: CHAPTER - II :

SYNTHESIS OF KEY INTERMEDIATE FOR EMMOTIN-G METHYL ETHER

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ABSTRACT

A key intermediate for the synthesis of Emmotin-G methyl ether (6.7), a phenolic bicarbocyclic sesquiterpene isolated from Emmotum nitenes (Icacinaceae) has been synthesised starting from p-Methoxy acetophenone. The Reformatskii reaction of p-methoxy acetophenone (6.1) with ethyl-4-bromocrotonate (6.2) followed by hydrogenation over palladium on carbon catalyst in presence of acetic acid gave ethyl-5-(p-methoxy phenyl) hexanoate (6.4) in high yield. Reduction of this saturated ester (6.4) with lithium aluminium hydride yielded the carbinol, 5-p-methoxy phenyl hexanol(6.5). PPA cyclization of the carbinol gave a product which appeared to be a mixture of isomers.

INTRODUCTION

Emmotin-G (1.1a) was isolated by Oliveira and co-workers[1] as one of the rearranged phenolic bicarbocyclic sesquiterpenic constituents from the trunk wood of Emmotum nitenes (Icacinaceae) along with emmotin-F (1.2a) and emmotin-H (1.3). On the basis of spectral evidences its structure has been established as 3-(2'-hydroxy isopropyl)-5, 8-dimethyl-2-naphthol (1.1a) which is also proved by correlation with other emmotins of identical carbon skeleton. The three emmotins (G, H and F) have

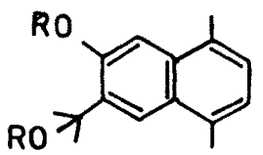
the identical carbon skeleton. The position of the hydroxy-isopropyl group and -OH group was established by correlation with emmotin-F (1.2a), Emmotin-G, $C_{15}H_{18}O_2$, is a white crystalline solid (M.P. = 112-115^{o}C).

Oliveira and co-workers[1] found that emmotin-G is a naphthol (λmax = 243 nm, ε 53900; λmax (NaOH), 254 nm, ε 55200) with a pair of ortho-related protons (δ = 7.18 and 7.08 doublets, J = 8 Hz) and a pair of para related protons (δ -7.73 and 7.42 singlets). The gem-dimethyl group was observed as a singlet at 1.78, and the two aromatic methyl groups at 2.59. As expected acetylation of emmotin-G to (1.1b) caused a strong paramagnetic shift (Δ = 0.59 ppm) of H_1 singlet and oxidation with fremy's salt yielded emmotin-H (1.3). Attempted direct acetylation of emmotin-H (1.3) under a variety of conditions led to mixtures.

Reductive acetylation of emmotin-H (1.3) in presence of zinc or acetylation of the quinoxaline derivative (1.4) gave better yields of isopropenyl compounds (1.6) and (1.7) respectively. As the dehydration product is equally available from emmotin-F (1.2a) it is assumed that the carbon skeleton of emmotin-F prevails in emmotin-G and emmotin-H. Therefore emmotin-G and H must possess the carbon skeleton of occidol (1.8).

The 3,S-configuration of emmotins is typical of the natural eudesmane type sesquiterpenoids, which suggests and

CHART-1



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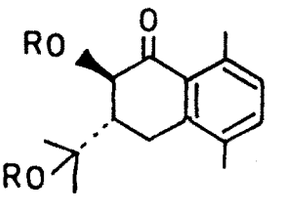
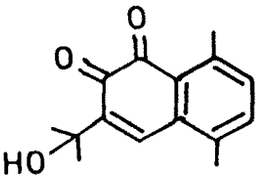
   b, R = Ac



2. a, R=H
   b, R=Ac



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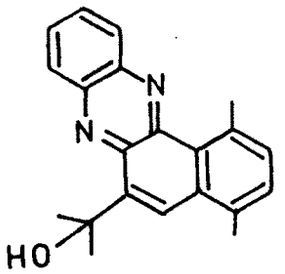

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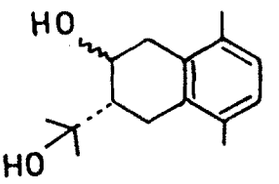
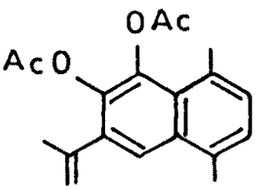


5 a, β-OH
  b, α-OH



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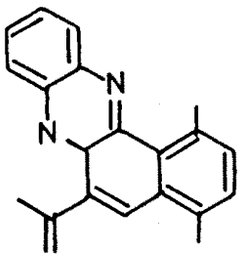

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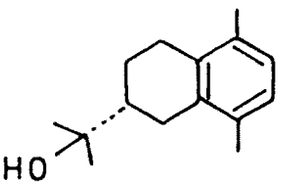

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confirms that there is biogenetic relationship between these compounds. Consequently, it is proposed that their bio-synthesis, by analogy with that of occidol[2] (1.8) should involve a one carbon shift dienol benzene rearrangement of an eudesmane type precursor.

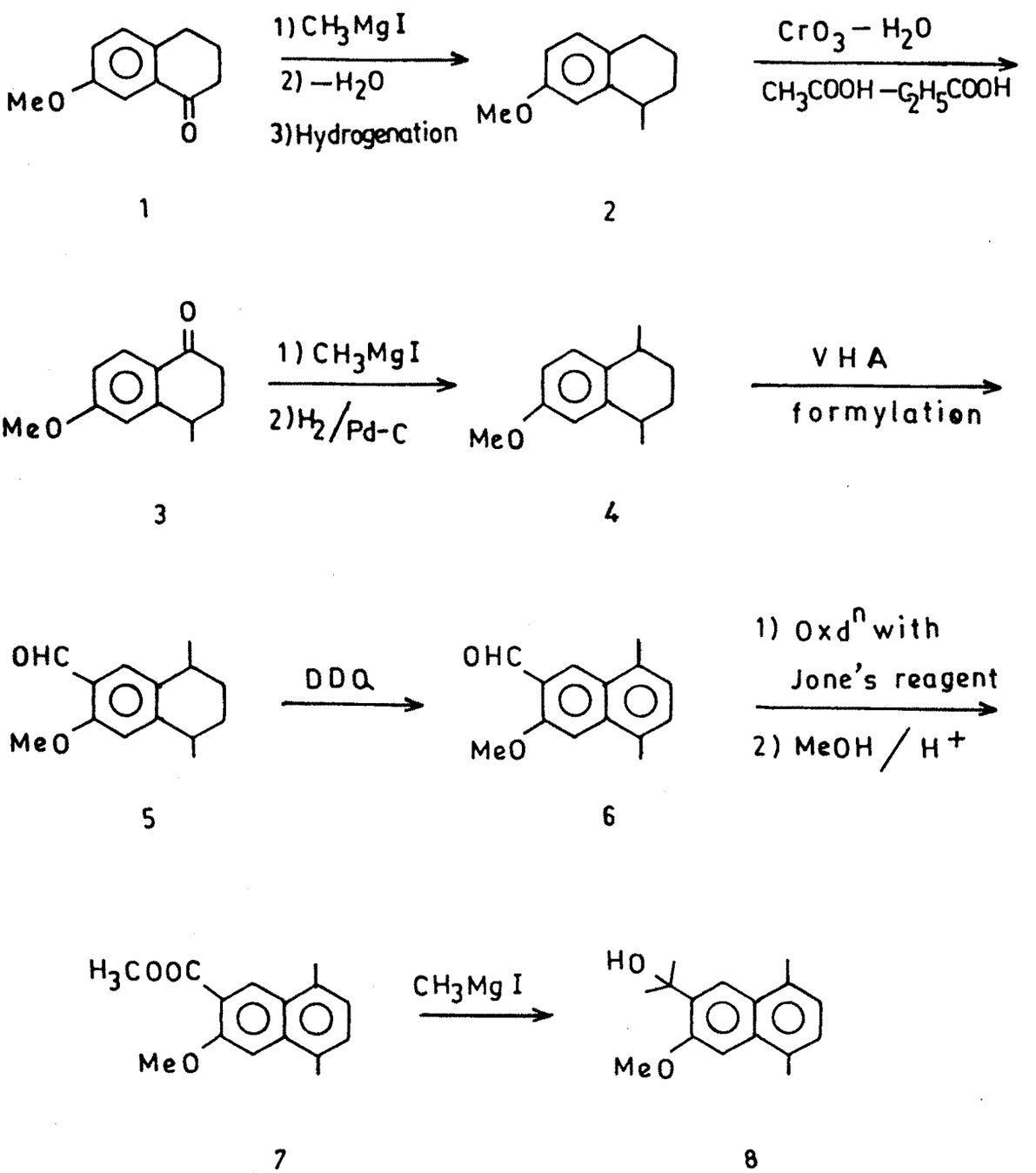
Out of reported syntheses of emmotin-G methyl ether the first synthesis reported by Reddy and Krishna Rao[3] (Chart-2); starting from a known 7-methoxy-1-tetralone[4] (2.1). The tetralone (2.1) on reaction with methyl magnesium iodide followed by hydrogenolysis gave 7- methoxy-1-methyl tetralin (2.2). The tetralin (2.2) on oxidation[5], with cromium trioxide in acetic acid - propionic acid mixture gives 6-methoxy-1-tetralone (2.3) which was then con- verted into the key intermediate in form of tetralin (2.4) by reaction of (2.3) with methylmagnesium iodide followed by hydrogenolysis.

