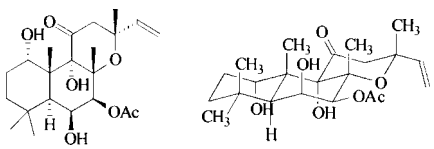
195.
8. Rekkas, S.; Rodios, N.; Alexandrou, N. E. *Synthesis* **1984**, 602.
9. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, 2H, J=8.7), 7.81-7.87 (m, 1H), 7.95-8.01 (m, 2H), 8.38 (d, 2H, J=8.7), 8.71-8.74 (m, 2H).
10. Any reference in Ref. (5) and (6).
11. Fox, M. A.; Dulay, M. T. *Chem. Rev.* **1993**, 341.
12. Omar, A.-M. M. E.; Kasem, M. G.; Laabota, I. M.; Bourdais, J. *J. Heterocyclic Chem.* **1981**, *18*, 499.

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

Kyunghae Lee and Hongbum Kim*

Department of Chemistry, College of Natural Sciences, Dongguk University, Seoul 100-715, Korea
Received June 19, 1998

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.

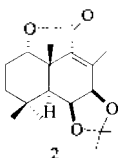


1
Forskolin

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.

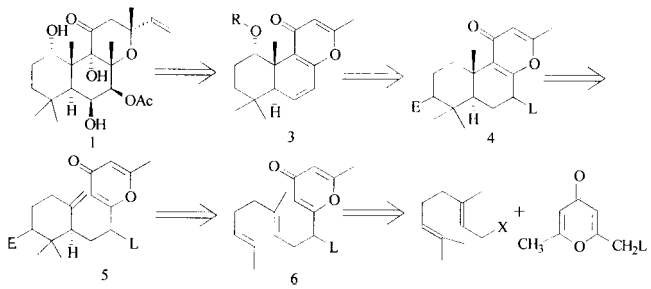


2

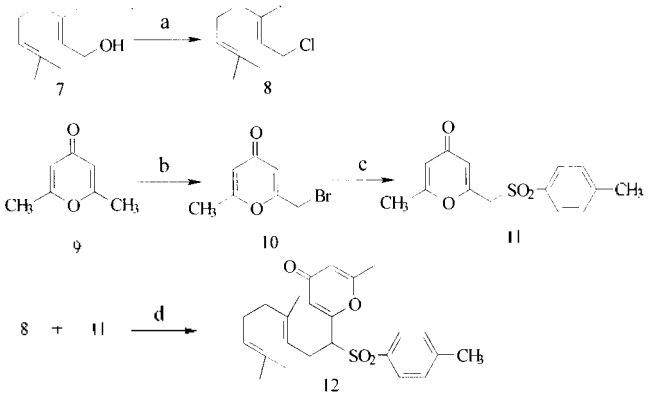
We have investigated a conceptually different approach to synthesize forskolin **1** utilizing polyene cyclization.[9] Our retrosynthetic analysis is depicted in Scheme 1. Forskolin **1** would be synthesized from the key intermediate **4**. The tetramethyl hexahydrobenzochromone of **4** would be constructed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

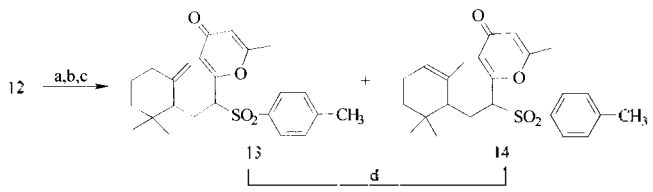
Treatment with (E)-1-chloro-3,7-dimethyl-octa-2,6-diene **8** with sodium hydride in THF followed by the addition of the sulfone-pyrone **11** gave rise to the triene **12** in 65.0% yield (Scheme 2). With a plausible key intermediate at hand, we have investigated an optimized cyclization reaction condition. 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.

Acknowledgment. We are grateful for the generous financial support from the Basic Science Research Institute Program (BSRI-97-3417) by the Ministry of Education and the Organic Chemistry Research Center (OCRC) in Sogang University.

References

1. Kim, B.; Lee, K.; Kim, H. *Bull. Korean Chem. Soc.* **1997**, *18*, 1139.
2. Lee, K.; Lee, C. H.; Kim, H. *ibid.* **1996**, *17*, 773.
3. Bhat, S. V.; Bajwa, B. S.; Dornauer, H.; de Souza, N. J. *Tetrahedron Lett.* **1977**, *27*, 1669.
4. (a) Khandelwal, Y.; Rajeshwari, K.; Rajagopalan, R.; Swamy, L.; Dohadwalla, A. N.; de Souza, N. J. *J. Med. Chem.* **1988**, *31*, 1872. (b) Tatee, T.; Narita, A.; Narita, K.; Izumi, G.; Takahira, T.; Sakurai, M.; Fujita, A.; Hosono, M.; Yamashita, K.; Enomoto, K.; Shirozawa, A. *Chem. Pharm. Bull.* **1996**, *44*, 2274.
5. (a) Bhat, S. V.; Dohadwalla, A. N.; Bajwa, B. S.; Dadkar, N. K.; Dornauer, H.; de Souza, N. J. *J. Med. Chem.* **1983**, *26*, 486. (b) Kogler, H.; Fehlohaber, H.-W. *Magn. Reson. Chem.* **1991**, *29*, 993.
6. (a) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107. (b) A review for forskolin; Colombo, M. I.; Zinczuk, J.; Ruveda, E. A. *ibid.* **1992**, *48*, 963. (c) Hanna, I.; Wlodyka, P. *J. Org. Chem.* **1997**, *62*, 6985.
7. (a) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115. (b) Corey, E. J.; Jardine, P. D. S.; Rohleff, J. C. *ibid.* **1988**, *110*, 3672. (c) Hashimoto, S-i.; Skata, S.; Sonegawa, M.; Ikegami, S. *ibid.* **1988**, *110*, 3670. (d) Delpech, B.; Calvo, D.; Lett, R. *Tetrahedron Lett.* **1996**, *37*, 1023.
8. (a) Blonchot-Courtois, V.; Fetizon, M.; Hanna, I. *Tetrahedron Lett.* **1992**, *33*, 5061. (b) Jordine, G.; Bick, S.; Möller, U.; Welzel, P.; Daucher, B.; Maas, G. *Tetrahedron* **1994**, *50*, 139. (c) Leclaire, M.; Pericaud, F.;. Lallemand, J.-Y. *J. Chem. Soc. Chem. Commun.* **1995**, 1333. (d) Aries, C.; Pancrazi, A.; Lallemand, J.-Y.; Prange, T. *Bull. Soc. Chem. Fr.* **1997**, *134*, 203.
9. (a) Sutherland, J. K. in *Comprehensive Organic Synthesis*, vol. 3, Trost, B. M. Ed., Pergamon Press, 1991, Chapter 1.9. (b) Gopalan, A. S.; Prieto, R.; Mueller, B.; Peters, D. *Tetrahedron Lett.* **1992**, *33*, 1579. (c) Harring, S. R.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 9229.
10. Nishizawa, M.; Monkuni, E.; Asoh, K.; Kan, Y.; Uenoyama, K.; Imagawa, H. *Synlett.* **1995**, 169 and references therein.
11. All compounds were isolated and fully characterized by spectroscopic methods. For example compound **13**. ^{1}H 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**. ^{1}H 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).