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SYNTHESIS OF NEW INTERMEDIATES OF PODOPHYLLOTOXIN ANALOGUES

Amos Victor and Y.B. Basavaraju*
Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore-570006

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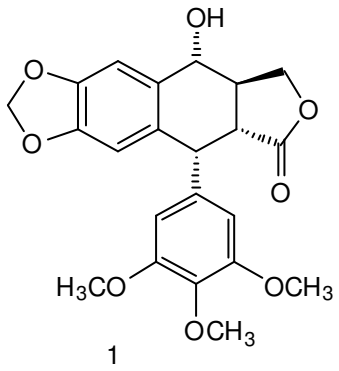
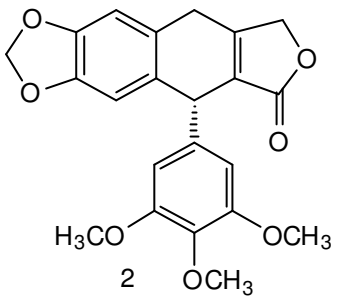
The new 3-ethyl carboxy-4-phenyl-6-fluoro-1-tetralone and 3-ethyl carboxy-4-(*p*-anisyl)-6-fluoro-1-tetralone were synthesized in good yields by chalcone route. They are key intermediates for the synthesis of analogues of podophyllotoxin a naturally occurring lignan compound. It exhibits antimitotic activity and other biological activity. The structure of new compounds were based on spectral and elemental analysis data.

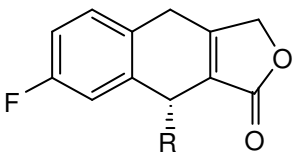
Podophyllotoxin **1** has been extracted from the medicinal plants such as *Podophyllum emodi* an Indian species, *Podophyllum peltatum* a North American species and from many other plants of *Podophyllum* species[1,2]. It belongs to the large family of natural products called lignans. Podophyllotoxin and its analogues exhibit strong biological activities such as antimitotic, anticancer, cathartic, cytotoxic, antitropical skin diseases, antimalarial, anti HIV (AIDS). β- Apopicropodophyllin **2**, a dehydrated product of podophyllotoxin showed stronger biological activity. With a view to study their structure activity relationship, it was decided to synthesize analogues **3** and **4** of podophyllotoxin by modifying methylenedioxy ring and ring C in **1** and **2**[3]. Several synthetic routes have been reported for the synthesis of podophyllotoxin analogues **3** and **4** *via* tetralone ester intermediates **5,6**. The chalcone route has been chosen with some change in experimental procedure[4]. The starting material *p*-fluoro acetophenone was



