

PREPARATION OF O-PROTECTED (2S,3S)-1,2-EPOXY-3-BUTANOLS. ENANTIOSELECTIVE
SYNTHESES OF (-)-RHODINOSE AND (+)-EPIMUSCARINE IODIDE

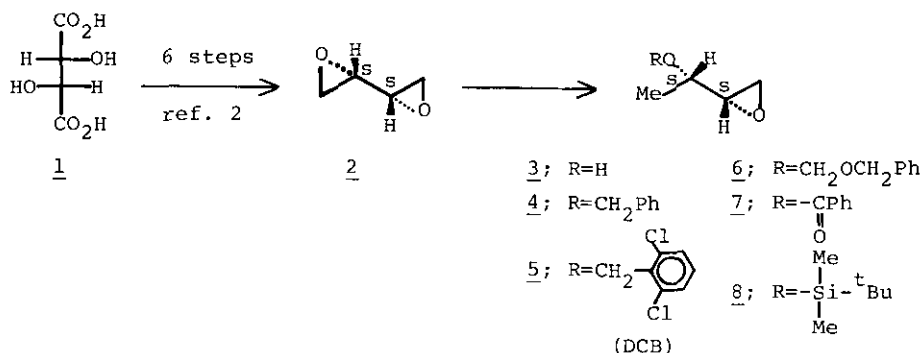
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Abstract — Reductive cleavage of (S,S)-1,2-3,4-diepoxybutane with lithium triethylborohydride, followed by protection gave O-protected (2S,3S)-1,2-epoxy-3-butanols, which were employed in chiral syntheses of (-)-rhodinoase and (+)-epimuscarine iodide.

In connection with a project directed toward the synthesis of biologically active natural products possessing 1,2-diol functionalities, an efficient method was sought for preparing (2S,3S)-1,2-epoxy-3-butanol derivatives. Very recently, Abushanab and co-workers¹ have developed the synthetic routes for (2S,3S)-3-benzyloxy-1,2-epoxybutane (**4**) starting with L-(+)-ascorbic acid, L-(+)-tartaric acid, and *Z*-butene-1,4-diol. However, all of these three methods are not efficient enough when a large quantity of **4** is required as a chiral building block. We now wish to report an effective preparation of O-protected (2S,3S)-1,2-epoxy-3-butanols and their transformations into (-)-rhodinoase (**11**) and (+)-epimuscarine iodide (**15**). Our approach to (2S,3S)-1,2-epoxy-3-butanol derivatives relied on reductive cleavage of the C₂ symmetry diepoxide **2**,² easily accessible from L-(+)-tartaric acid (**1**).

Treatment of the diepoxide **2** with one equivalent of lithium triethylborohydride (THF, -30 °C), followed by oxidative work up with methanolic trimethylamine *N*-oxide at room temperature and filtration of the reaction mixture through a silica gel short column without usual extractive work up gave (2S,3S)-1,2-epoxy-3-butanol (**3**).³ Without purification, **3** was then benzylated (NaH, PhCH₂Br, cat. ⁿBu₄NI, THF, rt)⁴ to afford (2S,3S)-3-benzyloxy-1,2-epoxybutane (**4**),^{5,6} bp_{0.25} 100 °C (Kugelrohr), [α]_D²² -13.7° (c 1.082, EtOH) (lit. -10.66°) in 45-60% overall yield.⁷ Similarly, the 2,6-dichlorobenzyl ether **5**, [α]_D²⁵ +7.6° (c 1.240, CHCl₃), the benzyloxymethyl ether **6**, [α]_D²⁵ -25.1° (c 1.092, CHCl₃), the benzoate **7**, [α]_D²⁵ +31.3° (c 1.221, CHCl₃), and the *tert*-butyldimethylsilyl ether **8**, [α]_D²⁵ +1.8° (c 1.115, CHCl₃) were prepared by the standard methods, respectively. Moreover, we examined reductive cleavage of **2** using other hydride reagents such as diisobutylaluminum hydride, lithium tri-*tert*-butoxyaluminum hydride, and sodium bis(2-methoxyethoxy)aluminum hydride. But the results were not encouraging.

