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A Study toward the Total Synthesis of Forskolin(III) A Synthesis of Monocyclized Key Intermediates

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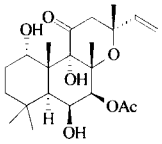
In connection with our continuing efforts[1,2] to utilize an polyene cyclization reaction to build up a carbon skeleton for forskolin **1**, we wish to report the synthesis of the monocyclized diene **13** as a key intermediate. Forskolin **1** is a diterpene obtained from the roots of *Coleus forskohlii* (Willd.)[3] Brig. (*Lamiaceae*), which was described in Ayurvedic materia medica as well as in ancient Hindu medicinal texts as a remedy for several complaints including heart diseases and central nervous system (CNS) disorders such as insomnia and convulsions.

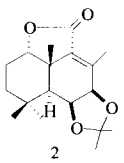


1
Forskolin

In clinical studies, forskolin **1** has shown a promising therapeutic potential as a novel drug for the treatment of diseases such as glaucoma, congestive heart failure, and bronchial asthma.[4] The absolute structure of **1** was determined from the crude methanolic extract of *Coleus forskohlii* in 1977 by the research group at Hoechest.[3,5] It has eight chiral centers and various oxygenated functional groups-hydroxyl, acetate, ketone, ether-with an ether linkage within its tricylic carbon skeleton.

Forskolin **1** has attracted considerable interests from many synthetic organic chemists[6] due to its unique structure and biological activities. The total synthesis of **1** involving a common key intermediate **2** was reported by Ziegler,[7a] Corey[7b] and Ikegami,[7c] respectively. Recently the Ziegler intermediate **2** has been elegantly synthesized by others.[8]

However, all of these synthetic routes required more than 20 steps for building the carbon skeleton with the necessary functional groups.

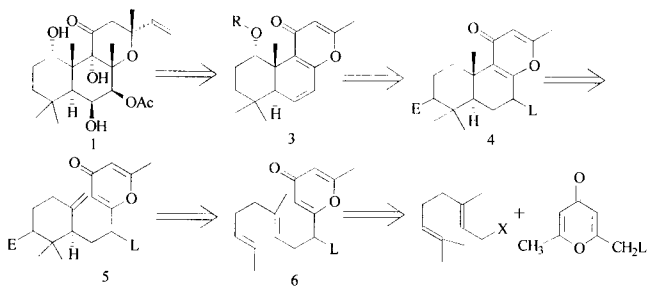


2

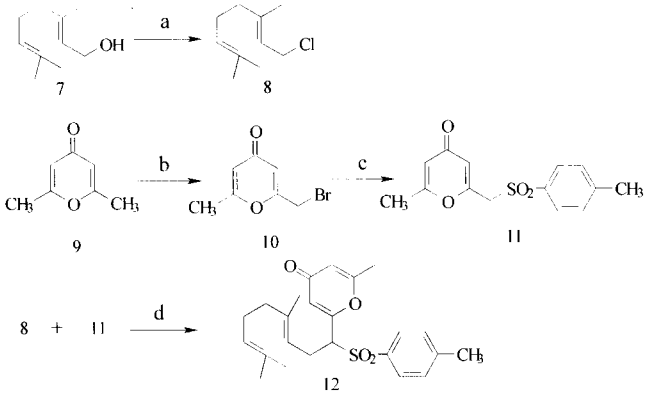
We have investigated a conceptually different approach to synthesize forskolin **1** utilizing polyene cyclization.[9] Our retrosynthetic analysis is depicted in Scheme 1. Forskolin **1** would be synthesized from the key intermediate **4**. The tetramethyl hexahydrobenzochromone of **4** would be constructed from the diene **5** by means of an adequate polyene cyclization reaction (Scheme 1).

