Tetrahedron Letters,Vol.30,No.21,pp 2751-2754,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A TWO-STEP SYNTHESIS OF (*R*)- AND (*S*)-BENZYLGLYCIDYL ETHER

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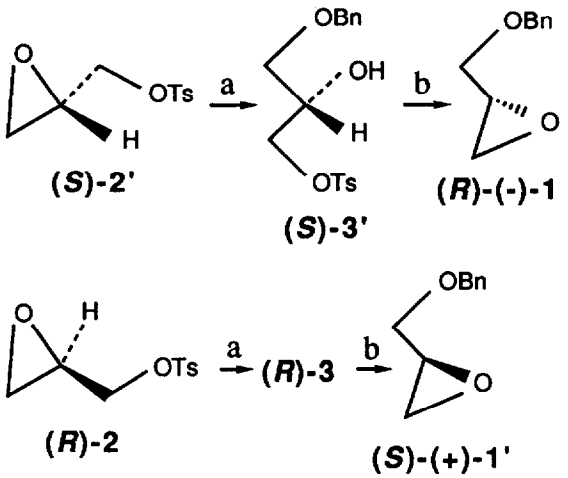
Abstract: Ring opening of (*R*)- and (*S*)-glycidyl tosylates with benzyl alcohol, followed by treatment with K_2CO_3/MeOH gave (*S*)-(+)- and (*R*)-(-)-benzylglycidyl ether in 90% overall yield.

(*R*)-(-)-Benzylglycidyl ether (**1**) and its enantiomer (*S*)-**1'** are useful chiral synthons. Recently, chiral epoxides **1** and **1'** have been used as the starting materials in enantioselective syntheses of a variety of natural products, including the polyol macrolides roflamycoin and mycoticins A and B,[1] the neuroexcitory amino acid arometic acid,[2] the alkaloid ratifine,[3] the terpenes (*S*)-lavandulol, (*R*)-santolinatriene, and (1*S*,2*S*)-rothrockene,[4] and other useful intermediates.[5]

Recent methods of preparing **1** and **1'** involve at least five steps beginning from natural sources such as D-mannitol and L-mannitol (via L-arabinose or L-inositol), respectively.[6] Alternative routes to **1** and **1'** are via inversion of (*R*)-benzylglycerol (prepared from D-mannitol)[7] and degradation of L-ascorbic acid.[8,9]

We report here a simple two-step route to **1** and **1'** from (*R*)-(-)- and (*S*)-(+)-glycidyl 4-toluenesulfonate (**2** and **2'**), which are prepared by asymmetric epoxidation of allyl alcohol and in situ derivatization.[10] Since the tosylates **2** and **2'** are available commercially in high optical purity,[11] our synthesis of (*R*)-**1** and (*S*)-**1'** represents a considerable advantage for small-scale procedures compared with reported routes. The key step in the procedure is the regio- and stereospecific opening of epoxide **2** (or **2'**) with benzyl alcohol in the presence of a catalytic amount of boron trifluoride etherate, giving the ring-opened 1-*O*-benzyl-3-*p*-toluenesulfonyl-*sn*-glycerol (**3**)[12] or its enantiomer (*S*)-**3'** in 93% yield.[13] *O*-Benzylglycidol is formed in nearly quantitative yield by treatment of **3** with potassium carbonate in methanol.



(a) 2.0 equiv of BnOH, catalytic $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 12 h, then 20 °C for 2 h; (b) 1.2 equiv of K_2CO_3/MeOH, -10 °C, 2 h, then 20 °C for 2 h.

(*S*)-(+)-**3'** was prepared as follows. To a solution of 10 g (43.8 mmol) of (+)-**2'** containing 1 g of type 3A molecular sieves[14] and 9.5 g (87.6 mmol) of freshly distilled benzyl alcohol in 100 mL of dichloromethane at 0 °C was added 10 drops (about 5 mol %) of boron trifluoride etherate. The mixture was stirred overnight under nitrogen at 0 °C, then at room temperature for 2 h, and filtered through a Celite pad. The filtrate was washed with 10% aqueous $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated to give a colorless oil. Removal of excess benzyl alcohol in vacuo left a residue, which was purified by two recrystallizations from ether-petroleum ether, giving 13.7 g (93%)[15] of (+)-**3'** as a white solid, mp 46-48 °C, $[\alpha]^{25}_D$ +6.79° (*c* 10, C_6H_6); lit.[16] $[\alpha]^{25}_D$ +6.64° (*c* 10, C_6H_6); 95.3,[17a] 94.0[17b] % ee. The enantiomer (*R*)-(-)-**3** was prepared from (-)-**2** in 92% yield using the same procedure; mp 48-50 °C, $[\alpha]^{25}_D$ -6.70° (*c* 10, C_6H_6); 96.2,[17a] 95.0[17b] % ee.