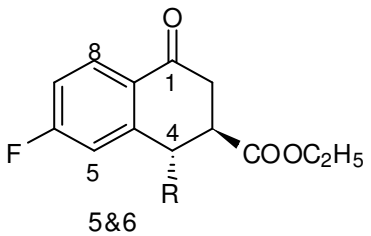
1



2

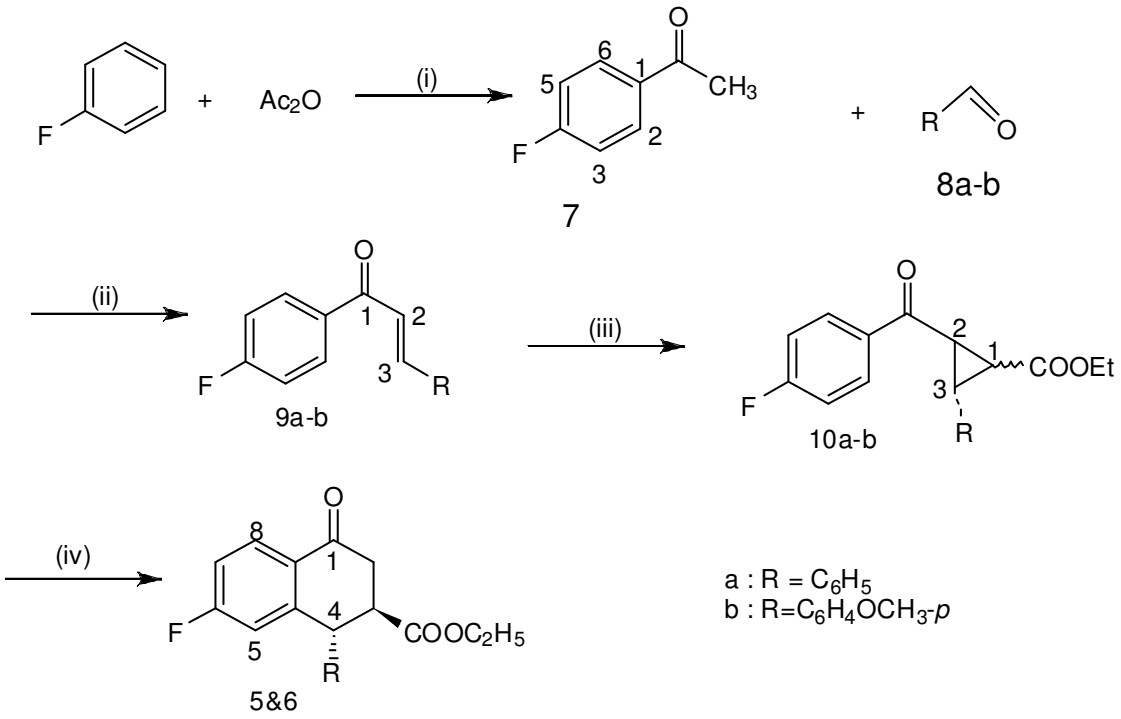


3&4



5&6

3&5 : R = C_6H_5
4&6 : R=$C_6H_4OCH_3$-*p*



(i) Anhyd. $ZnCl_2$, R.T.
(ii) KOH, C_2H_5OH-H_2O, R.T.
(iii) $ClCH_2COOC_2H_5$, Powdered Na, Dry C_6H_6, R.T.
(iv) Anhyd. $SnCl_4$, Ac_2O, dry CH_2Cl_2, 0^0-25^0

SCHEME-1

prepared in good yield by Friedel-Craft's acylation reaction of fluorobenzene with acetic anhydride in presence of fused zinc chloride[5]. Chalcones **8**a-b were prepared in excellent yields by Claisen condensation reaction of *p*-fluoro acetophenone with benzaldehyde **8**a-b in the presence of potassium hydroxide in water-ethanol mixture[6]. Cyclopropyl ketoesters **10**a-b were prepared in good yields by the reaction of chalcones **7**a-b with ethyl chloro acetate in the presence of powdered sodium in dry benzene[7,8,9]. The structure of the compounds were based on ^{1}H NMR, IR spectra and elemental analysis data.

Tetralone ester intermediates **5** and **6** were prepared in good yields by the intramolecular Friedel-Craft's acylation reaction of cyclopropyl keto ester **10**a-b in the presence of anhyd. stannic chloride and acetic anhydride in dry dichloromethane[10]. The structure of tetralone esters were based on ^{1}H NMR, IR mass spectra and elemental analysis data.

Experimental

Melting points of the compounds were taken in open capillary tubes and are uncorrected. The compounds were purified by column chromatography using silica gel (60-120 mesh) as adsorbent and benzene as eluent. The structures of the compounds were based on spectral and elemental analysis data.

1-(4-Fluoro phenyl-3-(phenyl)-prop-2-en-1-one 9a)

4-Fluoro acetophenone **7** (6g, 0.043 mol) and benzaldehyde (4.61g, 0.043 mol) were stirred in water (40 ml) and ethanol (20 ml) mixture in presence of potassium hydroxide (2.44g, 0.043 mol) at 15-30^0 for 4 hr. The reaction mixture was kept overnight in an ice bath. The precipitated product was filtered and

recrystallized from ethanol. The pale yellow crystalline compound was obtained in 84.52%, yield (8.3g), m.p. 73-76^0. IR (KBr): 1658 cm (C=O), 1599 (C=C), ^{1}H NMR ($CDCl_3$): 6.7-7.4 δ (m, 10H, ArH, C_2-H), 7.6 (d, J=12Hz, C_3-H). [Found : C, 79.52, H, 4.69 $C_{15}H_{13}FO$ requires C, 79.65, H, 4.87%].

The compound **9**b was obtained as yellow crystalline compound in 86.33%, yield (9.6g), m.p. 68-70^0. IR (KBr): 1660 (C=O), 1592 (C=C); ^{1}H NMR ($CDCl_3$): 3.8 (s, 3H, OCH_3), 6.6-7.2 (m, 7H, Ar-H, C_2-H), 7.3-7.6 (m, 2H, C_3-H, C_5-H). [Found : C, 74.86, H, 4.98 $C_{15}H_{13}FO_2$ requires C, 75.00, H, 5.08%].