Our retrosynthetic analysis led us to prepare (E)-1-chloro-3,7-dimethyl-octa-2,6-diene **8** and 2-methyl-6-[(p-tolylsulfonyl)methyl]-4*H*-pyran-4-one **11** (Scheme 2) which are obtained in a preparative scale as starting materials by optimized reaction conditions developed in our laboratory.[1,2]

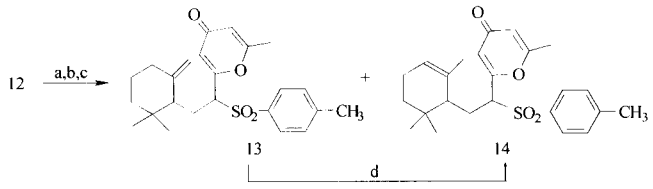
Treatment with (E)-1-chloro-3,7-dimethyl-octa-2,6-diene **8** with sodium hydride in THF followed by the addition of the sulfone-pyrone **11** gave rise to the triene **12** in 65.0% yield (Scheme 2). With a plausible key intermediate at hand, we have investigated an optimized cyclization reaction condition. Unfortunately, all attempts utilizing a Lewis acid promoted polyene cyclization-for example, BF_3-CH_3NO_2, BF_3-$CH_3CH_2NO_2$, I_2, $HgCl_2$, formic acid, etc-failed. After spending considerable amount of time, we finally have obtained mixture of exo olefin **13** in 46.0% and endo olefin **14** in 2.4% yield by using Nishizawa's reagent[10]-mercury(II) triflate and N,N-dimethylaniline-followed by $NaBH_4$ reduction (Scheme 3). Separation of **13** and **14** took a lot of time and care since their Rf values are very close. The reaction mixture of **13** and **14** was further submitted to an acid catalyzed isomerization condition to confirm structural



Scheme 1



Scheme 2. Reagents and conditions; (a) 1.50 eq. LiCl, 1.20 eq. MsCl, 1.20 eq. pyridine, DMF, RT, 2 hr, 94.7%, (b) 0.36 eq. BPO (x3), 0.52 eq. NBS (x4), Benzene, Reflux, 6 hr, 45.6%, (c) Sodium p-tolunesulfinate, EtOH, Reflux, 2 hr, 93.0%, (d) NaH, THF, 0 °C to RT, 2 hr, 65.0%.



Scheme 3. Reagents and conditions; (a) $Hg(OTf)_2$, DMA, CH_3NO_2, −20 °C, 1 hr; (b) Sat'd NaCl, RT, 3 hr; (c) $NaBH_4$-$NaOH/H_2O$, $EtOH/CH_2Cl_2$ (1 : 1), 45 min., 48.4% (3 steps); (d) 0.10 eq. p-Toluenesulfonic acid, Benzene, RT.

assignment. Treatment of the mixture with 0.10 equivalent of p-toluenesulfonic acid in benzene gave rise to the ratio change from (**13** : **14**=19.0 : 1.0) to (**13** : **14**=1.0 : 1.5) which was confirmed by comparison the integrations of olefinic protons (4.83, 4.43 ppm of exomethylene olefin in **13** and 5. 34 ppm of endomethylene in **14**). It showed that **14** is a thermodynamic product and our cyclization reaction was governed by kinetic control.

In summary, the key intermediate **13** was efficiently synthesized from geraniol **7** and 2,6-dimethy-γ-pyrone **9** in a convergent manner. The study for further elaboration to build carbon skeleton of forskolin **1** from **13** is currently under investigation in our laboratory.

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11. All compounds were isolated and fully characterized by spectroscopic methods. For example compound **13**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, 2H, 8.0 Hz), 7.32 (d, 2H, 8.0 Hz), 6.05 (br, 1H), 6.00 (s, 1H), 4.83 (s, 1H), 4.43 (s, 1H), 3.90 (dd, 1H, 12.5, 2.5 Hz), 2.45 (s, 3H), 2.39 (m, 1H), 2.21 (m, 1H), 2.07 (s, 3H), 2.05 (m, 1H), 2.09-1.94 (m, 2H), 1.21-1.28 (m, 1H), 1.61-1.45 (m, 3H), 0.88 (s, 3H), 0.86 (s, 3H). Anal. Calcd for $C_{24}H_{30}SO_4$: C, 69.53; H, 7.30; S, 7.72. Found: C, 69.31; H, 7.69; S, 7.57. Compound **14**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, 2H, 8.0 Hz), 7.32 (d, 2H, 8.0 Hz), 6.08 (br, 1H), 6.04 (1H), 5.34 (m, 1H), 4.09 (dd, 1H, 11.0, 4.5 Hz), 2.45 (s, 3H), 2.28-2.23 (m, 2H), 2.07 (s, 3H), 1.69 (m, 1H), 1.77 (dd, 1H, 13.0, 1 Hz), 1.45 (s, 3H), 1.43-1.39 (m, 3H), 0.92 (s, 3H), 0.83 (s, 3H).