Notes

Bimanes. 21. *syn*-(Methyl,fluoro)bimane Formation via Acetyl Hypofluorite

Edward M. Kosower,*[1a,b] David Hebel,[1a] Shlomo Rozen,[1a] and Annette E. Radkowski[1a]

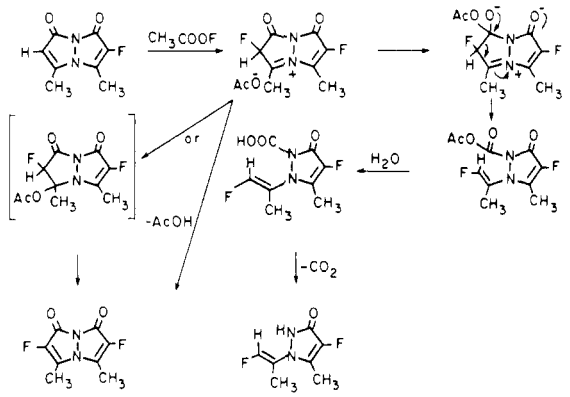
School of Chemistry, Sackler Faculty of Exact Sciences, Tel-Aviv University, Ramat-Aviv, 69978 Tel-Aviv, Israel, and Department of Chemistry, State University of New York, Stony Brook, New York 11794

Received February 19, 1985

Bimanes are bicyclic ring compounds that exhibit many interesting chemical,[2-6] photochemical,[7] and photophysical[8-13] properties along with useful applications in biology.[14-18] Ring-fluorinated bimanes were desired because (1) the small atomic size of fluorine would increase intermolecular interactions in the crystal over those observed for *syn*-(hydro, chloro)bimanes,[8-10] (2) the fluorine substituent would allow a stringent test of the Hammett $\rho-\sigma$ correlation for the rate constants of hydroxide-catalyzed bimane ring opening and (3) the fluoro derivative would extend the series of chloro-, bromo-, and iodobimanes for which a variety of physical properties have already been recorded.

Fluorinated heterocyclics cannot usually be synthesized by direct fluorination due to reaction of the fluorine at the heteroatom. Bimane derivatives are attractive as substrates for the electrophilic fluorination of heterocyclics with the new reagent acetyl hypofluorite.[19-22] The nitrogen atoms in bimanes are very low in basicity; the UV spectrum of *syn*-(CH_3,CH_3)B changes only a little in 6 N H_2SO_4, and the half-life of the bimane in this solution is more than 3 months at 25 °C.[2]

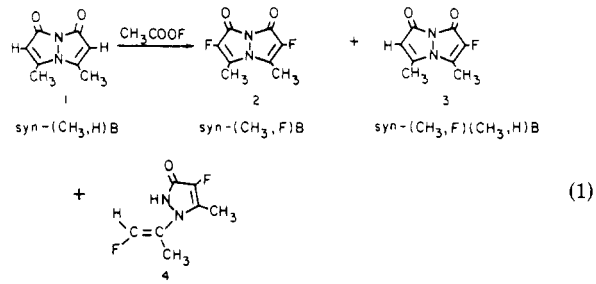
Scheme I



We report here the successful conversion of *syn*-(CH_3,H)B (1) to *syn*-(methyl,fluoro)bimane (2) via replacement of hydrogen by fluorine. The half-fluorinated derivative *syn*-(methyl,fluoro)(methyl,hydro)bimane (3) has also been isolated in low yield.

Results and Discussion

Synthesis. *syn*-(Methyl,hydro)bimane (1) reacts with acetyl hypofluorite in cold chloroform–nitromethane (2:1) solution (−75 °C) to form *syn*-(methyl,fluoro)bimane (2) (eq 1). Excess starting bimane is used to avoid further



(1)

reaction of the product bimane with acetyl hypofluorite or the small amounts (<15%) of other oxidizing materials that are present. Three products are isolated by chromatography of the solid after removal of the solvent. The desired bimane, *syn*-(CH_3,F)B (2), is obtained in ca. 25% yield along with the "mixed" bimane, *syn*-(CH_3,H)-(CH_3,F)B (3), in 5% yield. A major product is 2-((*Z*)-1-methyl-2-fluorovinyl)-3-methyl-4-fluoro-5-pyrazolinone (4). The strong fluorescence of the bimane is exhibited in the reaction solution.

