A Formal Synthesis of Forskolin: An Electrocyclization Approach

Hemalatha Venkataraman and Jin K. Cha*

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235

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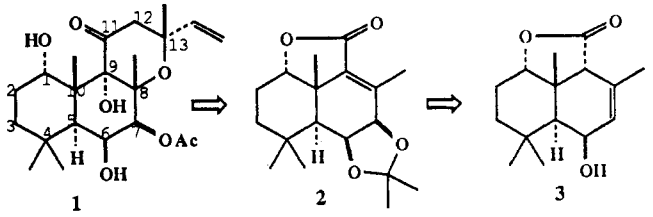
Summary: A formal synthesis of forskolin (1) is reported. A key intermediate, lactone acetonide **2**, was prepared by an efficient functional group transformation of lactol **16**, involving the hydroxyl-directed epoxidation, PCC oxidation, and deoxygenation.

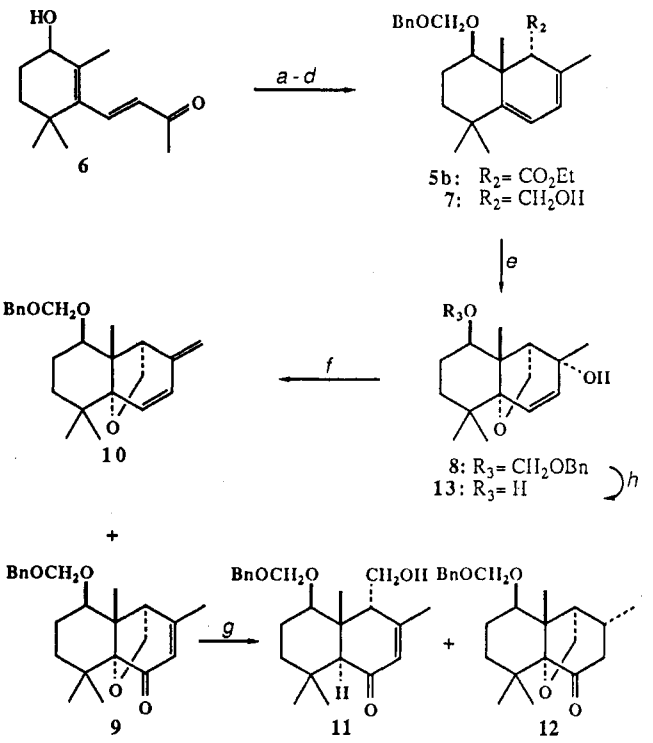
Sir: Forskolin (1), a highly oxygenated diterpene isolated from the roots of the Indian plant *Coleus forskohlii*,[1] has been shown to activate adenylate cyclase and exhibit a wide range of physiological effects. These include bronchospasmolytic, antihypertensive, antiglaucoma, and positive inotropic activities. In addition, forskolin has been demonstrated to inhibit platelet aggregation as well as the metastasis of tumors.[2] The considerable therapeutic potential of **1** and its unique structure have spurred intense synthetic investigations.[3] Most recently there have appeared three accounts of the total synthesis of (±)-forskolin.[4] The majority of previous studies hinge upon an intramolecular cycloaddition methodology, in particular the intramolecular Diels–Alder reaction.[3,4] These recent reports from other laboratories have prompted us to describe herein our synthetic studies of forskolin.



1 **2** **3**

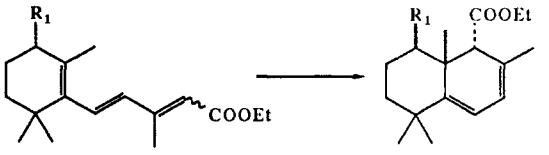
As outlined below, the well-known electrocyclization[5] of (*Z*)-hexa-1,3,5-trienes presents itself as an alternate, efficient route to the AB-ring framework of forskolin. In fact, Frâter previously reported such a cyclization of *Z*/*E*-trienecarboxylate **4a** to bicyclic farnesoate **5a**, along with its 1,5-shift product.[6] The application of the Frâter procedure to ester **4b**, which was readily prepared from

Scheme I[a]