Ethyl-2-(4-fluorobenzoyl)-3-(phenyl)-cyclopropane-1-carboxylate 10a

Chalcone **9**a (5g, 0.022 mol), freshly distilled ethyl chloro acetate (2.71g, 0.022 mol) and powdered sodium (1.02g, 0.044 mol) were stirred in dry benzene (160 ml) at room temp. for 26 hr. The unreacted sodium and its salts were filtered off. The filtrate was washed with 5% aq. sodium hydroxide solution (2x60 ml), 2% brine solution (75 ml) and dried over anhyd. sodium sulfate. After distilling off the solvent, a dark reddish brown semisolid was obtained. The product was purified by column chromatography using benzene as eluent. The product was obtained in 80.92% yield (5.3g) as brown semisolid. IR (KBr): 1739 (C=O of ester), 1679 (C=O), 1602 (aromatic C=C); ^{1}H NMR (DMSO-d_6): 4.1-4.4 d (q,2H, J=4Hz, $COOCH_2CH_3$, 1.0-1.3 (t, 3H, J=4 Hz, $COOCH_2CH_3$), 2.3-3.6 (m, 3H, C1-H, C_2-H & C_3-H), 7.3-7.6 (m, 4H, ArH), 6.7-7.2 (m, 5H, ArH). [Found : C, 72.96, H, 5.37 $C_{19}H_{17}FO_3$ requires C, 73.08, H, 5.45%].

Ethyl-2-(4-fluorobenzoyl)-3-(methoxyphenyl)-cyclopropane-1-carboxylate **10**b was obtained as a brown gummy product in 80.44% yield (5.4g). IR (KBr): 1743 (C=O of ester), 1670 (C=O), 1597 (C=C of aromatic); ^{1}H NMR ($CDCl_3$): 4.0-4.3 (q, 2H, J=4Hz, -$COOCH_2CH_3$), 1.2-1.4 (t, 3H, J=4Hz, $COOCH_2CH_3$), 2.8-3.8 (m, 3H, C_1-H, C_2-H & C_3-H), 6.8-7.6 (m, 8H, ArH), 3.9 (s, 3H, OCH_3). [Found : C, 70.02, H, 5.49 $C_{20}H_{19}FO_4$ requires C, 70.18, H, 5.56%].

3-Ethyl carboxy-4-(phenyl)-6-fluoro-1-tetralone 5

A solution of cyclopropyl ketoester **10**a (4.5g, 0.011 mol) in dry dichloromethane (60 ml) was added dropwise to a stirred solution of anhyd. stannic chloride (3.76g, 0.0144 mol) and acetic anhydride (2.94g, 0.0288 mol) in dichloromethane (60 ml) for half an hr at 0^0 and further stirred for 5 hr. After treating with 5N HCl (50 ml) solution, the organic layer was washed with 10% NaOH solution (2x50 ml) and finally with water. The product was purified by column chromatography using benzene as eluent to give a brown semi-solid compound in 80% yield (9.6g). IR (KBr): 1737 (C=O of ester), 1697 (C=O), 1598 (C=C of aromatic); ^{1}H NMR ($CDCl_3$): 3.7-4.1 (q, 2H, J=4Hz, $COOCH_2CH_3$), 0.9-1.3 (t, 3H, J=4Hz, $COOCH_2CH_3$), 2.1 (d, 1H, J=3H, C_4-H), 2.0-2.4 (dd, 2H, C_2-H), 3.3-3.6 (q, 1H, J=3Hz, C_3-H), 7.4 (d, 1H, J=3Hz, C_8-H), 7.5-7.8 (m, 2H, C_5-H, C_7-H), 6.7-7.1 (m, 5H, ArH). Mass spectrum : 312 (M^+, 28), 239 (34), 211 (16), 183 (43), 91(72). [Found : C, 73.01, H, 5.39 $C_{19}H_{17}FO_3$ requires C, 73.08, H, 5.45%].

3-Ethyl carboxy-4-(4-methoxy phenyl)-6-fluoro-1-tetralone **6** was obtained as brown semi-solid in 84-44%, yield (3.8g). IR (KBr): 1739 (C=O of ester), 1699 (C=O), 1601 (C=C of aromatic); ^{1}H NMR ($CDCl_3$): 3.8 (s, 3H, OCH_3), 6.6-7.0 (m, 4H, ArH), 2.1 (d, 1H, J=4Hz, C_4-H), 3.4-3.8 (q, 1H, C_3-H), 2.2-2.5 (dd, 2H, C_2-H), 7.4 (d, 1H, J=4Hz, C_8-H), 7.5-7.8 (m, 2H, C_5-H & C_7-H). Mass spectrum : 342 (M^+, 21), 286 (23), 238(18), 269(37), 210 (29), 122 (66). [Found : C, 69.98, H, 5.38 $C_{20}H_{19}FO_4$ requires C, 70.18, H, 5.56%].

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