The Preparation of Enantiomerically Pure 3,4-Epoxy-1-butene and 3-Butene-1,2-diol

Neil W. Boaz,* Stephen N. Falling, Mary K. Moore

Research Laboratories, Eastman Chemical Company, P.O. Box 1972, Kingsport, TN 37662, USA
Fax +1(423)2247582; E-mail: nwboaz@eastman.com

Received 11 March 2005

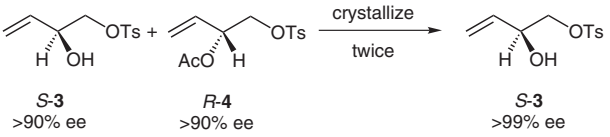
Abstract: Single enantiomer 2-hydroxy-3-butenyl tosylate is a key precursor for single enantiomer 3,4-epoxy-1-butene and 3-butene-1,2-diol. The epoxide results from ring-closure of the hydroxy-tosylate while the diol is obtained through the intermediacy of the corresponding cyclic carbonate. This latter sequence avoids the loss of enantiomeric purity observed through direct hydrolysis.

Key words: epoxides, asymmetric synthesis, chirality, diols, nucleophiles

Enantiomerically enriched 3-butene-1,2-diol (**1**) and various simple derivatives have been utilized for the preparation of a number of interesting chiral products, including 2-deoxy-D-ribose,[1] oscillatoxin A,[2] (*R*)-γ-caprolactone, 5-HETE, leukotriene B_4, lipoxin-B,[3] HIV protease inhibitor intermediates,[4] (–)-bestatin,[5] (–)-bulgecinine,[6] and (–)-tuliparin B.[7]

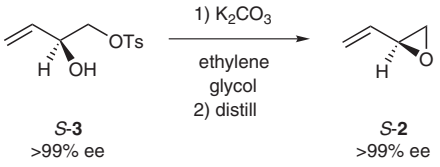
Early preparations of enantiomerically enriched diol **1** utilized multi-step syntheses from chiral pool materials such as D-mannitol,[8] L-ascorbic acid,[9] or tartaric acid.[10] More recent preparative methods of note include the hydrolytic kinetic resolution (HKR) of 3,4-epoxy-1-butene (**2**)[11] and the hydrolysis of racemic **2** using palladium-catalyzed dynamic kinetic resolution.[12] The HKR methodology is particularly noteworthy, as enantiomerically pure epoxide **2** can be obtained using HKR technology (run past 50% conversion) while enantiomerically pure diol **1** can be obtained using two sequential (but opposite in enantioselectivity) HKR reactions, using enantiomerically enriched epoxide **2** from the first HKR as substrate for the second. The enantiomeric purity of the diol itself cannot be readily enhanced, as it is a liquid.

The primary monotosylate of 3-butene-1,2-diol (**3**) is of interest as an alternative source for these enantiomerically enriched products, as it can be envisioned as a precursor of both 3-butene-1,2-diol (**1**) and 3,4-epoxy-1-butene (**2**). Tosylate **3** can be readily prepared in high enantiomeric purity by either enzymatic[13] or chemical (Sharpless epoxidation) resolution processes.[14] Enantiomerically enriched **3** is one of the very few derivatives of 3-butene-1,2-diol that we have been able to crystallize to enantiomeric purity. Indeed, the mixture of *S*-**3** and the enantiomeric acetate *R*-**4** (Equation 1) obtained from the enzymatic esterification reaction of racemic **3**[13] can be crystallized to remove the acetate and then recrystallized to obtain pure *S*-**3** with good recovery in >99% ee even starting with material as low as 80% ee. The antipodal *R*-**3** can be obtained in >99% ee from the mother liquors (see experimental).



Equation 1

Conversion of **3** to 3,4-epoxy-1-butene (**2**) has been effected on small scale by neat treatment with powdered potassium hydroxide and immediate distillation.[8b] The main complication with this protocol is the isolation of the volatile epoxide and its potential hydrolysis to the diol. Our optimized conditions for preparative scale utilized potassium carbonate in a high-boiling solvent (ethylene glycol), which allows the direct distillation of the epoxide from the reaction mixture. Drying and redistillation at atmospheric pressure afforded a 67% yield of highly pure *S*-**2** from *S*-**3** with no loss of enantiomeric purity (Equation 2).

