A Facile Synthetic Method for the Preparation of σ-Symmetric (1,2:4,5)-Diepoxypentane Equivalent†

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Optically active σ-symmetric (1,2:4,5)-diepoxypentane equivalent (10) has been synthesized in eight steps with moderate yields and diastereomeric excess by using Sharpless asymmetric dihydroxylation (AD reaction). Compound 10 can be used to prepare *syn* 1,3-diol subunit in natural product.

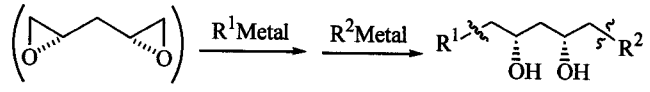
Keywords asymmetric synthesis, diastereoselectivity, dihydroxylation, diol, epoxide

The *syn* 1,3-diol subunit is common to a variety of natural products such as polyene macrolide antibiotics and has generated much synthetic interest.[1] A wide range of different methods have been used to prepare stereochemically defined *syn* 1,3-diols, ranging from hydroxylation of homoallylic alcohols to 1,2-Wittig rearrangement of allylic ethers.[2] Moreover, Rychnovsky[3] recently reported the preparation of *syn* 1,3-diols from *anti*-1,2:4,5-diepoxypentane following Mitsunobu procedure.[3] However, few examples have been reported for the preparation of *syn* 1,3-diols directly from *syn*-diepoxides or their equivalents without configurational inversion.

In our previous papers, we have utilized Sharpless asymmetric dihydroxylation (AD) reaction to prepare 1,2-diol and 1,4-diol subunits,[4,5] which have gained widespread use in the total syntheses of natural products. Then, we became interested in the σ-symmetric (1,2:4,5)-diepoxide (**1**) as a building block for *syn* 1,3-diols as a part of a convergent strategy to prepare alternative polyol chains. σ-Symmetric diepoxypentane is a *meso*-compound and has to be desymmetrized prior to the construction of the optically active *syn* 1,3-diols. We wish to report here the preparation of chiral σ-symmetric diepoxypentane desymmetric equivalent (**10**) utilizing Sharpless asymmetric dihydroxylation (AD reaction). Desymmetric synthon **1** can be used to build *syn* 1,3-diols through two-step epoxy-opening reactions, as is illustrated in Scheme 1.

The preparation of σ-symmetric diepoxypentane equivalent started from *p*-methoxylphenol (Scheme 2). *p*-Methoxylphenol was added to a stirred mixture of allyl bromide and K_2CO_3 in acetone and then refluxed for 5 h to give allyl ether **3** in 91% yield. Dihydroxylation of **3** with AD-mix-β in *tert*-butyl alcohol/water (1/1, *V*/*V*) at 0 ℃ furnished diol **4** in 82% yield, which was purified through recrystallization (>95% *ee* after recrystallization).[6] Compound **4** was then stirred in 30% HBr-HOAc at 50 ℃ for 30 min to give acetoxy bromide **5**, which was treated immediately with K_2CO_3 in methanol to afford epoxide **6**.[6]

Scheme 1



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Epoxide **6** was then reacted with vinylmagnesium bromide at −40 ℃ in the presence of catalytic amount of CuI to afford enol **7** in 98% yield. After masking the hydroxyl group with TBSCl and imidazole in DMF, the terminal alkene in **8** was dihydroxylated with AD-mix-β in *tert*-butyl alcohol-water (1/1, *V*/*V*) at 0 ℃ to afford diol **9** in 96% yield with 64% *de*,[7] which was treated with NaH, TsIm (p-$CH_3C_6H_4SO_2 \cdot C_3H_4N_2^+ + Cl^-$) to provide epoxide **10** in 83% yield. Thus, the equivalent of σ-symmetric (1,2:4,5)-diepoxide **10** was obtained from *p*-methoxylphenol as a colorless oil in high yields with moderate *de* (Scheme 2).

In conclusion, optically active σ-symmetric (1,2:4,5)-diepoxypentane equivalent (**10**) was synthesized in eight steps with high yields (53%) and moderate enantiomeric excess by using Sharpless asymmetric dihydroxylation (AD reaction) twice. Equivalent **10** can be used as an efficient precursor to a wide range of asymmetric optically active *syn* 1,3-diol subunits in a variety of natural products. Further investigations to prepare *syn* 1,3-diols and construct poly 1,3-diols using the methodology above are in progress.

