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TETRALONE ESTERS AS INTERMEDIATES FOR THE SYNTHESIS OF PODOPHYLLOTOXIN DERIVATIVES VIA CYCLOPROPANATION OF CHALCONES[1]

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Abstract: Cyclopropyl ester (**8a-f**) were synthesized by the cyclopropanation of chalcones (**7a-e**) in dry benzene using powdered sodium in 80-85% yield. Preparation of tetralone ester (**4a-e**), an intermediate for the synthesis of podophyllotoxin derivatives by Lewis acid ($SnCl_4$) catalyzed cyclization of (**8a-e**) is also described here.

Podophyllotoxin (**1**) and several of its analogous are used as cytotoxic spindle poisons and antitumor agents, some at clinical level.[2] Recently Lee et al[3]. discovered that some modified derivatives of podophyllotoxin possess anti-HiV (AIDS) property. In earlier parts of the series, we have reported the synthesis of analogous of **1** and β-apopicropodophyllin (**2**), with a view to study their structure-antimitotic activity relationship.[4] We found some of these derivatives possess higher activity and some have lower activity when compared to the parent molecules. Now we have envisaged that modifying ring A and pendent ring C in **1**

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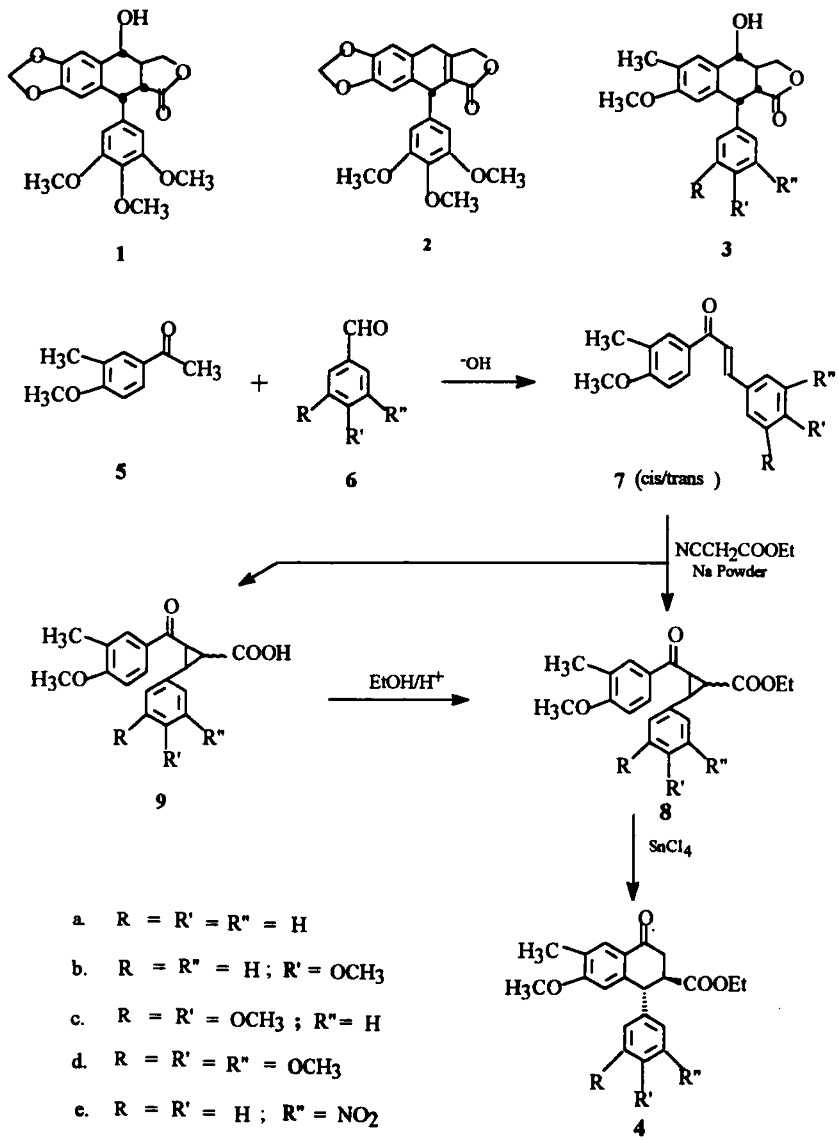
and **2** might enhance their biological activity and hence decided to synthesize the analogues **3a-e**.

