In general, our experience in the present work as well as for work in progress[13] would indicate most acidities in THF usually correspond reasonably well with those reported in Me_2SO. Perhaps the most important contribution of the data in THF is that when differences do occur it is the THF data that have direct application to synthetic problems.

The last compound in Table I, *N*-isopropylcyclohexanone imine, was found to have a p*K* of 31.3. Thus, for other imines whose p*K*'s have been previously measured relative to this imine[5] the values range from 28.9 for the benzylimine of acetone to 33.1 for the isopropyl imine of 3-pentanone. These data and the known effects of α-alkyl groups on decreasing acidity[5] would suggest that ketimines derived from branched ketones require LTMP to ensure complete deprotonation in a synthetic operation.

Experimental Section

The preparation of samples for ^{13}C NMR was the same as given in the following example except those few cases in which a second carbon acid rather than an amine was used as the reference acid.

Each sample was prepared in a 10-mm septum-capped NMR tube (Wilmad Glass, Buena, NJ) fitted with an argon inlet and outlet. To a solution of 1.5 mequiv of amine in 2 mL of freshly distilled THF at 0 °C was added 1.5 mequiv of methyllithium in ether. After 15 min, a solution of 1.5 mequiv of hydrocarbon in 1 mL of THF was added at 0 °C. The cap was wrapped in parafilm and the tube then warmed and transferred to the probe of a Varian FT-80 NMR spectrometer operating at 27 °C. Spectra were accumulated using a small pulse angle (30°) and a 2-s repetition rate. That differential relaxation times were unimportant was shown by extending repetition rate to 3 s without affecting integral ratios. Other factors of quantitative influence, such as differential NOE's, were eliminated by using an empirically derived correction factor. For example, this factor applied to the methylene signals of TMP and LTMP was arried at by measuring the integral for TMP prior to then after the addition of 0.5 equiv of methyllithium, as well as that of the LTMP produced (both relative to naphthalene present as an internal standard). We estimate the accuracy of all *K*'s to be ±30%, leading to an uncertainty in ΔpK of ±0.2 p*K* units or less.

Metalation of each hydrocarbon was shown to occur without decomposition or rearrangement by quenching the anion and recovering pure starting material as established by NMR and GC analysis. The site of metalation was, in each instance, clearly indicated by comparison of the ^{13}C shifts for each lithiated compound with its starting material. This ^{13}C shift data appear below. Some of the assignments for the lithio derivatives should be considered as tentative. They have been made on the basis of previously reported lithiation shifts for 2- and 4-picolyl anions[14] as well as by assuming the phenyl substituent effect in diphenylmethane vs. toluene[15] would be similar in the picolines. The less certain assignments are presented in square brackets.

^{13}C Chemical Shifts (in ppm from Me_4Si, Using the α-Carbon of THF 69.0 ppm). 4-Picoline: 151.0 (C_2), 126.2 (C_3) 149.3 (C_4), 20.2 (CH_3). Lithio derivative: 144.6 (C_2), 110.8 (C_3), 149.2 (C_4), 69.0 (CH_2). 3-Picoline: 151.9 (C_2), 134.4 (C_3), 137.4 (C_4), 124.5 (C_5), 148.6 (C_6), 19.2 (CH_3). Lithio derivative: 140.9 (C_2), [138.2] (C_3), 94.2 (C_4) [139.0] (C_5) 102.4 (C_6), 45.2 (CH_2). 2-Picoline: 160.0 (C_2), 124.2 (C_3), 137.2 (C_4), 121.7 (C_5), 150.8 (C_6), 20.2 (CH_3). Lithio derivative: 165.5 (C_2), 116.8 (C_3), 132.4 (C_4), 98.3 (C_5), 149.3 (C_6), 57.3 (CH_2). 4BP: 151.6 (C_2), 125.5 (C_3), 151.6 (C_4), 42.4 (CH_2), 140.1, 130.6, 130.1, 128.0, (phenyl group). Lithio derivative: 144.5, 147.2 (C_2 and C_6 nonequivalent), 116.2, 115.9 (C_3 and C_5), 144.8 (C_4), 88.6 (CH), 146.9, 128.7, 123.3, 107.4 (phenyl group). 3BP: 151.9 (C_2), 138.2 (C_3), 137.2 (C_4), 124.7 (C_5), 149.2 (C_6), 40.4 (CH_2), 142.1, 130.4, 130.1, 127.8 (phenyl group). Lithio derivative: 143.0 (C_2), 125.5 (C_4), 123.5 (C_5), 80.8 (CH), 147.4, 128.8, 120.2, 111.6 (phenyl group). 2BP: 162.6 (C_2), 124.1 (C_3), 137.4 (C_4), 122.3 (C_5), 150.7 (C_6), 46.1 (CH_2), 141.4, 130.4, 129.7, 127.4 (phenyl group). Lithio derivative: 159.4 (C_2), 114.7 (C_3, 134.0 (C_4), 101.4 (C_5) 149.3 (C_6), 86.3 (CH), 147.0, 129.2, 121.5, (phenyl group). Xanthene (see Table I for numbering): 124.5 (C_1), 129.1 (C_2), 122.3 (C_3), 130.5 (C_4), 117.8 (C_5), 153.7 (C_6), 29.1 (CH_2). Lithio derivative: 151.4 (C_1), 111.9 (C_2), 125.1 (C_3), 110.4 (C_4), 113.2 (C_5), 143.2 (C_6), 63.2 (CH). Benzhydryl phenyl sulfide: 143.1, 129.9, 130.3, 128.6 (benzhydryl), 58.7 (CH), 138.7, 130.1, 131.9, 127.9 (phenyl). Lithio derivative: 150.9, 121.4, 128.2, 112.2 (benzhydryl), 63.1 (quaternary), 128.6, 125.7, 122.5 (phenyl). The shifts for fluorenyllithium and for the lithiated ketimines have been reported previously.[16,17]

