(11) E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 809 (1976).
(12) Structural assignments for all stable synthetic intermediates are based upon proton magnetic resonance (^{1}H NMR), infrared, and mass spectra determined using purified, chromatographically homogeneous samples. In addition ultraviolet spectra were determined where appropriate and were also consistent with the formulations shown herein. All reactions involving air- or moisture-sensitive components were carried out in an atmosphere of dry argon.
(13) (a) H. M. Van Dort and H. J. Geursen, *Recl. Trav. Chim. Pays-Bas*, **86**, 520 (1967); (b) L. H. Vogt, Jr., J. G. Wirth, and H. L. Finkbeiner, *J. Org. Chem.*, **34**, 273 (1969).
(14) The quinone **4** could also be obtained in high yield from the phenol **3** by oxidation with 2 equiv of Frémy's salt in aqueous methanol; however, this procedure was less convenient largely because of the labor involved in preparing the reagent. Using the reactions outlined above the quinone **4** can be prepared reproducibly in 100-g lots.
(15) (a) R. G. Glushov and O. Y. Magidson, *Med. Prom. SSSR*, **16**, 27 (1962); (*Chem. Abstr.*, **58**, 4420 (1963)); (b) S. Oida and E. Ohki, *Chem. Pharm. Bull.*, **17**, 1990 (1969).
(16) The structure and stereochemistry of the adduct was anticipated to be that expressed by **6** on the basis of much precedent in the literature, and this expectation is fully confirmed by the data which follow.
(17) (a) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952). (b) For a subsequent application of one of the sequences developed in the course of our investigations, see J.-L. Gras, *Tetrahedron Lett.*, 4117 (1977).
(18) See S. K. Roy and D. M. S. Wheeler, *J. Chem. Soc.*, 2155 (1963).
(19) See J. E. McMurry and M. P. Fleming, *J. Org. Chem.*, **41**, 896 (1976). For a detailed account of the very extensive studies carried out on the cyclization of **7** and related substances with a wide range of reagents, see also ref 6.
(20) The less polar of the isomeric pinacols, mp 97–99 °C, is probably *cis*-**14** and the more polar isomer, mp 87.5–89 °C, *trans*-**14**, based upon previous experience with tricyclic analogues of known configuration (see, for example, ref 9a) and also on chemical data.
(21) See, E. J. Corey and C. U. Kim, *J. Org. Chem.*, **38**, 1233 (1973). The various known chromium(VI) reagents and many other standard oxidizing agents for alcohols afford mainly glycol fission products with substrates such as **14**.
(22) This is a useful modification of the procedure of Swern; see K. Omura, A. K. Sharma, and D. Swern, *J. Org. Chem.*, **41**, 957 (1976), and S. L. Huang, K. Omura, and D. Swern, *ibid.*, **41**, 3329 (1976).
(23) The ketol **15** is prone to 1,2 rearrangement of methylene at the bridgehead to form the stereoisomeric α-ketol upon exposure to base or acid or prolonged chromatography. This allogibberic → gibberic type rearrangement is driven by the relief of strain in going from cis-fused B/C rings (skew-boat C ring) to trans-fused B/C rings (chair C ring). The occurrence of the same rearrangement with 17-nor-17-oxoallogibberic acid represented an inconsistency in the originally assigned stereochemistry of gibberellic acid which led us to propose the X-ray crystallographic study (see ref 2d) that eventually produced the correction of the earlier configurational assignment at C(9).
(24) The β-methoxyethoxymethyl (MEM) protecting group[11] was originally developed for this specific application.
(25) For method see V. Van Rheenen, R. C. Kelly, and D. A. Cha, *Tetrahedron Lett.*, 1973 (1976).
(26) As might be expected the dialdehyde **18** is quite unstable (e.g., to water or silica gel).
(27) The use of this outstanding selective reagent (a crystalline solid) for this very demanding step (see ref 6) was arrived at by systematic experimental variation of secondary amine and acid components based on the idea of activating the methylene group α to the less hindered formyl group as an enamine by means of a not-too-basic, sterically discriminating secondary amine under almost neutral aprotic conditions. Other studies with this reagent will be published separately. Since these investigations one of the undersigned has successfully applied a similar reagent to the direct α methylenation of ketones; see J.-L. Gras, *Tetrahedron Lett.*, 2111 (1978).
(28) This investigation was supported financially by the U.S. National Science Foundation to whom we are deeply grateful.
(29) We are pleased to acknowledge helpful information and experimental data from the following colleagues: Drs. Sandor Barcza, Thomas M. Brennan, Robert L. Carney, Tetsuo Hiraoka, Masayuki Narisada, George Strunz, and Gerald L. Thompson.