The tetralin (2.4) was formylated using Vilsmeier-Haack-Arnold[6] reaction to obtain 6-formyl-7-methoxy-1,4-dimethyl tetralin (2.5), the dehydrogenation of (2.5) with DDQ[7] gave 3-methoxy-5,8-dimethyl-2-naphthaldehyde (2.6). The oxidation of (2.6) with Jone's reagent[8] followed by esterification gave methyl-3-methoxy-5,8-dimethyl-2-naphthoate (2.7) which was treated with excess of methyl magnesium iodide to furnish emmotin-G methyl ether (2.8).

Another synthesis has been reported by Velusamy and G.S. Krishna Rao[9] (Chart-3). It initiates with the use of a key

CHART-2

P. A. Reddy and G.S.K. Rao Synthesis (1980)



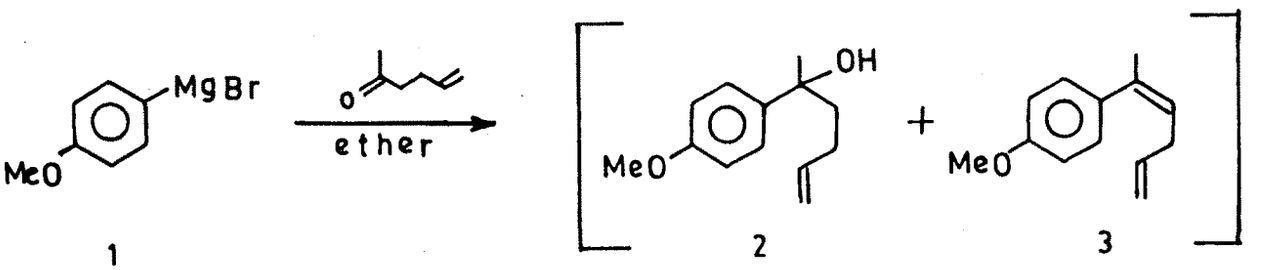
intermediate in form of 7-formyl-3 methoxy-1, 4-dimethyl naphthalene (3.6) which is synthesised by two routes, which has been converted into emmotin-G methyl ether as in first synthesis (Chart-2). In route 'A' p-anisyl magnesium bromide was reacted with allyl acetone which furnished a mixture of 5-(p-anisyl) hex-1-en-5-ol (3.2) and 5-(p-anisyl) hexan-1, 4-diene (3.3). Birch reduction[10,11] of hexenol (3.2)-hexadiene (3.3) mixture gave the 5-(p-anisyl) hex-1-ene (3.4) which on PPA cyclisation yielded the tetralin (3.5). The tetralin (3.5) was converted into 7-formyl-3-methoxy-1, 4-dimethyl naphthalene (3.6) as described earlier. The intermediate (3.6) was obtained by using another route 'B' in which 7-methoxy-4-methyl-1-tetralone[3] (3.7) was converted into the tetralol (3.8) by reaction with methyl magnesium iodide. The tetralol (3.8) on hydrogenation over Pd-C gave (3.5). Alternatively the tetralol (3.8) was converted into the key intermediate (3.6) directly by formylation followed by dehydrogenation with DDQ.

Another synthesis of emmotin-G methyl ether has been reported by M.T. Bachute and R.B. Mane.[12] (Chart-4). It starts with the aldol condensation of anisaldehyde (4.1) with ethyl methyl ketone. This gives p-methoxy styryl ethyl ketone (4.3), which is then subjected to conjugate addition of methyl magnesium iodide to obtain 5-(p-methoxy phenyl)-hexan-3-one (4.4). The ketone (4.4) was then reduced with sodium borohydride to give the alcohol 5-(p-methoxy phenyl) hexan-3-ol (4.5) which on PPA cyclization give 6-methoxy-1, 4-dimethyl

CHART–3

T. P. Velusamy and G. S. K. Rao Synthesis (1981)

Route–A :—



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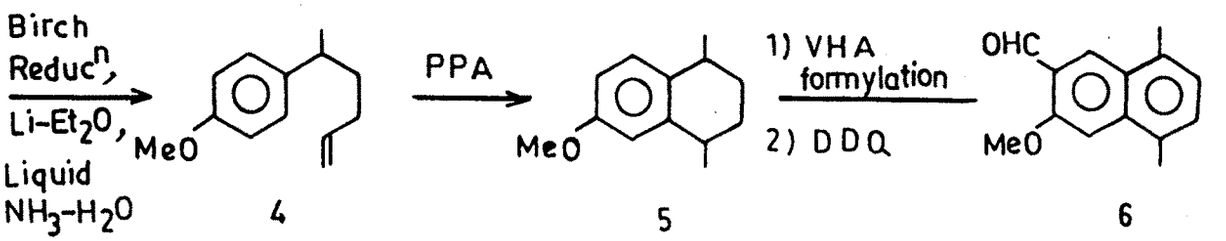
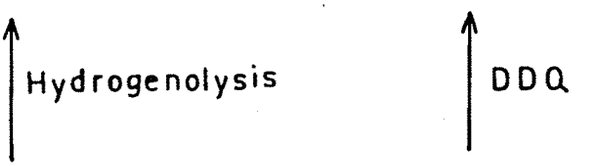
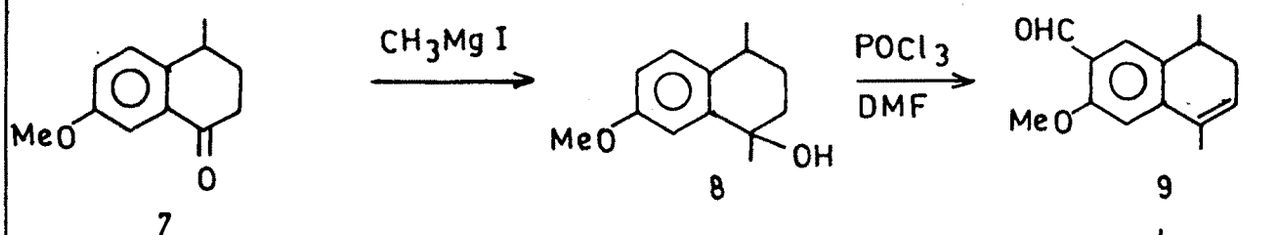


