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Regio- and Stereoselective Ring Opening of 2,3-Epoxyalcohols with Diethylaluminium Azide

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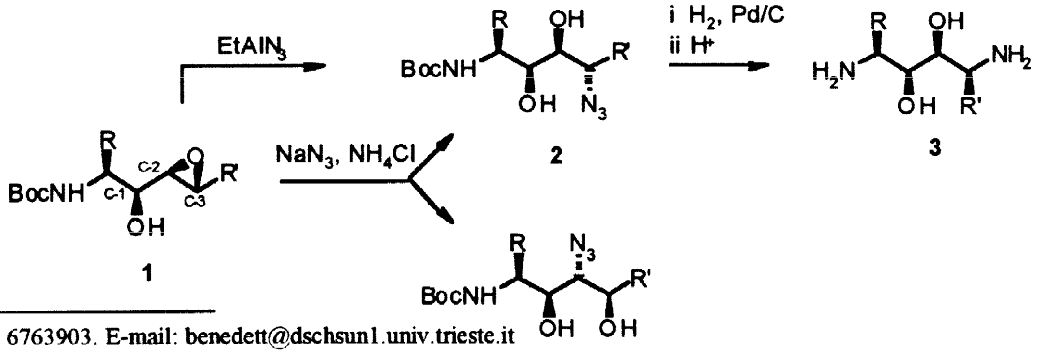
Abstract

2,3-Epoxyalcohols react with diethylaluminium azide under mild conditions to give 3-azido-1,2-diols resulting from the regio- and stereoselective attack of the nucleophile at the epoxide C-3. The high regioselectivity (>25:1) observed with both *cis* and *trans* substituted epoxides is not affected by bulky substituents at C-3. The method has been successfully applied also to the synthesis of diaminodiol dipeptide isosteres.

Keywords: Aluminium and compounds; Azides; Epoxides; Isosteres

The 3-amino-1,2-diol structure is present in several classes of biologically active compounds, such as, for example, β-blocker drugs [1,2], anti-hypertensive renin inhibitors [3,4] and aminosugars [5]. 3-Amino-1,2-diols are also valuable intermediates in the synthesis of a variety of other bioactive molecules, including α-aminoacids [6], α-hydroxy-β-aminoacids [7,8] and dipeptide isosteres [9,10]. A convenient approach to this structure is represented by the ring- opening of readily available 2,3-epoxyalcohols by ammonia or azide [11]. Recently we have followed this approach in the synthesis of a series of C_2-symmetric and pseudo-symmetric dihydroxyethylene dipeptide isosteres **3** with all-*S* configuration [10] (Scheme 1).

Scheme 1



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In the course of that work we found that ring opening of epoxides **1** with NaN_3 and NH_4Cl takes place selectively at the C-3 position to give the desired azidodiols **2** when R'= CH_2Ph or R'=CH_2*c*-Hex. However, when R' is the bulkier isopropyl group, the reaction is sluggish and yields a mixture of C-2 and C-3 regioisomers. Trimethylsilyl azide, in the presence of catalytic titanium tetraisopropoxide [12] also failed to afford the required product **2** (Scheme 1, R,R'=isopropyl), leading instead to the loss of the Boc protecting group. We thus turned to aluminium reagents whose ability to promote the nucleophilic ring opening of oxiranes is well established [13,14]; our initial attempt with trimethylsilyl azide and diethylaluminium chloride was not successful as this reagent gave a mixture of azido-alcohols and chlorohydrins [15]. Eventually the desired azidodiol **2** (R,R' = isopropyl) was obtained by the reaction of epoxide **1** with diethylaluminium azide (Scheme 1). This reagent was prepared and studied in the 60's [16,17], but it has been seldom used in organic synthesis [18,19]. In particular there appears to be only one report on the ring-opening of epoxides with Et_2AlN_3 [18], while, to the best of our knowledge, the use of this reagent in the cleavage of epoxyalcohols has never been reported. This prompted us to extend the investigation to a representative series of 2,3-epoxyalcohols; results are in the Table.

Treatment of 2,3-epoxyalcohols with diethylaluminium azide, prepared *in situ* from sodium azide and diethylaluminium chloride [15] gave the corresponding 3-azido-1,2-diols in good yields[1] (Table 1). The main by-products are the corresponding 3-chloro-1,2-diols which were identified from the ^1H and ^{13}C NMR spectra of the crude reaction mixtures and by comparison with the spectra of authentic samples obtained from the reaction of epoxyalcohols with diethylaluminium chloride. Regioisomeric 2-azido-1,3-diols were not detected by NMR and thus a regioselectivity higher than 25:1 can safely be assumed. As can be seen from the Table (entries 2, 4 and 8) protection of the hydroxy group as a benzyl ether does not affect the reactivity or the regioselectivity.

The very high C-3 selectivity displayed by diethylaluminium azide is not affected by substitution at the 3 position (entries 5, 7-12). Cyclic (*cis*-constrained) and acyclic *cis*-2,3-epoxyalcohols (entries 9, 10), when treated with this reagent, also gave the corresponding 3-azido-1,2-diols. The structures of these products were confirmed by comparison with literature data [12] (entry 9) or by the ^1H NMR analysis (400 MHz, $CDCl_3$) of the azidodiol and its di-trifluoroacetate (entry 10). Diethylaluminium azide is thus superior, in this respect, to titanium reagents whose C-3 selectivity is hampered by *cis*-substitution and by steric hindrance at the C-3 position [1].

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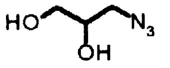
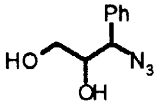
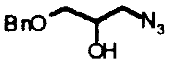
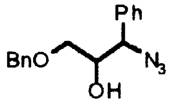
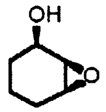
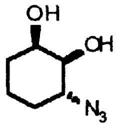
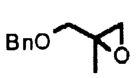
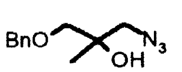
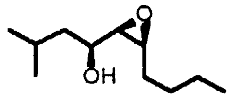
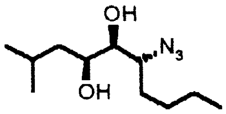
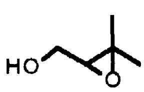
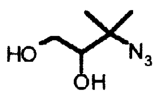
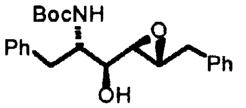
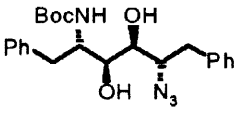
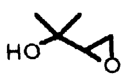
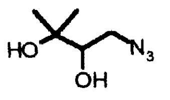
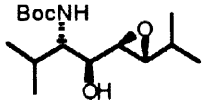
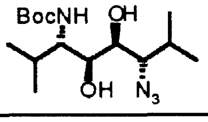
[1] Typical procedure. A 1.8M solution of diethylaluminium chloride in toluene (13.6 mmol) is added via syringe, under an argon atmosphere, to a well stirred suspension of sodium azide (15 mmol) in dry toluene and the resulting mixture is stirred for 4 h at 20 °C. The mixture is cooled to −78 °C and a solution of the epoxide (6.8 mmol) in 5 ml toluene is added dropwise. The reaction mixture is stirred for 1 h at −78 °C and for 16 h at 25 °C, then cooled to 5 °C and diluted with 30 ml ethyl acetate. Sodium fluoride (13 g) and water (1.8 ml) are added and the resulting suspension is stirred for 0.5 h at room temp. Filtration through a short pad of anhydrous sodium sulphate and solvent evaporation gives the crude product which is purified by column chromatography or crystallization.

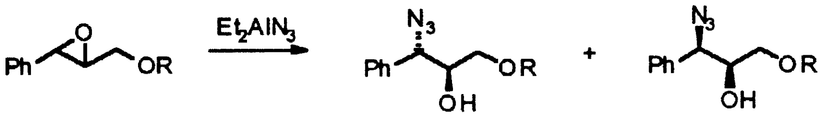
Table 1

Ring Opening of 2,3-Epoxyalcohols by Diethylaluminium Azide.[a]

Entry	Epoxyalcohol	Azidodiol	%Yield	Entry	Epoxyalcohol	Azidodiol	%Yield
1			38	7			74[b,c]
2			68[b]	8			65[b,c]
3			89	9[d]			83
4			69[b]	10[d]			84
5			69[b]	11			77
6			62[b]	12			79

[a] Yields refer to isolated products and are not optimized.
[b] 3-Chloro-1,2-diol is the main by-product.
[c] Mixture of *threo* and *erythro* diastereoisomers.
[d] Racemic mixture.