The conversion of 1 into 2 with acetyl hypofluorite represents the first reported electrophilic fluorination of a heterocyclic compound other than uracil or cytosine.[23-25]

(1) (a) Tel-Aviv University. (b) State University of New York, Stony Brook.
(2) Kosower, E. M.; Pazhenchevsky, B. *J. Am. Chem. Soc.* **1980**, *102*, 4983-4993.
(3) Kosower, E. M.; Pazhenchevsky, B.; Dodiuk, H.; Kanety, H.; Faust, D. *J. Org. Chem.* **1981**, *46*, 1666-1673.
(4) Kosower, E. M.; Pazhenchevsky, B.; Dodiuk, H.; Ben-Shoshan, M.; Kanety, H. *J. Org. Chem.* **1981**, 46, 1673-1679.
(5) Kosower, E. M.; Ben-Shoshan, M.; Faust, D.; Goldberg, I. *J. Org. Chem.* **1982**, *47*, 213-221.
(6) Kanety, H.; Kosower, E. M. *J. Org. Chem.* **1982**, *47*, 4222-4226.
(7) Kanety, H.; Dodiuk, H.; Kosower, E. M. *J. Org. Chem.* **1982**, *47*, 207-213.
(8) Kosower, E. M.; Kanety, H.; Dodiuk, H. *J. Photochem.* **1982**, *21*, 171-182.
(9) Kosower, E. M.; Kanety, H.; Dodiuk, H.; Hermolin J. *J. Phys. Chem.* **1982**, *86*, 1270.
(10) Shannon, V. L.; Strauss, H. L.; Kosower, E. M. *J. Org. Chem.* **1984**, *49*, 2815-2816.
(11) Kosower, E. M.; Hermolin, J.; Ben-Shoshan, M.; Faust, D. *J. Org. Chem.* **1981**, *46*, 4578-4580.
(12) Goldberg, I.; Kosower, E. M. *J. Phys. Chem.* **1982**, *86*, 332-335.
(13) Giniger, R.; Huppert, D.; Kosower, E. M. *Chem. Phys. Lett.* **1985**, *118*, 240-245.
(14) Kosower, N. S.; Kosower, E. M.; Newton, G. L.; Ranney, H. M. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 3382-3386.
(15) Gainer, H.; Kosower, N. S. *Histochemistry* **1980**, *68*, 309-315.
(16) Kosower, N. S.; Kosower, E. M.; Zipser, J.; Faltin, Z.; Shomrat, R. *Biochem. Biophys. Acta* **1981**, *640*, 748-759.
(17) Newton, G. L.; Dorian, R.; Fahey, R. C. *Anal. Biochem.* **1981**, *114*, 383-387.
(18) Vogel, F.; Lumper, L., *Biochem. J.* **1983**, *215*, 159-166
(19) Rozen, S.; Lerman, O.; Kol, M. *J. Chem. Soc., Chem. Commun.* **1981**, 443-444.
(20) Lerman, O.; Tor, Y.; Rozen, S. *J. Org. Chem.* **1981**, *46*, 4629-4631.
(21) Lerman, O.; Rozen, S. *J. Org. Chem.* **1983**, *48*, 724-727.
(22) Lerman, O.; Tor, Y., Hebel, D.; Rozen, S. *J. Org. Chem.* **1984**, *49*, 806-813.
(23) (a) Eckes, L.; Hanack, M. *Synthesis* **1978**, 217. (b) Baklouti, A.; Charbouni, M. M. *J. Fluorine Chem.* **1981**, *19*, 181.
(24) Barton, D. H. R.; Hesse, R. H.; Toh, H. T.; Pechet, M. M. *J. Org. Chem.* **1972**, *37*, 329-330.

0022-3263/85/1950-4152$01.50/0

The usual procedure for fluorination with CH_3COOF utilizes excess hypofluorite. In the case of reactive materials, excess substrate is required to avoid loss of the product through side reactions.[22] Bimanes are highly reactive toward electrophilic fluorinating agents. This is shown by the fact that the mixed bimane, i.e., *syn*-(CH_3,F)(CH_3,H)B (**3**), is produced in low yield, even though a substantial amount of starting material (**1**) is recovered. The simplest explanation is that **3** is formed and reacts further before the fluorinating agent can be completely dispersed. Bromination of *syn*-(CH_3,CH_3)B, under the usual conditions, yields both the monobromo derivative ($BrCH_2$,CH_3) (CH_3,CH_3)B and the dibromo compound ($BrCH_2$,CH_3)B. Rather high dilution during addition is needed to favor monobromination.