4 5 6

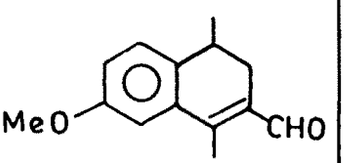


Route–B :—



7 8 9

+



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CHART–4

M. T. Bachute and R. B. Mane Synthesis (1991)

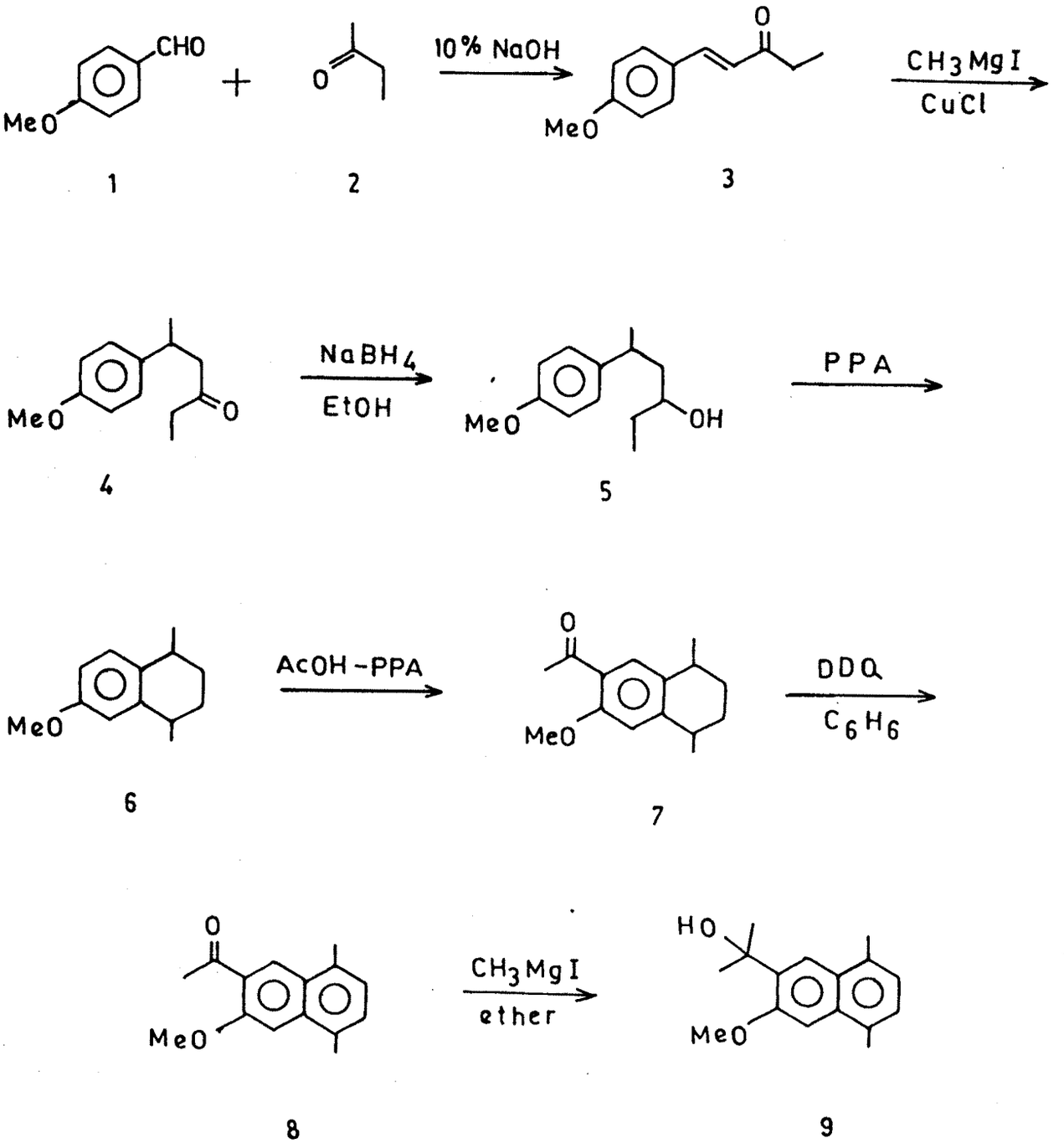


CHART-5

Abdus Sattar and R.B. Mane Synthesis (1993) —

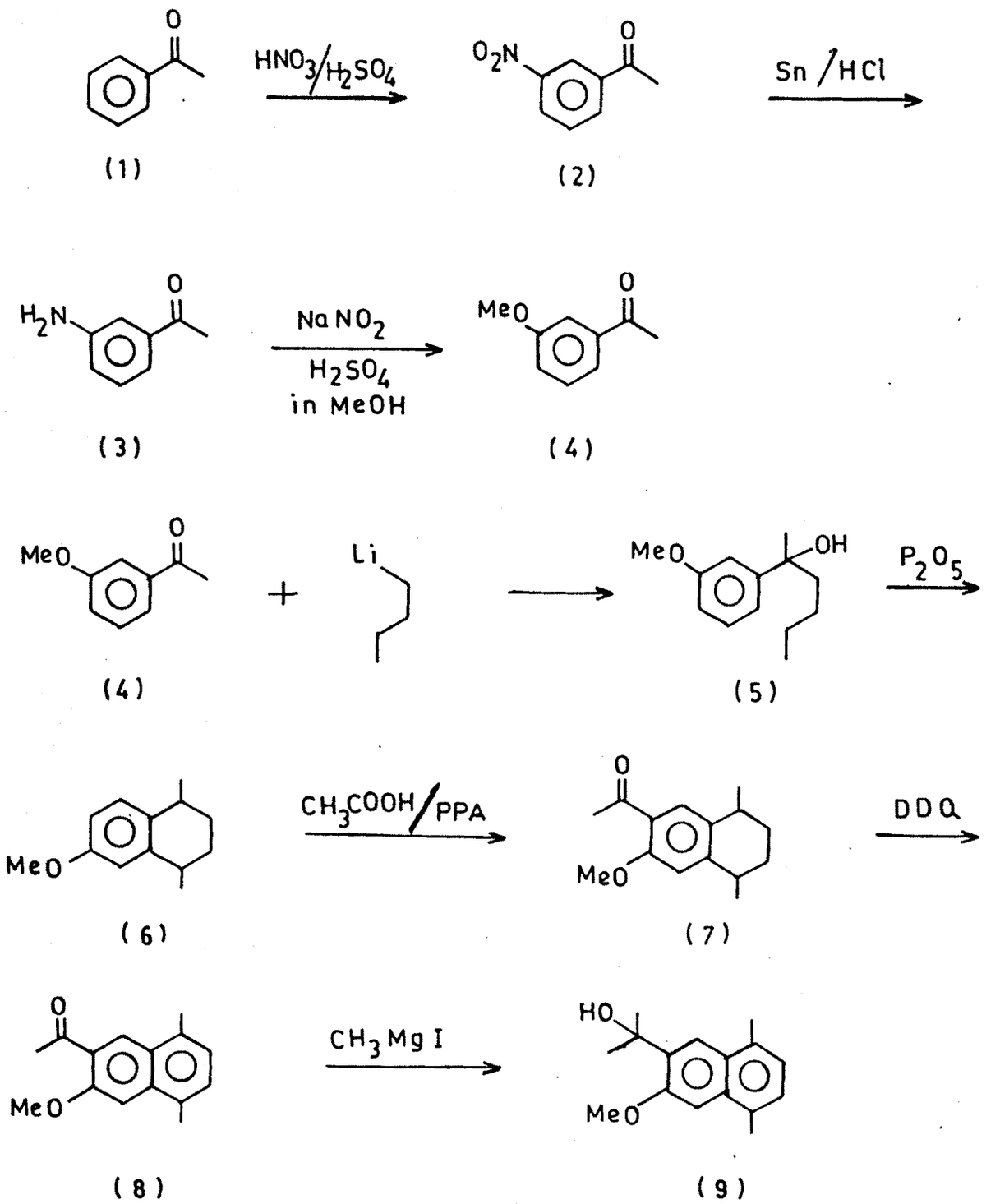
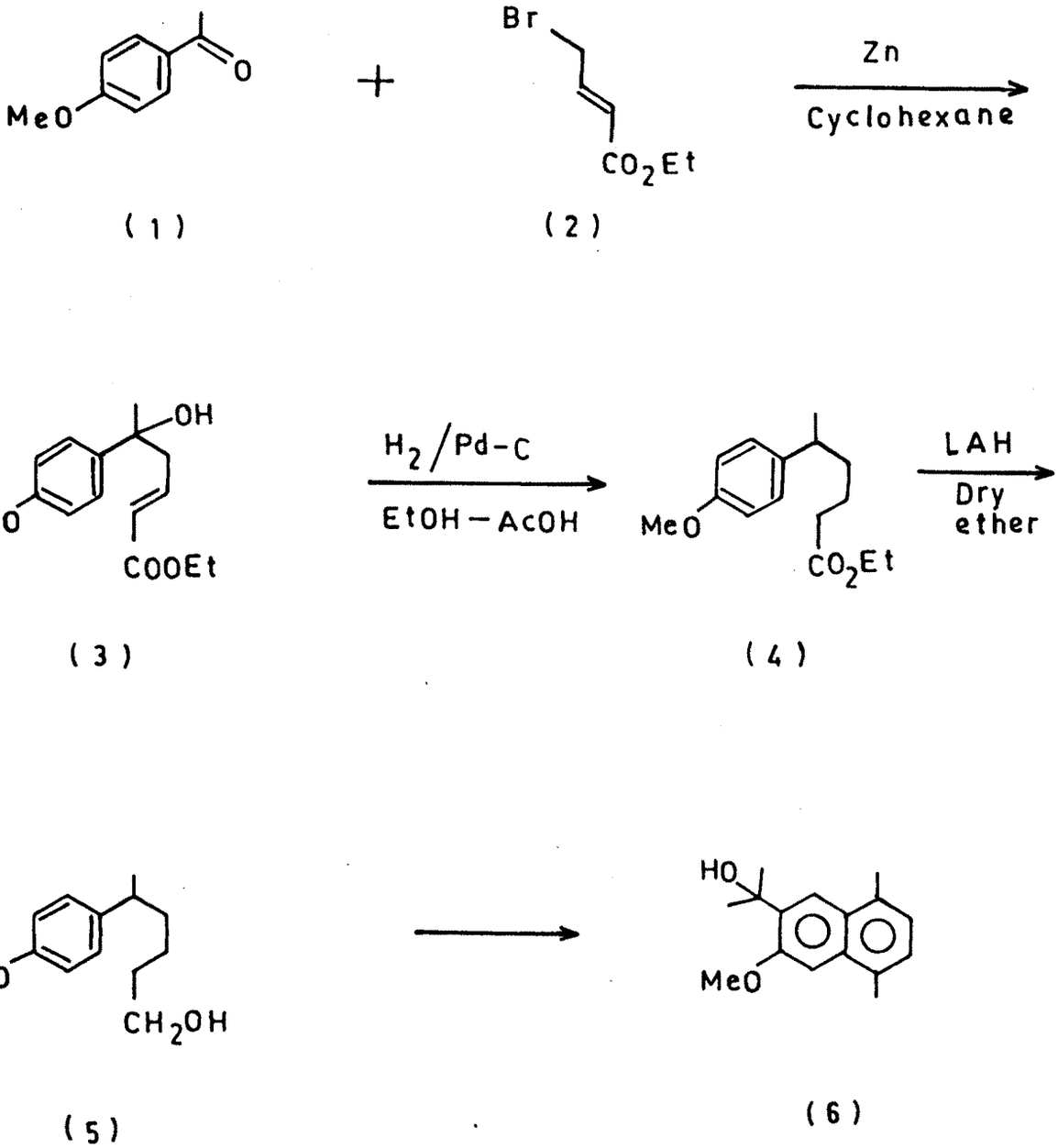


CHART-6


MeO
O
Br
CO_2Et
Zn
Cyclohexane
(1)
(2)
OH
MeO
COOEt
$H_2/Pd-C$
EtOH – AcOH
MeO
CO_2Et
LAH
Dry ether
(3)
(4)
MeO
CH_2OH
HO
MeO
(5)
(6)

tetralin (4.6) which was acetylated with acetic anhydride in PPA to furnish 6-methoxy-7-acetyl-1, 4-dimethyl tetralin (4.7). It was then aromatized with DDQ to obtain 6-methoxy-7-acetyl-1, 4-dimethyl naphthalene (4.8). The Grignard reaction of methyl magnesium iodide with the Ketone (4.8) gave emmotin-G methyl ether (4.9).

One more synthesis of emmotin-G methyl ether has been reported by Abdus Sattar and R.B. Mane[13] (Chart-5) in which butyl-lithium was reacted with 3-methoxy acetophenone (5.4) which gave 5-(3-methoxyphenyl) hexan-5-ol (5.5). This carbinol (5.5) on cyclodehydration with phosphorus pentoxide yielded a key intermediate 6-methoxy-1, 4-dimethyl tetralin (5.6). The tetralin (5.6) on acetylation with acetic acid and PPA gave 6-methoxy-7-acetyl-1, 4-dimethyl tetralin (5.7), which on aromatization with DDQ furnished 6-methoxy-7-acetyl-1, 4-dimethylnaphthalene (5.8) which on Grignard reaction with methyl magnesium iodide gave emmotin-G methyl ether (5.9).

We got interested in the new short route for a key intermediate for the synthesis of emmotin-G methyl ether which could be achieved by making use of a Reformatskii reaction of 4-bromocrotonate.[14]

PRESENT WORK

As discussed in the introductory part of this chapter, reported syntheses of emmotin-G methyl ether using different approaches are available. Our interest in the Reformatskii reaction of ethyl 4-bromocrotonate for the introduction of a 4-Carbon unit of the side chain and the elaboration of ester function into required functional group prompted us to explore a new route for the synthesis of emmotin-G methyl ether (6.7).

