# An Efficient Synthesis of Enantiomerically Pure (*R*)-(2-Benzyloxyethyl)oxirane from (*S*)-Aspartic Acid

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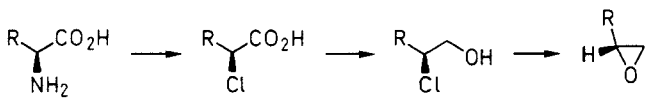
A 3-step synthesis of the title compound from (*S*)-aspartic acid is described. The overall yield of this process is 65% and the enantiomeric purity (ep) of the product is greater than 99%.

(2-Benzyloxyethyl)oxirane has been used as an intermediate in the preparation of a variety of biologically important compounds including compactin and milbemycin,[1] milbemycin $\beta_3$,[2] (*R*)- and (*S*)-lipoic acid,[3] 1,3-polyols (macrolide antibiotics)[4] and most recently, (*R*)- and (*S*)-*S*-adenosyl-1,8-diamino-3-thiooctane.[5]

Despite the extensive use of this chiral epoxide, there is still lacking a method for its preparation in both high yield and high enantiomeric purity. The typical chiral starting material for previously reported methods has been (*S*)-malic acid, which affords the (*S*)-epoxide directly[2,4,6-8] or can also give the (*R*)-epoxide with an intervening inversion sequence.[3,4] (*S*)-Erythrulose has also been used as a chiral starting material for the (*R*)-epoxide.[8,9] Typically, the overall yields of these processes from the chiral starting material are limited [12–53% for the (*S*)-epoxide and 17–32% for the (*R*)-epoxide] and many steps are required to prepare the target compound.

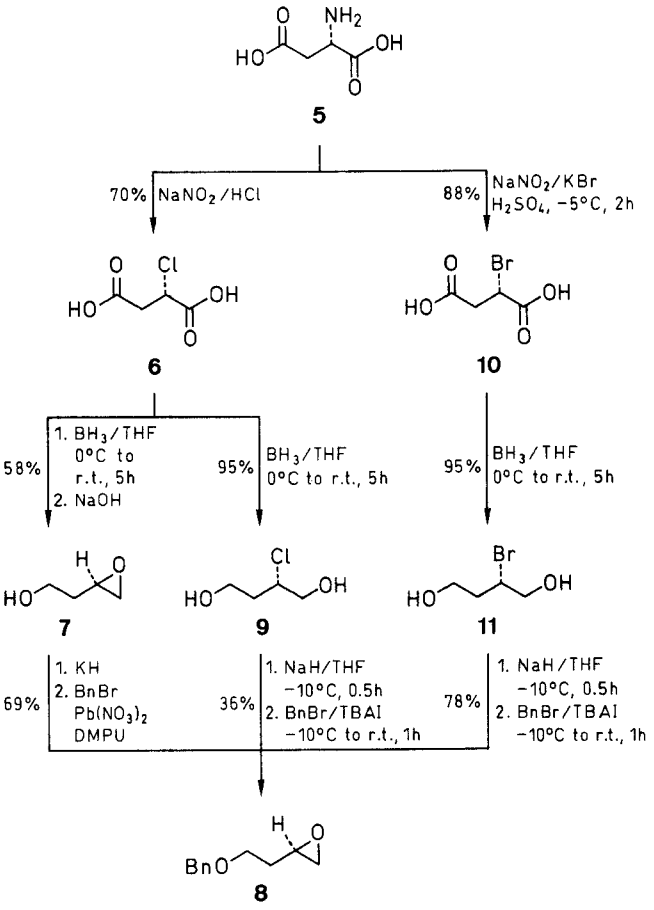
This state of the synthesis and our need for large quantities of (*R*)-(2-benzyloxyethyl)oxirane **(8)** led us to seek a better method for its preparation. Schurig and co-workers have reported the preparation of (*R*)-epoxides from (*S*)-amino acids.[10-12] Their methodology, as outlined below, involves conversion of the amine **1** into a halide **2** (with retention of configuration,[13] $NaNO_2$/HX) followed by reduction of the acid with lithium aluminum hydride and finally, base treatment to effect ring closure to the epoxide **4**.



