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Stereochemically Defined Cyclohexanediols through the Regioselective Ring-Opening of Silylated Epoxy Alcohols

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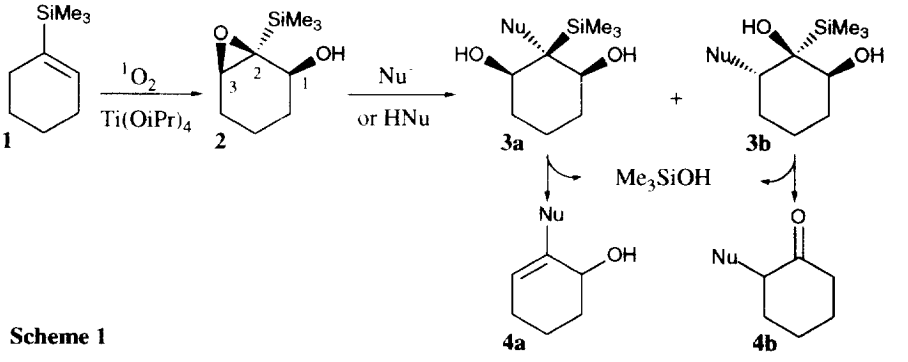
Abstract: The nucleophilic ring-opening of the silylated epoxy alcohol **2** leads to highly functionalized building blocks of defined stereochemistry, whereby the regioselectivity may be controlled through the proper choice of the nucleophile and the reaction conditions.

The photooxygenation of olefins in the presence of $Ti(OiPr)_4$ constitutes a convenient and simple one-pot procedure for the diastereoselective preparation of 2,3-epoxy alcohols.[1] The use of vinylsilanes enhances stereocontrol in this transformation and affords silylated epoxy alcohols, e.g. **2** from the cyclohexenyl derivative **1** (Scheme 1).[2] These epoxy alcohols possess synthetic potential as highly functionalized building



Scheme 1

blocks of defined stereochemistry. For example, nucleophilic epoxide ring-opening should lead to the diols **3a,b**, which can be further transformed by Peterson olefination to vinyl derivatives **4a** or substituted ketones **4b** (Scheme 1). Since the synthetic value depends on the regiocontrolled nucleophilic attack at the positions C-2 and C-3 in the epoxy alcohol **2** to generate the corresponding products **3a** and **3b**, it was our interest to explore the regioselectivity of the **2**→**3** transformation under a variety of reaction conditions. It is well documented that the trimethylsilyl substituent promotes stereo- and regioselective epoxide opening at the α position to the silicon atom both for acyclic [3] and for cyclic [3a,4] substrates through stereoelectronic control. Only for cyclic epoxy silanes, which are conformationally locked, can the tendency for transdiaxial ring-opening interfere and alter the regioselectivity. [4a] However, the presence of the hydroxy group in epoxide **2** creates additional uncertainties in the regiocontrol, since cyclic 2,3-epoxy alcohols are known [5] to undergo C-O cleavage preferably at the C-3 position. Consequently, the nucleophilic opening of the epoxide **2** should be governed by two counteracting effects, in that the silyl substituent should lead to diol **3a** by nucleophilic

attack at C-2, while the hydroxy group should promote formation of **3b** by attack at C-3.[6]

We treated the 2,3-epoxy-2-trimethylsilylcyclohexanol **2** with a variety of common nucleophiles under the reaction conditions summarized in Table 1. The resulting diols **3a,b** were conveniently distinguished by

Table 1: Product Distribution in the Epoxide Ring-Opening of Epoxy Alcohol **2**

Nu	Conditions	Product Distribution (%) **3a**	**3b**	**4a**	**4b**
H	$LiAlH_4$, Et_2O, 0° C, 5 h	≥ 95 (91)	-	-	-
N_3	NaN_3, NH_4Cl, $MeOH/H_2O$, 20 °C, 6 d [b]	≥ 95	-	-	-
SPh	PhSNa, THF, 20 °C, 46 h	-	-	≥ 95	-
OH	H_2O, H_2SO_4, THF, 20 °C, 5 h	10	90 (82)	-	-
OMe	MeOH, H_2SO_4, 20 °C, 20 min	11	82 (73)	-	7 [c]
Br	HBr (62 %), $CHCl_3$, 0 °C, 5 min	25	-	-	75

a) Determined by ^1H NMR analysis of the crude product mixture, conversion ≥ 95%, m.b. ≥ 90%, except where noted; yields of isolated material are given in parentheses; b) 66% conversion; c) as dimethoxy acetal.

