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REGIOSELECTIVE REDUCTIONS OF 2,3-EPOXY ALCOHOLS

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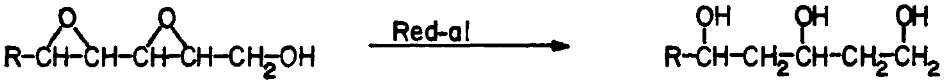
Abstract: Regioselective reduction of 3-substituted-2,3-epoxy alcohols to 1,3-diols with sodium bis(2-methoxyethoxy)aluminum hydride (Red-al) is shown to be a general reaction for these substrates.

In the studies of these laboratories, directed towards the stereospecific synthesis of polyhydroxylated natural products, we have demonstrated that Red-al is a remarkably regioselective reducing agent in the case of 2,3-epoxy alcohols and 2,3-4,5-bisepoxy alcohols.[1] In these reactions only 1,3-diols and 1,3,5-triols are formed, respectively, as seen in equations (1) and (2).

(1)



(2)

We reported earlier that the reaction depicted in equation (1) is selective with substrates possessing alkoxy substituents at C-4 and C-5 (see Figure 1).[2] The results of that study led us to believe that the electron withdrawing effect of the alkoxy substituent, deadening the C-3 position to nucleophilic attack, in concert with the intramolecular hydroxyl directing effect were both important factors in determining the site of reduction.

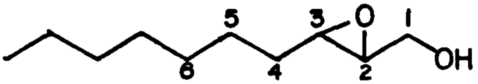


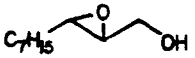
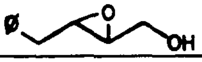
Figure 1

If the attack is intramolecular the stereoelectronic requirements are expected to greatly favor C-2 attack over C-3 attack. We have now found, provided a proper solvent selection is made (vide infra), that this reaction is general for 3-substituted-2,3-epoxy alcohols, with or without electron withdrawing substituents in the R-group.

Pursuing our original discovery[1], we sought conditions which would be selective for simple epoxy alcohols bearing no electron withdrawing substituents. The examples of this latter type (see 1, 2, and 3 in Table 1) were reported to give little or no selectivity in our first paper.[1] We immediately found a dramatic solvent effect.[3] In the earlier work CH_2Cl_2 was the solvent employed for the first three entries in the Table; the remaining entries (4 through 7) were performed in THF (see Table 1 in reference 1).[4] When the solvent was changed from CH_2Cl_2 to THF even the simplest epoxy alcohol 1 was reduced with high regioselectivity at C-2. The scope of this process for simple 3-substituted-2,3-epoxy alcohols (1, 4 and 5) is revealed in Table 2. Reduction using LAH gives only a slight predominance of the 1,3-diol, whereas Red-al reduction gives (for all practical purposes) only the 1,3-diol.

As expected, a methyl group in the C-3 position (see Figure 1) does not reduce the selectivity or make the substrate less reactive (entry 5, Table 2). On the other hand a methyl group in the two position (entry 6, Table 2) reversed the selectivity and greatly decreased the reaction rate. This latter result is easily attributed to the increased steric hindrance at C-2 in epoxy alcohol 8.

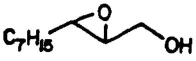
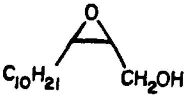
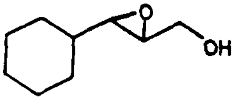
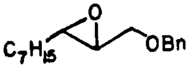
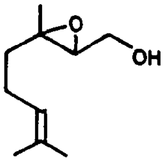
Table 1 Red-al Reductions

Entry	Epoxy Alcohol[a]		1,3:1,2 diol ratio	
			CH_2Cl_2[b,c]	THF[b,c]
1		1	1:1	>150:1[d]
2		2	5:1	40:1
3		3	5:1	∿100:1

a) Racemates were used. Concentrations of 0.1M-0.2M were used.
b) All reactions were run at 0°C as in reference 1.
   2-3 equivalents of Red-al were used in each reaction.
c) Ratio determined by High Field N.M.R. (250 MHz).[7]
d) Ratio determined by capillary G.C. High Field N.M.R. (250 MHz) showed no minor isomer.

The directing effect of an adjacent hydroxyl group in epoxide openings has been well studied in cyclic cases.[5] It now appears that for most acyclic cases the hydroxyl group will be important in achieving high regioselectivity for attack at C-2. Reduction of compound 1 with the hydroxyl group protected (as a benzyl ether) required refluxing THF and gave a slight predominance for reduction at C-3 (entry 4, Table 2).[6] Although it seems likely that the reaction proceeds by coordination of the aluminum reagent to the hydroxyl oxygen followed by intramolecular delivery (at least with THF as the solvent) of the hydride to the C-2 position, other important factors such as ethereal substituents and solvent complexation are not yet fully understood. Further investigations into more subtle effects governing these epoxy alcohol opening processes are now underway.

Table 2

Entry	Epoxy Alcohol[a]		Reductant[b]	1,3:1,2 diol ratio[c]	Yield[d]
1		1	LAH Red-al	4:1 ∿100:1	94% 90%
2		4	LAH Red-al	5:1 ∿100:1	77% 95%
3		5	LAH Red-al	6.4:1 125:1[e]	95% 95%
4		6	Red-al	1:1.5	50%
5		7	Red-al	∿100:1	95%
6		8	Red-al	∿1:100	70%

a) Racemates were used. Concentrations of 0.1M-0.2M were used.
b) All reactions were run in THF at $^-$15°C except entry 4 which was done in refluxing THF. 2-3 eq. of Red-al were used.
c) All ratios were determined by High Field N.M.R. (250 MHz).[7]
d) Yield represents isolated yields.
e) Ratio determined by capillary G.C. High Field N.M.R. (250 MHz) showed no minor isomer.

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References and Notes

1. P.Ma.,V.S.Martin, S.Masamune, K.B.Sharpless, S.M.Viti, *J.Org. Chem.* **1982**, *47*, 1378.
2. Finan and Kishi have also recently reported very similar results with alkoxy substituted 2,3-epoxy alcohols. J.M.Finan, Y.Kishi, *Tetrahedron Lett.* **1982**, 2719.
3. In their recent paper, reference 2, Finan and Kishi also note differences in selectivity when changing solvents.
4. Due to an unfortunate oversight one has the impression that all the reactions in reference 1 were performed in THF. This was not the case and stands corrected as described above.
5. (a) E.Glotter, S.Greenfield, D.Lavie, *Tetrahedron. Lett.* **1967**, 5261.
   (b) B.C.Hartman, B.Rickborn, *J.Org. Chem.* **1972**, *37*, 4246.
   (c) S.Danishefsky, M.Tsai, T.Kitahara, *J. Org. Chem.* **1977**, *42*, 394.
6. See reference 2 for an example of no reduction when the hydroxyl group is blocked.
7. We use $\sim$100:1 by High Field N.M.R. (250 MHz) to describe the result when a known peak for the minor isomer is totally unobservable.

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