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# Stereocontrolled Syntheses and Biological Profiles of (±)-6,7-Dideoxyforskolin and Its 13-Epimer

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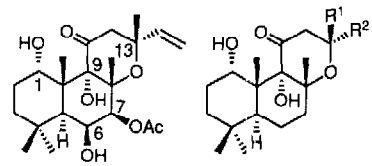
***Abstract:*** *A stereocontrolled synthesis of the hitherto unknown (±)-6,7-dideoxyforskolin has been accomplished, incorporating controlled C-ring annulation with simultaneous creation of the stereogenic center at C-13 via oxymercuration. An alternative attempt at C-ring elaboration via conjugate addition of a higher order vinyl cuprate reagent to dihydropyran-4-one resulted in the exclusive formation of its 13-epimer These analogues displayed no ability to stimulate adenylate cyclase in rat cerebral cortical membranes .*

Forskolin (**1**),[3] a highly oxygenated labdane diterpene isolated from the roots of the Indian herb *Coleus forskohlii*, has been demonstrated to exhibit antihypertensive, positive inotropic, bronchospasmolytic, and antithrombotic activity through a mechanism *via* the activation of adenylate cyclase in various tissues.[4] Due to its therapeutic potential for the treatment of glaucoma, congestive cardiomyopathy, and asthma coupled with its novel molecular architecture, forskolin (**1**) has presented itself as an unusually attractive target for synthetic investigations,[5] wherein three groups including our group have recently culminated in the total syntheses of this target molecule.[6] Our attention has now been turned to studies on the structure-activity relationships of **1**. Structure-activity studies with more than 50 semisynthetic derivatives of **1** and its congeners have demonstrated that the concomitant presence of the axially oriented 1α- and 9α-hydroxy groups should be essential for biological activity.[3b,7] With regard to 6β-hydroxy and 7β-acetoxy groups, it is documented that they are not critical for activity and may be able to tolerate a reasonable amount of modification, which has proven to be the case with a number of water-soluble forskolin analogues recently developed.[8] However, the precise nature of the 6β-hydroxy and 7β-acetoxy groups remains still open to question. Consequently, we directed synthetic efforts to forskolin analogues lacking these groups which are otherwise difficult to prepare from **1** and its congeners. Herein we wish to report stereocontrolled synthesis and biological profile of the hitherto unknown (±)-6,7-dideoxyforskolin (**2**) together with those of its 13-epimer (**3**).

