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A HIGHLY REGIO- AND STEREOSELECTIVE RING-OPENING OF 2,3-EPOXY ALCOHOLS WITH TRIMETHYLSILYL AZIDE-DIETHYLALUMINUM FLUORIDE SYSTEM

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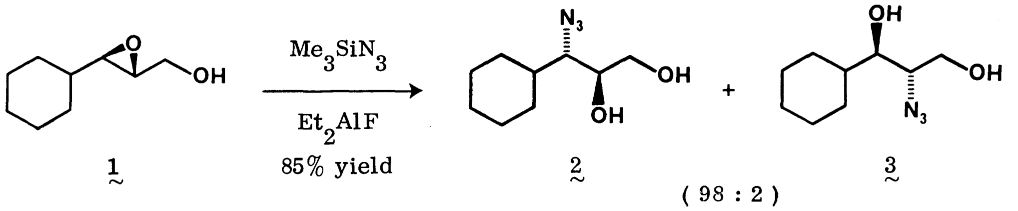
A new approach to the mild and selective synthesis of 3-azidodiols has been described which involves a highly regio- and stereoselective ring-opening of 2,3-epoxy alcohols with trimethylsilyl azide and diethylaluminum fluoride.

3-Aminoglycosides constitute one of the most critical elements in biologically active natural products including certain aminoglycoside antibiotics and antitumor agents.[1] The development of new synthetic processes of these 3-amino polyols depends crucially on the availability of efficient methods for the regio- and stereospecific arrangement of amino and hydroxy functions on a carbon chain of a substrate. The selective cleavage at the C-3 position of 2,3-epoxy alcohols with an amine or its synthetic equivalent seems to be highly promising for this purpose.[2,3] Here we wish to describe the realization of such a strategy by using trimethylsilyl azide-diethylaluminum fluoride system as illustrated in Eq. 1.



1 **2** **3** (1)

Treatment of 2,3-epoxy alcohol **1** in methylene chloride with trimethylsilyl azide (2 equiv.) and diethylaluminum fluoride[4] (4 equiv.) gave rise to a mixture of 3-azido-1,2-diol **2** and 2-azido-1,3-diol **3** in 85% yield.[5] The ratio of **2** and **3** was determined by GC analysis after converting to their diacetates to be 98:2.[6] In contrast, the nucleophilic ring-opening of 2,3-epoxy alcohols by a conventional method using azide anion reflects strongly the steric effect of all of the epoxide substituents, and cleavage of **1** with sodium azide is reported to furnish a mixture of **2** and **3** in a ratio of 1.7-2:1.[7] The effect of other Lewis acids was investigated in the reaction of **1** with trimethylsilyl azide. The use of boron trifluoride etherate resulted in formation of deteriorated reaction mixtures. Aluminum chloride, dimethyl- and diethylaluminum chloride afforded chlorinated diols as major products. While the combination of trimethylsilyl azide-diethylaluminum fluoride has proved to be most satisfactory, some variation in the experimental conditions was examined in detail. Thus, treatment of 1 with several equivalents of trimethylsilyl azide and diethylaluminum fluoride in halogenated hydrocarbon solvents gave results as revealed in Table 1.

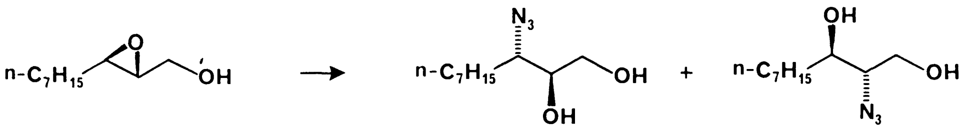
Table 1. Ring-Opening of Epoxy Alcohol 1 with Me_3SiN_3-Et_2AlF System [a)]

Entry	Me_3SiN_3/Et_2AlF (equiv.)	Solvent (temp, time)	Yield / % [b)]	Ratio [c)]
1	1.2 / 1.2	CH_2Cl_2 (RT, 3 d)	51	83 : 17
2	1.2 / 1.2	CH_2Cl_2 (40 °C, 9 h)	50	86 : 14
3	1.2 / 1.2	$ClCH_2CH_2Cl$ (80 °C, 9 h)	40	93 : 7
4	1.2 / 2	CH_2Cl_2 (RT, 2 d)	71	95 : 5
5	2 / 2	CH_2Cl_2 (RT, 2 d)	58	97 : 3
6	2 / 4	CH_2Cl_2 (RT, 18 h)	85	98 : 2

a) Reaction was carried out under argon atmosphere. b) Isolated yield of 2 and 3 after silica gel column chromatography. c) The ratio of 2 and 3 was determined by GC after converting to their diacetates.

