CO. Other distortions are understandable in terms of the bite angle of the phosphine. The overall geometry contrasts with that for R = Ph which was octahedral with an H_2 ligand *trans* to the CO. Thus, electronic control of H_2 activation on metal complexes has been achieved.

IR spectra of **1-Et** in Nujol showed a broad, medium-intensity Mo–H stretch at 1647 cm^{-1} shifting to 1194 cm^{-1} for the dideuteride. ^1H NMR {200 MHz, toluene-d_8} was consistent with a stereochemically nonrigid, 7-coordinate dihydride structure. At 25 °C, a sharp binomial quintet was observed at −5.40 ppm for the hydride ligands, in contrast to the broad singlets observed for the η^2-H_2 in **1-Ph**[2b] and the apparent η^2-H_2 in **1-(Ph–Et)** (Table I). Below −25 °C the hydride multiplet of **1-Et** broadened (Figure 2), behavior resembling that of $CrH_2[P(OMe)_3]_5$, which has been shown by NMR to be fluxional and possess the distal pentagonal bipyramidal structure.[11] In the slow exchange limit (< −66 °C) an A_2BCX_2 multiplet pattern (J_{PH} = 23, 49, 64 Hz) resulted, consistent with a pentagonal bipyramidal structure. ^1H NMR of $MoHD(CO)(Et_2P–PEt_2)_2$ displayed no observable HD coupling at 25 or −90 °C, while the Ph complex gave J_{HD} = 34 Hz, diagnostic[1,2a] of H_2 coordination.

The cone angles[12] of P(*i*-Bu)$_3$ and PPh_3 are similar (~145°) and both are larger than that for PEt_3 (132°). Thus the bulkiness of $R_2PC_2H_4PR_2$ should follow the same order, while the basicities of $R_2PC_2H_4PR_2$ for R = Et and *i*-**Bu** should be comparable but greater than that for R = Ph. Therefore, **1-*i*-Bu** provides an opportunity for separating steric and electronic factors. IR and NMR data (Table I) for **1-*i*-Bu** and its D_2 and HD isotopomers were similar to those for **1-Et**, indicating that **1-*i*-Bu** is also a dihydride. Since **1-*i*-Bu** is of comparable steric encumbrance to the H_2 complex **1-Ph**, it must follow that steric effects are of much less consequence than electronic influences in stabilizing H_2 coordination.

Several solution properties of **1-*i*-Bu**, including facile loss of H_2 in vacuo, relaxation time (T_1) of the hydride NMR signal, and collapse of the multiplet NMR pattern to a broad singlet below −55 °C, possibly indicate the presence of some η^2-H_2 tautomer. Crabtree has found that T_1 < 125 ms is characteristic of H_2 ligands while T_1 > 300 ms corresponds to hydride ligands.[4a,b,13] The T_1 for **1-Et** is 370 ms at −70 °C, consistent with a dihydride structure, while that for **1-Ph** is 20 ms, consistent with the known H_2 coordination. However, the T_1 for **1-*i*-Bu** (200 ms) is in the "gray area" between the values for H_2 and hydride complexes. Thus bulky ligands may favor H_2 ligation to a minor extent. Whether or not bulky ligands contribute to the *thermal* stability of η^2-H_2 complexes remains to be determined.

As in $Mo(CO)_3(PR_3)_2(H_2)$ and most other H_2 complexes, N_2 will displace the H_2 ligand in **1** to form the corresponding N_2 complexes **3** (the hydrides in **1-Et** and **1-*i*-Bu** are also displaceable). As a measure of the basicity of the metal center, Morris[14] has proposed that when ν_{NN} of N_2 complexes is in the range 2060–2160 cm^{-1}, H_2 complexes should result (upon "replacement" of the N_2 by H_2) versus hydrides for ν_{NN} <2060 cm^{-1} (electron-rich metal center). Interestingly, ν_{NN} for **3-Ph** is 2090 cm^{-1}, within the dihydrogen region, while ν_{NN} for **3-Et** (2050 cm^{-1}) and **3-*i*-Bu** (2060 cm^{-1}) are on the borderline (cf. 1950 cm^{-1} for the N_2 analogue of $MoH_2(PMe_3)_5$).

Further experiments are in progress to take advantage of this unique opportunity to map out the reaction coordinate for σ-bond activation at a metal center and to compare the chemistry of H_2 complexes with that of closely related dihydrides.

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Supplementary Material Available: Details of data collection, the structure determination, and refinement and tables of crystal data (Table II) and final coordinates and thermal parameters (Tables III and IV) (4 pages); listing of observed and calculated structure factors (Table V) (17 pages). Ordering information is given on any current masthead page.

