Experimental Section

The alkyl(trimethylsilyl)amines and (trimethylsilyl)aniline were all prepared according to the literature;[1] bis(trimethylsilyl)amine was purchased (Fisher Scientific) and distilled prior to use. Acid chlorides were purchased (Aldrich) and checked for purity by NMR and IR spectroscopy; if necessary they were purified by distillation or recrystallization. All solvents were distilled from calcium hydride immediately prior to use. All reactions were performed under an atmosphere of dry nitrogen with the aid of a vacuum manifold.

Products were characterized by ^1H NMR (Varian EM 360L) and IR (Perkin Elmer 735B) spectroscopy; melting points were taken with a Fisher-Johns melting point apparatus and checked against published values, agreeing in all cases to within ±3 °C. Elemental analyses were performed by Micanal of Tucson, AZ.

Preparation of Monofunctional Amides. A representative procedure for reactions of this type is given here for the synthesis of *N-tert*-butylacetamide. A 250-mL two-necked flask equipped with a magnetic stirrer and an addition funnel was evacuated and filled with dry N_2. *tert*-Butyl(trimethylsilyl)amine (5.81 g, 0.040 mol) was added along with 120 mL of hexane. Acetyl chloride (2.9 mL, 0.041 mol) was added dropwise to the room-temperature solution, resulting in the formation of a white precipitate; stirring was continued for 5 h. Vacuum filtration, washing with hexane to remove residual chlorotrimethylsilane, and recrystallization from isopropyl alcohol yielded 4.05 g (88%) of the product amide [mp 97–98 °C (lit.[7] mp 97 °C)].

Reactions of Diacid Chlorides with Alkyl(trimethylsilyl)amines. A. Preparation of Diamides. A typical reaction is described here for the synthesis of *N,N,N',N'*-tetraethyloxamide. Oxalyl chloride (4.68 g, 0.0369 mol) in 10 mL of hexane was slowly added to diethyl(trimethylsilyl)amine (10.90 g, 0.0750 mol) in 90 mL of hexane at room temperature under an atmosphere of N_2, resulting in the formation of an orange-red liquid mixture. Rotary evaporation of solvent and Me_3SiCl left a colored oily residue, which was recrystallized twice from CCl_4 to give the diamide [4.06 g = 55%; mp 33–35 °C (lit.[8] mp 35–36 °C)].

B. Preparation of *N-tert*-Butyloxamoyl Chloride. A solution of Me_3SiNH-*t*-Bu (3.78 g, 0.0260 mol) in 10 mL of hexane was added dropwise over a 15-min period to a stirred solution of oxalyl chloride (3.55 g, 0.0280 mol) in 35 mL of hexane under a nitrogen atmosphere at −23 °C; this temperature was maintained with a CCl_4/liquid N_2 slurry. Stirring was continued for 1.5 h as precipitation occurred. Solvent and Me_3SiCl were removed by low-pressure distillation under N_2 at 0 °C; the crystalline residue was washed with hexane and recrystallized from CCl_4 to give the product (1.83 g, 43%, mp 90–91 °C). Anal. Calcd for $C_6H_{10}ClNO_2$: C, 44.05; H, 6.16; N, 8.56. Found: C, 44.14; H, 6.28; N, 8.65.

C. Preparation of *N*-Isopropyloxamoyl Chloride. In a procedure similar to that described above, Me_3SiNH-*i*-Pr (4.61 g, 0.0351 mol) and $(COCl)_2$ (4.59 g, 0.0362 mol) were reacted to give a white precipitate identified as the expected product (1.89 g, 36%, mp 113 °C). Anal. Calcd for $C_5H_8ClNO_2$: C, 40.15; H, 5.39; N, 9.36. Found: C, 40.11; H, 5.37; N, 9.44.

Reactions of Bis(trimethylsilyl)amine with Acid Chlorides. A. Preparation of *N*-(Trimethylsilyl)benzamide. A solution of benzoyl chloride (34.71 g, 0.247 mol) in 50 mL of hexane was added dropwise to stirred $(Me_3Si)_2NH$ (40.35 g, 0.250 mol) in 90 mL of hexane, resulting in the formation of a white precipitate. Following reflux for 2 h under nitrogen, the mixture was cooled and filtered; the solid product was recrystallized from hot CCl_4 and identified as the desired silyl amide by NMR and IR spectroscopy. The yield was 40.69 g (85% based on C_6H_5COCl).