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Stereospecific Total Synthesis of Gibberellic Acid

Sir:

This communication describes the completion of the stereospecific total synthesis of gibberellic acid (GA_3) (**1**) from a key tricyclic intermediate (**2**) which is readily accessible by the approach detailed in the preceding publication.[1] In addition we disclose a new facet of the chemistry of gibberellic acid which allows access to derivatives in which the C(7) substituent on ring **B** is in the unnatural (and generally less stable[2]) α orientation and which also provided useful direct correlation of GA_3 with a number of advanced synthetic intermediates.

Deprotonation of the hydroxy diene **2** with 1.0 equiv of *n*-butyllithium in tetrahydrofuran (THF) at −40 °C followed by acylation with 1.55 equiv of *trans*-2-chloroacrylyl chloride[3] at −40 °C for 0.5 h afforded the ester **3** in ~80% yield (~62% overall from the THP ether of **2**).[4] When **3** was heated in benzene solution containing ~100 equiv of propylene oxide (as a hydrogen chloride scavenger) in a sealed tube at 160 °C for 45 h under argon the pure crystalline lactone **4**, mp 149–150 °C, could be obtained in 55% yield after recrystallization.[5] The stereochemistry of **4** is assigned from the supposition of concerted, α-face, "endo" internal Diels–Alder addition (there was no evidence for the formation of an appreciable amount of any stereoisomer of **4**); it is supported by ^{1}H NMR data and also by subsequent transformation to GA_3. Treatment of the adduct **4** with 2.2 equiv of lithium isopropylcyclohexylamide and 5 equiv of hexamethylphosphoramide in THF at −78 °C for 50 min followed by reaction with 5 equiv of methyl iodide at −78 to 0 °C over 12 h afforded cleanly the methylated lactone **5** (~75% yield). At this stage the MEM[6] protecting group was removed from **5** by stirring in dry chloroform–ether–nitromethane (15:5:1 by volume) with 25 equiv of finely powdered *anhydrous* zinc bromide at 23 °C for 3 h to yield hydroxy lactone **6** (~70% after chromatography). The IR, ^{1}H NMR, UV, and mass spectra and the TLC mobility of this material were identical with those of a sample of optically active **6** obtained from natural gibberellic acid as described below.

The synthetic (±)-hydroxy lactone **6** was resolved using a novel procedure designed to take advantage of the lone (tertiary bridgehead) hydroxyl in **6**. Exposure of **6** to a large excess of phosgene and 3 equiv of 4-dimethylaminopyridine in dry methylene chloride at 23 °C for 36 h gave, after rapid filtration through dry Celite and concentration in vacuo, crude chloroformate **7**[7] which was directly treated with (−)-α-phenylethylamine ($[\alpha]^{25}_D$ −41.7° in benzene) to provide after isolation a mixture of two diastereomeric urethanes (**8**) (95% total yield) which could be separated cleanly by chromatography on silica gel using 1:1 ethyl acetate–hexane for elution (TLC R_f values in this solvent system, 0.24 and 0.20). The less polar diastereomer, $[\alpha]^{25}_D$ +59° (*c* 0.44, $CHCl_3$), was identical spectroscopically (IR, ^{1}H NMR, mass spectrum) and chromatographically with urethane prepared from hydroxy lactone **6** from natural GA_3 and (−)-α-phenylethylamine which showed $[\alpha]^{25}_D$ +61° (*c* 0.42, $CHCl_3$). Reaction of this less polar synthetic urethane **8** with 5 equiv of triethylamine and 3 equiv of trichlorosilane in dry benzene at 25 °C for 60 h[8] afforded in 95% yield resolved hydroxy lactone **6**, mp 211–212 °C, $[\alpha]^{20}_D$ +162° (*c* 0.58, $CHCl_3$), identical in all respects (IR, ^{1}H NMR, mass spectrum, TLC high pressure liquid chromatography) with the hydroxy lactone **6** derived from natural GA_3 which showed $[\alpha]^{20}_D$ +161° (*c* 0.49, $CHCl_3$).

