A Short Stereospecific Synthesis of *dl*-Lycoramine. Control of Relative Stereochemistry by Dipole Effects

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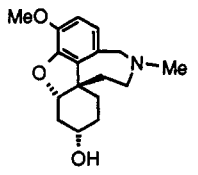
Received August 8, 1991

A distinguishing structural feature of several classes of phenylalanine- and tryptophan-derived alkaloids is the presence of a quaternary carbon bearing a substituted aromatic ring.[1] Establishment of this quaternary center[2] is a critical element in a plan for the chemical synthesis of any of these structurally diverse natural products.

For the morphine and *Amaryllidaceae* alkaloids,[3] an aryl radical cyclization approach seemed potentially well suited to the construction of functionally complex, advanced intermediates.[4] For example, the β,β-disubstituted dihydrobenzofuran structure of lycoramine (1) could be generated by cyclization of an *o*-(allyloxy)phenyl radical (Figure 1) so long as pendant functional groups proved compatible with the reaction conditions.



1

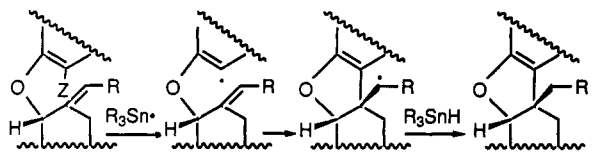
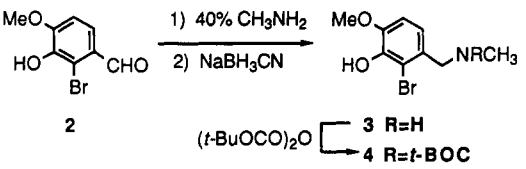


Figure 1.

Scheme I



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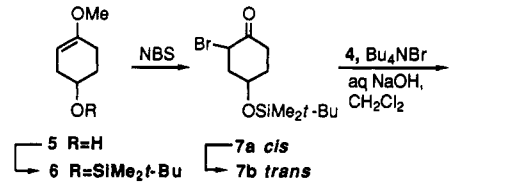
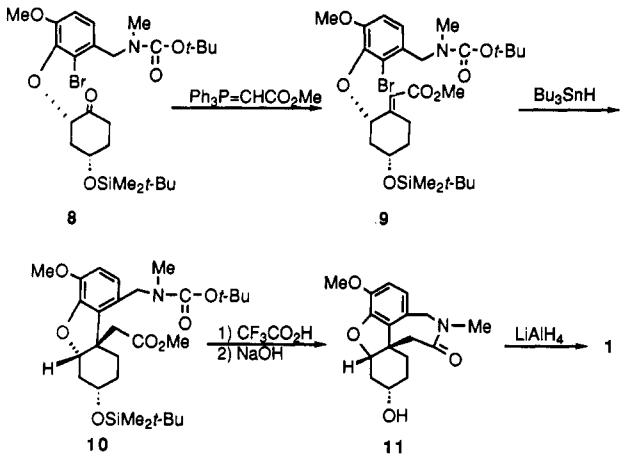
Scheme II





Investigation of this approach has now culminated in a seven-step synthesis of *dl*-lycoramine.[5,6] In this synthesis, the quaternary chiral center is introduced stereospecifically by cyclization of an (allyloxy)aryl radical and the carbinol center is controlled by an electrostatic effect.

Preparation of the cyclization substrate (see **9**) required alkylation of the functionalized phenol **4**,[7] which was easily prepared from bromoisovanillin (**2**) in two steps (Scheme I).

As it has been our experience that phenols are cleanly and efficiently alkylated by α-halo ketones, we sought a 4-oxygenated 2-halocyclohexanone with which to alkylate phenol **4**. Bromo ketone **7b** proved to be both stable and readily accessible (Scheme II).[8]

4-Methoxy-3-cyclohexenol (**5**, from the Birch reduction of *p*-methoxyphenol)[9] was converted to its *tert*-butyldi-

(1) For an excellent survey of alkaloid structures which includes discussions of chemistry, biosynthesis, and pharmacology, see: Cordell, G. A. *Introduction to Alkaloids – A Biogenetic Approach*; Wiley Interscience: New York, 1981. For phenylalanine- and tryptophan-derived alkaloids, see: Chapter 8, pp 275–573, and Chapter 9, pp 574–832.

(2) The general problem of synthesis of systems containing quaternary carbon atoms is the topic of a comprehensive review by Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(3) Recent interest in the *Amaryllidaceae* alkaloids has focussed on the activity of galanthamine as an acetylcholinesterase inhibitor. This class of compounds is considered to have potential in the treatment of the early stages of Alzheimer's disease. See the following: (a) Sweeney, J. E.; Puttfarcken, P. S.; Coyle, J. T. *Pharmacol. Biochem. Behav.* **1989**, *34*, 129. (b) Thomsen, T.; Kewitz, H. *Life Sciences* **1990**, *46*, 1553.

(4) Some model studies have been reported: (a) Parker, K. A.; Spero, D. M.; Van Epp, J. *J. Org. Chem.* **1988**, *53*, 4628. (b) Parker, K. A.; Spero, D. M.; Inman, K. C. *Tetrahedron Lett.* **1986**, *27*, 2833.

(5) For previous syntheses of lycoramine, see: (a) Barton, D. H. R.; Kirby, G. W. *J. Chem. Soc.* **1962**, 806. (b) Misaka, Y.; Mizutani, T.; Sekido, M.; Uyeo, S. *J. Chem. Soc. C* **1968**, 2954. Hazama, N.; Irie, H.; Mizutani, T.; Shingu, T.; Takada, M.; Uyeo, S.; Yoshitake, A. *J. Chem. Soc. C* **1968**, 2947. (c) Schultz, A. G.; Yee, Y. K.; Berger, M. H. *J. Am. Chem. Soc.* **1977**, *99*, 8065. (d) Martin, S. F.; Garrison, P. J. *J. Org. Chem.* **1982**, *47*, 1513. (e) Sanchez, I. H.; Soria, J. T.; Lopez, F. J.; Larraza, M. I.; Flores, H. J. *J. Org. Chem.* **1984**, *49*, 157. (f) Ackland, D. J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. I* **1987**, 2695.

(6) (a) For an ingenious synthesis of the related alkaloid narwedine, see: Holton, R. A.; Sibi, M. P.; Murphy, W. S. *J. Am. Chem. Soc.* **1988**, *110*, 314. (b) For the most recent synthesis of galanthamine (3,4-dehydrolycoramine) by the oxidative coupling approach, see: Szewczyk, J.; Lewin, A. H.; Carroll, F. I. *J. Heterocycl. Chem.* **1988**, *25*, 1809.

(7) The ^1H and ^{13}C NMR spectra of urethane **4** were temperature dependent. In the ^1H spectrum at room temperature, one of the aromatic protons appeared as a doublet and the other as a broad signal; furthermore, the *N*-methyl and *N*-methylene signals were broadened and the *tert*-butyl group appeared as two closely spaced singlets. At 60 °C, however, both aromatic protons appeared as clean doublets and the signals for the *N*-methyl, *N*-methylene, and *tert*-butyl groups were sharp singlets. Likewise, in the ^{13}C spectrum, the signal for one of the aromatic protons was doubled as was the signal for the methylene carbon; however, at 50 °C, both doubling phenomena disappeared. These effects are attributed to incomplete averaging, at room temperature, of the signals representing the aromatic proton ortho to the urethane substituent, the *N*-methyl protons, and *N*-methylene protons as the result of restricted rotation in the *tert*-butylurethane moiety. Similar broad and doubled signals appeared in the spectra of urethanes **8** and **9**. For complete data, see the Experimental Section.

(8) A *Chemical Abstracts* search (by name and by partial structure) revealed no known 2-halo-4-alkoxycyclohexanone. However, a report of the synthesis of 2-bromo-4-methoxycyclohexanone was called to our attention by a referee, see: Cook, J. W.; Graham, W.; Cohen, A.; Lapsley, R. W.; Lawrence, C. A. *J. Chem. Soc.* **1944**, 322.

(9) Marshall, J. A.; Flynn, G. A. *Synth. Commun.* **1979**, *9*, 123.

0022-3263/92/1957-0752$03.00/0

methylsilyl ether **6** by the standard silylation procedure. Treatment of enol ether **6** with NBS/NaOAc in aqueous THF afforded a mixture of bromo ketones **7**.

The ratio of isomers in the product could be determined by inspection of the NMR spectrum. This exhibited two pairs of signals between 4 and 5 ppm for the proton at C-2 and the proton on C-4; the signals at 4.85 and 4.23 ppm were assigned to the isomer designated "D" (for "downfield") and those at 4.58 and 4.12 ppm were assigned to the isomer designated "U" (for "upfield"). This ratio of D:U varied from 1:2 to 9:1 in the initially isolated mixture. However, on chromatography, stirring with silica gel, or simply on standing, the mixture was converted to isomer D, which contained only a trace (<5%) of isomer U.

Consideration of the chemical shift data[10] and complete assignment of proton–proton coupling constants[11] for isomer D in $CDCl_3$ allowed its unambiguous assignment as the trans isomer **7b**, in which the bromo substituent is equatorial and the siloxy substituent is axial.[12] Isomer U then is **7a**; examination of the coupling pattern for the proton at 4.58 ppm reveals that, in **7a** in $CDCl_3$, the bromo substituent is equatorial.

The predominance of isomer **7b** is qualitatively in agreement with the results of gas-phase MM2 calculations in which electrostatic interactions, correlated with the arrangement in space of the three dipoles of **7a** and **7b**, make significant contributions to the total energies. On the other hand, these gas-phase calculations[13] predict roughly equal populations of the two conformers of **7b**; the observed, overwhelming preference of isomer **7b** for the equatorial bromine, axial siloxy conformer in solution may be the result of solvent–dipole interactions which favor the conformer with the larger *net* dipole.

The functional group array in 4-oxygenated 2-halocyclohexanones contains interesting possibilities for a variety of synthetic transformations. Bromo ketone **7b** is especially attractive as a synthetic intermediate because it can be easily obtained free from its stereoisomer.

Alkylation of phenol **4** by bromo ketone **7b** in a two-phase system (Bu_4NBr, NaOH, CH_2Cl_2, H_2O) afforded cyclohexanone **8** in which the two alkoxyl substituents are cis (and equatorial).[11] The *cis*-2,4-dialkoxycyclohexanone is the kinetic product under the conditions of alkylation; alkylation of phenol **4** in a two-phase system of Bu_4NBr, NaOH, CH_2Cl_2, D_2O afforded ketone **8**[7] in which none of the three protons α to the ketone had been exchanged.

Condensation of ketone **8** with (carbomethoxymethylene)triphenylphosphorane gave unsaturated ester **9**,[7] our target intermediate, in which the aryloxy and siloxy substituents are still cis.[11] The tributyltin hydride initiated cyclization of substrate **9** proceeded without complication to afford the cis-fused dihydrobenzofuran **10**. In this reaction, the pivotal quaternary chiral center required for lycoramine has been generated by the addition of the hindered (ortho,ortho disubstituted) aryl radical to the hindered (trisubstituted, exocyclic), but electrophilic, olefin. With the stereocontrolled introduction of this center, the relative stereochemistry of the three chiral centers of lycoramine has been correctly established.

Treatment of tricyclic **10** with trifluoroacetic acid followed by aqueous sodium hydroxide effected deprotection of the amino and hydroxyl groups and lactamization in a single procedure. Lithium aluminum hydride reduction converted lactam **11** to *dl*-lycoramine (**1**). Our synthetic material was identical to an authentic sample of *dl*-lycoramine;[14] our synthetic material and the authentic sample had 400-MHz ^1H NMR and 100.6-MHz ^{13}C NMR spectra identical to those of natural (−)-lycoramine.[14]

The convergent, stereospecific preparation of lycoramine proceeds in seven steps from inexpensive, commercially available starting materials. It demonstrates the utility of aryl radical cyclizations in the synthesis of complex natural products. It also illustrates the potential of substituted α-halocyclohexanones as convenient intermediates for the solution of problems of 1,3-stereocontrol.

Experimental Section[15]

***N*-Methyl-2-bromo-3-hydroxy-4-methoxybenzenemethanamine (3).** To a stirred solution of 94 mg (0.41 mmol) of 2-bromo-3-hydroxy-4-methoxybenzaldehyde (**2**)[16] in 10 mL of MeOH was added 210 μL (2.44 mmol) of 40% methylamine. The pH of the solution was adjusted to 6–7 by the addition of HCl, and then 26 mg (0.41 mmol) of sodium cyanoborohydride was added. The mixture was stirred for 1.5 d and then the solvent was removed in vacuo. The residue was diluted with 10 mL of H_2O and acidified with 5% aqueous HCl, and the resulting solution was washed with Et_2O. The aqueous portion was neutralized with 15% aqueous NaOH solution, saturated with NaCl, and extracted with 2 × 15 mL of Et_2O. The combined organic solution was dried over $MgSO_4$ and concentrated to afford 34 mg (34%) of a light brown solid: mp 154–157 °C; IR (CH_2Cl_2) 3320 (m), 3060 (m), 2950 (s), 2840 (s), 1620 (m), 1490 (s), 1470 (s) cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 7.04 (d, 1 H, J = 8.4 Hz), 6.79 (d, 1 H, J = 8.4 Hz), 5.95 (br s, 1 H, D_2O exchange), 3.89 (s, 4 H), 3.64 (s, 2 H), 2.22 (s, 3 H); HRMS (EI) for $C_9H_{12}O_2NBr^{79}$ calcd 245.0051, found 245.0039.

(10) (a) Signals for protons in similar α-halocyclohexanone systems are shown in Garbisch, E. W., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 1780. (b) The conformational equilibria of α-halocyclohexanones are correlated with the dielectric constant of the solvent. For data on the parent α-halocyclohexanones, see: Pan, Y.-h.; Stothers, J. B. *Can. J. Chem.* **1967**, *45*, 2943. For a discussion of this solvent effect and of substituent effects on the chemical shifts of axial and equatorial protons in α-halocyclohexanones, see: Baretta, A.; Zahra, J. P.; Waegell, B.; Jefford, C. W. *Tetrahedron* **1970**, *26*, 15 and references therein.

(11) Tables containing complete decoupling data for compounds **7b** and **9** are contained in the supplementary material. Coupling constants for **7b**, **8**, and **9** are listed in the Experimental Section.

(12) The preference of a 4-alkoxy substituent on a cyclohexanone to assume the axial position is expected: for both 4-methoxy- and 4-(benzyloxy)cyclohexanone-d_4, the major conformation is the chair in which the 4-alkoxy group is axial; this preference is slightly solvent dependent. See: Stolow, R. D.; Giants, T. W. *J. Chem. Soc., Chem. Commun.* **1971**, 528.

(13) The calculated energies for two chair conformers of **7b** are close, with the axial bromine, equatorial siloxy conformer (in which the carbonyl and carbon–bromine dipoles are at an obtuse angle) favored by only 0.3 kcal. The equatorial bromine, axial siloxy conformer benefits from a transannular dipole–dipole interaction. For a discussion of this effect, see: Stolow, R. D.; Groom, T. *Tetrahedron Lett.* **1968**, 4069.

(14) We are grateful to Professor Arthur G. Schultz for the loan of a sample of synthetic *dl*-lycoramine[5c] and of a sample of (−)-lycoramine, originally isolated by W. C. Wildman. Spectroscopic data for lycoramine (from natural sources) have been reported: (a) Kobayashi, S.; Yuasa, K.; Imakura, Y.; Kihara, M.; Shingu, T. *Chem. Pharm. Bull.* **1980**, *28*, 3433. (b) Kihara, M.; Koike, T.; Imakura, Y.; Kida, K.; Shingu, T.; Kobayashi, S. *Chem. Pharm. Bull.* **1987**, *35*, 1070. (c) For NMR data for galanthamine, see ref 6b and Bastida, F. V.; Llabres, J. M.; Codina, C.; Feliz, M.; Rubiralta, M. *Phytochemistry* **1987**, *26*, 1519. Also: Vlahov, R.; Krikorian, D.; Spassov, G.; Chinova, M.; Vlahov, I.; Parushev, S.; Snatzke, G.; Ernst, L.; Kieslich, K.; Abraham, W.-R.; Sheldrick, W. S. *Tetrahedron* **1989**, *45*, 3329.

(15) Infrared spectra were recorded on a Perkin-Elmer 681 or Perkin-Elmer 1600 FT spectrometer. ^1H NMR spectra were recorded on either a 250- or 400-MHz Bruker FT spectrometer; ^{13}C NMR spectra were recorded on a 400-MHz Bruker FT (100.6 MHz) spectrometer. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. High resolution mass spectra were obtained on a Kratos MS-80 spectrometer under either electron impact (EI) or chemical ionization (CI) measurements. Thin-layer chromatography (TLC) was carried out on EM Science precoated silica gel 60F 254 plates. Flash column chromatography was performed with EM Science silica gel 60 (230–400 mesh). Tetrahydrofuran was distilled from sodium benzophenone ketyl in a recirculating still. All reactions were performed under an argon atmosphere.

(16) (a) Hlasta, D. J.; Bell, M. R. *Tetrahedron Lett.* **1985**, *26*, 2151. (b) Pauly, H. *Chem. Ber.* **1915**, *48*, 2010.

Benzyl Carbamate 4. To a solution of 986 mg (4.01 mmol) of amine 3 and 1.68 mL (12.0 mmol) of Et_3N in 60 mL of freshly distilled THF at −78 °C under Ar was slowly added 1.75 g (8.12 mmol) of di-*tert*-butyl dicarbonate in 30 mL of THF. The mixture was stirred for 3 h at −78 °C. Then it was warmed to rt and stirred for an additional 2 h. The reaction mixture was diluted with 100 mL of H_2O and extracted with 3 × 50 mL of EtOAc. The combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was subjected to hydrolysis in a solution of 4 g of NaOH in 30 mL of MeOH. Flash column chromatography (EtOAc/hexane, 3:7) afforded 886 mg (64%) of a white solid: mp 100–103 °C; IR (CH_2Cl_2) 3510 (br m), 3050 (m), 2980 (m), 2940 (m), 1685 (s), 1470 (s) cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 6.81 (d, 1 H, J = 8.4 Hz), 6.72 (m, 1 H), 6.14 (br s, 1 H, D_2O exchange), 4.49 (br s, 2 H), 3.89 (s, 3 H), 2.86 (br s, 3 H), 1.48 and 1.44 (2 s, 9 H); 250-MHz ^1H NMR ($CDCl_3$) at 60.3 °C δ 6.81 (d, 1 H, J = 8.4 Hz), 6.72 (d, 1 H, J = 8.4 Hz), 5.99 (br s, 1 H), 4.48 (s 2 H), 3.89 (s, 3 H), 2.83 (s, 3 H), 1.46 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 155.8 (s), 146.0 (s), 143.1 (s), 129.6 (s), 119.0 (d) and 118.1 (d), 110.6 (s), 109.5 (d), 79.6 (s), 56.2 (apparent q, presumably two overlapping t), 52.2 (d) and 51.4 (d), 34.0 (q), 28.3 (q); ^{13}C NMR ($CDCl_3$) at 50.6–50.9 °C δ 155.9, 146.2, 143.3, 129.9, 118.6 (br), 110.8, 109.8, 79.6, 56.3, 51.9 (br), 34.0, 28.3; HRMS (CI) for $C_{14}H_{21}Br^{79}NO_4$ (M + H) calcd 346.0653, found 346.0658.

1-Methoxy-4-(*tert*-butyldimethylsiloxy)cyclohexene (6). To solution of 2.30 g (17.9 mmol) of 4-methoxy-3-cyclohexen-1-ol (5)[9] in 4.6 mL of DMF at 0 °C were added 3.06 g (44.9 mmol) of imidazole and 3.25 g (21.5 mmol) of *tert*-butyldimethylsilyl chloride. The mixture was stirred for 1.5 d at rt under Ar, diluted with 200 mL of cold H_2O, and extracted with 4 × 50 mL of hexane. The combined organic solution was washed with cold brine, dried over Na_2SO_4, and concentrated to yield 4.08 g (quantitative yield) of a yellow oil: IR (neat) 3072 (w), 2996 (m), 2899 (s), 2855 (s), 1672 (s), 1507 (s), 1464 (s), cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 4.43 (dd, 1 H, J = 4.0, 2.9 Hz), 3.86 (m, 1 H), 3.47 (s, 3 H), 2.27–1.99 (m, 4 H), 1.81–1.61 (m, 2 H), 0.87 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 154.6, 90.1, 67.9, 53.9, 32.9, 31.6, 26.2, 25.8, 18.1, −4.8.

***cis*- and *trans*-2-Bromo-4-(*tert*-butyldimethylsiloxy)-cyclohexanones (7a and 7b) and Isolation of the Trans Isomer 7b.** To a solution of 2.01 g (11.3 mmol) of NBS and 128 mg (0.94 mmol) of NaOAc in 30 mL of THF and H_2O (1:1) at 0 °C was added dropwise a solution of 2.28 g (9.40 mmol) of enol ether 6 in 10 mL of THF. The mixture was stirred for 4 h at 0 °C and then poured into 200 mL of H_2O. Extraction with 4 × 70 mL of hexane gave a combined organic solution which was washed with brine, dried over $MgSO_4$, and concentrated to afford 2.82 g of crude material: 400-MHz ^1H NMR ($CDCl_3$) δ 4.85 (dd, 0.85 H, J = 10.6, 5.6 Hz), 4.58 (dd, 0.15 H, J = 11.6, 6.0 Hz), 4.23 (m, 1 H × 0.85), 4.12 (m, 1 H × 0.15), 2.81–2.64 (m, 2 H × 0.85), 2.64 (m, 1 H × 0.15), 2.52 (dddd, 1 H × 0.85, J = 13.7, 5.4, 5.3, 2.2 Hz), 2.39 (ddd, 1 H × 0.15, J = 14.6, 13.5, 10.6, 2.6 Hz), 2.21 (m, 1 H × 0.15), 2.12 (m, 1 H × 0.15), 2.02–1.92 (m, 2 H × 0.85), 1.92–1.77 (m, 2 H × 0.15), 0.91 (s, 9 H × 0.85), 0.87 (s, 9 H × 0.15), 0.12 (s, 3 H × 0.85), 0.10 (s, 3 H × 0.85), 0.06 (s, 3 H × 0.15), 0.04 (s, 3 H × 0.15). This was subjected to flash column chromatography (EtOAc/hexane, 1:9) to yield 1.92 g (67%) of a white solid (mp 47–48 °C): IR (KBr) 2954 (s), 2927 (s), 2894 (s), 2858 (s), 1729 (s), 1463 (s) cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 4.87 (dd, 1 H, J = 10.5, 5.8 Hz), 4.24 (m, 1 H), 2.74 (ddd, 1 H, J = 10.2, 6.3, 1.0 Hz), 2.72 (dd, 1 H, $J \approx$ 5.8, 5.2 Hz), 2.55 (dddd, 1 H, J = 13.7, 5.3, 5.3, 2.0 Hz), 2.28 (ddd, 1 H, J = 13.6, 10.6, 2.7 Hz), 2.04–1.92 (m, 2 H), 0.92 (s, 9 H), 0.13 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 201.8 (s), 66.6 (d), 51.5 (d), 45.9 (t), 35.2 (t), 34.5 (t), 25.7 (q), 18.0 (s), −4.9 (q); HRMS (CI) for $C_{12}H_{24}O_2Br^{79}Si$ (M + H) calcd 307.0728, found 307.0702.

Ketone 8. To 64 mg (0.20 mmol) of tetra-*n*-butylammonium bromide and 119 mg (2.96 mmol) of NaOH in a mixture of 20 mL of H_2O and 20 mL of CH_2Cl_2 at 0 °C was added 684 mg (1.98 mmol) of phenol 4. The reaction mixture was vigorously stirred for 30 min at rt and then 607 mg (1.98 mmol) of bromo ketone **7b** was added over 1 h. The mixture was stirred for 12 h at rt and then an additional 24 mg (0.60 mmol) of NaOH was added. Stirring was continued for a total of 1.5 d. Then the reaction mixture was poured into 100 mL of H_2O. Extraction with 3 × 50 mL of CH_2Cl_2 gave a solution which was washed with 2 × 20 mL of 10% aqueous NaOH and brine, dried over $MgSO_4$, and concentrated to afford 967 mg of crude product. Purification by flash column chromatography (EtOAc/hexane, 3:7) afforded 719 mg (64%) of a pale yellow oil: IR (neat) 3005 (w), 2950 (s), 2925 (s), 2890 (m) 2850 (s), 1735 (s), 1690 (s), 1590 (w), 1480 (s), 1460 (s) cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 6.85 (br s, 2 H), 4.94–4.78 (br, 1 H), 4.47 (br s, 2 H), 4.08 (tt, 1 H, J = 10.4, 4.1 Hz), 3.79 (s, 3 H), 2.85 (br s, 3 H), 2.54 (dt, 1 H, J = 13.8, ~4 Hz), 2.46 (m, 1 H), 2.34 (td, 1 H, J = 13.9, 5.6 Hz), 2.18–2.04 (m, 2 H), 1.80 (dddd, 1 H, J = 13.3, 13.3, 10.3, 4.8 Hz), 1.42 and 1.50 (2 br s, 9 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 205.0, 155.8, 151.5, 143.9, 130.2, 122.2 and 123.0, 118.5 and 118.9, 111.6, 80.7, 79.7, 67.8, 56.2, 51.7 and 52.5, 42.2, 35.8, 35.2, 34.2, 28.3, 25.7, 18.0, −4.7; HRMS (CI) for $C_{26}H_{42}O_6Br^{81}NSi$ (M + H) calcd 574.2022, found 574.2024.

Ester 9. A solution of 295 mg (0.52 mmol) of ketone 8 and 258 mg (0.77 mmol) of (carbomethoxymethylene)triphenylphosphorane in 20 mL of freshly distilled THF was stirred at reflux under Ar for 1 d. Then an additional 258 mg of Wittig reagent was added and refluxing was continued for a total of 3 d. The solvent was removed in vacuo and the residue was eluted from a column (15 g of flash silica) with EtOAc. The eluent was concentrated and the residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to yield 233 mg (77%) of a pale yellow oil: IR (neat) 3050 (w), 2930 (s), 2880 (s), 2850 (s), 1715 (s), 1690 (s), 1590 (w), 1480 (s) cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 6.87 (br s, 2 H), 6.41 (s, 1 H), 4.69 (br t, 1 H), 4.48 (br d, 2 H, J = 15.8 Hz), 3.99 (dt, 1 H, J = 14.2, 3.5 Hz), 3.80 (s, 3 H), 3.75 (m, 1 H), 3.72 (s, 3 H), 2.85 (br d, 3 H, J = 16.7 Hz), 2.23 (m, 1 H), 1.97 (br d, 1 H, J = 11.7 Hz), 1.79 (m, 1 H), 1.72 (ddd, 1 H, J = 11.8, 11.1, 11.8 Hz), 1.42 and 1.46 (2 br s, 10 H), 0.83 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H); 400-MHz ^1H NMR ($CDCl_3$) at 54.9–55.0 °C δ 6.90 (d, 1 H, J = 8.6 Hz), 6.86 (d, 1 H, J = 8.6 Hz), 6.40 (s, 1 H), 4.71 (dd, 1 H, J = 11.7, 4.1 Hz), 4.51 (d, 1 H, $J \approx$ 16 Hz), 4.46 (d, 1 H, $J \approx$ 16 Hz), 3.96 (dt, 1 H, J = 14.2, 3.7 Hz), 3.80 (s, 3 H), 3.75 (m, 1 H), 3.72 (s, 3 H), 2.85 (s, 3 H), 2.24 (dm, 1 H, J = 11.9 Hz), 1.97 (m, 1 H), 1.82 (td, 1 H, J = 14.4, 3.8 Hz), 1.73 (ddd, 1 H, J = 11.8, 10.8, 11.8 Hz), 1.46 (br s, 10 H), 0.84 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 157.9, 155.9, 152.2, 143.5, 130.2, 122.4, and 123.0, 119.0 and 119.4, 111.8, 111.3, 79.7, 79.4, 68.9, 56.1, 51.9 and 52.6, 50.9, 43.0, 35.9, 34.2, 28.4, 25.7, 24.0, 18.0, −4.6, −4.7; HRMS (CI) for $C_{29}H_{46}NO_7SiBr^{79}$ (M + H) calcd 628.2304, found 628.2324.

Siloxy Urethane 10. A mixture of 204 mg (0.32 mmol) of substrate 9, 170 μL (0.65 mmol) of Bu_3SnH, and 5 mg (0.03 mmol) of AIBN in 15 mL of benzene was stirred under a reflux condenser (bath temperature 130 °C) for 2 d under Ar. Catalytic amounts of AIBN were added several times during the course of the reaction. The solvent was removed in vacuo and the residue was purified by flash column chromotography (EtOAc/hexane, 3:7) to afford 158 mg of crude product. Distillative removal of low boiling impurities (Kugelrohr, 150 °C, 0.25 mmHg) left 108 mg (61%) of a yellow oil: IR (neat) 3050 (w), 2995 (s), 2934 (s), 2898 (s), 2856 (s), 1736 (s), 1695 (s), 1621 (m), 1583 (m) cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 6.85–6.57 (m, 2 H), 4.96 (dd, 1 H, J = 9.5, 6.4 Hz), 4.41–4.31 (br m, 2 H), 3.87 and 3.85 (2 s, 3 H), 3.67 (m, 1 H), 3.62 and 3.60 (2 s, 3 H), 2.79 and 2.76 (2 s, 3 H), 2.56 (d, 1 H, J = 14.6 Hz), 2.46 (d, 1 H, J = 14.6 Hz), 2.25–1.50 (m, 6 H), 1.48 (s, 9 H), 0.04, 0.03, 0.02, and 0.01 (4 s, 6 H); HRMS (EI) for $C_{29}H_{47}NO_7Si$ calcd 549.3121, found 549.3131.

7-Oxolycoramine (11). A solution of 26 mg (0.05 mmol) of siloxy urethane 10 in 0.5 mL of CF_3COOH and 0.5 mL of H_2O was stirred for 1 h at rt and the solvents were removed in vacuo. The residue was diluted with 1.5 mL of H_2O and this was washed with EtOAc. Aqueous sodium hydroxide solution (10%) was added until the pH of the phase reached 10–12. This was saturated with NaCl and solution was extracted with 3 × 5 mL of EtOAc. The combined organic solution was dried over K_2CO_3 and concentrated to afford 8 mg (56%) of a pale yellow oil: IR (CH_2Cl_2) 3412 (br), 3049 (s), 2842 (s), 1643 (s), 1536 (s) cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 6.63 (d, 1 H, J = 8.3 Hz), 6.60 (d, 1 H, J = 8.3 Hz), 4.35 (d, 1 H, J = 16.2 Hz), 4.32 (br s, 1 H), 4.26 (d, 1 H, J = 16.2 Hz), 4.05 (br s, 1 H), 3.81 (s, 4 H), 2.97 (s, 3 H), 2.80 (d, 1 H, J = 13.6 Hz), 2.75 (d, 1 H, J = 13.6 Hz), 2.50 (ddd, 1 H, J = 16.3, 4.7, 2.3 Hz), 1.90 (dt, 1 H, J = 16.2, 3.8 Hz), 1.87 (td, 1 H, J = 14.2, 3.6 Hz), 1.76 (ddd, 1 H, J = 14.2, 3.3, 2.4 Hz), 1.65–1.49 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 171.9, 146.4, 144.9, 137.0,

124.6, 119.7, 110.5, 89.2, 64.7, 56.2, 52.0, 41.7, 39.9, 36.2, 30.9, 29.7, 27.6; HRMS (EI) for $C_{17}H_{21}NO_4$ calcd 303.1470, found 303.1469.

(±)-Lycoramine (1). To a suspension of 10 mg of lithium aluminum hydride in 0.5 mL of freshly distilled THF was added a solution of 8 mg (0.03 mmol) of lactam 11 in 1 mL of THF. The reaction mixture was stirred at reflux 22 h under Ar, cooled, and quenched with 10% aqueous HCl solution. The aqueous solution was washed with EtOAc. Then NaOH pellets were added until the pH reached 10–12; the solution was saturated with sodium chloride and extracted with 3 × 10 mL of $CHCl_3$. The organic solution was washed with brine, dried over K_2CO_3, and concentrated to afford 6 mg (75%) of a pale yellow solid which was recrystallized from Et_2O: ^1H NMR ($CDCl_3$) 6.65 (d, 1 H, J = 8.0 Hz), 6.62 (d, 1 H, J = 8.0 Hz), 4.37 (br s, 1 H), 4.10 (br s, exch D_2O), 4.01 (d, 1 H, J = 15.3 Hz), 3.85 (s, 3 H), 3.70 (m, 1 H), 3.66 (d, 1 H, J = 15.3 Hz), 3.21 (t, 1 H, J = 13 Hz), 3.03 (d, 1 H, J = 14 Hz), 2.52 (d, 1 H, J = 15.3 Hz), 2.37 (s, 3 H), 2.01–1.65 (complex m, 9 H), 1.58 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 146.0, 144.2, 136.2, 125.8, 121.9, 110.8, 89.9, 65.3, 60.2, 55.8, 53.9, 46.7, 41.5, 31.5, 31.0, 27.6, 23.7; IR (CH_2Cl_2) 2934, 1626, 1503, 1441, 1415 cm^{-1}.