The structure of the important byproduct (2-((*Z*)-1-methyl-2-fluorovinyl)-3-methyl-4-fluoro-5-pyrazolinone (**4**) is based on hydrogen, fluorine, and ^{13}C NMR spectra. These spectra show three different hydrogens, 2 different fluorines, and seven different carbon atoms. A mechanism for the formation of **4** is shown in Scheme I. It is proposed that the acetyl hypofluorite acts as an F^+ donor, forming an intermediate iminium acetate ion pair. The ion pair can collapse through either (a) formation of an adduct at C_4 (C_6) which eventually leads to a ring-substituted bimane or (b) formation of a carbonyl addition product which yields **4** after a ring-opening step, hydrolysis, and decarboxylation.

Physical Properties. The physical properties of the fluorinated bimanes are in agreement with the proposed structures, as follows: *syn*-(methyl,fluoro)bimane (**2**), UVλ_{max} 340 nm (dioxane), NMR spectra (^1H NMR) [CH_3] 2.40, (^{19}F NMR) 168.3 ppm, mass spectrum, [M^+] *m/e* 200, fluorescence λ_{max} 433 nm (dioxane), IR spectrum [2930 (C–H), 1780 (C=O) cm^{-1}], and chromatographic behavior; *syn*-(methyl,fluoro)(methyl,hydro)bimane (**3**), UV λ_{max} 350 nm (dioxane), NMR spectra (^1H NMR) [CH_3] 2.39 and 2.40, [H] 5.53, (^{19}F NMR) 170.83 ppm, mass spectrum, [M^+] *m/e* 182, and fluorescence λ_{max} 408 nm (dioxane).

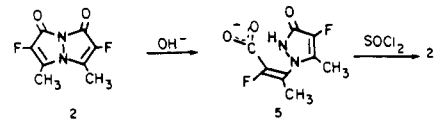
The chemical shift of the methyl group in **2** at 2.40 ppm seems somewhat unusual in comparison to what is seen for other related bimanes. In the series *syn*-(CH_3,X)B, the shifts (in ppm) are respectively CH_3, 2.31, H, 2.38, Cl, 2.47, Br, 2.47, I, 2.52. The coupling between the ^{19}F and the CH_3 hydrogens is 0.7 Hz, within the range of the values usually found.[26]

The absorption maximum for **2** in dioxane is at 340 nm, at much a shorter wavelength than that for **1** (354 nm) or for *syn*-(CH_3,Cl)B (364 nm). A detailed discussion of bimane conformations and photophysical properties will be given elsewhere together with a description of the photophysical properties of **2**.[27]

The carbonyl stretching frequency for **2** is at 1780 cm^{-1}, at a higher frequency than for all the bimanes in the series *syn*-(CH_3,X)B (1760 cm^{-1}) except for X = H (1765 and 1740 cm^{-1}) and X = CH_3 (1745 cm^{-1}). Decreased conjugation as in a "bent" bimane could account for the position of the band in **2**.

Chemical Properties. The rate constant for hydrolysis of **2** at 50 °C is 82.6 M^{-1}/s^{-1} and fits that expected for the σ_m constant (0.34). The ρ value for the Hammett correlation is 3.0, by using the sum of $\sigma_m + 0.5\sigma_m$ to account for the substituents in both rings.[6] Thus, the fluorine in the ground state acts as a purely electronegative substituent. The previous choice of σ_m to correlate the rate constants for the hydrolysis of bimanes bearing other substituents is reinforced and the validity of the correlation considerably enhanced.

The bimane is reformed on isolation of the hydrolysis product **5** and treatment with thionyl chloride (eq 2).



(2)

There is no observable reaction of *syn*-(CH_3,F)B with dilute bromine in CH_2Cl_2 at room temperature (the usual conditions for brominations of *syn*-(CH_3,CH_3)B) over a period of 1 week. *syn*-(CH_3,Cl)B is reported to have been converted to the monobromo derivative under these conditions in 2 months. Further studies on the bromination reaction will be carried out when adequate quantities of **2** are available.

The compound **2** darkens somewhat but is otherwise unchanged at the melting point (160 °C).

Experimental Section

The following instruments were used for the measurements: a Cary Model 17 spectrophotometer (ultraviolet–visible spectra), a Perkin-Elmer Model 257 instrument (infrared spectra), a Hitachi Perkin-Elmer spectrofluorimeter MPF-4 (fluorescence spectra), Du Pont mass spectrometer 21–491B (mass spectra), Bruker WH-90 and AM-360 NMR spectrometers (NMR spectra).

