tion of **20** with selenium dioxide in aqueous dioxane provided the known[6a] diosphenol **21** in 30% yield. The diosphenol **21** was heated to 155° for 1 hr with hydrazine hydrate in diethylene glycol. The product, separated on alumina, consisted of lycopodine (**1**, 26%), anhydrodihydrolycopodine (**22**, 40%), which is also a naturally occurring *Lycopodium* alkaloid,[8] and dihydrodeoxylycopodine[6a] (**1**, C=O replaced by CH_2, ~10%). Since lycopodine has been transformed into annofoline[9] and into alkaloid L.20[6b] this synthesis also represents, in a formal sense, a synthesis of these alkaloids.[10]

Acknowledgment. We wish to express our thanks to the National Research Council of Canada for supporting this study. We also thank J. F. McCutcheon and A. C. Soper for their help in various phases of this work.

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(9) W. A. Ayer, D. A. Law, and K. Piers, *Tetrahedron Letters*, 2959 (1964).

(10) G. Stork, R. A. Kretchmer, and R. H. Schlessinger, *J. Am. Chem. Soc.*, **90**, 1647 (1968), have also completed a synthesis of *dl*-lycopodine. Simultaneous publication has been arranged.

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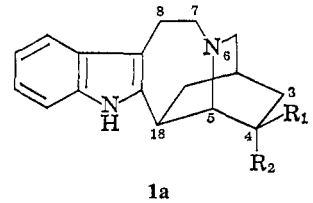
Received December 22, 1967

A Stereochemically Controlled Total Synthesis of *dl*-Ibogamine and *dl*-Epiibogamine

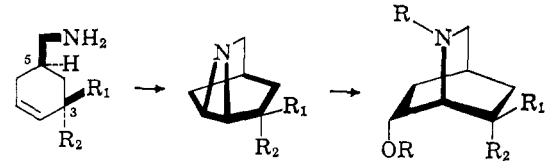
Sir:

A recent communication[1] on the stereocontrolled total synthesis of *dl*-ibogamine prompted us to disclose our own total synthesis of *dl*-ibogamine (**1a**) and *dl*-epiibogamine (**1b**).[2,3] Our synthesis is also stereochemically controlled, proving the assigned configurations of the ethyl side chains as depicted in **1a** and **1b**.

As was the case in our previous synthesis[4] of the alkaloid skeleton (desethylibogamine), the key reaction steps of the present synthesis comprise one-step conversion of *cis*- and *trans*-3-ethyl-5-aminomethylcyclohexenes (**2a,b**) into the bridged aziridines **3a,b** and cleavage of them to the isoquinuclidines **4a,b**.[4,5] For stereoselective synthesis of **2a**, the known compound **5a**,[6] after conversion into the tetrahydropyranyl ether **5b**[7] (83%), bp 123–129° (0.8–0.9 mm), was reduced with $LiAlH_4$ to **6a** (91%), bp 130–134° (0.5 mm), which on vinylation [**6b** (80% based upon the consumed **6a**), bp 110–115 (0.1 mm)] followed by pyrolysis[8] gave the aldehyde **7a**. The crude **7a** underwent the Huang-Minlon reduction giving **7b** (69% over-all yield from **6b**), bp 123–130° (6 mm), which on hydrolysis [**7c**, bp 97–100° (6 mm)] followed by tosylation (**7d**) and the Gabriel amination was transformed into pure **2a** in 67% over-all yield [**2a**, bp 104–106° (34 mm); picrate mp 153–154.5°]. The *cis* configuration in **2a** was based on the following evidence. On careful oxidation[9] followed by oximination and dehydration, **7c** was converted into the olefinic *cis*-nitrile **7e**,[10] bp 115–118° (32 mm), which was hydrogenated to *cis*-3-ethylcyclohexane-1-carbonitrile, bp 130° (bath temperature, 38 mm), identical with an authentic sample,[11] and reduced with $LiAlH_4$ to the amine **2a** identical with that prepared as described earlier. For the preparation of **2b**, the known compound **8a**[12] was reduced ($LiAlH_4$) giving **8b** (84%, *p*-