B. Preparation of Polyimides. In a representative procedure oxalyl chloride (4.82 g, 0.0380 mol) and $(Me_3Si)_2NH$ (6.13 g, 0.0380 mol) were mixed at room temperature in 20 mL of hexane under an atmosphere of dry N_2, resulting in the precipitation of a white solid. After stirring of the mixture for 5 h, volatile materials were removed by rotary evaporation, and the residue was washed several times with hexane, CCl_4, and $CHCl_3$. This crystalline solid did not melt below 240 °C and was insoluble in water and most organic solvents; it gave NMR and IR spectra consistent with those expected for a polyimide.

Registry No. EtNHCOMe, 625-50-3; EtNHCOEt, 5129-72-6; EtNHCOPh, 614-17-5; *i*-PrNHCOMe, 1118-69-0; *i*-PrNHCOEt, 10601-63-5; *i*-PrNHCOPh, 5440-69-7; *t*-BuNHCOMe, 762-84-5; *t*-BuNHCOEt, 1118-32-7; *t*-BuNHCOPh, 5894-65-5; PhNHCOMe, 103-84-4; PhNHCOEt, 620-71-3; PhNHCOPh, 93-98-1; $(Et)_2NCOEt$, 1114-51-8; $(Et)_2NCOPh$, 1696-17-9; EtNHTMS, 1735-00-8; *i*-BuNHTMS, 5577-65-1; *t*-BuNHTMS, 5577-67-3; PhNHTMS, 3768-55-6; $(Et)_2NTMS$, 996-50-9; MeCOCl, 75-36-5; EtCOCl, 79-03-8; PhCOCl, 98-88-4; $(Et)_2NCOCOCl$, 87039-68-7; $(Et)_2NCOCH_2COCl$, 87039-69-8; *o*-$(Et)_2NCOC_6H_4COCl$, 79422-68-7; *p*-$(Et)_2NCOC_6H_4COCl$, 87039-70-1; *i*-PrNHCOCOCl, 87039-71-2; *t*-BuNHCOCOCl, 87039-72-3; $((Et)_2NCO)_2$, 14288-05-2; $((Et_2NCO)_2CH_2$, 33931-42-9; *o*-$((Et)_2NCO)C_6H_4$, 83-81-8; *p*-$((Et)_2NCO)_2C_6H_4$, 15394-30-6; $(ClCO)_2$, 79-37-8; $(ClCO)_2CH_2$, 1663-67-8; *o*-$C_6H_4(COCl)_2$, 88-95-9; *p*-$C_6H_4(COCl)_2$, 100-20-9; TMSNHCOMe, 13435-12-6; TMSNHCOEt, 18140-08-4; TMSNHCOPh, 1011-57-0; $((ClCO)_2)$·(TMSNHTMS) (copolymer), 87039-67-6; $((ClCO)_2CH_2)$·(TMSNHTMS) (copolymer), 87050-06-4; (*p*-$(ClCO)_2C_6H_4$)·(TMSNHTMS) (copolymer), 87050-07-5; $(MeCO)_2NH$, 625-77-4; $(EtCO)_2NH$, 6050-26-6; $(PhCO)_2NH$, 614-28-8; $(TMS)_2NH$, 999-97-3.

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Stereospecific Synthesis of Hydroxyl-Differentiated (*E*)- and (*Z*)-1,4-Enediols

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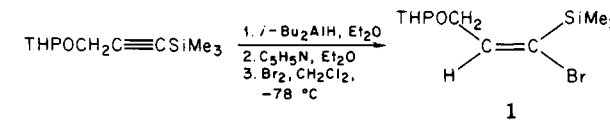
Hydroxyl-differentiated 1,4-enediols have significant potential as intermediates in the synthesis of complex organic molecules. Recently, Masamune and Sharpless[1] demonstrated the utility of such compounds in the synthesis of saccharides and related polyhydroxylated natural products via assymetric epoxidation. Also the potential exists for ultimate control of regiochemistry in Diels–Alder reactions by selective oxidation of the enediols to give regiocomplementary dienophiles. Therefore a general, stereospecific synthesis of hydroxyl-differentiated 1,4-enediols would be most useful; such a process is described in this paper.