**1** **2** **3** **4**

Thus, we projected applying this methodology to the preparation of **8** in relatively few steps starting with the readily available (*S*)-aspartic acid as outlined below. The corresponding mesylate has been prepared by a similar process.[14]

Initially, (*S*)-aspartic acid **(5)** was converted to (*S*)-chlorosuccinic acid **(6)** by treatment with sodium nitrite in hydrochloric acid. Diacid **6** was then reduced to the corresponding diol **9** with diborane and subsequently cyclized to the epoxide **7** when treated with sodium hydroxide in the same reaction vessel. Epoxide **7** was then purified by tedious chromatography followed by careful evaporation of the solvent, to avoid volatization of the product, prior to conversion to the benzyl ether **8** with potassium hydride/benzyl bromide. The overall yield of **8** was 27% from **5** using this sequence. We then discovered that recovered uncyclized **9** from this sequence could be converted to epoxide **8** in one pot by sequential treatment with sodium hydride then benzyl bromide/tetrabutylammonium iodide (TBAI).




Bn = benzyl

Recognizing that this method would eliminate the problematic isolation of hydroxy epoxide **7**, we explored this potential route further. When the sequence **5** to **6** to **9** to **8** was conducted on a preparative scale, the overall yield of **8** was 25%. Although this process facilitated the preparation of **8**, there was still much room for yield improvement. Epoxide formation seemed to be the limiting transformation. During the cyclization of **9** to **7** we had noted that, as time progressed, more products were forming (potentially inter- rather than intramolecular reaction products) and the amount of **7** was decreasing (TLC analysis). Therefore, we reasoned that if the cyclization step could be made to progress rapidly, the overall yield might show a dramatic increase. Hoping thus to increase the rate of epoxide formation, we turned our efforts to using bromide rather than chloride as the leaving group during epoxide formation.

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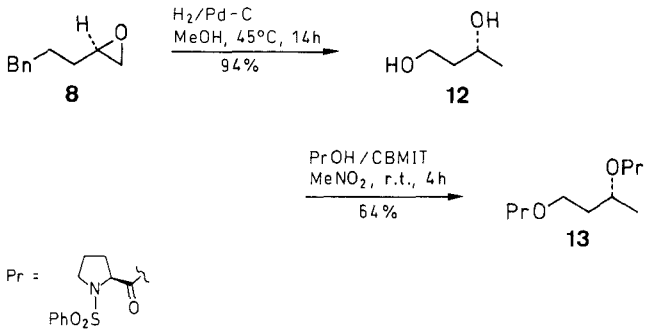
To this end, aspartic acid **(5)** was converted into (*S*)-bromosuccinic acid by treatment with sodium nitrite/potassium bromide/sulfuric acid in 88% yield. The diacid was then reduced with diborane to bromodiol **11** in 92% yield. Diol **11** was treated with sodium hydride in tetrahydrofuran to effect epoxide formation, which proceeded much more rapidly than with chlorodiol **9**. After consumption of the diol, the benzyl ether was formed in the same pot by addition of benzyl bromide/TBAI. The yield of this transformation is 78%. Thus we have succeeded in preparing (*R*)-(2-benzyloxyethyl)oxirane **(8)** in 3 steps from (*S*)-aspartic acid in an overall yield of 65%.

The optical purity of **8** was addressed by preparing diester **13**. Epoxide **8** was hydrogenolyzed in the presence of 30% Pd–C to provide (*S*)-1,3-butanediol **(12)** (a trace of the 1,4-diol was found to be present). The diol **12** was then converted to the bis-*N*-phenylsulfonyl-L-prolyl ester **13** by treatment with imidazolium-activated *N*-phenylsulfonyl-L-proline (prepared from 1,1′-carbonylbis(3-methylimidazolium) triflate, CBMIT,[15] and the *N*-protected L-proline derivative). The $^1$H NMR spectrum of **13** is used for determination of the diastereomeric purity (dp) of the bis-ester and therefore the ep of the epoxide **8**. At 500 MHz, the terminal diastereomeric methyl group is split into two doublets [$\delta$ = 1.33, $J$ = 6.30 Hz, (*S*)-configuration of the diol and $\delta$ = 1.31, $J$ = 6.29 Hz, (*R*)-configuration of the diol]. Doping experiments with racemic material indicated that the presence of 1% of the minor component could be detected and the relative intensities of the doublet at $\delta$ = 1.33 to the one at $\delta$ = 1.31 was at least 99:1. This indicated that the dp of the diol was greater than 99%. Therefore, the ep of **8** must also be greater than 99%.




In summary, an efficient and practical synthesis of (*R*)-(2-benzyloxyethyl)oxirane **(8)** has been conducted from (*S*)-aspartic acid **(5)** in three operations and 65% overall yield. The ep of epoxide **8** has been shown to be greater than 99%.