The optically active lactone **6** was hydrolyzed to the corresponding hydroxy acid salt by heating at reflux with excess 1.0 N aqueous potassium hydroxide for 45 min (argon atmosphere) and the resulting solution was treated at 23 °C with 2.07 equiv of 0.013 M sodium ruthenate[9] in 1 N aqueous sodium hydroxide for 2.5 h. Filtration through Celite, acidification to pH 3 at 0 °C, and extraction afforded upon isolation the diacid **9**, spectroscopically and chromatographically identical with the diacid obtained from GA_3 (see below); the corresponding dimethyl esters (from excess CH_2N_2 in ether) were also identical. The formation of diacid **9** clearly proceeds by way of the intermediate acid aldehyde which undergoes

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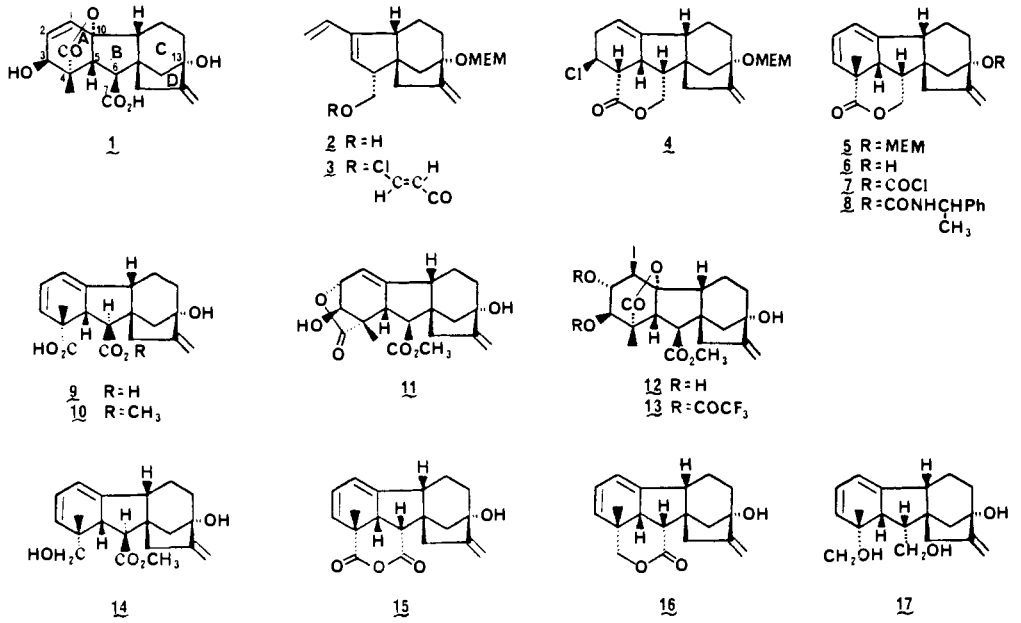

base-catalyzed epimerization to the more stable 6β-formyl derivative and then further oxidation to the observed product.[10] Selective monoesterification of the diacid was accomplished in THF by treatment with triethylamine (1.5 equiv) and *p*-toluenesulfonyl chloride (1 equiv) at −78 °C for 0.5 h and −50 °C for 2 h (to form the mixed sulfonic anhydride), subsequent quenching with excess methanol at −50 °C initially, and then, after warming to 23 °C, stirring for a further 2 h. Chromatography afforded the monoester **10** as a solid foam, $[\alpha]^{20}_D$ −21° (*c* 4.9, THF), identical in all respects with the compound obtained from GA_3 as described earlier.[11] From this optically active intermediate (**10**)[12] the synthesis of GA_3 is completed by the previously described[11] route which includes (1) hydroxylactonization of **10** with *m*-chloroperbenzoic acid to form **11**;[13] (2) lactone saponification and iodolactonization of **11** to give the iodolactone **12**; (3) in one flask, trifluoroacetylation of **12** to **13**, reduction with zinc to eliminate the 1-iodo and 2-trifluoroacetoxy substituents and bicarbonate treatment to saponify the 3-trifluoroacetate forming GA_3 methyl ester; and finally (4) conversion of GA_3 methyl ester to the free acid **1** using sodium *n*-propyl mercaptide in hexamethylphosphoramide[14] at 0 °C.