The key compounds for this study were the tetrahydropyranyl ethers of (*E*)- and (*Z*)-3-bromo-3-(trimethylsilyl)-2-propen-1-ol. The *E*-isomer **1** was prepared stereospecifically by hydroalumination–bromination[2] of the tetrahydropyranyl ether of 3-(trimethylsilyl)-2-propyn-1-ol.[3] The product **1** was obtained in 80% isolated yield.



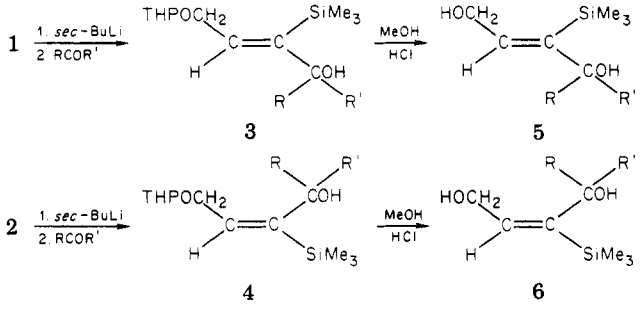
1

It was observed that ~5% cleavage of the tetrahydropyranyl ether was obtained in the crude reaction product. This material could either be separated from **1** by distillation or reprotected by treating the crude reaction product with dihydropyran and a catalytic amount of phosphorus oxychloride. In an attempt to suppress the cleavage of the tetrahydropyranyl ether, use of an equivalent amount of

(1) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373.
(2) Zweifel, G.; Lewis, W. *J. Org. Chem.* **1978**, *43*, 2739.
(3) Miller, R. B. *Synth. Commun.* **1972**, *2*, 267.

0022-3263/83/1948-4113$01.50/0

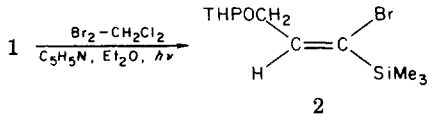
Table I



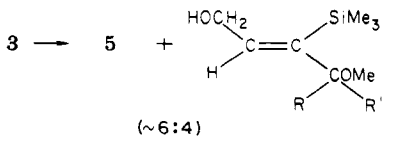
starting material	R	R'	% isolated yield 3	4	5	6
1	Et	H	78		80	
1	Me	Me	77		54	
1	Ph	H	69		70	
1	$(-CH_2-)_5$		80		51	
2	Et	H		75		81
2	Me	Me		75		70

tetrahydrofuran to diisobutylaluminum hydride was employed in the hydroalumination step in order to preferentially coordinate the aluminum by the tetrahydrofuranyl oxygen in analogy to a recent observation by Zweifel.[4] Under these conditions, no cleavage of the tetrahydropyranyl ether was observed, but unfortunately the yield of the desired product 1 dropped to 50%.

The *Z*-isomer 2 was prepared by isomerization of 1 using bromine in the presence of light.[2] Compound 2 was obtained in 82% isolated yield with 97% isomeric purity.



