

Synthetic studies towards forskolin

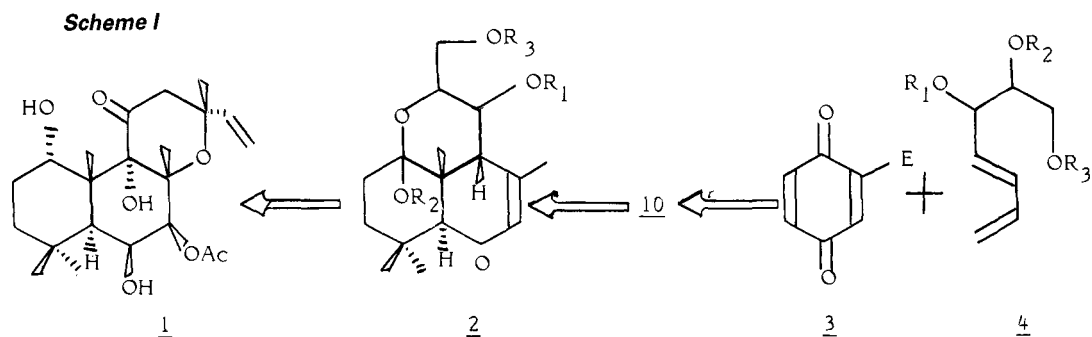
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Abstract - Forskolin (1), a novel labdane diterpenoid isolated from *Coleus forskohlii*, possesses, in addition to eight chiral centers, a novel tetrahydropyran-4-one moiety fused to a highly oxygenated *trans*-decalin system. This paper reports our progress towards the synthesis of AB ring system of forskolin.

Forskolin (1), a highly oxygenated labdane diterpenoid isolated from *Coleus forskohlii* (ref. 1, 2), displays a wide variety of physiological activities (ref. 3), such as bronchospasmolytic, antihypertensive, and inotropic activity. It also activates adenylate cyclase and reduces intraocular pressure in man.

The interesting biological properties coupled with the unique structural features of forskolin (1) have attracted much attention of synthetic chemists the worldover (ref. 5). Three syntheses of forskolin (1) have been achieved (ref. 6-8). Our new approach (ref. 9) is to synthesize the AB ring skeleton of forskolin (1) by intermolecular (4+2) cycloaddition (Scheme-1) of diene 4 derived from D-glucose and *in-situ* generated 2-methoxycarbonyl-*p*-quinone (3).

