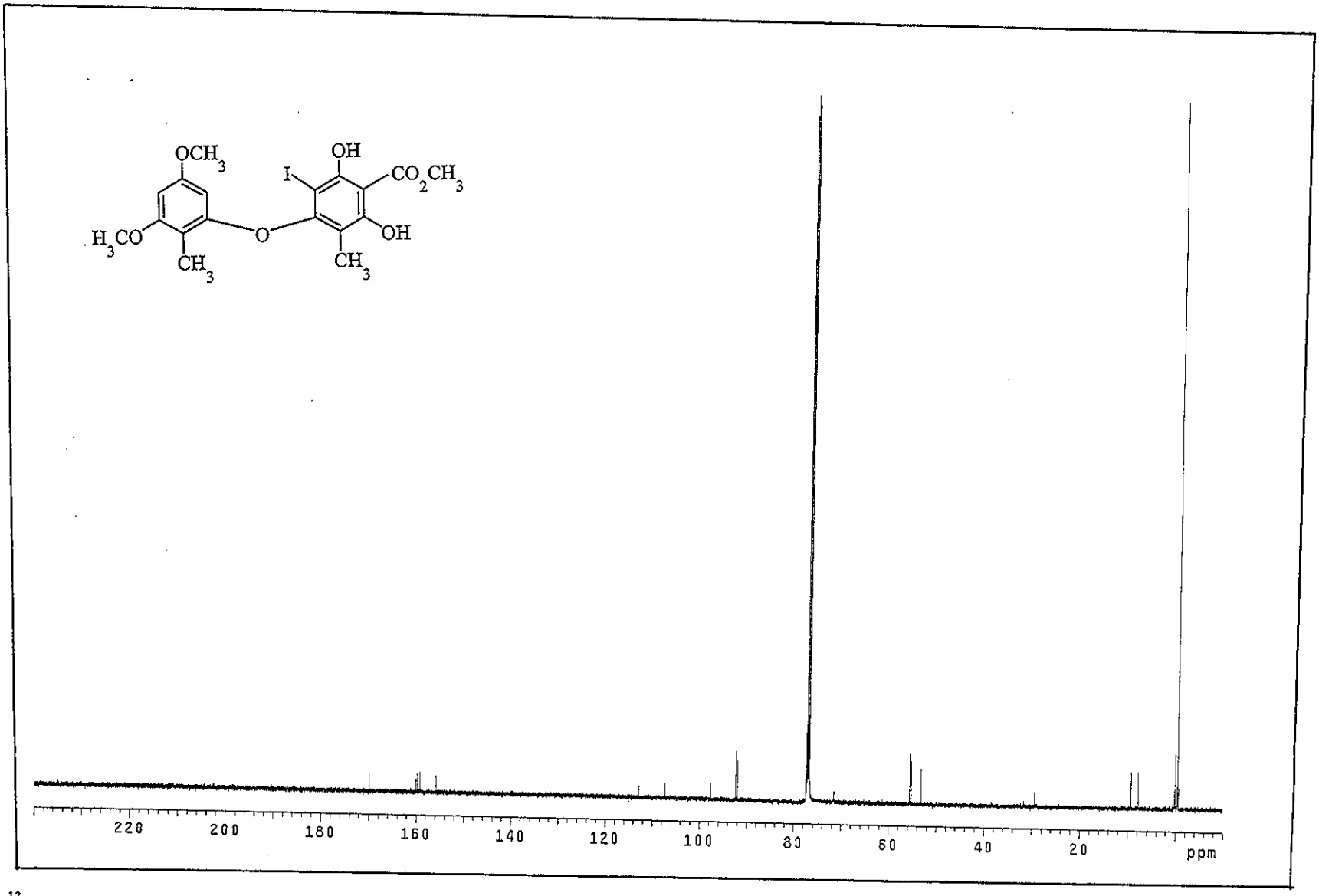


Figure 67. ^{13}C NMR spectrum of methyl 2,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy-5-methylbenzoate (129)

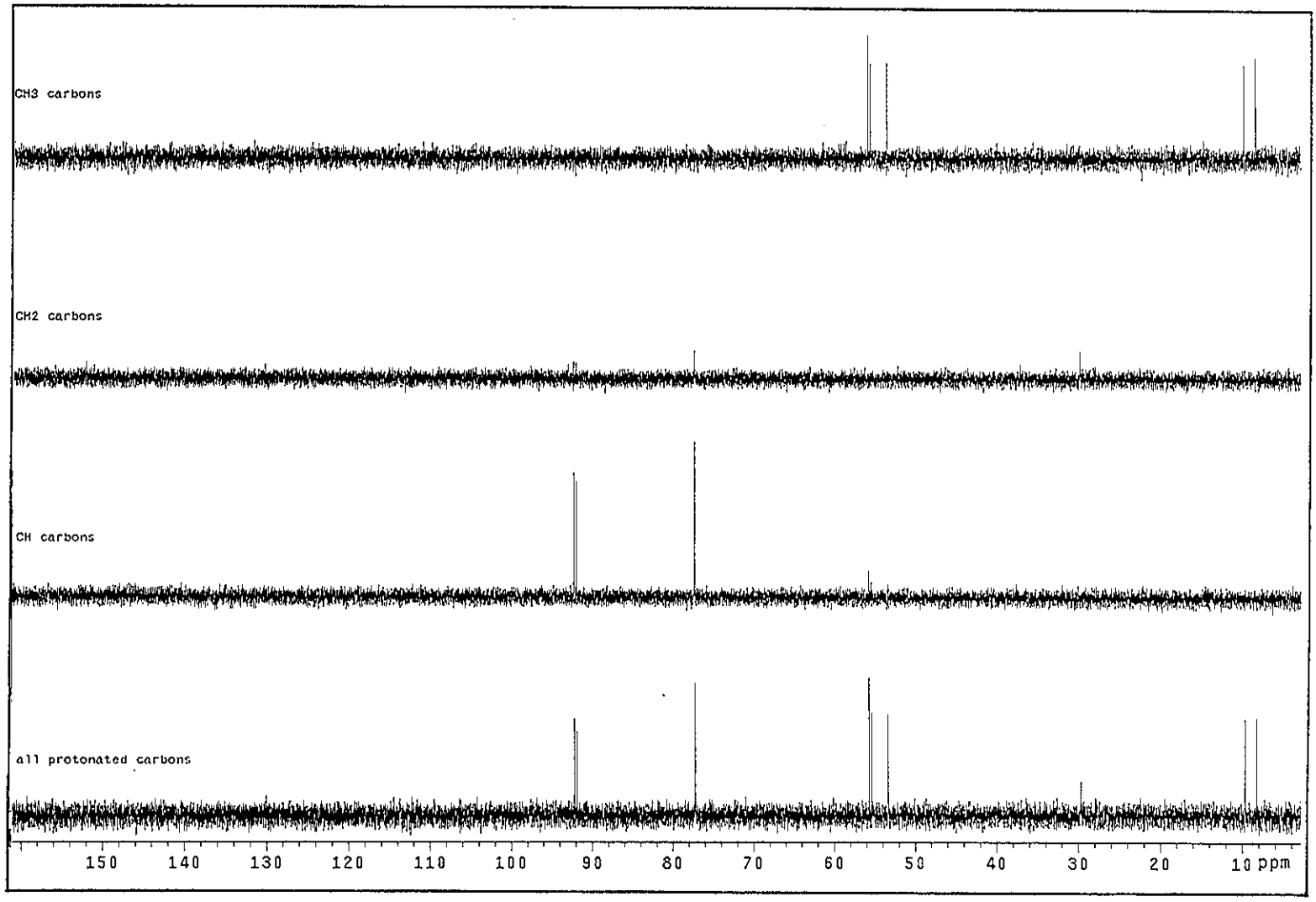


Figure 68. DEPT spectrum of methyl 2,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy)-5-methylbenzoate (129)