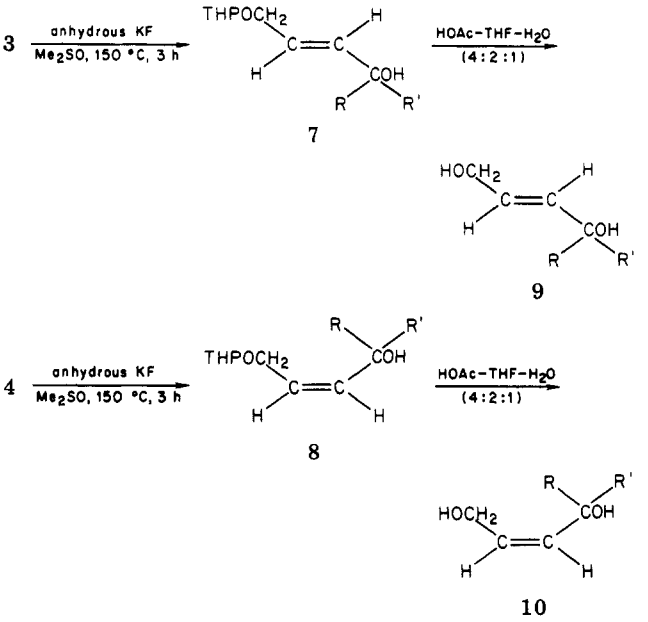
Next the bromovinylsilanes 1 and 2 were converted to the corresponding vinyllithium reagents by halogen–metal exchange with *sec*-butyllithium in tetrahydrofuran at −78 °C followed by reaction with an aldehyde or ketone to give the silylated 1,4-enediols 3 and 4 in which the two hydroxyl groups are differentiated. The results of this process are shown in Table I. It should be noted that, in order to maintain the stereospecific nature of the overall reaction, the vinyllithium reagent must be maintained below −65 °C during both its formation and reaction with the appropriate carbonyl compound.[5] For analytical purposes the tetrahydropyranyl ether was removed by exchange with methanol, using hydrochloric acid as a catalyst, to give the silylated 1,4-enediols 5 and 6. The lower yields obtained for 5 with R = R' = Me and R, R' = $(-CH_2-)_5$ in this exchange reaction are attributed to significant amounts of 4-methoxylated materials being formed.



[for R = R' = Me and R, R' = $(-CH_2-)_5$]

The vinyl carbon–silicon bond in the silylated 1,4-enediols 3 and 4 was stereospecifically cleaved with use of

Table II



starting material	R	R'	% isolated yield 7	8	9	10
3	Et	H	61		51	
3	Me	Me	77		48	
3	Ph	H	75		54	
3	$(-CH_2-)_5$		78		49	
4	Et	H		71		52
4	Me	Me		78		47

anhydrous potassium fluoride in dimethyl sulfoxide[6] to give the desired hydroxyl-differentiated (*E*)- and (*Z*)-1,4-enediols 7 and 8, respectively. The results of this process are shown in Table II. Again for analytical purposes it was desired to remove the tetrahydropyran group, but the conditions used previously (methanol and a few drops of hydrochloric acid) gave mostly methoxylated products. Therefore the cleavage was carried out with a mixture of acetic acid–tetrahydrofuran–water (4:2:1) at 45 °C.[7]

Summary

A general, stereospecific synthesis of hydroxyl-differentiated (*E*)- and (*Z*)-1,4-enediols has been achieved with the tetrahydropyranyl ethers of (*E*)- and (*Z*)-3-bromo-3-(trimethylsilyl)-2-propen-1-ol as the key intermediates by conversion to the corresponding vinyllithium reagents followed by reaction with aldehydes or ketones. The vinyl carbon–silicon bond of this addition product was cleaved stereospecifically with anhydrous potassium fluoride in dimethyl sulfoxide to give the desired hydroxyl-differentiated 1,4-enediols.

Experimental Section

Boiling points were recorded at gauge pressure and are reported uncorrected. Infrared spectra were obtained on a Beckman IR-8 spectrometer with only selected absorptions being reported. Nuclear magnetic resonance (^1H) spectra were obtained on a Varian EM390 instrument. Chemical shifts are reported as δ values in ppm downfield relative to internal tetramethylsilane or δ^* values in ppm downfield relative to the trimethylsilyl absorption of silicon-containing compounds. High-resolution mass

(4) Zweifel, G., Department of Chemistry, University of California, Davis, CA, personal communication, 1981.
(5) For the configurational stability of some (1-lithio-1-alkenyl)trimethylsilanes, see: Zweifel, G.; Murray, R. E.; On, H. P. *J. Org. Chem.* **1981**, *46*, 1292. Miller, R. B.; McGarvey, G. *Ibid.* **1979**, *44*, 4623.
(6) Chan, T. H.; Mychajlowskij, W. *Tetrahedron Lett.* **1974**, 3479. Fristad, W. E.; Bailey, T. R.; Paquette, L. A. *J. Org. Chem.* **1980**, *45*, 3028.
(7) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397. Bernady, K. F.; Floyd, M. B.; Poletto, J. F.; Weiss, M. J. *J. Org. Chem.* **1979**, *44*, 1438.

spectra were determined by Mr. Kei Miyano on a Varian M-60 mass spectrometer. Combustion analyses were performed by the Berkeley Microanalytical Laboratory, University of California, Berkeley. Analytical GLC was performed on a F & M Research Chromatograph Model 810 with a 50-m SE-30 glass capillary column.