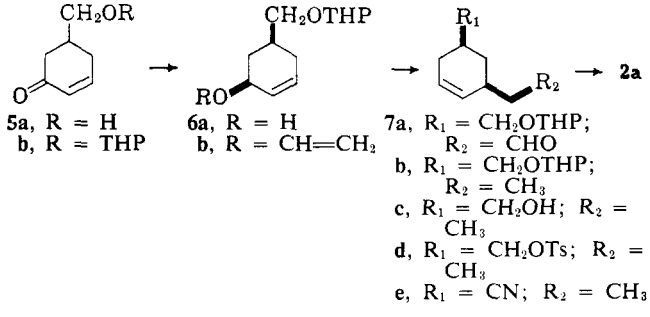


1a
b

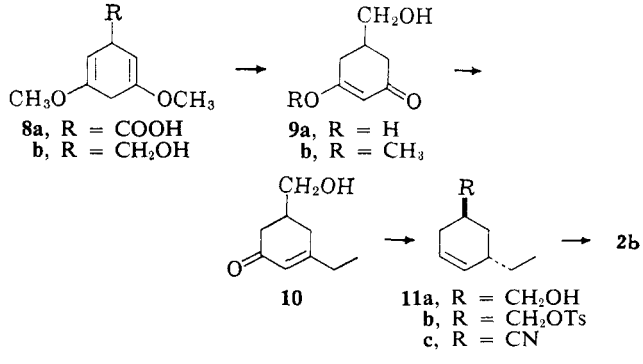


2a **3a** **4a** R = β-indolylacetyl
b **b** **b**

a, $R_1 = C_2H_5$; $R_2 = H$
b, $R_1 = H$; $R_2 = C_2H_5$



5a, R = H; **b**, R = THP
6a, R = H; **b**, R = $CH{=}CH_2$
7a, $R_1 = CH_2OTHP$; $R_2 = CHO$
b, $R_1 = CH_2OTHP$; $R_2 = CH_3$
c, $R_1 = CH_2OH$; $R_2 = CH_3$
d, $R_1 = CH_2OTs$; $R_2 = CH_3$
e, $R_1 = CN$; $R_2 = CH_3$



8a, R = COOH; **b**, R = CH_2OH
9a, R = H; **b**, R = CH_3
10
11a, R = CH_2OH; **b**, R = CH_2OTs; **c**, R = CN

(1) S. I. Sallay, *J. Am. Chem. Soc.*, **89**, 6762 (1967).

(2) The work was presented at the 11th National Symposium on the Chemistry of Natural Products, Oct 9, 1967, Kyoto, Japan. See the Abstracts, p 41.

(3) For previously reported total syntheses, see (a) G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Am. Chem. Soc.*, **87**, 2073 (1965); **88**, 3099 (1966); (b) J. P. Kutney, W. J. Cretney, P. Le Quesne, B. McKague, and E. Piers, *ibid.*, **88**, 4756 (1966). The formulas are shown in their absolute configuration. *Cf.* J. P. Kutney, R. T. Brown, and E. Piers, *Can. J. Chem.*, **44**, 637 (1966), and ref 3a.

(4) W. Nagata, S. Hirai, K. Kawata, and T. Okumura, *J. Am. Chem. Soc.*, **89**, 5046 (1967).

(5) W. Nagata, S. Hirai, K. Kawata, and T. Aoki, *ibid.*, **89**, 5045 (1967).

(6) E. E. Van Tamelen and G. T. Hildahl, *ibid.*, **78**, 4405 (1956).

(7) Satisfactory elemental analyses were obtained for all the compounds for which melting point or boiling point values are given. All the compounds cited showed reasonable spectral data.

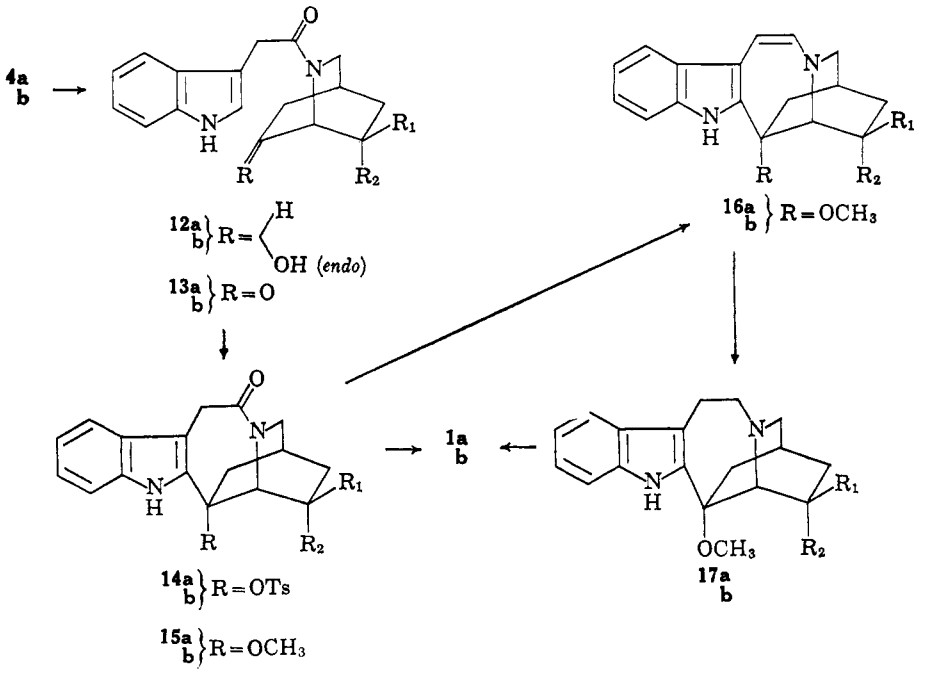
(8) A. W. Burgstahler and I. C. Nordin, *J. Am. Chem. Soc.*, **83**, 198 (1961).

