SHORT PAPER

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Alternative procedure for the synthesis of (±)-forskolin precursor†

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A concise synthesis of the enone (11), a potential intermediate for (±)-forskolin (**12**) synthesis is described.

Keywords: forskolin, *Coleus forskohlii*

Forskolin (**12**) is a highly oxygenated labdane diterpene, isolated[1] from the roots of the Indian herb *Coleus forskohlii*. It has shown promising potential as a novel drug[2] useful for the treatment of diseases such as glaucoma, heart failure and bronchial asthma. These interesting biological properties together with the unique structural features of forskolin (**12**) have prompted numerous synthetic studies. These efforts have culminated in four total syntheses[3-6] of this target molecule. In addition there have been a plethora of publications[7-10] directed towards the synthesis of forskolin. In connection with several planned terpene syntheses in our laboratory, we have tried to develop a concise synthesis of the enone (**11**) which has previously been reported by Ziegler[11] and ultimately[3] in the preparation of (±)-forskolin. The present communication describes the pathways that were developed to the find a route to the enone (**11**).

Our synthetic procedure begins with keto-alcohol (**1**) which was prepared by the published procedure[12]. Its benzoyl derivative (**2**), on reduction with borohydride in methanol, afforded a mixture of alcohols, as shown by NMR spectroscopy. On heating[13] in benzene with *p*-toluenesulfonic acid and silica these produced the olefin (**3**) in low yield. Therefore an alternative method was sought. It was found that the tosylates from the alcohols on heating with lithium bromide, lithium carbonate and dimethylformamide afforded the olefin (**3**) in 78% yield. Allylic oxidation[14] with chromium trioxide and 3,5-dimethylpyrazole in dichloromethane furnished the α,β-unsaturated ketone (**4**) in 40% yield. This was converted to the ketone (**5**) by catalytic hydrogenation with PtO_2 in acetic acid. Ketone (**5**) on subjection to (i) reduction with borohydride, (ii) tosylation of the resulting alcohols and (iiii) detosylation, provided the olefinic ketoester (**6**). Alkaline hydrolysis of this ester followed by Jones oxidation[15] of the resulting alcohol produced the unsaturated ketone (**7**) in 70% yield.

Having completed the synthesis of ketone (**7**), we turned our attention to its conversion to enone (**11**). In order to achieve this objective, ketone (**7**) was methylated[15] with methyl iodide in the presence of sodium hydride and triethylborane in tetrahydrofuran. No attempt was however made to assign the configuration of 7-Me group. The desired product (**8**) was obtained in excellent yield. This on bromination with N-bromosuccinimide in carbon tetrachloride followed by dehydrobromination[17] with aniline, produced the α,β-unsaturated ketone (**9**). The alcohol obtained by reduction of ketone (**9**) with sodium borohydride in ethanol, was converted to its tosyl derivative. Treatment of this with sodium cyanide in N-methylpyrrolidone[18] followed by saponification with potassium hydroxide in ethylene glycol produced the acid (**10**) in 35% yield. The conversion of ketone (**9**) to acid (**10**) was carried out without purification of the intermediates. The acid (**10**) showed a weak lactone carbonyl band (1665 cm^{-1}) in the IR spectrum. No attempt was made to assign the stereochemistry of the carboxyl group. Acid (**10**) in ethylene glycol was treated with sulphuric acid and stirred at room temperature for 5 h. The resulting product showed a strong band absorption for a lactone carbonyl in the IR spectrum. The crude material on oxidation[7] with pyridinium chlorochromate in dichloromethane yielded enone (**11**) whose spectroscopic properties satisfactorily matched those reported.[11] In addition of the enone (**11**), a thick dark oily material was obtained which showed the presence of α,β-unsaturated carbonyl and lactone carbonyl in IR spectrum. An attempt was made to purify and characterise the compounds obtained but we were unable to assign the structure of these compounds.

In summary we have developed a concise synthesis of enone (**11**) which proved to be a potential intermediate for the total synthesis of forskolin.

Experimental

Unless otherwise stated IR spectra were taken on Nicolet FT and NMR spectra were recorded on Varian A-90 and Brucker AM-300 spectrometer in $CDCl_3$ using TMS as an internal standard.

Mass spectra were run on Kratos NS25RFA and a gas chromatograph Hewlett Packard 5890 Quadrupolar 5972 series S. The expression "work-up" indicates that the solution was diluted with water, extracted with ether, washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography was carried out on silica gel 60, Merck, grade 60, 70–230 mesh, 60A° and TLC plates were coated with silica gel 60 F_{254}, layer thickness 0.2 mm and the spots were located by exposing to UV light. Microanalyses were carried out in the Department of Chemistry, IVIC.