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. MeOH was distilled from Mg. THF was distilled from $CaH_2$. All reactions involving air and/or $H_2O$ sensitive reagents were conducted under a dry $N_2$ or Ar atmosphere. Thin layer chromatography (TLC) was done on silica/F254 aluminum backed plates (E. Merck). Column chromatography was conducted utilizing 230–400 mesh silica gel (E. Merck). Melting points were determined using a Büchi melting point apparatus and are uncorrected. Chemical shifts for $^1$H and $^{13}$C NMR are referenced to internal TMS and the deuterated solvent peaks respectively. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

**(*S*)-(−)-Bromosuccinic Acid (10):**
A 3 L Morton flask equipped with a mechanical stirrer and a thermometer was charged with (*S*)-aspartic acid (**5**, 50.8 g, 0.38 mol) and KBr (20.7 g, 1.74 mol). $H_2SO_4$ (2.5 M, 990 mL) was added and the solution was cooled to −5°C. A solution of $NaNO_2$ (46.8 g, 0.68 mol) in $H_2O$ (90 mL) was added via an addition funnel being careful to maintain the temperature below 0°C during the 75 min addition period. The resulting dark brown mixture was stirred for 2 h at −5°C and then extracted with EtOAc (4 × 500 mL). The combined EtOAc extracts were dried ($Na_2SO_4$), filtered, and concentrated to a white solid; yield: 65.8 g (88%); mp 171–172°C $[\alpha]_D^{24}$ −40.4° ($c$ = 8.25), $H_2O$ [Lit.[14] mp 178–180°C $[\alpha]_D^{21}$ −43.0° ($c$ = 1.45, $H_2O$)].

$^1$H NMR ($CD_3OD$): $\delta$ = 2.95 (dd, $J$ = 17.2, 6.3, 1 H), 3.19 (dd, $J$ = 17.2, 8.7, 1 H), 4.61 (dd, $J$ = 8.5, 6.3, 1 H).

$^{13}$C NMR ($CD_3OD$): $\delta$ = 40.14, 40.77, 172.31, 173.12.

**(*S*)-2-Bromo-1,4-butanediol (11):**
In a 2 L Morton flask equipped with a mechanical stirrer, (*S*)-bromosuccinic acid (**10**, 52.4 g, 0.26 mol) was suspended in THF (400 mL). The mixture was cooled to 0°C in an ice-bath and $BH_3$ · THF (800 mL, 1 M, 0.8 mol) was added via a cannula over a 1 h period. After the addition, the cooling bath was removed and the reaction was stirred for 4 h. The excess borane was quenched by the addition of THF/$H_2O$ (100 mL, 1:1) and then calcined $K_2CO_3$ (160 g) was added. This mixture was stirred, then filtered, and the solid residue was washed with $Et_2O$ (3 × 100 mL). The combined filtrate and $Et_2O$ washes were concentrated to a mixture of an oil and borate salts and the oil was re-dissolved in $Et_2O$ (2 × 200 mL) and filtered away from the borate salts. The filtrate was dried ($MgSO_4$), filtered and evaporated to an oil which was chromatographed on silica gel (1:1, acetone/$CH_2Cl_2$) to give **11**; yield: 40.8 g (91%); $[\alpha]_D^{24}$ −31.9° ($c$ = 15.2, $CHCl_3$).

| | | | |
|---|---|---|---|
| $C_4H_9BrO_2$ | calc. | C 28.42 | H 5.37 |
| (169.0) | found | 28.31 | 5.64 |

$^1$H NMR ($CD_3OD$): $\delta$ = 1.85–1.96 (m, 1 H), 2.10–2.23 (m, 1 H), 3.68–3.84 (m, 4 H), 4.15–4.25 (m, 1 H), 4.86 (br s, 2 H).

$^{13}$C NMR ($CD_3OD$): $\delta$ = 38.90, 54.70, 60.45, 67.84.

**(*R*)-(2-Benzyloxyethyl)oxirane (8):**
NaH (15 g, 57% dispersion, 0.368 mol) was washed with hexanes (3 × 20 mL) and then suspended in dry THF (240 mL). The suspension was chilled in a bath to −10°C and bromodiol **11** (20 g, 0.12 mol) in dry THF (20 mL) was added over 5 min. After 25 min, BnBr (15.4 mL, 22.2 g, 0.13 mol) and TBAI (4.4 g, 11.8 mmol) were added. The mixture was allowed to stir for 5 min more at −10°C then the cold bath was removed and the reaction proceeded for 1 h while warming to r.t. Saturated $NH_4Cl$ (100 mL) was added and then the separated aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with $H_2O$ (200 mL) and brine (2 × 200 mL), dried ($Na_2SO_4$), filtered and evaporated. The crude product was purified by column chromatography (4:1, hexanes/EtOAc); yield: 17.1 g 78%); $[\alpha]_D^{22}$ +15.0° ($c$ = 3.37, $CH_2Cl_2$) [Lit.[8] $[\alpha]_D$ +16.9° ($c$ = 2.51, $CHCl_3$)].