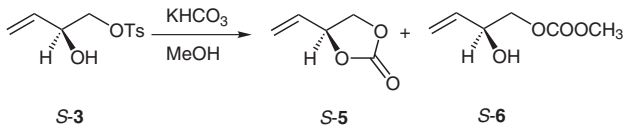


Equation 2

The conversion of tosylate **3** to the diol was more challenging than initially expected. In most circumstances treatment of a terminal diol monotosylate with aqueous base readily affords the diol through hydrolytic ring-opening of the intermediate epoxide. Unfortunately, the propensity of **2** to open in a regiorandom manner under basic conditions causes significant loss of enantiomeric purity, affording the diol **1** by treatment of **3** with aqueous hydroxide in as little as 5% ee.[15] Indeed, no simple hydration conditions have been found which will avoid some loss of enantiomeric purity.[15] Thus, we decided to find a method which would not involve the epoxide and would leave the stereogenic center undisturbed. The approach taken was to displace the tosylate with a hydroxyl surrogate under

SYNLETT 2005, No. 10, pp 1615–1617
Advanced online publication: 07.06.2005
DOI: 10.1055/s-2005-869867; Art ID: S03205ST

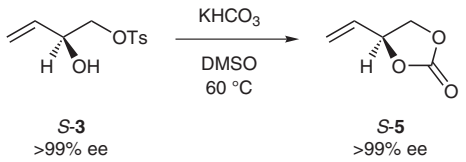
non-basic conditions. It is known that carbonate can function as a masked hydroxyl nucleophile for displacement reactions.[16] Unfortunately, this reagent is too basic for our circumstances, as its reaction with **3** results in epoxide formation as indicated above. However, we found that the less basic potassium bicarbonate effectively displaces the tosylate of **3** without affecting the stereogenic center. The reaction in alcoholic solvents is rather slow, affording a mixture of cyclic carbonate **5** and a mixed carbonate **6** from the alcohol solvent (Equation 3).



S-**3** *S*-**5** *S*-**6**

Equation 3

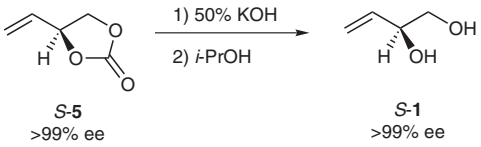
More satisfactory conditions were obtained when using DMSO as solvent, as the reaction was complete after heating to 60 °C overnight. (*S*)-Vinyl ethylene carbonate (*S*-**5**) was obtained in 74% yield from *S*-**3** after distillation with no loss of enantiomeric purity (Equation 4). The actual course of this reaction is not particularly clear. Possibilities include direct displacement of the tosylate with potassium hydrogen carbonate followed by further reaction with the secondary alcohol (or the alcohol solvent), reaction of potassium bicarbonate with the secondary alcohol of **3** (or solvent alcohol) with subsequent displacement of the tosylate, or reaction of the secondary alcohol of **3** (or of the alcohol solvent) with in situ generated carbon dioxide followed by displacement of the tosylate with the thus generated carbonate anion. The latter explanation may be the most likely, as similar reactions have been shown to be accelerated under a carbon dioxide atmosphere.[16b]



S-**3** >99% ee *S*-**5** >99% ee

Equation 4

The carbonate can be cleaved to the diol **1** by treatment with 50% aqueous potassium hydroxide by heating to 60 °C for two hours. Isolation of the diol proved problematic due to its water solubility. Treatment of the reaction mixture with ethyl acetate resulted in precipitation of the salts, which could be readily removed by filtration. However, the strongly basic conditions resulted in small amounts of transesterification between the product **1** and ethyl acetate, resulting in contamination of the desired product with the various acetates of **1**, which were difficult to separate from the desired product. A solvent survey indicated that isopropanol was a desirable replacement for ethyl acetate, as it completely precipitated the salts while avoiding any transesterification. Simple distillation of the isopropanol and distillation of the residue under reduced pressure afforded an 83% yield of highly pure *S*-**1** (>99%) from *S*-**5** on >50 g scale with no loss of enantiomeric purity (Equation 5).



