drolysis, affording the enone **18** as a 64:36 mixture of *E* to *Z* isomers in 59% yield. The crucial ring closure of **18** via oxyselenation furnished, after reductive workup, the desired tetrahydropyran-4-one **19** in 78% yield along with 6% yield of its epimer. In stark contrast to the result with a model system,[8a] the stereochemical outcome of this cyclization proved to be independent of the starting olefin geometry (**19** and its epimer: 79% and 5% from *E*-**18**; 80% and 6% from *Z*-**18**), implying that cyclization proceeded through the chair-preferred transition state involving a stable open carbocation allowing rotation about C-12/C-13 bond to direct the methyl group at an axial position. Transformation of **19** to **20** was quantitatively effected by a well-established Grieco method.[8a,b,24] Sequential removal of the *p*-methoxybenzyl group[25] and acetonide followed by selective acetylation[26] of 7β-OH completed the total synthesis of (±)-forskolin (mp 199-200 °C). The synthetic material was proven to be identical with an authentic sample of natural forskolin by comparison of the 400 MHz ^{1}H NMR, ^{13}C NMR, IR, MS, and TLC data.[27]

Acknowledgment. This research was supported in part by grants from Japan Research Foundation for Optically Active Compounds and the Ministry of Education, Science, and Culture. We are indebted to N. Matsuura and Y. Yanagiya for their technical assistance and the members of Instrumental Analysis Center of this faculty for spectral measurements. We are also grateful to Drs. K. Kamiya and Y. Wada of Takeda Chemical Industries, Ltd. for X-ray crystallographic determination.

Supplementary Material Available: Spectroscopic data and physical constants for **1-5**, **7-9**, and **11-20** and stereoviews and lists of atomic coordinates, thermal parameters, bond distances, and bond angles for **13** and **16** (21 pages). Ordering information is given on any current masthead page.

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(26) Bhat, S. V.; Bajwa, B. S.; Dornauer, H.; de Souza, N. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 767.
(27) After this paper was submitted, we knew that Ziegler and co-workers developed a synthetic route to forskolin: Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115.

Total Synthesis of (±)-Forskolin

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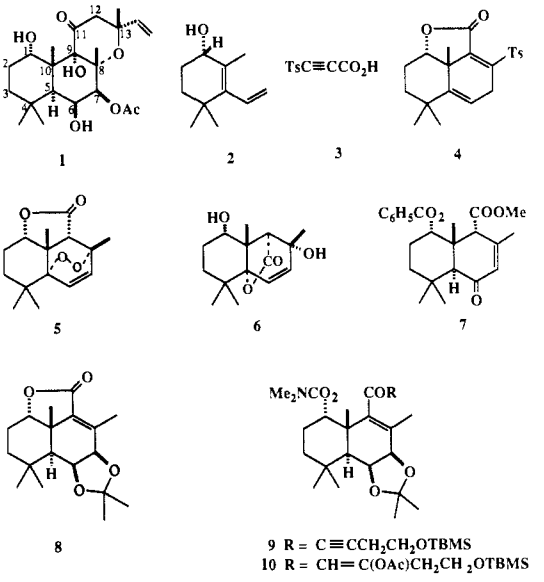
Forskolin (**1**), a diterpenoid isolated from *Coleus forskohlii*,[1] is an activator of adenylate cyclase which has a number of physiological effects (e.g., vaso- and bronchodilating, positive inotropic, and antiglaucoma) and considerable therapeutic potential.[2] Not surprisingly therefore, many laboratories have embarked on the synthesis of **1**. A spate of papers has appeared which describe initial stages of a variety of approaches,[3] and most recently a synthetic pathway has been reported which involves synthesis of a racemic intermediate, partial synthesis of the same intermediate in chiral form from forskolin, and reconversion of the degradation product to forskolin.[4] This paper contains an account of the first total synthesis of (±)-forskolin and a highly enantioselective method for obtaining the first synthetic intermediate **2** in chiral form, so that the approach described herein in principle amounts to a synthesis of the native form of forskolin.