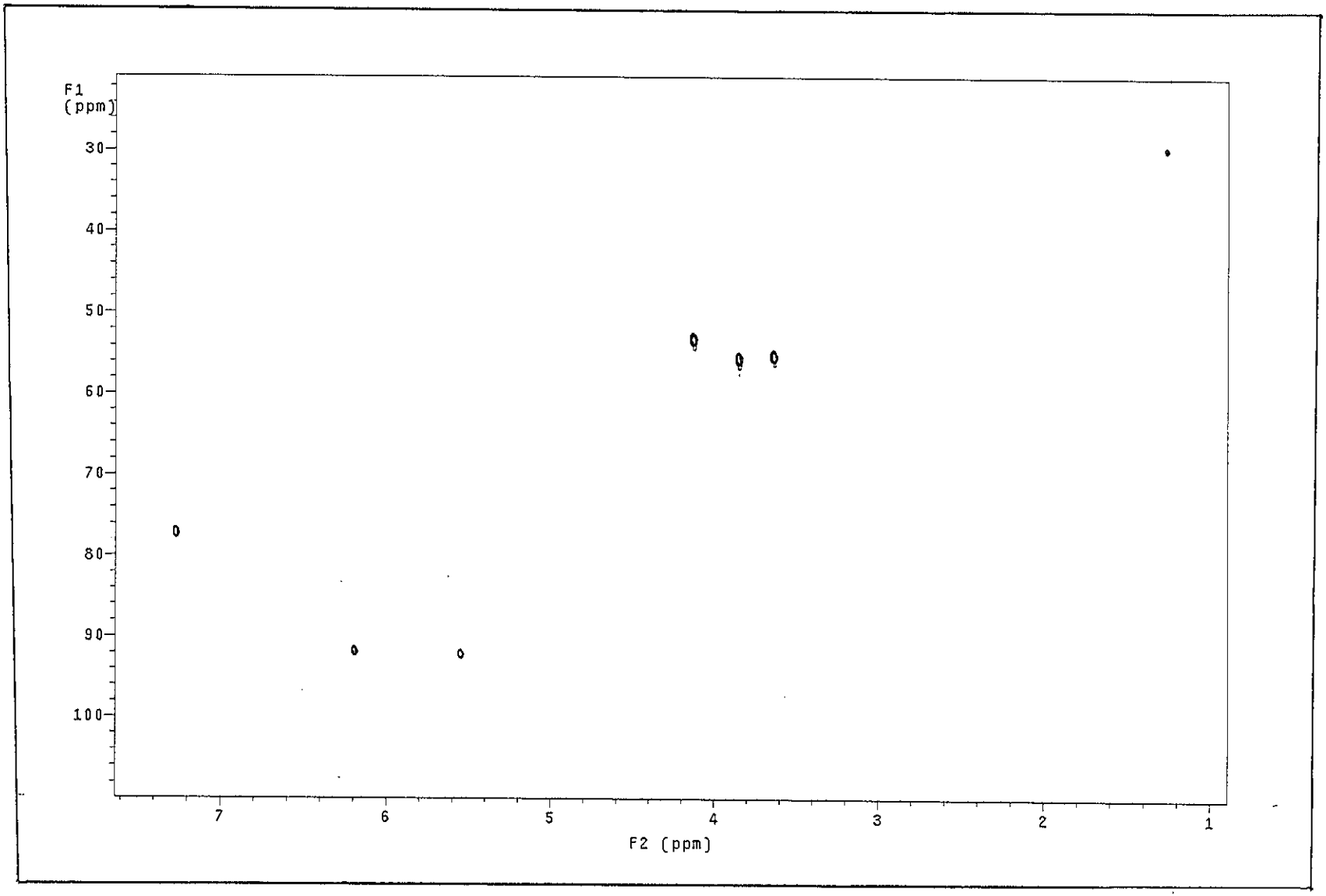


Figure 69. HMQC spectrum of methyl 2,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy)-5-methylbenzoate (129)

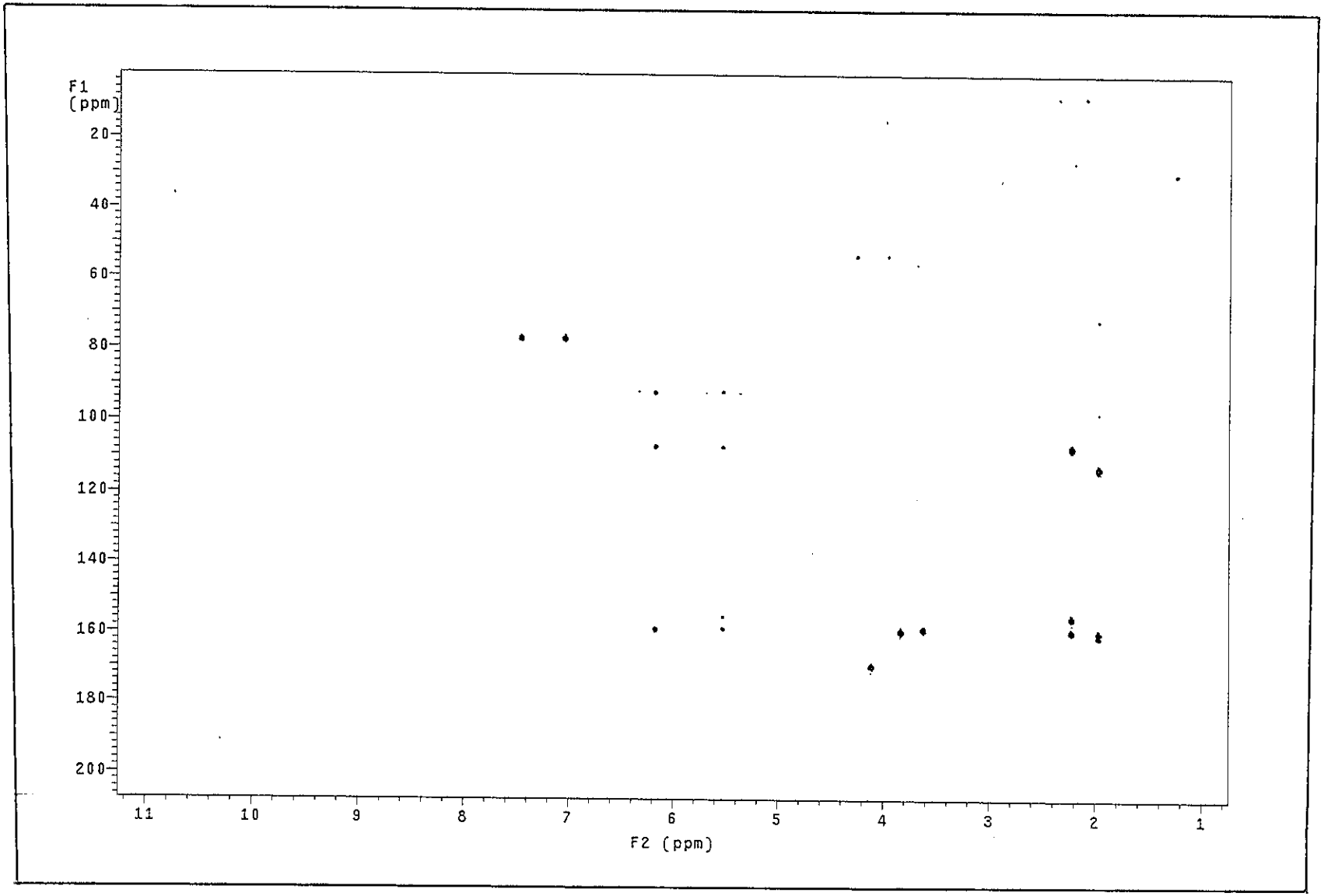


Figure 70. HMBC spectrum of methyl 2,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy)-5-methylbenzoate (129)

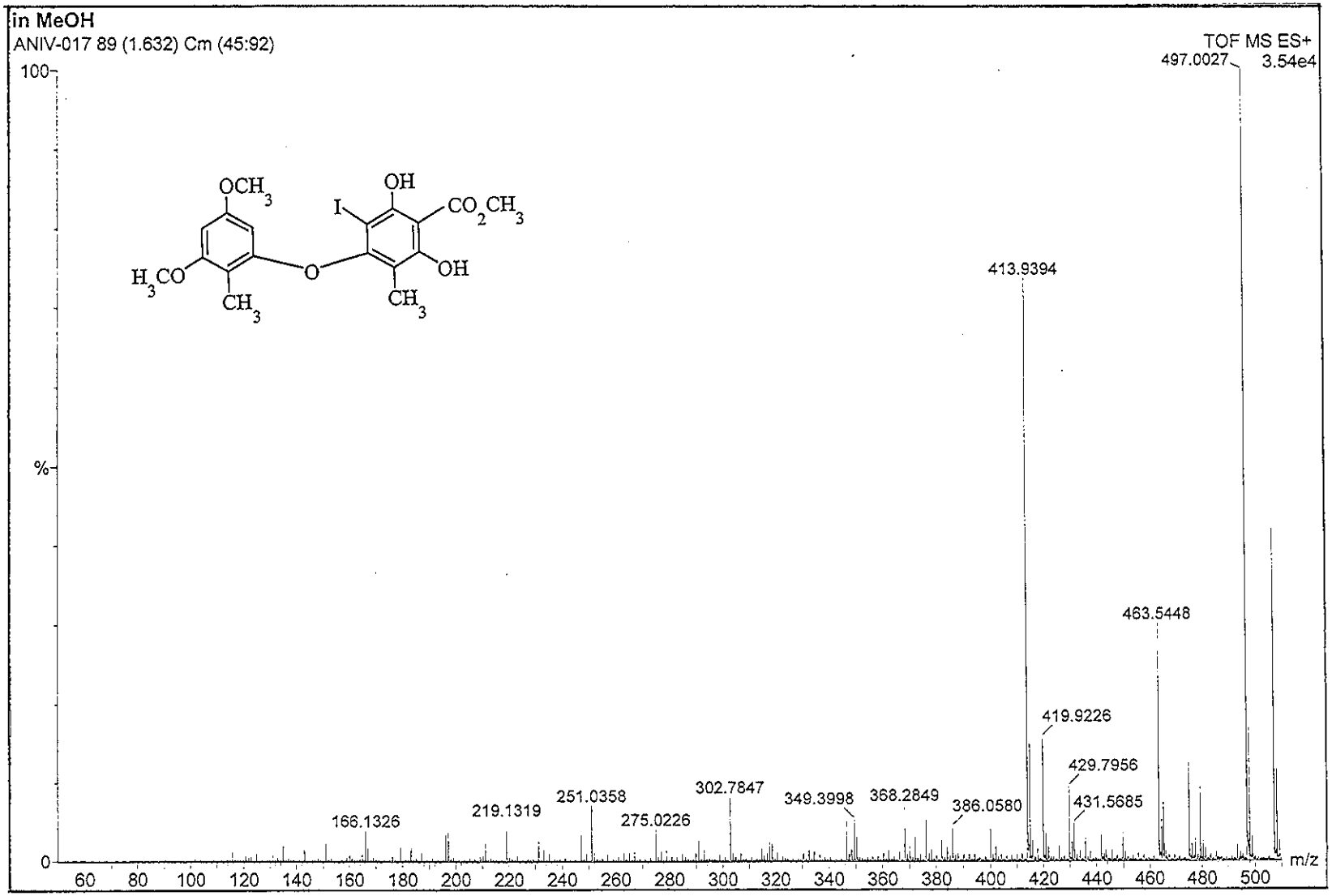


Figure 71. Mass spectrum (ESMS) of methyl 2,6-dihydroxy-3-iodo-4-(3',5'- dimethoxy-2'-methylphenoxy)-5-methylbenzoate (129)

