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

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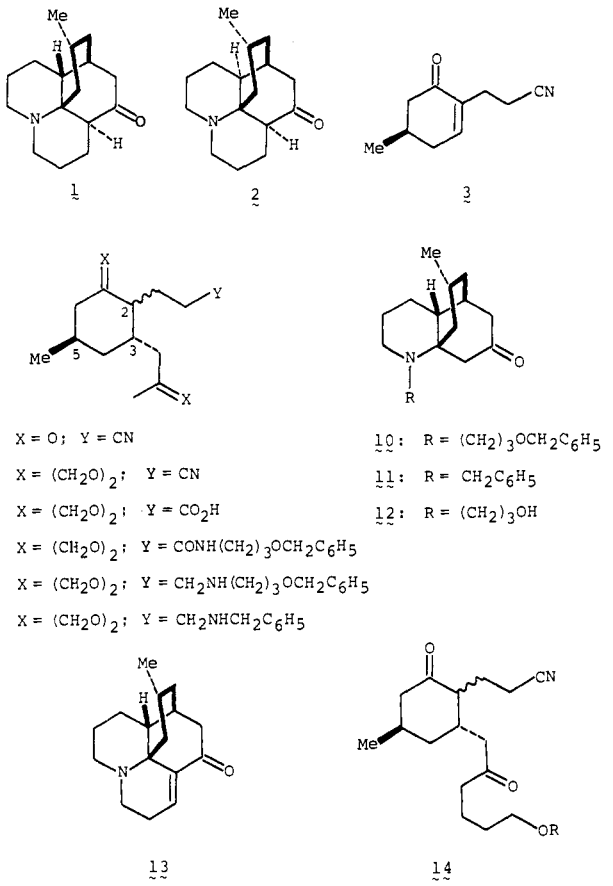
A Highly Efficient Total Synthesis of (±)-Lycopodine

Sir:

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

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



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

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

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

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analytically pure (±)-**1** from 4.5 g of cyanoenone **3**. Furthermore, the approach is readily amenable to modification for production of other *Lycopodium* alkaloids. For example, by using another cuprate in addition to enone **3**, we have prepared cyanodione **14**, which is an attractive intermediate for conversion into lycodine.[18] Further applications of the route in *Lycopodium* alkaloid synthesis are under investigation.

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Poly(I) Helix Formation. Dependence on Size-Specific Complexing to Alkali Metal Ions

Sir:

Poly(I) forms an ordered helical structure, originally thought to be three stranded[1] but more recently accepted as four stranded.[2,3] The hydrogen-bonding scheme (Figure 1) has a fourfold rotation axis in the center of the planar tetrameric array of inosines, and the polarity of the four strands is parallel. The observed stability of the helix (e.g., $T_m \simeq 25$ °C in 0.2 M Na^+)[4] has been surprising since only a single hydrogen bond joins each base to its neighbor, and a presumably destabilizing hole or cavity exists in the center of the tetrameric arrangement of bases (Figure 1). The results presented below suggest that an unoccupied central hole would indeed be destabilizing, but that the dimensions and chemical composition of the cavity permit stabilizing interactions which are essential for helix formation. The recent discovery[5] of specific alkali metal ion effects on formation of ordered complexes by a nucleotide, 5′-GMP, led us to examine the effect of these metals on helix formation by poly(I). In general, alkali metal ions show very little difference in their affinities for nuclei acid helices[6-9] or polyphosphates.[10] In contrast, we show here a striking dependence of poly(I) helix formation on the nature of the alkali metal cation. We believe this to be the first demonstration of control of ordered polynucleotide structures by size-selective complexation with alkali metal ions.

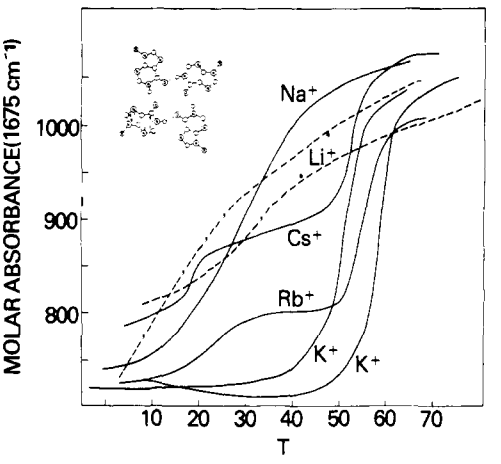

Figure 1. Inset: hydrogen bonding scheme of poly(I) helix. Infrared melting curves of helical poly(I) were measured at or slightly below the frequency maximum of the random coil polymer. Poly(I): 0.045 M Li^+ salt, unless otherwise indicated. Added salts: Li^+, upper curve, none: Li^+, lower curve 0.17 M LiCl; Na^+, 0.10 M NaCl; Cs^+, 0.10 M CsCl (measured at 1670 cm^{-1}); K^+ (left), 0.021 M KCl, 0.17 M LiCl, 0.042 M poly(I) Li salt; K^+ (right), 0.10 M KCl. The ordinate scale applies to the 0.1 M KCl curve, but numerical values are somewhat different for the others, plotted at lower frequencies. The first steps of the Rb and Cs curves are not equilibrium melting curves, but represent the conversion of a metastable to a stable helix (see text).

Helix formation of poly(I) was monitored by infrared spectroscopic observation of the inosine carbonyl stretching vibration[11] at 1676 cm^{-1}, using methods described and discussed previously.[4,12,13]

Poly(I) (P-L Biochemicals, lot no. 200-15, K^+ salt) was converted to the Li salt by extensive dialysis against LiCl. Alkali metal chlorides were the ultrapure grade of Alfa Inorganics.

The infrared spectrum of poly(I) Li^+ salt without added counterion shows no helix formation, and in 0.17 M LiCl, only ~50% helix at 0 °C (Figure 2).

In 0.1 M NaCl, the carbonyl band shifts to 1684.5 cm^{-1} at 4 °C (ϵ_{max} 1045, $\Delta\nu_{1/2}$ 26 cm^{-1}). Helix formation is slow, but is largely complete after 6 h at 4 °C. The melting curve (Figure 1) is cooperative though broad ($\sigma \simeq 28$ °C) with $T_m = 28$ °C.

The increase in helix stability on going to the next alkali metal, K^+, is dramatic. The K^+ salt of the polymer in the absence of added counterion is largely helical at 4 °C and still extensively structured at 40 °C (Figure 2). In 0.1 M KCl the thermal transition is highly cooperative ($\sigma = 8$ °C) with $T_m = 58$ °C (Figure 1). This T_m is 30 °C above that in 0.1 M NaCl, and at least 50 °C above that in 0.1 M LiCl. These results may be compared with differences of less than ~5 °C in T_m of double helical polynucleotides in 0.1 M solutions of the different alkali metal ions.[7-9]

Experiments with low concentrations of K^+ (0.02–0.0026 M) and a higher constant concentration of Li^+ (0.21 M) showed that K^+ controlled the formation of a stable helix with a cooperative transition (Figure 1). For 0.01, 0.005, and 0.0026 M KCl, $T_m = 46$, 43, and 36 °C, respectively, in 0.2 M Li^+. From these results we conclude that Li^+ and K^+ (at high ratios of Li^+ to K^+) have their effects at different binding sites, the former satisfying the electrostatic screening requirements of helix formation and the latter complexing at specific, size-selective binding sites (see below). With all sites occupied, the helix would have an axial channel filled with K^+ ions separated