Diisobutylaluminum hydride (Ethyl Corp.) was used as a neat liquid and assumed to be 5.4 M. *sec*-Butyllithium in cyclohexane (Aldrich) was standardized by titration with a standard solution of 2-butanol in xylene, using 1,10-phenanthroline as an indicator.[8] Bromine (Mallinckrodt) and anhydrous diethyl ether (Mallinckrodt) were used as received. Tetrahydrofuran (Mallinckrodt) was distilled from sodium benzophenone ketyl just prior to use. All aldehydes and ketones were distilled prior to use. Dimethyl sulfoxide (Mallinckrodt) was distilled from calcium hydride at reduced pressure. Anhydrous potassium fluoride was prepared by fusing the dihydrate (Mallinckrodt) prior to use. All reactions were stirred magnetically and carried out under an atmosphere of nitrogen in oven-dried (150 °C) glassware.

Preparation of the Tetrahydropyranyl Ether of (*E*)-3-Bromo-3-(trimethylsilyl)-2-propen-1-ol (1). In a 500-mL, three-necked, round-bottomed flask, fitted with two addition funnels and a low-temperature thermometer, was placed 20 g (94 mmol) of the tetrahydropyranyl ether of 3-(trimethylsilyl)-2-propyn-1-ol[3] in 95 mL of anhydrous diethyl ether. To this solution was added 19.21 mL of 5.4 M diisobutylaluminum hydride (103.7 mmol, 1.1 equiv) at such a rate that the temperature did not rise above 5 °C (ice bath). The resulting mixture was warmed to room temperature and stirred for 30 min and then stirred at 40 °C for 3 h. At the end of this time the solution was cooled at 0 °C (ice bath), and 95 mL of anhydrous diethyl ether and 15.2 mL (188 mmol) of pyridine were added. The yellow solution was next cooled to −78 °C (dry ice/acetone bath) and a solution of 22.6 g (141 mmol, 1.5 equiv) of bromine in 47 mL of methylene chloride was added at a rate such that a temperature <−60 °C was maintained. The resulting bright yellow suspension was washed into a separatory funnel containing 3 N sodium hydroxide, ice, and pentane. After the mixture was shaken and separated, the aqueous layer was thoroughly extracted with fresh pentane. The combined organic layers were washed twice with ice-cold 1 N sulfuric acid and once with saturated sodium bicarbonate solution. After the mixture was dried over anhydrous sodium sulfate, the solvent was removed by rotary evaporation in the presence of some solid sodium carbonate. The colorless residue was distilled under reduced pressure in the presence of solid sodium carbonate to afford 22 g (75 mmol, 80% yield) of colorless product. GLC analysis revealed the product to be >99% the *E* isomer: bp 68–69 °C (10^{-4} torr); IR (neat) 2970 (s), 2890 (m), 1600 (m), 1450 (m), 1250 (s), 1120 (s), 1020 (s), 840 (s), 740 (m) cm^{-1}; NMR (CCl_4) δ* 0.00 (s, 9 H, $(CH_3)_3Si$), 1.35 (m, 6 H, $-(CH_2-_3)$), 3.1–3.9 (m, 4 H), 4.35 (m, 1 H, OCHO), 6.6 (t, J = 7 Hz, HC=C). Anal. Calcd for $C_{11}H_{21}O_2Si$: C, 45.05; H, 7.22. Found: C, 44.96; H, 7.03.