***syn*-(CH_3,F)B (2).** A solution of acetyl hypofluorite (ca. 50 mmol) was generated according to Lerman et al.[22] and added in small portions (10 mL) to a well-stirred solution of the bimane *syn*-(CH_3,H)B (**1**; 560 mg, 3.5 mmol) in 700 mL of chloroform–nitromethane (2:1) at −75 °C. The progress of the reaction was monitored by TLC on silica gel. The reaction was usually very fast. The solvent was evaporated without warming and the residue chromatographed on silica gel with 20% ethyl acetate–petroleum ether.

The first compound eluted was 2-((*Z*)-1-methyl-2-fluorovinyl)-3-methyl-4-fluoro-5-pyrazolinone (**4**), obtained as white crystals from ethyl acetate (303 mg, 50%): mp 150–152 °C; IR (KBr) 3110, 3000, 2800–2300, 1595, 1440, 1400, 1370, 1340, 1270, 1220, 1170, 1130, 1085, 1040, 850, 715 cm^{-1}; ^1H NMR ($CDCl_3$) 1.98 [3 H, dd, $^4J_{HF}$ = 4.75 Hz, $^4J_{HH}$ = 1.45 Hz], 2.18 [3 H, d, $^4J_{HF}$ = 1.65 Hz], 6.88 [1 H, dq, J_{HF} = 78 Hz, $^4J_{HH}$ = 1.45 Hz] ppm; ^{19}F NMR ($CDCl_3$; $CFCl_3$ ref) −137.25 [1 F, d, J_{HF} = 78 Hz], −188.78 [1 F] ppm; ^{13}C NMR ($CDCl_3$) 8.57 [q], 13.48 [q], 123.1 [d, $^2J_{CF}$ = 28 Hz], 127.29 [d, $^2J_{CF}$ = 22 Hz], 133.86 [d, $^1J_{CF}$ = 241 Hz], 149.1 [dd, $^1J_{CF}$ = 263 Hz], 150.43 [s] ppm; mass spectrum *m/e* 174 [M^+], 115 [(M–CH_3CCHF)$^+$]. Anal. Calcd for $C_7H_8F_2N_2O$: C, 48.27; H, 4.60; F, 21.84. Found: C, 48.42; H, 4.48; F, 21.57.

The second compound eluted was *syn*-(methyl,fluoro)bimane [*syn*-(CH_3,F)B (**2**): 343 mg, 25%], obtained as light yellow crystals from CH_3CN or *i*-PrOH: mp 160 °C (darkens without dec); IR (KBr) 2930, 1780, 1705, 1670, 1420, 1330, 1220, 1030, 795, 740 cm^{-1}; UV (dioxane) λ_{max} 340 nm (ϵ_{max} 5000); fluorescence (dioxane) λ_{max} 433 nm (ϕ_F 0.86); ^1H NMR ($CDCl_3$) 2.40 [d, J_{HF} = 0.7 Hz] ppm; ^{19}F NMR $CDCl_3$; $CFCl_3$ ref) −168.3 ppm; mass spectrum, 200 [M^+]. Anal. Calcd for $C_8H_6F_2N_2O_2$: C, 48.00; H, 3.00; F, 19.00. Found: C, 47.82; H, 2.91; F, 19.21.

The third compound eluted was *syn*-(methyl,hydro)(methyl,fluoro)bimane [*syn*-(CH_3,H)(CH_3,F)B (**3**)], as light yellow crystals (31 mg, 5%): mp 197 °C (ethyl acetate); IR (KBr) 3120, 3110, 1750, 1675, 1580, 1440, 1395, 1370, 1230, 1145, 1030, 810 cm^{-1}; UV (dioxane) λ_{max} 350 nm (ϵ_{max} 4500); fluorescence (dioxane) λ_{max} 408 nm (ϕ_F 0.93); ^1H NMR ($CDCl_3$) 2.39 [3 H, s], 2.40 [3 H, d, J_{HF} = 3.5 Hz], 5.53 [m, 1 H] ppm; ^{19}F NMR ($CDCl_3$; $CFCl_3$ ref) −170.83 ppm; mass spectrum, *m/e* 182 [M^+]. Anal. Calcd for $C_8H_7FN_2O_2$: C, 52.75; H, 3.84; F, 10.44. Found. C, 52.93; H, 3.62; F, 10.85.

