To summarize our work, we have discovered that the phenyl Gilman reagent contains LiI incorporated in the cuprate cluster and should be represented as $Ph_2CuLi{\cdot}LiI$ or $Ph_2Cu(I)Li_2$,[16] just as the cyanocuprates have been represented as $R_2CuLi{\cdot}LiCN$[17] or more commonly as $R_2Cu(CN)Li_2$.[2a] Furthermore, Ph_3CuLi_2 in DMS is not merely a mixture of Ph_2CuLi and PhLi as it is in THF or ether, but rather it is a new "higher order" reagent, the first without CN. In this regard, chemical evidence and X-ray crystallography are not as reliable as NMR for the characterization of organocopper reagents.

Acknowledgment. We thank Drs. Heinz D. Roth and Peter A. Mirau of these laboratories for helpful discussions.

Registry No. CuI, 7681-65-4; CuBr, 7787-70-4; Ph_2Cu^6Li, 113811-10-2; Ph_2CuLi, 23402-69-9; $Ph_2Cu^6Li{\cdot}^6LiI$, 113811-11-3; Ph^6Li, 92382-42-8; PhLi, 591-51-5; $Ph_3Cu^6Li_2$, 113811-12-4; ^6Li, 14258-72-1; 2-cyclohexenone, 930-68-7; 3-phenylcyclohexanone, 20795-53-3; 1-phenylcyclohex-2-en-1-ol, 60174-90-5.

Supplementary Material Available: ^{13}C and ^6Li spectra of diphenylcopperlithium-6 at 195 K and ^{13}C spectra of $Ph_2CuLi{\cdot}LiBr$, $Ph_2CuLi{\cdot}LiBr$ + PhLi, and PhLi in ether at 173 K (3 pages). Ordering information is given on any current masthead page.

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A Total Synthesis of (±)-Forskolin†

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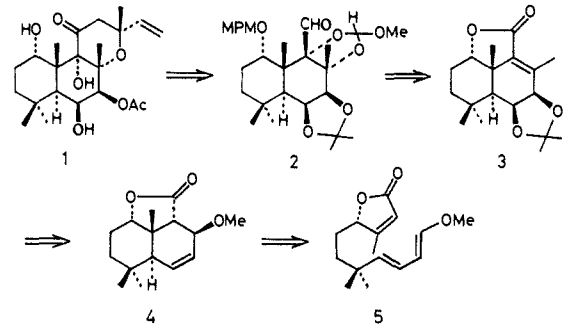
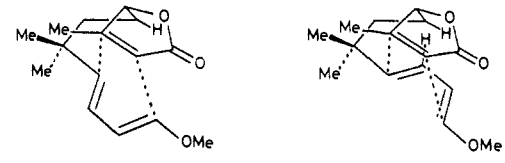
The labdane diterpene forskolin (**1**),[1] isolated from the roots of the Indian herb *Coleus forskohlii*, has been shown to be a hypotensive agent with spasmolytic, cardiotonic, and platelet aggregation inhibitory activity and also demonstrated to be a unique and potent stimulator of the enzyme adenylate cyclase in various tissues.[2] Owing to its therapeutic potential for glaucoma,[3] congestive heart failure,[4] and bronchial asthma[5] coupled with a substantial structural challenge, forskolin (**1**) has emerged as a highly attractive target for synthetic investigations.[6-9]

Scheme I



We report herein the total synthesis of (±)-forskolin, the strategy for which is outlined retrosynthetically in Scheme I.

The key intermediate **3** we envisaged became the same as Ziegler and co-workers reported,[7c] but the synthetic approach differs significantly from their efforts as detailed in Scheme II. The aldehyde **6**[10] was converted to the butenolide **7** by a series of routine manipulations in 56% overall yield. Subsequent addition of 3-methoxypropynyllithium (THF, −78 °C, 0.5 h) followed by sequential semihydrogenation over Lindlar catalyst (quinoline, benzene, 25 °C, 2 h), the allylic methyl carbonate formation (MeOCOCl, DMAP, CH_2Cl_2, reflux, 2 h), and palladium-catalyzed elimination[11] ($Pd(PPh_3)_4$ (0.1 equiv), Et_3N (2 equiv), THF, reflux, 5 h) afforded the desired *E,E*-diene **5** in 11% yield together with 35% yield of the *E,Z*-isomer. The key intramolecular Diels–Alder reaction[12] of **5** (toluene, 220–230 °C, sealed tube, 5 h) proceeded smoothly to give the desired trans fused decalin **4** in 85% yield. No evidence of the formation of any other isomeric cycloadducts was observed by 400 MHz ^1H NMR analysis of the crude reaction mixture. The relatively facile cyclization might be ascribed to the geminal dimethyl effect in favor of the proper orientation of the diene unit for cyclization[13] as well as the dominant HOMO–LUMO interaction in this highly activated system. The stereochemical outcome resulting from the exo transition state can be rationalized by the recently proposed nonsynchronous transition-state model,[12-14] in which bond formation between the olefinic termini with the largest FMO coefficients, the internal bond formation in this case, precedes bond formation at the other, so that steric interactions rather than electronic factors play a