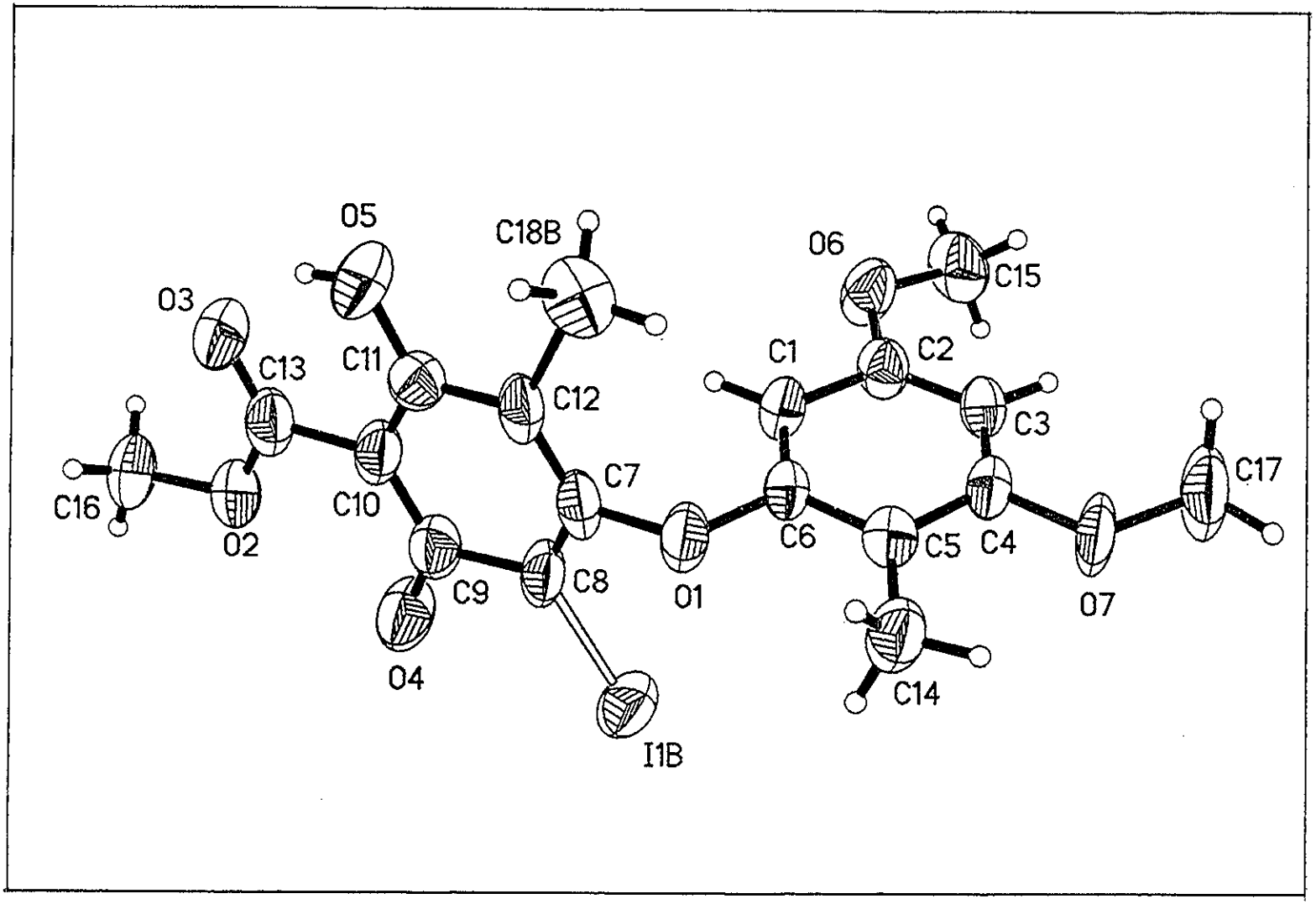


Figure 72. ORTEP drawing of methyl 2,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy)-5-methylbenzoate (129)

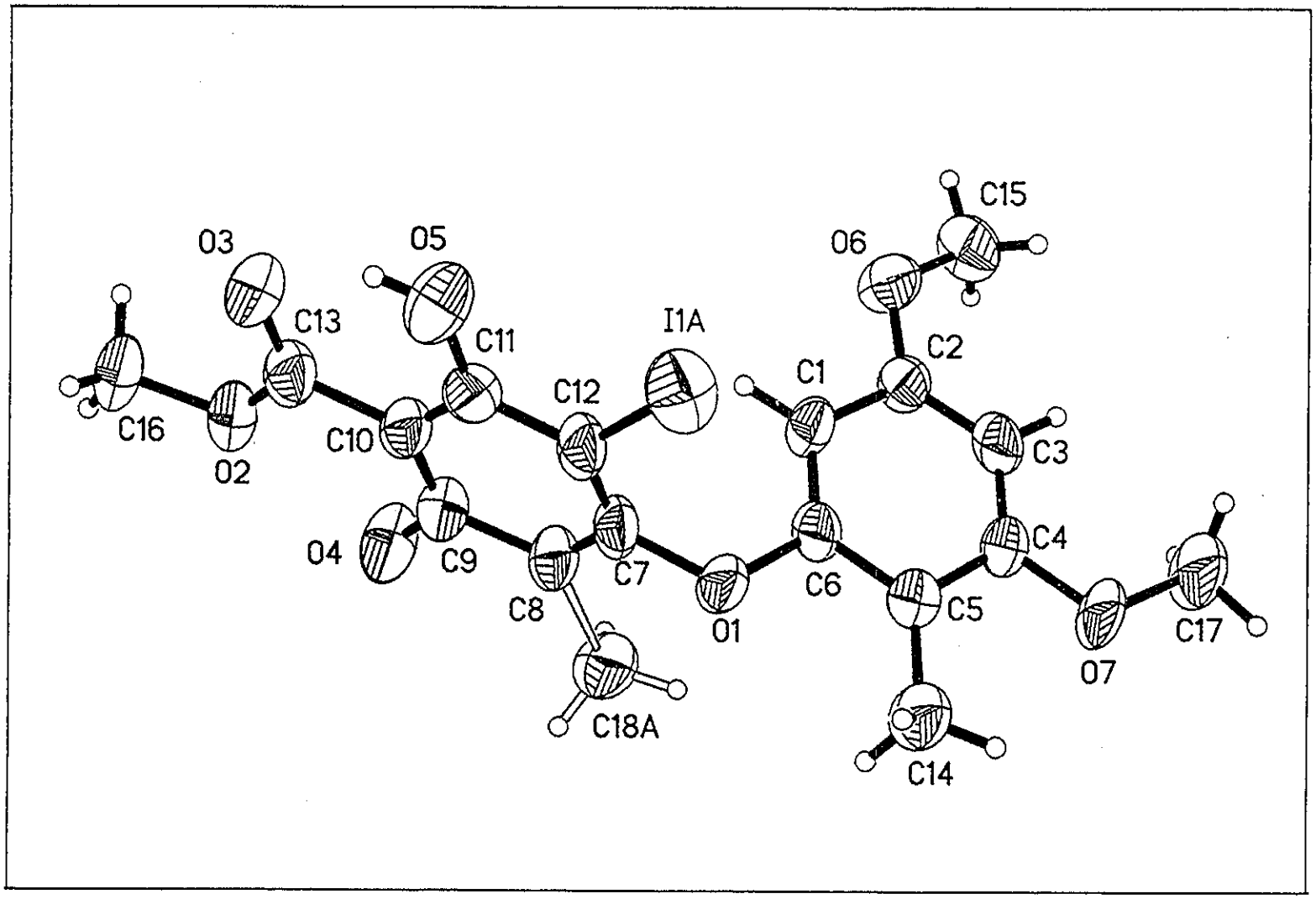


Figure 73. ORTEP drawing of methyl 2,6-dihydroxy-3-iodo-4-(3',5'-dimethoxy-2'-methylphenoxy)-5-methylbenzoate (129)