Registry No. 4BP, 2116-65-6; 4BP (lithio deriv), 81771-00-8; 3BP, 620-95-1; 3BP (lithio deriv), 97254-18-7; 2BP, 101-82-6; 2BP (lithio deriv), 56501-99-6; TMP, 768-66-1; TMP (lithio deriv), 38227-87-1; DA, 108-18-9; DA (lithio deriv), 4111-54-0; $[(CH_3)_3Si]_2NH$, 999-97-3; $[(CH_3)_3Si]_2NH$ (lithio deriv), 4039-32-1; $C_6H_8{=}NCH(CH_3)_2$, 13652-31-8; $C_6H_8{=}NCH(CH_3)_2$ (lithio deriv), 97254-20-1; *i*-Pr-NH-Pr-*i*, 5577-67-3; *i*-Pr-NH-Pr-*i* (lithio deriv), 18270-42-3; $(CH_3)_2CHNHSi(CH_3)_3$, 5577-65-1; $(CH_3)_2CHNHSi(CH_3)_3$ (lithio deriv), 42423-10-9; 4-picoline, 108-89-4; 4-picoline (lithio deriv), 26954-25-6; 3-picoline, 108-99-6; 3-picoline (lithio deriv), 26954-24-5; 2-picoline, 109-06-8; 2-picoline (lithio deriv), 1749-29-7; xanthene, 92-83-1; xanthene (lithio deriv), 40102-97-4; benzhydryl phenyl sulfide, 21122-20-3; benzhydryl phenyl sulfide (lithio deriv), 81771-01-9; 4-methylquinoline, 491-35-0; 4-methylquinoline (lithio deriv), 97254-19-8; fluorene, 86-73-7; fluorene (lithio deriv), 881-04-9.

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(17) Fraser, R. R.; Chuaqui-Offermanns, N. *Can. J. Chem.* **1981**, *59*, 3007.

An Apparent, Deep-Seated, Carbonium-Ion-Mediated Sesquiterpene Rearrangement

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The bicyclic cation **1**, based on a himachalane-type carbon skeleton and readily derivable from *cis,trans*-farnesyl pyrophosphate **2**, has long been recognized as the biogenetic progenitor of a variety of bi- and tricyclic sesquiterpenoid carbon skeletons.[1] Among notable natural products derived from **1** are longifolene (**3**)[2], α-longipinene (**4**)[3], vulgarone (**5**)[4], and allohimachalol (**6**)[5] (Scheme I). The biomimetic cationic cylization of **1** or a derivative, therefore, presents interesting possibilities, but much effort in this direction has not been forthcoming, due perhaps, to the relative inaccessibility of **1** in its correct stereochemical form.[6] In this note, we delineate on the fate of a derivative of **1**, which after initially taking a biomimetic route to longipinene system (**4**), charters an unanticipated