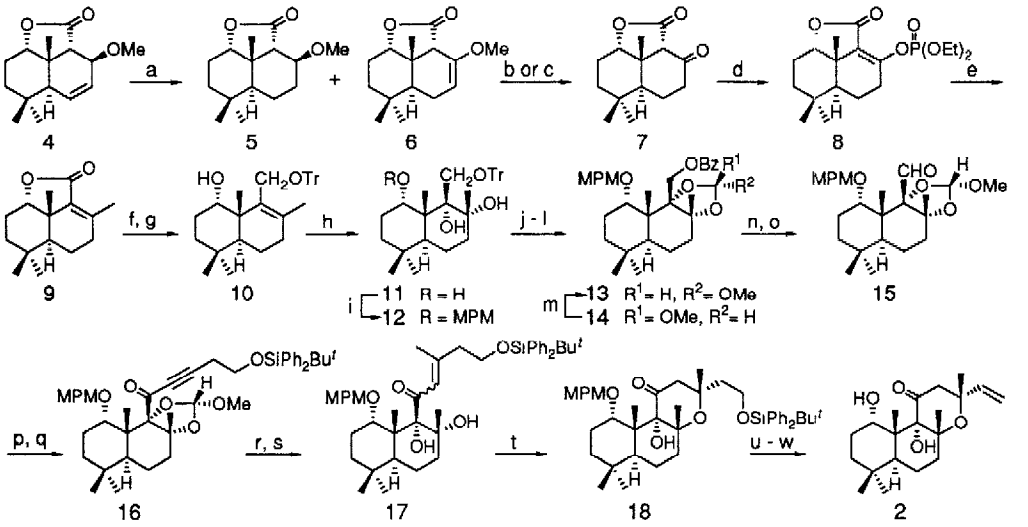



**1**

**2** $R^1$ = Me, $R^2$ = $CH_2$=CH
**3** $R^1$ = $CH_2$=CH, $R^2$ = Me

The synthetic sequence to **2** starting with the tricyclic lactone **4** , a key intermediate for our total synthesis of (±)-**1**,[6b] was detailed in Scheme 1. Catalytic hydrogenation of **4** afforded the methyl ether **5**[9] in 64% yield along with 35% of the enol methyl ether **6**. Demethylation of **5** with $BBr_3$ followed by Jones oxidation produced the β-keto lactone **7** in 90% yield, while treatment of **6** with $BBr_3$ at -40 °C gave the same lactone **7** in 88% yield. To elaborate the methyl-substituted olefinic moiety, **7** was converted into the enol phosphate **8** in 96% yield. Coupling reaction of **8** with dimethylcuprate reagents such as $Me_2CuLi$ and $Me_2Cu(CN)Li_2$ in both the absence and presence of $BF_3{\cdot}OEt_2$ gave less satisfactory results,[10] whereas the palladium(0)-catalyzed

**Scheme 1**



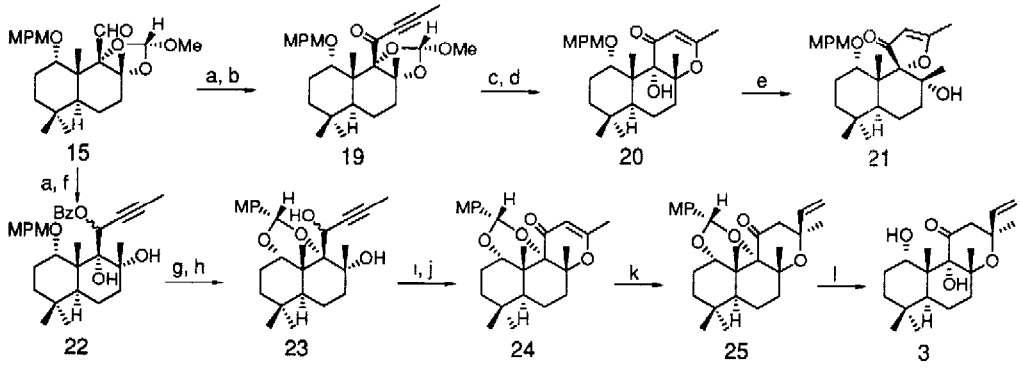
(a) $H_2$, 10% Pd-C, MeOH, 1 h, 64% of **5** and 35% of **6** (b) $BBr_3$, $CH_2Cl_2$, 0.5 h; Jones reagent, acetone, 0 °C, 0 5 h, 90% from **5** (c) $BBr_3$, $CH_2Cl_2$, -40 °C, 1 h, 88% from **6**. (d) NaH, THF-HMPA (8·1), 0.5 h; $(EtO)_2P(O)Cl$, 0.5 h, 96%. (e) $Me_3Al$ (2.0 equiv.), $Pd(PPh_3)_4$ (0.1 equiv.), $ClCH_2CH_2Cl$, sealed tube, 60 °C, 86%. (f) $LiAlH_4$, ether, reflux, 1 h, 87%. (g) TrCl, DMAP, $CH_2Cl_2$, reflux, 30 h, 89% (h) $OsO_4$ (1.2 equiv.), pyridine, 40 h; $H_2S$, 0 °C, 10 min, 83%. (i) NaH, THF-HMPA (1:2), 5 min; MPMCl, 10 h, 93%. (j) TsOH, MeOH, 3 h, 96%. (k) PhCOCl, DMAP, pyridine, 2 h, 95% (l) $HC(OMe)_3$, TsOH, 10 min, 95%. (m) $HC(OMe)_3$, TsOH (n) $K_2CO_3$, MeOH, 60 °C, 3 h, 94%. (o) $SO_3$·pyridine, $Et_3N$, DMSO, 3 h, 87% (p) $LiC{\equiv}CCH_2CH_2OSiPh_2Bu^t$, THF, -78~-25 °C, 2 5 h, 84%. (q) $MnO_2$, benzene, 10 h, 86% (r) $Me_2CuLi$, ether, -78 °C, 20 min, 87%. (s) 10% aq. HCl-THF (1.50), 20 min, $K_2CO_3$, MeOH, 1.5 h, 98% (t) $Hg(OCOCF_3)_2$ (2.7 equiv ), $CH_2Cl_2$, -78~-23 °C, 3 h; LiI, ether, $Et_3N$, 70%. (u) 10% aq HCl-THF-MeOH (1:1:3), 3 h, 81% (v) *o*-$NO_2C_6H_4SeCN$, *n*-$Bu_3P$, THF, 0 5 h, $H_2O_2$, $CH_2Cl_2$, 0 5 h, 86%. (w) DDQ, $CH_2Cl_2$-$H_2O$ (10·1), 3 h; $K_2CO_3$, MeOH, 2 h, 84%.

