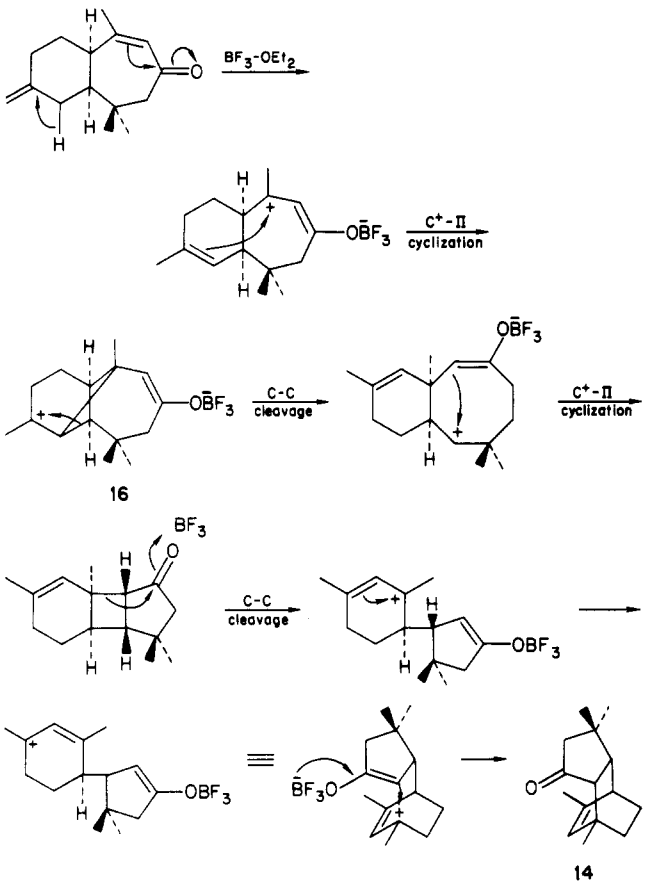
Scheme III



till it finds its sink in stable **14**.

Experimental Section

BF_3–OEt_2-Catalyzed Rearrangement of 7. A mixture of bicyclic ketone **7** (0.5 g) and BF_3–OEt_2 (0.6 mL) in 30 mL of dry benzene was refluxed with stirring. After 30 h, the reaction mixture was quenched with ice-cold saturated sodium carbonate (20 mL). Separation of the benzene layer, washing with brine, and removal of solvent furnished 0.5 g of an oily residue. This material was adsorbed on a silica gel (20 g) column and chromatographed. Elution with benzene–pentane (1:4) afforded 0.29 g (58%) of pure tricyclic ketone **14**: bp 90–95 °C (0.6 torr); $[\alpha]^{25}_D$ +260° ($CHCl_3$); IR (neat) 1730 (s), 1640 (w), 1405 (m), 1370 (m), 1360 (m), 1280 (m), 1220 (m), 1175 (s), 1120 (m), 790 (s) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 5.6 (1 H, br t), 2.67 (1 H, m), 2–2.4 (2 H, m), 1.90 (3 H, d, J = 2 Hz), 1.75 (2 H, m), 1.1–1.6 (4 H, m), 1.30 (3 H, s), 1.15 (3 H, s), 0.91 (3 H, s); ^{13}C NMR (22.63 MHz, $CDCl_3$) δ 220.4 (s), 141.0 (s), 130.3 (d), 58.1 (d), 53.5 (t), 51.99 (d), 37.6 (2 C, s), 37.3 (d), 33.3 (t), 31.9 (q), 28.5 (t), 25.3 (q), 22.9 (q), 20.7 (q); MS (70 eV), m/e (relative intensity) 218 (M^+, 4.9), 190 (M – CO, 14.8) 108 (C_8H_{12}, 43.2), 106 (C_8H_{10}, 1,3-dimethyl benzene, 100), 93 ($C_7H_9^+$, 32.1), 91 ($C_7H_7^+$, 41.3), 79 (11), 77 (16), 57 (25.9).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.56; H, 10.09. Found: C, 82.25; H, 10.0.