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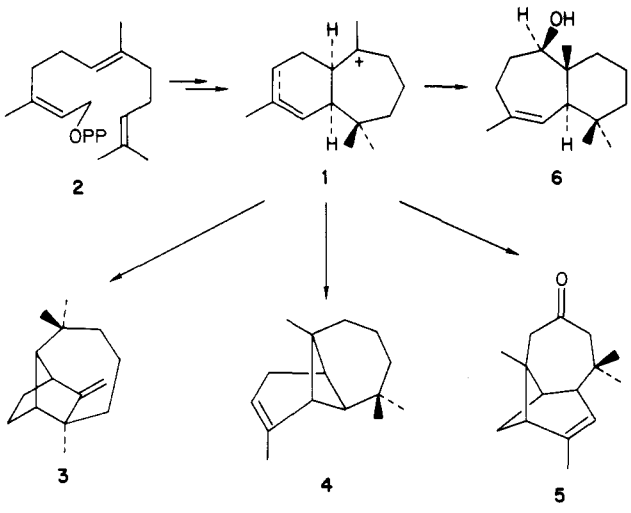
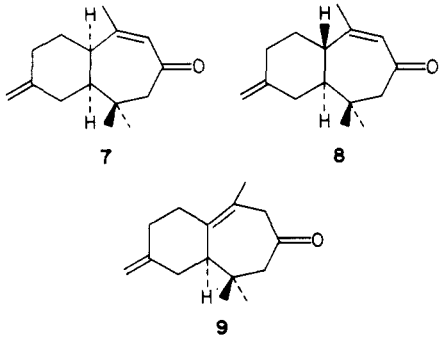
Scheme I

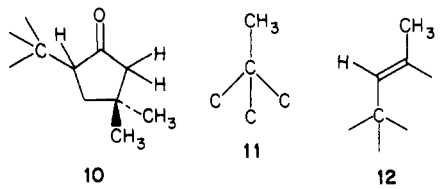


course and unfolds a series of fascinating carbonium ion rearrangements.

Sometime back, in connection with our synthesis of himachalene sesquiterpenes, we had reported[7,8] the preparation of optically active cis bicyclic enone **7** and showed



that it could be readily equilibrated with its trans isomer **8** and β,γ-unsaturated isomer **9**. In order to effect biomimetic cyclization of **7**, its reaction with various Lewis acids was explored. When either **7** or more conveniently an equilibrated mixture of **7–9** was exposed to BF_3–OEt_2 in refluxing benzene, a new liquid ketone, $C_{15}H_{22}O$ (M^+ 218), was isolated in 55–60% yield as the only major product of the reaction. Its spectral data revealed the presence of three rings and substructures **10**, **11**, and **12**. The IR



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(4) Uchio, Y.; Matsuo, A.; Nakayama, M.; Hayashi, S. *Tetrahedron Lett.* **1976**, 2963.
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(6) Narula, A. P. S.; Dev, S. *Tetrahedron* **1977**, *33*, 813.
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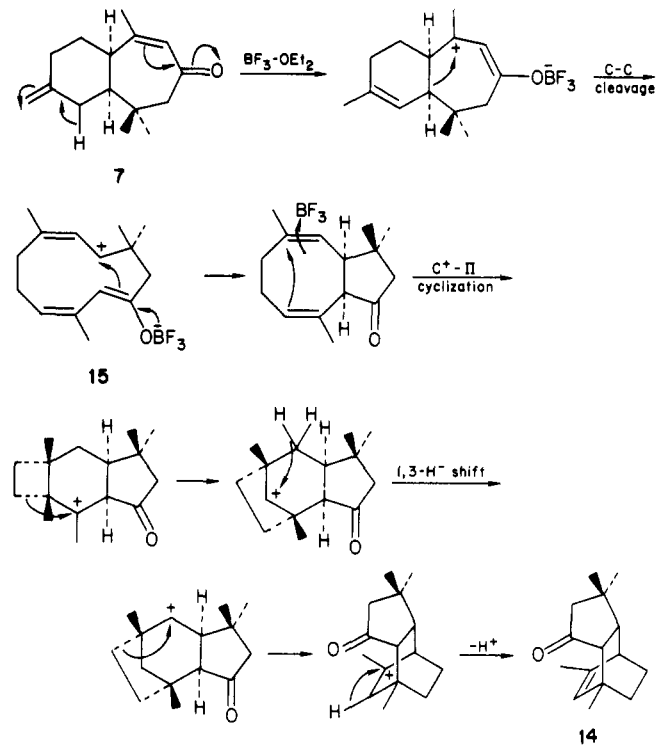
Scheme II