Preparation of the Tetrahydropyranyl Ether of (*Z*)-3-Bromo-3-(trimethylsilyl)-2-propen-1-ol (2). A solution of 7 g (23.9 mmol) of (*E*)-bromovinylsilane 1 in 25 mL of anhydrous diethyl ether was immersed in a water bath and 0.45 mL of pyridine was added. The mixture was bathed in a 275-W sunlamp while 0.193 g (1.2 mmol, 0.05 equiv) of bromine in 0.56 mL of methylene chloride was added over a 90-min period. Following addition of another 0.45 mL of pyridine, a second portion of 0.193 g (1.2 mmol, 0.05 equiv) of bromine in 0.56 mL of methylene chloride was added over a 60-min period. A third portion of pyridine and bromine (0.05 equiv) was added over a 60-min period and the mixture was stirred an additional 30 min. During this whole process the reaction temperature was maintained at ~30 °C by adding ice to the water bath as necessary. The reaction mixture was next poured into 10% sodium sulfite solution, shaken, and separated. The aqueous layer was thoroughly extracted with pentane, and the organic extracts were washed twice with ice-cold 1 N sulfuric acid and once with saturated sodium bicarbonate solution. After the mixture was dried over anhydrous sodium sulfate, the solvent was removed by rotary evaporation. The residue was distilled at reduced pressure to afford 5.74 g (19.6 mmol, 82% yield) of colorless product. GLC analysis revealed the product to be 97% the *Z* isomer: bp 67–68 °C (10^{-4} torr); IR (neat) 2970 (s), 2880 (m), 1600 (m), 1450 (m), 1250 (s), 1120 (s), 1020 (s), 840 (s), 740 (s) cm^{-1}; NMR (CCl_4) δ* 0.00 (s, 9 H, $(CH_3)_3Si$), 1.35 (m, 6 H, $-(CH_2-_3)$), 3.1–4.1 (m, 4 H), 4.3 (m, 1 H, OCHO), 6.15 (t, 1 H, J = 6 Hz, HC=C).

For analysis a small portion of compound **2** was hydrolyzed to the corresponding alcohol. To 0.586 g (2 mmol) of tetrahydropyranyl ether **2** in 4 mL of methanol were added a few drops of 3 N hydrochloric acid. The mixture was stirred for 3 h at room temperature and worked up. The solvent was removed by rotary evaporation to afford a residue, which was chromatographed. Elution from 14 g of silica gel with 50% methylene chloride–50% pentane gave 0.355 g (1.7 mmol, 85% yield) of (*Z*)-3-bromo-3-(trimethylsilyl)-2-propen-1-ol: IR (neat) 3390 (s), 2995 (s), 2910 (s), 1620 (m), 1253 (s), 1040 (s), 845 (m), 762 (m) cm^{-1}; NMR (CCl_4) δ* 0.00 (s, 9 H, $(CH_3)_3Si$), 2.62 (br, 1 H, OH), 4.07 (d, 2 H, J = 5 Hz, OCH_2C=C), 6.21 (t, 1 *H*, J = 5 Hz, HC=C); high-resolution mass spectrum[9] calcd for $C_6H_{13}BrOSi$ m/e 207.9919, found 207.9896.

General Procedure for Preparation of Hydroxyl-Differentiated Silylated 1,4-Enediols 3 and 4 (Table I). A solution of bromovinylsilane 1 or **2** in dry tetrahydrofuran (2 mL/mmol of 1 or **2**) was cooled to −78 °C (dry ice/acetone bath) and *sec*-butyllithium (1.2 equiv) in cyclohexane was added at a rate such that the temperature was maintained below −65 °C. After stirring of the resulting solution for 4 min at −78 °C, the aldehyde or ketone (2 equiv) was added again at a rate such that the temperature was maintained below −65 °C. After addition was complete, the solution was stirred for 1 h at −78 °C, allowed to warm to room temperature, and then stirred an additional hour. At the end of this time, the reaction mixture was poured into saturated ammonium chloride solution, shaken, and separated. The aqueous layer was thoroughly extracted with pentane, and the combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation to afford a residue, which was distilled at reduced pressure. (See paragraph at the end of paper about supplementary material.)

General Procedure for Hydrolysis of the Tetrahydropyranyl Ethers in Table I. To 2 mmol of the tetrahydropyranyl ether **3** or **4** in 4 mL of methanol was added a few drops of 3 N hydrochloric acid. The mixture was stirred for 3 h at room temperature and then solid sodium bicarbonate was added to neutralize the acid. After removal of the methanol by rotary evaporation, the residue was washed with water and the aqueous layer was thoroughly extracted with diethyl ether. The combined organic extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation to give a residue, which was either recrystallized or chromatographed. (See paragraph at the end of paper about supplementary material.)