We decided to use p-methoxy acetophenone (6.1) as the starting material for the synthesis of emmotin-G methyl ether because of the easy elaboration of the Ketonic functionality into the desired side chain.

Lot of improvements have been reported recently in the Reformatskii reaction of ethyl 4-bromocrotonate. We decided to use this reaction for introduction of a 4-carbon unit of the side chain and then elaborate it into the desired functionality. The Reformatskii reaction of p-methoxy acetophenone (6.1) with ethyl 4-bromocrotonate (6.2) in presence of zinc dust gave the hydroxyester, ethyl 5-hydroxy-5-p-methoxy phenyl-2-hexenoate (6.3) in high yield. Boiling cyclohexane was used as the reaction medium as it is known that the normal adduct formed by attack at the γ-carbon predominates in presence of such solvents. The spectral data of the hydroxyester (6.3) was in

complete agreement with the structure. The I.R. spectrum (Fig.1) showed a broad peak for the hydroxyl at 3500 cm^{-1} and the ester carbonyl at 1710 cm^{-1}. The PMR spectrum (Fig.2) showed a triplet at δ 1.20 for the methyl of the ethyl ester group, a singlet for the benzylic methyl at 1.70, the -OH proton appeared as a broad peak at 1.55, the allylic methylene group appeared as a broad peak at 2.19, a sharp singlet for the methoxyl group at 3.84, a quartet for the ester methylene group at 4.18. The vinylic proton α- to the ester group appeared as broad singlet at 5.22 a multiplet for the other olefinic proton at 6.9 was merged with aromatic protons,and a multiplet for four aromatic protons at 7.19. The unsaturated hydroxyester (6.3) was converted into the saturated ester ethyl 5-p-methoxy phenyl hexanoate (6.4) by hydrogenation over palledium on carbon (10%) in ethanol in the presence of acetic acid. The I.R. spectrum showed absence of the hydroxyl group and the double bond. The PMR Spectrum (Fig.3) was in agreement with the structure. It exhibited a triplet for the methyl of the ethyl ester group at δ 1.17, a doublet for the benzylic methyl at 1.22, a multiplet for the four methylene protons at 1.52, a broad triplet for the methylene group adjacenet to the ester carbonyl group at 2.32, a multiplet for the bezylic methine proton at 2.64, a quartet for the methylene of the ethyl ester at 3.51, a sharp singlet for the aromatic methoxy group at 3.86 and 7.08 to 7.25 double doublet for aromatic protons. Reduction of the above saturated ester (6.4) with lithium

aluminium hydride in dry ether yielded the carbinol 5-(p-Methoxy phenyl)hexanol (6.5). I.R. spectrum (fig.5) showed a broad peak for the hydroxyl at 3375 cm^{-1}. PMR ($CDCl_3$) showed a doublet at δ 1.25 for benzylic methyl, a multiplet for six methylene protons at 1.4 - 1.9, a multiplet for benzylic methine proton at 2.65, a triplet for methylene adjacent to hydroxy at 3.6, a sharp singlet for aromatic methoxy group at 3.8, a broad peak for hydroxy at 5.15, and a doublet for aromatic protons ortho to -OMe at 6.85, another doublet for aromatic protons meta to -OMe at 7.1. The PPA cyclization of the carbinol (6.5) gave the mixture of isomers,probably six membered and seven membered ring compounds.