4,4,8aβ-trimethyl-8β-benzoyl-trans-perhydronaphthalene-3-one (**2**): To a solution of keto alcohol (1) (9.01 g) in pyridine (21 ml) was added benzoyl chloride (13 ml). The mixture was stirred for 20 h at room temperature and diluted with water. The work-up afforded a yellow oil which was chromatographed (hexane:Et_2O) to obtain the keto-benzoate (2) (11.98 g, 89%), m.p. 90–93°C (from Et_2O), *m/z* 314 (M^+–C_6H_5CO), and 192 (M^+–C_6H_5COOH); ν_{max} 1720 cm^{-1} (unresolved ester and ketonic carbonyl); δ 1.07 (s, 3H), 1.09 (s, 3H), 1.21 (s, 3H) (4,4,10-Me), 4.79 (dd, J_{aa}=11 Hz and J_{ae}=3Hz, 1H, 9-H), 7.41–8.19 (m, 5H, aromatic protons) (Found: C, 76.71; H, 8.52. $C_{20}H_{26}O_3$ requires C, 76.40; H, 8.34%).

4,4,8aβ-trimethyl-8β-benzoyl-trans-1,4,4a,5,6,7,8,8a-octahydronaphthalene (**3**): To a solution of benzoate (2) (3.82 g) in ethyl alcohol (80 ml) Sodium borohydride (585 mg). The mixture was stirred for 20 h at room temperature, cold water was added and extracted with chloroform. The work-up afforded an alcohol (3.05 g), ν_{max} 3520 cm^{-1} (OH) and 1714 (CO).

The alcohol was dissolved in dry pyridine (30 ml) and *p*-toluenesulfonyl chloride (5.46 g) was added. The mixture was stirred for 48 h at room temperature, cold water added and extracted with ether. The mixture lithium bromide (3.58 g) was added to the resulting tosylate (3.48 g) dissolved in N,N-dimethylformamide (45 ml) heated for 6 h at 120–130°C. The reaction mixture was cooled, diluted with water and extracted with ether. The work-up

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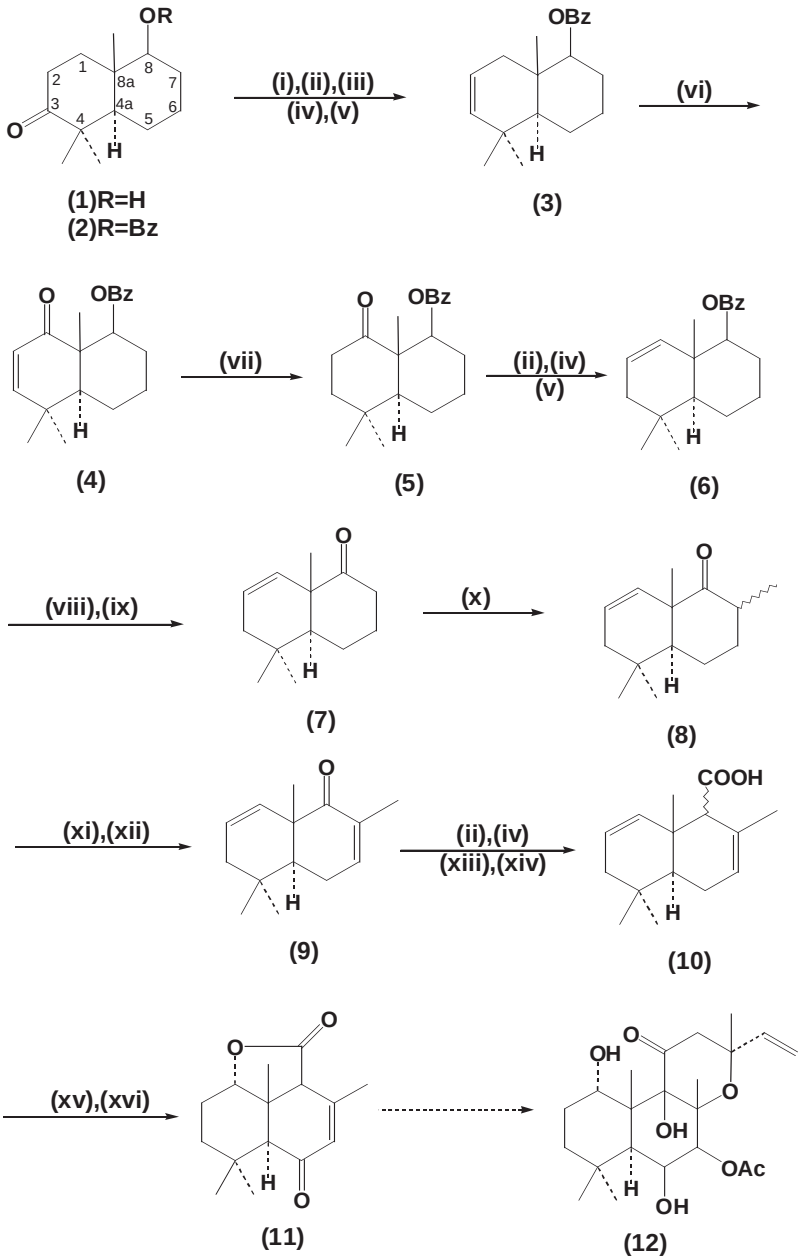

