2 mL of NH_4OH and heated at 50 °C for 20 h. The orange heterogeneous mixture was evaporated, and the residue was dissolved in 17 mL of H_2O and 4 mL of AcOH (decolorization). Extraction with EtOAc (10, 5, 5 mL) and $CHCl_3$ (5 mL) left an aqueous layer which contained two products by reversed phase HPLC (see text) (15-min gradient, 1-15% CH_3CN in 0.1 M NH_4OAc, pH 5.7, 2 mL/min). After preparative injections and the pooling of fractions, the eluant containing the tetranucleotide **1** (the major peak) was diluted with three volumes of water and passed through a Sep-Pak (prewashed with 80% CH_3CN and H_2O). A 5-mL wash with H_2O removed excess AcOH and NH_4OAc, and the product was eluted with 5 mL of 50% CH_3CN. Lyophilization and solution of the product in water gave 17 AU_{260}: UV max (H_2O) 265 nm, 254 (sh) (relative ϵ 1.0:0.98).

Approximately 4 AU_{260} of the tetramer **1** in 0.5 mL of 0.10 M Tris/2mM $MgCl_2$ pH 8.2 buffer was treated with 80 μg of venom phosphodiesterase, 160 μg of bacterial alkaline phosphates, and 440 μL of buffer to make a total of 1 mL.[20] The reaction was incubated at 37 °C for 17.5 h, 2.5 mL of cold EtOH was added, and after 1 h at −20 °C the proteins were pelleted by centrifugation and the supernatant was evaporated under a stream of argon. The residue was dissolved in 0.5 mL of H_2O and analyzed on a reversed-phase HPLC column (1% CH_3CN, 0.1 M NH_4OAc, pH 5.7, μ-Bondapak C_{18}, 2 mL/min), showing dC (2.3 min), dT (3.6 min), dA (8.6 min), and d(O^6-Me)G (16.5 min) by comparison with authentic standards. The peaks were collected and compared by UV with authentic nucleosides.

5′-Phosphorylation with γ-^{32}P ATP and polynucleotide kinase,[20] HPLC purification (see text), and partial digestion with snake venom phosphodiesterase and endonuclease P_1 (see text) gave a mixture of fragments which were pooled and submitted to homochromatography.[21] Figure 4 shows the expected sequence including an unusual mobility shift for the second base.

^{1}H NMR (D_2O, in ppm downfield from DSS): 8.31 (1 H, s, H8 of A), 8.08 (s, 2, H2 A + H8 (O^6-Me)G), 7.58 (d, 1, J = 7.4 Hz, H6 C), 7.34 (d(m?), 1, J = 1.1 Hz, H6 T), 6.36 (t, 1, J = 6.6 Hz, H1′), 6.14 (t, 1, J = 5.5 Hz, H1′), 6.11 (t, 1, J = 5.5 Hz, H1′), 5.96 (dd, 1, J = 8.5, 5.9 Hz, H1′), 5.84 (d, 1, J = 7.4 Hz, H5 C), 4.4-3.6 (m's, 16, H3′, H4′, H5′). 4.00 (s, 3, OCH_3 of O^6-MeG), 2.9-1.7 (m's, 8, H2′), 1.82 (s, 3, CH_3 T).

Acknowledgment. We express our gratitude to Professor Paul S. Miller of the Johns Hopkins University Division of Biophysics for invaluable discussions and for a large-scale deprotection of the tetranucleotide for NMR, to Professor Lou-sing Kan of JHU for obtaining the 300-MHz NMR spectrum at the JHU-Baltimore NMR Biomedical Research Center, supported by the National Institutes of Health (GM 27512), to Professor U. L. RajBhandary, Mr. David Russell, and Mr. San Yin of the Massachusetts Institute of Technology for assistance in homochromatography, and to Professor David B. Ludlum of Albany Medical College for providing a reference sample of phosphorylated O^6-methyldeoxyguanosine. We also wish to express our appreciation to Professors Gerald N. Wogan and Jonathan A. King of the Massachusetts Institute of Technology for their continued interest and support of this work. High resolution and field desorption mass spectra were provided by Dr. Catherine E. Costello at the facility, supported by the National Institutes of Health (Grant RR 00317, Professor Klaus Biemann, principal investigator), for the Biotechnology Resources Branch, Division of Research Resources. This work was supported by a National Research Service Award (Grant 2 T32 CA09112) from the National Cancer Institute, DHEW, the National Institutes of Health (Grants GM 09868 and PO1 ES 00597), and the Hoffmann-LaRoche Foundation.

Registry No. **1**, 80228-05-3; **2**, 964-21-6; **3**, 80228-06-4; **4**, 80228-07-5; **5**, 80228-08-6; **6**, 80228-09-7; **7**, 80228-10-0; **8**, 80228-11-1; **9**, 80228-12-2; **10**, 80228-13-3; 2-amino-6-chloropurine, 10310-21-1; 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentosyl chloride, 3601-89-6; dDMTrTpCE, 67221-57-2; dDMTrC^{Bz}pCE, 80228-14-4; dA^{Bz}Ac, 25152-95-8.

Total Synthesis of Lycopodium Alkaloids: (±)-Lycopodine, (±)-Lycodine, and (±)-Lycodoline[1]

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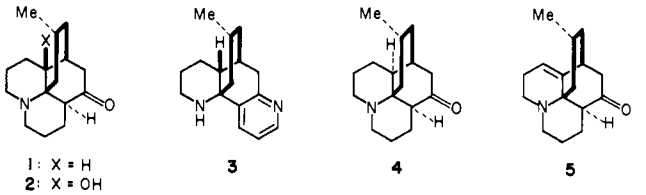
Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received June 4, 1981*

Abstract: Intramolecular Mannich condensation is shown to be a powerful method for the synthesis of lycopodium alkaloids (eq 2). Two syntheses of (±)-lycopodine (**1**) have been developed. In the first (Scheme II), compound **1** is produced in 13 steps from 5-methyl-1,3-cyclohexanedione (16.6% overall yield). In this synthesis, rings A and B are formed in the Mannich cyclization, and ring D is closed by aldol condensation. The alternative lycopodine synthesis (Scheme IV) is more convergent and produces (±)-**1** in only eight operations from the same starting point (13% overall yield). In this synthesis, primary amine **41** is employed in the Mannich reaction, and ring D is closed by intramolecular alkylation of a bromo amine. The synthesis of (±)-lycodine (**3**) also requires eight steps and provides the alkaloid in 13.2% overall yield (Scheme V). This synthesis features an efficient, one-pot conversion of δ,ϵ-unsaturated ketone **46** into pyridine **3**. (±)-Lycodoline (**3**) is produced by an 11-step route in 3.2% overall yield as shown in eq 16, 18, and 22. In this synthesis, the angular hydroxyl is introduced by the stereoselective autoxidation of an octahydroquinoline (eq 16). The Mannich cyclization is completed by a novel method which utilizes the base-catalyzed polymerization of 3-bromo-1-propanol as a method for slow delivery of HBr, thus allowing the reaction to be carried out under essentially neutral conditions (eq 18). The lycodoline synthesis is completed by use of a novel variant of the Oppenauer oxidation (**61** → **62**).

The lycopodium alkaloids are a family of about 100 biogenetically related compounds elaborated by the genus *Lycopodium* (club mosses).[2] The first known,[3] most abundant, and most widely distributed member of the family is lycopodine (**1**). The structure



of lycopodine was established by MacLean in 1960[4] and confirmed

(1) Portions of this work have been reported in preliminary form: (a) C. H. Heathcock, E. Kleinman, and E. S. Binkley, *J. Am. Chem. Soc.*, **100**, 8036 (1978); (b) E. Kleinman and C. H. Heathcock, *Tetrahedron Lett.*, 4125 (1979); (c) C. H. Heathcock and E. F. Kleinman, *J. Am. Chem. Soc.*, **103**, 222 (1981).

(2) For reviews of lycopodium alkaloid chemistry, see: (a) K. Wiesner, *Fortschr. Chem. Org. Naturst.*, **20**, 271 (1962); (b) D. B. MacLean *Alkaloids (N.Y.)* **10**, 305 (1968); (c) *ibid.*, **14**, 347 (1973).

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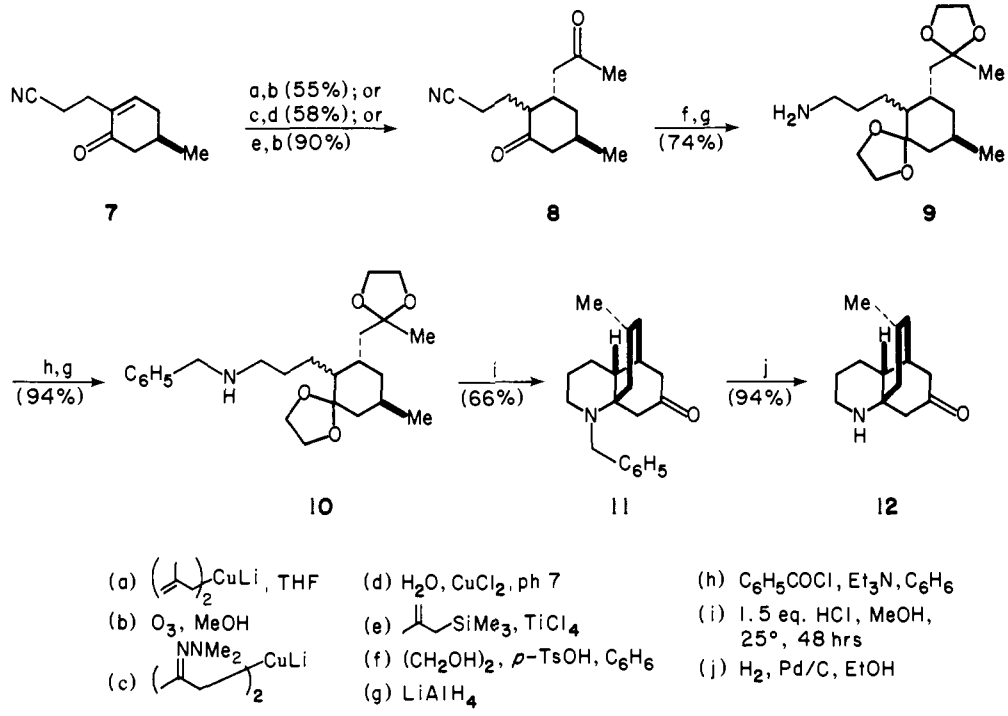
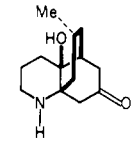
Scheme I



by single-crystal X-ray analysis in 1974.[5] Lycodoline (**2**) is the second most widely occurring member of the family. It was discovered in 1943 by Manske and Marion,[6] and its structure was elucidated by Ayer and Iverach in 1961.[7] Lycodine (**3**), first isolated by Anet and Eves,[8] is the simplest member of a small group of dinitrogen lycopodium alkaloids which also includes *N*-methyllycopodine,[9] α-obscurine,[10] and β-obscurine.[10]

Lycopodine has been the target of a number of synthetic investigations. The only successful syntheses have been those of Stork[11] and Ayer,[12] which were communicated in 1968. An attempted synthesis by Wiesner provided the unnatural isomer 12-epilycopodine (**4**).[13] Several other interesting approaches were either unsuccessful or were not pursued to completion.[14] In addition, Horii has reported a synthesis of racemic anhydrolycodoline (**5**).[15] Since natural anhydrolycodoline may be hydrogenated to a 6.5:1 mixture of **4** and **1**,[7a] the Horii route could, in principle, also be used to synthesize these compounds.[16] The only reported attempt to prepare lycodoline is the work of Horii, which led to the tricycle **6**.[17] Unfortunately, attempts to add the

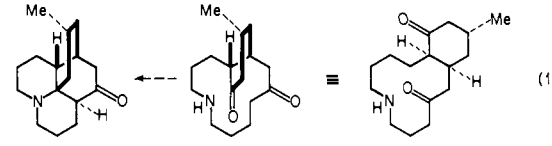


6

fourth ring were unsuccessful.[15] There have been no reports of synthetic attacks specifically directed at lycodine.

Synthetic Design

Our approach to the synthesis of lycopodine and its congeners was based on the recognition that **1** is a β-amino ketone and hence the product of a Mannich condensation (eq 1).[18] The Mannich

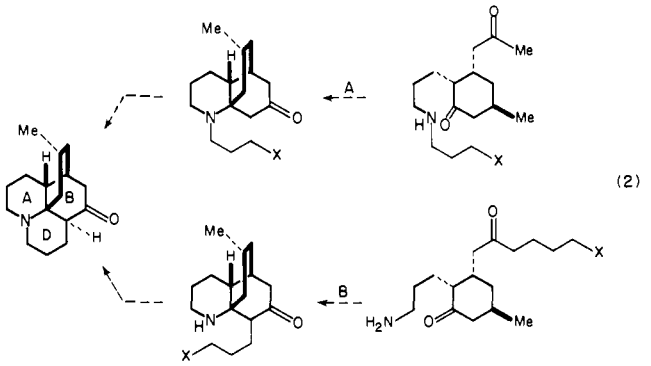


(1)

condensation is a member of the relatively select group of organic reactions which can result in the formation of two or more skeletal

(3) K. Bödeker, *Justus Liebigs Ann. Chem.*, **208**, 363 (1881).
(4) (a) W. A. Harrison and D. B. MacLean, *Chem. Ind. (London)*, 261 (1960); (b) W. A. Harrison, M. Curcumelli-Rodostamo, D. F. Carson, L. R. C. Barclay, and D. B. MacLean, *Can. J. Chem.*, **39**, 2086 (1961).
(5) D. Rogers, A. Quick, and M.-U. Hague, *J. Chem. Soc., Chem. Commun.*, 522 (1974).
(6) R. H. Manske and L. Marion, *Can. J. Res., Sect. B*, **21**, 92 (1943).
(7) (a) W. A. Ayer and G. G. Iverach, *Tetrahedron Lett.*, 87 (1962); (b) W. A. Ayer, and G. G. Iverach, *Can. J. Chem.*, **42**, 2514 (1964).
(8) F. A. L. Anet and C. R. Eves, *Can. J. Chem.*, **36**, 902 (1958).
(9) W. A. Ayer, J. A. Berezowsky, and G. G. Iverach, *Tetrahedron*, **18**, 567 (1962).
(10) B. P. Moore and L. Marion, *Can. J. Chem.*, **31**, 952 (1953).
(11) (a) G. Stork, R. A. Kretchmer, and R. H. Schlessinger, *J. Am. Chem. Soc.*, **90**, 1647 (1968); (b) G. Stork, *Pure Appl. Chem.*, **17**, 383 (1968).
(12) W. A. Ayer, W. R. Bowman, T. C. Joseph, and P. Smith, *J. Am. Chem. Soc.*, **90**, 1648 (1968).
(13) K. Wiesner, V. Musil, and K. J. Wiesner, *Tetrahedron Lett.*, 5643 (1968).
(14) (a) F. Bohlmann and O. Schmidt, *Chem. Ber.*, **97**, 1354 (1964); (b) H. Dugas, R. A. Ellison, Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Lett.*, 1279 (1965); (c) E. Colvin, J. Martin, W. Parker, and R. A. Raphael, *J. Chem. Soc., Chem. Commun.*, 596 (1966); (d) E. Wenkert, B. Chauncy, K. G. Dave, A. R. Jeffcoat, F. M. Schell, and H. P. Schenk, *J. Am. Chem. Soc.*, **95**, 8427 (1973).
(15) (a) S.-W. Kim, Y. Bando, and Z.-I. Horii, *Tetrahedron Lett.*, 2293 (1978); (b) T. Momose, S. Uchida, T. Imanishi, S. Kim, N. Takahashi, and Z.-I. Horii, *Heterocycles*, **6**, 1105 (1977).
(16) Although the Horii synthesis of **5** has been referred to as constituting a formal total synthesis of lycopodine, we demur from this description. If racemic anhydrolycodoline had previously been hydrogenated and shown to provide racemic lycopodine, or if the Horii synthesis had incorporated a resolution, so that enantiomerically homogeneous anhydrolycodoline was produced in the end, then it would be accurate to say that this route, appending the final hydrogenation, carried out on the identical substrate, would surely provide the natural product. In some cases, this seemingly trivial distinction may actually be quite important. For example, it is well-known that racemates may have very different melting points and solubilities than the pure enantiomers. Suppose that natural anhydrolycodoline had been hydrogenated in a solvent in which its racemate is insoluble. Suppose further that all solvents in which the racemate are soluble exert an effect upon the diastereoselectivity of the hydrogenation such that only 12-epilycopodine is produced. Under this set of hypothetical conditions, then, it is clear that a *total* synthesis would not have been achieved.
(17) Z.-I. Horii, S.-W. Kim, T. Imanishi, and T. Momose, *Chem. Pharm. Bull.*, **18**, 2235 (1970).
(18) For reviews of the Mannich condensation, see: (a) F. H. Blicke, *Org. React. (N.Y.)*, **1**, 303 (1942); (b) H. Hellmann and G. Opitz, *Angew. Chem.*, **68**, 265 (1956); (c) M. Tramontini, *Synthesis*, 703 (1975).

bonds in one process. Other, more familiar examples are the Diels–Alder reaction (and 1,3-dipolar cycloaddition), Robinson annelation, 2 + 2 photoaddition, and cationic polyene π cyclization. Generally, the application of one of these powerful reactions in a synthesis will lead to considerable economy in the total length of the synthesis (witness the ubiquity of the Diels–Alder and Robinson processes in the construction of carbocyclic systems). Indeed, such simplification is apparent in the case of lycopodine, since the starting material for the hypothetical reaction shown in eq 1 contains only two rings rather than four. On the other hand, this postulated reactant is more complicated than lycopodine in having a 12-membered ring. However, if we first take into account that the ring-D bonds adjacent to the nitrogen and the carbonyl could be formed by appropriate intramolecular alkylations, we arrive at two possible schemes whereby the Mannich condensation could serve as a key to an efficient synthesis of lycopodine (eq 2).[19]



(2)

The Intramolecular Mannich Condensation. To test the efficacy of an intramolecular Mannich condensation for synthesis of the lycopodine skeleton, we carried out the synthesis shown in Scheme I starting with the known cyano enone **7**.[22] The acetonyl side chain may be added by way of lithium dimethallylcuprate, followed by ozonolytic cleavage of the double bond. The addition is highly stereoselective with respect to the C-5 methyl group, as expected.[23] The side chain may also be introduced by the Corey–Enders method,[24] which employs the cuprate derived from the *N,N*-dimethylhydrazone of acetone, or by the Sakurai method,[25] which utilizes methallyltrimethylsilane and titanium tetrachloride.[26] The Sakurai method provides the best overall yield of cyano dione **8**. It appears that these conversions provide the first information on the stereochemistry of the Corey–Enders and Sakurai methods.[26] In each case, compound **8** is obtained as an approximately equimolar mixture of C-2 epimers. After protection of the two carbonyl groups, the cyano function is reduced and an *N*-benzyl group installed by reduction of the benzamide of amine **9**. The crucial Mannich cyclization proceeds smoothly when amino diketal **10** is heated with methanolic HCl for 48 h. A single tricyclic amino ketone (**11**) is obtained in 66% yield. Catalytic debenzylation of **11** provides the secondary amine **12**.