The transformation of gibberellic acid **1** to the key intermediate **6** and several other gibberellins having the C(7) substituent α-oriented at C(6) was achieved by the use of a novel strategy for effecting the 6β → 6α epimerization which is normally contrathermodynamic in this series.

Saponification of the acid ester **10**[15] by heating at reflux with excess 1 N aqueous potassium hydroxide for 40 min afforded after acidification and isolation the diacid **9** (95% yield), $[\alpha]^{20}_D$ −25.5° (*c* 2.4, THF), which could be reesterified with excess diazomethane to the same dimethyl ester obtained by methylation of **10** (indicating that no epimerization at C(6) occurs in the saponification). Reaction of the diacid **9** with 10 equiv of triethylamine and 1 equiv of *N,N'*-dicyclohexyl carbodiimide in THF at reflux for 7 h furnished, upon workup and chromatography on silica gel, the anhydride **15**, mp 167–168 °C, $[\alpha]^{20}_D$ +268° (*c* 9.3, $CHCl_3$) (73% yield). The stereochemistry of the anhydride, anticipated to be as shown in **15** on geometrical grounds, was shown by methanolysis (CH_3OH–C_5H_5N) and methylation of the resulting acid-ester with diazomethane to produce a dimethyl ester stereoisomeric with that obtained by methylation of **9** or **10**.[16] The success of the 6β → 6α epimerization involved in the formation of the anhydride **15** depends on activation of the C(6) carboxylic acid function under equilibrating conditions (triethylamine catalysis) and subsequent capture of the C(6) α-oriented carbonyl by the 4α-carboxylic group. Reduction of **15** with ~0.6 mol equiv of lithium borohydride in dimethoxyethane at −25 °C for 1.5 h yielded, upon acidification with acetic acid, workup, and chromatography on silica gel, the lactone **6** (50%) together with a structurally isomeric lactone (**16**, 16%); R_f values for **6** and **16** were 0.74 and 0.85, respectively (silica gel plates, ethyl acetate–acetic acid, 95:5). The isomeric lactone **16**, mp 171 °C, $[\alpha]^{20}_D$ +133° (*c* 8.7, $CHCl_3$), was synthesized unambiguously from the ester acid **10** by the following sequence: (1) reaction of the tetra-*n*-butylammonium salt of **10** in dry THF with 1 equiv of mesitylenesulfonyl chloride at −78 → 23 °C over 2 h to form the mixed sulfonic anhydride; (2) reduction of the activated 4-carboxylic group to a 4-hydroxymethyl group (without isolation) at 0 °C by addition of excess sodium borohydride and reaction at 0 °C for 1 h; and (3) epimerization at C(6) and concomitant lactonization of the resulting dihydroxy ester (**14**) by heating at reflux with sodium methoxide in absolute methanol for 48 h.

Lithium borohydride reduction of either lactone **6** or **16** afforded the triol **17** (colorless, foam), $[\alpha]^{20}_D$ −17.0° (*c* 3.5, THF), oxidation of which with chromic acid (two phase, ether–water) led exclusively to lactone **16** (no detectible **6**).[17]

The research results described in this and the foregoing paper mark the achievement of one of the more intriguing and salient objectives in the area of organic synthesis. They also provide a basis for further synthetic and transformational investigations relating to gibberellic acid, and we hope to report on the ongoing work in this area in due course.[18,19]

References and Notes

(1) E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, and J.-L. Gras, *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) (a) J. F. Grove, *Q. Rev. (London)*, **15**, 56 (1961); (b) E. J. Corey and R. L. Danheiser, *Tetrahedron Lett.*, 4477 (1973).

(3) (a) A. N. Kurtz, W. E. Billups, R. B. Greenlee, H. F. Hamil, and W. T. Pace, *J. Org. Chem.*, **30**, 3141 (1965); (b) P. K. Freeman, B. K. Stevenson, D. M. Balls, and D. H. Jones, *ibid.*, **39**, 546 (1974).

(4) Satisfactory infrared (IR), proton magnetic resonance (^{1}H NMR), and mass spectral data were obtained on purified, chromatographically homogeneous samples of the synthetic intermediates described herein. All reactions involving air- or moisture-sensitive components were carried out in an atmosphere of dry argon.