their ^{13}C spectra, since the symmetrical products **3a** show only four resonances for the six-membered ring, while six signals were observed for the **3b** regioisomers. The preferred site of attack depends on the nucleophile employed; e.g. the hydride, azide and thiophenolate nucleophiles entered exclusively at C-2, in the last case the corresponding vinyl sulfide **4a** (Nu = SPh) was formed by an *in situ* Peterson olefination of the *cis*-hydroxy silane **3a** (Nu = SPh) under the basic reaction conditions. In contrast, the acid-catalyzed solvolysis in water or methanol gave preferably the regioisomeric diols **3b**. The epoxide-opening with hydrogen bromide constitutes a moderately regioselective case. In the acidic medium, partial (Nu = OMe) or complete (Nu = Br) formation of the corresponding α-substituted ketones **4b** (Nu = OMe, Br) was observed by elimination of trimethylsilanol from the *trans*-β-hydroxy silanes **3b**. [7]

The regioselectivity of the ring-opening of the epoxy silane **2** can be explained by the degree of positive charge development in the transition state. Thus, strong nucleophiles under basic or neutral conditions give clean S_N2 attack at C-2, since no positive charge is involved and the stereoelectronic control by the silyl substituent operates, which preferrably weakens the C_2-O bond.[8] In contrast, under acid-catalyzed conditions (Nu = OH, OMe), the solvolysis proceeds through the protonated epoxide as an S_N2/S_N1 borderline case with substantial cationic character in the transition state. Consequently, the regioselectivity is controlled by the inductive effect of the neighboring hydroxy group. In these cases, the positive charge is less destabilized for nucleophilic attack the at C-3 position and the formation of diols **3b** is preferred. Finally, the more nucleophilic bromide ion gives also an appreciable amount of ring-opening at the C-2 position even under acidic conditions.

In summary, the present study has shown that the regioselectivity of ring-opening in silylated epoxy alcohols can be efficiently directed by the proper choice of the nucleophile and reaction conditions. In this way, the highly functionalized, stereochemically defined diols **3** have been made available for synthesis in two steps from readily accessible vinylsilanes.

EXPERIMENTAL

General Aspects

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 1420 ratio recording infrared spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250 or a Bruker AC 200 spectrometer by using $CDCl_3$ as internal standard. Combustion analyses were carried out by the Microanalysis Division of the Institute of Inorganic Chemistry, University of Würzburg. Column chromatography was run on silica gel (63 - 200 μm) from Woelm as stationary phase, with an absorbant / substrate ratio of ca. 100 : 1. For thin layer chromatography

(TLC), Polygram SIL G/UV_{254} (40x80 mm) plates from Macherey and Nagel were employed. All commercial compounds were used as received, solvents were purified and dried by reported standard methods. Epoxy alcohol **2** was prepared according to the previously described procedure. [2] The reactions were run to complete conversion of the epoxide **2** (TLC control) and the crude product mixtures were directly analyzed by NMR, for product ratios cf. Table 1.

(*1α,2α,3α*)-2-Trimethylsilyl-1,3-cyclohexanediol (**3a**, Nu = H)
A solution of 202 mg (1.08 mmol) epoxy alcohol **2** in ether (4 mL) was added dropwise to a suspension of $LiAlH_4$ (47.0 mg, 1.23 mmol) in ether (5 mL). The mixture was stirred at 0 °C for 5 h, carefully hydrolyzed with brine (15 mL) and the aqueous layer was extracted with ether (3x15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was evaporated at 20 °C/20 Torr. The residue was recrystallized from pentane to give 184 mg (91%) diol **3a** as colorless prims, mp 48-49 °C. IR (KBr): ν = 3570-3240 cm^{-1} (OH), 2950, 2890, 1450, 1250, 1050, 955. ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.00 (s, 9 H), 0.65 (m, 1 H), 1.10-2.15 (m, 6 H), 2.61 (br s, 2 H), 4.12 (m, 2 H). ^{13}C-NMR (63 MHz, $CDCl_3$): δ = -1.4 (3xq), 14.1 (t), 34.9 (2xt), 36.3 (d), 69.0 (2xd). Anal Calcd for $C_9H_{20}O_2Si$ (188.3): C, 57.39; H, 10.70. Found: C, 57.26; H, 10.82.