General Procedure for Fluoride Cleavage of Vinyl Carbon–Silicon Bond (Table II). A solution of **3** or **4** in dry dimethyl sulfoxide (5 mL/mmol of **3** or **4**) was added to anhydrous potassium fluoride (2 equiv). The mixture was heated at 150 °C for 3 h and partitioned between diethyl ether and water and separated. The aqueous layer was thoroughly extracted with diethyl ether, and the combined organic extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation to afford a residue, which was chromatographed. (See paragraph at the end of paper about supplementary material.)

General Procedure for Hydrolysis of the Tetrahydropyran Ethers in Table II. The tetrahydropyran ether (1 mmol) **7** or **8** was dissolved in 10 mL of a 4:2:1 mixture of acetic acid–tetrahydrofuran–water. The resulting solution was stirred for 6 h at 45 °C and then poured into a separatory funnel containing 10 N sodium hydroxide, ice, and ether. After the mixture was shaken and separated, the aqueous layer was thoroughly extracted with ether, and the combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation to give a residue, which was either chromatographed

(8) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

(9) All samples on which high-resolution mass spectral data were obtained were shown to be homogeneous (one peak) on a 50-m SE-30 glass capillary column.

or recrystallized. (See paragraph at the end of paper about supplementary material.)

Acknowledgment. We thank the Committee on Research, University of California, Davis, for partial support of this work.

Registry No. 1, 87070-85-7; 2, 87070-86-8; 3 (R = Et; R' = H), 87070-87-9; 3 (R, R^1 = Me), 87088-26-4; 3 (R = Ph; R^1 = H), 87070-88-0; 3 (R, R^1 = $(CH_2)_5$), 87070-89-1; 4 (R = Et; R^1 = H), 87070-90-4; 4 (R, R^1 = Me), 87070-91-5; 5 (R = Et; R^1 = H), 87070-92-6; 5 (R, R^1 = Me), 87070-93-7; 5 (R = Ph; R^1 = H), 87070-94-8; 5 (R, R^1 = $(CH_2)_5$), 87070-95-9; 6 (R = Et; R^1 = H), 87070-96-0; 6 (R, R^1 = Me), 87070-97-1; 7 (R = Et; R^1 = H), 87070-98-2; 7 (R, R^1 = Me), 64841-63-0; 7 (R = Ph; R^1 = H), 87070-99-3; 7 (R, R^1 = $(CH_2)_5$), 87071-00-9; 8 (R = Et; R^1 = H), 87071-01-0; 8 (R, R^1 = Me), 64841-62-9; 9 (R = Et; R^1 = H), 87071-02-1; 9 (R, R^1 = Me), 50546-22-0; 9 (R = Ph; R^1 = H), 74141-11-0; 9 (R, R^1 = $(CH_2)_5$), 87071-03-2; 10 (R = Et; R^1 = H), 83726-18-5; 10 (R, R^1 = Me), 50407-79-9; 3-(trimethylsilyl)-2-propyn-1-ol tetrahydropyranyl ether, 36551-06-1; propaldehyde, 123-38-6; acetone, 67-64-1; benzaldehyde, 100-52-7; cyclohexanone, 108-94-1; (Z)-3-bromo-3-(trimethylsilyl)-2-propen-1-ol, 87071-04-3.

Supplementary Material Available: Full experimental details including scale, IR data, NMR data, and analyses for each entry in Table I and II (8 pages). Ordering information is given on any current masthead page.