(5) In earlier model studies of this internal Diels–Alder step,[1b] satisfactory cyclization was obtained both with *trans*-2-chloroacrylate and propiolate esters. In contrast to the earlier studies the conversion of **3** to **4** *failed completely* in the absence of propylene oxide. The cyclization of the

propiolate ester of **2** was not studied since we were unable to find conditions for its formation in high yield (from propiolic anhydride or other carboxyl-activated derivatives of propiolic acid), again in contradistinction to earlier model studies or model experiments with other primary or secondary alcohols.

(6) E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 809 (1976).
(7) The chloroformate **7** reacted rapidly with water to re-form **6**, with various alcohols to form the corresponding mixed carbonates as well as with primary amines to form the expected urethanes.
(8) Method of W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **42**, 2781 (1977).
(9) D. G. Lee, D. T. Hall, and J. H. Cleland, *Can. J. Chem.*, **50**, 3741 (1972). As the orange solution containing the reagent was added to the reaction mixture a black precipitate developed.
(10) Analogous $\alpha \rightarrow \beta$ epimerization of 6 α-formyl derivatives in a number of related structures has been observed in these laboratories (see also ref 2b); it occurs readily and completely even under mild conditions (triethylamine, Oediger's base, or chromatography on silica gel).
(11) E. J. Corey, T. M. Brennan, and R. L. Carney, *J. Am. Chem. Soc.*, **93**, 7316 (1971). For another less direct synthesis of **10** from **6**, see R. L. Danheiser, Ph.D. Dissertation, Harvard Universtiy, 1978.
(12) The optically active ester acid **10** may also be obtained by resolution of racemic **10** using (−)-α-(1′-napthyl)ethylamine with ethyl acetate–ether for crystallization.
(13) Hydroxy lactone **11** could also be obtained from diacid **9** by hydroxylactonization (1.05 equiv of peracetic acid in water–ethyl acetate at pH 9) followed by esterification with diazomethane.
(14) P. A. Bartlett and W. S. Johnson, *Tetrahedron Lett.*, 4459 (1970).
(15) Derived from naturally occurring GA_3.
(16) The dimethyl ester corresponding to diacid **9** had R_f 0.27, whereas the 6α epimer had R_f 0.25 (silica gel plates with 1:1 ethyl acetate–hexane); the epimeric dimethyl esters were very easily separable by high pressure liquid chromatography (1-min difference in retention time with heptane–ether–isopropyl alcohol (100:10:1)).
(17) The naturally derived triol **17** was spectroscopically and chromatographically identical with the triol obtained by lithium borohydride reduction of synthetic (±)-**6**.
(18) We are indebted to the following colleagues for experimental help at various times: Drs. Yoshihiro Hayakawa, Thomas M. Brennan, and Robert L. Carney. Our sincere thanks are extended to Imperial Chemical Industries Ltd., Merck and Co., Abbott Laboratories, and Chas. Pfizer and Co. for their generosity in donating samples of gibberellic acid.
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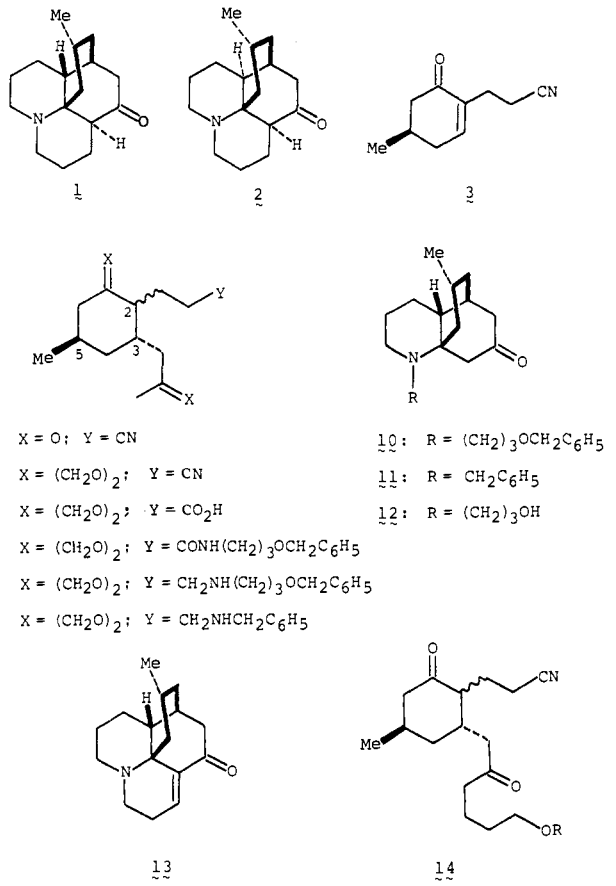
A Highly Efficient Total Synthesis of (±)-Lycopodine