A portion of the above ketone **14** was converted to the semicarbazone derivative by the pyridine method, and recrystallization from ethanol furnished colorless crystals, mp 229–230 °C.

Anal. Calcd for $C_{16}H_{25}N_3O$: C, 69.81; H, 9.09; N, 15.27. Found: C, 70.16; H, 9.26; N, 15.47.

Crystal Data for 13. The 2,4-dinitrophenylhydrazone derivative **13** of **14** was prepared according to standard procedure, and crystals for X-ray studies were grown from acetonitrile: mp 163–64 °C; $C_{21}H_{26}N_4O_4$; a = 6.933 (1) Å, b = 7.933 (4) Å, c = 18.832 (2) Å, β = 93.75 (11)°; space group P_21; Z = 2, DC = 1.28 g cm^{-3}, Mo Kα radiation, λ = 9.70926 Å, μ = 0.54 cm^{-1}. Of the 1759 unique reflections recorded, 1482 had $I > 3(I)$. The data were collected on a CAD-4 four-circle diffractometer, and the structures were solved by automatic centrosymmetric direct methods and refined by large-block least squares. The final refinement converged at R = 0.0491.[10]

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Registry No. **7**, 51704-15-5; **8**, 97059-12-6; **9**, 51704-14-4; **13**, 96999-76-7; **14**, 96999-75-6.

(10) Further details on the X-ray crystal structure work can be obtained from the Dalhousie University group.

Communications

Total Synthesis of (±)-Catharanthine

Summary: A total synthesis of (±)-catharanthine is detailed.

Sir: Catharanthine (**1**), an *Iboga* alkaloid isolated from *Catharanthus roseus*, is an important synthetic target[1] since it is now possible to prepare the clinically useful cancer chemotheraputic dimeric *Catharanthus* alkaloids[2] vinblastine and vincristine by the coupling of catharanthine *N*-oxide with vindoline and subsequent functional group manipulation.[3]

We report a short total synthesis of (±)-catharanthine which features as key steps the formation of **4** by the Diels–Alder reaction of 1-carbomethoxy-5-ethyl-1,2-dihydropyridine (**2**)[4] with **3**, and the photochemical cyclization[5] of the α-chloro ester **7** to the pentacyclic compound

(1) Previous total syntheses of (±)-catharanthine: (a) Buchi, G.; Kulsa, P.; Ogasawara, K.; Rosati, R. *J. Am. Chem. Soc.* **1969**, *92*, 999. (b) Marazano, C.; LeGoff, M. T.; Fourrey, J. L.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1981**, 389. Relay synthesis: (c) Kutney, J. P.; Bylsma, F. *Helv. Chim. Acta* **1975**, *58*, 1672. Formal total syntheses: (d) Trost, B. M.; Godleski, S. A.; Belletire, J. L. *J. Org. Chem.* **1979**, *44*, 2052. (e) Imanishi, T.; Shin, H.; Yagi, N.; Hanaoka, M. *Tetrahedron Lett.* **1980**, *21*, 3285.

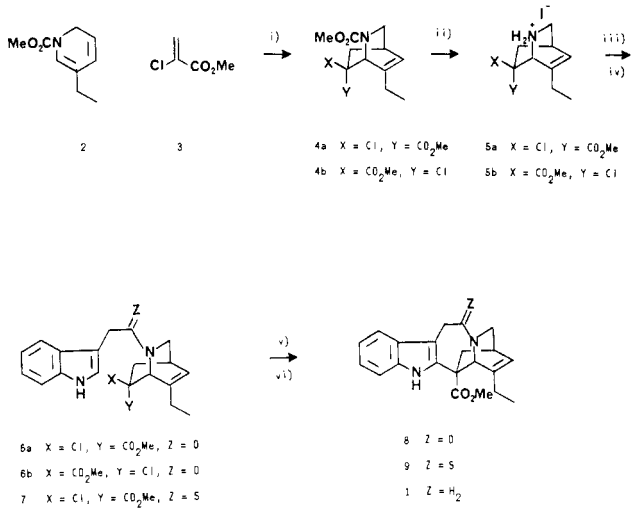
(2) (a) Neuss, N.; Johnson, I. S.; Armstrong, J. G.; Jansen, C. J. *Adv. Chemother.* **1964**, *1*, 133. (b) Taylor, W. I.; Farnsworth, N. R. "The Catharanthus Alkaloids": Marcell Dekker: New York, 1975. (c) Gerzon, K. In "Anticancer Agents Based on Natural Products Models", Medicinal Chem.; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1981; Vol. 16. (d) Jewers, K. *Progr. Drug Res.* **1981**, *25*, 275. (e) "Antineoplastic Agents"; Remers, W. A., Ed.; Wiley: New York, 1984.