[a] (a) $PhCH_2OCH_2Cl$, iPr_2NEt, CH_2Cl_2; (b) $(iPrO)_2P(O)CH_2CO_2Et$, NaH, THF, reflux; (c) Δ; (d) $LiAlH_4$, ether; (e) tBuOOH, $VO(acac)_2$, PhH; (f) PCC, CH_2Cl_2; (g) Na, anthracene, THF; (h) Li, NH_3.

the known hydroxy-β-ionone **6**[7] gave cleanly a single product **5b** (60–70%).[8,9] The stereochemical assignment of the (benzyloxy)methoxy group was based upon the presence of the diaxial coupling constant (δ 3.82 ppm, dd, J = 11.3 and 4.6 Hz), which clearly indicates H-C(1) to be in the axial position. As noted by Frâter for **5a**, the adduct **5b** was found to be resistant to the alkaline hydrolysis.[6]



4a: R_1 = H
4b: R_1 = OCH_2OBn

5a: R_1 = H
5b: R_1 = OCH_2OBn

The $LiAlH_4$ reduction of ester **5b**, followed by the hydroxyl-directed epoxidation,[10] gave tricyclic alcohol **8** in

(1) (a) Bhat, S. V.; Bajwa, B. S.; Dornauer, H.; de Souza, N. J.; Fehlhaber, H. W. *Tetrahedron Lett.* **1977**, 1669. (b) Bhat, S. V.; Bajwa, B. S.; Dornauer, H.; de Souza, N. J. *J. Chem. Soc., Perkin Trans. 1*, **1982**, 767.

(2) Seamon, K. B. *Ann. Rep. Med. Chem.* **1984**, *19*, 293 and references cited therein.

(3) (a) Jenkins, P. R.; Menear, K. A.; Barraclough, P.; Nobbs, M. S. *J. Chem. Soc., Chem. Commun.* **1984**, 1423. (b) Nicolaou, K. C.; Li, W. S. *Ibid.* **1985**, 421. (c) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *Tetrahedron Lett.* **1985**, *26*, 3307. (d) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Polo, E.; Simoni, D. *J. Chem. Soc., Chem. Commun.* **1986**, 757. (e) Kulkarni, Y. S.; Snider, B. B. *Org. Prep. Proc. Int.* **1986**, *18*, 7. (f) Hutchinson, J. H.; Pattenden, G.; Myers, P. L. *Tetrahedron Lett.* **1987**, *28*, 1313. (g) Bold, G.; Chao, S.; Bhide, R.; Wu, S. H.; Patel, D. V.; Sih, C. J.; Chidester, C. *Ibid.* **1987**, *28*, 1973. (h) Koft, E. R.; Kotnis, A. S.; Broadbent, T. A. *Ibid.* **1987**, *28*, 2799. (i) Liu, Z.-Y.; Zhou, X.-R.; Wu, Z.-M. *J. Chem. Soc., Chem. Commun.* **1987**, 1868. See also: (j) Saksena, A. K.; Green, M. J.; Shue, H.-J.; Wong, J. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1748. (k) Hrib, N. J. *Tetrahedron Lett.* **1987**, *28*, 19.

(4) (a) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115. (b) Hashimoto, S.; Sakata, S.; Sonegawa, M.; Ikegami, S. *Ibid.* **1988**, *110*, 3670. (c) Corey, E. J.; Da Silva Jardine, P.; Rohloff, J. C. *Ibid.* **1988**, *110*, 3672.

(5) (a) Marvell, E. N.; Caple, G.; Schatz, B. *Tetrahedron Lett.* **1965**, 385. (b) Vogel, E.; Grimme, W.; Dinné, E. *Ibid.* **1965**, 391. (c) Marvell, E. N.; Caple, G.; Schatz, B.; Pippin, W. *Tetrahedron* **1973**, *29*, 3781.

(6) Frâter, G. *Helv. Chim. Acta* **1974**, *57*, 2446. Frâter, G.; Muller, U. *Ibid.* **1988**, *71*, 808.