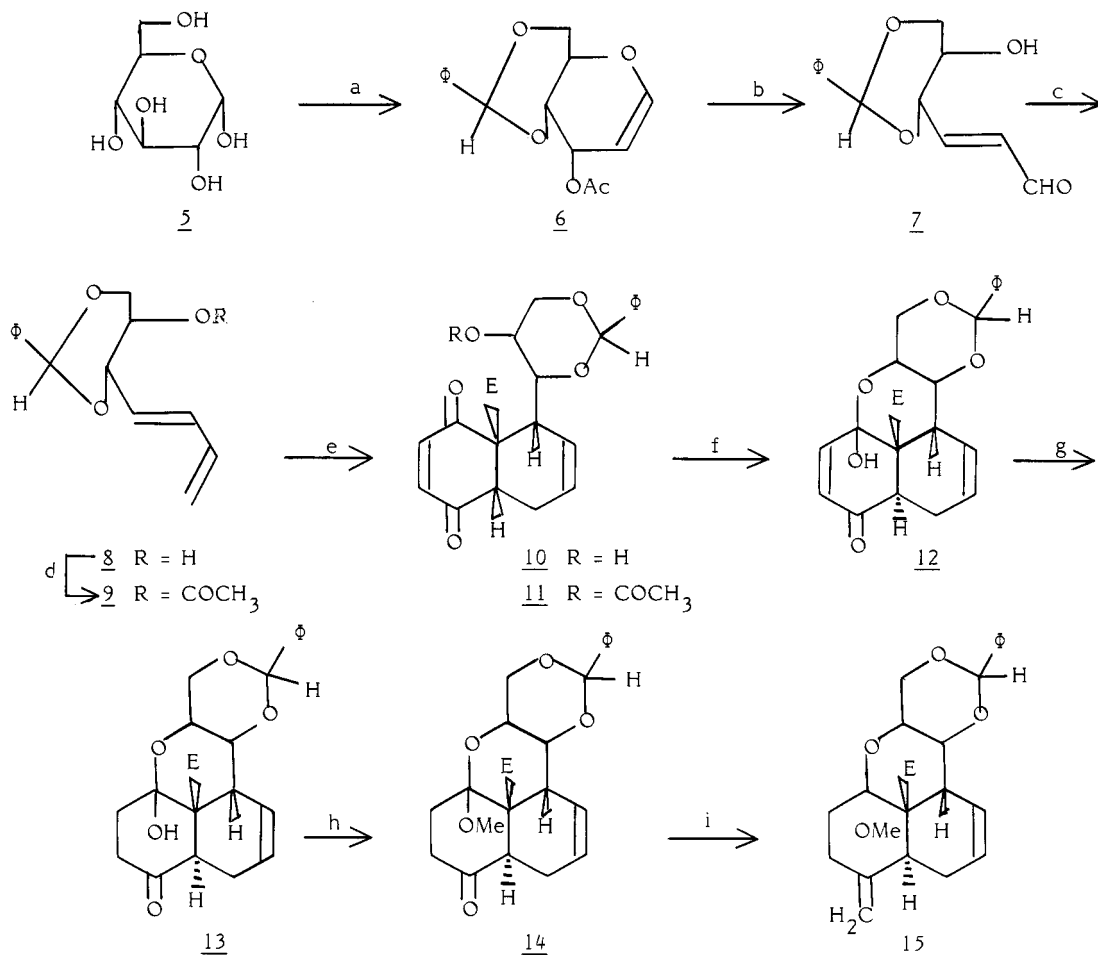


The easily available 3-*O*-acetyl-4,6-*O*-benzylidene-D-allal 6 (ref. 10) on a mercuration-demercuration reaction (ref. 11) afforded the aldehyde 7, which on Wittig olefination gave diene 8 in quantitative yield. The Diels-Alder reaction of diene 8 with 2-methoxycarbonyl-*p*-quinone in the presence of silver oxide (ref. 12) (RT, 24 hr) furnished 10 in 80% yield as a crystalline compound, mp 224–26°, $[\alpha]_D^{20} -346^\circ$ (c 0.5, methanol). The stereo- and regiochemistry of the *cis*-adduct 10 was determined by decoupling experiments which confirmed the assigned structure. Epimerization of 10 with basic alumina (ref. 13) furnished *trans*-adduct 12 in quantitative yield. Examination of the ^1H and ^{13}C NMR spectra of 12 established the stereo- and regiochemical nature of the Diels-Alder reaction. The ^1H NMR spectrum of 12 displayed a doublet of doublets centered at 3.35 ppm ($J_{9,11} = 10.00$, $J_{9,8} = 5.00$ Hz) for the H-9 proton, and a doublet of doublets at 3.06 ppm ($J_{5,6} = 10.00$, $J_{5,6'} = 3.50$ Hz) for the ring junction proton. Such a pattern is consistent only with the stereo- and regiochemistry of 12. The ^{13}C NMR spectrum of 12 showed absorptions at 204 (carbonyl), 105 (hemiketal) and 56 ppm for the C-10 carbon. Further, an upfield shift of 5 to 6 ppm of C-10 carbon in the ^{13}C NMR of 12, 13

[†] Dhar and co-workers (ref. 1) first isolated coleonol from *Coleus forskohlii*, subsequently its identity with forskolin has now been established convincingly (ref. 4).

and 14 as compared to ketones 20, 21 and 22 is very much consistent with the ketal structures and supported the assigned regiochemistry. Treatment of 12 with Zn-AcOH (ref. 13) furnished hemiketal 13 in quantitative yield as a colourless crystalline solid.