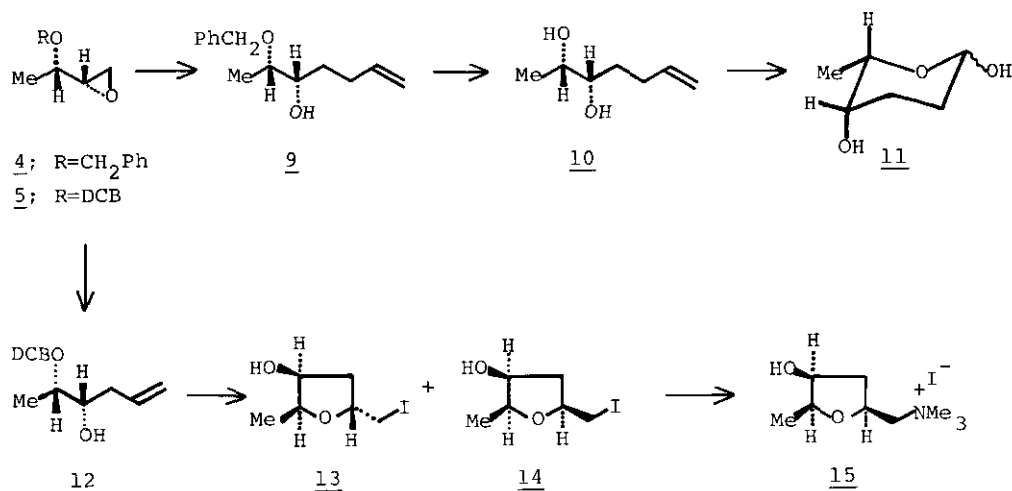


The utility of (2S,3S)-1,2-epoxy-3-butanol derivatives as a chiral building block was at first demonstrated in the synthesis of (-)-rhodinose (**11**), a sugar component of the antibiotics such as rhodomycin and streptolydigin.^{8,9} The reaction of **4** with allylmagnesium chloride in the presence of cuprous iodide (THF, -60 °C) gave the alcohol **9**,¹⁰ bp_{0.15} 120 °C (Kugelrohr), $[\alpha]_{\text{D}}^{26} +36.4^\circ$ (c 1.006, CHCl_3), which, upon debenzoylation (Li, liq. NH_3 , -33 °C), afforded the diol **10**,¹¹ bp_{0.3} 50 °C (Kugelrohr), $[\alpha]_{\text{D}}^{25} -19.2^\circ$ (c 1.104, CHCl_3), in 73% overall yield. Ozonolysis (CH_2Cl_2 , -78 °C and then Me_2S), followed by treatment with 10% hydrochloric acid (acetone, 55 °C) furnished (-)-rhodinose (**11**), bp_{0.3} 80 °C (Kugelrohr), $[\alpha]_{\text{D}}^{27} -11.8^\circ$ (c 0.660, acetone) (lit.^{9b} -11°), in 53% overall yield.

Furthermore, we examined the synthesis¹² of (+)-epimuscarine iodide (**15**), which is one of the natural stereoisomeric muscarines so far isolated,^{12,13} utilizing (2S,3S)-1,2-epoxy-3-butanol derivative **5** as a chiral precursor. Thus, the reaction of **5** with vinylmagnesium bromide in the presence of cuprous iodide (THF, -60 °C) afforded the alcohol **12**,¹⁴ $[\alpha]_{\text{D}}^{28} +45.0^\circ$ (c 1.130, CHCl_3), in 96% yield.

Application¹⁵ of the stereoselective iodoetherification methodology developed by Bartlett and co-worker¹⁶ to **12** allowed formation of **13**,¹⁷ $[\alpha]_{\text{D}}^{29} +39.0^\circ$ (c 0.508, CHCl_3), and **14**,¹⁸ mp 62 °C (n_{hexane}), $[\alpha]_{\text{D}}^{30} -0.34^\circ$ (c 1.164, CHCl_3), in a ratio of 5:95 in 59% yield, after separation by column chromatography (SiO_2 , $\text{Et}_2\text{O}-n_{\text{hexane}}$ 1:5). Finally, the iodide **14** was treated with ethanolic trimethylamine at refluxing temperature¹² to yield (+)-epimuscarine iodide (**15**), mp 175 °C (acetone), $[\alpha]_{\text{D}}^{28} +32.0^\circ$ (c 0.550, H_2O) (lit.¹⁰ -38.9° for the antipode), in 73% yield.

The study outlined above demonstrates an effective chiral construction of 1,2-diol functionalities using (2S,3S)-1,2-epoxy-3-butanol derivatives and further investigations for the synthesis of other natural products using these chiral precursors are underway.