S-**5** >99% ee *S*-**1** >99% ee

Equation 5

Thus, either of the enantiomers of epoxide **2** or diol **1** can be readily obtained with absolute retention of configuration from the appropriate enantiomer of 2-hydroxy-3-butenyl tosylate (**3**).

(*S*)-2-Hydroxy-3-butenyl Tosylate (*S*-3)

A ca. 1:1 mixture of (*S*)-2-hydroxy-3-butenyl tosylate (*S*-**3**, >95% ee) and (*R*)-2-acetoxy-3-butenyl tosylate (*R*-**4**, >95% ee, 185.55 g, combined 0.70 mol maximum) from an enzymatic esterification resolution reaction[13] was dissolved in toluene (85 mL, 1 mL/g of **3**) at ambient temperature. Heptane (85 mL, 1 volume) was added with vigorous stirring. The mixture was stirred at r.t. for 30 min at which time crystallization had begun. The mixture was cooled to 4 °C overnight and the resulting precipitate was collected, washed with cold toluene, and dried to afford 61.41 g of **3** contaminated with about 1% of **4**. The filtrate and wash were set aside for further use. Recrystallization of the precipitate from warm (ca. 40 °C) toluene (122 mL, 2 mL/g) by cooling to 4 °C afforded 53.13 g (31%) of >99% ee *S*-**3** free of any detectable acetate. ^{1}H NMR ($CDCl_3$): δ = 7.800 (2 H, d, *J* = 8.25 Hz), 7.356 (2 H, d, *J* = 8.19 Hz), 5.751 (1 H, ddd, *J* = 5.38, 10.46, 16.55 Hz), 5.378 (1 H, br d, *J* = 17.05 Hz), 5.247 (1 H, br d, *J* = 10.48 Hz), 4.396 (1 H, m), 4.066 (1 H, dd, *J* = 3.39, 10.20 Hz), 3.906 (1 H, dd, *J* = 7.41, 10.22 Hz), 2.451 (3 H, s), 2.276 (1 H, d, *J* = 4.50 Hz). Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82; N, 0. Found: C, 54.84; H, 5.86; N, <0.3. Chiral HPLC [250 × 4.6 mm Chiralcel OB (Chiral Technologies), 90:10 hexane–*i*-PrOH, 1 mL/min, 254 nm): t_R = 30.9 min (*S*-**3**), t_R = 41.3 min (*R*-**3**). $[\alpha]_D^{20}$ –8.10 (*c* 1.05, MeOH).

The initial filtrate and wash were stripped to afford 123.97 g of *R*-**4** and *S*-**3** in about a 75:25 ratio, respectively. This material can be freed of **3** by the selective reaction of the secondary hydroxyl with succinic anhydride and extractive removal of the resulting succinate half ester.[17] Deacylation of *R*-**4** (concd HCl/MeOH)[17] and recrystallization as above afforded *R*-**3** in 35% overall yield with >99% ee.

(*S*)-3,4-Epoxy-1-butene (*S*-2)

Ethylene glycol (2610 mL) was charged to a three-neck round bottom flask, which was placed under full vacuum for 1.5 h to remove any residual water. *S*-**3** (652.5 g, 2.69 mol) was added and the mixture was stirred until most of **3** had dissolved. Then, K_2CO_3 (400 g, 2.89 mol, 1.08 equiv) was added and the reaction mixture was stirred at r.t. for 2 h to completely consume **3**. After the reaction was complete, vacuum was slowly applied to distill the desired product. A double trap was employed to capture the distillate, with the first trap filled with ice water and the second with *i*-PrOH/dry ice. Both receiving flasks were cooled to below –75 °C using *i*-PrOH/dry ice. The distillation was started at 100 mm Hg and the vacuum was reduced at a rate of approximately 20 mm Hg every 15 min until reaching 50 mm Hg and distilled for 2.5 h. The stirring rate was adjusted to assist in the reduction of foaming. The vacuum was further decreased to 10 mm Hg and the mixture was stirred vigorously for 2 h to afford additional material for a total of 167.8 g (90%) of *S*-**2**.