(9) K. E. Pfitzner and J. G. Moffat, *ibid.*, **85**, 3027 (1963); **87**, 5661, 5670 (1965).

(10) Separation of the *cis* and *trans* isomers by glpc was effective only for the olefinic nitriles **7e** and **11c**. This is the reason for this transformation.

(11) Preparation of the authentic sample will be described in a full paper.

(12) A. J. Birch, P. Hextall, and S. Sternkell, *Australian J. Chem.*, **7**, 256 (1954).



a, $R_1 = C_2H_5$; $R_2 = H$
b, $R_1 = H$; $R_2 = C_2H_5$

nitrobenzoate mp 101–103°), which on hydrolysis (**9a**) followed by methylation gave **9b** (41% from **8b**), mp 71–72.5°. Treatment of **9b** with ethylmagnesium bromide gave **10** (68%), which underwent the Wolff–Kishner reduction giving crude **11a** (65%), bp 85–90° (5 mm). This crude material was found to be contaminated with *ca.* 25% of the *cis* isomer **7c** from glpc[10] of the corresponding olefinic nitrile **11c**. Basic treatment of a pure sample of **11c**, bp 118–121° (32 mm), obtained by preparative glpc, gave a 6:5 equilibrium mixture of **7e** and **11c**, and this fact proves the *trans* configuration of the latter. Reduction ($LiAlH_4$) of pure **11c** gave the *trans* amine **2b**, bp 101–104° (30 mm); picrate mp 158–159.5°. From the preparative viewpoint, the crude material of **11a** was used for transformation into crude **2b** (*ca.* 75% purity, 58% over-all yield), bp 95–98° (24 mm), by tosylation (**11b**) and subsequent Gabriel amination.

Compounds **2a** and **b** were oxidized with lead tetraacetate[5] giving the bridged aziridines **3a,b** (**3a**: picrate mp 152–154°, flavianate mp 173–176°; **3b**: picrate mp 142–144°, flavianate mp 167–169°), which without purification were cleaved with β-indolylacetic anhydride to give **4a,b**. On alkaline hydrolysis, the last compounds were led to the crystalline **12a,b** (33 and 20% over-all yield from **2a,b**, respectively) (**12a**: mp 206–208°; **12b**: mp 193–196°), which on oxidation by the Oppenauer method or, better, with dimethyl sulfoxide and acetic anhydride[13] were converted into the keto lactams **13a,b**. Cyclization of **13a** and **13b** without rearrangement was effected by refluxing (5–10 min) the benzene solution in the presence of 1.3–1.5 molar equiv of *p*-toluenesulfonic acid to give the lactam tosylates **14a,b** (**14a**: amorphous; **14b**: mp 175–178°) which were converted[4] into the methoxy lactams **15a,b** (30 and 34% over-all yield from **12a,b**, respectively) (**15a**: mp 283–285°; **15b**: mp 275–278°) Reduction of **15a** and **15b** with $LiAlH_4$ gave carbinolamines which without purification were dehydrated with alumina to the enamines **16a** (40%) and **16b** (32%) (**16a**: mp 185–187°, λ_{max}^{EtOH} 235 (ε 25,200), 285 mμ (ε 14,100); **16b**: mp 178–182°, λ_{max}^{EtOH} 234.5 (ε 21,100), 244 (shoulder), 285 mμ (ε 12,500). Catalytic hydrogenation of **16a,b** gave methoxyibogamine (**17a**; 55%) and methoxyepiibogamine (**17b**; 67%) (**17a**: mp 152–154°; **17b**: mp 144–147°), which were reduced[14] smoothly to *dl*-ibogamine (**1a**) and *dl*-epiibogamine (**1b**) (**1a**: mp 127–128°; **1b**: mp 196.5–197.5°). The samples of **1a** and **1b** were proven to be identical with authentic samples of *dl*-ibogamine and *dl*-epiibogamine (mixture melting point, infrared spectra, and tlc).[15] The present synthesis is parallel to our previous skeleton synthesis,[4] confirming the correctness of the latter synthesis and of the synthesis reported by Huffman and his coworkers.[16] *dl*-Ibogamine (**1a**) was directly obtained together with the unstable enamine **16a** (R = H instead of OCH_3) by diisobutylaluminum hydride reduction of the lactam tosylate **14a**. Conversion of this enamine into **1a** is currently being studied.

(13) J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **89**, 2416 (1967).

(14) *Cf.* G. Büchi and R. E. Manning, *ibid.*, **88**, 2532 (1966).

(15) The authors wish to express their sincere thanks to Professor G. Büchi for his courtesy in providing an authentic sample of *dl*-ibogamine and performing the identification of *dl*-epiibogamine.

(16) J. W. Huffman, C. B. S. Rao, and T. Kamiya, *J. Am. Chem. Soc.*, **87**, 2288 (1965); *J. Org. Chem.*, **32**, 697 (1967).

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A New Convenient Reagent for Peptide Syntheses

Sir:

The preparation and biological activity of the pseudobase N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline