The easy synthesis of fluoroalkanes from alkenes, alcohols, and other precursors with HF or with our HF/pyridine reagent[7] makes the present method an attractive route to iodoalkanes through the corresponding fluoroalkanes.

Experimental Section

General Procedure. Iodotrimethylsilane (2.21 g, 11 mmol) was added to a stirred solution of the alkyl fluoride (chloride) (10 mmol) in dichloromethane (25 mL), and the reaction mixture was stirred under a dry nitrogen atmosphere for 16 h. The reaction mixture was quenched with aqueous sodium bicarbonate solution and extracted with dichloromethane. The organic extract was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated and the product isolated by distillation or crystallization.

Reaction with hexamethyldisilane/iodine or with chlorotrimethylsilane/sodium iodide was performed as described previously.[6]

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

Registry No. Iodotrimethylsilane, 16029-98-4; 1-hexyl fluoride, 373-14-8; 1-decyl fluoride, 334-56-5; benzyl fluoride, 350-50-5; cyclohexyl fluoride, 372-46-3; 1-adamantyl fluoride, 768-92-3; 2-norbornyl fluoride, 694-95-1; 1-adamantyl chloride, 935-56-8; 2-methyl-2-propyl chloride, 507-20-0; 1-iodohexane, 638-45-9; 2-iodohexane, 18589-27-0; benzyl iodide, 620-05-3; cyclohexyl iodide, 626-62-0; 1-adamantyl iodide, 768-93-4; 2-norbonyl iodide, 55924-26-0; 2-methyl-2-propyl iodide, 558-17-8.

(7) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3872-3881.

Azetidinium Intermediate in the Reaction of 2-[(Dimethylamino)methyl]cyclopent-1-yl Mesylate with 3,4-Dichloroaniline

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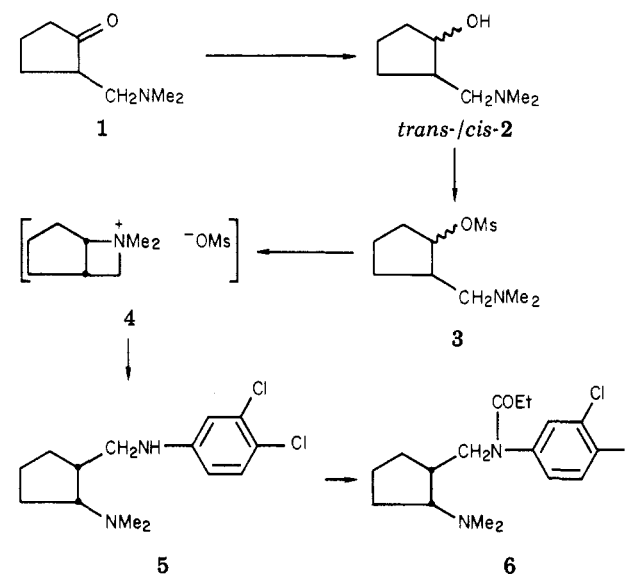
There have been many examples of aziridinium intermediates reported in the literature[1] but comparatively few examples of azetidinium intermediates.[2] While conducting a search for biologically active agents, we encountered an interesting example of the latter intermediate.

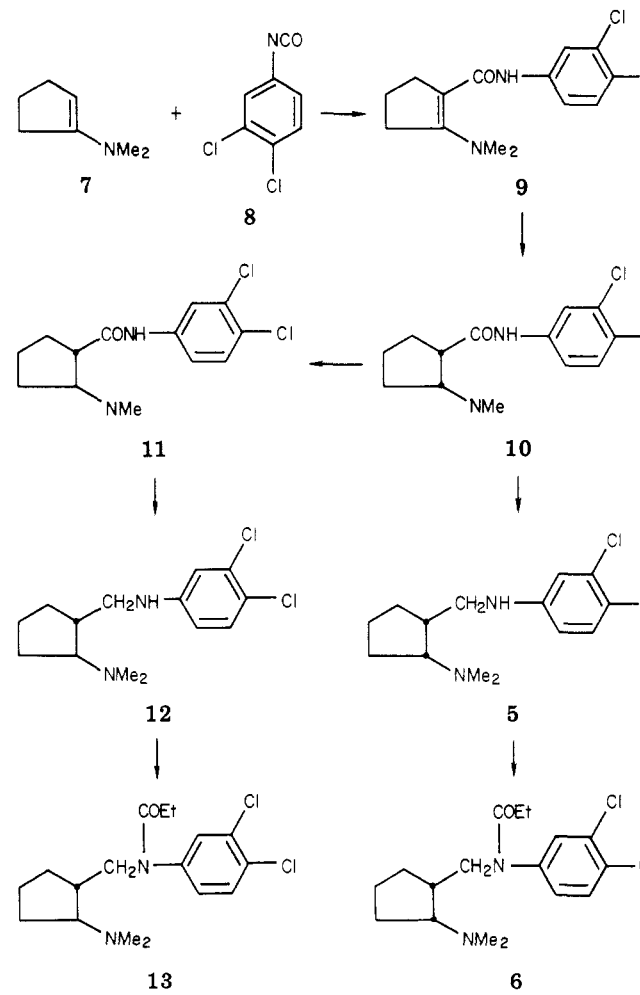
Treatment of the isomeric mixture of amino alcohols **2**,[3] obtained by lithium aluminum hydride reduction of Mannich base **1**, with sodium hydride and methanesulfonyl chloride and subsequent reaction of the resulting unstable mesylate **3** with 3,4-dichloroaniline produced diamine **5** as the only aniline-containing product (Scheme I). The structure of the product was established by comparison of the propionanilide **6**, obtained by acylation with propionic anhydride, with material produced in an alternate synthesis.

Reaction of 1-(dimethylamino)cyclopentene (**7**) with 3,4-dichlorophenyl isocyanate (**8**) in benzene[4] followed by PtO_2 hydrogenation gave cis amide **10**[5] (Scheme II).

Scheme I



Scheme II



(1) (a) S. Ikegami, K. Uoji, and S. Akaboshi, *Tetrahedron*, **30**, 2077 (1974); (b) C. F. Hammer, S. R. Leller, and J. H. Craig, *ibid.*, **28**, 239 (1972); (c) P. E. Fanta, *Chem. Heterocycl. Compd.*, **19**, 548-551 (1964).

(2) J. A. Moore, *Chem. Heterocycl. Compd.*, **19**, 894-895 (1964).

(3) (a) Cf. C. Mannich and P. Schaller, *Arch. Pharm. (Weinheim, Ger.)*, **276**, 575 (1938); R. Ratouis and G. Combes, *Bull Soc. Chim. Fr.*, 576 (1959). (b) The stereochemistry of the major isomer could not be assigned definitively but is most likely trans since similar reduction of aminocyclohexanones produces *predominantly the trans alcohol*. (a) E. Costes, C. Bénard, and A. Lattes, *Tetrahedron Lett.*, 1185 (1976); (b) C. L. Stevens, K. J. TerBeek, and P. Madhavan Pilla, *J. Org. Chem.*, **39**, 3943 (1974).

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Diborane reduction followed by acylation gave propionanilide **6**. Isomerization of cis amide **10** with potassium *tert*-butoxide to the more stable trans amide **11** followed by diborane reduction and acylation yielded the corresponding *trans*-propionanilide **13**.

Formation of diamine **5** can be best explained as proceeding through initial displacement of mesylate ion to form azetidinium intermediate **4** followed by nucleophilic displacement at the least hindered position.

Experimental Section

Melting points were taken in capillary tubes and are corrected. Ultraviolet spectra were determined on a Cary Model 14 spectrophotometer, IR spectra on a Perkin-Elmer Model 421 spectrophotometer, mass spectra at 70 eV on an Atlas Model CH-4 spectrometer, and NMR spectra on a Varian Model A-60A or XL-100 spectrometer. NMR peaks are recorded in parts per million downfield from tetramethylsilane.

***cis*-3′,4′-Dichloro-2-(dimethylamino)cyclopentanecarboxanilide (10).** A solution of 3,4-dichlorophenyl isocyanate (**8**; 59.8 g, 0.32 mol) in benzene (100 mL) was added in 30 min to a solution of 1-(dimethylamino)cyclopentene[6] (**7**; 41.1 g, 0.37 mol) in benzene (400 mL). The mixture was refluxed 1 h and then transferred to a Parr hydrogenation bottle. Platinum oxide (2.0 g) was added and the mixture hydrogenated at 30 psi of H_2 until uptake ceased (0.33 mol in 20 min). The mixture was filtered through Celite and evaporated to a yellow solid. Recrystallization from ether gave amide **10**: 61.6 g (64%); mp 68–70 °C; UV (EtOH) λ_{max} (end absorption) 212 nm (ϵ 29 550), 254 (20 000), 284 (sh, 1680), 295 (1150); mass spectrum, *m/e* 300/302/304 (M^+); IR NH 3000 (br, NH), 2780 (*N*-alkyl), 1680 (C=O), 1595, 1545 (C=C/amide II), 905, 865, 800 cm^{-1} (other); NMR ($CDCl_3$) δ 12.25 (m, 1 H, NHCO), 7.8 (m, 1 H, aromatic), 7.35 (m, 2 H, aromatic), 2.86 (m, 1 H, CH), 2.59 (m, 1 H, CH), 2.45 (s, 6 H, NMe_2), 1.5–2.1 (m, 6 H, ring hydrogens).

Anal. Calcd for $C_{14}H_{22}Cl_2N_2O$: C, 55.82; H, 6.02; N, 9.30; Cl, 23.54. Found: C, 55.86; H, 6.03; N, 9.22; Cl, 23.77.

***trans*-3′,4′-Dichloro-2-(dimethylamino)cyclopentanecarboxanilide (11).** A solution of amide **10** (22.6 g, 0.075 mol) and potassium *tert*-butoxide (8.4 g, 0.075 mol) in *tert*-butyl alcohol (200 mL) was refluxed for 5 h. The solution was evaporated, and the residue was treated with methylene chloride (250 mL) and water (200 mL). The organic layer was washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to a yellow solid. Recrystallization from ether–petroleum ether gave amide **11**: 13.9 g (62%); mp 102–103 °C; UV (EtOH) λ_{max} (end absorption) 212 nm (ϵ 30 550), 254 (20 950), 284 (1700), 295 (1250); mass spectrum, *m/e* 300, 302 (M^+); NMR ($CDCl_3$) δ 10.6 (m, 1 H, NHCO), 7.75 (m, 1 H, aromatic), 7.3–7.4 (m, 2 H, aromatic), 3.1 (m, 1 H, CH), 2.7 (m, 1 H, CH), 2.4 (s, 6 H, NMe_2), 1.6–2.2 (m, 6 H, ring hydrogens).

Anal. Calcd for $C_{14}H_{20}Cl_2N_2O$: C, 55.82; H, 6.02; N, 9.30; Cl, 23.54. Found: C, 55.81; H, 5.90; N, 9.15; Cl, 23.42.

***cis*-3,4-Dichloro-*N*-[[2-(dimethylamino)cyclopentyl]methyl]benzenamine (5).** A solution of borane in THF (130 mL, 1.0 M, 0.13 mol) was added in 30 min to a solution of amide **10** (10.0 g, 0.033 mol) in THF (100 mL). After the solution was refluxed for 3 h, concentrated hydrochloric acid (67 mL) was added to destroy excess borane. The solution was refluxed 15 min and then evaporated to remove THF. The residue was made basic with 40% potassium hydroxide and extracted with ether. The extract was washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated to a yellow oil. The hydrochloride salt was prepared with excess ether–HCl and recrystallized from methanol–ether: 10.1 g (85%); mp 180–183 °C; UV (EtOH) λ_{max} (end absorption) 210 nm (ϵ 27 200), 256 (16 700), 311 (2200); mass spectrum, *m/e* 286/288; IR 2660, 2480, 2340 (NH^+), 1600, 1590, 1570, 1560 (NH_2^+/C=C), 1135, 1035, 1005, 1000, 875, 830, 825 cm^{-1} (other); NMR (D_2O) δ 7.35 (m, 1 H, aromatic) 6.9 (m, 1 H, aromatic), 6.7 (m, 1 H, aromatic), 3.68 (m, 1 H, CH), 2.8–3.2 (m, 8 H, CH_2N and NMe_2), 1.7–2.0 (m, 6 H, ring hydrogens).

Anal. Calcd for $C_{14}H_{20}Cl_2N_2 \cdot 2HCl$: C, 46.68; H, 6.16; N, 7.78; Cl, 39.38. Found: C, 46.29; H, 6.17; N, 7.63; Cl, 39.01.

***trans*-3,4-Dichloro-*N*-[[2-(dimethylamino)cyclopentyl]methyl]benzenamine (12).** Reduction of amide **11** with borane–THF as above gave diamine **12** (hydrochloride): 9.0 g (76%); mp 172–185 °C; UV (EtOH) λ_{max} (end absorption) 211 nm (ϵ 26 550), 257 (17 800), 313 (2300); mass spectrum, *m/e* 286, 288 (M^+); IR 3500, 3440 (OH/NH), 2640, 2480 (NH^+), 1590, 1565 (NH_2^+/C=C), 1135, 1035, 1015, 825, 710 (other); NMR (D_2O) δ 7.5 (m, 1 H, aromatic), 7.3 (m, 1 H, aromatic), 7.05 (m, 1 H, aromatic), 3.1–3.6 (m, 3 H, CH_2N and CH), 2.9 (s, 6 H, NMe_2), 2.5 (m, 1 H, CH), 1.5–2.3 (m, 6 H, ring hydrogens).

Anal. Calcd for $C_{14}H_{20}Cl_2N_2 \cdot 2HCl \cdot 0.25H_2O$: C, 46.10; H, 6.22; N, 7.68; Cl, 38.89. Found: C, 46.12; H, 6.26; N, 7.59; Cl, 38.83.

***cis*-3′,4′-Dichloro-*N*-[[2-(dimethylamino)cyclopentyl]methyl]propionanilide (6).** A mixture of diamine **5** (9.0 g, 0.02 mol) and propionic anhydride (30 mL) was heated on a steam bath overnight. Water (100 mL) was added and heating continued for 30 min. The solution was cooled, made basic with 20% sodium hydroxide, and extracted with ether. The extract was washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated to a tan solid. Recrystallization from ether–petroleum ether gave amide **6**: 3.65 g (41%); mp 127–128 °C; UV (EtOH) λ_{max} (end absorption) 242 nm (ϵ 6100), 274 (sh, 714), 281 (546); mass spectrum, *m/e* 342, 344; IR 3060 (=CH), 2780 (*N*-alkyl), 1660 (C=O), 1590, 1560 (C=C), 1355, 1275, 1245, 1175, 1130, 1055, 1030 (CN/other); NMR ($CDCl_3$) δ 7.5 (m, 1 H, aromatic), 7.3 (m, 1 H, aromatic), 7.05 (m, 1 H, aromatic), 3.35–3.45 (m, AB of ABX, 2 H, CH_2NCO), 2.25 (m, 1 H, CH), 2.1 (q and s, 8 H, CH_3CH_2CO and NMe_2), 1.95 (m, 1 H, CH), 1.4–1.9 (m, 6 H, ring hydrogens), 1.05 (t, 3 H, 7.0 Hz, CH_3CH_2CO).

Anal. Calcd for $C_{17}H_{24}Cl_2N_2O$: C, 59.47; H, 7.05; N, 8.16; Cl, 20.66. Found: C, 59.16; H, 7.16; N, 8.10; Cl, 20.63.

***trans*-3′,4′-Dichloro-*N*-[[(2-dimethylamino)cyclopentyl]methyl]propionanilide (13).** Treatment of diamine **12** (6.5 g, 0.023 mol) with propionic anhydride as above gave amide **13**: 4.25 g (53%); mp 79–80 °C; UV (EtOH) λ_{max} (end absorption) 230 nm (sh, ϵ 6950), 237 (6400), 272 (sh, 669), 281 (518); mass spectrum, *m/e* 342, 344; IR, 3060 (=CH), 2780, 2760 (*N*-alkyl), 1655 (C=O), 1590, 1565 (C=C), 1350, 1285, 1240, 1230, 1130, 1030 (CN/other); NMR ($CDCl_3$) δ 7.5 (m, 1 H, aromatic), 7.4 (m, 1 H, aromatic), 7.05 (m, 1 H, aromatic), 3.45–4.0 (m, AB of ABX, 2 H, CH_2NCO), 2.4 (m, 1 H, CH), 2.0–2.2 (m, 1 H, CH), 2.15 (s, 6 H, NMe_2), 2.05 (q, 2 H, J = 7.0 Hz, CH_3CH_2CO), 1.2–1.8 (m, 6 H, ring protons), 1.05 (t, 3 H, 7.0 Hz CH_3CH_2CO).

Anal. Calcd for $C_{17}H_{24}Cl_2N_2O$: C, 59.47; H, 7.05; N, 8.16; Cl, 20.66. Found: C, 59.83; H, 7.11; N, 8.13; Cl, 20.98.

2-[(Dimethylamino)methyl]cyclopentanol (2). A solution of 2-[(dimethylamino)methyl]cyclopentanone (**1**;[7] 70.6 g, 0.50 mol) in ether (200 mL) was added dropwise with stirring to a suspension of lithium aluminum hydride (30.0 g) in ether (1500 mL). The mixture was refluxed overnight and cooled in ice, and the excess lithium aluminum hydride was decomposed by dropwise addition of water (30 mL), 15% sodium hydroxide (30 mL), and water (90 mL). The mixture was filtered, dried ($MgSO_4$), and evaporated to a colorless oil. Distillation gave amino alcohol **2**: 59.7 g (83%); bp 76–85 °C (14 mm); IR 3400 (OH), 1460 (CH), 1100, 1040, 1020 (CO/CN); NMR ($CDCl_3$) δ 5.1 (m, 1 H, CHOH), 4.7 (m, 1 H, exchanges with D_2O, OH), 4.4 (m, 1 H, CH), 3.7 (m, 2 H, AB of ABX, CH_2NMe_2), 2.25 (s, 6 H, NMe_2), 1.0–2.2 (m, 6 H, ring hydrogens). VPC/MS on a Chromosorb 101 column showed two components in a 96:4 ratio with molecular weight *m/e* 143.

Reaction of 2-[(Dimethylamino)methyl]cyclopent-1-yl Mesylate with 3,4-Dichloroaniline. A mixture of amino alcohol **2** (28.6 g, 0.20 mol) and sodium hydride (50% oil dispersion; 9.6 g, 0.20 mol) in THF (150 mL) was refluxed for 1 h. The mixture was cooled in ice while methanesulfonyl chloride (22.9 g, 0.20 mol) was added in 30 min. When the addition was complete, 3,4-dichloroaniline (64.8 g, 0.4 mol) was added in one portion. The solvent was removed by distillation and the residue heated overnight on a steam bath. Sodium hydroxide (15%, 200 mL) was added and heating continued for 1 h. The mixture was extracted

(5) Catalytic hydrogenation to produce exclusively the cis isomer was shown previously in six-membered-ring analogues. R. H. Rynbrandt, F. L. Schmidt, and J. Szmuszkovicz, *J. Med. Chem.*, 14, 985 (1971).

(6) W. A. White and H. Weingarten, *J. Org. Chem.*, 32, 213 (1967).

(7) H. Booth, *J. Chem. Soc.*, 1050 (1959).

with ether. The extract was washed with water and extracted with 10% hydrochloric acid (200 mL). The aqueous layer was washed with ether, made basic with 40% sodium hydroxide, and extracted with ether. The extract was washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to a brown oil. Short-path, vacuum distillation gave diamine **5** as a yellow oil: 25.4 g (42%); bp 160–170 °C (0.1 mm). Treatment with propionic anhydride as above gave the propionanilide, identical with *cis*-propionanilide **6** as shown by spectroscopic comparison and mixture melting point.

Registry No. **1**, 6947-99-5; *cis*-**2**, 78089-75-5; *trans*-**2**, 78089-84-6; **5**, 78089-76-6; **5**·2HCl, 78089-77-7; **6**, 78089-78-8; **7**, 4840-12-4; **8**, 102-36-3; **10**, 78089-79-9; **11**, 78089-80-2; **12**·2HCl, 78089-81-3; **13**, 78089-82-4; propionic anhydride, 123-62-6; 2-[(dimethylamino)-methyl]cyclopent-1-yl mesylate, 78089-83-5; methanesulfonyl chloride, 124-63-0; 3,4-dichloroaniline, 95-76-1.

Borohydride and Cyanoborohydride Reduction of Thioimonium Salts. A Convenient Route for Transformation of Amides to Amines

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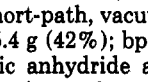
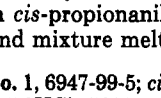
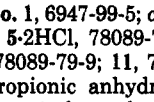
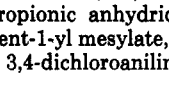
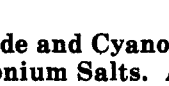
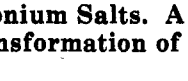
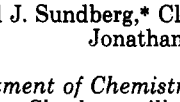
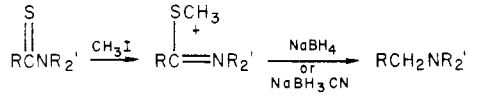
In the synthesis of deethylcatharanthine via the chloroacetamide photocyclization route recently reported from our laboratory,[1] the final stage of the synthesis required reduction of a lactam to an amine in the presence of an ester group, a carbon–carbon double bond, and the electrophile-sensitive indole ring. A sequence involving conversion to the thiolactam, methylation with methyl iodide, and reduction with sodium cyanoborohydride proved to be a very effective method for the overall reduction. Since thioamides have recently been shown to be useful synthetic intermediates,[2] we decided to explore the generality of this reduction sequence. While our work was in progress, Roush reported[3] the use of a similar reaction in one of his synthetic approaches to dendrobine. Raucher and Klein have also independently developed the reaction.[4] The procedure is the sulfur analogue of the Borch method for reduction of amides to amines via imino ethers formed by O-alkylation with trialkyloxonium ions.[5] The principal advantage of the thioamides over amides is their higher nucleophilicity. While the work of Roush and Raucher was carried out using triethyloxonium tetrafluoroborate as the alkylating reagent, we have found that alkylation of the thioamides proceeds to completion at room temperature with methyl iodide in a period of a few hours.

The reduction of tertiary aliphatic amides to amines proceeded smoothly under our conditions. The thioamides were prepared by the standard P_2S_5 method. These were alkylated with methyl iodide in tetrahydrofuran, and the precipitated salts were reduced in methanol with either sodium borohydride or sodium cyanoborohydride. Table I gives the yield of amines.

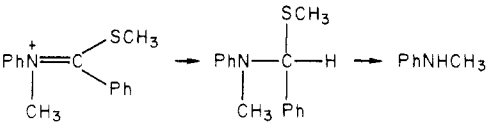
Table I. Reduction of Thioamides

thioamide	yield of amine: $NaBH_4$	yield of amine: $NaBH_3CN$
1a, 	80	70
1b, 	96	89
1c, 	61	77
1d, 	98	69
1e,	60	
1f, 	44[a,b]	
1g, 	44	
1h, 	65[c]	

[a] Reduction in the presence of $ZnCl_2$. [b] Yield determined by NMR. [c] Reduction in the presence of $SnCl_4$.



Under our standard conditions *N*-methylthiobenzanilide gave a considerably lower yield than was observed for the aliphatic amides, and some effort was devoted to examining the reaction conditions to see if the yield could be improved. Under the standard conditions *N*-methylaniline was found to be the major product, suggesting hydrolysis of the partially reduced intermediate. Inclusion of zinc



chloride to promote elimination of methanethiol improved the yield somewhat, but the yield remained below that obtained for the aliphatic amides. Similarly, the reduction of thioacetanilide proceeded in low yield under the standard conditions, but inclusion of stannic chloride in the reduction mixture resulted in a 65% yield of *N*-ethylaniline.

In the case of deethylcatharanthine we had noted enamine formation rather than complete reduction when $NaBH_4$ (basic solution) was used, while $NaBH_3CN$ (under acidic conditions) gave complete reduction to the amine. No enamine formation was noted for the compounds **1b** or **1d**. The result with deethylcatharanthine, therefore, is evidently a reflection of the special bridgehead nature of the thiolactam.[6] Placement of a carboethoxy group on the 2-position of the thioacyl moiety resulted in partial reduction to the conjugated enamine intermediate in

(1) R. J. Sundberg and J. D. Bloom, *J. Org. Chem.*, **45**, 3382 (1980).
(2) Y. Tamaru, T. Harada, and Z. Yoshida, *J. Am. Chem. Soc.*, **101**, 1316 (1979); Y. Tamaru, T. Harada, and Z. Yoshida, *ibid.*, **102**, 2392 (1980); Y. Tamaru, M. Kagotani, and Z. Yoshida, *J. Org. Chem.*, **45**, 5221 (1980); Y. Tamaru, M. Kagotani, and Z. Yoshida, *ibid.*, **44**, 2816 (1979); Y. Tamaru, T. Harada, H. Iwamoto, and Z. Yoshida, *J. Am. Chem. Soc.*, **100**, 5221 (1978); Y. Tamaru, T. Harada, and Z. Yoshida, *ibid.*, **100**, 1923 (1978).
(3) W. R. Roush, *J. Am. Chem. Soc.*, **102**, 1390 (1980).
(4) S. Raucher and P. Klein, *Tetrahedron Lett.*, 4061 (1980).
(5) R. F. Borch, *Tetrahedron Lett.*, 61 (1968).
(6) Even lithium aluminum hydride reduction gives only partial reduction of lactams in this skeletal system: W. Nagata, S. Hirai, K. Kawata, and T. Okumura, *J. Am. Chem. Soc.*, **89**, 5046 (1967); W. Nagata, S. Hirai, T. Okumura, and K. Kawata, *ibid.*, **90**, 1650 (1968).

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