(*1α2α,3α*)-2-Azido-2-trimethylsilyl-1,3-cyclohexanediol (**3a**, Nu = N_3)
A solution of 302 mg (1.62 mmol) epoxy alcohol **2**, 527 mg (8.10 mmol) sodium azide and 190 mg (3.56 mmol) ammonium chloride in MeOH/water (10 : 1, 10 mL) was stirred at room temperature (ca. 20 °C) for 6 d. The mixture was extracted with ether (3x15 mL) and the combined organic layers were washed with brine (2x10 mL) and dried over $MgSO_4$. Removal of the solvent at 20 °C/20 Torr afforded 320 mg of a colorless oil, which contained diol **3a** (Nu= N_3) and unchanged starting material (54%). Column chromatography on silica gel [Et_2O/pentane (1:3) as eluent] gave 136 mg (80% based on recovered starting material) **3a** as colorless oil. IR (Film): ν = 2540-3270 cm^{-1} (OH), 2950, 2100 (N_3), 1450, 1260, 1080, 840. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.16 (s, 9 H), 1.03-1.95 (m, 6 H), 2.51 (br s, 2 H), 3.95 (m, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ = -1.4 (3xq), 12.6 (t), 29.0 (2xt), 56.8 (s), 70.3 (2xd). Anal Calcd for $C_9H_{19}N_3O_2Si$ (229.4): C, 47.13; H, 8.35; N 18.32. Found: C, 46.96; H, 8.63; N 18.19.

2-Phenylthio-2-cyclohexenol (**4a**, Nu = SPh)
Thiophenol (551 mg, 5.00 mmol) was added to a suspension of sodium hydride (40.0 mg, 2.00 mmol) in THF (20 mL) and the mixture was stirred at 0 °C for 15 min. A sample of epoxy alcohol **2** (186 mg, 1.00 mmol) was added and the mixture was stirred for 48 h at room temperature (ca. 20 °C). Concentrated NH_4Cl (10 mL) was added, the solution was stirred for 15 min and the solvents were evaporated at 20 °C/0.1 Torr. The residue was taken up in ether (30 mL) and undissolved material was removed by filtration. The ether solution was dried over $MgSO_4$ and the solvent was evaporated at 20 °C/20 Torr to afford 290 mg of a yellow solid. Vinylsulfide **4a** (Nu = SPh) was identified by comparison with the known [9] NMR data as the sole ring-opening product, contaminated with diphenyl disulfide (ca. 30%).

(*1α,2α,3α*)-2-Trimethylsilyl-1,2,3-cyclohexanetriol (**3a**, Nu = OH) and **(*1α,2α,3β*)-2-Trimethylsilyl-1,2,3-cyclohexanetriol** (**3b**, Nu = OH)
A sample of epoxy alcohol **2** (372 mg, 2.00 mmol) was dissolved in THF (3.5 mL) and water (1.5 mL), 2 N H_2SO_4 (1.5 mL) was added and the mixture was stirred at room temperature (ca. 20 °C) for 5 h. Water (10 mL) was added and the aqueous layer was extracted with ether (5x15 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (2x10 mL) and brine (10 mL), dried over $MgSO_4$ and the solvent was evaporated at 20 °C/20 Torr. The residue (397 mg, colorless solid, **3a** : **3b** = 10 : 90) was recrystallized from Et_2O/pentane to give 336 mg (82%) triol **3b** as colorless powder, mp 125-126 °C. **3a** (Nu = OH, only resolved resonances are listed): ^{1}H-NMR (250 MHz, CD_3OD): δ = 0.02 (s, 9H), 3.68 (m, 2 H). ^{13}C-NMR (63 MHz, CD_3OD): δ = -1.4 (3xq), 29.1 (2xt) 74.0 (2xd). **3b** (Nu = OH): ^{1}H-NMR (250 MHz, CD_3OD): δ = -0.03 (s, 9 H), 1.08-2.07 (m, 6 H), 3.72 (m, 2 H). ^{13}C-NMR (63 MHz, CD_3OD): δ = -1.7 (3xq), 19.8 (t), 28.8 (t), 29.9 (t), 71.9 (d), 72.7 (s), 73.8 (d). Anal Calcd for $C_9H_{20}O_3Si$ (204.3): C, 52.90; H, 9.86. Found: C, 52.41; H, 9.68.