Acknowledgment. This work was supported by the National Science Foundation (Grant No. 8705647) and by a Biomedical Research Support Grant (PHS 2 S07 RR07085-24) administered by Brown University. NMR spectra were acquired with a Bruker AM400WB spectrometer, purchased with funds from the National Science Foundation, and with a Bruker WM250 spectrometer, purchased with funds from NSF and the Montedison Group of Milan. The Kratos MS-80 mass spectrometer was purchased with funds from the Division of Research Resources of the National Institutes of Health. We are grateful to Mr. Craig A. Coburn for conducting several experiments which defined conditions for the equilibration of ketones 7 and we thank John S. Oliver, Richard M. Stratt, and Dennis Liotta for helpful discussions.

Registry No. (±)-1, 18797-70-1; 2, 2973-58-2; 3, 137718-76-4; 4, 137718-77-5; (±)-5, 124549-69-5; (±)-6, 137718-78-6; (±)-7, 137718-79-7; (±)-7, 137718-83-3; (±)-8, 137718-80-0; (±)-9, 137718-81-1; (±)-10, 137718-82-2; (±)-11, 137742-02-0.

Supplementary Material Available: Tables of ^1H NMR decoupling data for compounds 7b and 9 and spectra for new compounds 3, 4, 6–11, synthetic lycoramine (1), and authentic (–)-lycoramine (33 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Photochemistry of Steroidal Ketones: Formation of an Exceptionally Stable Ketene by an α-Cleavage Reaction

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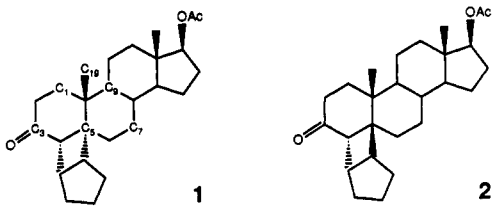
Received June 11, 1991

Upon irradiation, saturated cyclic ketones undergo preferential Norrish type I cleavage of the C–C bond between the carbonyl group and the more substituted α-carbon.[1] Exceptions to this general reactivity pattern are limited.[2-4] There is much evidence that the key intermediate is a triplet biradical,[5] which after a spin flip either recombines to give starting material or undergoes intramolecular hydrogen abstraction via a cyclic transition state.[6,7] Here we report that the isomeric testosterone acetate–cyclopentene adducts[8] 1 and 2 (Scheme I) not only undergo a Norrish type I cleavage toward the less substituted α-carbon in high yields, but also differ considerably in the fate of the intermediate 1,6-biradical.

Scheme I



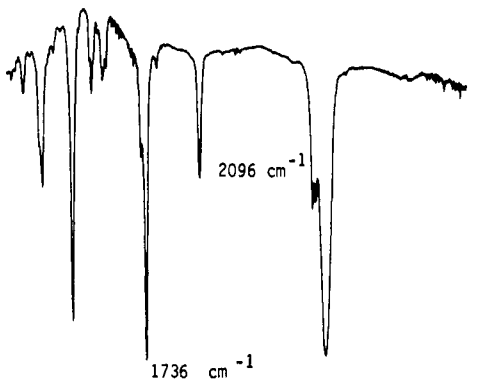


Figure 1. IR spectrum showing the presence of ketene 6 after irradiation of 2 in ethyl acetate for 45 min.

The cis-fused adduct 1 was irradiated in ethyl acetate. The major photoproduct (>80%) was identified as 4 (Scheme II) by ^1H NMR, ^{13}C NMR, IR, and GC–MS, indicating that cleavage toward the less substituted α-carbon atom had occurred.

The photoreactivity of 1 can be attributed to differences in the strength of the bonds between the carbonyl group and the adjacent carbon atoms, i.e., the higher s-character in the bond between the four-membered ring and the carbonyl carbon results in a stronger bond than the less substituted alkyl–acyl bond which preferably cleaves. A similar type of regioselective Norrish type I cleavage has been observed with *cis*- and *trans*-4,7,7-trimethylbicyclo-[4.1.0]heptan-3-one,[9] *cis*-4,6,6-trimethylbicyclo[3.1.1]heptan-2-one,[2] and 22,29,30-trinorhopan-21-one.[4] In photo-CIDNP experiments, the proton of aldehyde 4 displays enhanced NMR absorption,[10] which further indicates that the triplet 1,6-biradical 3 (Scheme II) is indeed an inter-

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