(25) A detailed study of the reactions of acetyl hypofluorite with various alkenes will be submitted in the near future for publication.

(26) (a) Lovey, A. J.; Pawson, B. A. *J. Med. Chem.* **1982**, *25*, 71. (b) Jackman, L. M.; Sternhell, S. In "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969; p 350.

(27) Kosower, E. M., Hebel, D.; Radkowski, A.; Giniger, R.; Shusterman, A., submitted for publication.

The conversion of *syn*-(methyl,hydro)bimane (1) to products was between 50% and 100%, based on the recovery of 1. The yields of 2 were between 25% and 30%, of 3 between a trace and 5%, and of 4 from 50% to 60%.

Kinetic Measurements. *syn*-(CH_3,F)B (2) was dissolved in CH_3CN. An aliquot (100 μL) was added rapidly to aqueous buffer, pH 10.2, maintained at 50.0 °C in a thermostated quartz cell located in the cell compartment of a Cary 17 spectrophotometer. The decrease of absorption at 360 nm was followed with time for more than 10 half-lives. The second-order rate constant for the reaction of the bimane with hydroxide ion was obtained from the experimental curve from the slope of the plot of log ($D_t - D_{inf}$) vs. time and dividing by the temperature corrected hydroxide ion concentration.

Regeneration of 2 from the Pyrazolinoylacrylic Acid. A mixture of the acid (obtained from base-catalyzed ring opening of *syn*-(CH_3,F)B and acidification) (1 mg) and thionyl chloride (10 μL) was stirred for 24 h. After removal of thionyl chloride under vacuum, the residue was shown to be identical with authentic *syn*-(CH_3,F)B (2) in absorption maximum (340 nm; dioxane), emission maximum (433 nm; dioxane), and thin-layer chromatographic behavior.

Acknowledgment. The aid of M. Ben-Shoshan and Y. Menachem in preparing the *syn*-(CH_3,H)B is acknowledged. Partial support of the work by the donors of the Petroleum Research Fund, administered by the American Chemical Society, the U.S.-Israel Binational Science Foundation, and the European Research Office, U.S. Army, is appreciated.

Registry No. 1, 74235-71-5; 2, 98194-60-6; 3, 98194-61-7; 4, 98194-62-8; 5, 98194-63-9; acetyl hypofluorite, 78948-09-1.

A Convenient Method for Obtaining *trans*-2-Aminocyclohexanol and *trans*-2-Aminocyclopentanol in Enantiomerically Pure Form

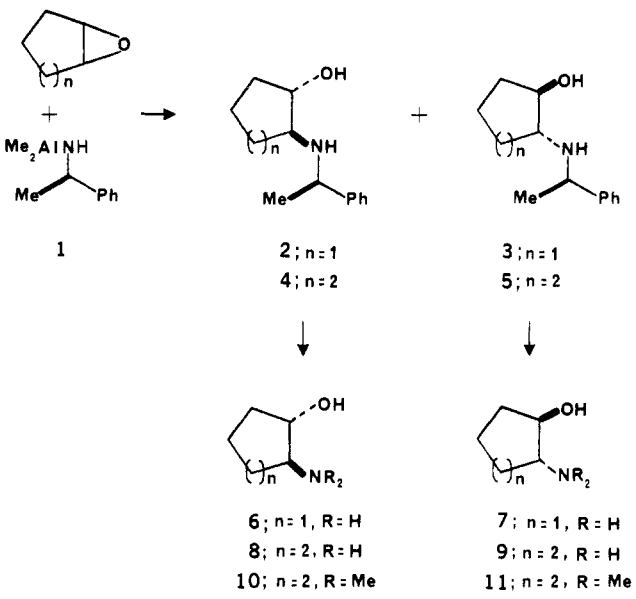
L. E. Overman* and S. Sugai[1]

Department of Chemistry, University of California, Irvine, California, 92717

Received February 19, 1985

We recently reported[2] that Amaryllidaceae alkaloids could be prepared in good yield from 2-aminocyclopentanones by a sequence whose key step was a cationic aza-Cope rearrangement. In order to extend this approach to the preparation of these alkaloids in enantiomerically pure form,[3] we required a method for preparing (1*R*,2*R*)-*trans*-2-aminocyclopentanol on a large scale. This intermediate had previously been obtained by classical resolutions, which proceeded, however, in low overall efficiency.[4,5] In this paper, we report that both enantiomers of *trans*-2-aminocyclopentanol and *trans*-2-aminocyclohexanol can be conveniently obtained by the chromatographic separation of the diastereomeric *trans*-amino alcohols resulting from the reaction of cyclopentene oxide or cyclohexene oxide with the reagent[6] formed from (*R*)-α-methylbenzylamine and trimethylaluminum.