(*1α,2α,3α*)-2-Methoxy-2-trimethylsilyl-1,3-cyclohexanediol (**3a**, Nu = OMe) and **(*1α,2β,3β*)-3-Methoxy-2-trimethylsilyl-1,2-cyclohexanediol** (**3b**, Nu = OMe)
A sample of epoxy alcohol **2** (397 mg, 1.97 mmol) was dissolved in dry methanol (15 mL) and one drop of conc. H_2SO_4 was added. The mixture was stirred at room temperature (ca. 20 °C) for 20 min and solid

Na_2CO_3 (100 mg) was added. The solution was filtered and the solvent evaporated at 20 °C/20 Torr. Recrystallization of the oily residue [415 mg, **3a** : **3b** : **4b** (as dimethoxy acetal [10]) = 11 : 82 : 7] from pentane gave 315 mg (73%) diol **3b** (Nu = OMe) as colorless powder, mp 91-92 °C. **3a** (Nu = OMe, only resolved resonances are listed): ^{1}H-NMR (250 MHz, $CDCl_3$): δ = -0.11 (s, 9 H), 2.98 (br s, 2 H), 3.18 (s, 3 H), 3.92 (m, 2 H). ^{13}C-NMR (63 MHz, $CDCl_3$): δ = 0.6 (3xq), 15.8 (t), 26.9 (2xt), 50.6 (q), 70.8 (2xd). **3b** (Nu = OMe): IR (CCl_4): ν = 3630 cm^{-1} (OH), 3600 (OH), 2950, 1500, 1245, 1100, 985. ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.09 (s, 9 H), 1.50-1.75 (m, 6 H), 1.90 (br s, 1 H), 2.07 (br s, 1 H), 3.24 (s, 3 H), 3.46 (br t, *J* = 4.1 Hz, 1 H), 3.91 (dd, *J* = 9.2 Hz, 3.5 Hz, 1 H, 2-H). ^{13}C-NMR (63 MHz, $CDCl_3$): δ = -2.0 (3xq), 18.1 (t), 22.2 (t), 29.0 (t), 55.8 (q), 71.0 (d), 71.2 (s), 84.6 (d). Anal Calcd for $C_{10}H_{22}O_3Si$ (218.4): C, 55.00; H, 10.15. Found: C, 55.23; H, 10.45.

(*1α,2β,3α*)-**2-Bromo-2-trimethylsilyl-1,3-cyclohexanediol** (**3a**, Nu = Br)
A sample of epoxy alcohol **2** (186 mg, 1.00 mmol) was dissolved in $CHCl_3$ (5 mL) and aqueous HBr (62%, 2 mL) was added at 0 °C. The mixture was vigorously stirred for 5 min and water (10 mL) was added. The aqueous layer was extracted with $CHCl_3$ (4x15 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was removed at 20 °C/20 Torr and the oily residue was analyzed by ^{1}H NMR spectroscopy (**3a** : **4b** = 25 : 75). Diol **3a** (Nu = Br) was unstable under the conditions of silica gel chromatography and could, therefore, not be isolated in pure form for complete characterization.**3a** (Nu = Br): ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.29 (s, 9 H), 1.35-2.25 (m, 6 H), 2.45 (br s, 2 H), 4.17 (m, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ = -0.5 (3xq), 14.6 (t), 28.8 (2xt), 74.33 (2xd), 76.4 (s).

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