The A/B ring system of **1** was constructed simply by allowing hydroxy diene **2**[5] and acetylenic acid **3**[6] to react in $CHCl_3$ solution (0.44 M) at 23 °C for 30 h to give **4** (72%) as the product of sequential esterification and Diels-Alder reaction. Lactone **4** was transformed into endoperoxide **5** in three steps: (1) replacement of tosyl by methyl (76%) by using 2.7 equiv of Me_2CuLi and 1.2 equiv of BF_3·Et_2O (-35 °C 1 h, to 0 °C 15 min); (2) α,β → β,γ-double bond isomerization (0.1 equiv of diazabicyclononene (DBN), 23 °C, 45 min); and (3) photoperoxidation of the conjugated diene lactone (O_2, tungsten lamp irradiation, $CHCl_3$, 0.1% methylene blue; 0 °C, 144 h) to give **5**[7] (95% over two steps). Reduction of **5** (10 equiv of AlHg in 20:1 THF-H_2O at 23 °C for 10 min) afforded dihydroxy lactone **6** (97%) which was converted to enone **7** by the following sequence: (1) benzoylation (2 equiv each of benzoic anhydride pyridine, and 4-(dimethylamino)pyridine (DMAP) in $ClCH_2CH_2Cl$ at 50 °C for 2 h; 85% yield of 1-monobenzoate); (2) oxidation by pyridinium chlorochromate (9 equiv, $ClCH_2CH_2Cl$, 80-90 °C for 5 h; 60% yield);[8] (3) lactone reductive cleavage using 13 equiv of AlHg in 20:1 THF-H_2O at 20 °C for 18 min (85% yield); and (4) esterification with ethereal CH_2N_2 (99%). Lactone acetonide **8** was obtained from **7** in four steps (69% overall): (1) enone and benzoate reduction with lactonization (4.4 equiv of diisobutylaluminum hydride in toluene at -78 °C for 75 min; 80%); (2) stereoselective



1 2 3 4 5 6 7 8

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(4) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115-8116.
(5) Prepared from α-ionone by the sequence (1) epoxidation by 1.5 equiv of peroxyacetic acid in ethyl acetate (2.9 M) at 23 °C for 3 h (100%); (2) carbonyl reduction using 1 mol equiv of sodium borohydride and 1 equiv of cerium trichloride in methanol at 23 °C for 10 min (100%); (3) ozonolysis in CH_3OH-CH_2Cl_2 followed by treatment with Me_2S and subsequent treatment of the aldehyde product with base to afford 2,4,4-trimethyl-3-formyl-2-cyclohexen-1-ol (90%); and (4) Wittig methylenation in THF at 0 °C for 1 h (71%).
(6) Prepared from *p*-toluenesulfonylacetylene (Bhattacharya, S. N.; Josiah, B. M.; Walton, D. R. M. *Organomet. Chem. Synth.* **1970**, *1*, 145-149) by metalation in THF at -105 to -95 °C with BuLi (90 min), reaction with excess CO_2 (-95 °C to 0 °C), acidification and rapid extractive isolation at 0 °C. The acid **3** was used immediately for reaction with **2** since it undergoes rapid (base-catalyzed) decarboxylation.
(7) The stereochemistry of **5** was confirmed by the observation of a positive NOE effect between the β-proton at C(9) and the olefinic protons (at C(6) and C(7)).
(8) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682-685.

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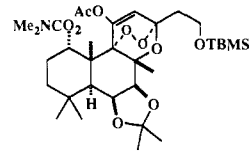
7,8-β epoxidation with 2.5 equiv of *tert*-butyl hydroperoxide and 0.05 equiv of $Mo(CO)_6$ in C_6H_6 at 68 °C for 1 h;[9] (3) elimination of H from C(9) and O from C(8) using 4 equiv of KOH in CH_3OH at 23 °C for 10 min (86% yield for two steps); and (4) ketalization with excess 2,2-dimethoxypropane–acetone with tosic acid as catalyst at 23 °C for 90 min (99% yield).

The highly reactive lactone carbonyl of **8** was readily ethynylated by slow addition of 2.8 equiv of $LiC{\equiv}CCH_2CH_2OTBMS$ (TBMS = *tert*-butyldimethylsilyl) to **8** in THF at 0 °C (80%), and the resulting 1-hydroxy ketone was carbamoylated by reaction with 10 equiv each of dimethylcarbamoyl chloride, 2,6-lutidine, and silver triflate in CH_2Cl_2 (0.06 M) at 23 °C (addition of the silver salt to the other two reactants) to give **9** (60%). Ynone **9** was converted to enol acetate **10** (60% overall)[10] by the following steps: (1) conjugate addition of hydroxyl to C≡C (10 equiv of 0.3 M K_2CO_3 in 1:1 THF–ethylene glycol at 23 °C for 2 h followed by exposure to 1:1 2 N aqueous oxalic acid and acetone at 60 °C for 7 h); (2) resilylation (10 equiv of TBMSCl, 30 equiv of imidazole in DMF at 23 °C for 30 min; 73% overall); and (3) acetylation of the resulting β-hydroxy enone by reaction first with thallous ethoxide at 23 °C for 30 min and then acetyl chloride (−78 °C to −45 °C over 1 h; 82%).