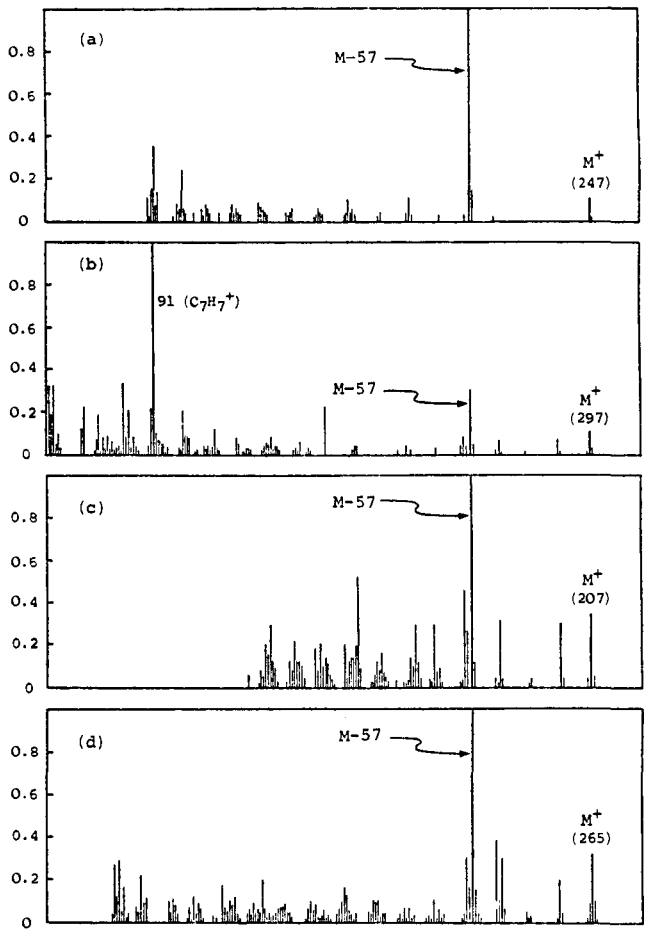
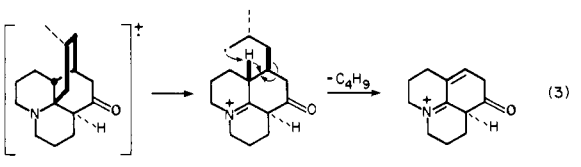


Figure 1. Mass spectra of (a) lycopodine, (b) amino ketone **11**, (c) amino ketone **12**, and (d) hydroxy amino ketone **19**.

The structures of tricyclic amino ketones **11** and **12** were readily assigned on the basis of their mass spectra. MacLean has shown that lycopodine (**1**) and other lycopodium alkaloids having the C_4H_8 bridge give prominent M − 57 peaks, which presumably arise by the mechanism depicted in eq 3.[27] Indeed, both **11** and **12**

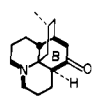


(3)

show major M − 57 fragments in their mass spectra (Figure 1). However, examination of the high-resolution mass spectra of **11** and **12** shows that in each case the M − 57 fragment is a composite of M − C_4H_9 and M − C_3H_5O peaks, which are formed in approximately equal amounts. This is readily understood in terms of the competing fragmentations shown in eq 4.

The Mannich cyclization depicted in Scheme I proceeds not only in good yield but also with high stereoselectivity. The stereoselection of the reaction may be understood in terms of an

(19) In one of his papers in the classic series on the application of machine logic to synthesis design, Corey introduces the heuristic of strategic bonds.[20] As an illustration of the concept, lycopodine is analyzed and the following strategic bonds are identified:



The indicated ring-B bonds are selected because they are exocyclic to a second ring and are contained in a "maximally bridging" ring. The bonds to nitrogen are selected because of a special proviso that all ring bonds to O, S, or N are strategic if their rupture does not lead to formation of a medium or large ring.

The strategic bond heuristic eliminates further consideration of path A. However, Corey has also defined a heuristic which in essence directs initial attention to paths utilizing selected powerful methods such as the Robinson annelation.[21] If a Mannich transform were included in the logical planning process with a high priority, paths A and B would clearly emerge as the only two reasonable paths to **1**.

(20) E. J. Corey, W. J. Howe, H. W. Orf, D. A. Pensak, and G. Peterson, *J. Am. Chem. Soc.*, **97**, 6616 (1975).

(21) E. J. Corey, A. P. Johnson, and A. K. Long, *J. Org. Chem.*, **45**, 2051 (1980).

(22) Compound **7** is prepared in three steps (60% overall yield) from 5-methyl-1,3-cyclohexanedione by a published procedure: R. D. Clark and C. H. Heathcock, *J. Org. Chem.*, **41**, 636 (1976).

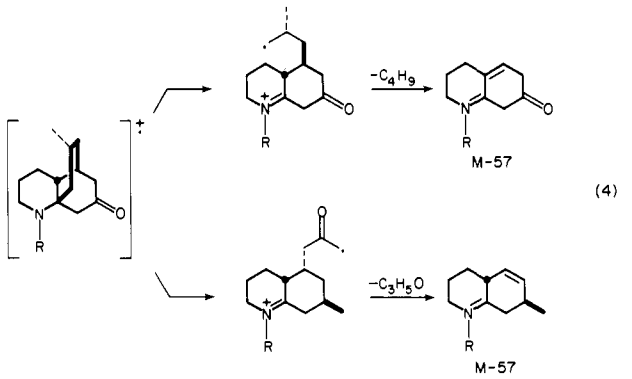
(23) H. O. House and W. F. Fischer, *J. Org. Chem.*, **33**, 949 (1968).

(24) (a) E. J. Corey and D. Enders, *Tetrahedron Lett.*, 11 (1976); (b) E. J. Corey and D. Enders, *Chem. Ber.*, **111**, 1362 (1978).

(25) A. Hosomi and H. Sakurai, *J. Am. Chem. Soc.*, **99**, 1673 (1977).

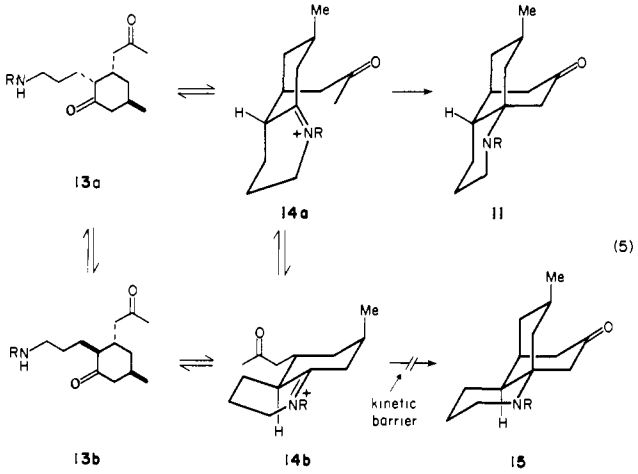
(26) We thank Todd Blumenkopf for carrying out this transformation. Further studies on the stereochemistry of the Sakurai reaction will be published separately.

(27) D. B. MacLean, *Can. J. Chem.*, **41**, 2654 (1963).



(4)

argument first put forth by Stork to account for the stereochemical outcome of a related cyclization.[11] As shown in eq 5, diastereomer



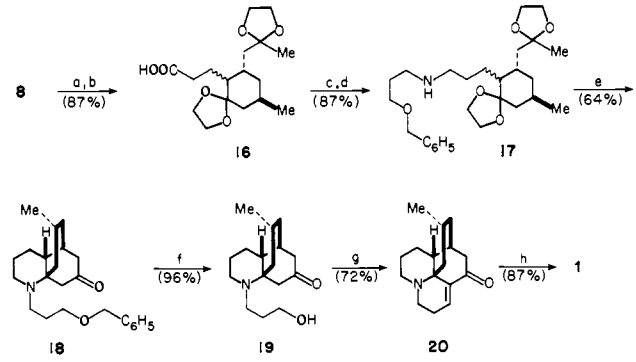
(5)

13a and **13b** can cyclize to give bicyclic immonium ions **14a** and **14b**. However, ions **14a** and **14b** are each constrained to a single conformation in which the cyclohexylidene ring is in a chair conformation. Furthermore, the angular hydrogen *must* be axial with respect to the cyclohexylidene ring in this conformation. Therefore, the acetonyl appendage is axial in isomer **14a** and equatorial in **14b**. The former ion can readily cyclize, leading to **11**. However, for geometric reasons, **14b** cannot cyclize, even though the product (**15**) should be perfectly stable.

The First Lycopodine Synthesis: Path A. For the synthesis of lycopodine, it is necessary that a functionalized three-carbon appendage that can later be used to fashion ring D be incorporated into the Mannich cyclization substrate (paths A and B, eq 2). We first examined path A, as is shown in Scheme II. Ketalization of cyano dione **8**, followed by alkaline hydrolysis of the nitrile function, provides acid **16** which is transformed, via the intermediate amide, into amine **17**. As with amino diketal **10**, treatment of **17** with methanolic HCl results in smooth Mannich cyclization, giving a single tricyclic amino ketone (**18**) in 64% yield. However, in the case of **17** the cyclization requires stronger acid (3 N HCl) and is much slower (14 days). We are at a loss to explain the difference in the rates of cyclization of **10** and **17**. However, it should be noted that the two reactions only differ in rate by a factor of about ten. In fact, of the various Mannich cyclizations we have carried out in this system (vide infra), compound **10** cyclizes most rapidly and compound **17** most slowly.

The sluggishness of the Mannich cyclization is probably due to the fact that enolization of immonium ion **14a** (see eq 5) requires that this intermediate accept a proton and thus become a dication. It occurred to us that, under the relatively acidic conditions, ions **14a** and **14b** might not equilibrate very rapidly. Thus, while **14a** could cyclize to product, part of the material might be trapped in the form of the unreactive ion **14b**. To test this hypothesis, we prepared the two diastereomers of amino diketal **17** and submitted them separately to the conditions of Mannich cyclization. However, the two diastereomers gave amino ketone **9** in essentially identical yields (50 ± 5% after 10 days).

Scheme II



(a) $(CH_2OH)_2$, *p*-TsOH, C_6H_6. (b) KOH, EtOH. (c) $ClCO_2Et$, Et_3N, $H_2N(CH_2)_3OCH_2C_6H_5$. (d) $LiAlH_4$, THF. (e) 3 *N* HCl, MeOH, 65°, 14 days. (f) H_2, Pd/C, HCl, EtOH. (g) *t*-BuOK, $(C_6H_5)_2C{=}O$, C_6H_6. (h) H_2, Pt, EtOH.

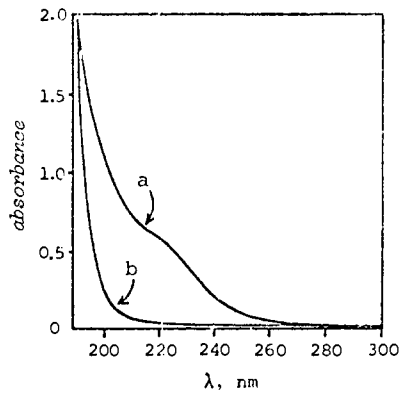
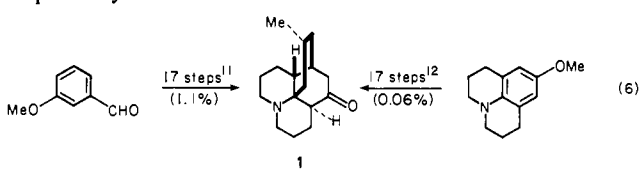


Figure 2. Ultraviolet spectrum of (a) hydroxy amino ketone **19** and (b) the hydrochloride salt of **19**.

Hydrogenolysis of benzyl ether **18** provides the crystalline alcohol **19**. The mass spectrum of **19** (Figure 1) also contains the M − 57 fragment as the base peak. The ultraviolet spectrum of **19** (Figure 2) contains an absorption at 220 nm (ϵ 900) which disappears upon protonation. This weak absorption has also been noticed in lycopodine and other lycopodium alkaloids having the "12-normal" configuration, but not in 12-epilycopodine.[28]

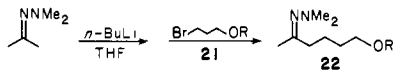
Treatment of hydroxy ketone **19** with potassium *tert*-butoxide and benzophenone in refluxing benzene[29] provides (±)-dehydrolycopodine (**20**),[30] which is smoothly hydrogenated to obtain (±)-lycopodine (**1**).[31] The synthesis of lycopodine which is summarized in Schemes I and II is exceedingly efficient, providing the racemic alkaloid in 16.6% overall yield for the 13 steps beginning with 5-methyl-1,3-cyclohexanedione. For comparison, the pioneering syntheses of Stork[11] and Ayer[12] both require 17 steps from the indicated starting materials (eq 6) and provide (±)-lycopodine in approximate overall yields of 1.1% and 0.06%, respectively.[32]



(6)

(28) W. A. Ayer, B. Altenkirk, R. H. Burnell, and M. Moinas, *Can. J. Chem.*, **47**, 449 (1969).
(29) (a) R. B. Woodward, N. L. Wendler, and F. J. Brutschy, *J. Am. Chem. Soc.*, **67**, 1425 (1945); (b) H. Rapoport, R. Naumann, E. R. Bissell, and R. M. Borner, *J. Org. Chem.*, **15**, 1103 (1950).
(30) M. Curcumelli-Rodostamo and D. B. MacLean, *Can. J. Chem.*, **40**, 1068 (1962).
(31) For a discussion of an unsuccessful attempt to close ring D by intramolecular alkylation of a bromo ketone, see: C. H. Heathcock, E. F. Kleinman, and E. S. Binkley *Int. Congr. Ser.-Excepta Med.*, **457**, 71–82 (1979).

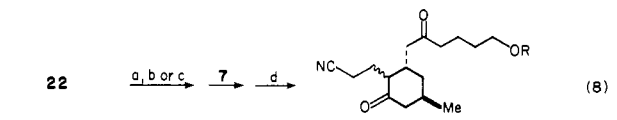
The Second Lycopodine Synthesis: Path B. For the synthesis of lycodine (**3**), it is obviously necessary that the elements of the pyridine ring be attached to the methyl ketone, rather than the nitrogen atom, of the Mannich cyclization substrate (see eq 2, path B). In addition to providing a route to lycodine, path B is more convergent, since the total elements of rings B and D would be added to the cyano enone in one step. Thus, the path B approach should also lead to a simplification of the lycopodine synthesis. To investigate path B, we prepared hydrazone **22a** by alkylating the *N,N*-dimethylhydrazone of acetone with 1-(benzyloxy)-3-bromopropane (eq 7).[33] However, this material turns



(7)

a: R = $CH_2C_6H_5$ b: R = $CH_2OCH_2CH_2OCH_3$ c: R = CH_3

out to be unsuitable for use in the conjugate addition; reaction of **22a** with *n*-butyllithium followed by cuprous iodide and enone **7** provides a 1:1 mixture of cyano dione **23** and the corresponding alcohol **24** (eq 8). To determine whether this unexpected de-



(8)

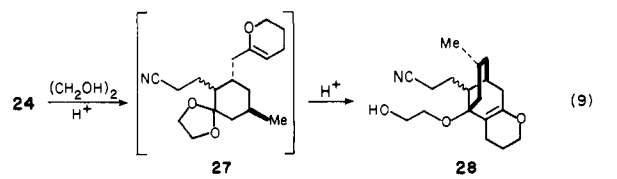
a: R = $CH_2C_6H_5$
b: R = $CH_2OCH_2CH_2OCH_3$
c: R = CH_3

23: R = $CH_2C_6H_5$ } (68%)
24: R = H
25: R = $CH_2OCH_2CH_2OCH_3$ (57%)
26: R = CH_3 (60%)

(a) *n*-BuLi; (b) CuI, $(i\text{-}C_3H_7)_2S$; (c) C_6H_5SCu; (d) $CuCl_2$, H_2O, pH 7

benzylation occurs in the cuprate step or in the hydrolysis step, we subjected hydrazone **22a** to the hydrolysis conditions ($CuCl_2$, H_2O, pH 7) and obtained the corresponding ketone in good yield. Thus, the cleavage probably occurs during formation or reaction of the cuprate reagent. Although to our knowledge cuprate-initiated debenzylation is not precedented, it is not totally unexpected, since cuprates are known to be effective electron-transfer reagents.[34]

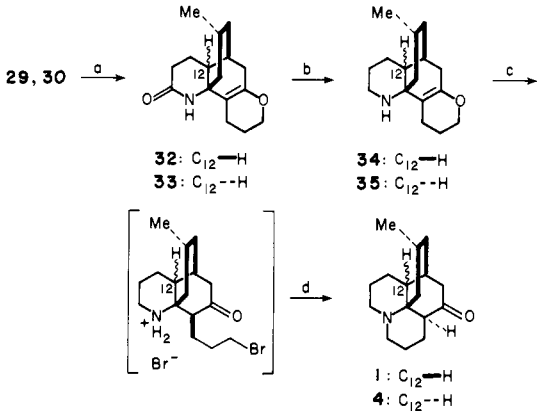
The second addend we examined was the (methoxyethoxy)methyl (MEM)[35] ether **22b**. The mixed cuprate reagent was formed from lithiated **22b** and thiophenoxycopper.[36] As expected, the conjugate addition proceeds smoothly, affording adduct **25** in 57% yield (eq 8). Since we anticipated problems with the MEM protecting group under the acidic conditions of the ketalization process or later under the rather vigorous acidic conditions of the Mannich cyclization, we elected to remove it at this point under controlled conditions. Deblocking is conveniently achieved by treatment of **25** with HCl in aqueous THF at 69 °C; diketo alcohol **24** is obtained in 69% yield. However, treatment of **24** to the standard ketalization conditions affords a mixture of diastereomeric dihydropyrans **28** in quantitative yield. These compounds are presumably formed via dihydropyran **27**, as shown in eq 9.