(3) Reviews: (a) Kutney, J. P. *Lect. Heterocycl. Chem.* **1978**, *4*, 59. (b) Potier, P. *J. Nat. Prod. (Lloydia)* **1980**, *43*, 72. (c) Lounasmaa, M.; Nemes, A. *Tetrahedron* **1982**, *38*, 223.

(4) Raucher, S.; Lawrence, R. F. *Tetrahedron Lett.* **1983**, *24*, 2927.

0022-3263/85/1950-3236$01.50/0

Scheme I[a]



[a] (i) 2 equiv of **3**, 5 mol % hydroquinone, 90 °C, 22 h, 2.5 M in toluene; (ii) 2.2 equiv of $Me_3SiSiMe_3$, 1.1 equiv of I_2 120 °C, 15 min; **4**, 25 °C, 20 h; excess MeOH; (iii) 2.2 equiv of *O,N*-bis(trimethylsilyl)acetamide, 0 °C, 30 min, CH_2Cl_2; 1.2 equiv of indole-3-acetyl chloride, 25 °C, 2.5 h; (iv) 0.8 equiv of Lawesson's reagent, 65 °C, 1 h, 0.1 equiv of HCl, 65 °C, 3 h; (v) irradiation of 8×10^{-4} M solution of **7** in CH_3CN/H_2O (30:70) containing $NaHCO_3$ (20 equiv) with a 450-W Hanovia mercury lamp/Pyrex filter, 6 h; (vi) 1.3 equiv of Et_3OBF_4, CH_2Cl_2, 0 to 25 °C, 45 min; 5 equiv of $NaBH_3CN$, 5 equiv of HOAc, MeOH, 0 to 25 °C, 5 h.

9 (Scheme I).

Diels–Alder reaction of **2**, available in five steps and 63% overall yield from 3-ethylpyridine,[4] and methyl α-chloroacrylate (**3**) gave a 1:1.4 mixture of the isomers **4a** and **4b** in 96% yield.[6] Although it is possible to separate **4a** and **4b** by careful flash chromatography,[7] and thus assign stereochemistry,[8] this separation is unnecessary for the synthesis of **1**. Treatment of the mixture of **4a** and **4b** with excess freshly prepared trimethylsilyl iodide[9] gave a mixture of **5a** and **5b** which was reacted without purification first with *O,N*-bis(trimethylsilyl)acetamide[10] and then with indole-3-acetyl chloride[11] to provide the indoles **6a** and **6b** as a 1:1.4 mixture of isomers in 97% overall yield from **4**. The above transformations were also carried out on pure samples of **4a** and **4b** in order to obtain pure samples of **6a** and **6b**. Solutions of pure **6a** or **6b** in $CDCl_3$ were found to equilibrate to a 1:1 mixture of **6a** and **6b** when exposed to catalytic amounts of anhydrous HCl.

Numerous attempts to effect photochemical cyclization[5] by irradiation of dilute solutions of **6a** or **6b** (or mixtures of **6a** and **6b**) in $MeOH/H_2O$ or CH_3CN/H_2O containing $NaHCO_3$ under argon with a 450-W Hanovia mercury lamp, with or without Pyrex or Vycor filters, afforded only trace amounts of **8**, despite the fact that the corresponding 20-deethyl compound (mixture of endo/exo isomers) provides 5-oxo-20-deethylcatharanthine in moderate yield under these reaction conditions.[12]

The isomer **6a** could be readily converted to the thioamide **7** in 85% yield by treatment with Lawesson's reagent;[13] in contrast, **6b** could not be converted to a thioamide with either Lawesson's reagent or P_2S_5. However, when a 1:1.4 mixture of the isomers **6a** and **6b** was reacted with Lawesson's reagent in dimethoxyethane containing a catalytic amount of anhydrous HCl, the thioamide **7** was obtained in 70% yield, presumably via isomerization of **6b** to **6a** and subsequent thionation.