A Synthetic Route to Forskolin†

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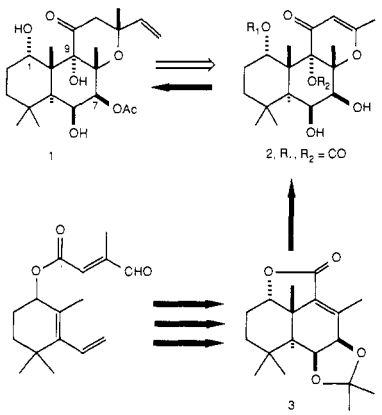
Forskolin **1**, isolated from the Indian plant *Coleus forskohlii*,[2] has been the subject of intense medicinal and chemical interest[3] owing to its pronounced inotropic,[4] antihypertensive,[4] and bronchospasmolytic[5] activity and its ability to effect adenylate cyclase activation in the absence of the guanine nucleotide-binding protein.[6] Forskolin and its derivatives lower intraocular pressure



in humans by topical application.[7] In this communication, we report the formal synthesis of forskolin by the transformation of racemic lactone **3**, which had been previously synthesized by an

† Dedicated to Professor Kenneth B. Wiberg on the occasion of his 60th birthday.

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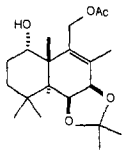
intramolecular Diels–Alder strategy,[3c] into dihydropyranone **2**, prepared in enantiomerically pure form by degradation of natural forskolin. Enantiomerically pure dihydropyranone **2** had been converted by photochemical means to forskolin.[3n]

Reduction of lactone **3** ($LiAlH_4$, Et_2O, 25 °C, 1 h) and subsequent, selective acetylation (*N*-acetylimidazole, DBU, C_6H_6, 25 °C, 1 h)[8] afforded allylic acetate **4** in 95% yield. Stoichiometric osmylation of tetrasubstituted olefin **4** (OsO_4, pyridine, 25 °C, 5 days; H_2S; 85%) produced the C_8,C_9-*cis*-diol **5a**, whose stereochemistry was confirmed by subsequent transformations.



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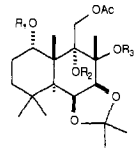
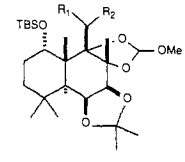
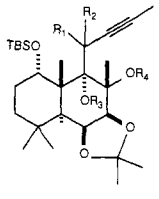


5a, $R_1 = R_2 = R_3 = H$
b, R_1 = TBS, $R_2 = R_3 = H$
c, R_1 = TBS, R_2, R_3 = CHOMe

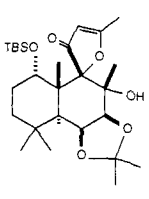


6a, R_1, R_2 = H, OH
b, R_1, R_2 = O

Protection of the C_1-hydroxyl of triol **5a** as its *tert*-butyldimethylsilyl ether **5b** was achieved (TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 35 min) in 75% yield. To set the stage for the elaboration of the ring C carbon framework, the C_8,C_9-diol of silyl ether **5b** was protected (neat $CH(OMe)_3$, *p*-TsOH, 25 °C, 2 h; 97%) as its orthoformates **5c** (12:1 mixture; ^1H NMR (major isomer) δ 2.06 (s, 3 H, OAc), 3.33 (s, 3 H, OMe)); saponification (2 N KOH/MeOH/THF, 1:5:1, 25 °C, 5 h) gave the alcohols **6a**; and Collins–Ratcliffe–Rodehorst oxidation[9] (CrO_3·2pyr, CH_2Cl_2, 25 °C, 30 min; 88% (two steps)) afforded the aldehydes **6b** (^1H NMR (major isomer) δ 3.40 (s, 3 H, OMe), 9.73 (1 H, s, CHO)). Selective addition of 1-lithiopropyne[3j] (THF, −10 °C, 1 h; 84%) to the major aldehyde gave rise to a single propargyl alcohol **7a** (IR (CCl_4) 3619 cm^{-1}; ^1H NMR δ 1.84 (d, 3 H, J = 2.4 Hz, CCMe), 3.32 (s, 3 H, OMe)). A second Collins oxidation realized



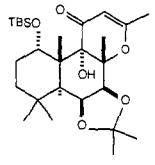
7a, R_1, R_2 = H, OH, R_3, R_4 = CHOMe
b, R_1, R_2 = O, R_3, R_4 = CHOMe
c, R_1, R_2 = O, R_3, R_4 = H, CHO
d, R_1, R_2 = O, R_3 = R_4 = H



8

the acetylenic ketone **7b** (IR (CCl_4) 2208, 1676 cm^{-1}; ^1H NMR δ 2.01 (s, 3 H, CCMe), 3.40 (s, 3 H, OMe)) in 94% yield. Liberation of the $C_{8,9}$-diol functionality was accomplished in two operations. Exposure of orthoformate **7b** to aqueous acid (3 N HCl/THF, 1:25, 25 °C, 2 h) produced hydroxyformates **7c** that underwent rapid formolysis (half-saturated ammoniacal methanol, 25 °C, 30 min) to produce diol **7d** (^1H NMR δ 2.02 (s, 3 H, CCMe), 3.95 (m, 1 H, C_1–H)) in 74% yield for the two steps.

When conditions (Cs_2CO_3, CH_3CN, 45 °C, 9 h) devised by Deslongchamps[10] for the intramolecular addition of β-keto ester anions to acetylenic ketones were applied to diol **7d**, exclusive formation of furanone **8** occurred;[11] the NMR spectrum (^1H NMR δ 2.15 (s, 3 H, vinyl Me), 5.48 (s, 1 H, vinyl H)) was not in accord with that of dihydropyranone **2**. Rehybridization of the acetylene group without alteration of the oxidation level (i.e., 1,4-addition of HX) was expected to eliminate the formation of furanone **8**, as the transition state for ring closure would be of the 6-endo-trig type.[12] Rewardingly, exposure of acetylenic ketone **7d** to methanolic potassium methoxide (0.03 M, 25 °C, 6 h) produced a mixture of the desired dihydropyranone **9** (^1H NMR δ 1.96 (s, 3 H, vinyl Me), 5.11 (s, 1 H, vinyl H); 44% yield) and *E* vinylogous ester **10** (^1H NMR δ 2.25 (s, 3 H, vinyl Me), 3.65 (s, 3 H, OMe), 6.34 (s, 1 H, vinyl H); 34% yield),[13] which proved to be stable



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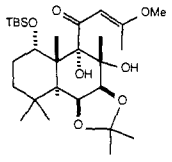

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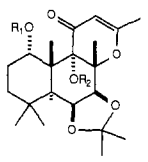

11a, R_1 = R_2 = H
b, R_1, R_2 = CO

to the reaction conditions. The putative, penultimate precursor of dihydropyranone **9** is assumed to be the *Z* isomer of **10**, which, if the transition state for closure is chairlike, experiences a 1,3-Me/OMe diaxial interaction, whereas the *E* isomer requires a seemingly more demanding Me/Me interaction. However, acid-catalyzed cyclization (*p*-TsOH, benzene, 25 °C, 5 h) of the *E* isomer **10** provided the desired dihydropyranone **9** in 97% yield (total of 76% yield from acetylenic ketone **7d**).

Final linkage with the degradation product required a series of functional group manipulations. Desilylation ($Bu_4N^+F^-$, THF, 25 °C, 20 min, 76%) of dihydropyranone **9** provided alcohol **11a** (^1H NMR δ 1.97 (s, 3 H, vinyl Me), 5.08 (m, 1 H, C_1-H), 5.16 (s, 1 H, vinyl H)) which in turn was converted ($COCl_2$, pyridine, CH_2Cl_2, 0 °C, 20 min) to the cyclic carbonate **11b** (^1H NMR δ 2.02 (s, 3 H, vinyl Me), 5.26 (s, 1 H, vinyl H), 5.52 (m, 1 H, C_1-H)) in 90% yield.[14] Finally, deketalization (3 N HCl/THF, 1:5, 50 °C, 12 h) of cyclic carbonate **11b** afforded racemic dihydropyranone **2** (72% yield), identical by comparison of its 250-MHz ^1H NMR spectrum and TLC mobility with that derived from enantiomerically pure, natural forskolin.[15]

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Supplementary Material Available: Spectral and analytical data for **2**, **4**, **5a–c**, **6b**, **7a,b,d**, **8**, **9**, **10**, and **11a,b** (4 pages). Ordering information is given on any current masthead page.

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(13) An NOE experiment showed a 7% enhancement of the vinyl hydrogen upon irradiation of the methoxyl hydrogens. For ^1H NMR values of (*E*)- and (*Z*)-4-methoxy-3-penten-2-one, see: Awang, D. V. C. *Can. J. Chem.* **1971**, *49*, 2672. See, also: Stork, G.; Kraus, G. A. *J. Am. Chem. Soc.* **1976**, *98*, 2351.

(14) While the formation of the cyclic carbonate demonstrated the cis relationship of the C_1-C_9 hydroxyls, synthetically unsuitable, cyclic protecting groups involving the C_1-C_9 hydroxyls proved this point earlier in the work.

(15) The overall conversion of lactone **3** to dihydropyranone **2** was accomplished in 11% yield. The dihydropyranone **2** was transformed into forskolin in 10% yield.[3n]