(9)

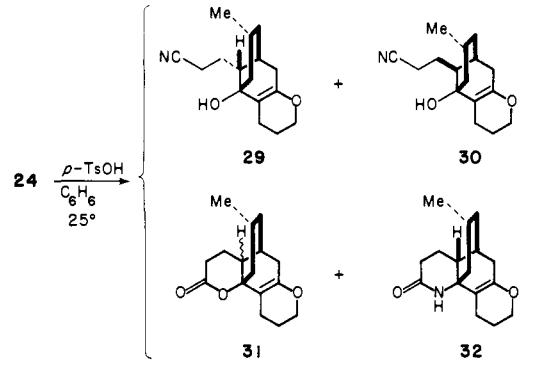
The aldol-like cyclization of **24** may also be accomplished by simple acid treatment (*p*-toluenesulfonic acid in benzene); enol

Scheme III



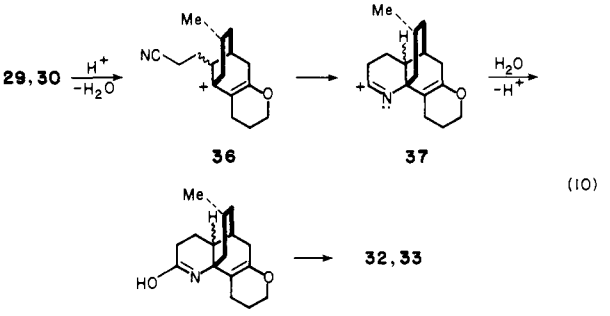
(a) 2-Naphthalenesulfonic acid, C_6H_6, Δ. (b) $LiAlH_4$, THF, Δ. (c) 25% HBr/HOAc, 25°. (d) K_2CO_3, MeOH.

ethers **29** and **30** are formed in a combined yield of 54%, along with 3% of lactone **31** and 2% of lactam **32**.



The stereostructures of **29**, **30**, and **31** were determined as outlined in Scheme III. The separated cyano alcohols **29** and **30** were each converted, by treatment with 2-naphthalenesulfonic acid in refluxing benzene, into the corresponding lactams (**32** and **33**). In the case of **29**, lactam formation is highly stereoselective; lactam **32** is produced as the only diastereomer in 79% yield. However, isomer **30** gives 65% of lactam **33** and 15% of **32**. Reduction of lactams **32** and **33** provides the corresponding amines (**34** and **35**), which are treated with 25% HBr in glacial acetic acid at 25 °C. The intermediate ammonium bromide salt is basified, whereupon spontaneous cyclization occurs, leading to (±)-lycopodine (**1**) and (±)-12-epilycopodine (**4**), respectively.

The conversion of cyano alcohols into lactams **32** and **33** appears to be an example of the well-known Ritter reaction (eq 10).[37]

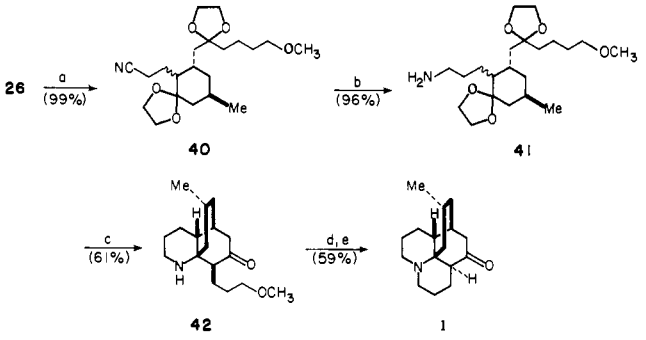


(10)

However, in the present case, we think that this mechanism is unlikely. Although the solvolysis of various 1-substituted bicyclo[3.3.1]nonanes to give bridgehead carbocations analogous to **36** is well precedented,[38,39] the lone-pair electrons of the nitrile

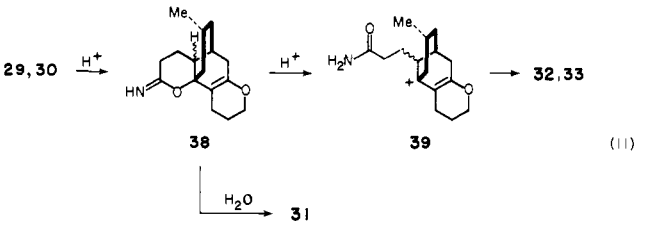
(32) Yields were not reported for all steps in the Stork and Ayer syntheses. All such steps were assumed to proceed in 95% yield for the purpose of this comparison.
(33) E. J. Corey and D. Enders, *Tetrahedron Lett.*, 3 (1976).
(34) H. O. House, *Acc. Chem. Res.*, **9**, 59 (1976).
(35) E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 809 (1976).
(36) E. J. Corey and D. L. Boger, *Tetrahedron Lett.*, 4597 (1978).
(37) L. I. Krimen and D. J. Cota, *Org. React.* (*N.Y.*), **17**, 213 (1969).

Scheme IV



(a) $(CH_2OH)_2$, *p*-TsOH, C_6H_6. (b) $LiAlH_4$. (c) 3 *N* HCl, MeOH, Δ, 18 days. (d) 25% HBr/HOAc, 25°. (e) K_2CO_3, MeOH.

nitrogen in **36** are not well disposed to attack the cationic center. Furthermore, the geometry of ion **37** is such that the lone-pair electrons cannot assist in delocalizing the positive charge. A more plausible mechanism is summarized in eq 11. Acid-catalyzed

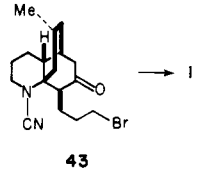


(11)

addition of the bridgehead hydroxy group to the nitrile may afford iminolactone **38**, which undergoes solvolysis to bridgehead carbocation **39**, followed by cyclization to lactams **32** or **33**. Hydrolysis of iminolactone leads to lactone **31**.

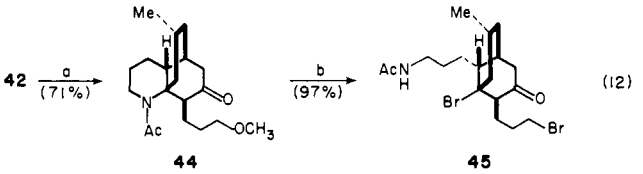
Although the conversion of enone **7** to (±)-lycopodine via enol ether **24** is relatively straightforward (six steps) and proceeds in reasonable overall yield (ca. 6%), this approach suffers from lack of stereochemical control, since both (±)-lycopodine and (±)-12-epilycopodine are produced. The problem is solved by using a more stable protecting group than MEM for the primary alcohol. Thus, methyl ether **26** is smoothly diketalized to cyano diketal **40**, which is reduced to amino diketal **41**. This material undergoes the Mannich closure reaction, providing tricyclic amino ketone **42**, which is converted into (±)-lycopodine by treatment with HBr in glacial acetic acid followed by basification. Thus, path B is shown to be viable. (±)-Lycopodine is produced in this manner in eight operations (13% overall yield) from 5-methyl-1,3-cyclohexanedione (Scheme IV).

Synthesis of Lycodine. In 1960, Anet and Rao[40] reported the conversion of bromo ketone **43**, a key intermediate in MacLean's degradation of lycopodine,[4] into lycodine. It therefore seems that



the methoxy ketone **42** should be a viable intermediate for synthesis of (±)-lycodine, since we have established in the second lycopodine synthesis that the primary methyl ether can be conveniently converted into a primary bromide. However, it is necessary to protect the amino group before cleavage of the ther, since simple neutralization of the ammonium salt leads to lycopodine.

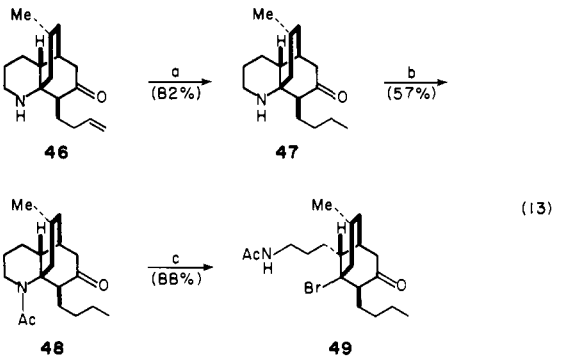
Amino ketone **42** undergoes N-acylation with reluctance. A variety of standard methods (acetic anhydride/pyridine, acetic anhydride/triethylamine, benzoyl chloride/triethylamine, and ethyl chloroformate/pyridine) are unsuccessful. The unreactivity of **42** is probably due to a combination of factors. First, the nitrogen is rather hindered, particularly by the equatorial 3-methoxypropyl appendage. Second, the inductive effect of the proximate carbonyl undoubtedly reduces the intrinsic basicity of the nitrogen lone pair. However, acetylation is accomplished with acetyl chloride in triethylamine, a process which probably involves ketene as the acylating species. Treatment of amide **44** with 25% HBr in acetic acid at room temperature leads to a rather unexpected transformation. In addition to conversion of the methyl ether to primary bromide, the bridgehead amido function is replaced by bromide (eq 12). To provide evidence that the terminal methoxy group



(12)

(a) CH_3COCl, Et_3N, CH_2Cl_2, 25° (b) 25% HBr/HOAc, 25°

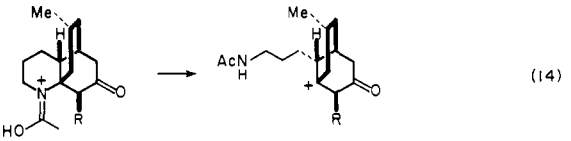
is not involved in the surprising scission of ring A, we carried out the same sequence of steps on the butylated amino ketone **47**, which was prepared by catalytic hydrogenation of tricyclic amino ketone **46** (vide infra). As shown in eq 13, the same result is obtained; bromo ketone **49** is produced in 88% yield.



(13)

(a) H_2, Pd/C, ethanol (b) CH_3COCl, Et_3N, CH_2Cl_2, 25° (c) 25% HBr/HOAc, 25°

The formation of the bridgehead bromides **45** and **49** probably involves ionization of the protonated amide to the bridgehead carbocation (eq 14).[38] At least part of the driving force for this



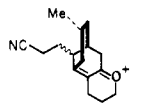
(14)

ionization must come from relief of steric interference between the equatorial alkyl group adjacent to the ketone and the protonated amide (a form of $A^{(1,3)}$ strain[41]), since lactam **32** does not undergo the reaction (eq 15).

The unexpected problem in cleaving the methyl ether of **44** led us to consider other possible appendages which could be used to

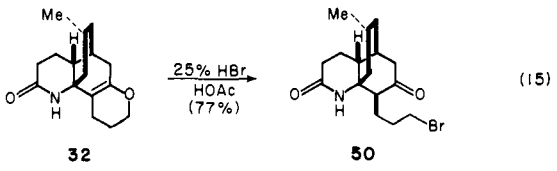
(38) See, inter alia, (a) R. C. Bingham and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **93**, 3189 (1971); (b) H. O. House, W. A. Kleschick, and E. J. Zaiko, *J. Org. Chem.*, **43**, 3653 (1978); (c) H. O. House, R. F. Sieloff, T. V. Lee, and M. B. DeTar, *ibid.*, **45**, 1800 (1980).

(39) Cation **36** may also be considered as an analogue of the bicyclo[3.3.1]non-1-en-3-one system studied recently by House and co-workers:[38b,c]



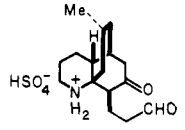
(40) F. A. Anet and M. V. Rao, *Tetrahedron Lett.*, **No. 9**, 9 (1960).

(41) (a) F. Johnson and S. K. Malhotra, *J. Am. Chem. Soc.*, **87**, 5492 (1965); (b) *ibid.*, 5493; (c) F. Johnson, *Chem. Rev.*, **68**, 375 (1968); (d) F. Johnson and D. T. Dix, *J. Am. Chem. Soc.*, **93**, 5391 (1971).



32 50 (15)

fashion ring D of lycodine. One such synthon would be a homoallyl group, which could be degraded oxidatively to the required 3-functionalized propyl substituent.[42] Hydrazone **51**, readily obtained by alkylation of the *N,N*-dimethylhydrazone of acetone with 4-bromo-1-butene, is converted into the mixed cuprate,[36] which undergoes smooth 1,4 addition to enone **7** to yield cyano dione **52**. Standard manipulation of this material, as summarized in Scheme V, provides tricyclic amino ketone **46**. At this point, it is necessary to protect the nitrogen against the oxidant to be used in cleaving the homoallyl double bond. For this purpose the simplest possible protecting group, a proton, suffices admirably. Thus, ozonization of **46** in acidic methanol followed by reduction of the ozonide with dimethyl sulfide gives a methanol solution presumably containing **55** (or some hemiacetal derived therefrom).



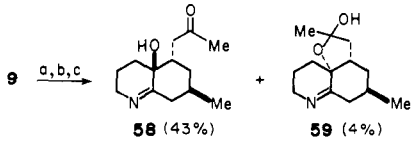
55

However, no attempt was ever made to isolate **55**, which is expected to be highly unstable in any case. Instead, the methanolic solution containing **55** is treated with excess hydroxylamine hydrochloride and boiled for 2 days,[43] whereupon (±)-lycodine (**3**) is obtained in 70% yield. The overall yield of crystalline (±)-lycodine is 13.2% for the eight steps from 5-methyl-1,3-cyclohexanedione.

Synthesis of Lycodoline. For synthesis of lycodoline (**2**), it is necessary to introduce a hydroxy group at the eventual C_{12} position. A possible means of achieving this goal was suggested by the work of Cohen and Witkop,[44] who found that $\Delta^{1(9)}$-octahydroquinoline (**56**) undergoes facile autoxidation to give hydroperoxide **57**. In fact, when amino diketal **9** is treated briefly

56: X = H
57: X = OOH

with aqueous acid and the acidic solution then basified, there is obtained an unstable imine which reacts rapidly with atmospheric oxygen. In practice, it is best to extract the basic solution with ethyl acetate and to stir the resulting solution under an atmosphere of pure oxygen until uptake ceases. The solution is then hydrogenated over palladized carbon to reduce the hydroperoxy group. In this manner, crystalline hydroxy ketone **58** is obtained in 43% yield, along with 4% of hemiketal **59** (eq 16). The stereostructure

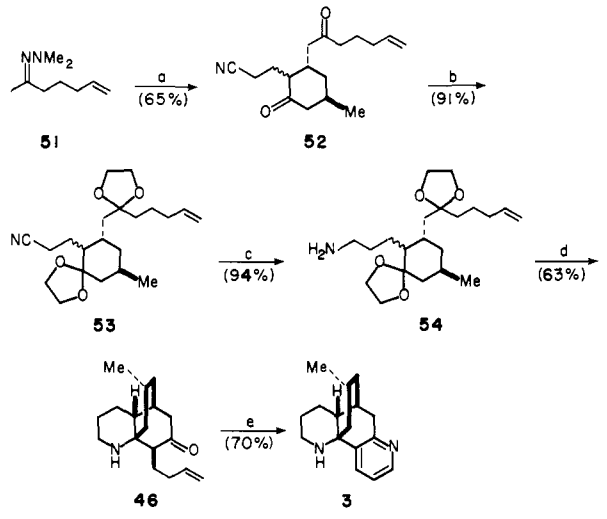


58 (43%) + **59** (4%) (16)

(a) 10% HCl, NaOH, EtOAc (b) O_2 (c) H_2/Pd/C

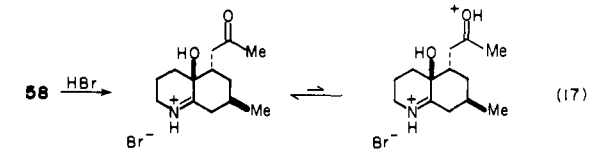
of **58** is vouchsafed by the observation that it exists in an open form, while **59** is in the cyclic hemiketal form indicated. The major stereoisomer is thus produced by attack of oxygen on the intermediate free radical trans to the acetonyl side chain.

Scheme V



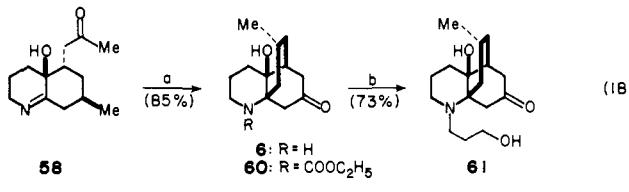
(a) *n*-BuLi, THF; C_6H_5SCu; **7**; $CuCl_2$, H_2O, pH 7. (b) $(CH_2OH)_2$, *p*-TsOH, C_6H_6. (c) $LiAlH_4$, ether. (d) 3 *N* HCl, MeOH, Δ, 14 days. (e) H_2SO_4, MeOH; O_3, −78°C; Me_2S; $NH_2OH \cdot HCl$; 65°, 48 hr; NaOH, H_2O.

Compound **58** is obviously an attractive intermediate for conversion into lycodoline. However, there is one problem—the tertiary hydroxyl. In fact, it is known that lycodoline is dehydrated to anhydrolycodoline under rather mild conditions.[7] Indeed, treatment of **58** with 3 N methanolic HCl results only in the formation of complex mixtures. For conversion of **58** to the corresponding tricyclic amino ketone, acid catalysis is required, and a full equivalent of acid must eventually be consumed, since the product is considerably more basic than the reactant (amine vs. imine). However, when the immonium bromide formed from **58** and 1 equiv of HBr is heated in toluene to 120 °C, no cyclization occurs. Presumably, this unreactivity stems from the difficulty of enolizing the acetonyl group, which requires attachment of a second proton to the molecule, thus converting it into a dication (eq 17).



(17)

A tidy solution to this difficult problem was found in an unexpected reaction. When imine **58** is dissolved in a 5:1 mixture of toluene and 3-bromo-1-propanol and the resulting solution refluxed for 24 h, a crystalline ammonium salt separates from solution. Neutralization of this salt provides the desired tricyclic hydroxy amino ketone **6** in 85% yield (eq 18). Treatment of



58 **6**: R = H **60**: R = $COOC_2H_5$ **61** (18)

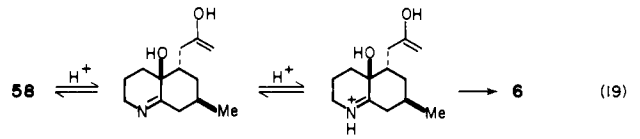
(a) 5:1 Toluene: 3-bromo-1-propanol, 120°, 24 hr; then 1 *N* NaOH
(b) 3-Iodo-1-propanol, acetone, $NaHCO_3$, K_2CO_3, Δ

compound **6** with 3-iodo-1-propanol in refluxing acetone affords diol **61** in good yield.