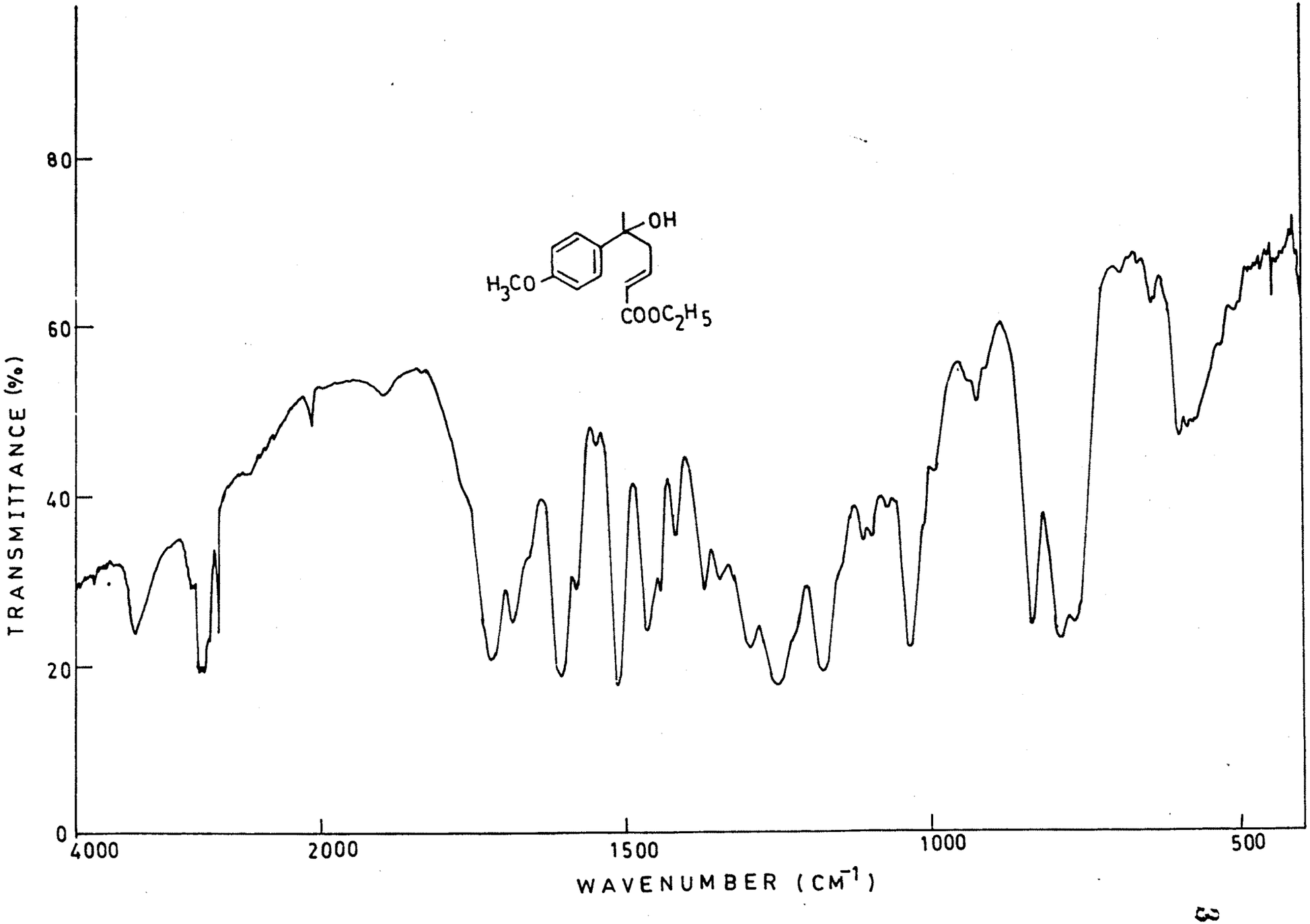

80
60
40
20
0
TRANSMITTANCE (%)
4000
2000
1500
1000
500
WAVENUMBER (CM⁻¹)
OH
H3CO
COOC2H5

FIG. 1

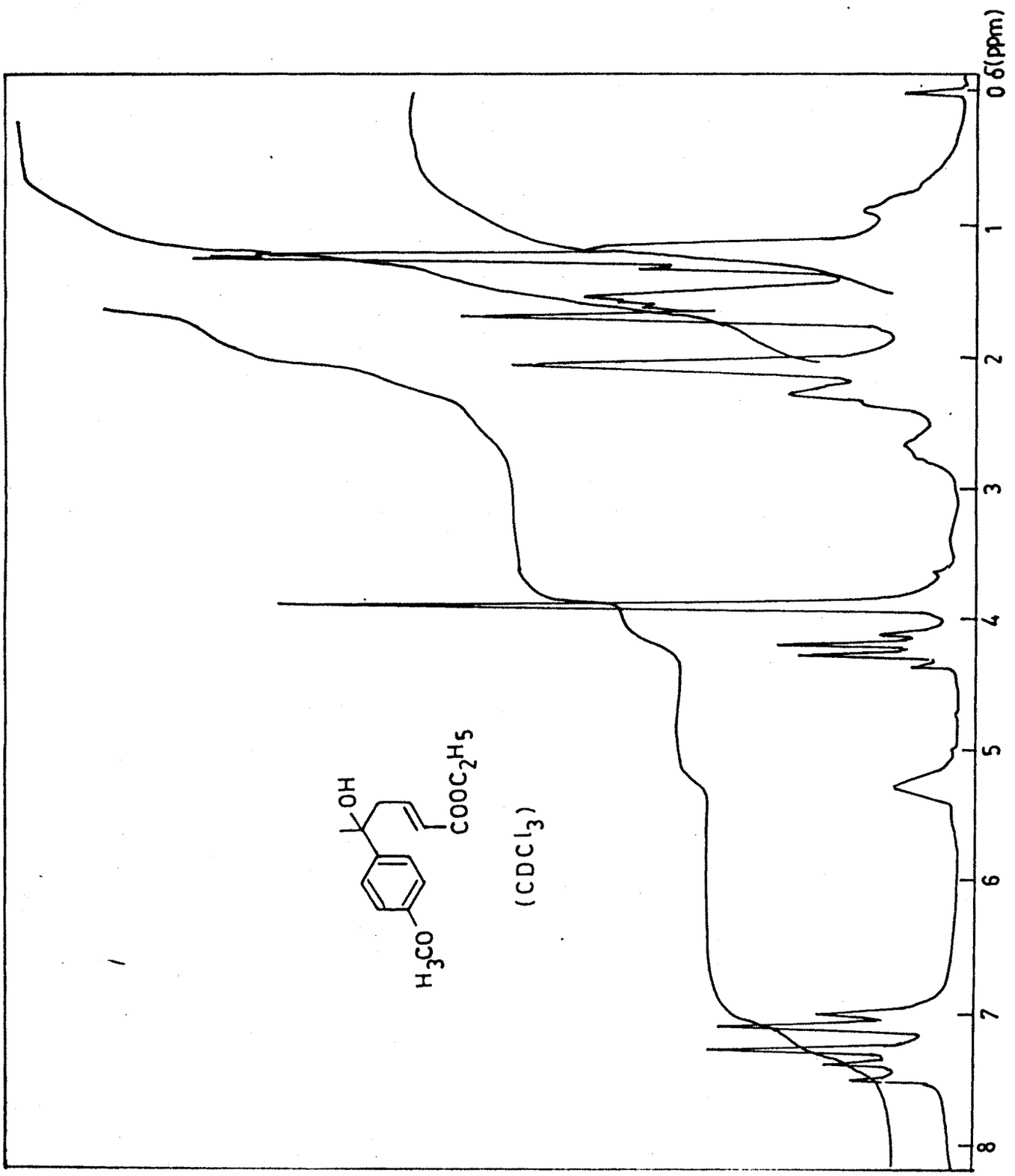


FIG. 2

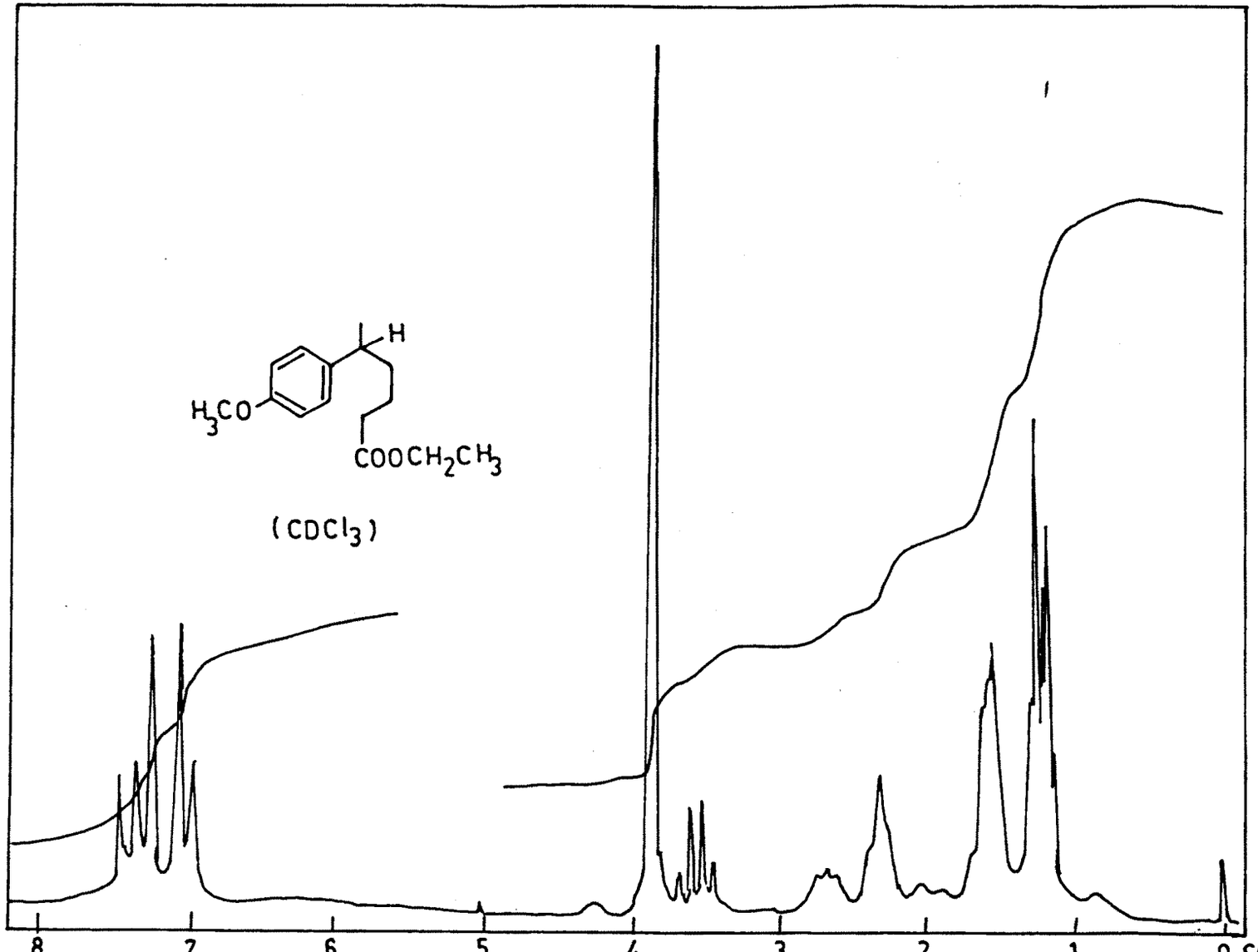


FIG. 3

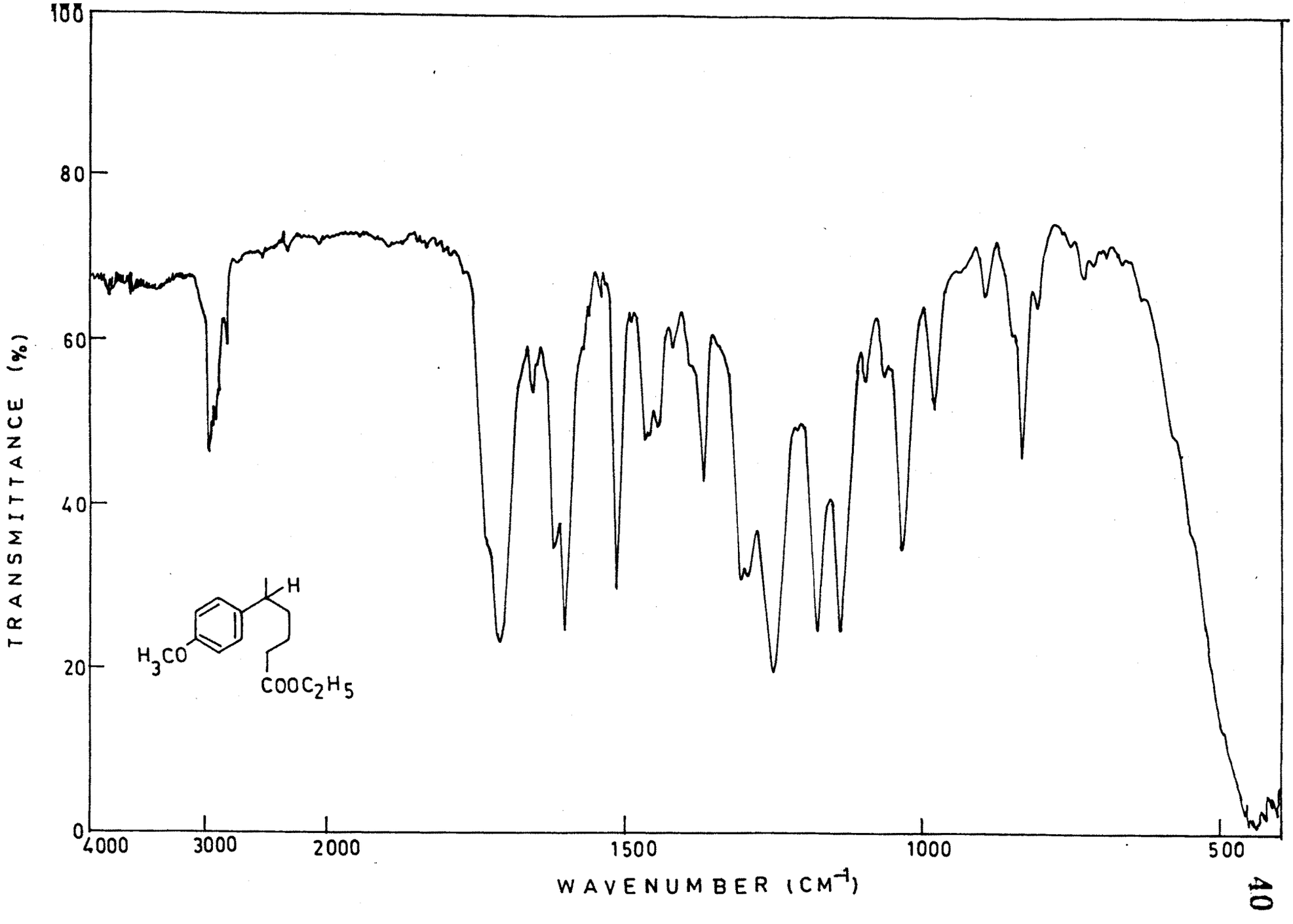

100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3000
2000
1500
1000
500
WAVENUMBER (CM⁻¹)
H
H3CO
COOC2H5
40

FIG. 4

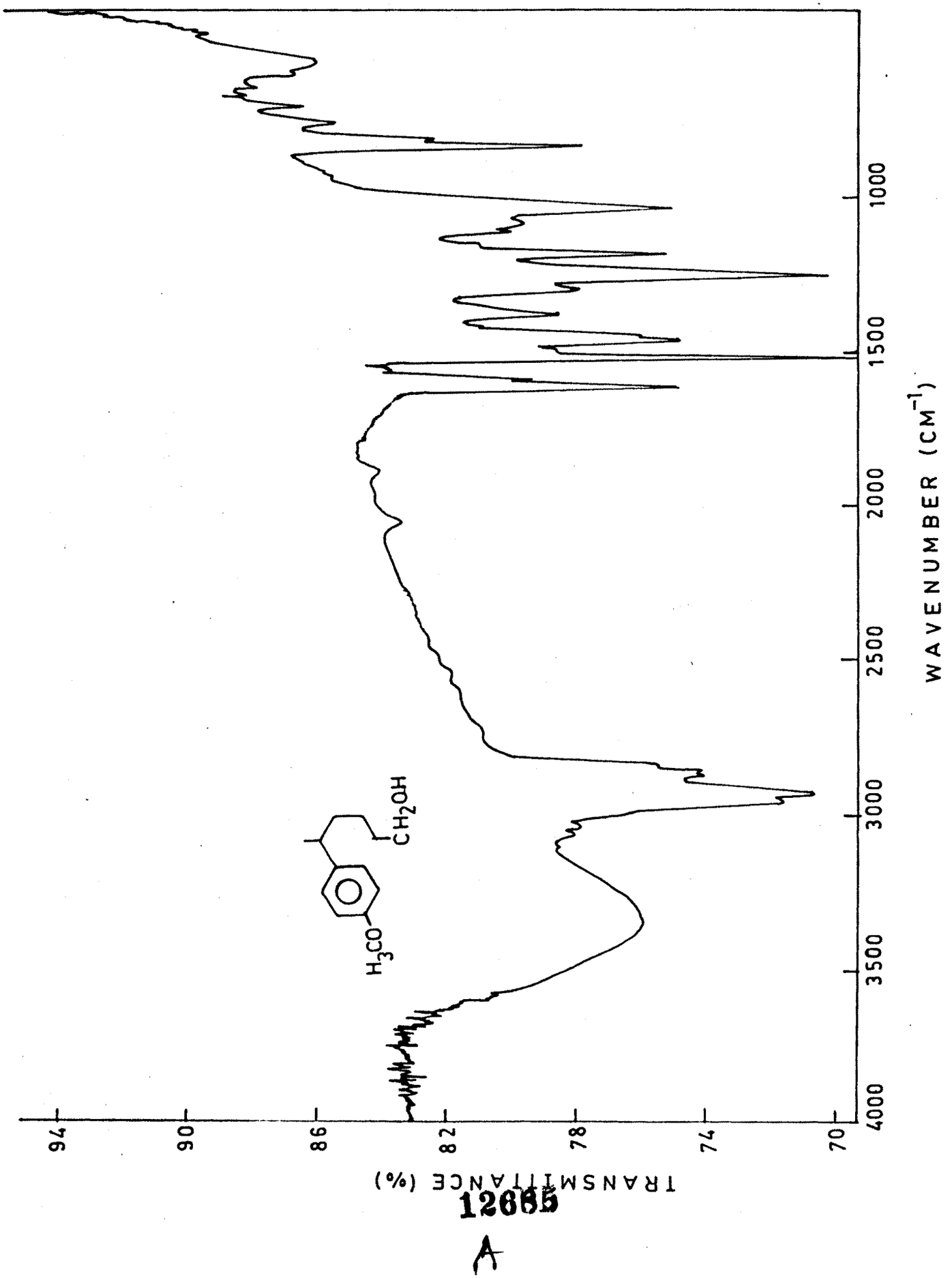

TRANSMITTANCE (%)
94
90
86
82
78
74
70
4000
3500
3000
2500
2000
1500
1000
WAVENUMBER (CM^{-1})
CH_2OH
H_3CO

FIG. 5

12665

A

EXPERIMENTAL

GENERAL :