Sir:

Lycopodine (**1**), the archetypal *Lycopodium* alkaloid,[1] has been known since 1881,[2] although its full structure was not established until 1960.[3] Intensive synthetic work during the 1960s[4] resulted in two total syntheses of the alkaloid which were communicated in 1968.[5] An earlier approach resulted in the synthesis of the unnatural diastereomer 12-epilycopodine (**2**).[6] A recent communication reports a synthesis of racemic anhydrolycodoline.[7] Since natural anhydrolycodoline is hydrogenated to **2** and **1** in a ratio of 6.5:1,[8] this work constitutes a further formal synthesis of lycopodine. We wish to communicate a highly efficient stereospecific total synthesis of lycopodine which is promising for application to the synthesis of some of the many other members of this important class of alkaloids.[1]

Cyanoenone **3**[9] is converted into cyanodione **4** by stereoselective trans addition[10] of lithium dimethallylcopper (ether, −78 °C; 64%),[11] followed by ozonolysis (O_3, CH_3OH, −78 °C; 87%), or by conjugate addition of the cuprate derived from the lithiated *N,N*-dimethylhydrazone of acetone, followed by aqueous hydrolysis ((1) THF, −78 °C, 4 h; (2) Cu_2Cl_2, THF, H_2O, pH 7, 25 °C, 16 h; 60%).[12] Both procedures afford cyanodione **4** as a separable mixture of C_2 epimers, in an approximate equimolar ratio. However, we have been unable to detect, at this stage or any subsequent stage, C_3–C_5 cis diastereomers. Cyanodione **4** is converted via cyano diketal **5** ($HOCH_2CH_2OH$, *p*-TsOH, C_6H_6, reflux; 99%) to diketal acid **6** (KOH, H_2O, C_2H_5OH, reflux, 16 h; 90%). Treatment of acid **6** with ethyl chloroformate in the presence of triethylamine, followed by 3-benzyloxypropylamine (THF, −10 °C; 88%),[13] affords amide **7** which is reduced to secondary amine **8** ($LiAlH_4$, THF, reflux, 16 h; 99%).



Treatment of amino diketal **8** with HCl in methanol results in slow intramolecular Mannich cyclization (3.2 M HCl, reflux, 14 days), affording a single tricyclic amino ketone (**10**) in 65% yield. Although compound **8**, like compounds **4–7**, is an equimolar mixture of C_2 epimers, none of the 12-epi diastereomer (lycopodine numbering) has been found in the reaction product. This kinetic stereoselectivity was anticipated[14] and is also observed in cyclization of the analogous *N*-benzylamine **9**, which affords tricyclic amino ketone **11**, uncontaminated by its diastereomer, under similar (but less stringent) conditions (2.2 equiv of HCl, CH_3OH, reflux, 48 h; 66%).

Catalytic debenzylation of **10** (H_2O, C_2H_5OH, HCl, H_2, Pd; 96%) affords crystalline alcohol **12** (mp 86–87 °C), which undergoes Oppenauer oxidation (benzophenone, *t*-C_4H_9OK, C_6H_6, reflux, 30 min)[15] with subsequent intramolecular aldolization and dehydration to afford racemic dehydrolycopodine[16] (**13**, mp 104–105 °C; λ_{max} 245 nm (ϵ 5000)) in 72% yield. Catalytic hydrogenation of **13** (H_2, Pt, C_2H_5OH) affords racemic lycopodine (**1**, mp 130–131 °C (lit.[5a] mp 130–131 °C)) in 87% yield. The synthetic material produced in this manner is identical with a sample of natural lycopodine by infrared and 180-MHz ^1H NMR spectroscopy.

The efficiency of the current synthesis is demonstrated by the high overall yield (17.7% from enone **3**, 11.1% from dihydroorcinol[17]) and by the fact that no other lycopodine diastereomer may be detected in the final product, even though isomer separations are not carried out at any point during the synthesis. In one continuous run, we have prepared 1.2 g of

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