Several synthetic routes[5]other than Gensler's[6] have been reported for the synthesis of **1** via the tetralone ester **4**. In the present paper, we adopted Murphy's method[7] because it requires easily available starting materials. Starting material for the synthesis of **4** is the chalcone (**7**), which was easily prepared by stirring a equal molar solution of 3-methyl-4-methoxy-acetophenone (**5**) and aromatic aldehyde (**6**) in methanol containing one equivalent of sodium hydroxide pellets at room temperature for 5 to 10 minutes. Cyclopropyl ketoesters (**8**) were synthesized via cyclopropanation of **7** using cyano ethyl acetate by employing the method of Rai ital.[8] In a typical procedure, a solution of **7** in benzene containing cyanoethyl acetate was treated with sodium powder at room temperature and then was refluxed for 12 hrs. After the workup gave 82% of cyclopropyl ester (**8**) and 10% of ketoacid (**9**). The formation of **9** was confirmed by its conversion to **8** in almost quantitative yeild using ethanol and sulphuric acid. Formation of the cyclopropyl ring system in **8** was confirmed by ^{1}H NMR, (multiplet at δ 2.20-2.35 ppm). The products isolated were characterized by IR, ^{1}H NMR, and also mass spectra, which showed the acyl cation as base peak and other fragments formed through a identical fragmentation pattern.

In the present paper we adopted Murpy,s[7] method for the cyclization of **8** to give tetralone **4**. In a typical procedure, reaction of cyclopropyl esters **8** with two equivalents of $SnCl_4$ in nitrobenzene at room temperature for 6 to 7 hr. yielded


1
2
3
5
6
7 (cis/trans)
NCCH2COOEt
Na Powder
9
EtOH/H+
8
SnCl4
4
a. R = R' = R" = H
b. R = R" = H ; R' = OCH3
c. R = R' = OCH3 ; R" = H
d. R = R' = R" = OCH3
e. R = R' = H ; R" = NO2

tetralone ester **4** in 60-65% yield. The NMR spectrum of **4a** exhibited a doublet at δ 4.55 ppm (J=6Hz) for the dibenzylic proton C_1-H. The large J value of 6 Hz indicated that C_2-H and C_1-H in **4a** were diaxial. Hence, the C_2-ethoxycarbonyl and C_1-phenyl groups should be *trans* to each other, a configuration being thermodynamically more stable.

Experimental Section:

Melting points were taken on open capillary and are uncorrected. IR spectra were recorded on a Perkin Elmer 399 spectrometer. ^{1}H NMR spectra were recorded on Jeol 60 MHz NMR spectrometer using $CDCl_3$ as solvent and TMS as internal reference The chemical shifts are expressed in δ ppm. Mass spectra were recorded on Hitachi RMU-6I spectrophotometer and important fragments are given with the relative intensities in the bracket. Thin layer chromatography were obtained on Merk silica gel G coated on glass plates.

General procedure for the preparation of chalcones (7a-e): A typical procedure is described for the preparation of ***1-(3'-methyl-4'-methoxyphenyl)-3-phenyl-prop-2-ene-1-one*** (**7a**) :- A solution of 3-methyl-4-methoxy acetophenone (**5**, 1.0 g, 6.2 mmol) and benzaldehyde (**6a**, 0.65 g, 6.2 mmol) in methanol (25 mL) was treated with sodium hydroxide pellets (0.25 g) and stirred for 15 minutes at room temperature, wherein chalcone **7a** precipitated. The precipitate was then filtered off, washed thoroughly with water and dried to yield **7a**. It was then recrystallized from 50% aqueous ethanol give a light yellow, crystalline compound in 80% (1.22 g) yield, m.p.= 86°C, IR (KBr): 1600 (C=C), 1605, 1657 (CO) cm^{-1};

^1H NMR ($CDCl_3$): δ 2.25 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 6.80 (bd, 2H, -HC=CH-), 7.0-7.20 (m, 5H, Ar-H), 7.20-7.30 (d, 1H, Ar-H), 7.50-7.65 (bd, 2H, Ar-H); Anal. Calcd. for $C_{17}H_{16}O_2$ C, 80.92; H, 6.40%: Found C, 80.86; H, 6.42%.