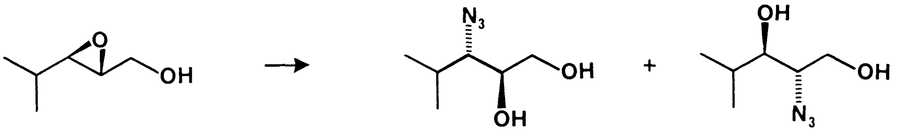
Some other examples are illustrated in Eq. 2-4, which uniformly exhibited the excellent C-3 regioselectivity of the epoxide opening as well as the rigorous stereospecificity of the contiguous centers. The results with sodium azide-ammonium chloride in aqueous 2-methoxyethanol are also included for comparison. Clearly, the aluminum reagent has played an important role for the regioselective activation of epoxy moiety upon coordination of epoxy alcohols,[8)] thereby facilitating their opening at the C-3 position exclusively with trimethylsilyl azide. The reaction in Eq. 4 demonstrates the firm establishment of three contiguous chiral centers by combination of our approach with Sharpless epoxidation.[9)] Since the azide can serve as a protected amino group as well as be useful for further elaboration, the present method will find broad applications in the synthesis of biologically active 3-amino polyols by manipulating the substitution pattern of the starting epoxy alcohols.

A typical experimental procedure for the organoaluminum-promoted ring-opening of 2,3-epoxy alcohols follows. A 1 M hexane solution of diethylaluminum fluoride[4)] (4 mmol) was added to a stirred solution of the epoxy alcohol 1 (156 mg, 1 mmol) and trimethylsilyl azide (265 μL, 2 mmol) in methylene chloride (5 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 18 h. The mixture was poured into 1 mol dm^{-3} HCl and extracted with methylene chloride. The combined extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (ether/hexane, 5:1 as eluant) to furnish a mixture of azidodiols 2 and 3 (169 mg, 85% yield) as a



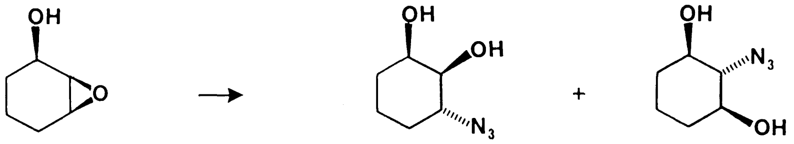
(2)

Me_3SiN_3-Et_2AlF :	98 : 2	(81%)
NaN_3-NH_4Cl :	78 : 22[2b]	



(3)

Me_3SiN_3-Et_2AlF :	98 : 2	(84%)
NaN_3-NH_4Cl :	53 : 47	(90%)



(4)

Me_3SiN_3-Et_2AlF :	96 : 4	(89%)
NaN_3-NH_4Cl :	93 : 7	(89%)

colorless oil.[5)] This mixture was then converted to the corresponding diacetates[6)] by treatment with acetic anhydride (0.5 mL) and pyridine (0.5 mL) in methylene chloride (0.5 mL) in the presence of catalytic 4-(N,N-dimethylamino)pyridine. The isomeric ratio of **2** and **3** was determined to be 98:2 by GC analysis: (25-m PEG-HT capillary column, 190 °C) $t_R(\mathbf{2}) = 19.5$ min; $t_R(\mathbf{3}) = 17.3$ min.

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2) Recent synthesis of 2-amino sugars from 2,3-epoxy alcohols: a) N. Minami, S. S. Ko, and Y. Kishi, J. Am. Chem. Soc., **104**, 1109 (1982); b) C. H. Behrens and K. B. Sharpless, Aldrichimica Acta, **16**, 67 (1983).

3) A similar strategy using trimethylsilyl cyanide-zinc iodide was also reported. See: P. G. Gassman and R. S. Gremban, Tetrahedron Lett., **25**, 3259 (1984). Recently, Sharpless found the Ti(OPr^i)$_4$-mediated regioselective opening of 2,3-epoxy alcohols at the C-3 position with a variety of nucleophiles including trimethylsilyl azide (private communication by M. Caron and K. B. Sharpless). We are very grateful to Professor Sharpless for valuable informations prior to his publication.

4) We appreciate Toyo Stauffer Chemical Co., Ltd. for generous gift samples of diethylaluminum fluoride.

5) IR of **2** and **3** (neat) 3380 (OH), 2115 (N_3) cm^{-1}.

6) Diacetates of **2** and **3**: IR (neat) 2060 (N_3), 1740 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ2.02 (s, 3H), 2.06 (s, 3H), 3.37 (broad t, 1H), 3.85-4.52 (m, 2H), 4.99-5.33 (m, 1H). Both the regio- and stereochemistry of the diacetates of **2** and **3** were determined by comparison with the authentic samples which were synthesized by treatment of **1** with sodium azide-ammonium chloride in aqueous 2-methoxyethanol followed by acetylation using acetic anhydride-pyridine.

7) Sharpless reported the ratio of **2** and **3** to be 1.7:1 by sodium azide-ammonium chloride in aqueous 2-methoxyethanol, or 2:1 by sodium azide-magnesium sulfate in methanol. See Ref. 2b.

8) A similar regioselective ring-opening was observed in the alkylation of 2,3-epoxy alcohols with trialkylaluminums. S. Danishefsky, M.-Y. Tsai, and T. Kitahara, J. Org. Chem., **42**, 394 (1977); T. Suzuki, H. Saimoto, H. Tomioka, K. Oshima, and H. Nozaki, Tetrahedron Lett., **23**, 3597 (1982); W. R. Roush, M. A. Adam, and S. M. Peseckis, ibid., **24**, 1377 (1983).

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