Scheme II

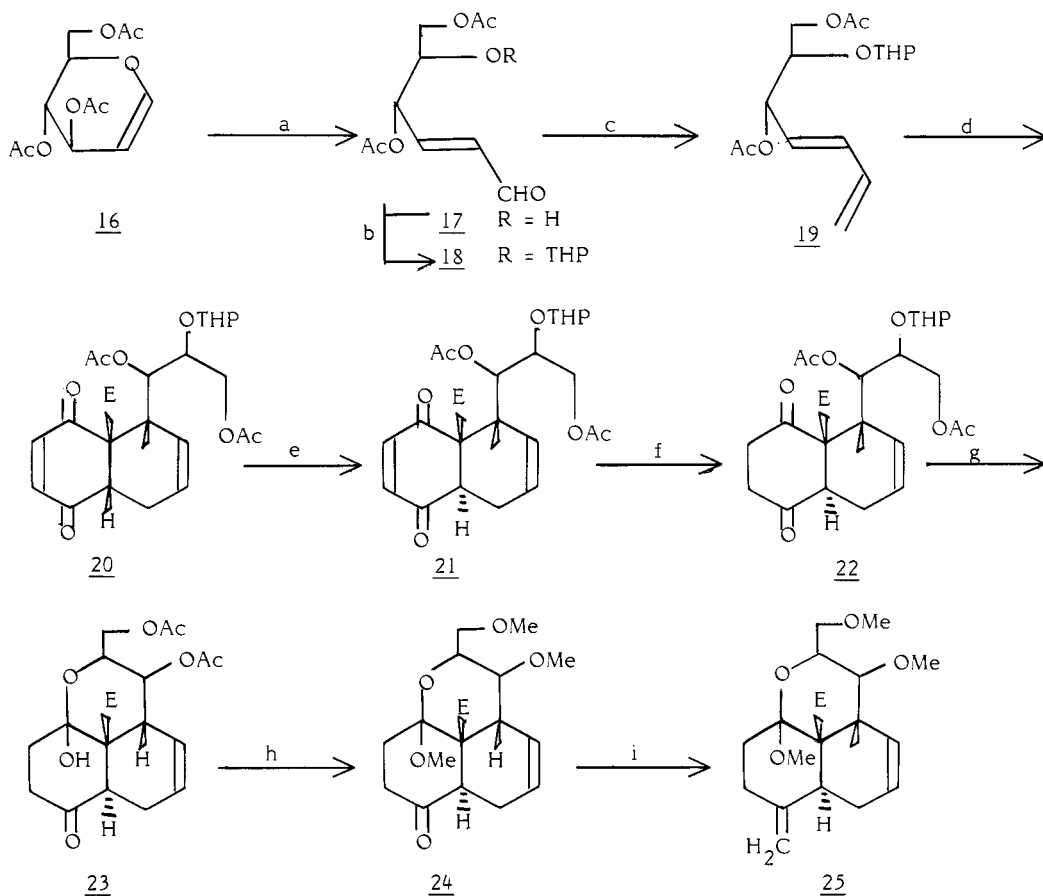


a, Ref. 10; b, $\text{Hg}(\text{OAc})_2$, aq. THF, NaCl; c, $\Phi_3\text{P} = \text{CH}_2$; d, Ac_2O , TEA; e, 2-methoxy-carbonyl-*p*-quinol, ΦH , Ag_2O ; f, Al_2O_3 ; g, Zn-AcOH; h, MeI, NaOH, TBAI; i, $\Phi_3\text{P} = \text{CH}_2$

Thermodynamically more stable hemiketal 13, with a built-in protection of C-1 ketone function was chosen for C-4 alkylation studies. It failed to react with ethylcyanoacetate under various modified reaction conditions. It also failed to react with methylenetriphenylphosphorane, while forcing conditions led to decarboxylation. The failure of the Knoevenagel and Wittig reaction on hemiketal 13 appeared due to side reactions involving the opening of the hemiketal function at C-1. It was, therefore, thought worthwhile to protect the hemiketal function with the base stable protecting group. The hemiketal 13 failed to react with *tert*-butyldimethylsilyl chloride (ref. 14), while conventional method (methanol, PTSA) also failed to give the methoxyhemiketal 14. The protection of the hemiketal function 13 was then attempted under phase transfer catalysed conditions. In the instance, reaction of the hemiketal 13 with methyl iodide and finely powdered sodium hydroxide in the presence of tetrabutylammonium iodide furnished methoxyhemiketal 14 in excellent yield (97%). After successfully protecting hemiketal function in 13, the Wittig reaction was then employed to get alkylated product. Treatment of 14 with base free methylenetriphenylphosphorane (to suppress the enolization and ester hydrolysis) furnished the required olefin 15 in 67% yield.