coupling with trimethylaluminum by the method of Oshima[11] proved to be the superior choice for the high-yielding construction of the conjugated lactone **9**. Since it was anticipated through the synthesis of (±)-**1** that osmylation of the olefin present in the conjugated lactone with a tricyclic system would occur exclusively from the β-side, **9** was reduced with lithium aluminum hydride and then protected as the trityl ether **10**. Indeed, osmylation of **10** proceeded uneventfully from the α-side to afford the 8α,9α-diol **11** in 83% yield, 1α-hydroxy group of which was protected as *p*-methoxybenzyl ether **12**. Protective group interchange followed by treatment with $HC(OMe)_3$ and *p*-toluenesulfonic acid furnished an easily separable 1:1 mixture of the orthoformates **13**[12] and **14**[12] in 86% yield. Since the β-methoxy isomer **14** was found to be a substrate relatively unsuitable for the subsequent steps, particularly at the stage of addition of the lithium acetylide (*vide infra*), **14** was recycled *via* equilibration. Debenzoylation of the α-methoxy isomer **13** and subsequent Parikh-modified Moffatt oxidation[13] afforded the aldehyde **15** in 83% yield, which underwent smooth addition of 4-(*tert*-butyldiphenylsiloxy) butynyllithium and subsequent oxidation with $MnO_2$ to give the ynone **16** in 72% yield. Conjugate addition of $Me_2CuLi$ to **16** followed by hydrolysis afforded the enone **17** as a 70:30 mixture of *E* to *Z* isomers in 85% yield. The C-ring closure of **17** was cleanly effected by oxymercuration with $Hg(OCOCF_3)_2$ or oxyselenation with PhSeCl to give, after reductive workup, the tetrahydropyran-4-one **18**,

with no trace of other cyclization products. It is worthy to mention that the virtually complete control of correct stereochemistry at C-13 *via* oxymercuration proved to be irrespetive of the starting olefin geometry (the ratio of **18** to its 13-epimer: >99: <1 with either *E*- or *Z*-**17**), thus the tedious separation of both isomers being avoided. On the other hand, the ratio of **18** to its 13-epimer *via* oxyselenation was found to be >99: <1 with *E*-**17** and 55:45 with *Z*-**17**. These results can be understood based on the previously proposed model[14] *via* chair-preferred transition states; the oxymercuration proceeds *via* the attack of 8α-hydroxy group on a carbocation allowing rotation about C-12/C-13 bond to orient the methyl group at an axial position, while the oxyselenation proceeds through the intermediacy of both an episelenonium ion and a carbocation. Desilylation of **18** and subsequent elaboration of a vinyl group by a well-established Grieco method[15] was followed by a removal of *p*-methoxybenzyl ether protection,[16] affording (±)-6,7-dideoxyforskolin (**2**), mp 144-145 °C, in 59% yield. Stereochemical proof of **2** was unambiguously established based on nuclear Overhauser effect difference spectra, which showed enhancements of the C-8 methyl signal by the C-10 and C-13 methyl signals.