exo-transition state endo-transition state

crucial role in transition-state selection. Somewhat surprisingly,

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

‡ Visiting scientist from Yamasa Shoyu Co. Ltd., Choshi, Chiba, Japan, 1983–1985.

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(10) Prepared from dimethyl 2,2-dimethylglutarate in 49% overall yield by the following sequence: (1) $LiAlH_4$, Et_2O, 0 °C, 2 h; (2) *t*-BuCOCl, pyridine, 0 °C, 2.5 h; (3) dihydropyran, TsOH catalyst, CH_2Cl_2, 0 °C, 1 h; (4) NaOMe, MeOH, reflux, 2 h; (5) CrO_3/pyridine, CH_2Cl_2, 0 °C, 2 h.

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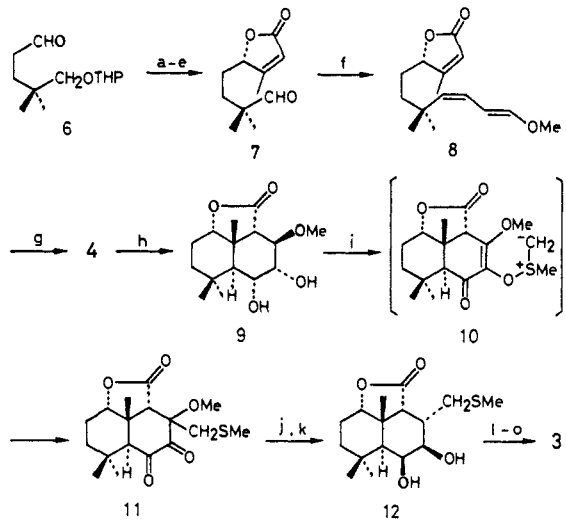
Scheme II[a]