Scheme 2



4a R = H
4b R = Bn

5a 7 : 3 **6a**
5b 5 : 1 **6b**

Ring-opening of 3-substituted 2,3-epoxyalcohols (entries 7-12) is highly stereoselective, leading to the formation of the corresponding azidodiols with inversion of configuration at C_3, with the exception of the phenyl substituted epoxides **4** (Scheme 2). In this case we obtained a mixture of diastereoisomers **5** and **6** from *anti* and *syn* attack. A similar behaviour has been observed in the reaction of the same epoxide with trimethylsilyl azide in the presence of catalytic $Ti(O\text{-}iPr)_4$; the formation of the *syn* product **6** can be attributed either to an intramolecular attack by an azide-containing metal species co-ordinated to the epoxide oxygen or to an S_N1 reaction at the benzylic center, following ring opening of the epoxide promoted by co-ordination of the Lewis acid [12, 20]. It is noteworthy that the corresponding chlorodiol, which is a byproduct of the reaction, is also formed as a mixture of diastereoisomers in a similar ratio.

Finally, entries 11 and 12 show that this methodology can be efficiently applied to the ring-opening of highly substituted, homochiral epoxy alcohols leading, in this case, to 3-azido-1,2-diols in which four contiguous chiral centers have been established in a stereocontrolled way [10]. Catalytic hydrogenation of the azides over palladium and deprotection (Scheme 1) gave the corresponding, enantiomerically pure, C-2 symmetric diaminodiols **3** (R,R'=CH_2Ph; $CH(CH_3)_2$), thus unambiguously confirming the regio- and stereochemical features of the Et_2AlN_3 promoted ring opening.

We have thus demonstrated that diethylaluminium azide is a mild and efficient reagent for the regio- and stereoselective ring opening of epoxyalcohols; as the C-3 selectivity is not affected by *cis* or hindered substituents, this method should find general application in the synthesis of 3-amino-1,2-diols.

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References

[1] Rama Rao AV, Gurjar MK, Joshi SV. Tetrahedron: Asymmetry 1990;1:697.

[2] Klunder JM, Ko SY, Sharpless KB. J.Org.Chem. 1986;51:3710.

[3] Kleinert HD, Rosenburg SH, Baker WR, Stein HH, Klinghofer V, Barlow J, Spina K, Polakowski J, Kovar P, Cohen J, Denissen J Science 1992;257:1940.

[4] Luly JR, BaMaung N, Soderquist J, Fung AKL, Stein H, Kleinert HD, Marcotte PA, Egan DA, Bopp B, Merits J, Bolis G, Greer J, Perun TI, Plattner JJ. J. Med. Chem. 1988;31:2264.

[5] Jurczak J. In: Hanessian S. editor. Preparative Carbohydrate Chemistry. New York: Marcel Dekker, 1997:595.

[6] Caron M, Carlier PR, Sharpless KB. J. Org. Chem. 1988;53:5187.

[7] Pastó M, Moyano A, Pericàs MA, Riera A. Tetrahedron: Asymmetry 1996;7:243.

[8] Pastó M, Castejón P, Moyano A, Pericàs MA, Riera A. J. Org. Chem. 1996;61:6033.

[9] Brånalt J, Kvarnström I, Classon B, Samuelsson B, Nillroth U, Danielson UH, Karlén A, Hallberg A. Tetrahedron Lett. 1997;38: 3483.

[10] Benedetti F, Miertus S, Norbedo S, Tossi A, Zlatoidzky P. J. Org. Chem. 1997;62:9349.

[11] Mitsunobu O. In: Trost BM, Fleming I, editors. Comprehensive Organic Synthesis Vol. 6. Oxford: Pergamon Press, 1991:65-101.

[12] Sutowardoyo KI, Sinou D. Bull. Soc. Chim. Fr. 1991;128:387.

[13] Gorzynski Smith J. Synthesis 1984:629.

[14] Rao AS, Paknikar SK, Kirtane JG. Tetrahedron 1983;39:2323.

[15] Maruoka K, Sano H, Yamamoto H. Chem. Lett. 1985:599.

[16] Dehnicke K, Strähle J, Seybold D, Müller J. J. Organomet. Chem. 1966;6:298.

[17] Müller J. J. Organomet. Chem. 1973;51:119.

[18] Mereyala HB, Frei B. Helv. Chim. Acta 1986, 69, 415.

[19] Rawal VH, Zhong HM. Tetrahedron Lett. 1994;35:4947.

[20] Sutowardoyo KI, Emziane M, Lhoste P, Sinou D. Tetrahedron 1991;47:1435.