The distilled material was dried with Na_2SO_4, filtered and re-distilled at atmospheric pressure to further purify the product. The H_2O/*S*-**2** azeotrope (36.3 g) was collected as a forerun at 50–62 °C, and *S*-**2** (126.5 g, 67%) was collected at 63 °C. Chiral GC analysis indicated >99% chemical purity and 99.4% ee. ^{1}H NMR ($CDCl_3$): δ = 5.522 (1 H, m), 5.298 (2 H, m), 3.345 [1 H, m (5), *J* = 3.15 Hz], 2.967 (1 H, t, *J* = 4.43 Hz), 2.657 (1 H, dd, *J* = 2.31, 5.17 Hz). Chiral GC [30 m × 0.25 mm Cyclosil-B (J & W Scientific), 0.25 μm film thickness, 40 °C, 7 min; 40–120 °C, 70 °C/min; 120 °C, 12 min, 8.0 psi, 7 min; 8.0–13.0 psi, 80 psi/min; 13.0 psi, 7.72 min]: t_R(*S*-**2**) 6.37 min, t_R(*R*-**2**) 6.67 min. $[\alpha]_D^{25}$ +9.6 (*c* 6.33, *i*-PrOH). The literature value for *S*-**2** is $[\alpha]_D^{25}$ +8.3 (*c* 6.96, *i*-PrOH).[8b]

(*S*)-Vinyl Ethylene Carbonate (*S*-5)

(*S*)-2-Hydroxy-3-butenyl tosylate (*R*-**3**, >99% ee, 241 g, 1.04 mol), DMSO (166 mL), and $KHCO_3$ (208 g, 2.08 mol, 2.0 equiv) were charged to a 500-mL flask. The solution was heated to 60 °C overnight to completely consume **3** according to TLC analysis. The mixture was cooled to ambient temperature and poured into 1040 mL of EtOAc. The EtOAc solution was washed with four 420-mL portions of H_2O, and the combined aqueous washes were back-extracted with two 625-mL portions of EtOAc. The combined organic solution was washed once more with H_2O, dried with $MgSO_4$, and concentrated. The residue was distilled at 13 mm Hg and the material collected at 114 °C. This afforded 84.0 g (74%) of *S*-**5** with 99.4% chemical purity (GC) and 99.4% ee (chiral GC). ^{1}H NMR ($CDCl_3$): δ = 5.917 (1 H, ddd, *J* = 7.00, 10.38, 17.21 Hz), 5.526 (1 H, d, *J* = 17.02 Hz), 5.459 (1 H, d, *J* = 10.37 Hz), 5.141 (1 H, q, *J* = 7.28 Hz), 4.614 (1 H, t, *J* = 8.37 Hz), 4.171 (1 H, t, *J* = 7.84 Hz). Chiral GC [30 m × 0.25 mm Cyclosil-B (J & W Scientific), 0.25 μm film thickness, 120 °C isothermal]: t_R 15.26 min (*R*-**5**), t_R 15.85 min (*S*-**5**). $[\alpha]_D^{22}$ –26.1 (*c* 1.15, MeOH).

(*S*)-3-Butene-1,2-diol (*S*-1)