The interesting formation of compound **6** may involve slow delivery of HBr by base-catalyzed polymerization of the bromo alcohol. As was mentioned above, it is necessary that a full equivalent of HBr must eventually be provided. However, the failure of the immonium bromide to cyclize (eq 17) shows that the HBr must be added slowly. Under these conditions, there are

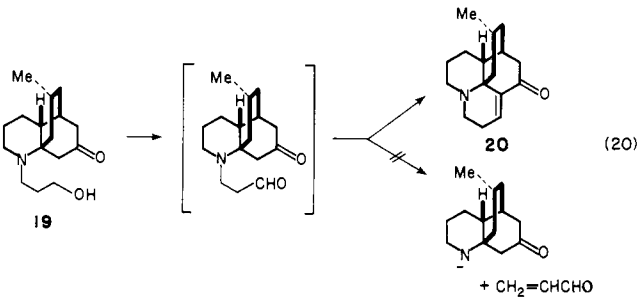
(42) See: D. N. Brattesani and C. H. Heathcock, *J. Org. Chem.*, **40**, 2165 (1975).
(43) E. Knoevenagel, *Liebigs Ann. Chem.*, **281**, 25 (1894).
(44) L. A. Cohen and B. Witkop, *J. Am. Chem. Soc.*, **77**, 6595 (1955).

never enough mobile protons to protonate all the imine molecules. Thus, there is a greater opportunity for enolization to occur on a molecule which does not bear a proton on nitrogen. When the resulting enol subsequently acquires a proton on nitrogen, cyclization presumably occurs rapidly (eq 19).



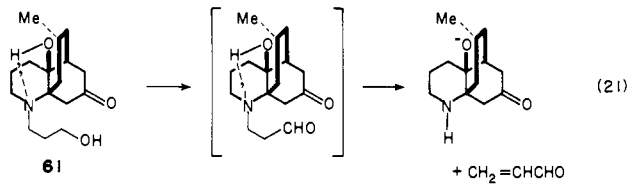
(19)

With keto diol **61** in hand, it remained only to carry out the modified Oppenauer cyclization to obtain dehydrolycodoline (see Scheme II). However, when **61** is treated with potassium *tert*-butoxide and benzophenone in refluxing benzene,[29] the only product which may be isolated is the dealkylated tricyclic amino ketone **6**. The probable mechanism for this dealkylation is reverse Michael reaction of the intermediate keto aldehyde. Recall that this possible side reaction does not intervene in the course of conversion of keto alcohol **19** to enone **20**, presumably because amide ion is such a poor leaving group (eq 20). However, in the



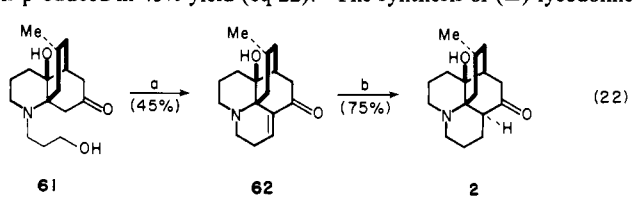
(20)

case of **61**, the tertiary hydroxyl is able to protonate the amide nitrogen, so that the leaving group of the reverse Michael reaction is essentially an alkoxide ion (eq 21).



(21)

The solution to the problem is clearly to remove the offending hydroxy proton. However, the tertiary alcohol appears to be rather hindered, since various attempts to functionalize it were unsuccessful (acetyl chloride, trifluoroacetic anhydride, *N,O*-bis(trimethylsilyl)acetamide). However, the problem is solved in a straightforward fashion by simply substituting potassium hydride for potassium *tert*-butoxide in the modified Oppenauer oxidation. In this way, both the primary and the tertiary alcohol are deprived of their protons. Thus, the intermediate keto aldehyde cannot undergo reverse Michael reaction, for to do so would involve expulsion of a dianion. In this manner, dehydrolycodoline (**62**) is produced in 45% yield (eq 22). The synthesis of (±)-lycodoline



(22)

(a) KH, $(C_6H_5)_2C{=}O$, $C_6H_5CH_3$. (b) H_2/PtO_2.

is completed by catalytic hydrogenation of **62**, whereupon (±)-**2** is produced in 75% yield. In all, the synthesis of **2** requires 11 steps from 5-methyl-1,3-cyclohexanedione and proceeds in 3.2% overall yield.

Summary. The present work has demonstrated the viability of the intramolecular Mannich condensation for construction of the tetracyclic network of the lycopodium alkaloids. The method is highly stereoselective and yields the racemic alkaloids (±)-lycopodine (**1**), (±)-lycodoline (**2**), and (±)-lycodine (**3**) in syntheses requiring only 8–13 steps from the readily available starting material 5-methyl-1,3-cyclohexanedione.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Ether, benzene, toluene, and tetrahydrofuran (THF) were distilled from sodium/benzophenone prior to use. All reactions involving organometallic reagents were performed under a nitrogen atmosphere. Solvents were removed with a rotary evaporator unless otherwise stated. Boiling points and melting points (Pyrex capillary) are uncorrected. Infrared (IR) spectra were determined with a Perkin-Elmer Model 297 infrared recording spectrophotometer. Ultraviolet (UV) spectra were determined with a Cary Model 118 ultraviolet spectrophotometer. Results are expressed as λ_{max} in nm (log ϵ). ^{1}H NMR spectra were determined on the following spectrometers: Varian T-60, Varian EM-390, UCB-180, or UCB-250 (superconducting, FT instruments operating at 180 and 250 MHz, respectively). Significant ^{1}H NMR data are tabulated in order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) in hertz. ^{13}C NMR spectra were measured at 25.14 MHz on a Nicolet TT-23 spectrometer. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. All NMR spectra were taken in $CDCl_3$ unless otherwise noted. Mass spectra were obtained with AEI MS-12 and Consolidated 12-110B mass spectrometers. Mass spectral data are tabulated as *m/e* (intensity expressed as percent of total ion current). Gas–liquid partition chromatography (GLC) was done with Varian Aerograph A-90P, 920, and 940 gas chromatographs. High-performance liquid chromatography (HPLC) was performed with a Waters PrepLC/System 500 on μPorasil columns. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, CA. Unless otherwise noted, no special purifications were used in preparing analytical samples.

2-(2-Cyanoethyl)-5-methyl-1,3-cyclohexanedione. The sodium salt of 5-methyl-1,3-cyclohexanedione,[45] prepared from 115.3 g (0.914 mol) of dione and 36.5 g (0.914 mol) of sodium hydroxide in 305 mL of methanol, was condensed with 410 g (8.6 mol) of acrylonitrile according to the procedure of Gruber and Lutz.[46] The product (162.4 g, 99%) was obtained as a white powder, mp 147–153 °C (lit. 154–158 °C).[47]

2-(2-Cyanoethyl)-3-chloro-5-methylcyclohex-2-en-1-one was prepared from 2-(2-cyanoethyl)-5-methyl-1,3-cyclohexandione on a 0.51-mol scale in 74% yield by the procedure of Clark and Heathcock.[22]

2-(2-Cyanoethyl)-5-methylcyclohex-2-en-1-one (7) was prepared from 2-(2-cyanoethyl)-3-chloro-5-methylcyclohex-2-en-1-one on a 0.373-mol scale in 81% yield by the procedure of Clark and Heathcock.[22]

(1*RS*,4*RS*,6*SR*)- and (1*SR*,4*RS*,6*SR*)-4-Methyl-6-[2-(2-methyl)propenyl]-2-oxocyclohexanepropanenitrile. Method A. A solution of 22.6 g (110 mmol) of $(CH_3)_2S{\cdot}CuBr$[48] in 200 mL of ether was cooled to −78 °C, and 218 mmol of methallyllithium (260 mL of a 0.84 M ether solution) was added dropwise over a 4-min period. After 1 equiv of methallyllithium had been introduced, the product was a bright red slurry, which changed to a clear pale yellow solution upon addition of the second equivalent. This resulting lithium dimethallylcuprate solution was allowed to stir for an additional 15 min at −78 °C, and then a mixture of 12.10 g (74.1 mmol) of enone **7** in 100 mL of ether was added over a 10-min period. The resulting red-orange mixture was allowed to stir for an additional 5 min, and the reaction mixture was poured into 400 mL of pH 9 ammonium chloride–ammonia buffer solution. The reaction flask was rinsed with additional buffer solution, which was added to the initial mixture. The layers were separated, the ether layer was washed with an additional 200 mL of buffer, and the combined aqueous layers were backwashed with 300 mL of ether. The organic layers were combined, washed with brine, dried ($MgSO_4$), and evaporated to obtain a yellow oil, shown by ^{1}H NMR to be a mixture of 1,2- and 1,4-addition products. The isomers were partially separated by distillation through a 6-in. Vigreux column. The tertiary alcohol resulting from 1,2 addition is more volatile than the 1,4 adduct. After a forerun of the 1,2 adduct, 9.3 g of semipure 1,4 product was collected over the range 127–144 °C (1.0 torr). The material was further purified by chromatography on 350 g of silica gel, eluting with hexane:ether (7:3 to 6:4). In this way was

(45) (a) A. W. Crossley and N. Renouf, *J. Chem. Soc.*, **107**, 602 (1915); (b) G. Blanchard, *J. Am. Chem. Soc.*, **73**, 5863 (1951).
(46) C. A. Gruber and H. J. Lutz, *Helv. Chim. Acta*, **48**, 799 (1965).
(47) H. Reinshagen, *Liebigs Ann. Chem.*, **681**, 84 (1965).
(48) H. O. House and J. M. Wilkens, *J. Org. Chem.*, **43**, 2443 (1978).

obtained 7.97 g of pure product (66%): IR (neat) 2280, 1710, 890 cm^{-1}; ^1H NMR (CCl_4) δ 1.00 (3 H, d), 1.70 (3 H, s), 4.73 (2 H, d); mass spectrum, *m/e* 219 (M^+), 164. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.43; H, 9.39; N, 6.47.

Method B. A stirred solution of 122.6 mg (0.75 mmol) of enone **7** in 2.6 mL of dry methylene chloride was cooled to −78 °C. Titanium tetrachloride (0.10 mL, 0.173 g, 0.91 mmol) was added in one portion, giving rise to a deep red solution in which a yellow precipitate was evident. After 5 min, 144 mg (1.12 mmol) of methallyltrimethylsilane in 2 mL of dry methylene chloride was added dropwise over a 45-min period at such a rate as to maintain the solution temperature below −70 °C. The dark purple mixture was stirred an additional 30 min, at which time 1.5 mL of water was added dropwise over a 30-min period. The reaction mixture was allowed to warm to room temperature, during which time the color of the solution turned from purple to orange, then to yellow, and finally became colorless. The reaction mixture was partitioned between ether and brine. The ethereal layer was dried over Na_2SO_4 and the solvent was evaporated. The residue (187 mg) was purified by chromatography on 11 g of silica gel with an ether–hexane (1:4 to 1:2) eluant to afford 158 mg (96%) of a colorless oil identical by ^1H NMR, IR, and TLC behavior with a sample of the methallylated intermediate prepared in method A.

(1*RS*,4*RS*,6*SR*)- and (1*SR*,4*RS*,6*SR*)-4-Methyl-2-oxo-6-(2-oxopropyl)cyclohexanepropanenitrile (8). Method A. A solution of 1.0 g (4.56 mmol) of the methallyl adduct dissolved in 10 mL of methanol was placed in an ozonolysis tube and cooled to −78 °C. This solution was then treated for 16.65 min with a stream of ozone generated at a rate of 0.3 mmol/min (5.0 mmol total) by a Welsbach ozonator. The cold solution was then flushed with nitrogen to remove any excess ozone (~30 min). At the end of this time, 0.425 g (6.85 mmol) of dimethyl sulfide was added, and the resulting solution was warmed to −10 °C and stirred for 1 h at this temperature. This treatment was followed by stirring at 0 °C for 1 h and finally at room temperature for 1 h. The solvent was removed at reduced pressure and the resulting material was dissolved in 100 mL of ether. This solution was washed with four 25-mL portions of water and then dried over $MgSO_4$. Solvent removal afforded 0.84 g (83%) of dione **9**: IR (neat) 2280, 1710 cm^{-1}; ^1H NMR (CCl_4) δ 1.07 (3 H, d), 2.13 (3 H, s).

Method B. In a dry 2-L, 4-neck flask under nitrogen, fitted with a 200-mL jacketed addition funnel, a mechanical stirring apparatus, a low-temperature thermometer, and a rubber septum, was placed a mixture of 124 mL (190 mmol) of a 1.53 M solution of *n*-butyllithium in hexane and 750 mL of dry THF. After the contents were chilled to −78 °C, 19.03 g (24.37 mL, 190 mmol) of acetone dimethylhydrazone[49] was added dropwise at such a rate that the reaction temperature was maintained below −65 °C. The resulting white suspension of α-lithioacetone dimethylhydrazone was stirred an additional 0.5 h at −78 °C and then treated with a precooled (−78 °C) liquid complex of 18.28 g (96 mmol) of CuI, 28.2 mL (23.85 g, 384 mmol) of freshly distilled dimethyl sulfide, and 100 mL of THF at such a rate that the reaction temperature did not exceed −70 °C. When the addition was complete (0.5 h), the resulting mixture of cuprate reagent was stirred an additional 10 min at −70 °C, 20 min at −30 to −20 °C, and 15 min at −10 to −5 °C. After the yellow-brown mixture was rechilled to −70 °C, a solution of 15.26 g (93.5 mmol) of enone **7** in 10 mL of THF was added dropwise at such a rate that the reaction temperature did not exceed −67 °C. After additional stirring for 4 h at −78 °C and 45 min with slow warming to 0 °C, the brown mixture was poured onto 1 L of a pH 8.9 aqueous NH_4Cl–NH_4OH buffer solution with vigorous stirring. The blue mixture was diluted with 600 mL of methylene chloride, and the upper (organic) layer was washed with 500 mL of additional buffer solution. After the combined aqueous layers were backwashed with methylene chloride (2 × 600 mL), all the organic layers were combined, dried ($MgSO_4$), and evaporated to 25.2 g of a dark oil. This crude mixture of dimethylhydrazone adduct was dissolved in a mixture of 1.3 L of THF and 284 mL of an aqueous pH 7 buffer and treated with a solution of 23.9 g (140 mmol) of $CuCl_2 \cdot 2H_2O$ in 464 mL of water. A dark green suspension initially formed which, after 16 h of additional stirring at 25 °C, became a clear, light green solution. The THF was then evaporated and the residue was diluted with 500 mL of water and extracted with methylene chloride (3 × 500 mL). The combined organic extracts were filtered through a plug of glass wool, dried ($MgSO_4$), and evaporated to 23.1 g of a dark oil. Distillation through a 6-in. Vigreux column afforded 12.35 g (60%) of dione **8** as a yellow liquid, bp 152–155 °C (0.33 torr). The NMR spectrum, except for minor differences corresponding to the difference in the ratio of C-2 diastereomers, was identical with a spectrum of the product prepared by the procedure outlined in part A. Slightly higher yields, 65–70%, were obtained when the reaction was run on a smaller scale and the product was purified by silica gel chromatography. An analytical sample was prepared by preparative GLC (10 ft, silicone, 170 °C). Anal. Calcd for $C_{13}H_{19}O_2N$: C, 70.57; H, 8.66; N, 6.33. Found: C, 70.70; H, 8.50; N, 5.99.

(6*RS*,7*SR*,9*RS*)- and (6*SR*,7*SR*,9*RS*)-9-Methyl-7-[(2-methyl-1,3-dioxolan-2-yl)methyl]-1,4-dioxaspiro[4.5]decane-6-propanenitrile (Diketal of 8). A mixture of 3.51 g (15.86 mmol) of dione **8**, 18.6 g (300 mmol) of ethylene glycol, 0.57 g (3.0 mmol) of *p*-$TsOH \cdot H_2O$, and 75 mL of benzene was heated to reflux under nitrogen for 6 h with water separation (Dean–Stark trap). The cooled mixture was then poured onto 250 mL of saturated aqueous $NaHCO_3$ solution with stirring, and the organic layer was extracted with ether (1 × 300 mL, 2 × 150 mL), dried (K_2CO_3), and evaporated to obtain 4.86 g (99%) of cyano diketal as a viscous oil: IR (neat) 2285 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (3 H, d), 1.23 (3 H, s), 3.90 (8 H, br s). Anal. Calcd for $C_{17}H_{27}O_4N$: C, 65.99; H, 8.80; N, 4.53. Found: C, 66.15; H, 8.73; N, 4.63.

In one run, a fraction of the pure diketal diastereomers was separated by column chromatography (ether–hexane eluant) followed by preparative HPLC (ether–hexane, 45:55). From 13.3 g of starting dione **8**, 2.50 g of the less polar (R_f 0.30 in ether–hexane, 1:1) and 1.10 g of the more polar (R_f 0.22 in ether–hexane, 1:1) diastereomer were obtained. The two diastereomers have identical IR and ^1H NMR spectra.

(6*RS*,7*SR*,9*RS*)- and (6*SR*,7*SR*,9*RS*)-9-Methyl-7-[(2-methyl-1,3-dioxolan-2-yl)methyl]-1,4-dioxaspiro[4.5]decane-6-propanamine (9). To a solution of 0.058 g (1.53 mmol) of lithium aluminum hydride in 3 mL of anhydrous ether was carefully added 0.472 g (1.53 mmol) of cyano diketal dissolved in 3 mL of ether. The resulting mixture was allowed to stir at room temperature for 2 h. At the end of this time, 0.058 mL of water, 0.058 mL of 15% NaOH, and 0.17 mL of water were added in succession. The resulting white solid was filtered off and washed repeatedly with ether. The ether was then removed to afford 0.464 g (97.5%) of analytically pure amine **9**: ^1H NMR (CCl_4) δ 0.87 (3 H, s), 1.23 (3 H, s); mass spectrum, *m/e* 313 (M^+). Anal. Calcd for $C_{17}H_{31}O_4N$: C, 65.14; H, 9.96; N, 4.47. Found: C, 64.99, H, 9.66; N, 4.69.

The reduction has also been carried out on a 9.86-mmol scale, affording 3.04 g (98%) of amine **9**.

(6*RS*,7*SR*,9*RS*)- and (6*SR*,7*SR*,9*RS*)-*N*-(Phenylmethyl)-9-methyl-7-[(3-methyl-1,3-dioxolan-2-yl)methyl]-1,4-dioxaspiro[4.5]decan-6-propanamine (10). To a solution of 0.244 g (1.732 mmol) of benzoyl chloride and 0.176 g (1.732 mmol) of triethylamine in 10 mL of anhydrous benzene was added 0.494 g (1.575 mmol) of amino diketal **9**. The resulting solution, which immediately turned cloudy, was allowed to stir for 12 h at room temperature. At the end of this time, the hydrochloride salt was removed by filtration and washed with ether. The combined organic solutions were diluted with 100 mL of ether and washed with two 50-mL portions of a saturated $NaHCO_3$ solution. After drying over $MgSO_4$, the solvent was removed and the resulting material maintained at 1.0 torr and 50–60 °C for 2 h. This afforded 0.658 g (98%) of analytically pure amide: IR (neat) 1640, 1545 cm^{-1}; ^1H NMR (CCl_4) δ 0.87 (3 H, d), 1.23 (3 H, s), 3.84 (8 H, s), 7.50 (5 H, m). Anal. Calcd for $C_{24}H_{35}NO$: C, 69.04; H, 8.45; N, 3.35. Found (ultra-micro): C, 68.9; H, 8.4; N, 3.2.