1-(3'-Methyl-4'-methoxyphenyl)-3-(4"-methoxyphenyl)-prop-2-ene-1-one (**7b**):- Obtained from 3-methyl-4-methoxy acetophenone (**5**, 1.0 g, 6.2 mmol) and p-anisaldehyde (**6b**, 0.84 g, 6.2 mmol) as pale yellow crystalline solid in 85% (1.47 g), m. p.= 62-64°C, IR (KBr): 1605 (C=C), 1610, 1667 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.30 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.80 (bd, 2H, -HC=CH-), 6.90-7.0 (bd, 1H, Ar-H), 7.50-7.70 (d, 4H, Ar-H), 7.80-7.90 (d, 2H, Ar-H); Anal. Calcd. for $C_{18}H_{18}O_3$ C, 76.56; H, 6.43%: Found C, 76.46; H, 6.47%.

1-(3'-Methyl-4'-methoxyphenyl)-3-(3",4"-dimethoxyphenyl)-prop-2-ene-1-one (**7c**) :- Obtained from 3-methyl-4-methoxy acetophenone (**5**, 1.0 g, 6.2 mmol) and 3,4-dimethoxybenzaldehyde (**6c**, 1.03 g, 6.2 mmol) as pale yellow crystalline solid in 82% (1.56 g), m. p.= 93-95°C, IR (KBr): 1600 (C=C), 1605, 1657 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.30 (s, 3H, CH_3), 3.85 (s, 6H, OCH_3), 3.92 (s, 3H, OCH_3), 6.70-6.95 (d, 2H, -HC=CH-), 7.10-7.30 (bd, 1H, Ar-H), 7.50-7.55 (d, 2H, Ar-H), 7.60-7.75 (d, 1H, Ar-H), 7.80-7.90 (d, 2H, Ar-H); Anal. Calcd. for $C_{19}H_{20}O_4$ C, 73.06; H, 6.45% Found C, 73.01; H, 6.44%.

1-(3'-Methyl-4'-methoxyphenyl)-3-(3",4",5"-trimethoxyphenyl)-prop-2-ene-1-one (**7d**) :- Obtained from 3-methyl-4-methoxy acetophenone (**5**, 1.0 g, 6.2 mmol) and 3,4,5-trimethoxybenzaldehyde (**6d**, 1.22 g, 6.30 mmol) as pale yellow crystalline solid in 85% (1.78 g), m. p.= 88-89°C, IR (KBr): 1605 (C=C), 1616, 1662 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.30 (s, 3H, CH_3), 3.85 (s, 9H, OCH_3), 3.90 (s, 3H, OCH_3), 6.80 (bd, 2H, -HC=CH-), 6.40 (s, 2H, Ar-H), 6.50 (s, 1H, Ar-H), 7.70-7.80 (d, 2H, Ar-H) ; Anal. Calcd. for $C_{20}H_{22}O_5$ C, 70.16; H, 6.48%: Found C, 70.10; H, 6.50%.

1-(3'-Methyl-4'-methoxyphenyl)-3-(3"-nitrophenyl)-prop-2-ene-1-one (**7e**) :- Obtained from 3-methyl-4-methoxy acetophenone (**5**, 1.0 g, 6.2 mmol) and 3-nitrobenzaldehyde (**6e**, 0.94 g, 6.2 mmol) as pale brown crystalline solid in 78% (1.47 g), m. p.= 134-36°C, IR (KBr): 1605 (C=C), 1610, 1672 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.30 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 6.70-6.90 (bd, 2H, HC=CH-), 7.20 (s, 1H, Ar-H), 7.30-8.00 (m, 6H, Ar-H) ; Anal. Calcd. for $C_{17}H_{15}NO_4$ C, 68.66; H, 5.09; N, 4.71%: Found C, 68.74; H, 6.39; N, 4.75%.

General procedure for the preparation of cyclopropyl ketoesters (8): A typical procedure is described for the preparation of ***ethyl-2-(3'-methyl-4'-methoxybenzoyl)-3-phenyl cyclopropane-1-carboxylate*** (**8a**) :- Freshly distilled cyanoethyl acetate (0.45 g, 4.0 mmol) was added into a magnetically stirred suspension of powdered sodium (0.18 g, 8 m atom) in dry benzene (25 mL) in a 100 ml round bottomed flask fitted with guard tube. Chalcone (**7a**, 1.02 g, 4.0

mmol) was added and the mixture stirred at room temperature. After 24 hrs, reaction mixture was washed successively with 5% NaOH (2 X 15 mL), brine solution (2 X 15 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure yielded a pasty mass, which after purification over chromatography yielded the cyclopropyl ester in 82% (1.12 g) yield as a pale yellow oil. Alkaline extract on acidification with conc. HCl at 5°C gave a pasty mass, which was then extracted into ether layer and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave keto acid (**9a**) as a pale yellow oil in 10% (0.125 g) yield.