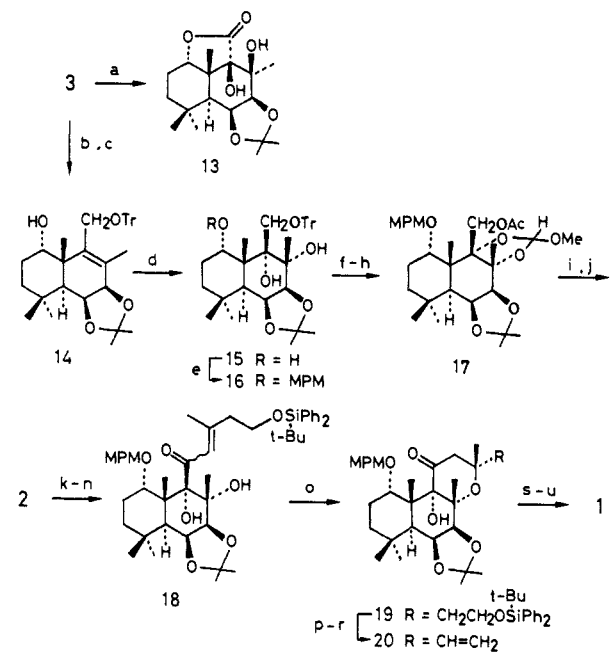


[a] Reagents and conditions: (a) $LiC{\equiv}CCO_2Me$ (1.1 equiv), THF, −78 °C, 1 h, 91%; (b) dihydropyran (1.5 equiv), TsOH catalyst, CH_2Cl_2, 0 °C, 0.5 h, 96%; (c) $LiMe_2Cu$ (1.1 equiv), THF, −70 °C, 1 h, 87%; (d) TsOH catalyst, MeOH, 23 °C, 2 h, 90%; (e) PCC (2.2 equiv), CH_2Cl_2, 23 °C, 2 h, 81%; (f) $MeOCH{=}CHCH_2P^+Ph_3Br^-$ (1.5 equiv), *n*-BuLi (1.5 equiv), THF, −25 °C, 1 h, then add **7**, −78 to −25 °C, 1 h, 76%; (g) PhSH (0.01 equiv), toluene, sealed tube, 220 to 230 °C, 15 h, 81%; (h) OsO_4 (0.05 equiv), $Me_3N \rightarrow O$ (1.4 equiv), pyridine (0.5 equiv), *t*-BuOH–H_2O (4:1), reflux, 18 h, 90%; (i) SO_3–pyridine (15 equiv), Et_3N (16 equiv), DMSO, 20 °C, 20 h, 81%; (j) NaTeH (2.5 equiv), EtOH, 23 °C, 0.5 h, 85%; (k) *t*-$BuNH_2$–BH_3 (6 equiv), MeOH, 23 °C, 21 h, 87%; (l) $Me_2C(OMe)_2$ (7 equiv), TsOH catalyst, benzene, 23 °C, 1 h, 95%; (m) MCPBA (1.1 equiv), CH_2Cl_2, −25 °C, 0.5 h, 94%; (n) $CaCO_3$ (1 equiv), toluene, reflux, 70 h, 68%; (o) LiOMe (5 equiv), THF, 23 °C, 72 h, 92%.

the *E,Z*-isomer was found to cyclize under the foregoing conditions to **4** in 23% yield, wherein the recovered diene (65%) was contaminated with ca. 1% of the *E,E*-isomer **5**.[15] On the favorable note that this cyclization occurred only after isomerization to the *E,E*-isomer, we then attempted a tandem olefin isomerization/intramolecular Diels–Alder reaction with the *Z,E*-diene **8** conveniently prepared from **7** via Wittig coupling with (3-methoxy-2*E*-propenylidene)triphenylphosphorane[16] in 76% yield. Indeed, thermolysis of **8** in the presence of 1 mol % thiophenol as an equilibrating catalyst[17] in toluene at 220–230 °C for 15 h led to an 81% yield of **4**.[18]

With convenient access to **4** secure, we then focused on the elaboration of the 6β,7β-diol. Osmium tetroxide catalyzed hydroxylation[19] of **4** proceeded uneventfully from the less hindered, concave face of the molecule to afford the 6α,7α-diol **9** as the exclusive product in 90% yield. An inversion of configurations at these centers was then achieved as follows. Parikh-modified Moffatt oxidation[20] of **9** was accompanied by [2,3] sigmatropic rearrangement[21] of the sulfur ylide **10** to give the 6,7-diketone **11** with the methylthiomethyl group at C-8 in 81% yield. Reductive removal of the methoxy group with sodium hydrogen telluride[22] was followed by a stereocontrolled reduction with *tert*-butylamineborane[23] to produce the 6β,7β-diol **12** in 74% yield.

Scheme III[a]



[a] Reagents and conditions: (a) OsO_4 (1.1 equiv), pyridine, 20 °C, 24 h, then H_2S, $CHCl_3$–dioxane (1:1), 23 °C, 0.5 h, 83%; (b) $LiAlH_4$ (5 equiv), Et_2O, reflux, 1 h, 89%; (c) TrCl (1.2 equiv), DMAP (2.4 equiv), $ClCH_2CH_2Cl$, reflux, 6 h, 90%; (d) OsO_4 (1.1 equiv), pyridine, 20 °C, 30 h, then H_2S, $CHCl_3$–dioxane (1:1), 23 °C, 0.5 h, 83%; (e) NaH (5 equiv), *p*-$MeOC_6H_4CH_2Cl$ (5 equiv), HMPA, THF, 23 °C, 3 h, 91%; (f) TsOH catalyst, $CHCl_3$–MeOH (2:1), 20 °C, 40 min, 95%; (g) Ac_2O (5 equiv), pyridine, 20 °C, 2 h, 96%; (h) $HC(OMe)_3$, TsOH catalyst, 20 °C, 15 min, 95%; (i) $LiAlH_4$ (4 equiv), Et_2O, 0 °C, 10 min, 95%; (j) SO_3–pyridine (7 equiv), Et_3N (36 equiv), DMSO, 23 °C, 16 h, 78%; (k) $LiC{\equiv}CCH_2CH_2OSi$-*t*-$BuPh_2$ (4.5 equiv), THF, −78 to 20 °C, 2 h, 83%; (l) MnO_2, benzene, 23 °C, 3 h, 79%; (m) $LiMe_2Cu$ (3 equiv), Et_2O, −78 °C, 15 min, 93%; (n) 3 N HCl–THF (1:40), 23 °C, 1 h, then 0.2 N KOH–THF–MeOH (1:4:4), 23 °C, 20 min, 95%; (o) PhSeCl (2 equiv), CH_2Cl_2, 0 °C, 38 h, then Ra-Ni(W-2), EtOH, reflux, 5 min, 78%; (p) *n*-Bu_4NF (3.5 equiv), THF, 23 °C, 5 h, 97%; (q) *o*-$O_2NC_6H_4SeCN$ (3 equiv), *n*-Bu_3P (3 equiv), THF, 23 °C, 0.5 h, 89%; (r) 30% H_2O_2, CH_2Cl_2, 18 °C, 20 h, 84%; (s) DDQ (3 equiv), CH_2Cl_2–H_2O (18:1), 23 °C, 48 h, then K_2CO_3, MeOH, 23 °C, 40 min, 96%; (t) 10% aqueous $HClO_4$–THF (1:2), 23 °C, 60 h, 77% (based on the consumed starting material, 21% conversion); (u) Ac_2O, pyridine, 0 °C, 9 h, 85%.