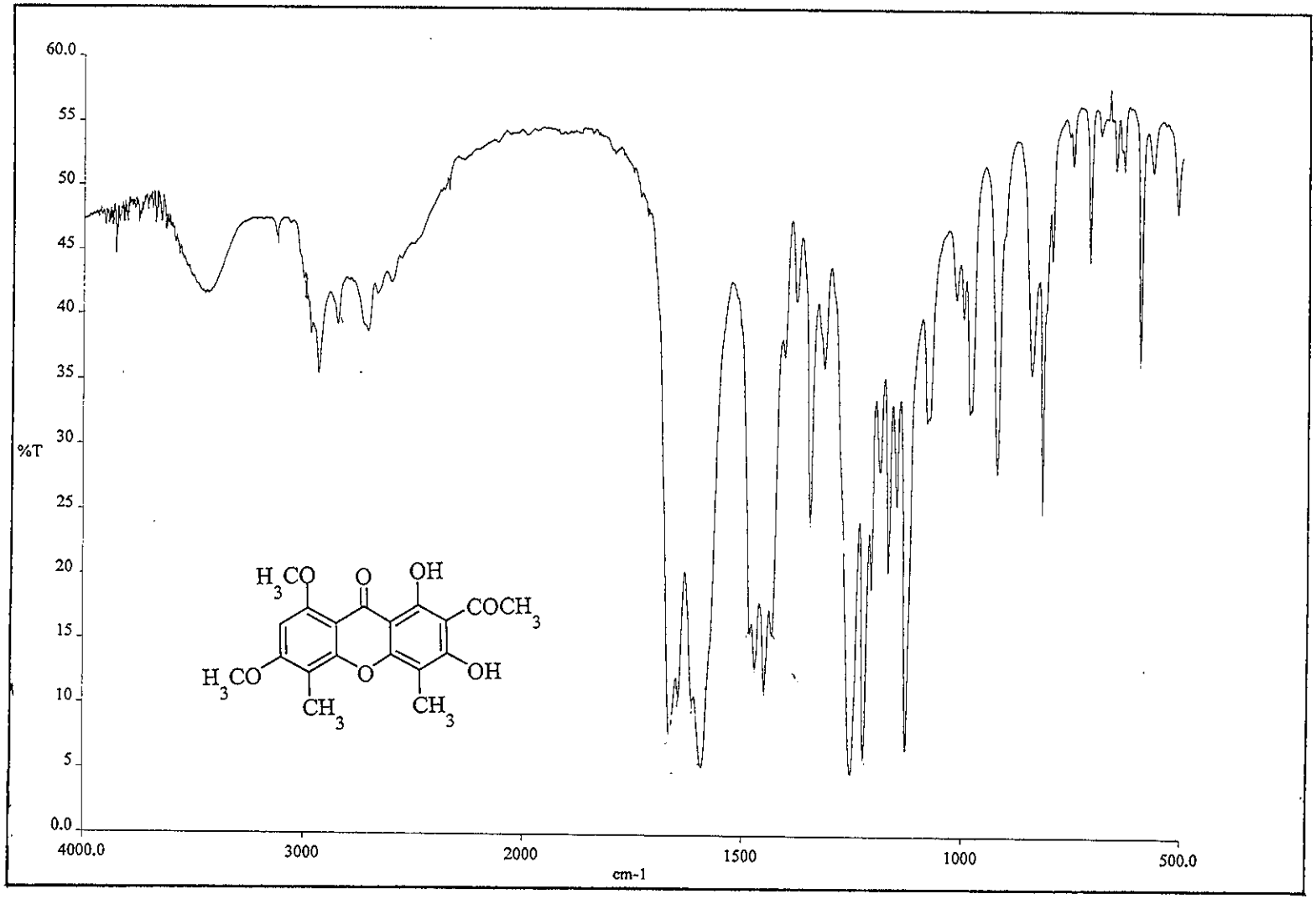


Figure 74. FTIR spectrum of 2-acetyl-1,3-dihydroxy-6,8-dimethoxy-4,5-dimethylxanthone (127)

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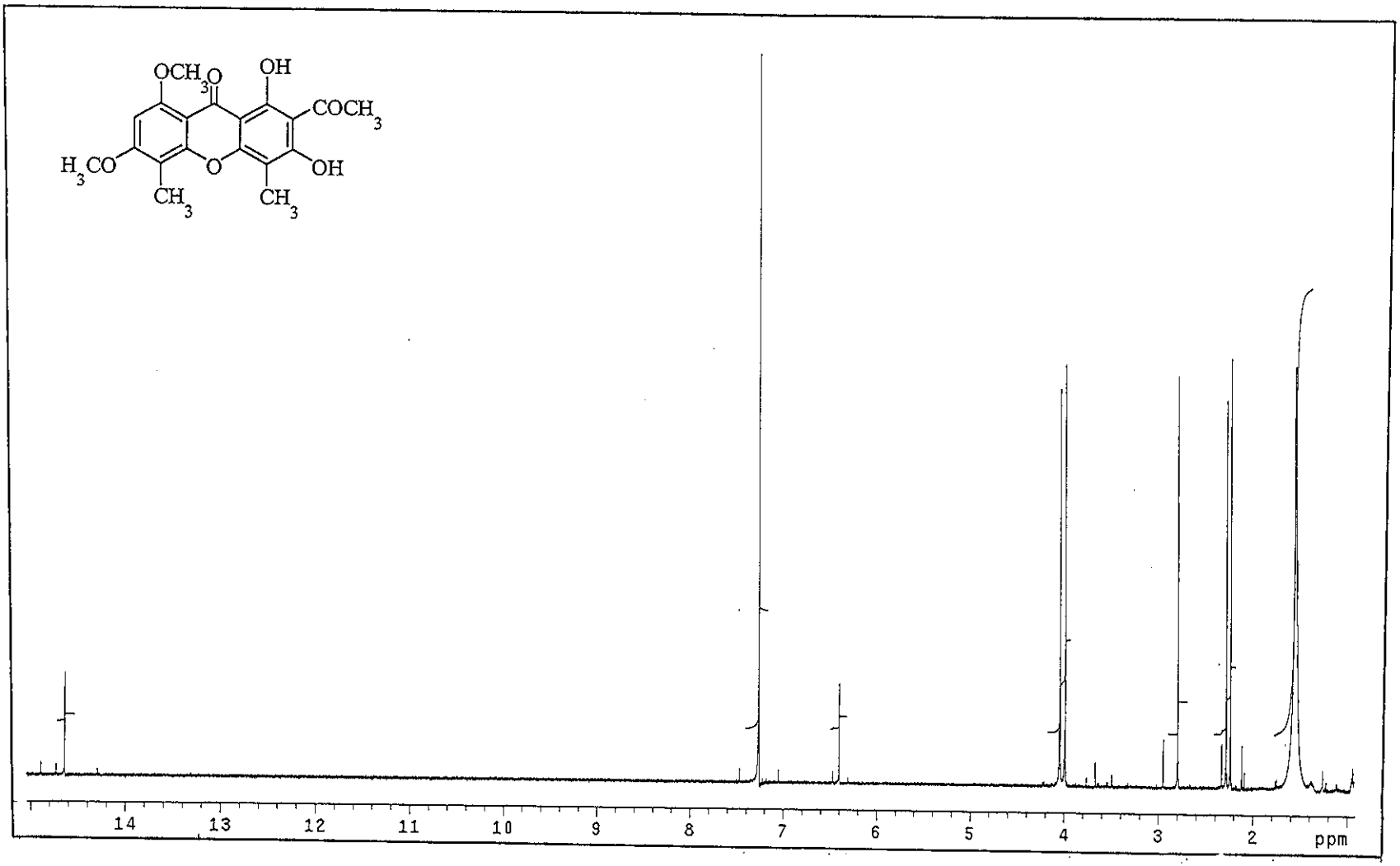

Figure 75 . ^{1}H NMR spectrum of 2-acetyl-1,3-dihydroxy-6,8-dimethoxy-4,5-dimethylxanthone (127)

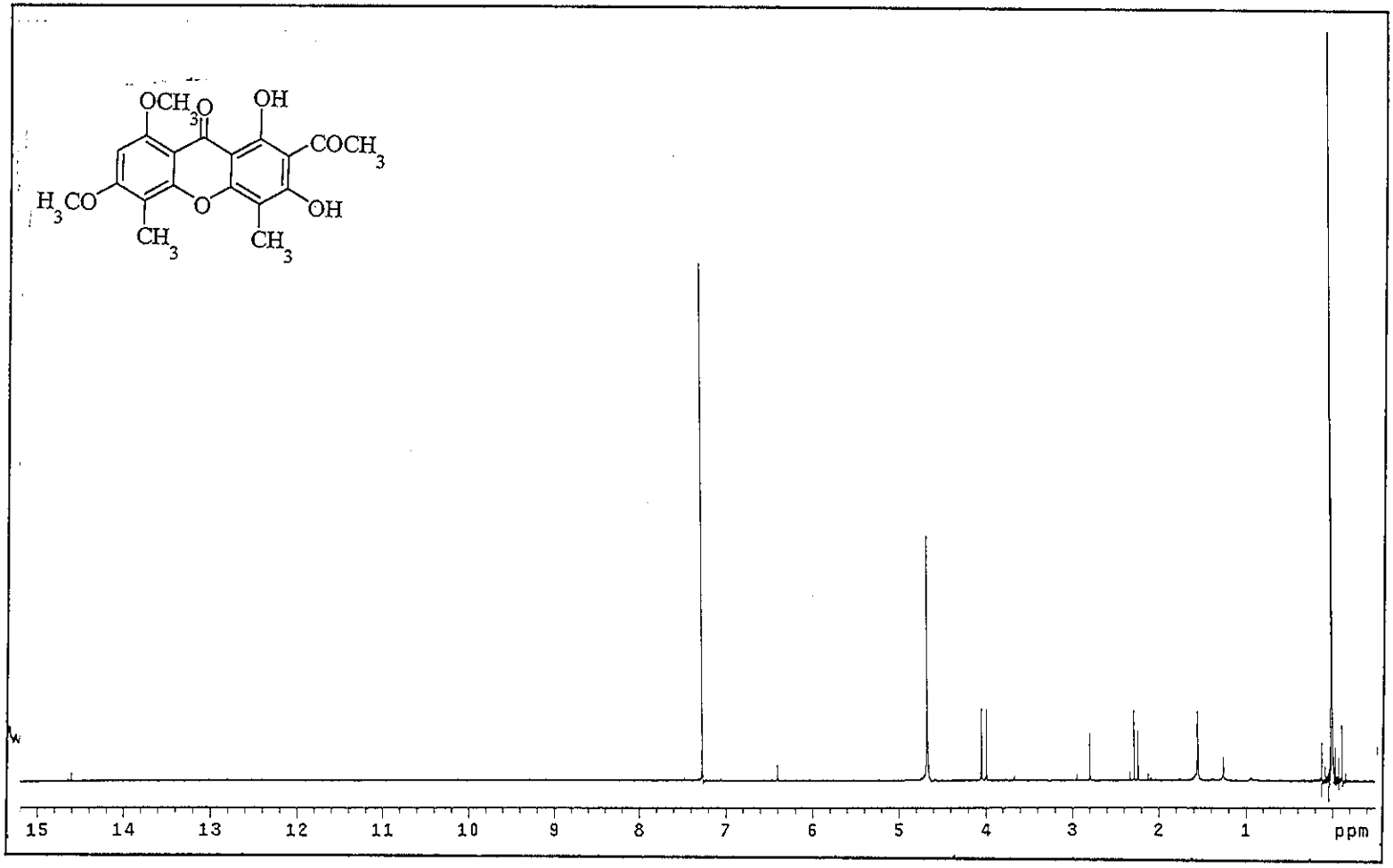

Figure 76. ^{1}H NMR spectrum of 2-acetyl-1,3-dihydroxy-6,8-dimethoxy-4,5-dimethylxanthone (127) (D_2O)