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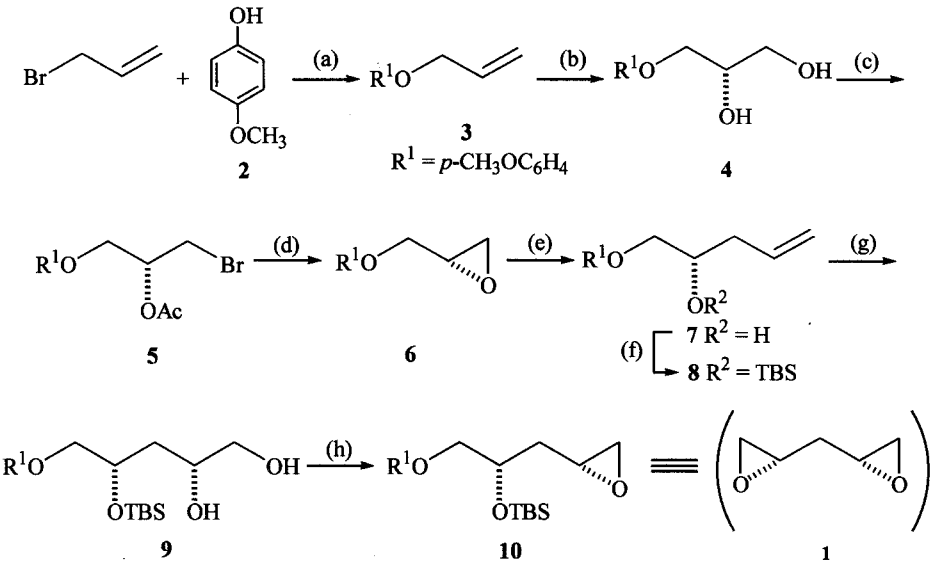
Scheme 2



Reagents and conditions: (a) K_2CO_3, acetone, reflux (91%); (b) AD-mix-β, *t*-BuOH-H_2O (1:1), 0 ℃ (82%); (c) 30% HBr/HOAc, 50 ℃; (d) K_2CO_3, CH_3OH (overall yields: 92% from **4**); (e) $CH_2CHMgBr$, CuI, −40 ℃, THF (98%); (f) TBSCl, imidazole, DMF (99%); (g) AD-mix-β, *t*-BuOH-H_2O (1:1), 0 ℃ (96%); (h) NaH, TsIm, THF (83%).

Experimental

Melting points were uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer with TMS as an internal standard and $CDCl_3$ as solvent. Coupling constants, *J* values, were given in Hz. IR spectra were taken on a Shimadzu 440-IR spectrophotometer. MS and HRMS spectra were run respectively on a Finnigan 4021 GC MS/DC and Varian MAT 21 instrument with an ionizing voltage of 70 eV. $[\alpha]_D^{20}$ was tested on a Perkin-Elmer 241MC auto rotationer.

Preparation of p-methoxyphenyl allyl ether (**3**)

To a solution of subsrate **2** (50 g, 0.4 mol) in 600 mL of acetone was added allyl bromide (52 mL, 0.6 mol). The reaction mixture was heated at reflux 5 h and then filtered. Concentration of the filtrate followed by flash column chromatography (eluted with petroleum ether/EtOAc = 200/1) gave **3** (60 g, 91%) as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.90—6.80 (m, 4H), 5.87 (m, 1H), 5.17 (m, 2H), 4.07 (m, 2H), 3.78 (s, 3H); IR (neat) ν: 2961, 1507, 1473, 1243, 952, 837, 758 cm^{-1}; EIMS *m/z* (%): 164 (M^+, 35.85), 149 (5.68), 137 (9.24), 124 (100.0), 109 (55.23); HRMS calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0831.

Preparation of (*S*)-3-(*p-methoxyphenoxy*)*-propane*-1,2-*diol* (**4**)

To a solution of K_2CO_3 (41.4 g, 300 mmol) and $K_3Fe(CN)_6$ (98.7 g, 150 mmol) in 500 mL of *t*-BuOH/H_2O (1/1, *V/V*) was added $K_2OsO_2(OH)_4$ (75 mg, 0.2% equiv.), $(DHQD)_2PHAL$ (780 mg) and substrate **3** (16.4 g, 100 mmol). The reaction mixture was stirred at 0 ℃ for 9 h, and the reaction was quenched by the addition of Na_2SO_3 (150 g). After filtration, the filtrate was extrated with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and filtered. After removal of the solvent, the crude product was purified by flash column chromatography on silica gel (eluted with petroleum ether/EtOAc = 1/1) to give **4** (16.3 g, 82%) as a white solid: m.p. 79—83 ℃; $[\alpha]_D^{20}$ + 5.07 (*c* 1.20, EtOH); ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.59—6.52 (m, 4H), 4.10—3.98 (m, 3H), 3.79—3.73 (m, 2H), 3.77 (s, 3H), 2.36 (br s, 2H); IR (KBr) ν: 3395, 2950, 1508, 1472, 1391, 1300, 1250, 1120, 1055, 834 cm^{-1}; EIMS *m/z* (%): 198 (M^+, 40.90), 180 (1.04), 149 (3.66), 137 (2.93), 124 (100.00), 109 (62.59); HRMS calcd for $C_{10}H_{14}O_4$ 198.0892, found 198.0903.