spectrum exhibited an absorption at 1730 cm^{-1} (cyclopentanone), while ^1H NMR [δ 5.6 (br, 1 H), 1.9 (d, J = 2 Hz, 3 H)] and ^{13}C NMR [δ 141.0 (s), 130.3 (d)] spectra showed the presence of only one trisubstituted olefinic linkage. Furthermore, the ^1H NMR spectrum exhibited the presence of three quaternary methyl groups (δ 0.91, 1.15, and 1.30) and three exchangeable (D_2O) protons α to the carbonyl group. Double-resonance experiments and LIS studies fully established the substructures **10–12** in the rearranged product. It was thus clear that a deep-seated structural reorganization had occurred, and this necessitated an unambiguous solution of the structure using singe-crystal X-ray technique. After considerable effort, a crystalline 2,4-dinitrophenylhydrazone derivative **13**, mp 163–164°C, was prepared, and its crystals proved suitable for X-ray diffraction studies. The crystal structure showed it to be the 2,4-DNP derivative of **14**.

The mechanism of formation of rearranged ketone **14** from **7** posed some intriguing possibilities. Our initial hunch was that this rearrangement proceeded through a sequence depicted in Scheme II, involving an 11-membered humulenetype intermediate **15**. The rest of the steps from **15** to **14** bear close resemblance to the pathway through which a variety of carbocyclic systems are derived from humulene, both in vivo and in vitro.[9] However, the rearranged ketone **14** obtained by us was optically active, [α^{25}_D +260° ($CHCl_3$), and this completely ruled out of contention the intermediacy of **15** and the mechanism shown in Scheme II. An alternate mechanism for the genesis of **14** from **7**, which involves a series of cyclization–fragmentation steps, in tandem, is depicted in Scheme III. It is significant that the initial cyclization of cation **16** takes a biomimetic course with the formation of the longipinene-based cation **17**. However, instead of eliminating a proton to give a longipinene derivative, the strained cyclobutylcarbinyl cation **17** rearranges further

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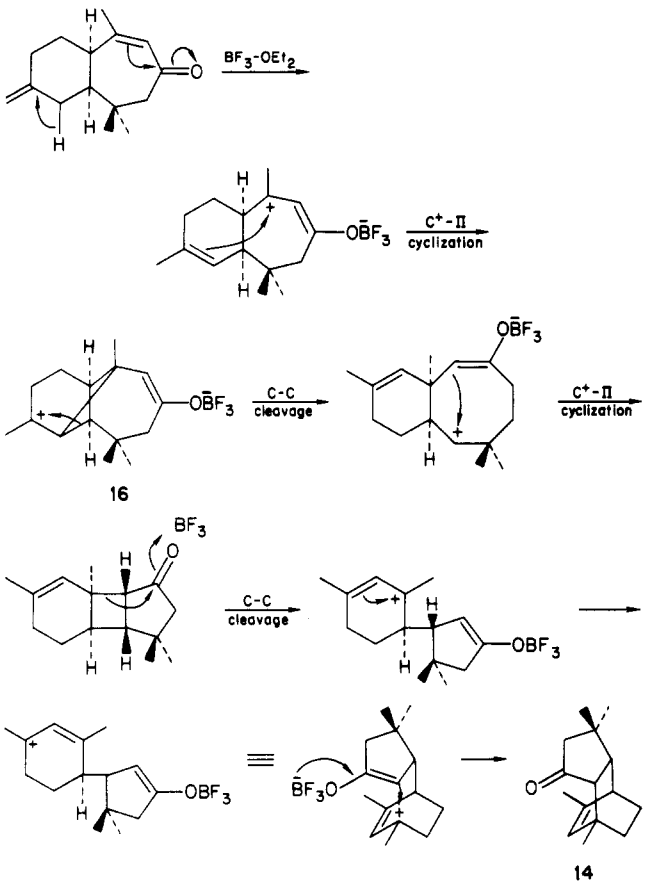
Scheme III



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]

Acknowledgment. We thank Dr. Suresh C. Suri and A. N. Murthy for their help. ^{13}C NMR spectral data were obtained through the kind courtesy of Dr. G. Lukacs, Institut de Chemie des Substances Naturelles, Gif-Sur-Yvette. We thank him for his help.

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.

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

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