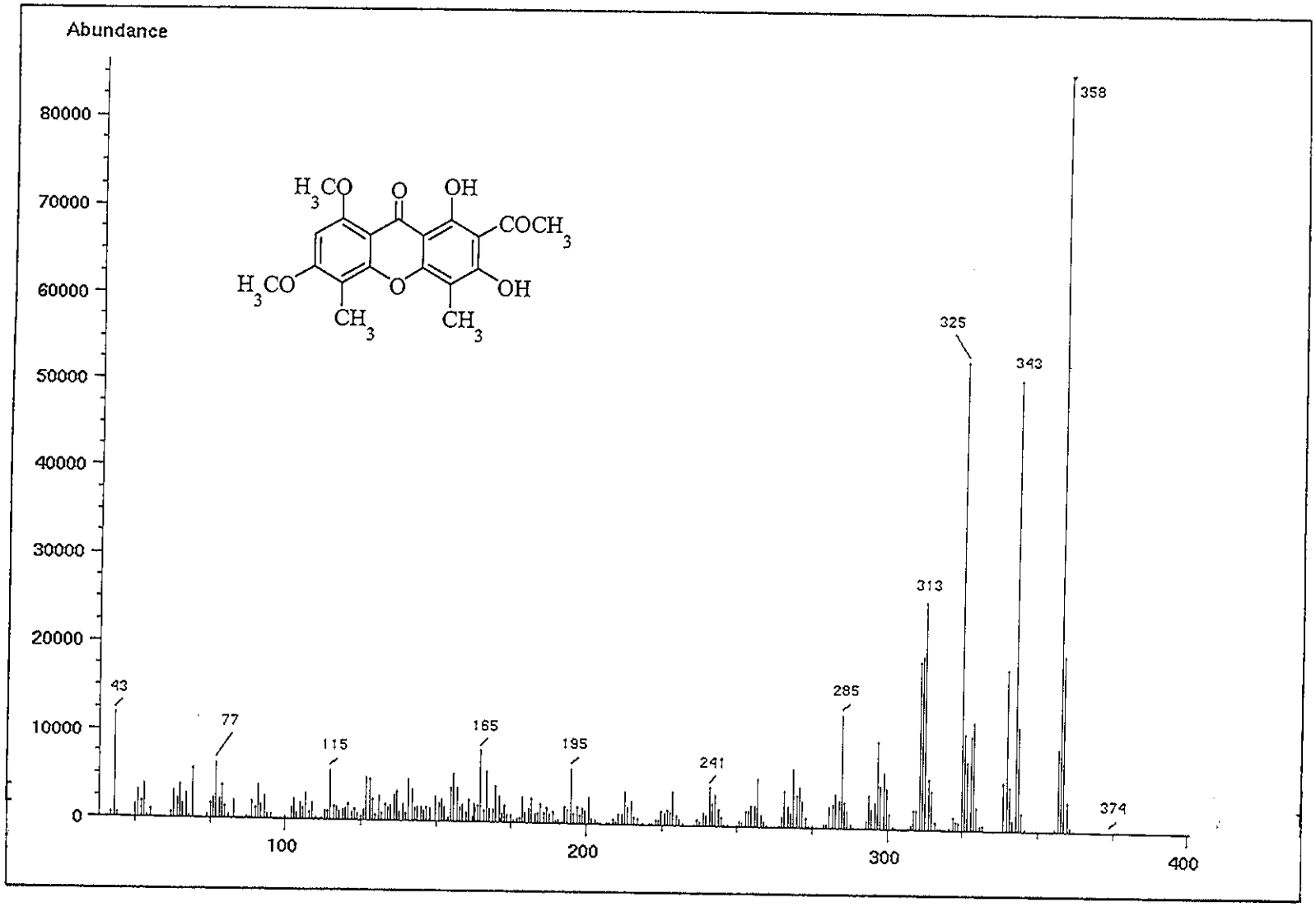

Figure 77. Mass spectrum (EIMS) of 2-acetyl-1,3-dihydroxy-6,8-dimethoxy-4,5-dimethylxanthone (127)

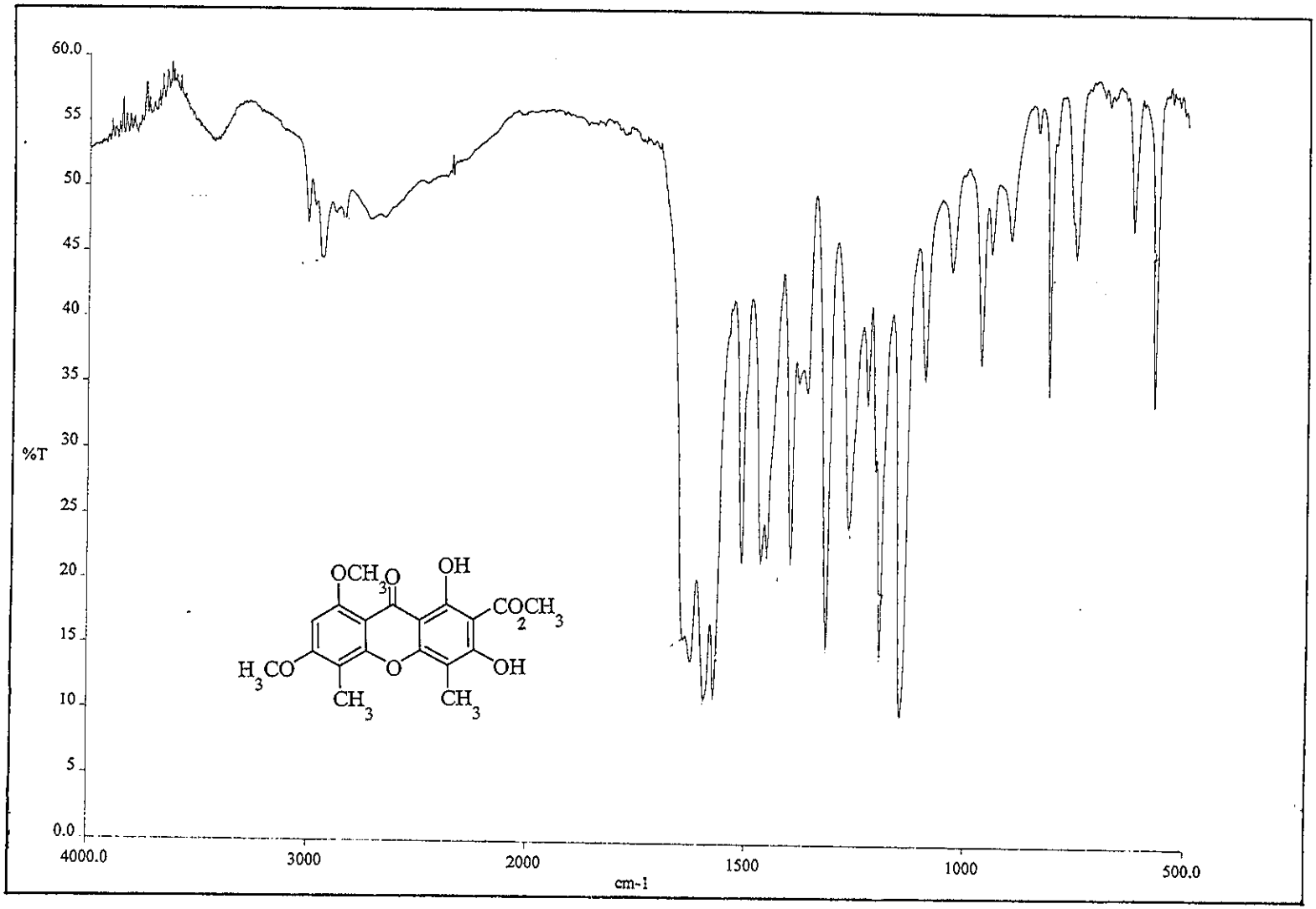

Figure 78. FTIR spectrum of 1,3-dihydroxy-2-methoxycarbonyl-6,8-dimethoxy-4,5-methylxanthone (131)