(*R*)-(-)-Benzylglycidyl ether (**1**) was prepared from (*S*)-(+)-**3'** as follows. To a solution of 1.68 g (5.0 mmol) of (+)-**3'** in 20 mL of methanol at -10 °C was added 0.83 g (6.0 mmol) of powdered K_2CO_3. The mixture was stirred for 2 h at -10 °C, then 2 h at room temperature. Ether (20 mL) was added, and the mixture was filtered through a pad of silica gel and washed with ether (30 mL). Removal of solvents under reduced pressure gave 0.8 g (98%) of (*R*)-(-)-**1**;[18] $[\alpha]^{25}_D$ -5.40° (*c* 5, C_6H_6); lit.[16] $[\alpha]^{25}_D$ -5.35° (*c* 5, C_6H_6). (*S*)-(+)-**1'** was prepared in 97% yield in the same way from (*R*)-(-)-**3**; $[\alpha]^{25}_D$ +5.43° (*c* 5, C_6H_6).

In summary, we have shown a simple and efficient two-step procedure for conversion of glycidyl tosylate into (*R*)-**1** and (*S*)-**1'**, which are useful chiral C_3 synthons for many natural products of current interest.

Acknowledgment. This research was supported by National Institutes of Health Grant HL 16660.

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11. Tosylates **2** and **2'** are available from Aldrich Chemical Co. After this work was completed, (*R*)-(-)- and (*S*)-(+)-glycidyl 3-nitrobenzenesulfonates became available (*Aldrichimica Acta* **1988,** *21*, 54), which reach 99% ee after two recrystallizations from ethanol (Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989,** *54*, 1295-1304). The latter reference reports 97% ee for **2** after several recrystallizations. For large-scale work glycidyl sulfonates can be prepared by reaction of commercially available (Aldrich, Arco) chiral glycidol with arenesulfonyl chloride at -10 °C, followed by multiple recrystallizations.

12. For the *sn* (stereospecific numbering) system for designating the configuration of glycerol derivatives, see *Chem. Phys. Lipids* **1978,** *21*, 163.

13. We recently reported the ring opening of (*R*)-**2** and (*S*)-**2'** by 1-hexadecanol catalyzed by $BF_3{\cdot}OEt_2$: Guivisdalsky, P. N.; Bittman, R.; *Tetrahedron Lett.* **1988,** *29*, 4393-4396.

14. Molecular sieves were heated at 160 °C (0.05 mm) for at least 3 h.
15. IR ($CHCl_3$) 3528, 1597, 1495, 1360, 1193, 1181, 1101, 991, 941 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.79 (d, 2H, J = 8.3 Hz), 7.2-7.4 (m, 5H), 7.30 (d, 2H, J = 8.3 Hz), 4.49 (s, 2H), 4.0-4.2 (m, 3H), 3.51 (d, 2H, J = 4.7 Hz), 2.44 (s, 3H; br s, 1H). Anal. Calcd for $C_{17}H_{20}O_5S$: C, 60.70; H, 5.99; S, 9.53. Found: C, 60.61; H, 6.06; S, 9.29.
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17. Analysis of the diastereomeric (*R*)-(+)-Mosher ester derived from **3** by (a) HPLC (Pirkle type 1-A column, hexanes-2-PrOH 85:15) and (b) ^1H NMR (400 MHz, $CDCl_3$) (Guivisdalsky, P. N.; Bittman, R. *J. Am. Chem. Soc.* **1989,** *111*, in press).
18. IR ($CHCl_3$) 1606, 1589, 1479, 1102, 861, 853 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.2-7.5 (m, 5H), 4.60 and 4.52 (AB q, 2H, J = 12.0 Hz), 3.75 (dd, 1H, J = 3.0, 11.3 Hz), 3.40 (dd, 1H, J = 5.9, 11.3 Hz), 3.12-3.20 (m, 1H), 2.76 (t, 1H, J = 5.0 Hz), 2.58 (dd, 1H, J = 2.7, 5.0 Hz).

(Received in USA 13 January 1989)