Irradiation of **10** (GE sunlamp) in the presence of 2% of methylene blue in O_2-saturated $CHCl_3$ at 10 °C for 4–5 h resulted in photocyclization to a pyran and subsequent 4 + 2 addition of $^1\Delta_gO_2$ to form endoperoxide **11** in 55–63% yield. This key step



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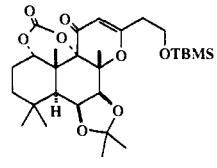

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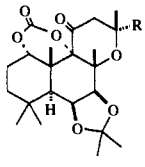
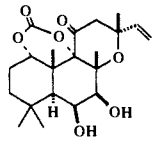


13 R = CH_2CH_2OTBMS
14 R = $CH{=}CH_2$



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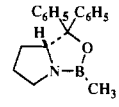

16

to form the C ring of the forskolin system was completely stereoselective.[11] Enone **12** was obtained from endoperoxide **11** by the following sequence: (1) β-elimination–hydroperoxide reduction using sodium ethoxide (0.05 M, 2.2 equiv)–tributylphosphine (10 equiv) in ethanol at 0 °C for 2.5 h (80%) and (2) cyclic carbonate formation by reaction with 10:1 acetic acid–acetic anhydride at 100–105 °C (sealed tube) for 23 h. β-Face stereospecific conjugate addition of methyl to enone **12** was effected by reaction with excess $MeCuPBu_3$ and $BF_3{\cdot}Et_2O$ (each 0.2 M) in ether at −78 °C for 4 h and −50 °C for 15 min to provide keto carbonate **13** in 85% yield. Conversion of **13** to vinyl ketone **14** was carried out in >90% yield by (1) desilylation using 2% HF in 50:1 acetonitrile–water at 0 °C for 15 min, (2) reaction with *o*-nitrophenylselenocyanide[12] and tri-*n*-butylphosphine (each 0.02 M) in THF at 0 °C for 2 h, and (3) treatment with 10 equiv of 30% aqueous hydrogen peroxide in THF (0.16 M) at 23 °C for 4 h. Deketalization of **14** (2:1 acetic acid–water, 10 equiv of semicarbazide, 70 °C, 4 h) gave carbonate **15** (>95%). Reaction of **15** with 0.14 M LiOH in 4:2:1 THF–H_2O–*i*-PrOH at 23 °C for 5 min produced (±)-desacetyl forskolin (>95%) which upon treatment with excess Ac_2O–pyridine at 0 °C for 4 h gave (±)-forskolin (**1**) in 90% yield. Synthetic (±)-forskolin thus obtained was identical with an authentic sample of forskolin[13] by 500 MHz ^1H NMR, infrared, and high resolution mass spectral comparison as well as by thin layer chromatography by using several different solvent systems.

Reduction of the ketone corresponding to **2** by 0.6 equiv of borane in the presence of 10 mol% of the (*R*)-oxazaborolidine **16** as catalyst[14,15] in THF solution proceeded with 95/5 enantioselectivity to afford the (*S*)-enantiomer of **2** (as shown), the form required for enantioselective synthesis of the natural form of forskolin, and this alcohol has been converted to the chiral lactone **4**. Thus the synthetic approach reported herein can provide the natural form of forskolin as well as the racemate.

A number of the steps of this synthesis are noteworthy or novel including (1) the enantioselective synthesis of **2**, (2) the facile one-step synthesis of **4** from **2** and **3** at room temperature, (3) the functional group transformation in the conversion **4** → **5**, **5** → **7**, **9** → **11**, and **11** → **12**. The stereospecificity of the C-ring annulation **10** → **12** and the conjugate methylation **12** → **13** also stand out.[16]

Supplementary Material Available: Spectroscopic data for compounds **1–15** and other reaction intermediates mentioned herein (4 pages). Ordering information is given on any current masthead page.

(9) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137.

(10) The ^1H NMR spectrum of **10** indicates rapid interconversion of the two position isomeric β-acetoxyenones (acetyl migration) at 23 °C which becomes slow on the NMR time scale at 227 K.

(11) For related photocyclizations, see: (a) Büchi, G.; Yang, N. C. *Helv. Chim. Acta* **1955**, *38*, 1338–1341. (b) Cerfontain, H.; van Noort, P. C. M.; Geenevasen, J. A. J. *J. Chem. Soc., Perkin Trans. II* **1980**, 1057–1062. (c) Barker, A. J.; Begley, M. J.; Mellor, M.; Otieno, D. A.; Pattenden, G. *J. Chem. Soc., Perkin Trans. I* **1983**, 1893–1900.

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(13) We thank Drs. R. H. Rupp, W. Bartmann, and J. Knolle of the Hoechst Co. for a generous supply of plant-derived forskolin.

(14) Corey, E. J.; Bakshi, R.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.

(15) We are indebted to Dr. Tetsuya Mohri of these laboratories for carrying out the enantioselective synthesis of **2** which will be reported separately.

(16) We are grateful to the National Institutes of Health for support of this research and to Dr. Keith Kyler for experimental contributions to an early stage of our program.

Hexagonal Lattice Hosts for Urea. A New Series of Designed Heterocyclic Receptors

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Beginning with crown ethers,[1] the field of host–guest,[2] or supramolecular,[3] chemistry focused initially on complexation of cations.[4] Although hydrogen bonds between neutral molecules are generally weaker than charge/dipole attraction and polar hydrogen bonds,[5] several recent reports indicate that networks of hydrogen bonds may be used to form neutral complexes that

(1) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495–2496.

(2) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039–1057, and references therein.

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