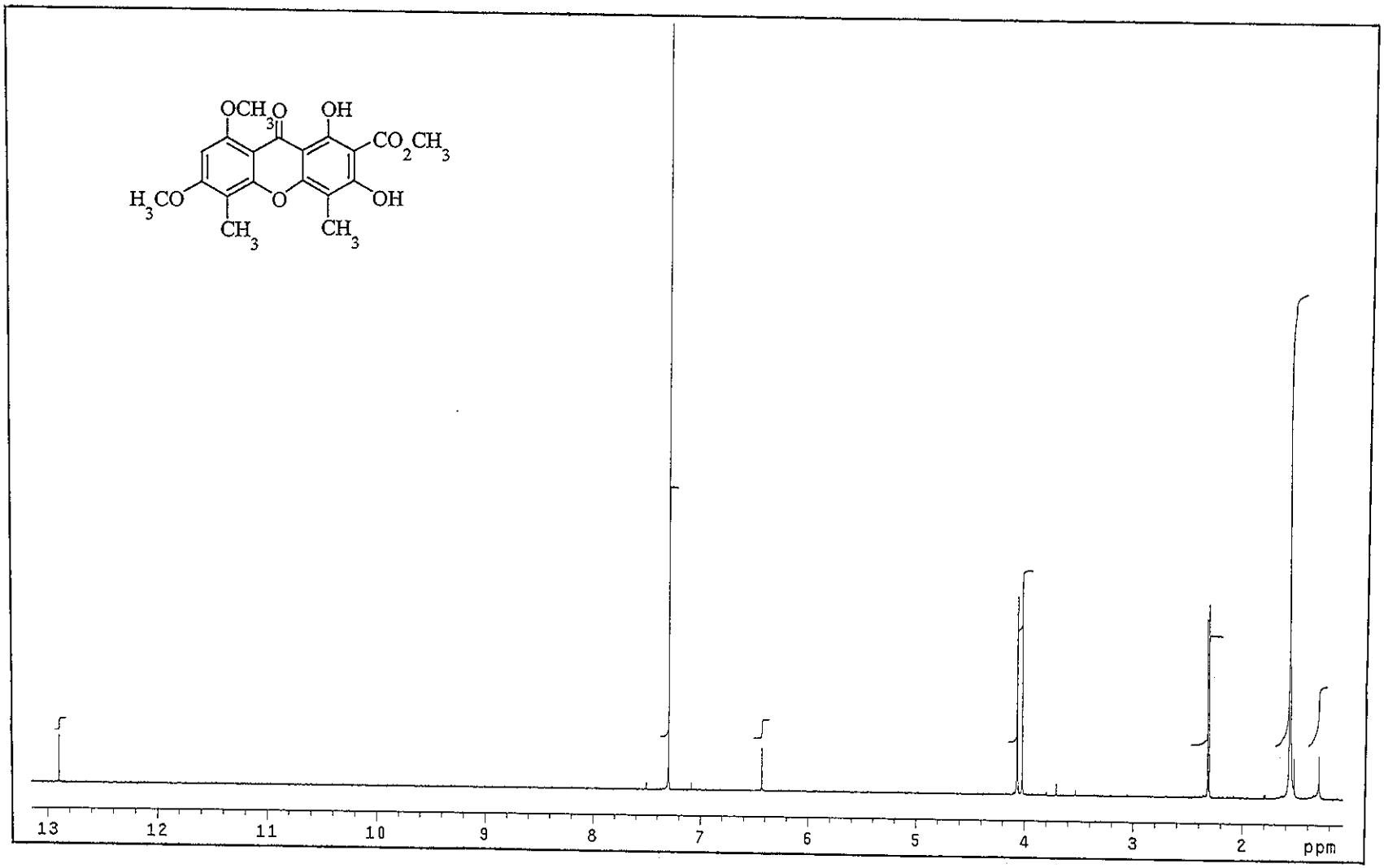

Figure 79. ^{1}H NMR spectrum of 1,3-dihydroxy-2-methoxycarbonyl-6,8-dimethoxy-4,5-methylxanthone (131)

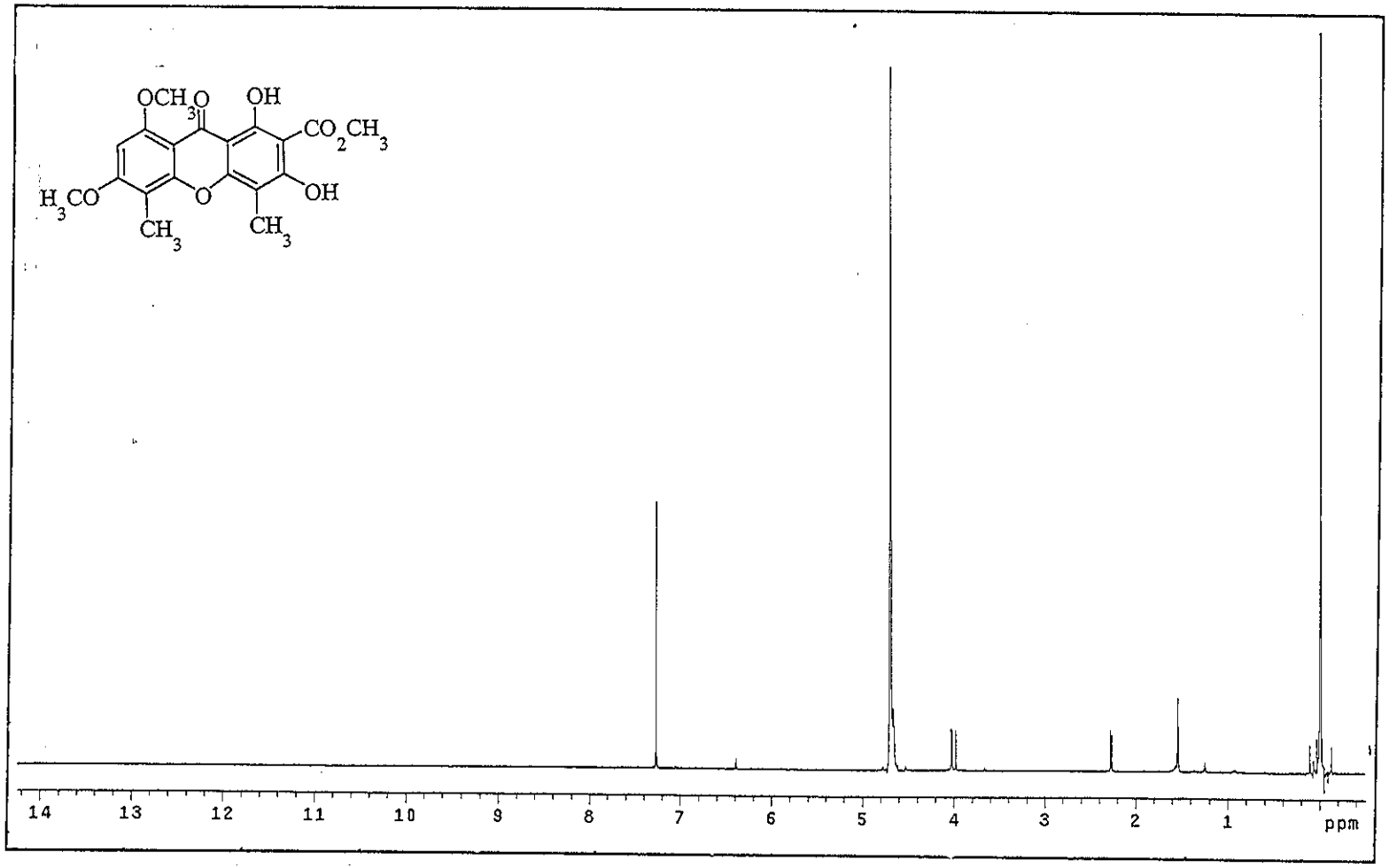

Figure 80. ^{1}H NMR spectrum of 1,3-dihydroxy-2-methoxycarbonyl-6,8-dimethoxy-4,5-methylxanthone (131) (D_2O)

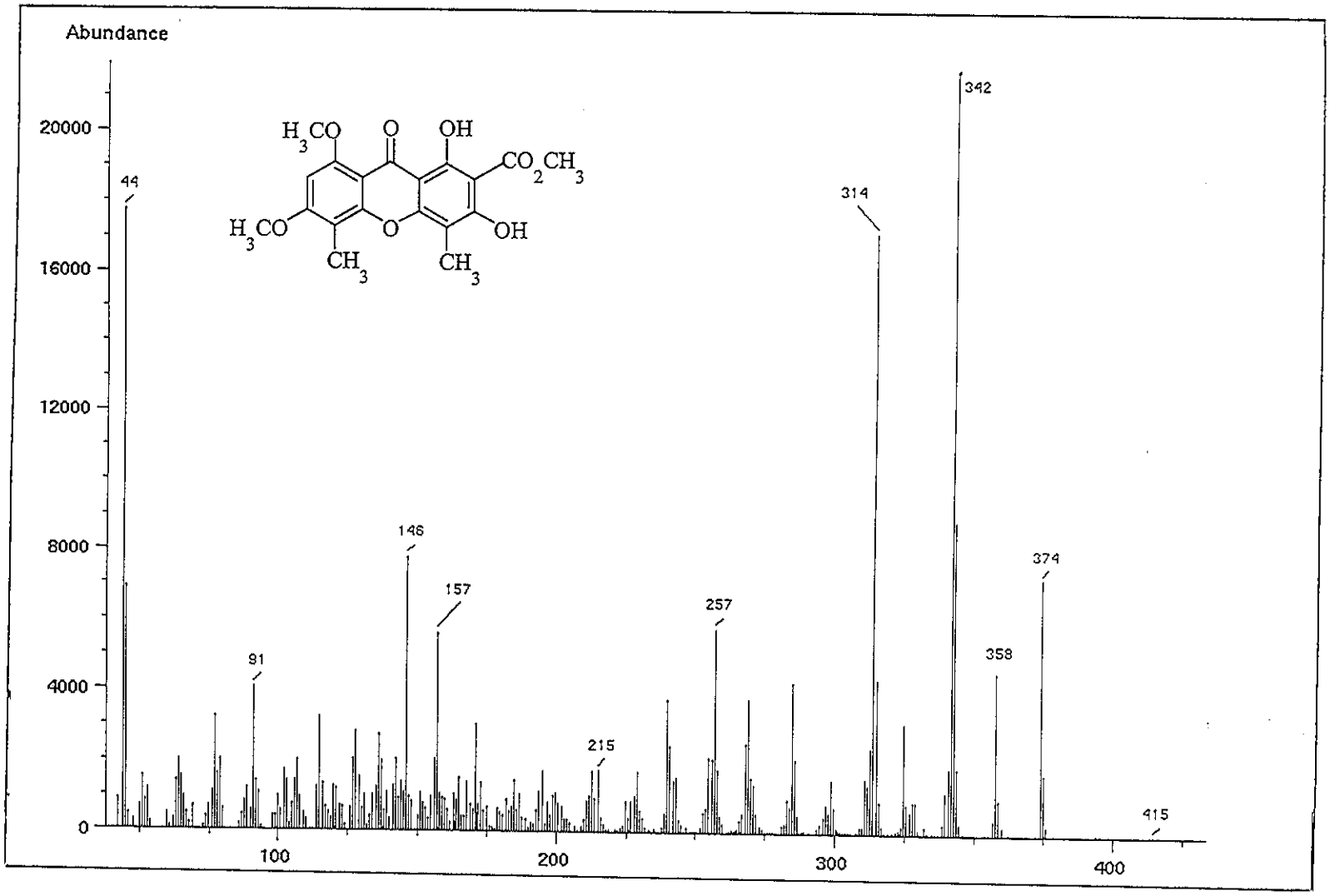

Figure 81. Mass spectrum (EIMS) of 1,3-dihydroxy-2-methoxycarbonyl-6,8-dimethoxy-4,5-methylxanthone (131)