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2. D. Seebach, H.-O. Kalinowski, B. Bastani, G. Grass, H. Daum, H. Dorr, N. P. DuPreez, V. Ehrig, W. Langer, C. Nussler, H.-A. Oei, and M. Schmidt, *Helv. Chim. Acta*, **60**, 301 (1977).
3. Since the compound 3 is very volatile and water-soluble, the standard work up including treatment with aqueous hydrogen peroxide and extraction gave 3 in lower than 30% yield.
4. S. Czernecki, C. Georgoulis, and C. Provelenghiou, *Tetrahedron Lett.*, **39**, 3535 (1976).
5. All new compounds gave satisfactory spectral (¹H-NMR, IR, MS) and analytical (high resolution MS) data.
6. (2S,3S)-1,2-Epoxy-3-butanol derivatives exhibited the following ¹H-NMR spectra in CDCl₃: 4: δ 1.23 (3H, d, 8 Hz), 2.36-3.33 (4H, m), 4.53 (1H, d, 12 Hz), 4.76 (1H, d, 12 Hz), 7.30 (5H, br.s); 5: δ 1.23 (3H, d, 6 Hz), 2.27-3.16 (3H, m), 3.36 (1H, quint, 6 Hz), 4.67 (1H, d, 10 Hz), 5.00 (1H, d, 10 Hz), 7.03-7.33 (3H, m); 6: δ 1.23 (3H, d, 7 Hz), 2.37-3.17 (3H, m), 3.81 (1H, quint, 7 Hz), 4.60 (2H, s), 4.76 (1H, d, 6 Hz), 4.93 (1H, d, 6 Hz), 7.23 (5H, br.s); 7: δ 1.43 (3H, d, 7 Hz), 2.59-2.91 (2H, m), 3.10-3.33 (1H, m), 5.04 (1H, quint, 7 Hz), 7.19-7.59 (3H, m), 7.93-8.16 (2H, m); 8: δ 0.08 (6H, s), 0.88 (9H, s), 1.19 (3H, d, 7 Hz), 2.42-3.10 (3H, m), 3.56 (1H, m).
7. Any chromatographical purifications were not necessary through the whole synthetic sequence from 1 to 4.
8. a) C. L. Stevens, P. Blumbergs, and D. L. Wood, *J. Am. Chem. Soc.*, **86**, 3592 (1964); b) H. Brockmann and H. Greve, *Tetrahedron Lett.*, 831 (1975) and references therein.

9. For the synthesis of (-)-rhodnose (11), see: a) A. H. Haines, Carbohydr. Res., 21, 99 (1972); b) R. Knollman and I. Dyong, Chem. Ber., 108, 2021 (1975); c) T. R. Kelly and P. N. Kaul, J. Org. Chem., 48, 2775 (1983). For the synthesis of the antipode of 11, see ref. 8a.
10. $^1\text{H-NMR}$ (CDCl_3): δ 1.19 (3H, d, 6 Hz), 1.60 (2H, m), 2.20 (3H, m, 1H exchangeable with D_2O), 3.42 (2H, m), 4.38 (1H, d, 11 Hz), 4.66 (1H, d, 11 Hz), 4.73-5.25 (2H, m), 4.49-6.23 (1H, m), 7.28 (5H, s).
11. $^1\text{H-NMR}$ (CDCl_3): δ 1.19 (3H, d, 6 Hz), 1.50 (2H, m), 2.20 (2H, m), 2.76 (2H, br.s, exchangeable with D_2O), 3.18-3.85 (2H, m), 4.80-5.30 (2H, m), 5.50-6.25 (1H, m).
12. Although Bollinger and Eugster reported the synthesis of optically active epimuscarine involving resolution of ($\pm$)-epimuscarine iodide, no report of its enantioselective synthesis has yet been made: H. Bollinger and C. H. Eugster, Helv. Chim. Acta, 54, 2704 (1971).
13. H. Bollinger and C. H. Eugster, Helv. Chim. Acta, 54, 1332 (1971).
14. $^1\text{H-NMR}$ (CDCl_3): δ 1.16 (3H, d, 7 Hz), 2.30 (2H, m), 2.70 (1H, br.d, exchangeable with D_2O), 3.25-3.70 (2H, m), 4.66 (1H, d, 11 Hz), 4.92 (1H, d, 11 Hz), 4.65-5.30 (2H, m), 5.52-6.25 (1H, m), 7.22 (3H, m).
15. The similar stereoselective route to ($\pm$)-muscarine based upon the iodoetherification methodology has already been developed; R. Amouroux, B. Gerin, and M. Chastrette, Tetrahedron Lett., 23, 4341 (1982).
16. S. D. Rychnovsky and P. A. Bartlett, J. Am. Chem. Soc., 103, 3963 (1981).
17. $^1\text{H-NMR}$ (CDCl_3): δ 1.18 (3H, d, 5.5 Hz), 1.62-2.50 (3H, m, 1H exchangeable with D_2O), 3.29 (2H, d, 6 Hz), 3.98-4.60 (3H, m).
18. $^1\text{H-NMR}$ (CDCl_3): δ 1.29 (3H, d, 6 Hz), 1.74 (1H, ddd, 12, 6, and 2 Hz), 1.87 (1H, br.s, exchangeable with D_2O), 2.43 (1H, ddd, 12, 8, and 6 Hz), 3.36 (2H, d, 5 Hz), 3.60-4.50 (3H, m).

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