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

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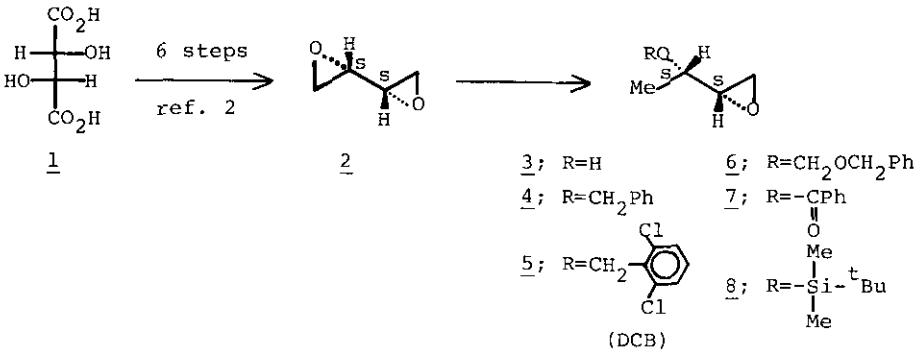
Abstract —— Reductive cleavage of (S,S)-1,2-3,4-diepoxybutane with lithium triethylborohydride, followed by protection gave O-protected (2S,3S)-1,2-epoxy-3-butanols, which were employed in chiral syntheses of (-)-rhodinose and (+)-epimuscarine iodide.

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-workers[1] 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 (-)-rhodinose (*11*) and (+)-epimuscarine iodide (*15*). Our approach to (2S,3S)-1,2-epoxy-3-butanol derivatives relied on reductive cleavage of the C_2 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, $PhCH_2Br$, cat. $^nBu_4NI$, THF, rt)[4] to afford (2S,3S)-3-benzyloxy-1,2-epoxybutane (4),[5,6] $bp_{0.25}$ *100* °C (*Kugelrohr*), $[\alpha]_D^{22}$ *-13.7°* (c 1.082, EtOH) (lit. -10.66°) in 45-60% overall yield.[7] Similarly, the 2,6-dichlorobenzyl ether 5, $[\alpha]_D^{25}$ +7.6° (c 1.240, $CHCl_3$), the benzyloxymethyl ether 6, $[\alpha]_D^{25}$ -25.1° (c 1.092, $CHCl_3$), the benzoate 7, $[\alpha]_D^{25}$ +31.3° (c 1.221, $CHCl_3$), and the tert-butyldimethylsilyl ether 8, $[\alpha]_D^{25}$ +1.8° (c 1.115, $CHCl_3$) 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.

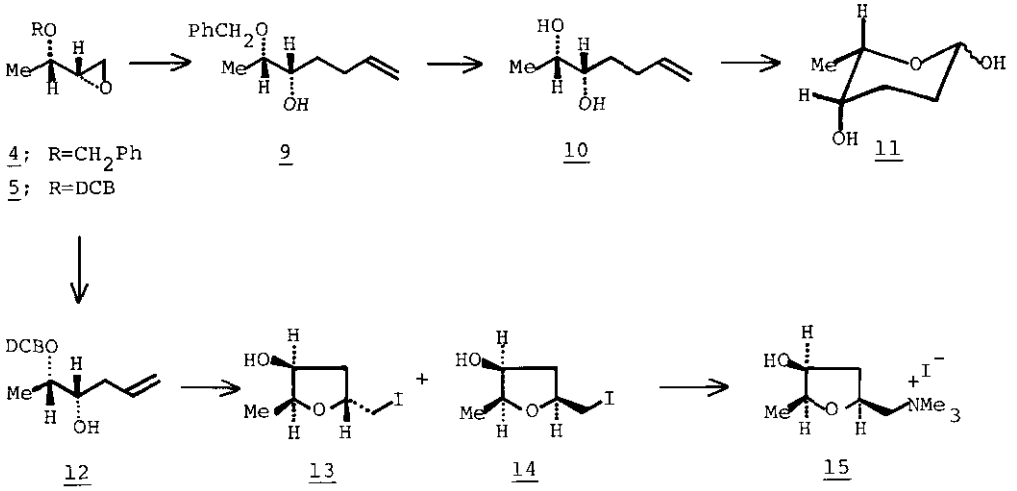


The utility of (2S,3S)-1,2-epoxy-3-butanol derivatives as a chiral building block was at first demonstrated in the synthesis of (-)-rhodinose (11), a sugar component of the antibiotics such as rhodomycin and streptolydigin.[8,9] The reaction of 4 with allylmagnesium chloride in the presence of cuprous iodide (THF, -60 °C) gave the alcohol 9,[10] $bp_{0.15}$ 120 °C (Kugelrohr), $[\alpha]_D^{26}$ +36.4° (c 1.006, $CHCl_3$), which, upon debenzylation (Li, liq. NH_3, -33 °C), afforded the diol 10,[11] $bp_{0.3}$ 50 °C (Kugelrohr), $[\alpha]_D^{25}$ -19.2° (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), $[\alpha]_D^{27}$ -11.8° (c 0.660, acetone) (lit.[9b] -11°), in 53% overll yield.

Furthermore, we examined the synthesis[12] 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] $[\alpha]_D^{28}$ +45.0° (c 1.130, $CHCl_3$), in 96% yield.

Application[15] of the stereoselective iodoetherification methodology developed by Bartlett and co-worker[16] to 12 allowed formation of 13,[17] $[\alpha]_D^{29}$ +39.0° (c 0.508, $CHCl_3$), and 14,[18] mp 62 °C (^{n}hexane), $[\alpha]_D^{30}$ -0.34° (c 1.164, $CHCl_3$), in a ratio of 5:95 in 59% yield, after separation by column chromatography (SiO_2, Et_2O-^{n}hexane 1:5). Finally, the iodide 14 was treated with ethanolic trimethylamine at refluxing temperature[12] to yield (+)-epimuscarine iodide (15), mp 175 °C (acetone), $[\alpha]_D^{28}$ +32.0° (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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1. E. Abushanab, M. Bessodes, and K. Antonakis, Tetrahedron Lett., 25, 3841 (1984).
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 (^{1}H-NMR, IR, MS) and analytical (high resolution MS) data.
6. (2S,3S)-1,2-Epoxy-3-butanol derivatives exhibited the following ^{1}H-NMR spectra in $CDCl_3$; 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 (-)-rhodinose (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}H-NMR ($CDCl_3$): δ1.19 (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}H-NMR ($CDCl_3$): δ1.19 (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 (±)-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}H-NMR ($CDCl_3$): δ1.16 (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 (±)-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}H-NMR ($CDCl_3$): δ1.18 (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}H-NMR ($CDCl_3$): δ1.29 (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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