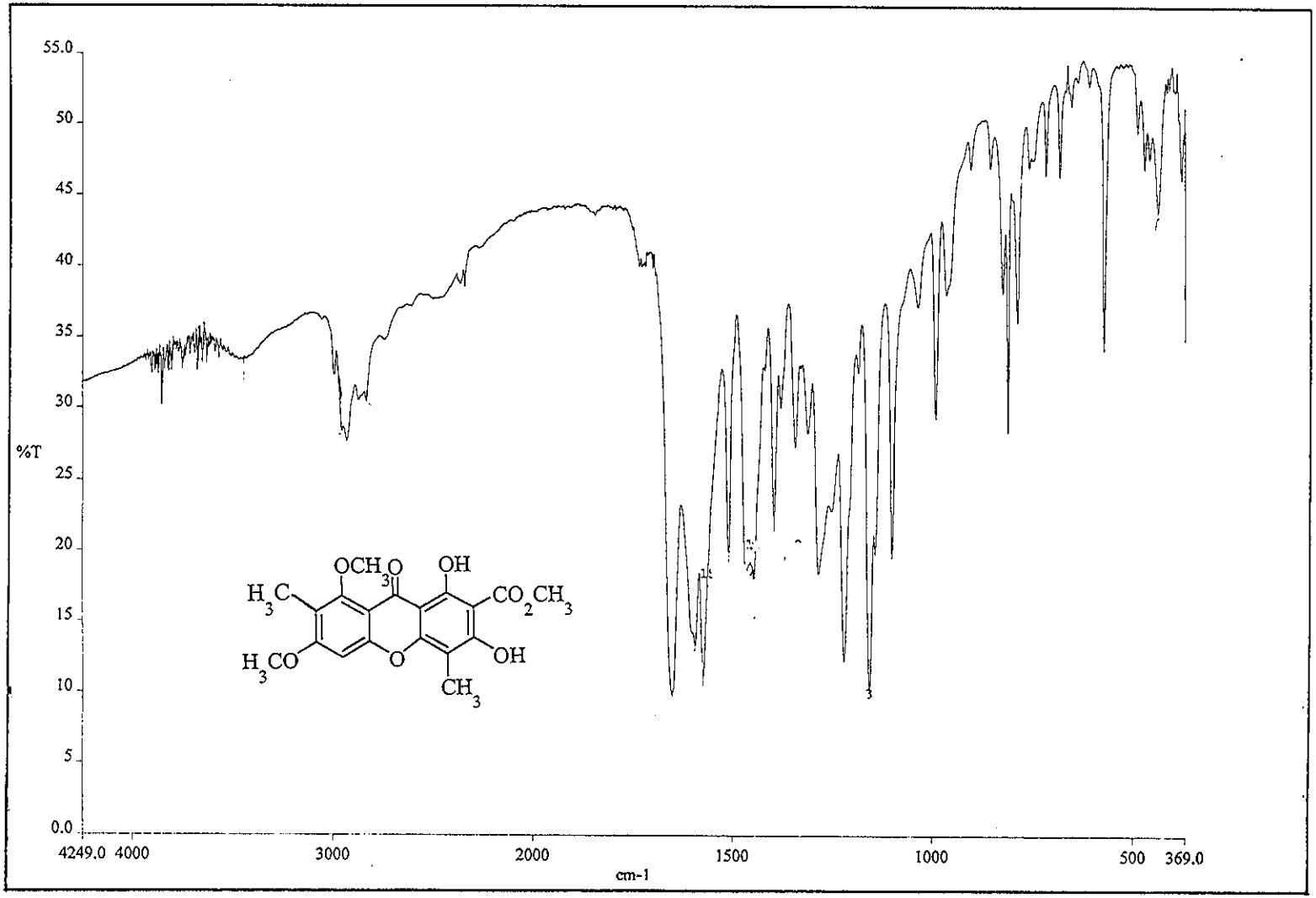

Figure 82. FTIR spectrum of 1,3-dihydroxy-2-methoxycarbonyl-6,8-dimethoxy-4,7-dimethylxanthone (133)

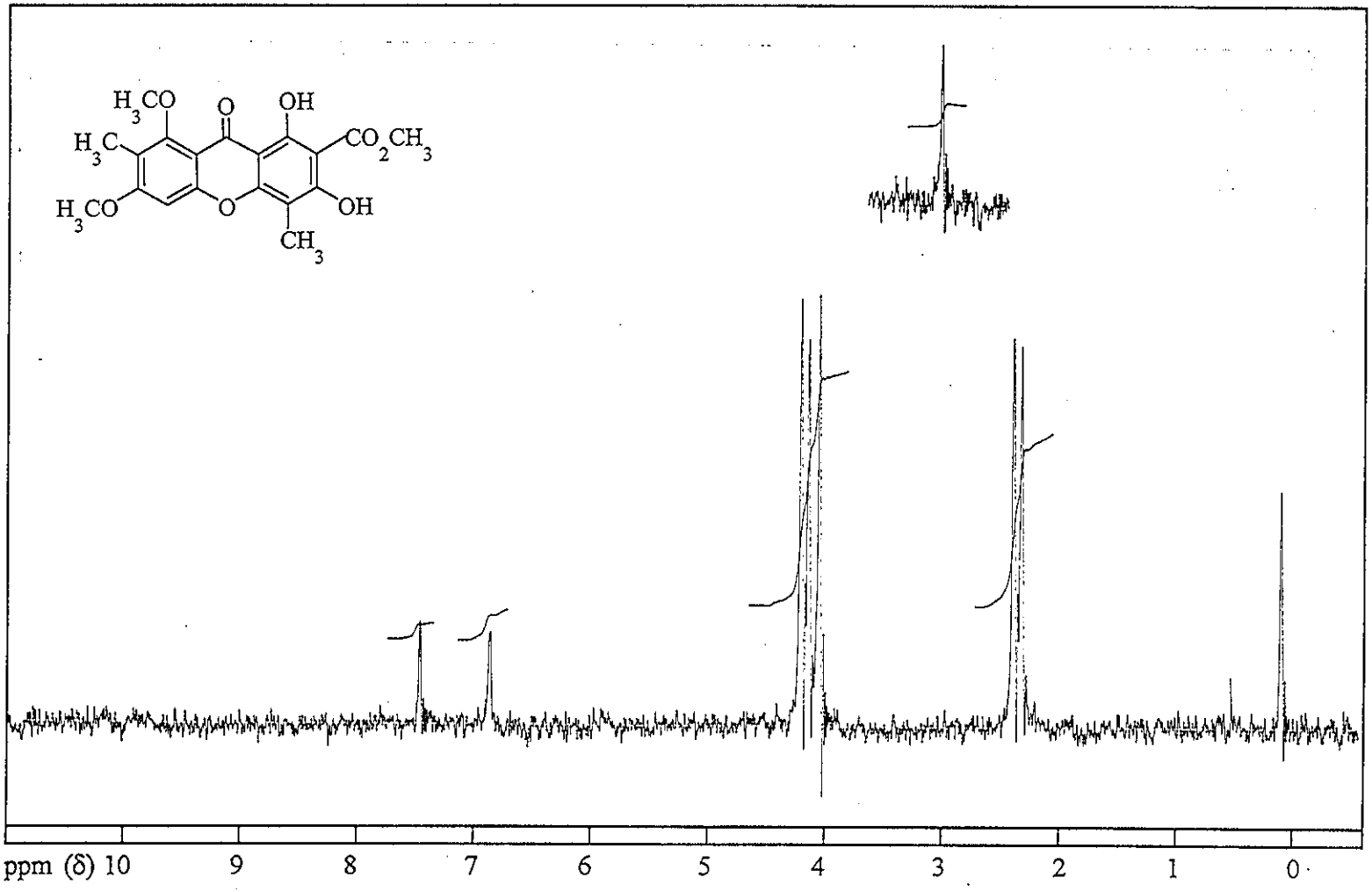

Figure 83. ^{1}H NMR spectrum of 1,3-dihydroxy-2-methoxycarbonyl-6,8-dimethoxy-4,7-dimethylxanthone (133)