(7) (a) Heather, J. B.; Mittal, R. S. D.; Sih, C. J. *J. Am. Chem. Soc.* **1976**, *98*, 3661. (b) Brooks, D. W.; Bevinakatti, H. S.; Kennedy, E.; Hathaway, J. *J. Org. Chem.* **1985**, *50*, 628. (c) He, J.-F.; Wu, Y.-L. *Synth. Commun.* **1985**, *15*, 95. (d) Henbest, H. B. *J. Chem. Soc.* **1951**, 1074.

(8) (a) The ring closure (50–70% yield) was carried out by the direct pyrolysis (240 °C, *N*,*N*-dimethylaniline) of **4b**, or more conveniently in two steps [(1) photolysis (benzanthrone, THF); (2) thermolysis (140 °C, DMF, 2 days)]. (b) *N*,*N*-Dimethylaniline was reported to be a superior solvent for intramolecular Diels–Alder reactions as well. See: Parker, K. A.; Iqbal, T. *Tetrahedron Lett.* **1986**, *27*, 6291.

(9) All new compounds were fully characterized by IR spectra, ^1H and ^{13}C NMR spectra, and HRMS.

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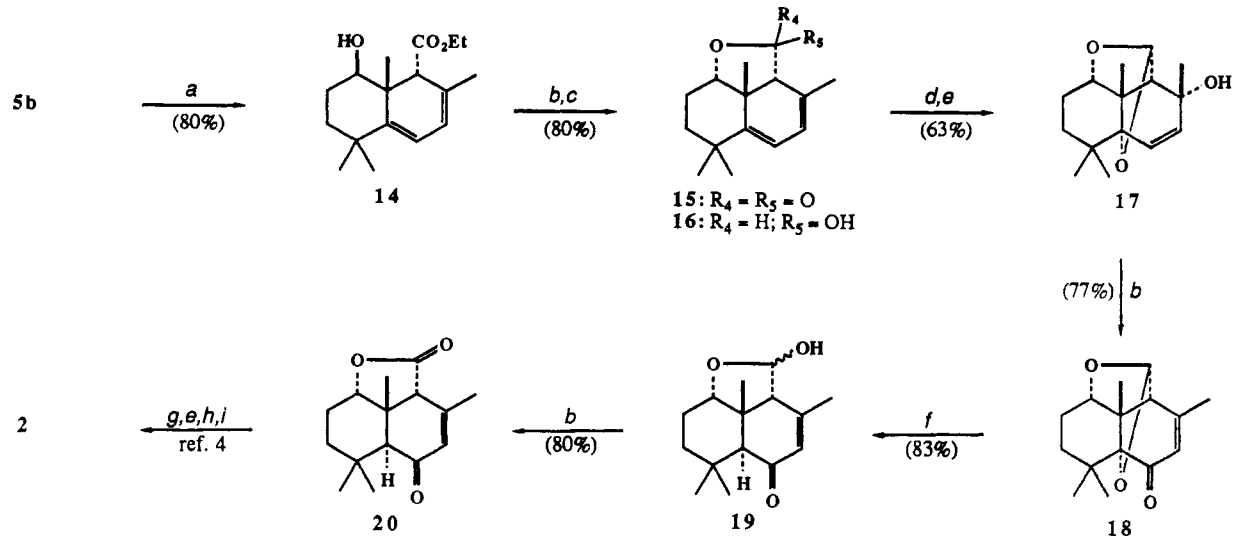
Scheme II[a]



[a] (a) W-2 Raney nickel, EtOH, room temperature; (b) PCC, CH_2Cl_2; (c) $NaBH_4$, EtOH; (d) $LiAlH_4$, ether, 0 °C; (e) tBuOOH, $VO(acac)_2$, PhH; (f) Na, anthracene, THF; (g) $LiBH_4$, Li_2CO_3, EtOH; (h) KOH, MeOH; (i) 2,2-dimethoxypropane, *p*TsOH.

an overall 65% yield (Scheme I). Subsequent conversion of the latter to ketone **9** (60%), contaminated with diene **10** (15%), was achieved by PCC oxidation.[11] The selective reductive cleavage of **9** with sodium anthracenide then afforded the key intermediate **11** in 50–60% yield (based on the recovered starting material). On the other hand, its treatment with Al–Hg in aqueous THF gave a mixture of **11** and **12**.