Scheme I



Aminolysis[6] of cyclopentene oxide or cyclohexene oxide with aluminum amide 1 proceeded in nearly quantitative yield at room temperature. Although this reaction occurred, not surprisingly, with virtually no diastereoselectivity, the amino alcohol products were easily separated in high yield (see Table I) by simple flash chromatography on silica gel. Hydrogenolysis[7] then provided highly enantiomerically pure samples of **6**–**9**[8] (Scheme I) in overall yields from the starting epoxide of 36–41%.

The general resolution method reported here should be useful for the preparation of other optically active β-amino alcohols.[10]

Experimental Section[11]

(1*S*,2*S*)-*trans*-2-[(*R*)-(α-Methylbenzyl)amino]cyclohexanol (4) and (1*R*,2*R*)-*trans*-2-[(*R*)-(α-Methylbenzyl)amino]cyclohexanol (5). A solution of Me_3Al (6.2 mL of a 2.0 M solution in toluene, 12.4 mmol) was added dropwise at 0 °C to a rapidly stirred solution of (+)-(*R*)-α-methylbenzylamine (1.50 g, 12.4 mmol)[11] and CH_2Cl_2 (10 mL). The resulting solution was maintained for 1 h at 0 °C and then a solution of cyclohexene oxide (1.28 g, 13.1 mmol) and CH_2Cl_2 (10 mL) was added dropwise. The resulting solution was maintained for an additional 3 h at 0 °C and then left overnight at 25 °C. The aluminate salt was decomposed[12] at 0 °C by adding 2.2 g (52 mmol) of NaF followed

(1) On sabbatical leave from the Agricultural Chemicals Research Laboratory, Sankyo Company, Tokyo, Japan.

(2) Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629.

(3) For a report of the total synthesis of (-)-crinine, see: Overman, L. E.; Sugai, S. *Helv. Chem. Acta* **1985**, *68*, 745.

(4) See, inter alia: (a) *trans*-2-Aminocyclopentanol: Godchot, M.; Mousseron, M *Bull. Soc. Chim. Fr.* **1932**, *51*, 1270. (b) *trans*-2-(Benzylamino)cyclopentanol: Barr, A. A.; Frencel, I.; Robinson, J. B. *Can. J. Chem.* **1977**, *55*, 4180.

(5) Optically active β-amino alcohols, including *trans*-2-(dimethylamino)cyclohexanol, have recently been obtained by the Sharpless kinetic resolution procedure: Miyano, S.; Lu, L. D.-L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3611.

(6) (a) Overman, L. E.; Flippin, L. A. *Tetrahedron Lett.* **1981**, *22*, 195. (b) This aminolysis can be accomplished with the reagent prepared from (*R*)-α-methylbenzylamine and triethylaluminum; however, the reaction is considerably slower.

(7) Anwer, M. K.; Spatola, A. F. *Synthesis* **1980**, 929.

(8) The absolute configuration of the *trans*-2-aminocyclopentanols[4b] and the *trans*-2-(dimethylamino)cyclohexanols[9] have been established.

(9) Kay, J. B.; Robinson, J. B. *J. Chem. Soc. C* **1969**, 248. Robinson, J. B. *J. Pharm. Pharmacol.* **1970**, *22*, 222.

(10) A similar resolution procedure was recently employed in the synthesis of a fortimycin aglycone: Schubert, J.; Schwesinger, R.; Prinzbach, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 167.

(11) For general experimental details, see: Overman, L. E.; Jacobsen, E. J.; Doedens, R. J. *J. Org. Chem.* **1983**, *48*, 3393. (+)-(*R*)-α-Methylbenzylamine ($[\alpha]^{25}_D$ +39.4°, neat) was purchased from *Norse Laboratories*, Newbury Park, CA. Flash chromatography was carried out with E. Merck silica gel, 230–400 mesh.

(12) Yamamoto, H.; Muruoka, K. *J. Am. Chem. Soc.* **1981**, *103*, 4186.

0022-3263/85/1950-4154$01.50/0