Irradiation of an 8×10^{-4} M solution of the thioamide **7** in CH_3CN/H_2O (30:70) containing $NaHCO_3$ under argon with a 450-W Hanovia mercury lamp with a Pyrex filter for 6 h provided **9** in 30% crude yield. The thiolactam **9** was reduced[14] without further purification by treatment with Et_3OBF_4 followed by $NaBH_3CN$ to provide (±)-catharanthine (**1**) in 21% overall yield from **7**.

This synthesis of (±)-catharanthine requires a total of 11 steps and proceeds in an overall yield of 9% from commercially available 3-ethylpyridine. We are currently pursuing an enantioselective synthesis of (+)-catharanthine through the use of chiral auxiliaries in the Diels–Alder reaction.

Acknowledgment. We thank Professor J. P. Kutney (University of British Columbia) for providing us with an authentic sample of (+)-catharanthine and Professor R. J. Sundberg (University of Virginia) for providing us with a sample of 5-oxo-20-deethylcatharanthine. This investigation was supported by PHS Grant Number CA-32976, awarded by the National Cancer Institute, DHHS. MS data were obtained on a VG 7070 GC/MS and associated VG 2035F/B data system funded by NIH Biomedical Research Development Grant 1 508 RR 09082.

(5) α-Chloroacetamide photocyclization review: (a) Sundberg, R. J. "Organic Photochemistry"; Padwa, A., Ed.; Marcel Dekker: New York, 1983; Vol. 6. Synthesis of 20-deethylcatharanthine: (b) Sundberg, R. J.; Bloom, J. D. *Tetrahedron Lett.* **1978**, 5157. (c) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1980**, *45*, 3382.

(6) All new compounds gave spectra in accord with their proposed structures. Elemental compositions were determined by high resolution mass spectroscopy. **6**: HREIMS calcd for $C_{21}H_{23}ClN_2O_3$ 386.1395 (^{35}Cl), found 386.1367. **7**: HREIMS calcd for $C_{21}H_{23}ClN_2O_2S$ 402.1166 (^{35}Cl), found 402.1155. **9**: HREIMS calcd for $C_{21}H_{22}N_2O_3$ 366.1399, found 366.1386. **1**: HREIMS calcd for $C_{21}H_{24}N_2O_2$ 336.1838, found 336.1839.

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(8) For the assignment of stereochemistry of carbomethoxy groups at the 7-position of 2-azabicyclo[2.2.2]oct-5-ene derivatives, see: Lawrence, R. F. Ph.D. Thesis, University of Washington, 1984.

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(10) The *O,N*-bis(trimethylsilyl)acetamide functions as an acid scavenger in this reaction, and the acylation may proceed via the *N*-silylamine corresponding to **5**. For the use of *O,N*-bis(trimethylsilyl)acetamide in the formation of carbamates from amines and alkyl chloroformates, see: Raucher, S.; Jones, D. S. *Synth. Commun.*, in press.

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(14) Raucher, S.; Klein, P. *Tetrahedron Lett.* **1980**, *21*, 4061. Also see, ref 5b,c.

(15) Fellow of the Alfred P. Sloan Foundation (1980–1984). Recipient of NIH Research Career Development Award CA 00864 (1983–1988).

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Efficient Asymmetric Reduction of Acyl Cyanides with *B*-3-Pinanyl-9-BBN (Alpine-Borane)

Summary: Acyl cyanides are effectively reduced to optically active β-amino alcohols by using Alpine-Borane followed by sodium borohydride/cobaltous chloride.

Sir: The trialkylborane *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane[1]) is an effective asymmetric

0022-3263/85/1950-3237$01.50/0