Ethyl crotonate (Fluka), N-Bromosuccinimide (Riedel), p-Methoxy acetophenone (SRL), Zinc dust (SRL), Dry cyclohexane (BDH), Palladium charcoal (10%, J & M), LAH (Fluka), Phosphorus Pentoxide (BDH), orthophosphoric acid (BDH) were used. Dry cyclohexane was prepared by distillation over phosphorus pentoxide and stored over sodium metal wire.

ETHYL 4-BROMOCROTONATE (6.2) :

A mixture of N-Bromosuccinimide (18g), ethyl crotonate (20g) and dry redistilled carbontetrachloride (30 ml) in a round bottom flask was refluxed on water bath for 12 hrs. By this time all the solid floats on the surface of the liquid. It was filtered off to remove the succinimide and washed with a little dry carbon tetrachloride. Solvent was removed and the residue distilled to yield product (13g) b.p. 91-93^{o}/12 mm.

ETHYL 5-HYDROXY-5 (p-METHOXY PHENYL)-2-HEXENOATE (6.3) :

A mixture of p-methoxy acetophenone 6.1(3.28 g) and ethyl 4-bromocrotonate 6.2 (3.86 g) in dry cyclohexane (8 ml) was added dropwise during 30 min. to zinc dust (7 g) covered with dry cyclohexane (10 ml) with stirring. The reaction mixture was refluxed for 1 hr, cooled, decomposed with saturated ammonium

chloride solution and extracted with ether. The ether layer was washed with water, dried and the solvent removed to obtain the crude ethyl-5-hydroxy-5-(p-methoxy phenyl) 2-hexenoate 6.3 (3.9 g).

The unsaturated ester (0.500 g) was purified by preparative t.l.c. (Silica gel-G, 9:1 - Pet ether : ethyl acetate). IR (neat, Fig.1) : 3500 cm^{-1} (OH), 1710 cm^{-1} (ester carbonyl), 1638 cm^{-1} (Olefinic double bond); PMR ($CDCl_3$, Fig.2) : δ 1.20 (3H,t, J=7 Hz,$-CO_2-CH-\underline{CH_3}$), 1.70 (3H, $ArCH\underline{CH_3}$) 1.55 (1H,bs, Ar$C-\underline{OH}$), 2.19 (2H,d J=7 Hz, Ar $C-\underline{CH_2}$), 3.84 (3 H,S, $Ar-O\underline{CH_3}$), 4.18 (2H, q J = 7 Hz,CO_2 - $\underline{CH_2}-$), 5.22(1H, bs, CH = $\underline{CH}-CO_2C_2H_5$), 6.9 (1H, m, $CH_2-\underline{CH}$ = CH),7.19 (4H, m, Ar-H).

Analysis Found : C, 68.15 ; H 7.60%

$C_{15}H_{20}O_4$ requires : C, 68.18 ; H 7.57%

ETHYL-5-(P-METHOXY PHENYL) HEXANOATE (6.4) :

The hydrogenation of Ethyl-5-hydroxy-5- (p-methoxy phenyl) hexenoate (6.3) was carried out by dissdolving it (3.4 g) in absolute ethanol (30 ml) containing a few drops of acetic acid and shaking under hydrogen atmosphere with palladium charcoal (10%) catalyst. The reaction mixture was filtered and the ethanol removed under vacuum. The crude saturated ester was extracted with ether, washed with aqueous sodium bicarbonate and then with water. The organic layer was dried and the solvent distilled to furnish crude ethyl-5-hydroxy-5-(p-methoxy

phenyl) hexanoate, 6.4 (2.8 g) as a liquid and was purified by chromatography over silica gel column (60-120 mesh, 60 g) Elution with benzene gave the pure saturated ester (2.0 gm). I.R. (neat) : 1708 cm^{-1} (ester carbonyl); PMR ($CdCl_3$, Fig.3) : δ 1.17 (3H, t, J = 7 Hz, CO_2CH_2 - $\underline{CH_3}$), 1.22 (3H, d, J = 7 Hz, Ar CH- CH_3) 1.52 (4 H,m, - $\underline{CH_2}$ - $\underline{CH_2}$), 2.32 (2H, t, J = 7Hz, $\underline{CH_2}$-CO_2 C_2H_5), 2.64 (1 H, m, Ar-$\underline{CH}$-CH_3) 3.51 (2H,q, J=7 Hz, $CO_2\underline{CH_2}CH_3$) 3.85 (3H, s, Ar-OMe), 7.08 (2H, d, J=8 Hz, Ar-H Ortho to - OCH_3), 7.25 (2H, d, J=8 Hz <u>meta</u> to OCH_3),

Analysis Found : C, 72.10; H, 8.70 %

$C_{15}H_{22}O_3$ requires : C, 72.00; H, 8.80 %

<u>5-(p-METHOXY PHENYL) HEXANOL (6.5)</u> :

To a stirred suspension of Lithium aluminium hydride (1g) in anhydrous ether (10 ml) was added dropwise with stirring saturated ester (6.5), (1 g) in anhydrous ether (10 ml). The reaction mixture was left overnight at room temperature and then refluxed for 1 Hr. The contents were cooled and then sat. Na-K-tartrate added to quench the reaction. It was extracted twice with ether. The usual workup of the combined organic extracts gave an oil 0.825 gm which on short path vacuum distillation gave alcohol (b.p. - 130-135°/11 mm).(0.640 gm). The structure was confirmed by spectral analysis.

IR (neat, fig.5) : 3375 cm^{-1} (-OH).PMR ($CDCl_3$) : δ 1.25 (3H,d, ArCH-CH_3), 1.4-1.9 (6H,m,methylene protons), 2.65 (1H,m, benzylic methine proton), 3.6 (2H,t, methylene adjacent to hydroxy), 3.8 (3H,s,Ar-OMe), 5.15 (1H, bs, -OH), 6.85 (2H, d,

J=8 Hz Ar-H ortho to OMe), 7.1 (2H, d, J=8 Hz Ar-H meta to -OMe).

PPA cyclization of 5-(p-METHOXY PHENYL) HEXANOL (6.5) :

To plyphosphoric acid (prepared from phosphorus pentoxide (5 g) and ortho-phosphoric acid (3 ml) was added Crude Carbinol (1 g) at room temperature with stirring. The reaction mixture was stirred for 30 min. and heated at 100°C for 1 hr. The mixture was then cooled, poured on crushed ice and extracted with ether. After usual work up the ether was distilled off to yield the crude product which was purified by Column Chromatography.

NMR spectrum of the product indicated that it is a mixture of isomers.

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