Reagents: (i) BzCl, Pyr; (ii) $NaBH_4$, MeOH; (iii) PTsOH, SiO_2, C_6H_6; (iv) TsC1, Pyr; (v) LiBr, DMF; (vi) CrO_3, 3,5-dimethylpyrazole; (vii) H_2, PtO_2, MeCOOH; (viii) KOH, EtOH; (ix) H_2SO_4-CrO_3; (x) Et_3B, NaH, MeI; (xi) NBS; (xii) C_6H_7N, CCl_4; (xiii) NaCN, $C_6H_{13}N$; (xiv) KOH, $(CH_2OH)_2$; (xv) H_2SO_4, $(CH_2OH)_2$; (xvi) PCC, PH_2Cl_2.

followed by chromatographic purification (hexane: Et_2O 9:1) yielded the olefinic ester (3) (2.82 g, 78%); *m/z* 298 (M^+), 176 (M-C_6H_5COOH) and 161 (M-C_6H_5COOH-Me); ν_{max} 1719 cm^{-1} (CO); δ 0.95 (s, 3H), 1.01 (s, 3H), 1.17 (s,3H) (4,4,10-Me), 4.78 (dd, J_{ae}= 9 Hz, J_{aa}=3.2 Hz, 1H, 9-H), 5.38–5.47 (m, 2H, 2-H, 3-H), 7.44–8.05 (m, 5H, aromatic protons); Found: C, 80.87; H, 8.99. $C_{20}H_{26}O_2$ requires C, 80.49; H, 8.78%).

*4,4,8a*β-*Trimethyl-8*β-*benzoyl-trans-1,4,4a,5,6,7,8,8a-tetrahydronaphthalene-1-one* (**4**): To dry chromium trioxide (4.92 g) in dry methylene chloride (71 ml) at –25°C was added rapidly 3,5-dimethylpyrazole (4.91 g). This was stirred at the same temperature for 35 min and then added dropwise a solution of olefinic ester (**3**) (1.11 g) in dichloromethane (56 ml). The reaction mixture was stirred at –20°C for 5 h and 20 h at room temperature. A solution of aqueous sodium hydroxide (5 M, 20 ml) was added and again stirred for 2 hr. The organic extract was washed with dilute hydrochloric acid, aqueous sodium bicarbonate solution and saturated ammonium chloride solution. The organic extract was dried and evaporated. The resulting residue on chromatographic purification (hexane:Et_2O 9:1) furnished the unsaturated ketone (4) (464 mg, 56%), *m/z* 312 (M^+), 190 (M^+-C_6H_5COOH) and 175 (M^+-C_6H_5COOH-Me); ν_{max} 1716 cm^{-1} (CO) and 1669 (α,β-unsaturated ketone); δ 1.14 (s, 3H), 1.21 (s, 3H), 1.39 (s, 3H) (4,4,10-Me), 4.90 (dd, J_{aa}= 11 Hz, J_{ae}= 4 Hz, 1H, 9-H), 5.94 (dd, *J*=10 Hz, 1H, 2-H), 6.96 (dd, *J*=10 Hz, 1H, 3-H) and 7.49–8.10 (m, 5H, aromatic protons). (Found: C, 76.51; H, 8.02. $C_{20}H_{24}O_3$ requires C, 76.89; H, 7.74%).