Esterification of keto acid (9a): Solution of keto acid (**9**, 0.125 g) in absolute ethanol (10 mL) was treated with conc. H_2SO_4 acid (0.5 mL) and refluxed for 4 hrs. After 4 hr, solvent was evaporated off, neutralized with 5% sodium bicarbonate solution and then extracted into ether. The ethereal layer was washed thoroughly with water (2 X 20 mL), brine solution (1 X 15 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure yielded a pasty mass, which after purification over chromatography yielded the cyclopropyl ester (**8a**) in 95% (0.128 g) yield as a pale yellow oil, IR (KBr): 1605 (C=C), 1680 (CO), 1750 (ester CO) cm^{-1}, ^1H NMR ($CDCl_3$); δ 0.95-1.12 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.20-3.35 (m, 3H, C_1, C_2, C_3-H), 3.70-3.95 (q, 2H, OCH_2), 3.90 (s, 3H, OCH_3), 7.00-7.20 (m, 5H, Ar-H), 7.25-2.35 (d, 1H, Ar-H), 7.80-7.90 (d, 2H, Ar-H); Mass spectrum, m/z (relative intensity): 338 (M^+, 10), 310 (M^+, $-C_2H_4$, 8), 265 (M^--73, 14), 252(M^+-86, 52), 237(M^+-101, 32), 149($ArCO^+$, 100); Anal. Calcd. for $C_{21}H_{22}O_4$ C, 74.52; H, 6.56%: Found C, 74.59; H, 6.39%.

Ethyl-2-(3'-methyl-4'-methoxybenzoyl)-3-(4"-methoxyphenyl)- cyclopropane-1-carboxylate **(8b)** :-Obtained from (**7b**, 1.0 g, 3.2 mmol) and cyanoethyl acetate (0.36 g, 3.2 mmol) as pale yellow oily product in 85% (1.08 g) yield, IR (KBr): 1605 (C=C), 1678 (CO), 1755 (ester CO) cm^{-1}, ^1H NMR ($CDCl_3$); δ 0.95-1.10 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.20-3.35 (m, 3H, C_1, C_2, C_3-H), 3.70-3.90 (q, 2H. OCH_2), 3.90 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 7.00-7.20 (d, 2H, Ar-H), 7.25-2.35 (d, 1H, Ar-H), 7.60-7.80 (bd, 4H, Ar-H); Mass spectrum, m/z (relative intensity): 368(M^+, 12), 340(M^+,-C_2H_4, 11), 295(M^+-73, 20), 282(M^+-86, 71), 267(M^+-101,15), 149($ArCO^+$, 100); Anal. Calcd. for $C_{22}H_{24}O_5$ C, 71.72; H, 6.57%: Found C, 71.78; H, 6.425%.

Ethyl-2-(3'-methyl-4'-methoxybenzoyl)-3-(3",4"-dimethoxyphenyl)-cyclopropane-1-carboxylate **(8c)** :-Obtained from (**7c**, 1.0 g, 3.2 mmol) and cyanoethyl acetate (0.36 g, 3.2 mmol) as pale yellow oily product in 85% (1.08 g) yield, IR (KBr): 1605 (C=C), 1678 (CO), 1755 (ester CO) cm^{-1}, ^1H NMR ($CDCl_3$); δ 1.00-1.10 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.20-3.30 (m, 3H, C_1, C_2, C_3-H), 3.70-3.95 (q, 2H. OCH_2), 3.85 (s, 6H, OCH_3), 3.90 (s, 3H, OCH_3), 7.00-7.10 (s, 2H, Ar-H), 7.25-7.35 (d, 1H, Ar-H), 7.60-7.75 (d, 1H, Ar-H), 7.80-7.90 (d, 2H, Ar-H); Mass spectrum, m/z (relative intensity):

398(M^+, 11), 370($M^+-C_2H_4$,7), 325(M^+-73, 18), 312(M^+-86,55), 297(M^+-101, 32), 149($ArCO^+$, 100); Anal. Calcd. for $C_{23}H_{26}O_6$ C, 69.33; H, 6.58%: Found C, 69.40; H, 6.55%.