Protection of the diol as the acetonide followed by thermolysis of the sulfoxide and subsequent isomerization afforded the targeted conjugated lactone **3** in 56% yield.

With the efficient synthesis of **3** realized, the stage was now set for the completion of the synthesis as shown in Scheme III. Osmylation of **3** was expected to occur preferentially from the less hindered α-face, but, surprisingly, 8β,9β-diol **13** was obtained as the sole product in 83% yield, the structure of which was confirmed by a single-crystal X-ray analysis. The tricyclic system seemed to be in part responsible for this unusual result, and so we attempted the osmylation with a bicyclic system. Toward this end, the lactone **3** was transformed into the bicyclic compound **14** by reduction with lithium aluminum hydride and subsequent tritylation in 85% yield. We were gratified to observe that treatment of **14** with a stoichiometric amount of osmium tetroxide provided exclusively the desired 8α,9α-diol **15** in 83% yield, the structural proof of which was unambiguously established based upon a single-crystal X-ray analysis of the *p*-methoxybenzyl ether **16**. Detritylation of **16** followed by selective acetylation of the primary alcohol and ortho ester formation furnished **17** in 91% yield, which underwent deacetylation and Parikh oxidation[20] to give the aldehyde **2** in 74% yield. Addition of 4-(*tert*-butyldiphenylsiloxy)butynyllithium to **2** was followed by sequential oxidation with MnO_2, conjugate addition of $LiMe_2Cu$, and hy-

(15) During the course of our studies, Burke and co-workers found that intramolecular Diels–Alder reaction of the butenolide derivatives bearing oxygenated *E,E*- or *Z,E*-dienes proceeded stereospecifically via exo transition state to produce the trans and cis fused hydrindenes, respectively: Burke, S. D.; Magnin, D. R.; Oplinger, J. A.; Baker, J. P.; Abdelmagid, A. *Tetrahedron Lett.* **1984**, *25*, 19.

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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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Total Synthesis of (±)-Forskolin

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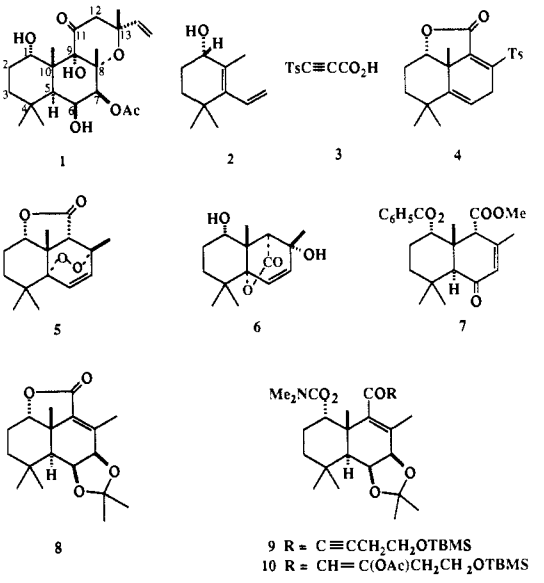
Forskolin (**1**), a diterpenoid isolated from *Coleus forskohlii*,[1] is an activator of adenylate cyclase which has a number of physiological effects (e.g., vaso- and bronchodilating, positive inotropic, and antiglaucoma) and considerable therapeutic potential.[2] Not surprisingly therefore, many laboratories 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 $BF_3{\cdot}Et_2O$ (−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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(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)).
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