Preparation of (*S*)-3-(*p-methoxyphenoxy*)-1,2-*epoxypropane* (**6**)

Substrate **4** (9 g, 45.5 mmol) was treated with 30% HBr-HOAc (23 mL) at 50 ℃ for 45 min. The reaction mixture was poured slowly into a solution of $NaHCO_3$ in ice water and was then neutralized with aqueous NaOH (1.0 mol/L) and was extracted with ethyl ether (3 × 50 mL). The combined organic phases were washed with water and brine in turn, dried over Na_2SO_4, and filtered inturn. After removal of the solvent, the crude product **5** was obtained as a brown oil.

Unpurified crude product **5** was treated with K_2CO_3 (10 g) in 100 mL of CH_3OH for 2 h at r.t. The reaction mixture was concentrated. The residue was dissolved with 200 mL of distilled water and extracted with ethyl ether (3 × 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and filtered. After removal of the solvent, the crude product was purified by flash column chromatography on silica gel (eluted with petroleum ether/EtOAc = 6/1) to give **6** (7.5 g, 92%) as a white solid: m.p. 63—65 ℃; $[\alpha]_D^{20}$ + 5.14 (*c* 1.22, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.88—6.81 (m, 4H), 4.16 (dd, *J* = 11.0, 3.2 Hz, 1H), 3.91 (dd, *J* = 11.0, 5.6 Hz, 1H), 3.76 (s, 3H), 3.32 (m, 1H), 2.88 (t, *J* = 4.9 Hz, 1H), 2.73 (dd, *J* = 4.9, 2.7 Hz, 1H); IR (KBr) 2933, 1510, 1235, 1037, 825 cm^{-1}; EIMS *m/z* (%): 180 (M^+, 100.00), 163 (9.77), 151 (11.89), 137 (9.32), 123 (33.93), 109 (12.48), 95 (17.03); HRMS calcd for $C_{10}H_{12}O_3$ 180.0786, found 180.0805.

Preparation of (*S*)-1-(*p-methoxyphenoxy*)-4-*penten*-2-*ol* (**7**)

To a solution of CuI (546 mg, 2.87 mmol) in anhydrous THF (25 mL) was slowly added vinylmagnesium bromide (1 mol/L in THF, 54.7 mL). After stirring for 5 min, subsrate **6** (4.88 g, 27 mmol) in anhydrous THF (10 mL) was added dropwise and the reaction mixture was stirred at − 40 ℃ for 2 h. The reaction mixture was diluted with 200 mL of EtOAc and washed with distilled water (50 mL) and brine in turn, dried over Na_2SO_4 and filtered. After removal of the solvent, the crude product was purified by flash column chromatography on silica gel (eluted with petroleum ether/EtOAc = 4/1) to give **7** (5.55 g, 98%) as a colorless oil: $[\alpha]_D^{20}$ + 10.7 (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.88—6.82 (m, 4H), 5.87 (m, 1H), 5.22—5.14 (m, 2H), 4.07 (m, 1H), 3.97 (dd, *J* = 9.3, 3.3 Hz, 1H), 3.85 (dd, *J* = 9.3, 7.3 Hz, 1H), 3.78 (s, 3H), 2.38 (m, 2H); IR (neat) ν: 3446, 2961, 1507, 1473, 1243, 952, 837, 758 cm^{-1}; EIMS *m/z* (%): 208 (M^+, 35.85), 191 (1.11), 167 (2.27), 164 (2.00), 149 (5.68), 137 (9.24), 124 (100.00), 109 (55.23), 95 (10.95), 81 (7.55), 77 (9.79), 43 (9.99); HRMS calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1088.