(*S*)-Vinyl ethylene carbonate (*S*-**5**, 79.0 g, 0.69 mol) was charged to a 1-L flask and cooled in an ice bath. A solution of potassium hydroxide (45.0 g, 0.80 mol, 1.15 equiv) in 45 mL of H_2O was added dropwise over 35 min. The ice bath was removed and the mixture was heated to 60 °C for 2 h. After cooling to ambient temperature, *i*-PrOH (370 mL) was added and the mixture was stirred for 20 min. The inorganic salt precipitate was removed by filtration and the solids were washed with 50 mL of *i*-PrOH. The combined organic solution was concentrated and the residue was distilled at 10 mm Hg with material collected at 80 °C. This afforded 50.4 g (83% yield) of *S*-**1** with >98% chemical purity (GC) and 99.5% ee (chiral GC). ^{1}H NMR ($CDCl_3$): δ = 5.842 (1 H, ddd, *J* = 5.52, 10.51, 16.89 Hz), 5.350 (1 H, dd, *J* = 1.67, 17.08 Hz), 5.222 (1 H, dd, *J* = 1.07, 10.38 Hz), 4.250 (1 H, m), 3.670 (1 H, dd, *J* = 3.34, 11.26 Hz), 3.493 (1 H, dd, *J* = 7.42, 11.26 Hz), 2.572 (2 H, br s). MS (EI): *m/z* = 70 [$M^+ - H_2O$], 57 [$M^+ - CH_2OH$]. Chiral GC [30 m × 0.25 mm Cyclosil-B (J & W Scientific), 0.25 μm film thickness, 40 °C, 7 min, 40–120 °C, 70 °C/min, 120 °C, 12 min; 8 psi, 7 min, 8–80 psi, 13 psi/min, 80 psi, 7.72 min]: t_R 14.28 min (*S*-**1**), t_R 14.36 min (*R*-**1**). $[\alpha]_D^{20}$ –44.4 (*c* 3.02, *i*-PrOH).

References

(1) (a) Kozikowski, A. P.; Ghosh, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 5788. (b) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1984**, *49*, 2762.

(2) Walkup, R. D.; Cunningham, R. T. *Tetrahedron Lett.* **1987**, *28*, 4019.

(3) (a) Rama Rao, A. V.; Reddy, E. R.; Joshi, B. V.; Yadav, J. S. *Tetrahedron Lett.* **1987**, *28*, 6497. (b) Rama Rao, A. V.; Bose, D. S.; Gurjar, M. K.; Ravindranathan, T. *Tetrahedron* **1989**, *45*, 7031.

(4) Gurjar, M. K.; Devi, N. R. *Tetrahedron: Asymmetry* **1994**, *5*, 755.

(5) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852.

(6) Maeda, M.; Okazaki, F.; Murayama, M.; Tachibana, Y.; Aoyagi, Y.; Ohta, A. *Chem. Pharm. Bull.* **1997**, *45*, 962.

(7) Ohgiya, T.; Nishiyama, S. *Heterocycles* **2004**, *63*, 2349.

(8) (a) Baer, E.; Fischer, H. O. *J. Biol. Chem.* **1939**, *128*, 463. (b) Crawford, R. J.; Lutener, S. B.; Cockcroft, R. D. *Can. J. Chem.* **1976**, *54*, 3364.

(9) (a) Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304. (b) Marco, J. L.; Rodriguez, B. *Tetrahedron Lett.* **1988**, *29*, 1997. (c) Takano, S.; Numata, H.; Ogasawara, K. *Heterocycles* **1982**, *19*, 327. (d) Hubschwerlen, C. *Synthesis* **1986**, 962.

(10) Howes, D. A.; Brookes, M. H.; Coates, D.; Golding, B. T.; Hudson, A. T. *J. Chem. Res., Synop.* **1983**, 9; *J. Chem. Res., Miniprint* **1983**, 217.

(11) (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.

(12) (a) Trost, B. M.; McEachern, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 8649. (b) Cheeseman, N.; Fox, M.; Jackson, M.; Lennon, I. C.; Meek, G. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5396.

(13) Boaz, N. W.; Zimmerman, R. L. *Tetrahedron: Asymmetry* **1994**, *5*, 153.

(14) Neagu, C.; Hase, T. *Tetrahedron Lett.* **1993**, *34*, 1629.

(15) Boaz, N. W. *Tetrahedron: Asymmetry* **1995**, *6*, 15.

(16) (a) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Synthesis* **1981**, 793. (b) Myers, A. G.; Widdowson, K. L. *Tetrahedron Lett.* **1988**, *29*, 6389.

(17) Boaz, N. W. US Patent No. 5312950, **1994**.