Having developed an efficient route to a fully functionalized AB-ring unit of **1**, we turned our attention to establishing the correct stereochemistry at the C(1)-OH group.[12] Consequently, deprotection of the (benzyloxy)methyl group in **5b** was achieved (80%) by W-2 Raney nickel, without concomitant reduction of the double bond, to provide **14**.[13] The PCC oxidation of alcohol **14** followed by reduction with $NaBH_4$ gave, in 80% overall yield, a 3:1 mixture of tricyclic lactone **15**, mp 87–89 °C (lit.[3h] mp 80–82 °C) and lactol **16**, mp 112–114 °C. Lactone **15** was then reduced by $LiAlH_4$ (refluxing THF) to the corresponding diol, which did not undergo the transition-metal-catalyzed epoxidation [$VO(acac)_2$, tBuOOH]. However, lactol **16**, which was also readily available (97%) from **15** [$LiAlH_4$, ether, 0 °C], gave tetracyclic alcohol **17** in 63% yield under identical reaction conditions (Scheme II). Alcohol **17** was then smoothly converted to lactol **19** (overall 64% yield) by means of our synthetic protocol as described for ketone **11**. Subsequent PCC oxidation of **19** afforded the corresponding tricyclic lactone **20**, mp 117–118 °C (lit.[3c] mp 109–110 °C), in 80% yield. The latter was then converted, according to the procedures of Ziegler and Corey,[4a,c] to lactone acetonide **2**, mp 95–96 °C (lit.[4c] mp 99–101 °C), which was found to exhibit IR and ^1H and ^{13}C NMR spectra identical with published data. Since acetonide **2** has previously been converted into forskolin (**1**), our work reported herein constitutes its formal synthesis.

It should also be noted that the ready resolution of α-ionone and related compounds (e.g., cyclocitral and cyclogeranic acid) into their antipodes renders our synthetic strategy potentially enantioselective.[14,15] Studies are currently in progress to further elaborate **2** to forskolin, as well as to prepare the initial synthetic intermediate **6** in optically pure form.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Institutes of Health (Grant GM35956) for support of this research.

Supplementary Material Available: Experimental and spectroscopic data for compounds **5b**, **7**, **8**, **9**, **11**, **15**, **17–20**, and **2** and NMR spectra of **2**, **11**, and **20** (12 pages). Ordering information is given on any current masthead page.

(10) (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136. (b) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

(11) (a) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682. (b) Babler, J. H.; Coghlan, M. J. *Synth. Commun.* **1976**, *6*, 469. (c) Liotta, D.; Brown, D.; Hoekstra, W.; Monahan, R. III *Tetrahedron Lett.* **1987**, *28*, 1069.

(12) As the (benzyloxy)methyl group of **8** was removed cleanly by treatment with Li in NH_3 to furnish diol **13**, the correct stereochemistry of the C(1)-OH group can, in principle, be obtained at this stage.

(13) Oikawa, Y.; Tanaka, T.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5397.

(14) The fact that only one diastereomer **5b** was obtained in the electrocyclization reaction demonstrates an efficient stereocontrol by an allylic oxygen substituent. Furthermore, this indicates the possibility of achieving asymmetric synthesis of forskolin starting from an optically active hydroxy-β-ionone **6**.

(15) (a) Sobotka, H.; Bloch, E.; Cahnmann, H.; Feldbau, E.; Rosen, E. *J. Am. Chem. Soc.* **1943**, *65*, 2061. (b) Eugster, C. H.; Buchecker, R.; Tscharner, Ch.; Uhde, G.; Ohloff, G. *Helv. Chim. Acta* **1969**, *52*, 1729. (c) Buchecker, R.; Egli, R.; Regel-Wild, H.; Tscharner, Ch.; Eugster, C. H.; Uhde, G.; Ohloff, G. *Ibid.* **1973**, *56*, 2548. (d) Haag, A.; Eschenmoser, W.; Eugster, C. H. *Ibid.* **1980**, *63*, 10. (e) Bennett, D. J.; Ramage, G. R.; Simonsen, J. L. *J. Chem. Soc.* **1940**, 418.