To a solution of 0.052 g (1.36 mmol) of lithium aluminum hydride in 4 mL of anhydrous ether was added 0.569 g (1.36 mmol) of the benzamide dissolved in 4 mL of ether, and the resulting mixture was stirred for 48 h at room temperature. At the end of this time, 0.052 mL of water, 0.052 mL of 15% NaOH, and 0.156 mL of water were added successively. The resulting white solid was filtered off and washed with ether. Solvent removal afforded 0.540 g of amine **10** that was contaminated with a small amount of unreduced amide. This mixture was separated by column chromatography with 25 g of silica gel using ether as the eluant to yield 0.526 g (96%) of pure **10**: ^1H NMR (CCl_4) δ 0.87 (3 H, s), 1.23 (3 H, s), 3.83 (8 H, br s), 7.27 (5 H, br s); mass spectrum, *m/e* 403 (M^+), 388, 91. Anal. Calcd for $C_{24}H_{37}O_4N$: C, 71.53; H, 9.24; N, 3.47. Found: C, 71.08; H, 9.14; N, 3.56.

(4a*RS*,5*SR*,8a*SR*,10*RS*)-10-Methyl-1-(phenylmethyl)hexahydro-1*H*-5,8a-propanoquinolin-6(8*H*)-one (11). Method A. A solution of 0.328 g (0.815 mmol) of amino diketal **10** in 5 mL of methanol was treated with 0.6 mL of a 3 M HCl solution (1.8 mmol), and the resulting mixture was heated to reflux for 48 h. At the end of this time, the solution was cooled, poured into 50 mL of a saturated $NaHCO_3$ solution, and extracted with four 50-mL portions of ether. After the combined ether extracts were dried over $MgSO_4$, the solvent was removed to yield 0.238 g of material. TLC analysis (ether) indicated this product was a mixture of **11** (R_f 0.7) and the bicyclic enamine resulting from incomplete cyclization (R_f 0.3). These products were separated by column chromatography (12 g of silica gel, 5% ether–hexane eluant) to yield 0.104 g (52%) of **11**, which was isolated as an oil. Subsequent attempts to

(49) R. H. Wiley, S. C. Slaymaker, and H. Kraus, *J. Org. Chem.*, **22**, 204 (1957).

crystallize this product were unsuccessful. IR (neat) 1700 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (3 H, d, J = 7), 2.87 (1 H, d, J = 14), 4.13 (1 H, d, J = 14), 7.23 (5 H, br s); mass spectrum, m/e 297 (M^+), 240, 91 (Figure 1b).

Method B. A solution of 0.264 g (0.655 mmol) of **10** in 10 mL of ether was extracted with 10 mL of 10% HCl. The layers were separated, and the acid portion was immediately brought to pH 9 with 5% NaOH. The resulting cloudy solution was then extracted with four 50-mL portions of ether, which were combined and dried over $MgSO_4$. Removal of solvent afforded 0.204 g (100%) of material that was identified as *N*-benzyl-2-aza-7-(2-propionyl)-8-methylbicyclo[4.4.0]dec-1(6)-ene. TLC indicated this sample was identical with that isolated in part A. IR (neat) 1710, 1645 cm^{-1}; ^1H NMR (acetone-d_6) δ 0.87 (3 H, d, J = 7), 2.10 (3 H, s), 3.93 (1 H, d, J = 16), 4.23 (1 H, d, J = 16), 7.34 (5 H, br s).

This material was dissolved in a solution of 4 mL of methanol and 0.4 mL of 3 M HCl (1.2 mmol), and the resulting solution was heated to reflux for 48 h. This solution was then worked up as in part A to yield 0.177 g of a mixture of **11** and recovered enamine. Column chromatography afforded 0.130 g (66%) of **11**, identical in every respect with the product isolated in part A.

(4a*RS*,5*SR*,8a*SR*,10*RS*)-10-Methylhexahydro-1*H*-5,8a-propanoquinolin-7(8*H*)-one (12). To a solution of 41.8 mg (0.142 mmol) of **11** dissolved in 2 mL of absolute ethanol was added 40 mg of 5% palladium on carbon, and the resulting mixture was hydrogenated at room temperature and atmospheric pressure. The solution absorbed the required volume of hydrogen (3.1 mL) in 1 h. The catalyst was removed by filtration through a plug of filter aid and the solvent evaporated to obtain 33 mg (94%) of secondary amine **12** as a viscous oil: IR (neat) 1700 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (3 H, d, J = 7); mass spectrum, m/e 207 (M^+), 192, 150 (Figure 1c).

(6*RS*,7*SR*,9*RS*)- and (6*SR*,7*SR*,9*RS*)-9-Methyl-7-[(2-methyl-1,3-dioxolan-2-yl)methyl]-1,4-dioxaspiro[4.5]decane-6-propanoic Acid (16). The diketal nitrile (4.68 g, 15.7 mmol) was dissolved in 70 mL of a 15% KOH in 95% ethanol solution, and the mixture was heated to reflux for 16 h under nitrogen. The ethanol was then removed, and the residue was diluted with 200 mL of water. After this mixture was washed with ether (2 × 100 mL), 50 mL of methylene chloride was added, followed by aqueous 6 N HCl solution, dropwise at 0 °C, until the aqueous layer was acidic (pH 2). The organic layer was extracted with methylene chloride (3 × 150 mL), and the combined extracts were washed with brine (1 × 150 mL) and dried ($MgSO_4$). Removal of the solvent afforded 4.61 g (90%) of acid **16** as a gummy solid, which was of suitable purity for the next step. The analytical sample was obtained as white crystals, mp 172–176 °C, by trituration and subsequent recrystallization from ether and was most likely enriched in one diastereomer. IR ($CHCl_3$) 3300, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, d), 1.30 (3 H, s), 3.90 (8 H, s), 9.96 (1 H, s). Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59. Found: C, 61.80; H, 8.47.

The less polar diastereomer of the diketal nitrile (2.45 g, 7.92 mmol) was hydrolyzed with 39 mL of 15% ethanolic KOH solution to afford 2.45 g (94%) of the corresponding diastereomer of acid **16**, mp 172–174 °C. The analytical sample, mp 178–179 °C, was obtained by recrystallization from methylene chloride–ether. The NMR and IR spectra were identical with the spectra obtained from the diastereomeric mixture. Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59. Found: C, 62.12; H, 8.66.

The more polar diastereomer of the diketal nitrile (1.07 g, 3.46 mmol) was hydrolyzed with 17 mL of 15% ethanolic KOH solution to afford 1.12 g (99%) of the corresponding diastereomer of acid **16**, as an oil which slowly crystallized. Trituration in hexane gave 778 mg of a tan solid, mp 76–79 °C. The analytical sample, mp 86.5–87.5 °C, was obtained by recrystallization from ether–hexane. The NMR and IR spectra were identical with the spectra obtained from the diastereomeric mixture. Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59. Found: C, 62.06; H, 8.69.

(6*RS*,7*SR*,9*RS*)- and (6*SR*,7*SR*,9*RS*)-9-Methyl-7-[(2-methyl-1,3-dioxolan-2-yl)methyl]-*N*-[3-(phenylmethoxy)propyl]-1,4-dioxaspiro[4.5]-decane-6-propanamine (17). A mixture of 4.61 g (14.0 mmol) of acid **16** and 2.93 mL (2.13 g, 21.1 mmol) of triethylamine in 115 mL of THF under nitrogen was chilled to −15 °C, and 2.01 mL (3.38 g, 21.1 mmol) of ethyl chloroformate was added dropwise so as to maintain the reaction temperature close to −15 °C. After stirring for an additional 5 min at −15 °C, 3.71 g (22.5 mmol) of 3-(benzyloxy)-1-propylamine[50] was added dropwise at such a rate that the reaction temperature did not exceed −10 °C. The mixture was then stirred for an additional 5 min at −15 °C, 0.5 h at 0 °C, and 0.5 h at 25 °C before being filtered. The salts were washed well with ether and the solvent was evaporated under vacuum without external heating. The residue was diluted with 375 mL of ether and washed with 150 mL of water and aqueous 10% K_2CO_3 solution (2 × 90 mL). After drying (K_2CO_3) and removal of the solvent, the residue was purified by chromatography on 175 g of silica gel with a $CHCl_3$–ether (6:4 to 100% ether) eluant to afford 5.90 g (88%) of the amide (R_f 0.12 in $CHCl_3$–ether, 1:1) as a viscous oil: IR (film) 3300, 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3 H, d), 1.28 (3 H, s), 3.32 (2 H, overlapping double t, J = 6), 3.52 (2 H, t, J = 6), 3.90 (8 H, s), 4.47 (2 H, s), 6.23 (1 H, br t), 7.28 (5 H, s). Anal. Calcd for $C_{27}H_{41}NO_6$: C, 68.18; H, 8.69; N, 2.95. Found: C, 68.07; H, 8.42; N, 3.09.

The individual diastereomers of acid **16** (500 mg each) were converted into the corresponding amide derivatives by using the foregoing procedure. Both pure amides are viscous oils and have spectral properties which are virtually identical with those of the mixture of diastereomers.

A mixture of 5.90 g (12.4 mmol) of the amide, 1.41 g (37.2 mmol) of $LiAlH_4$, and 145 mL of THF was heated at reflux for 16 h under nitrogen. After cooling to 25 °C, 1.4 mL of H_2O, 1.41 mL of aqueous 15% NaOH solution, and 4.5 mL of water were carefully added dropwise. The salts were removed by filtration and washed well with ether. After the filtrate was dried (K_2CO_3), the solvent was removed to afford 5.68 g (99%) of amine **17** as a viscous oil: ^1H NMR ($CDCl_3$) δ 0.85 (3 H, d, J = 6), 1.22 (3 H, s), 2.3–2.8 (5 H, m), 3.47 (2 H, t), 3.83 (8 H, s), 4.42 (2 H, s), 7.22 (5 H, s). Anal. Calcd for $C_{27}H_{43}NO_5$: C, 70.24; H, 9.39; N, 3.03. Found: C, 70.27; H, 9.35; N, 3.17.

The individual diastereomers of the amide (710 mg) were each reduced with 178 mg of $LiAlH_4$ in 18 mL of THF to afford 496 (72%) and 489 mg (71%) of amine **17** derived respectively from the less and more polar diketal nitriles.

The ^1H NMR and IR spectra of each diastereomer are identical with those of the epimeric mixture. For the diastereomer derived from the less polar diketal nitrile, ^{13}C NMR ($CDCl_3$) δ 138.2, 127.8, 127.0, 110.7, 110.4, 72.3, 68.3, 64.7, 64.0, 63.6, 49.9, 46.6, 43.4, 38.4, 35.1, 31.1, 29.7, 27.4, 24.6, 23.8, 22.1, 21.5; and for the amine derived from the more polar diketal nitrile, δ 138.2, 127.7, 126.9, 111.2, 110.2, 72.2, 68.3, 63.7, 63.5, 62.9, 49.5, 46.6, 44.8, 41.9, 39.3, 34.3, 32.3, 29.6, 28.8, 27.0, 25.0, 23.7, 21.7.

(4a*RS*,5*SR*,8a*SR*,10*RS*)-10-Methyl-1-[3-(phenylmethoxy)propyl]-hexahydro-1*H*-5,8a-propanoquinolin-7(8*H*)-one (18). A mixture of 5.68 g (12.3 mmol) of amine **17**, 220 mL of a 3.2 M methanolic HCl solution (prepared by bubbling HCl gas into reagent grade methanol), and 10 mL of water was refluxed for 14 days under nitrogen. The methanol was then evaporated, and the residue was diluted with 175 mL of saturated aqueous $NaHCO_3$ solution and extracted with methylene chloride (3 × 150 mL). The combined extracts were dried (K_2CO_3) and the solvent was evaporated. Purification of the residue on 170 g of silica gel with a methanol–chloroform (0.5–4%) eluant afforded 2.61 g (60%) of tricyclic amine **18** (R_f 0.55 in 5:95 methanol–chloroform) as a viscous oil: IR (film) 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (3 H, d, J = 6), 3.52 (2 H, t, J = 6), 4.43 (2 H, s), 7.28 (5 H, s); mass spectrum, m/e 355 (0.72, M^+), 2.98 (4.65), 264 (4.71), 220 (3.63), 91 (4.99, base). Anal. Calcd for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.52; H, 9.19; N, 3.79.

The more polar fractions gave 0.14 g (3%) of a 4:1 mixture of alcohol **19** and benzyl ether **18**. This material was combined with the pure benzyl ether (above) for use in the next step.

Each of the diastereomers of diketal amine **17** were similar subjected to the Mannich cyclization for 10 days. The yield in each case for tricyclic benzyl ether **18**, containing a minor amount of alcohol **19**, was 50 ± 5%.

(4a*RS*,5*SR*,8a*SR*,10*RS*)-1-(3-Hydroxypropyl)-10-methylhexahydro-1*H*-5,8a-propanoquinolin-7(8*H*)-one (19). A mixture of 2.61 g of benzyl ether **18** and 0.14 g of a 4:1 mixture of **19** and **18** (total of 6.41 mmol) was dissolved in 45 mL of absolute ethanol and treated with 4.94 mL (14.8 mmol) of an aqueous 3 N HCl solution. At this point 200 mg of 10% Pd on charcoal was added, and the mixture was stirred under 1 atm of hydrogen until uptake ceased (2 h). After filtration of the catalyst and removal of the solvent, the residue was dissolved in 15 mL of water and made basic with 35 mL of saturated aqueous $NaHCO_3$ solution. The precipitate was extracted with methylene chloride (3 × 50 mL) and the combined extracts were dried (K_2CO_3). Removal of the solvent afforded 2.0 g (96%) of alcohol **19** as an oil which slowly solidified and was of suitable purity for the next step. The analytical sample, mp 86–87 °C, was obtained by trituration of the solid in hexane to obtain tan crystals, which were recrystallized from ether: IR ($CHCl_3$) 3300, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3 H, d, J = 5), 3.6–3.9 (2 H, m), 5.07 (1 H, s); mass spectrum, m/e 265 (0.67, M^+), 250 (2.37), 220 (3.36), 208 (11.85); UV_{max} (H_2O) 220 nm (inf, ϵ 900). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.26; N, 5.28. Found: C, 72.43; H, 10.03; N, 5.14.

(±)-3,4-Dehydrolycopodine (20). To a mixture of 13.50 g (75.20 mmol) of benzophenone and 2.53 g (22.6 mmol) of potassium *tert*-butoxide in 39 mL of dry benzene under nitrogen was added a solution of

(50) W. P. Utermohlen, *J. Am. Chem. Soc.*, **67**, 1505 (1945).

2.00 g (7.52 mmol) of alcohol **19** in 39 mL of dry benzene. The resulting mixture was heated at reflux for 40 min as the progress of the reaction was monitored by TLC. After cooling to 25 °C and dilution with 100 mL of benzene, the mixture was extracted with aqueous 1 N HCl solution (2 × 75 mL, 1 × 50 mL). The combined aqueous extracts were washed with ether (2 × 70 mL), made basic (pH 11) with aqueous 6 N NaOH solution, and extracted with methylene chloride (3 × 150 mL). The combined organic extracts were dried (K_2CO_3) and the solvent was removed. Chromatography of the residual red oil (1.71 g) on 96 g of silica gel with a methanol–chloroform (1:99 to 3:97) eluant afforded 1.32 g (72%) of enone **20** (R_f 0.20 in MeOH–$CHCl_3$, 5:95) as a yellow-brown solid, mp 98–105 °C. This material was of suitable purity for use in the next step. The analytical sample, mp 104–105 °C, was prepared by recrystallization from hexane. IR ($CHCl_3$) 1680, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, d), 6.95 (1 H, t); mass spectrum, m/e 245 nm (ϵ 5000). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.33; H, 9.45; N, 5.71. Found: C, 78.07; H, 9.27; N, 5.59.

3-(Benzyloxy)-1-propanol was prepared by the published procedure.[51] On a 1.18-mol scale, we obtained 95.8 g of product (53%), bp 120–123 °C (2.3 torr).

3-Methoxy-1-propanol was prepared by the published procedure.[52] On a 1.1-mol scale, we obtained 67 g of product (74%), bp 150–151 °C.

1-(Benzyloxy)-3-bromopropane. To a chilled (5–10 °C) mixture of 35.7 g (0.215 mol) of 1-(benzyloxy)-3-propanol and 56.4 g (0.215 mol) of triphenylphosphine with mechanical stirring was added 38.2 g (0.215 mol) of *N*-bromosuccinimide in small portions at such a rate that the reaction temperature did not exceed 10 °C. After 16 h of additional stirring at 25 °C, the resulting suspension was filtered and the precipitated triphenylphosphine oxide was washed with 250 mL of benzene. The filtrate was washed with 525 mL of 5% sodium thiosulfate solution, 0.5 N NaOH (2 × 850 mL), and brine (1 × 500 mL) and dried ($MgSO_4$). The solvent was evaporated and the residual sludge was triturated with 200 mL of ether. Concentration of the supernatant and distillation of the residue afforded 33.2 g (67%) of the bromide as a colorless liquid: bp 128–130 °C (5 torr) (lit.[53] bp 159–160 °C (3 torr)); ^1H NMR (CCl_4) 2.02 (2 H, quintet, J = 6), 3.42 (2 H, t, J = 6), 3.46 (2 H, t, J = 6), 4.40 (2 H, s), 7.18 (5 H, s).

1-Bromo-3-methoxypropane. Following the same procedure as that described for preparation of the bromobenzyl ether, a mixture of 30.0 g (0.33 mol) of 3-(methoxy)-1-propanol and 57.3 g (0.33 mol) of triphenylphosphine in 350 mL of benzene was treated with 59.3 g (0.33 mol) of *N*-bromosuccinimide. Obtained was 26 g (51%) of bromide as a colorless liquid: bp 140–142 °C (lit.[54] bp 139 °C); ^1H NMR ($CDCl_3$) δ 2.08 (2 H, quintet), 3.37 (3 H, s), 3.50 (4 H, t).

1-Bromo-3-[2-(methoxyethoxy)methoxy]propane. To a mixture of 14.05 g (0.101 mol) of 3-bromo-1-propanol (Eastman) and 18.93 g (17.35 mL, 0.152 mol) of (β-methoxyethoxy)methyl chloride (MEM chloride, Aldrich) in 180 mL of methylene chloride was added 19.6 g (0.152 mmol) of *N,N*-diisopropylethylamine (Aldrich). A moderate exotherm ensued, and after 2 h of additional stirring at 25 °C, the mixture was washed with 180 mL of water, 200 mL of aqueous 5% HCl solution, and 200 mL of saturated aqueous $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and the solvent was evaporated. Distillation of the residue (21 g) afforded 12.1 g (53%) of the bromide as a colorless liquid, bp 52–54 °C (0.3 torr). The analytical sample was prepared by preparative GLC (OV-101): ^1H NMR ($CDCl_3$) δ 2.13 (2 H, quintet, J = 5), 3.43 (3 H, s), 2.8–3.4 (8 H, m), 4.70 (2 H, s). Anal. Calcd for $C_7H_{15}BrO_3$: C, 37.02; H, 6.66; Br, 35.19. Found: C, 37.17; H, 6.69; Br, 35.40.

6-(Benzyloxy)-2-hexanone Dimethylhydrazone (22a). To a suspension of α-lithioacetone dimethylhydrazone, prepared by the dropwise addition of 11.2 mL (8.74 g, 87.3 mmol) of acetone dimethylhydrazone to a mixture of 43.6 mL (65.5 mmol) of a 1.5 M solution of *n*-butyllithium in hexane and 125 mL of THF at −78 °C followed by 0.5 h of additional stirring at −78 °C, was added 10.0 g (44.6 mmol) of 1-(benzyloxy)-3-bromopropane dropwise at −78 °C. The resulting mixture was stirred for 0.5 h at −78 °C, 1 h with slow warming to 0 °C, 3 h at 0 °C, and 0.5 h at 25 °C. A few milliliters of methanol was then added to quench the excess anion, and the solvent was removed. The residue was diluted with 100 mL of water and extracted with 150 mL of ether. The ether layer was washed with an additional 100 mL of water, combined with a 100-mL backwash of the combined aqueous layers, washed with 100 mL of brine, and dried (K_2CO_3). Evaporation of the solvent and distillation of the residue afforded 7.3 g (68%) of dimethylhydrazone **22a** as a colorless liquid: bp 100–101 °C (0.5 torr); ^1H NMR ($CDCl_3$) δ 1.5–1.8 (4 H, m), 1.85 and 1.90 (3 H, two s), 2.17 (2 H, br t), 2.35 and 2.40 (6 H, two s), 3.42 (2 H, br t), 4.92 (2 H, s), 7.20 (5 H, s). Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.36; H, 9.63; N, 11.28.

6-[2-(Methoxyethoxy)methoxy]-2-hexanone Dimethylhydrazone (22b). Following the same procedure as was used for the preparation of dimethylhydrazone **22a**, we used 12.1 g (53 mmol) of 1-bromo-3-[2-(methoxyethoxy)methoxy]propane to alkylate the anion derived from 13.6 mL (10.7 g, 106 mmol) of acetone dimethylhydrazone, 53.2 mL (80 mmol) of a 1.5 M solution of *n*-butyllithium in hexane, and 150 mL of THF. Dimethylhydrazone **22b** (10.3 g, 79%) was obtained as a colorless liquid: bp 85–90 °C (0.15 torr); ^1H NMR ($CDCl_3$) δ 1.60 (4 H, quintet, J = 5), 1.90 and 1.93 (3 H, two s), 2.20 (2 H, br t), 2.42 (3 H, s), 2.43 (6 H, s), 3.38 (3 H, s), 3.5–3.7 (6 H, m), 4.67 (2 H, s). Anal. Calcd for $C_{12}H_{26}N_2O_3$: C, 58.51; H, 10.64; N, 11.37. Found: C, 58.70; H, 10.55; N, 11.33.

6-Methoxy-2-hexanone Dimethylhydrazone (22c). Following the same procedure as that used for the preparation of dimethylhydrazone **22a**, we used 11.59 g (76 mmol) of 1-bromo-3-methoxypropane to alkylate the anion prepared from 15.17 g (0.151 mol) of acetone dimethylhydrazone, 74.2 mL (114 mmol) of a 1.53 M solution of *n*-butyllithium in hexane, and 200 mL of THF. Dimethylhydrazone **22c** (8.95 g, 69%) was obtained as a colorless liquid: bp 80–82 °C (6 torr); ^1H NMR ($CDCl_3$) δ 1.4–1.7 (4 H, m), 1.93 and 1.95 (3 H, two s), 2.0–2.4 (2 H, m), 2.38 and 2.43 (6 H, two s), 3.30 (3 H, s), 3.36 (2 H, br t). Anal. Calcd for $C_9H_{20}N_2O$: C, 62.75; H, 11.70; N, 16.26. Found: C, 62.69; H, 11.37; N, 15.86.

6-Hepten-2-one Dimethylhydrazone (51). Following the same procedure as that used for the preparation of dimethylhydrazone **22a**, we used 20.0 g (148 mmol) of 4-bromo-1-butene (Aldrich) to alkylate the anion prepared from 37.9 mL (26.95 g, 296 mmol) of acetone dimethylhydrazone and 148 mL (222 mmol) of a 1.5 M *n*-butyllithium solution in hexane and 400 mL of THF. Dimethylhydrazone **51** (14.1 g, 62%) was obtained as a colorless liquid: bp 89–81 °C (20 torr); ^1H NMR ($CDCl_3$) δ 1.88 and 1.93 (3 H, two s), 2.38 (3 H, s), 2.43 (3 H, s), 4.7–6.2 (3 H, m); IR (CCl_4, 1%) 3080, 1640, 910 cm^{-1}. Anal. Calcd for $C_9H_{18}N_2$: C, 70.08; H, 11.76; N, 18.16. Found: C, 70.30; H, 11.69; N, 18.06.

(1*RS*,4*RS*,6*SR*)- and (1*SR*,4*RS*,6*SR*)-4-Methyl-2-oxo-6-[2-oxo-6-(phenylmethoxy)hexyl]cyclohexanepropanenitrile (23) and (1*RS*,4*RS*,6*SR*)- and (1*SR*,4*RS*,6*SR*)-6-[6-Hydroxy-2-oxohexyl]-4-methyl-2-oxocyclohexanepropanenitrile (24). Following the same procedure for the preparation of dione **8** by the dimethylhydrazne cuprate method, we added 1.22 g (7.5 mmol) of enone **7** to the cuprate reagent prepared from 3.72 g (15 mmol) of dimethylhydrazone **22a**, 9.8 mL (15 mmol) of a 1.53 M solution of *n*-butyllithium in hexane, 1.43 g (7.4 mmol) of CuI, 4.36 mL (3.55 g, 30 mmol) of diisopropyl sulfide, and 75 mL of THF. Hydrolysis of the crude dimethylhydrazone adduct with 3.88 g of $CuCl_2 \cdot 2H_2O$, 35 mL of aqueous pH 7 buffer, 58 mL of water, and 175 mL of THF gave 3.7 g of a dark oil. Chromatography of this material on 125 g of silica gel using an ether–hexane–methanol (4:6:0 to 1:0:0 to 0:6:94) afforded 952 mg (34%) of benzyl ether **23** as a viscous oil (R_f 0.47 and 0.41 in ether): IR (film) 2250, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.42 (2 H, t), 4.43 (2 H, s), 7.23 (5 H, s); mass spectrum, m/e 369 (0.07, M^+), 164 (3.81), 91 (6.58). The more polar fractions gave 704 mg (34%) of alcohol **24** (R_f 0.44 and 0.35 in methanol:chloroform, 5:95) as a viscous oil. The NMR and IR spectra were identical with a sample prepared by hydrolysis of ether **25** (vide infra).

(1*RS*,4*RS*,6*SR*)- and (1*SR*,4*RS*,6*SR*)-6-[6-(2-Methoxyethoxy)-methoxy-2-oxohexyl]-4-methyl-2-oxocyclohexanepropanenitrile (25). A lithium thiophenoxide solution, prepared by the dropwise addition of 27.6 mL (82.8 mmol) of a 1.5 M solution of *n*-butyllithium in hexane to a solution of 4.25 mL (4.56 g, 41.4 mmol) of thiophenol in 18.5 mL of THF at 0 °C under nitrogen with 15 min of additional stirring at 0 °C, was added dropwise via syringe to a suspension of 7.88 g (41.4 mmol) of CuI in 69 mL of THF at −78 °C under nitrogen at such a rate that the reaction temperature did not exceed −70 °C (15 min). After warming to 0 °C, the resulting yellow-green solution of (thiophenoxy)copper was added dropwise, precooled to 0 °C in a jacketed addition funnel, to a solution of lithiated dimethylhydrazone **22b**, which was already prepared by the dropwise addition of 10.20 g (41.4 mmol) of **22b** under nitrogen to a mixture of 27.6 mL (41.4 mmol) of a 1.5 M solution of *n*-butyllithium in hexane and 280 mL of THF at −78 °C. After the resulting cuprate reagent was stirred for 45 min at −78 °C, a solution of 6.44 g (39.5 mmol) of enone **7** in 5 mL of THF was added to the grey-brown mixture at such a rate that the reaction temperature did not exceed −70 °C. Following additional stirring for 4 h at −78 °C and 2.5 h with slow warming to −10 °C, the mixture was poured onto 350 mL

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(52) L. Smith and J. Spring, *J. Am. Chem. Soc.*, **65**, 1271 (1943).
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(54) P. M. Laughton and R. E. Robertson, *Can. J. Chem.*, **39**, 2155 (1961).

of an aqueous pH 8.2 NH_4Cl–NH_4OH buffer solution with vigorous stirring. The mixture was then diluted with 465 mL of methylene chloride, stirred for an additional 15 min, and filtered to remove the precipitated (thiophenoxy)copper. From the filtrate, the organic layer was separated, washed with 250 mL of additional buffer, combined with a 300-mL methylene chloride backwash of the combined aqueous layers, and dried (K_2CO_3). The solvent was evaporated, and the residue (19.1 g) was diluted with 550 mL of THF and 120 mL of an aqueous pH 7 buffer solution. A solution of 10.10 g (58.3 mmol) of $CuCl_2 \cdot 2H_2O$ in 185 mL of water was then added. After stirring for 16 h at 25 °C, the light green mixture was concentrated to remove most of the THF, and the residue was diluted with 250 mL of water and extracted with methylene chloride (4 × 300 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated. Chromatography of the residual oil (16.1 g) on 200 g of silica gel with an ether–hexane (4:10 to 1:0) eluant afforded 8.25 g (57%) of dione **25** (R_f 0.27 and 0.22 in ether) as a viscous oil: IR (film) 2250, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.42 (3 H, s), 3.4–3.7 (6 H, m), 4.70 (2 H, s). Anal. Calcd for $C_{20}H_{33}NO_5$: C, 65.37; H, 9.05; N, 3.81. Found: C, 65.15; H, 8.95; N, 3.74.

(1*RS*,4*RS*,6*SR*)- and (1*SR*,4*RS*,6*SR*)-6-[6-Methoxy-2-oxohexyl]-4-methyl-2-oxocyclohexanepropanenitrile (26). Following the same procedure as was used for the preparation of dione **25**, we added 6.93 g (42.5 mmol) of enone **7** to the cuprate reagent prepared from 7.69 g (44.6 mmol) of dimethylhydrazone **22c**, 29.7 mL (44.6 mmol) of 1.5 M solution of *n*-butyllithium in hexane, (thiophenoxy)copper (44.6 mmol), and 400 mL of THF. After hydrolysis of the dimethylhydrazone adduct with 10.87 g (63.8 mmol) of $CuCl_2 \cdot 2H_2O$, the crude product (14 g) was purified on 200 g of silica gel with an ether–hexane eluant (35:100 to 100:0) to afford 5 g of the pure dione. Rechromatography of the impure fractions afforded a combined total of 7.4 g (60%) of dione **26** as a viscous oil: IR (film) 2250, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.1–3.5 (2 H, m), 3.33 (3 H, s); mass spectrum, *m/e* 293 (0.11, M^+), 275 (0.08), 261 (0.40), 164 (2.62). Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.78. Found: C, 69.81; H, 9.18; N, 4.88.

(1*RS*,4*RS*,6*SR*)- and (1*SR*,4*RS*,6*SR*)-4-Methyl-2-oxo-6-(2-oxohept-6-enyl)cyclohexanepropanenitrile (52). Following the same procedure as was used for the preparation of dione **25**, we added 1.93 g (11.8 mmol) of enone **7** to the cuprate reagent prepared from 2.28 g (14.8 mmol) of dimethylhydrazone **51**, 9.85 mL (29.6 mmol) of a 1.5 M solution of *n*-butyllithium in hexane, (thiophenoxy)copper (14.8 mmol), and 135 mL of THF. Following hydrolysis of the dimethylhydrazone adduct with 3.70 (21.7 mmol) of $CuCl_2 \cdot 2H_2O$, the crude product was purified on 150 g of silica gel with an ether–hexane eluant (2:8 to 5:5) to afford 2.14 g (65%) of dione **52** as a viscous oil: IR (film) 3080, 2250, 1708, 1640, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9–1.2 (3 H, m), 5.7–6.0 (3 H, m). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.04; H, 9.03; N, 5.16.

Diketo Alcohol 24 from Hydrolysis of 25. A mixture of 7.06 g (19.2 mmol) of ether **25**, 65 mL of aqueous 5% HCl solution, and 130 mL of THF was heated to 60 °C over a 1-h period. After additional heating at 60 °C, the cooled mixture was diluted with 500 mL of ether and the aqueous layer was separated. The organic layer was washed with 100 mL of water and 150 mL of aqueous 1 N NaOH solution and then combined with a 300-mL ether backwash of the combined aqueous layers. Drying ($MgSO_4$) of the organic layer, evaporation of the solvent, and chromatography of the residue (5.3 g) on 160 g of silica gel with a methanol–chloroform eluant (0.5:99.5 to 2:90) afforded 3.70 g (69%) of diketo alcohol **24** as a viscous oil: IR (film) 3500, 2250, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.57 (2 H, t); mass spectrum, *m/e* 279 (0.05 M^+), 261 (0.28), 164 (1.67). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.92; H, 8.92; N, 5.00.

(5*RS*,6*RS*,7*SR*,10*RS*)- and (5*RS*,6*SR*,7*SR*,10*RS*)-5-[(2-Hydroxy)ethoxy]-10-methyl-3,4,5,6,7,8-hexahydro-5,7-propano-2*H*-1-benzopyran-6-propanenitrile 28. A mixture of 550 mg (1.97 mmol) of diketo alcohol **24**, 2.22 g (35.8 mmol) of ethylene glycol, 68 mg (0.36 mmol) of *p*-TsOH·H_2O, and 12 mL of benzene was heated at reflux for 5 h under nitrogen with water separation (Dean–Stark trap). The cooled mixture was then poured onto 20 mL of saturated aqueous $NaHCO_3$ solution, and the organic layer was extracted with ether (4 × 20 mL). The combined organic extracts were dried (K_2CO_3), and the solvent was removed to obtain 587 mg (98%) of cyano alcohol **28** (R_f 0.40 and 0.45 in 5:95 methanol–chloroform) as a viscous oil: IR (film) 3450, 2250, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.2–4.1 (6 H, m); mass spectrum, *m/e* 305 (1.45, M^+), 195 (12.06); HRMS: calcd for $C_{18}H_{27}NO_3$, 305.1990; found, 305.1995.

Acid Cyclization of Diketo Alcohol 24. A solution of 3.25 g (11.63 mmol) of diketo alcohol **24** in 80 mL of benzene was treated with 0.233 g (0.116 mmol) of *p*-TsOH·H_2O. After stirring for 16 h at 25 °C, an additional 0.100 g (0.522 mmol) of *p*-TsOH·H_2O was added (the disappearance of starting material was monitored by TLC). After a further 32 h, the mixture was diluted with 100 mL of ether and washed with saturated aqueous $NaHCO_3$ solution (2 × 100 mL). After the combined aqueous layers were washed with 100 mL of ether, the combined organic extracts were dried ($MgSO_4$) and the solvent was removed. The residue was separated on 145 g of silica gel with ether–hexane (3:10 to 10:0) as eluant. After a 300-mL forerun, the eluant was collected in 100-mL fractions. Fractions 12–15 afforded 85 mg (3%) of (5*SR*,10b*RS*,12*RS*)-12-methyl-4,4a,5,6,9,10-hexahydro-5,10b-propano-8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-2(3*H*)-one (**31**), as a solid. Trituration in hexane gave the analytical sample: mp 102.5–103.5 °C; IR ($CHCl_3$, 1%) 1725, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3 H, d), 3.6–4.3 (2 H, m); mass spectrum, *m/e* 262 (5.76, M^+), 205 (15.58). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.30; H, 8.43.

Fractions 16–19 gave 895 mg of an oil which crystallized from ether–hexane to afford 646 mg (21%) of (5*RS*,6*RS*,7*SR*,10*RS*)-5-hydroxy-10-methyl-3,4,5,6,7,8-hexahydro-5,7-propano-2*H*-1-benzopyran-6-propanenitrile (**29**): R_f 0.57 in ether; mp 105–105.5 °C; IR ($CHCl_3$, 1%) 3600, 2250, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, d), 3.7–4.1 (2 H, m); mass spectrum, *m/e* 261 (2.50, M^+), 221 (3.85), 204 (16.65, base), 163 (16.00), 151 (4.13). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.70; H, 8.72; N, 5.32.

Fractions 24–28 gave 181 mg of an oil which crystallized from ether–hexane to afford 115 mg (4%) of (5*RS*,6*SR*,7*SR*,10*RS*)-5-hydroxy-10-methyl-3,4,5,6,7,8-hexahydro-5,6-propano-2*H*-1-benzopyran-6-propanenitrile (**30**): R_f 0.44 in ether; mp 107–109 °C; IR ($CHCl_3$, 1%) 3600, 2250, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, d), 3.7–4.1 (2 H, m); mass spectrum, *m/e* 261 (1.24, M^+), 2.08 (2.17), 204 (4.79), 163 (5.40), 151 (6.15, base). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.29; N, 8.73; N, 5.34.

The mother liquors from crystallization of **29** and **30** were combined with the residue from fractions 20–23 to afford 1.00 g (33%) of a mixture of the two diastereomers which was enriched in isomer **30**.

Elution of the column with MeOH–ether (5:95) gave 208 mg of a foam which crystallized from ether to afford 48 mg (2%) of lactam **32**, mp 212–217 °C. The spectral data were identical with those of a sample prepared from cyano alcohol **29** (vide infra). An undepressed mixture melting point was also observed.

(4a*RS*,5*SR*,10b*RS*,12*RS*)-12-Methyl-4,4a,5,6,9,10-hexahydro-3*H*,8*H*-5,10b-propanopyrano[2,3-*h*]quinolin-2(1*H*)-one (32). A mixture of 100 mg (0.382 mmol) of cyano alcohol **29**, 100 mg (0.48 mmol) of 2-naphthalenesulfonic acid, and 15 mL of benzene was heated at reflux under nitrogen for 1 h. After cooling, the mixture was poured onto 50 mL of saturated aqueous $NaHCO_3$ solution, and the organic layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated. Chromatography of the residue (121 mg) on 6 g of silica gel with ethyl acetate as eluant afforded 79 mg (79%) of lactam **32**: R_f 0.41 in 5:95 methanol–chloroform; mp 215–218 °C; IR ($CHCl_3$, 0.8%) 3400, 1686, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (3 H, d, J = 6), 3.5–4.1 (2 H, m), 7.30 (1 H, br s); mass spectrum, *m/e* 261 (3.88, M^+), 205 (5.26), 204 (25.77, base). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.18; H, 8.68; N, 5.27.

(4a*SR*,5*SR*,10b*RS*,12*RS*)-12-Methyl-4,4a,5,6,9,10-hexahydro-3*H*,8*H*,5,10b-propanopyrano[2,3-*h*]quinolin-2(1*H*)-one (33). Following the same procedure as was used for the preparation of lactam **32** from **29**, we treated 100 mg (0.382 mmol) of cyano alcohol **30** with 100 mg (0.48 mmol) of 2-naphthalenesulfonic acid in 15 mL of refluxing benzene. After workup and silica gel chromatography (ethyl acetate), 79 mg of a 4:1 mixture of lactams **33** and **32** was obtained as a white foam. Fractional crystallization from ether afforded 31 mg (31%) of pure **33**: R_f 0.44 in 5:95 methanol–chloroform; mp 172–174 °C; IR ($CHCl_3$, 0.8%) 3400, 1680, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3 H, d, J = 6), 3.5–4.1 (2 H, m), 6.07 (1 H, br s); mass spectrum, *m/e* 261 (2.83, M^+), 205 (4.04), 204 (16.30, base). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.52; H, 8.87; N, 5.36. Found: C, 73.38; H, 8.78; N, 5.31.

(6*RS*,7*SR*,9*RS*)- and (6*SR*,7*SR*,9*RS*)-7[2-(4-Methoxybutyl)-1,3-dioxolan-2-yl)methyl]-9-methyl-1,4-dioxaspiro[4.5]decan-6-propanenitrile (40). A mixture of 7.49 g (25.5 mmol) of dione **26**, 22.8 g (4.65 mmol) of ethylene glycol, 884 mg (4.65 mmol) of *p*-TsOH·H_2O, and 155 mL of benzene was heated at reflux for 5 h under nitrogen with water separation (Dean–Stark trap). The cooled mixture was poured onto 200 mL of saturated aqueous $NaHCO_3$ solution with vigorous stirring, and the organic layer was extracted with ether (1 × 150 mL, 2 × 200 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution (1 × 150 mL) and water (2 × 150 mL). After being combined with an ether backwash (2 × 150 mL) of the combined aqueous layer, the organic layers were dried (K_2CO_3). Removal of the solvent afforded 9.67 g (99%) of diketal **40** as a viscous oil: IR (film) 2250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3 H, d, J = 7), 3.3–3.6 (2 H, m), 3.36 (3 H, d), 3.98 (8 H, s); mass spectrum, *m/e* 381 (0.09, M^+), 336 (0.40), 294 (2.82),

159 (5.6, base), 113 (5.15). Anal. Calcd for $C_{21}H_{35}NO_5$: C, 66.11; H, 9.25; N, 3.67. Found: C, 66.11; H, 9.01; N, 3.76.

(6*RS*,7*SR*,9*RS*)- and (6*SR*,7*SR*,9*RS*)-7-[(2-(4-Methoxybutyl)-1,3-dioxolan-2-yl)methyl]-9-methyl-1,4-dioxaspiro[4.5]decane-6-propanamine (41). To a suspension of 1.01 g (25.35 mmol) of 95% $LiAlH_4$ in 50 mL of ether under nitrogen was added dropwise a solution of 9.49 g (24.9 mmol) of diketal **40** in 55 mL of ether. After stirring for 3 h at 25 °C, the cooled mixture was quenched by the careful addition of 1.01 mL of water, 1.01 mL of 15% aqueous NaOH solution, and 3.03 mL of water. The salts were removed by filtration (washed well with ether), and the filtrate was dried (K_2CO_3). Removal of the solvent afforded 9.19 g (96%) of amine **41** as a viscous oil: ^1H NMR ($CDCl_3$) δ 0.92 (3 H, d, J = 6), 3.3–3.6 (2 H, m), 3.40 (3 H, s), 4.00 (8 H, s); mass spectrum, m/e 385 (0.07, M^+), 340 (2.28), 298 (1.33), 212 (1.73), 159 (8.21, base), 113 (6.55). Anal. Calcd for $C_{21}H_{39}NO_5$: C, 65.42; H, 10.20; N, 3.63. Found: C, 65.77; H, 10.06; N, 3.47.

(4a*RS*,5*SR*,8*SR*,8a*RS*,10*RS*)-8-(3-methoxypropyl)-10-methylhexahydro-1*H*-5,8a-propanoquinolin-7(8*H*)-one (42). A mixture of 8.89 g (23.3 mmol) of diketal amine **41** and 400 mL of 3.2 M methanolic HCl solution was heated at reflux under nitrogen for 18 days. The solvent was then removed and the residue was diluted with 250 mL of water and brought to pH 10 with aqueous 10 N NaOH solution. The oily precipitate was extracted with methylene chloride (3 × 250 mL), and the combined extracts were dried (K_2CO_3). Removal of the solvent and chromatography of the oily residue (7.1 g) on 200 g of silica with methanol–chloroform as eluant (0.5 to 10% MeOH) gave 3.93 g (61%) of tricyclic amino ketone **42** as a viscous oil: IR (film) 3350, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, d), 3.33 (3 H, s), 3.40 (2 H, t); mass spectrum, m/e 279 (1.96, M^+), 264 (2.89), 220 (1.92), 164 (1.03), 150 (5.78). Anal. Calcd for $C_{17}H_{29}NO$: C, 73.07; H, 10.46; N, 5.01. Found: C, 72.77; H, 10.32; N, 4.82.

(±)-Lycopodine (1). (a) From 3,4-Dehydrolycopodine (20). To a solution of 1.32 g (5.36 mmol) of enone **20** in 50 mL of methanol was added 50 mg of 86% PtO_2, and the resulting mixture was stirred under 1 atm of hydrogen until uptake ceased. The catalyst was removed by filtration and the solvent evaporated to obtain 1.30 g of crude product as a yellow solid, mp 126–128 °C. Sublimation of this solid (100 °C, 0.001 torr) afforded 1.16 g (87%) of analytically pure (±)-lycopodine as white needles, mp 127–129 °C. The ^1H NMR (180 MHz) and IR (CCl_4) spectra of this material were superimposable with spectra of natural lycopodine. Recrystallization of the sublimed material gave white needles, mp 130–131 °C (lit.[11] mp 130–131 °C). Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.91; H, 10.17; N, 5.69.

(b) From Lactam 32. To a solution of 10 mg (0.382 mmol) of lactam **32** in 4 mL of THF was added 22 mg (0.55 mmol) of 95% $LiAlH_4$, and the resulting mixture was heated at reflux under nitrogen for 21 h. After cooling, the mixture was quenched by the careful addition of 22 μL of water, 22 μL of aqueous 15% NaOH solution, and 66 μL of water. The salts were removed by filtration and washed well with ether, and the filtrate was dried (K_2CO_3). Removal of the solvent gave 11 mg of the crude secondary amine **34** as an oil: IR (CCl_4, 1%) 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, d, J = 5), 3.4–3.1 (2 H, m). This material was stirred for 16 h in 1.5 mL of 25% HBr in acetic acid at 25 °C in a sealed flask. Following removal of the solvent under aspirator pressure at 40–50 °C, we dissolved the residue in 6 mL of aqueous 10% HCl solution, washed it with ether (3 × 6 mL), made it basic (pH 10) with aqueous 10 N NaOH solution, then extracted it with methylene chloride (3 × 10 mL). The combined organic extracts were dried (K_2CO_3), and the solvent was removed. Sublimation of the residual solid (80 °C, 0.001 torr) afforded 5.0 mg (53%) of (±)-lycopodine (**1**), mp 122–125 °C, which was identical by IR, NMR, and TLC with the synthetic lycopodine prepared in part a.

(c) From Amino Ether 42. A mixture of 345 mg (1.24 mmol) of methyl ether **42** and 20 mL of 25% HBr in AcOH was stirred for 22 h at 25 °C in a sealed flask. The solvent was then removed under aspirator pressure at 40–50 °C, and the residue was dissolved in 75 mL of 2:1 water–methanol. This mixture was made basic (pH 9) with solid K_2CO_3 and kept warm on a steam bath for 15 min to keep the salts in solution. After dilution with 100 mL of water, the mixture was extracted with methylene chloride (3 × 75 mL). The combined extracts were dried (K_2CO_3) and the solvent was removed. Sublimation of the yellow-orange solid residue (30–90 °C, 0.001 torr), afforded 179 mg (59%) of (±)-lycopodine, mp 128–129 °C. This sample was identical by IR, ^1H NMR (90 MHz), TLC, and mixture melting point with the (±)-lycopodine prepared in part a.

(±)-12-Epilycopodine (4). To a solution of 17 mg (0.065 mmol) of lactam **33** in 5 mL of THF was added 22 mg (0.55 mmol) of 95% $LiAlH_4$, and the resulting mixture was heated at reflux under nitrogen for 4 days. After cooling, the mixture was quenched by the careful addition of 45 μL of water, 45 μL of aqueous 15% NaOH solution, and 135 μL of water. The salts were removed by filtration (washed well with ether), and the filtrate was dried (K_2CO_3). Removal of the solvent gave 20 mg of the crude secondary amine as an oil: IR (CCl_4, 1%) 1678 cm^{-1}. This residue was stirred for 16 h in 2 mL of 25% HBr in AcOH at 25 °C in a sealed flask. After removal of solvent under aspirator pressure at 40–50 °C, the residue was dissolved in 10 mL of aqueous 10% HCl solution, washed with ether (3 × 10 mL), made basic (pH 10) with aqueous 10 N NaOH solution, and extracted with methylene chloride (3 × 20 mL). The combined organic extracts were dried (K_2CO_3), and the solvent was removed. The oily residue (16 mg) was purified by silica gel chromatography, sublimation, and alumina chromatography, respectively, to afford 4 mg (25%) of (±)-12-epilycopodine (**4**) as a clear oil. This sample was identical by IR and TLC with an authentic sample of 12-epilycopodine even though it failed to crystallize after repeated attempts (lit. mp 56–58 °C for (±)-12-epilycopodine[13]).

(4a*RS*,5*SR*,8*SR*,8a*SR*,10*RS*)-1-Acetyl-8-(3-methoxypropyl)-10-methylhexahydro-1*H*-5,8a-propanoquinolin-7(8*H*)-one (44). A mixture of 156 mg (0.558 mmol) of methoxy ketone **42** and 467 μL (339 mmol) of triethylamine in 4 mL of methylene chloride at 25 °C under nitrogen was treated with 0.118 mL (131 mg, 1.67 mmol) of acetyl chloride. After stirring for an additional 0.5 h, the mixture was diluted with 30 mL of methylene chloride and washed with aqueous 5% HCl solution (3 × 20 mL), aqueous 10% K_2CO_3 solution (1 × 25 mL), and brine (1 × 25 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed. Chromatography of the solid residue (179 mg) on 8 g of silica gel with an ether–$CHCl_3$ (1:1) eluant afforded 127 mg (71%) of amide **44** as an oil which slowly crystallized, mp 86–95 °C. The analytical sample was prepared by trituration in ether to obtain a white solid, mp 118–124 °C, which was recrystallized from ether to provide material, mp 126.5–127.5 °C; IR ($CHCl_3$, 1%) 1700, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3 H, d), 2.13 (3 H, s), 3.32 (3 H, s), mass spectrum, m/e (2.95, M^+), 306 (0.91), 278 (5.71), 1.92 (6.79), 150 (6.73). Anal. Calcd for $C_{19}H_{31}NO_3$: C, 70.99; H, 9.72; N, 4.36. Found: C, 71.18; H, 9.63; N, 4.40.

(1*RS*,2*RS*,5*SR*,7*RS*,9*RS*)-9-(3-Acetamidopropyl)-1-bromo-2-(3-bromopropyl)-7-methylbicyclo[3.3.1]nonan-3-one (45). A mixture of 19 mg (0.059 mmol) of amide **44** and 3 mL of 25% HBr in acetic acid was stirred for 16 h at 25 °C in a sealed flask. The solvent was removed under aspirator pressure at 40–50 °C, and the residue was diluted with water, made basic with saturated aqueous $NaHCO_3$ solution, and extracted with methylene chloride. The organic extracts were dried ($MgSO_4$), and the solvent was removed to afford 26 mg (97%) of dibromide **45** as a viscous oil: IR ($CHCl_3$, 1%) 3450, 1705, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (3 H, d), 1.99 (3 H, s), 3.2–3.5 (4 H, m), 5.66 (1 H, br s); mass spectrum, m/e 371 and 369 (0.92, 0.94), 289 (3.67), 232 (12.37, base), 192 and 190 (2.84, 2.87), 150 (2.53), 82 and 80 (4.05 and 4.06).

(4a*RS*,5*SR*,8*SR*,8a*RS*,10*RS*)-8-Butyl-10-methylhexahydro-1*H*-5,8a-propanoquinolin-7(8*H*)-one (47). To a solution of 498 mg (1.905 mmol) of amino olefin **46** (vide infra) in 20 mL of absolute ethanol was added 50 mg of 10% Pd on charcoal. The mixture was then stirred under 1 atm of hydrogen until the uptake had ceased. Filtration of the catalyst and removal of the solvent from the filtrate gave an oil which was purified by distillation using a Kugelrohr apparatus (100 °C, 0.01 torr) to afford 411 mg (82%) of saturated ketone **47**: IR (CCl_4, 1%) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (3 H, d, J = 6), 0.91 (3 H, t, J = 6); mass spectrum, m/e 263 (4.31, M^+), 220 (7.17), 150 (12.24). Anal. Calcd for $C_{17}H_{29}NO$: C, 77.51; H, 11.05; N, 5.32. Found: C, 77.68; H, 11.07; N, 5.21.

(4a*RS*,5*SR*,8*SR*,8a*RS*,10*RS*)-1-Acetyl-8-butyl-10-methylhexahydro-1*H*-5,8a-propanoquinolin-7(8*H*)-one (48). Following the same procedure as was used for the preparation of methoxy amide **44**, we acylated 411 mg (1.56 mmol) of amine **47** with 0.333 mL (0.367 g, 4.68 mmol) of acetyl chloride and 1.31 mL (0.947 g, 9.36 mmol) of triethylamine in 12 mL of methylene chloride. After workup and chromatography (ether–hexane, 1:4 to 1:0, eluant), 271 mg (57%) of amide **48** was obtained, mp 94–98 °C. The analytical sample, mp 103–104 °C, was prepared by recrystallization from petroleum ether: IR ($CHCl_3$, 0.8%) 1700, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (3 H, s); mass spectrum, m/e 305 (2.88, M^+), 2.62 (5.95), 220 (1.82), 192 (5.59), 150 (5.06). Anal. Calcd for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.58. Found: C, 74.88; H, 10.20; N, 4.54.

(1*RS*,2*RS*,5*SR*,7*RS*,9*RS*)-9-(3-Acetamidopropyl)-1-bromo-2-butyl-7-methylbicyclo[3.3.1]nonan-3-one (49). A mixture of 200 mg (0.655 mmol) of amide **48** in 8 mL of 25% HBr in acetic acid was stirred for 20 h at 25 °C in a sealed flask. After removal of the solvent under aspirator pressure at 40–50 °C, the residue was diluted with a mixture of 30 mL each of methylene chloride and water. The aqueous layer was made basic (pH 10) with aqueous 1 N NaOH solution, and the organic layer was separated and then combined with two 30-mL methylene

chloride extracts of the aqueous layer. The combined organic layers were dried ($MgSO_4$) and the solvent was removed. Chromatography of the residue on 10 g of silica gel with methanol–chloroform (0.1–0.6% methanol) afforded 223 mg (88%) of bromide **49** as a colorless foam: IR ($CHCl_3$, 0.8%) 3450, 1707, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (3 H, d, J = 5), 0.93 (3 H, t, J = 6), 1.96 (3 H, s), 3.24 (2 H, overlapping double t, J = 6), 6.14 (1 H, br t); mass spectrum, m/e 305 (2.81), 262 (3.08), 220 (1.68), 1.92 (2.96), 150 (3.17). Anal. Calcd for $C_{19}H_{33}BrNO_2$: C, 59.06; H, 8.36; Br, 20.68; N, 3.63. Found: C, 59.06; H, 8.31; Br, 20.52; N, 3.59.

(4a*RS*,5*SR*,8*SR*,8a*RS*,10*RS*)-8-(3-Bromopropyl)-10-methylhexahydro-1*H*-5,8a-propanoquinolin-2,7(8*H*)-dione (50). A mixture of 31 mg (0.118 mmol) of lactam **32** and 2 mL of 25% HBr in HOAc was stirred at 25 °C in a sealed flask for 16 h. Following the same workup procedure as was used for the preparation of bromide **49**, we obtained 42 mg of crude product as an oil which was crystallized from ether–hexane to provide 31.3 mg (77%) of bromide **50**: mp 122–123 °C; IR ($CHCl_3$, 1%) 3480, 1703, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (3 H, d, J = 6), 3.4 (2 H, t, J = 6), 7.80 (1 H, br s); mass spectrum, m/e 343 and 341 (0.09, 0.08, M^+), 261 (1.05), 204 (8.17, base). Anal. Calcd for $C_{16}H_{29}BrNO_2$: C, 56.15; H, 7.07; Br, 23.35; N, 4.09. Found: C, 56.24; H, 7.14; Br, 23.10; N, 4.02.

(6*RS*,7*SR*,9*RS*)- and (6*SR*,7*SR*,9*RS*)-9-Methyl-7-[(2-pent-4-enyl-1,3-dioxolan-2-yl)methyl]-1,4-dioxaspiro[4.5]decane-6-propanenitrile (53). A mixture of 4.21 g (15.3 mmol) of dione **52**, 17.25 g (278 mmol) of ethylene glycol, 0.531 g of p-TsOH·H_2O, and 80 mL of benzene was refluxed for 21 h under nitrogen with water separation by using a Dean–Stark trap for 5 h and a Soxhlet extractor with calcium hydride in the thimble for 16 h, respectively. The cooled mixture was poured onto 150 mL of saturated aqueous $NaHCO_3$ solution with vigorous stirring, and the organic layer was extracted with ether (3 × 150 mL). The combined organic extracts were dried (K_2CO_3) and the solvent was removed to obtain 5.07 g (91%) of diketal **53** as a viscous oil: IR (film) 3075, 2250, 1640, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, d), 3.90 (8 H, s), 4.7–5.9 (3 H, m). Anal. Calcd for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 69.44; H, 9.11; N, 3.84.

(6*RS*,7*SR*,9*RS*)- and (6*SR*,7*SR*,9*RS*)-9-Methyl-7-[(2-pent-4-enyl-1,3-dioxolan-2-yl)methyl]-1,4-dioxaspiro[4.5]decane-6-propanamine (54). Following the same procedure as was used for the preparation of amine **41**, we reduced 5.00 g (13.7 mmol) of diketal nitrile **53** with 687 mg (17.2 mmol) of 95% $LiAlH_4$ in 60 mL of ether to afford 4.73 g (94%) of amine **54** as a viscous oil: IR (film) 2275, 1640, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, d, J = 6), 2.67 (2 H, br t), 3.87 (8 H, s), 4.8–5.1 (2 H, m), 5.5–5.9 (1 H, m). Anal. Calcd for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81. Found: C, 68.98; H, 9.82; N, 3.43.

(4a*RS*,5*SR*,8*SR*,8a*RS*,10*RS*)-8-(But-3-enyl)-10-methylhexahydro-1*H*-5,8a-propanoquinolin-7(8*H*)-one (46). A mixture of 4.69 g (12.8 mmol) of diketal amine **54** and 250 mL of 3 M methanolic HCl solution was heated at reflux for 14 days under nitrogen. The solvent was then removed and the residue was diluted with 150 mL of saturated aqueous $NaHCO_3$ solution. The oily precipitate was extracted with methylene chloride (3 × 125 mL) and the combined extracts were dried (K_2CO_3). Removal of the solvent and chromatography of the oily residue (3.7 g) on 110 g of silica gel with an ether–$CHCl_3$ eluant (1:1 to 1:0) afforded 2.11 g (63%) of tricyclic olefin **46** as a viscous oil: IR (CCl_4, 1%) 3080, 1702, 1640, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (3 H, d, J = 6), 4.8–5.1 (2 H, m), 5.5–5.9 (1 H, m); mass spectrum, m/e 261 (1.15, M^+), 220 (12.26), 150 (9.55). Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 77.84; H, 10.09; N, 5.11.

The *N*-acetyl derivative of **46** was prepared in the same manner as was used to prepare amide **48**; 48 mg (0.184 mmol) of amine **46** was acylated with 39 μL (43 mg, 0.551 mmol) of acetyl chloride and 153 μL (111 mg, 1.10 mmol) of triethylamine in 1.5 mL of methylene chloride. After workup and chromatography (ether–chloroform, 1:3 eluant), 29 mg (52%) of amide was obtained, mp 84–87.5 °C. The analytical sample, mp 99–100 °C, was prepared by recrystallization from petroleum ether. IR ($CHCl_3$, 1%) 1700, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3 H, d), 2.12 (3 H, s), 4.8–5.1 (2 H, m), 5.5–6.0 (1 H, m). Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62. Found: C, 75.30; H, 9.81; N, 4.67.

(±)-Lycodine (3). To a solution of 756 mg (2.89 mmol) of keto olefin **46** in 75 mL of methanol was added 9.64 mL (28.9 mmol) of an aqueous 3 M H_2SO_4 solution. After the mixture was cooled to −78 °C, a stream of ozone (generated by a Welsbach ozonator) was bubbled in until the starting material was consumed, as shown by TLC (small aliquots were quenched with dimethyl sulfide and neutralized). The mixture was then flushed by bubbling nitrogen through it, and a solution of 4.02 g (57.8 mmol) of NH_2OH·HCl in 30 mL of 1:1 aqueous methanol was added at −78 °C. After the mixture was stirred for 1 h at −78 °C and 1 h at 0 °C, 10 mL of dimethyl sulfide was added. The resulting mixture was stirred for 0.5 h at 0 °C and 0.5 h at 25 °C before being heated at reflux under nitrogen for 48 h. The solvent was removed, and the residue was diluted with 150 mL of H_2O, made basic (pH 10) with aqueous 10 N NaOH solution, and extracted with CH_2Cl_2 (4 × 100 mL). After drying of the combined organic extracts (K_2CO_3) and removal of the solvent, the oily residue (695 mg) was chromatographed on 45 g of silica gel with 1–5% methanol in chloroform as eluant to afford 490 mg (70%) of (±)-lycodine, mp 74–76 °C. The analytical sample was prepared by sublimation (50 °C, 0.001 torr), and recrystallization from pentane, mp 86–87 °C. This sample was identical by IR, ^1H NMR (180 MHz), and TLC with a sample of natural lycodine. Anal. Calcd for $C_{16}H_{22}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.24; H, 9.15; N, 11.56.

(4a*SR*,5*SR*,7*RS*)-4a-Hydroxy-7-methyl-5-(2-oxopropyl)-2,3,4,4a,5,6,7,8-octahydroquinoline (58), (4a*RS*,5*SR*,7*RS*)-4a-Hydroxy-7-methyl-5-(2-oxopropyl)-2,3,4,4a,5,6,7,7-octahydroquinoline (59), and (4a*SR*,5*SR*,7*RS*)-4a-(Hydroperoxy)-7-methyl-5-(2-oxopropyl)-2,3,4,4a,5,6,7,7-octahydroquinoline. A solution of 2.30 g (7.34 mmol) of diketal amine **9** in 80 mL of ether was extracted with aqueous 10% HCl solution (1 × 60 mL, 1 × 20 mL). The combined acid extracts were then made basic (pH 10) with aqueous 10 N NaOH while nitrogen was being bubbled through the solution, and the oily precipitate was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (1 × 100 mL), dried over Na_2SO_4, filtered, and stirred under 1 atm of oxygen at 25 °C until the uptake had ceased (2 h). At this point 260 mg of 10% Pd on charcoal was added, and the mixture was stirred under 1 atm of hydrogen until the uptake ceased (3 h). After filtration of the catalyst and removal of the solvent, the yellow solid residue was triturated with ethyl acetate to afford 528 mg of keto imine **58** as a white powder, mp 161.5–163 °C. The analytical sample, mp 164–165 °C, was prepared by recrystallization from ethyl acetate: IR ($CHCl_3$, 1%) 3600, 1715, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3 H, d, J = 5), 2.10 (3 H, s), 3.2–3.7 (2 H, m), 3.83 (1 H, br s); mass spectrum, m/e 223 (0.29, M^+), 204 (0.86), 180 (0.73). Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.91; H, 9.48; N, 6.27. Found: C, 70.03; H, 9.31; N, 6.31.

Chromatography of the mother liquor on 55 g of silica gel with 1–10% methanol in chloroform as eluant gave 68 mg (4%) of *cis*-hydroxy keto imine **59** as a viscous oil: IR (CCl_4, 1%) 3450, 1715, 1658 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (3 H, d, J = 6), 1.58 (3 H, s); mass spectrum, m/e 223 (1.11, M^+), 205 (0.50), 180 (1.72); HRMS, calcd for $C_{13}H_{21}NO_2$, 223.1572; found, 223.1577.

The more polar fractions provided 178 mg of additional imine **58**, mp 159–160 °C. The total yield was thus 706 mg (43%).

In one run, a crystalline precipitate formed during the autoxidation step when the imine derived from 646 mg of diketal **9** was stirred under oxygen in 10 mL of ethyl acetate. Filtration afforded 112 mg (23%) of hydroperoxide: mp 110 °C dec; mass spectrum, m/e 239 (0.08, M^+), 221 (0.61), 204 (1.08), 178 (1.66). Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85; N, 5.85. Found: C, 65.06; H, 8.75; N, 5.79.

Catalytic reduction of this hydroperoxide (93 mg, 0.387 mmol) in 20 mL of ethyl acetate with 10 mg of Pd on charcoal under 1 atm of hydrogen afforded 87 mg (99%) of hydroxy imine **58**, mp 156–158 °C, which was identical by TLC, NMR and mixture melting point with the sample prepared above.

(4a*SR*,5*SR*,8a*SR*,10*RS*)-4a-Hydroxy-10-methylhexahydro-1*H*-5,8a-propanoquinolin-7(8*H*)-one (6). Bicyclic imine **58** (1.00 g, 4.48 mmol) was dissolved in 10 mL of 3-bromo-1-propanol (Eastman) and then diluted with 50 mL of toluene. The mixture was gradually heated to 85 °C over a period of 1 h and to 105 °C over a further 3-h period under nitrogen. At this time a white precipitate began to form, and heating at 105 °C was continued for a further 22 h. Filtration of the solid afforded 1.18 g (87%) of hydrobromide salt, mp >270 °C. An analytical sample was prepared by recrystallization from ethanol: mass spectrum, m/e 225 (0.34), 224 (0.97), 223 (1.25), 148 (8.25). Anal. Calcd for $C_{13}H_{22}BrNO_2$: C, 51.32; H, 7.29; Br, 26.27; N, 4.60. Found: C, 51.26; H, 7.32; Br, 26.02; N, 4.48.

The salt was dissolved in 30 mL of water, and this solution was made basic (pH 9) with aqueous 1 N NaOH. Extraction with methylene chloride (3 × 30 mL), drying (K_2CO_3) of the combined extracts, and removal of the solvent afforded 851 mg (85%) of tricyclic alcohol **6** as fluffy white crystals, mp 164–165 °C. The analytical sample, mp 165–166 °C, was prepared by recrystallization from ether: IR (CCl_4, 0.8%) 3520, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (3 H, d, J = 7); mass spectrum, m/e 233 (1.77, M^+), 148 (12.02). Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.91; H, 9.48; N, 6.27. Found: C, 70.20; H, 9.54; N, 6.24.

To a suspension of 54 mg (0.18 mmol) of the hydrobromide salt of amine **6** in 1 mL of methylene chloride was added 101 μL (74 mg, 0.73 mmol) of triethylamine followed by 52 μL (58 mg, 0.54 mmol) of ethyl chloroformate. After 45 min, an additional 101 μL of triethylamine and

52 μL of ethyl chloroformate were added. After 1 h, the mixture was diluted with 20 mL of methylene chloride and washed with aqueous 5% HCl solution (3 × 15 mL), water (1 × 20 mL), and saturated aqueous $NaHCO_3$ solution. The organic layer was dried (K_2CO_3) and the solvent was removed. The residual oil (31 mg) was chromatographed on 3 g of silica gel with 1:4 ether–chloroform eluant to obtain 16 mg of carbamate **60** as a clear oil, which was crystallized from ether–hexane: mp 131–132 °C (lit.[17] mp 130–132 °C); IR ($CHCl_3$, 0.8%) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, d, J = 6), 1.22 (3 H, t, J = 7), 3.97 (2 H, q, J = 7).

(4a*SR*,5*SR*,8a*SR*,10*RS*)-4a-Hydroxy-1-(3-hydroxypropyl)-10-methylhexahydro-1*H*-5,8a-propanoquinolin-7(8*H*)-one (61). To a mixture of 668 mg (3.00 mmol) of amine **6** in 19 mL of acetone was added 750 mg each of $NaHCO_3$ and anhydrous K_2CO_3 followed by 2.78 g (15.0 mmol) of 3-iodo-1-propanol.[55] The mixture was then heated at reflux for 6 h under nitrogen with vigorous stirring. After cooling, the salts were removed by filtration (washed well with acetone) and the solvent was removed. The residue was diluted with 50 mL of aqueous 5% HCl solution, washed with ether (3 × 50 mL), neutralized with solid K_2CO_3, and extracted with methylene chloride (3 × 50 mL). The organic extracts were dried (K_2CO_3) and the solvent was removed. Trituration of the solid residue in ether afforded 612 mg (73%) of diol **61**, mp 140.5–141 °C; IR ($CHCl_3$, 1%) 3620, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (3 H, br s), 3.62 (2 H, t, J = 6); mass spectrum, m/e 281 (2.33, M^+), 266 (2.07), 2.36 (6.15, base), 2.06 (4.13). Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.08; H, 9.57; N, 4.92.

(±)-3,4-Dehydrolycodoline (62). To a suspension of 157 mg (3.91 mmol) of potassium hydride (prepared by washing 628 mg of 25% KH in mineral oil with three portions of ether) in 6 mL of toluene was added 160 mg (0.59 mmol) of diol **61** under nitrogen. After stirring for 15 min at 25 °C, 1.075 g (5.90 mmol) of benzophenone was added and the resulting mixture was heated at reflux for 17 h. The resulting brown suspension was allowed to cool to 25 °C, diluted with 6 mL of benzene, and extracted with aqueous 5% HCl solution (1 × 10 mL, 1 × 2 mL). The aqueous extracts were neutralized with solid K_2CO_3 and extracted with ethyl acetate (4 × 15 mL). Drying of the extracts (Na_2SO_4) and removal of the solvent gave 144 mg of a red solid. Chromatography of this solid on 7 g of silica gel with 1–3% methanol in chloroform as eluant gave 95 mg of an orange solid which was triturated in ether to afford 67 mg (45%) of enone **62** as a yellow solid, mp 150–154 °C. An analytical sample, mp 155–157 °C, was prepared by recrystallization from ether: IR ($CHCl_3$, 1%) 3530, 1675, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, d, J = 5), 6.87 (1 H, t, J = 3); UV_{max}(MeOH) 248 nm (ε 8800); mass spectrum, m/e 261 (3.27, M^+), 244 (1.65), 233 (4.01), 204 (6.88, base). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.86; H, 9.04; N, 5.29.

(±)-Lycodoline (2). To a solution of 66 mg (0.25 mmol) of enone **62** in 5 mL of absolute EtOH was added 7 mg of 86% PtO_2, and the resulting mixture was stirred under 1 atm of hydrogen until uptake ceased. The catalyst was removed by filtration and the solvent evaporated. Trituration of the residue with ethanol afforded 18 mg of (±)-lycodoline as yellow crystals, mp 197–199 °C. Sublimation (110 °C, 10^{-4} torr) of the mother liquor gave an additional 34 mg of analytically pure (±)-lycodoline as white crystals, mp 192–195 °C. The total yield was thus 52 mg (78%). The ^1H NMR (250 MHz) and IR ($CHCl_3$) spectra of this material were superimposable with spectra of natural lycodoline. Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 72.78; H, 9.51; N, 5.14.

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Registry No. (±)-**1**, 18688-24-9; (±)-**2**, 69832-13-9; (±)-**3**, 73677-04-0; (±)-**4**, 33190-30-6; (±)-**6**, 69787-46-8; (±)-**6** HBr, 76465-86-6; (±)-**7**, 69060-78-2; (±)-**8** isomer I, 69060-79-3; (±)-**8** isomer II, 69060-80-6; (±)-**8** diketal isomer I, 69060-81-7; (±)-**8** diketal isomer II, 69088-57-9; (±)-**9** isomer I, 80513-57-1; (±)-**9** isomer II, 80513-58-2; (±)-**10** isomer I, 69060-86-2; (±)-**10** isomer II, 69088-61-5; **10** amide, 80471-21-2; (±)-**11**, 69060-87-3; (±)-**12**, 72058-83-4; (±)-**16** isomer I, 69060-82-8; (±)-**16** isomer II, 69088-58-0; (±)-**16** amide isomer I, 69060-83-9; (±)-**16** amide isomer II, 69088-59-1; (±)-**17** isomer I, 69060-84-0; (±)-**17** isomer II, 69088-60-4; (±)-**18**, 69060-85-1; (±)-**19**, 69060-88-4; (±)-**20**, 69060-89-5; (±)-**22a**, 80471-22-3; **22b**, 80471-23-4; **22b** Li, 80471-24-5; **22c**, 73677-05-1; (±)-**23** isomer I, 80471-25-6; (±)-**23** isomer II, 80471-26-7; (±)-**24** isomer I, 80471-27-8; (±)-**24** isomer II, 80471-28-9; (±)-**25** isomer I, 80471-29-0; (±)-**25** isomer II, 80471-30-3; (±)-**26** isomer I, 80471-31-4; (±)-**26** isomer II, 80471-32-5; (±)-**28** isomer I, 80471-33-6; (±)-**28** isomer II, 80513-59-3; (±)-**29**, 80471-34-7; (±)-**30**, 80513-60-6; **31**, 80471-35-8; (±)-**32**, 80471-37-0; (±)-**33**, 80513-97-9; (±)-**34**, 80471-38-1; (±)-**35**, 80513-64-0; (±)-**40** isomer I, 80471-36-9; (±)-**40** isomer II, 80513-61-7; (±)-**41** isomer I, 80513-62-8; (±)-**41** isomer II, 80513-63-9; (±)-**42**, 73677-06-2; (±)-**44**, 80485-77-4; (±)-**45**, 80471-39-2; (±)-**46**, 73677-03-9; (±)-**46** *N*-acetyl, 80485-78-5; (±)-**47**, 80471-40-5; (±)-**48**, 80471-41-6; (±)-**49**, 80471-42-7; (±)-**50**, 80471-43-8; **51**, 73676-99-0; (±)-**52** isomer I, 80471-44-9; (±)-**52** isomer II, 80471-45-0; (±)-**53** isomer I, 80471-46-1; (±)-**53** isomer II, 80513-65-1; (±)-**54** isomer I, 73711-98-5; (±)-**54** isomer II, 83677-02-8; (±)-**58**, 76405-06-6; **59**, 76405-05-5; (±)-**61**, 76405-03-3; (±)-**62**, 76405-04-4; **76**, 2172-73-8; 5-methyl-1,3-cyclohexanedione sodium salt, 80471-47-2; 2-(2-cyanoethyl)-3-chloro-5-methylcyclohex-3-en-1-one, 80471-48-3; (1*RS*,4*RS*,6*SR*)-4-methyl-6-[2-(2-methyl)-propenyl]-2-oxocyclohexanepropanenitrile, 80471-49-4; (1*SR*,4*RS*,6*SR*)-4-methyl-6-[2-(2-methyl)propenyl]-2-oxocyclohexanepropanenitrile, 80471-50-7; *N*-benzyl-2-aza-7-(2-propionyl)-8-methylbicyclo[4.4.0]dec-1(6)-ene, 80471-51-8; 3-(benzyloxy)-1-propanol, 4799-68-2; 3-methoxy-1-propanol, 1589-49-7; 1-(benzyloxy)-3-bromopropane, 54314-84-0; 1-bromo-3-methoxypropane, 36865-41-5; 1-bromo-3-[2-(methoxyethoxy)methoxy]propane, 80471-52-9; 3-bromo-1-propanol, 3970-21-6; (β-methoxyethoxy)methyl chloride, 3970-21-6; (4a*SR*,5*SR*,7*RS*)-4a-(hydroperoxy)-7-methyl-5-(2-oxopropyl)-2,3,4,4a,5,6,7,8-octahydroquinoline, 5162-44-7; 3-iodo-1-propanol, 80471-53-0; 3-(benzyloxy)-1-propylamine, 627-32-7; acetone dimethylhydrazone, 16728-64-6; (±)-**58** HBr, 13483-31-3; (±)-**60**, 80471-54-1, 69787-44-6.

(55) F. L. M. Pattison and G. M. Brown, *Can. J. Chem.*, **34**, 879 (1956).