*4,4,8a*β-*Trimethyl-8*β-*benzoyl-trans-perhydronaphthalene-1-one* (**5**): Ketone (4) (750 mg) was dissolved in ethanol (8 ml) and hydrogenated at 500 psi using Pd-C (160 mg, 10%) as catalyst for 4 h. The catalyst and solvent were filtered off and concentrated to obtain (5) (704 mg, 94%), m.p. 141–143°C (from Et_2O), *m/z* 314 (M^+), 192 (M^+-C_6H_6COOH) and 177 (M^+-C_6H_6COOH-Me); ν_{max} 1715 cm^{-1} (unresolved ester and carbonyl); δ 0.92 (s, 3H), 1.08 (s, 3H), 1.45 (s, 3H), 5.35 (dd, J_{aa}= 12 Hz, J_{ae}= 5 Hz, 1H, 9-H) and 7.35–7.96 (m, 5H, aromatic protons). (Found: C, 76.71; H, 8.53. $C_{20}H_{26}O_3$ requires C, 76.40; H, 8.34%).

*4,4,8a*β-*Trimethyl-8*β-*benzoyl-trans-3,4,4a,5,6,7,8,8a-octahydronaphthalene* (**6**): To a solution of ketoester (5) (2.12 g) in ethanol (30 ml) was added sodium borohydride (625 mg), stirred at room temperature for 20 h, acidified with acetic acid and extracted with chloroform. The work-up afforded an alcohol (2.02 g), m.p. 145–151°C, ν_{max} 3405 cm^{-1} (OH).

To the alcohol (2.02 g) dissolved in pyridine (20 ml) was added *p*-toluene-sulfonyl chloride (3.62 g). The mixture was stirred for 48 h, cold water added and extracted with ether. The work-up afforded a yellow solid (2.56 g), m.p. 151–155°C which was dissolved in dimethylformamide (30 ml) and treated with lithium bromide (2.38 g). The reaction mixture was heated in oil bath for 6 h at 120–130°C, cooled, diluted with cold water and extracted with ether. The work-up followed by chromatographic purification (hexane: Et_2O 9:1) yielded olefinic ester (**6**) (1.44 g, 72%) as yellow oil; *m/z* 176 (M^+-C_6H_5OOH) and 161 (M^+-C_6H_5COOH-Me); ν_{mas} 1717 cm^{-1} (CO); δ 0.95 (s, 3H), 1.01 (s, 3H), 1.16 (s, 3H) (4,4,10-Me), 4.76 (dd, J_{aa}= 11 Hz, J_{ae}= 4.3 Hz, 1H, 9-H), 5.40–5.45 (m, 2H, 1-H and 2-H), and 7.43–8.07 (m, 5H, aromatic protons). (Found: C, 80.85; H, 8.99. $C_{20}H_{26}O_2$ requires C, 80.49; H, 8.78%).

*4,4,8a*β*-Trimethyl-trans-3,4,4a,5,6,7,8,8a-octahydronaphthalene-8-one* (**7**): To olefinic ester (6) (1.08 g) dissolved in an alcoholic solution of potassium hydroxide (1.44 g KOH, 22 ml ethanol) was heated under reflux for 6 h, cooled, diluted with water and extracted with ether. The work-up followed by chromatographic purification (hexane: Et_2O 7:3) afforded an alcohol as yellow oil (625 mg); *m/z* 176 (M^+-H_2O); ν_{mas} 3405 cm^{-1} (OH).

To alcohol (624 mg) dissolved in acetone (12 ml), cooled at 0°C, was added Jones reagent (1ml), and the mixture was stirred for 30 min at 0°C. To the resulting dark brown solution was added 2-propanol (5 ml), diluted with water and extracted with ether. The work-up followed by chromatographic purification (hexane: Et_2O 6:4) yielded olefinic ketone (**7**) (486 mg, 70%); *m/z* 192 (M^+) and 177 (M^+-Me); ν_{mas} 1708 cm^{-1} (CO); δ 0.96 (s, 3H), 0.98 (s, 3H), 1.14 (s, 3H) (4,4,10-Me), 5.31–5.34 (m, 1H, 2-H), 5.45–5.48 (m, 1H, 1-H). (Found: C, 81.52; H, 10.34. $C_{13}H_{20}O$ requires C, 81.20; H, 10.48%).

*4,4,8a*β*-Trimethyl-3,4,4a,5,8,8a-hexahydronaphthalene-8-one* (**9**): To a suspension of sodium hydride (4.22 g) in dry tetrahydrofuran (10 ml) was added triethylborane (1.22 ml) (Aldrich), stirred for 3 min and added ketone (**7**) (525 mg) dissolved in dry tetrahydrofuran (5 ml). The resulting solution was stirred for 1 hr at room temperature, added methyl iodide (3 ml) and again stirred 30 min at room temperature. To the resulting dark brown solution was slowly added hydrochloric acid (4 ml, 10%) and the mixture was extracted with ether. The work-up followed by chromatographic purification (hexane: Et_2O 9:1) afforded the oily ketone (**8**) (417 mg); *m/z* 206 (M^+).