With the synthesis of **2** completed, we then attempted at an alternative, more efficient construction of the C-ring by the method developed in the synthesis of (±)-1,6,7-trideoxyforskolin[14] as outlined in Scheme 2. Toward this end, the aldehyde **15** was converted into the dihydropyran-4-one **20** under the previously described conditions. However, conjugate addition to **20** with vinyl cuprate reagents such as $(CH_2{=}CH)_2Cu(CN)Li_2$,[17] $(CH_2{=}CH)_2CuLi$,[18] $(CH_2{=}CH)_2CuMgBr$[19] *etc.* under a variety of conditions[20] was found to afford none of the desired product but instead the rearranged dihydrofuran-3-one **21** as the sole product in 70-80% yield. It is of interest to note that conjugate addition of $(CH_2{=}CH)_2Cu(CN)Li_2$ to dihydropyran-4-ones with hydroxy group at C-9 was successful in the syntheses of (±)-1,6,7-trideoxyforskolin[14] and (±)-**1**.[21] Thus, we next examined the feasibility of conjugate addition with the *p*-methoxybenzylidene acetal **24**[12] which was elaborated from the common intermediate **15**. We have now found that conjugate addition to **24** with $(CH_2{=}CH)_2Cu(CN)Li_2$ in the presence of $BF_3OEt_2$ proceeds exclusively from the β-side to give the adduct **25** in 95% yield.[22] This compound was converted under the foregoing conditions into (±)-6,7-dideoxy-13-epiforskolin (**3**),[12] mp 197-198 °C, in 84% yield.

**Scheme 2**




(a) $LiC{\equiv}CCH_3$, THF, -40~0 °C, 1 5 h, 76%. (b) $MnO_2$, benzene, 4 h, 95%. (c) 5% aq. HCl-THF (1.30), 40 °C, 6 h, 77% (d) $Hg(OCOCH_3)_2$ (1.1 equiv.), $MeNO_2$, 0.5 h, LiI, 0 5 h, 72% (e) $(CH_2{=}CH)_2Cu(CN)Li_2$ (20 equiv.), ether, -78~-30 °C, 0.5 h, 80%. (f) 10% aq $HClO_4$-THF (1:4), 10 h; PhCOCl, DMAP, pyridine, 1.5 h, 77% (g) DDQ (1.2 equiv ), $CH_2Cl_2$, 0 °C, 10 h, 86%. (h) $K_2CO_3$, MeOH, 2 5 h, 93% (i) $SO_3$·pyridine, $Et_3N$, DMSO, 3 h, 68%. (j) $Hg(OCOCH_3)_2$ (1 1 equiv ), $MeNO_2$, 0 5 h; LiI, 0 5 h, 79%. (k) $(CH_2{=}CH)_2Cu(CN)Li_2$ (10 equiv.), $BF_3{\cdot}OEt_2$ (10 equiv ), ether, -78 °C, 20 min, 95% (l) DDQ, $CH_2Cl_2$-water (10·1), 10 h; $K_2CO_3$, MeOH, 5 h, 84%

Neither (±)-6,7-dideoxyforskolin (**2**) nor its 13-epimer (**3**) showed ability to stimulate adenylate cyclase in rat cerebral cortical membranes.[23] Based on this result, it has now been disclosed that both or either of hydroxy and acetoxy groups at C-6 and C-7 should be critical for the activation of adenylate cyclase by forskolin.

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