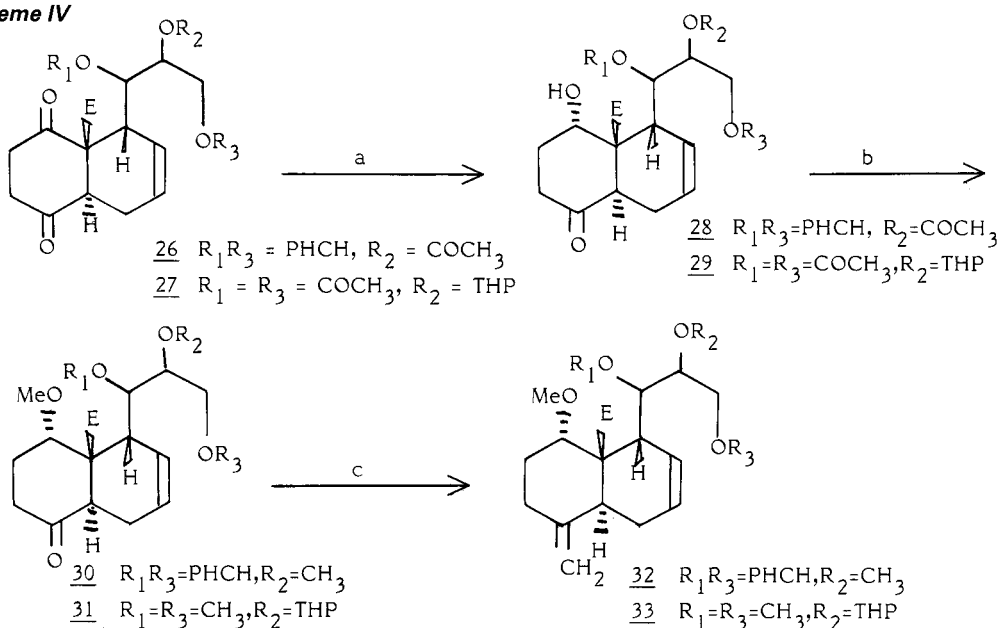
To circumvent the circuitous synthesis of hemiketal 14, simultaneously, we investigated 21, which is available from *D*-glucal 16 (Scheme-III). Easily available *D*-glucal 16 (ref. 15) from *D*-glucose on Perlin reaction (ref. 16) provided aldehyde 17. Protection of the hydroxyl function in 17 (DHP, PTSA) gave 18. Wittig olefination of 18 furnished diene 19 in quantitative yield. The Diels-Alder

Scheme III



a, 0.02N H₂SO₄, Hg(SO₄)₂; b, DHP, PTSA; c, $\Phi_3P = CH_2$; d, 2-methoxycarbonyl-p-quinol, ΦH , Ag₂O; e, Al₂O₃; f, zn-AcOH; g, MeOH, PTSA; h, MeI, NaOH, TBAI; i, $\Phi_3P = CH_2$

Scheme IV



a, NaBH₄, THF; b, MeI, NaOH, TBAI; c, $\Phi_3P = CH_2$

reaction of diene 19 with 2-methoxycarbonyl-p-quinol in the presence of silver oxide (RT, 8 days) furnished 20 in quantitative yield. The *cis*-adduct 20 failed to crystallize, but on epimerization over basic alumina followed by recrystallization (ether-hexane) furnished 21 as a pale yellow crystalline solid (84%). The reaction of 21 with Zn-AcOH furnished diketone 22 in quantitative yield. Deprotection of THP in 22 (MeOH, PPTS) gave hemiketal 23. Treatment of 23 with methyl iodide under PTC conditions afforded 24 in quantitative yield, which on further reaction with methylenetriphenylphosphorane (base free) furnished 25 in 80% yield.

Our next objective was to achieve reduction of C-1 carbonyl function in the presence of C-4 carbonyl function in 26 and 27. Diketone 26 was made available from diene 9 via standard Diels-Alder, epimerization and reduction sequence. Reduction of diketones 26 and 27 with sodium borohydride (ref. 17) in THF was not only chemoselective but it furnished alcohols 28 and 29 in a stereospecific fashion in quantitative yield. Protection of 28 and 29 with methyl iodide under PTC conditions furnished methoxyhemiketals 30 and 31 in excellent yield. Wittig olefination of 30 and 31 with methylenetriphenylphosphorane furnished exomethylene compounds 32 and 33 in more than 80% yield.

In conclusion, we have synthesized four key intermediates 15, 25, 32 and 33, and their further investigations are in progress towards the targeted total synthesis of forskolin.

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