Ethyl-2-(3'-methyl-4'-methoxybenzoyl)-3-(3",4",5"-dimethoxyphenyl)-cyclopropane-1-carboxylate **(8d)** :-Obtained from (**7d**, 1.0 g, 2.9 mmol) and cyanoethyl acetate (0.33 g, 2.9 mmol) as pale red oily product in 82% (1.02 g) yield, IR (Nujol): 1605 (C=C), 1678 (CO), 1760 (ester CO) cm^{-1}, ^1H NMR ($CDCl_3$); δ 0.95-1.10 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.20-3.35 (m, 3H, C_1, C_2, C_3-H), 3.70-3.85 (q, 2H. OCH_2), 3.85 (s, 9H. OCH_3), 3.90 (s, 3H, OCH_3), 7.00-7.20 (d, 2H, Ar-H), 7.25-2.35 (d, 1H, Ar-H), 7.80-7.90 (d, 2H, Ar-H); Mass spectrum, m/z (relative intensity): 428(M^+,12), 400 ($M^+-C_2H_4$, 9), 355(M^+-73,25), 342(M^+-86, 56), 327(M^+-101,15), 149($ArCO^+$, 100); Anal. Calcd. for $C_{24}H_{28}O_7$ C 67.26; H, 6.59%: Found C, 67.20; H, 6.63%.

Ethyl-2-(3'-methyl-4'-methoxybenzoyl)-3-(3"-nitrophenyl)-cyclopropane-1-carboxylate **(8e)** :-Obtained from (**7e**, 1.0 g, 3.4 mmol) and cyanoethyl acetate (0.38 g, 3.4 mmol) as pale red oily product in 80% (1.03 g) yield, IR (Nujol): 1362 (sym NO_2), 1522 (asym NO_2), 1600 (C=C), 1678 (CO), 1745 (ester CO) cm^{-1}, ^1H NMR ($CDCl_3$); δ 0.95-1.12 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.20-3.35 (m, 3H, C_1, C_2, C_3-H), 3.70-3.95 (q, 2H. OCH_2), 3.90 (s, 3H, OCH_3), 7.00-7.20 (m, 4H, Ar-H), 7.25-2.35 (d, 1H, Ar-H), 7.80-7.90 (d, 2H, Ar-H); Mass spectrum, m/z (relative intensity): 383(M^+,10), 355($M^+-C_2H_4$, 12), 310(M^+-73,16), 297(M^+-86,56), 282(M^+-101,21), 149($ArCO^+$, 100); Anal. Calcd. for $C_{21}H_{21}NO_6$ C, 65.77; H, 5.52; N, 3.65%: Found C, 65.73; H, 5.44; N, 3.69%.

General procedure for the preparation of tetralone esters (4): A typical procedure is described for the preparation of ***ethyl-6-methyl-7-methoxy-1-phenyl-4-oxo-2-naphthoate*** **(4a)** :-Solution of cyclopropyl ketoester (**8a**, 0.80 g, 2.36 mmol) in nitrobenzene (10 mL) was added dropwise to a magnetically stirred solution of anhydrous stannic chloride (0.54 g, 4.6 mmol) in nitrobenzene (10 mL) for half an hour at 0°C and further stirred for 6 hrs. After treating with 5N HCl (5 mL), the organic layer was washed with 10% NaOH (2 X 10 mL) and finally with water. Brown gummy product obtained after steam distillation of the solvent was purified by coloumn chromatography using chloroform as eluant to yield tetralone ester **4a** as red semisolid in 65% (0.52 g) yield, IR (KBr): 1605 (C=C), 1670 (CO), 1725 (ester CO) cm^{-1}, ^1H NMR ($CDCl_3$): δ 0.9-1.2 (t, 3H, CH_3), 2.1 (s, 3H, CH_3), 2.85 (d, 2H, J=6Hz, C_3-H), 3.1-3.25 (m, 1H, C_2-H), 3.70-3.90 (q, 2H, OCH_2), 3.95 (s, 3H, OCH_3), 4.55 (d, 1H, J=6Hz, C_1-H), 7.1-7.8 (m, 7H, Ar-H); Anal. Calcd. for $C_{21}H_{22}O_4$ C, 74.52; H, 6.56%: Found C, 74.47; H, 6.55%