| | | | |
|---|---|---|---|
| $C_{11}H_{14}O_2$ | calc. | C 74.13 | H 7.92 |
| (178.2) | found | 74.12 | 7.99 |

$^1$H NMR ($CDCl_3$): $\delta$ = 1.69–1.97 (m, 1 H), 2.51 (dd, $J$ = 5.0, 2.7, 1 H), 2.76 (pseudo t, $J$ = 4.5, 1 H), 3.02–3.09 (m, 2 H), 3.61 (t, $J$ = 6.1, 2 H), 4.51 (s, 2 H), 7.29–7.39 (m, 5 H).

$^{13}$C NMR ($CDCl_3$): $\delta$ = 33.31, 47.41, 50.39, 67.36, 73.39, 127.91, 128.69, 138.58.

**(*S*)-1,3-Butanediol (12):**
Epoxide **8** (60 mg, 0.35 mmol) and Pd–C (20 mg, 30%) in MeOH (7 mL) were stirred at 45°C under a $H_2$ atmosphere for 14 h. The catalyst was removed by vacuum filtration through celite and the solvent was removed in vacuo; yield: 28 mg (94%). This product was used directly in the next step without further purification.

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$^1$H NMR ($CDCl_3$): $\delta$ = 1.18 (d, $J$ = 6.32, 3 H), 1.61–1.67 (m, 2 H), 3.25 (br s, 2 H), 3.61–3.85 (m, 2 H), 3.97–4.03 (m, $J$ = 6.22, 1 H).

**(*S*)-1,3-Bis-(*N*-phenylsulfonyl)prolyoxybutane (13):**
To an ice cold solution of carbonyldiimidazole (220 mg, 1.36 mmol) in $MeNO_2$ (2.1 mL) was added, dropwise, freshly distilled methyl triflate (0.292 mL, 437 mg, 2.66 mmol) and the resulting solution was stirred for 10 min. Solid *N*-phenylsulfonyl-L-proline (341 mg, 1.34 mmol)[16] was added in one portion, stirring was continued for 10 min, then (*S*)-1,3-butanediol (**12**, 20 mg, 0.22 mmol) in $MeNO_2$ (0.4 mL) was added. After stirring for 4 h, the reaction was quenched by adding 1 M citric acid (5 mL) and EtOAc (10 mL). The separated organic layer was washed with sat. aq $NaHCO_3$ (2 × 25 mL), dried ($MgSO_4$), and evaporated. The residue was purified by chromatography[17] on silica gel (1:1 hexanes/EtOAc); yield: 80 mg (64%); $[\alpha]_D^{24}$ − 50.0° ($c$ = 3.5, $CHCl_3$).

| | | | | |
|---|---|---|---|---|
| $C_{26}H_{32}N_2O_8S_2$ | calc. | C 55.30 | H 5.71 | N 4.96 |
| (564.5) | found | 55.10 | 5.83 | 4.88 |

$^1$H NMR ($CHCl_3$): $\delta$ = 1.33 (d, $J$ = 6.29, 3 H), 1.71–1.78 (m, 2 H), 1.91–2.05 (m, 8 H), 3.27–3.32 (m, 2 H), 3.48–3.54 (m, 2 H), 4.15–4.21 (m, 2 H), 4.24–4.37 (m, 2 H), 5.04–5.10 (m, $J$ = 6.25, 1 H), 7.62–7.73 (m, 6 H), 7.87–7.89 (m, 4 H).

$^{13}$C NMR ($CDCl_3$): $\delta$ = 20.01, 24.63, 30.88, 31.01, 34.62, 48.44, 60.40, 60.66, 61.34, 68.72, 127.44, 129.05, 132.78, 138.16, 171.60, 171.94, 178.19.

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The *N*-phenylsulfonyl-L-proline was shown to be > 99% ep.
(17) When racemic benzyloxy epoxide **8** was converted to a diastereomeric mixture of diol derivatives **13**, the diastereomers were not separable under the conditions employed for the isolation of **13**. Therefore, the undesired diastereomer, if present, would not be removed during the chromatographic purification.

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