Ketone (**8**) (415 mg), without further purification and characterization was dissolved in carbon tetrachloride (8 ml). To the resulting solution was added N-bromosuccinimide (125 mg), and heated at 90°C for 3 h. The reaction mixture was cooled, filtered and to the filtrate was added distilled aniline (95 mg) and stirred for 15 h at room temperature. The reaction mixture was washed with hydrochloric acid (15%), saturated solution of sodium chloride, solution of sodium carbonate (5%) and water respectively. The organic extract was dried and evaporated to obtain a yellow oil which on chromatographic purification (hexane: Et_2O 9:1) yielded the α,β-unsaturated ketone (**9**) (417 mg, 75%); *m/z* 204 (M^+) and 189 (M^+–Me);); ν_{mas} 1709 cm^{-1} (CO); δ 0.93 (s, 3H), 0.95 (s, 3H), 1.25 (s, 3H) (4,4,8a-Me), 1.88 (s,3H, 7-Me) 5.37 (dd, 1H, 1-H), 5.80–5.88 (m, 1H, 2-H), 6.29–6.38 (m, 1H, 6-H). (Found: C, 82.67; H, 10.08. $C_{14}H_{20}O$ requires C, 82.30; H, 9.87%).

5-oxo-1,2,3,4,4a,5,8,8a-octahydro-4,4,7,8a-tetramethyl-2H-naphthol 1,8-bc furan-2-one (**11**): Ketone (9) (412 mg) in ethanol (20 ml) was stirred with sodium borohydride (105 mg) for 12 h at room temperature. Work-up afforded alcohol (408 mg); ν_{mas} 3310 cm^{-1} (OH).

The resulting alcohol (408 mg) in pyridine was stirred with p-toluene-sulphonylchloride (502 mg) for 24 h at room temperature. The mixture was diluted with cold water and extracted with ether. Work-up afforded tosylate (580 mg) which exhibited the complete absence of hydroxyl group in the IR spectrum.

To a solution of tosylate (575 mg) in dry N-methyl pyrollidone (15 ml) was added sodium cyanide (210 mg) and heated at 90°C for 24 h. The cooled mixture was treated with ice-water and extracted with ether. The resulting product (152 mg) in TLC (hexane: Et_2O 4:6) indicated that it was a mixture of three compounds; ν_{max} 2260 cm^{-1} (CN).

The crude product (152 mg) and potassium hydroxide (100 mg) in ethylene glycol (8 ml) was heated at 170°C for 18 h. The cooled solution was diluted with water and extracted with ether. The aqueous phase was cooled to 0°C and was acidified with hydrochloric acid (3%), and extracted with dichloromethane. The usual work-up afforded the acid (**10**), contaminated with γ-lactone, as dense liquid (145 mg, 35%); *m/z* 189 (M^+-COOH), 236 (lactonic structure); ν_{max} 1765 cm^{-1} (lactone carbonyl), 1710 (CO) and 3121–2500 (acid OH).

Acid (**10**) (140 mg) was dissolved in ethylene glycol (8 ml) and sulphuric acid (25%, 6 ml) added and was stirred at 35–40°C for 24 h. The reaction mixture was diluted with cold water and extracted with ether. The organic extract was washed several times with a brine solution, dried and evaporated to obtain a dark oil (119 mg); ν_{max} 1745 cm^{-1} (lactone carbonyl) and 1655 (CO).

The oily compound (118 mg), *t*-butylhydroperoxide (70%, 60 μl), pyridinium dichromate (235 mg) and Celite (252 mg) in benzene (15 ml) was stirred at room temperature for 24 h. A further amount of t-butyl hydroperoxide (60 μl) was added and stirred for another 24 h at room temperature. The mixture was diluted with ether (30 ml), then Celite (802 mg) was added and the mixture was filtered through a column of Celite. The column of Celite was washed with ether (3 × 15 ml). The combined ethereal extract was washed with brine, dried and evaporated to obtain a green oil which on chromatographic purification (hexane: Et_2O 7:3) yielded the enone (11) (12 mg) (2.4% from ketone **9**), as a colourless crystal, m.p. 111–113°C (hexane) (lit.[11] 109–110°C); *m/z* 248 (M^+); ν_{mas} 1765 cm^{-1} (lactone CO), 1652 (CO) and 1625 (C=C) ; δ 1.12 (s, 3H), 1.14 (s, 3H), 1.22 (s, 3H) (4,4,8a-Me), 1.46–2.24 (m, 4H, 2-H and 3-H), 2.19 (s, 3H, 7-Me), 5.72 (s, 1H, 6-H). (Found: C, 72.78; H, 8.31. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%).

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