Preparation of (*S*)-1-(*p-methoxyphenoxy*)-2-*tert-butyldimethylsilyloxy*-4-*pentene* (**8**)

A solution of **7** (3.77 g, 18.1 mmol) in dry DMF (25 mL) was treated with imidazole (1.85 g, 27.2 mmol) and TBSCl (3.28 g, 21.2 mmol) at r.t. overnight. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with distilled water and brine in turn, dried over Na_2SO_4 and filtered. Concentration of the filtrate followed by flash column chromatography on silica gel (eluted with petroleum ether/EtOAc = 20/1) provided **8** (5.77 g, 99%) as a colorless oil: $[\alpha]_D^{20}$ + 9.96 (*c* 1.78, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.83 (s, 4H), 5.83 (m, 1H), 5.13—5.05 (m, 2H), 4.05 (m, 1H), 3.81—3.79 (m, 2H), 3.77 (s, 3H), 2.45—2.27 (m, 2H), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); IR (neat) ν: 2950, 1516, 1472, 1243, 1120, 1060, 1004, 837, 786 cm^{-1}; EIMS *m/z* (%): 322 (M^+, 2.13), 265 (63.05), 223 (5.29), 209 (31.86), 191 (3.39), 181 (100.00), 149 (20.25), 137 (3, 13), 123 (18.44), 101 (5.30), 89 (4.55), 73 (32.26), 57 (4.06), 45 (2.04); HRMS calcd for $C_{18}H_{30}O_3Si$ 322.1964, found 322.1983.

Preparation of (2*R*,4*S*)-5-(*p-methoxyphenoxy*)-4-*tert-butyldimethylsilyloxy-pentane*-1,2-*diol* (**9**)

To a solution of K_2CO_3 (4.9 g, 75 mmol) and $K_3Fe(CN)_6$ (12.9 g, 75 mmol) in *t*-BuOH/H_2O (500 mL, *V*/*V* = 1/1) was added $K_2OsO_2(OH)_4$ (20 mg, 0.2% equiv.), $(DHQD)_2PYR$ (230 mg, 1.0 % equiv.) and substrate **8** (8.4 g, 26 mmol). The reaction mixture was stirred at 0 ℃ for 13 h. The reaction was quenched by the addition of Na_2SO_3 (39 g) and then filtered. The filtrate was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and filtered. After removal of the solvent, the crude product was purified by flash column chromatography on silica gel (eluted with petroleum ether/EtOAc = 1/1) to give **9** (8.9 g, 96%) as a white solid: m.p. 178—182 ℃; $[\alpha]_D^{20}$ − 7.9 (*c* 1.26, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.81 (s, 4H), 4.27 (m, 1H), 3.97 (m, 1H), 3.91 (m, 1H), 3.84 (m, 1H), 3.77 (s, 3H), 3.65 (dd, *J* = 11.1, 3.4 Hz, 1H), 1.81—1.79 (m, 2H), 0.90 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H); IR (KBr) ν: 3400, 1515, 1475, 1244, 1100, 1057, 840, 833, 795 cm^{-1}; EIMS *m/z* (%): 357 (M^+ + 1, 6.47), 3.07 (3.62), 299 (4.86), 207 (17.81), 189 (22.74), 175 (58.36), 157 (100.00), 149 (45.66), 123 (58.94); HRMS calcd for $C_{18}H_{32}O_5Si$ 356.2019, found 356.2032.

Preparation of (2*R*,4*S*)-5-(*p-methoxyphenoxy*)-4-*tert-butyldimethylsilyloxy*-1-*epoxy-pentane* (**10**)

To a suspension of NaH (1.725 g, 60% suspension in mineral oil, 43.1 mmol) in anhydrous THF (100 mL) was added substrate **9** (8.9 g, 25 mmol) in 50 mL of THF at − 10 ℃ in drops. After stirring for 30 min, TsIm (1.85 g × 3, 25 mmol) was added in three portions and the resulting mixture was stirred for additional 2 h. Saturated aqueous NH_4Cl was added to quench the reaction. After removal of the THF, the aquous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and filtered. Concentration of the filtrate followed by flash column chromatography on silica gel (eluted with petroleum ether/CH_2Cl_2 = 5/1) yielded **10** (7.0 g, 83%) as a white solid:

m.p. 165—167 ℃; $[\alpha]_D^{20}$ − 5.0 (*c* 0.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.83 (s, 4H), 4.22 (m, 1H), 3.91 (dd, J = 6.5 Hz, 3.9 Hz, 1H), 3.84 (m, 1H), 3.77 (s, 3H), 3.14 (m, 1H), 2.80 (m, 1H), 2.51 (m, 1H), 1.86—1.77 (m, 2H), 0.90 (s, 9H), 0,01 (s, 6H); IR (KBr) ν: 2949, 2854, 1507, 1464, 1389, 1363, 1234, 1110, 986, 752 cm^{-1}; EIMS *m/z* (%): 338 (2.25, M^+), 281 (4.10), 240 (58.48), 222 (34.98), 181 (58.89), 149 (100.00), 124 (56.60), 109 (10.68); HRMS calcd for $C_{18}H_{30}O_4Si$ 338.1913, found 338.1897.

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7 The diastereomeric excess was determined by HPLC of σ-symmetric (1,2:4,5)-diepoxide equivalent (**10**).

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