Ethyl-6-methyl-7-methoxy-1-(4'-methoxyphenyl)--4-oxo-2-naphthoate **(4b)** :-Prepared from (**8b**, 0.80 g, 2.17 mmol) in dry benzene containing stannic chloride (0.5g, 4.2 mmol) as brown gummy product in 60% (0.48 g) yield, IR (KBr): 1610 (C=C), 1678 (CO), 1750 (ester CO) cm^{-1}, ^1H NMR ($CDCl_3$): δ 0.9-1.10 (t, 3H,

CH_3), 2.2 (s, 3H, CH_3),), 2.80 (d, 2H, J=5.5Hz, C_3-H), 3.1-3.25 (m, 1H, C_2-H), 3.65-3.80 (q, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.55 (d, 1H, J=5.5Hz, C_1-H), 6.7-7.8 (m, 6H, Ar-H); Anal. Calcd. for $C_{22}H_{24}O_5$ C, 71.72; H, 6.57%: Found C, 71.69; H, 6.62%.

Ethyl-6-methyl-7-methoxy-1-(3',4'-dimethoxyphenyl)—4-oxo-2-naphthoate **(4c)** :-Prepared from (**8c**, 0.80 g, 2.01 mmol) in dry benzene containing stannic chloride (0.50 g, 4.2 mmol) as brown gummy product in 62% (0.49 g) yield, IR (KBr): 1613 (C=C), 1670 (CO), 1750 (ester CO) cm^{-1}, ^1H NMR ($CDCl_3$) δ 0.9-1.1 (t, 3H, CH_3), 2.15 (s, 3H, CH_3),), 2.85 (d, 2H, J=6Hz, C_3-H), 3.1-3.25 (m, 1H, C_2-H), 3.60-3.75 (q, 2H, OCH_2), 3.80 (s, 6H, OCH_3), 3.85 (s, 3H, OCH_3), 4.55 (d, 1H, J=6Hz, C_1-H), 6.8-7.8 (m, 5H, Ar-H); Anal. Calcd. for $C_{23}H_{26}O_6$ C, 69.33; H, 6.58%: Found C, 69.32; H, 6.59%.

Ethyl-6-methyl-7-methoxy-1-(3',4',5'-trimethoxyphenyl)—4-oxo-2-naphthoate **(4d)** :-Prepared from (**8d**, 0.80 g, 1.86 mmol) in dry benzene containing stannic chloride (0.5 g, 4.2 mmol) as brown gummy product in 62% (0.49 g) yield, IR (Nujol): 1605 (C=C), 1678 (CO), 1755 (ester CO) cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.0-1.3 (t, 3H, CH_3), 2.2 (s, 3H, CH_3),), 2.85 (d, 2H, J=6Hz, C_3-H), 3.1-3.25 (m, 1H, C_2-H), 3.60-3.80 (q, 2H, OCH_2), 3.82 (s, 6H, OCH_3), 3.85 (s, 6H, OCH_3), 4.55 (d, 1H, J=6Hz, C_1-H), 6.4-7.5 (bm, 4H, Ar-H); Anal. Calcd. for $C_{24}H_{28}O_7$ C 67.26; H, 6.59%: Found C, 67.30; H, 6.56%.

Ethyl-6-methyl-7-methoxy-1-(3'-nitrophenyl)—4-oxo-2-naphthoate **(4e)** :- Prepared from (**8e**, 0.81 g, 2.08 mmol) in dry benzene containing stannic chloride

(0.5 g, 4.2 mmol) as brown gummy product in 60% (0.49 g) yield, IR (KBr): 1600 (C=C), 1683 (CO), 1734 (ester CO) cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.0-1.3 (t, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.85 (d, 2H, J=6Hz, C_3-H), 3.1-3.25 (m, 1H, C_2-H), 2.95 (d, 2H, CH_2), 3.60-3.75 (q, 2H, OCH_2), 3.80 (s, 3H, OCH_3), 4.55 (d, 1H, J=6Hz, C_1-H), 6.7-8.1 (m, 6H, Ar-H); Anal. Calcd. for $C_{21}H_{21}NO_6$ C, 65.77; H, 5.52; N, 3.65% Found C, 65.81; H, 5.55; N, 3.63%.

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