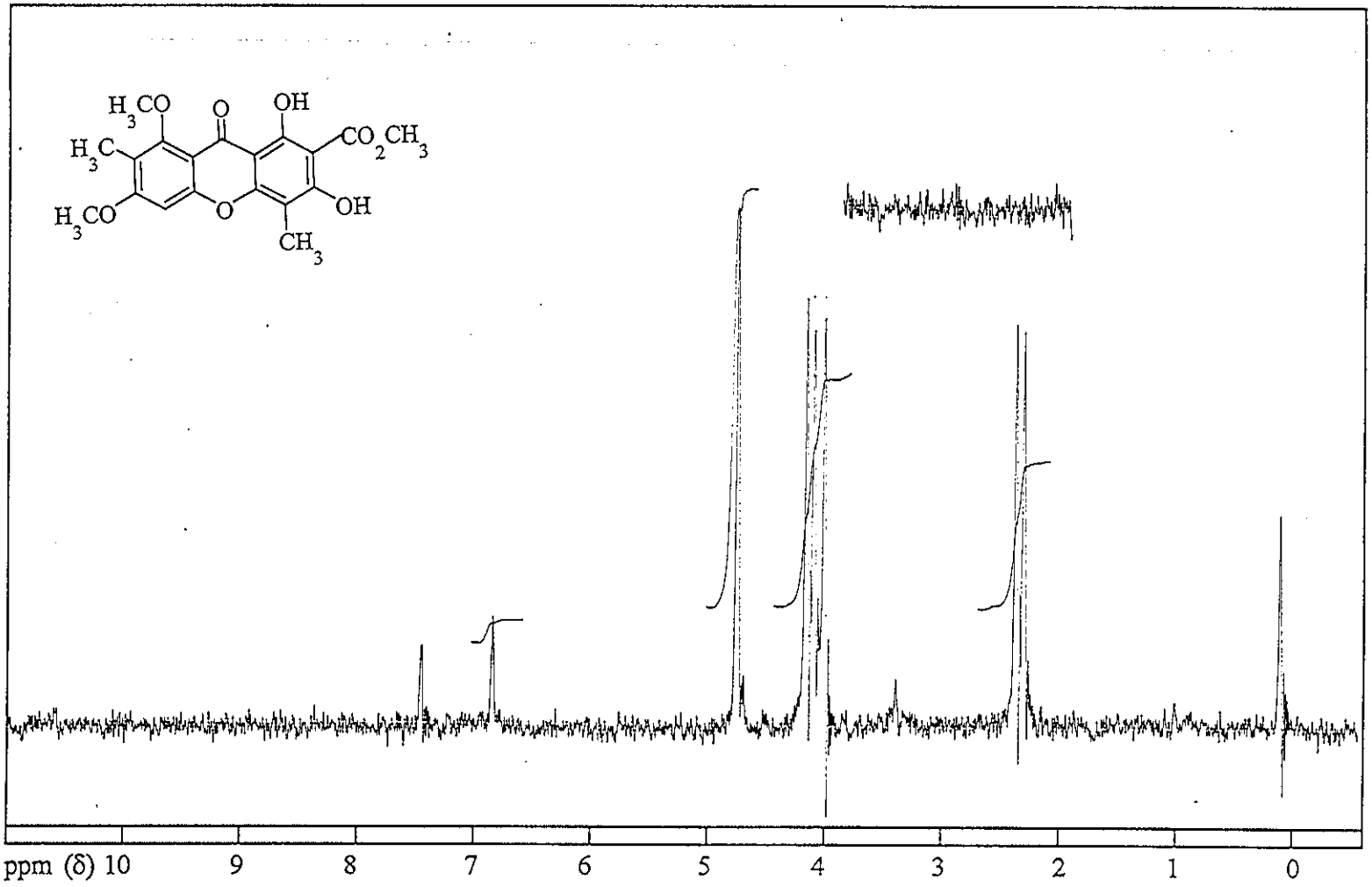

Figure 84. ^{1}H NMR spectrum of 1,3-dihydroxy-2-methoxycarbonyl-6,8-dimethoxy-4,7-dimethylxanthone (133) (D_2O)

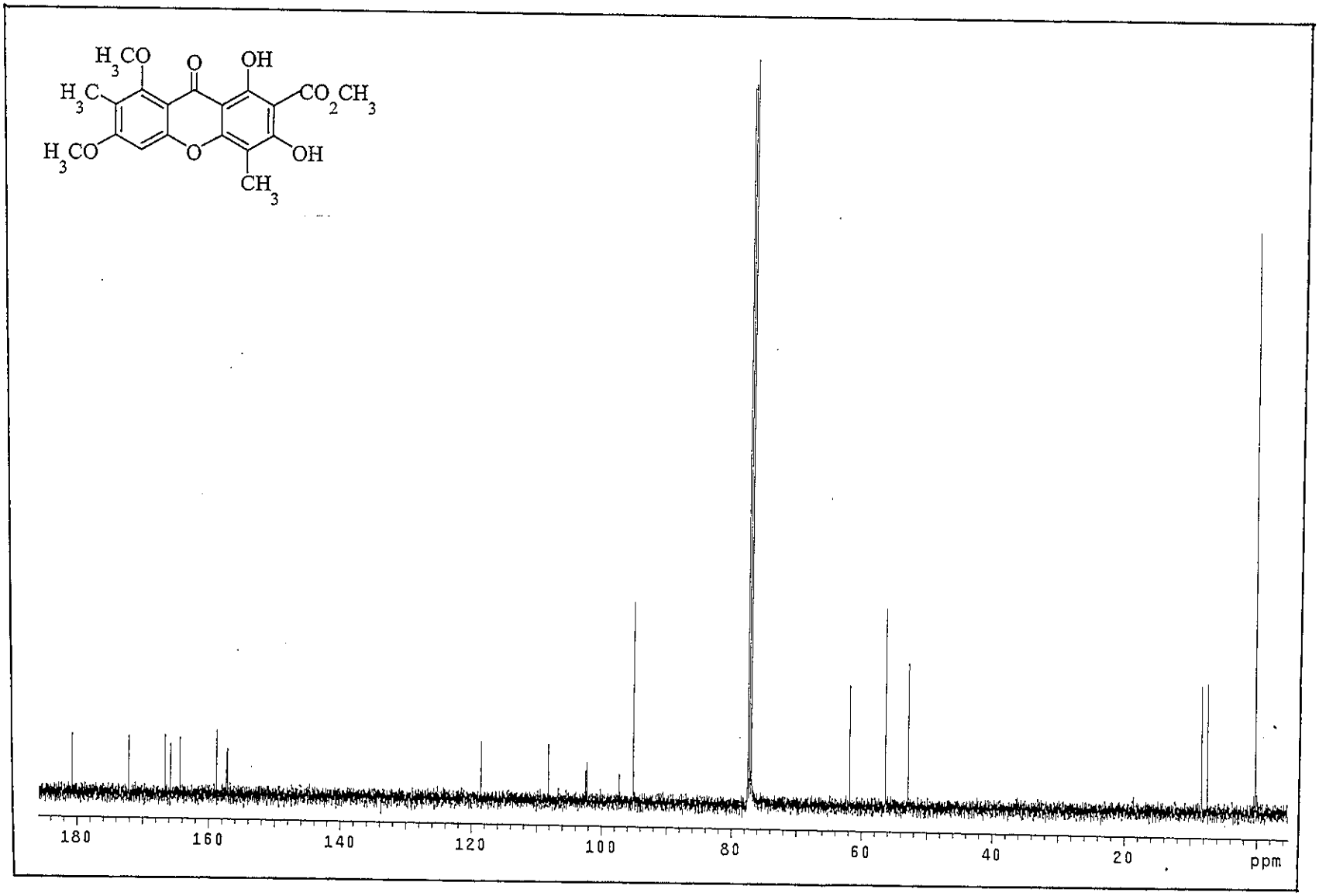

Figure 85. ^{13}C NMR spectrum of 1,3-dihydroxy-2-methoxycarbonyl-6,8-dimethoxy-4,7-dimethylxanthone (133)

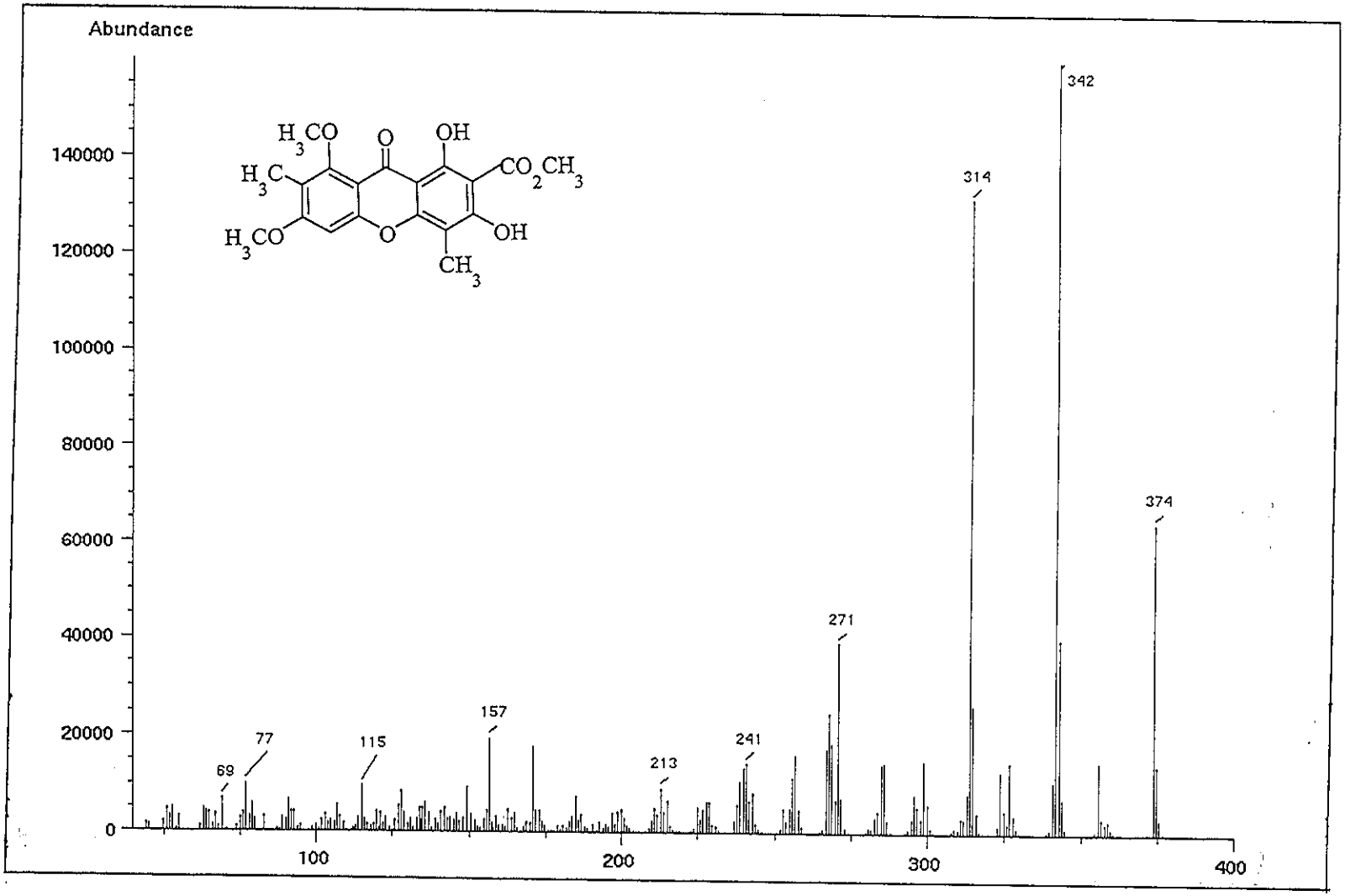

Figure 86. Mass spectrum (EIMS) of 1,3-dihydroxy-2-methoxycarbonyl-6,8-dimethoxy-4,7-dimethylxanthone (133)

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