Formation of Nitrosamines by Alkylation of Diazotates

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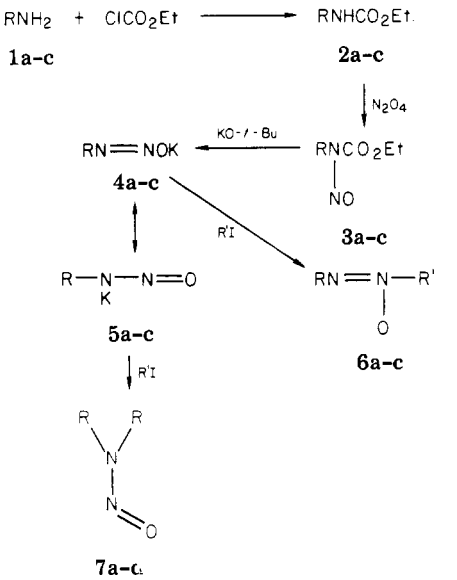
In the study of the metabolic activation of procarbazine, a chemotherapeutic agent used in the treatment of Hodgkins disease (tumors of the brain and other neoplasms), two azoxy isomers were identified as metabolites.[1-4] Further metabolism of these azoxy compounds should lead to an alkylating species.[4,5] A regiospecific synthesis of each of these unsymmetrical compounds or their unsubstituted analogues was desired to provide an opportunity to study the metabolism of the individual azoxy isomers to determine their relative importance. Moss and co-workers have reported that alkylation of diazotates can be used for the regiospecific synthesis of unsymmetrical azoxyalkanes.[6] Attempts were made to prepare the individual azoxy isomers benzyl-*NNO*-azoxymethane (**6a**) and benzyl-*ONN*-azoxymethane (**6b**) by using this methodology, but with THF rather than HMPA as the solvent (see Scheme I). The *N*-nitrosourethane **3a** used in these reactions was prepared by the sequence shown in Scheme I. The *N*-nitrosourethane **3a** was then used to generate the diazotate in situ. The diazotate was prepared by reaction of **3a** with KO-*t*-Bu (2 equiv) in dry THF under N_2 at −30 °C followed by alkylation with methyl iodide at 35 °C.

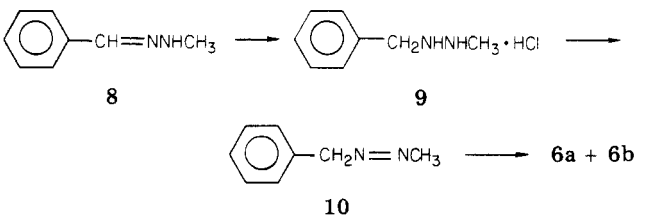
In the case of **6b** the diazotate was generated from *N*-methyl-*N*-nitrosourethane (**3b**), which was obtained by the sequence shown in Scheme I. The diazotate was generated in situ by the method described above and was alkylated with benzyl iodide at 35 °C.

Scheme I[a]



[a] a, R = $C_6H_5CH_2$, R' = CH_3; b, R = CH_3, R' = $C_6H_5CH_2$; c, R = $C_6H_5(CH_3)CH$, R' = CH_3CH_2; d, R = CH_3CH_2, R' = $C_6H_5(CH_3)CH$.

Scheme II



When the alkylation product from the reaction of the diazotate from **3a** with methyl iodide and the product from the reaction of the diazotate of **3b** with benzyl iodide were compared they were found to be the same. Both products had GC retention times of t_R = 28.0 min.[7a] The two products also had identical ^1H NMR spectra and were observed as a mixture of two isomers. One isomer had chemical shifts at δ 2.85 (s, 3 H), 4.79 (s, 2 H), and 7.30 (s, 5 H), and a second isomer with chemical shifts at δ 3.59 (s, 3 H), 5.28 (s, 2 H), and 7.31 (s, 5 H) was also observed. The isomers were in a ratio of 78/22. These chemical shift values were found to be identical with those reported for the syn and anti isomers of benzylmethylnitrosamines **7a** and **7b**, and the reported syn/anti isomer ratio (79/21), was also the same.[8] A sample of benzylmethylnitrosamines **7a,b** was prepared by nitrosation of *N*-methylbenzylamine with aqueous $NaNO_2$ in acetic acid.[9] The GC retention time of this authentic sample of benzylmethylnitrosamine was also found to be t_R = 28.0 min.[7a]

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(7) (a) On a 6 ft × 4 mm i.d. column with 3% OV-225 on 100/120 Supelcoport at 90–135 °C at 1 °C/min. (b) Same as ref. 11a except 90–135 °C at 10 °C/min.
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