Johns or Electrothermal melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with IBM AF 100, Bruker AC 200, or Bruker AM 400 FTNMR spectrometers. Proton chemical shifts are expressed in parts per million (ppm) downfield from internal tetramethylsilane (TMS). ^{13}C chemical shifts are also expressed in ppm relative to the solvent chemical shift. Infrared data (IR and FTIR) are reported in reciprocal centimeters and were recorded either with a Perkin-Elmer 283B spectrophotometer or an IBM IR/44 FTIR spectrophotometer. Mass spectra were obtained with a Hewlett-Packard 5985A mass spectrometer. Elemental analyses were performed either by Desert Analytics of Tuscon, AZ, or by Oneida Research Services of Whitesboro, NY.

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Dioxane and tetrahydrofuran (THF) were distilled from a mixture of sodium and potassium. Reagent grade dimethyl sulfoxide (DMSO) was stored over molecular sieves (4 Å) for 24 h before use. Phenylenediamine was recrystallized from hexane and sublimed under vacuum before use. Phenylenediamine dihydrochloride and methyl salicylate were used as received. Chloroacetonitrile was distilled and stored over molecular sieves before use.

(2-Carbomethoxyphenoxy)acetonitrile (3). Under nitrogen, a solution of methyl salicylate (6.5 mL, 50.0 mmol) in 50 mL of DMSO was added dropwise over a period of 2 and 1/4 h to a stirring solution of anhydrous K_2CO_3 (7.0 g, 55.0 mmol) in 50 mL of DMSO at room temperature, and the resulting solution was stirred for 1 h. Then a solution of chloroacetonitrile (4.7 mL, 75.0 mmol) in 100 mL of DMSO was added dropwise over a period of 5 and 1/4 h at room temperature. After completion of the addition, the reaction mixture was stirred for 1 h. The resulting mixture was filtered, and the filtrate was poured into 300 mL of cold water. The precipitate that formed was filtered, washed with cold water, and air dried, giving 7.13 g (76%) of **3** as a white powder with a melting point of 53.0–54.0 °C. Recrystallization from hexane yielded colorless needles with mp 54.5–55.0 °C (lit.[27] mp 53–54 °C): IR (KBr) 1725 (C=O), 1599 (C=C), 1276, 1232, and 1090 cm^{-1} (alkyl and/or aryl C–O); ^1H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, CO_2CH_3, 3 H), 4.86 (s, OCH_2CN, 2 H), 7.10–7.20 (m, Ar H, 2 H), 7.47–7.56 (m, Ar H, 1 H), 7.83–7.88 (m, Ar H, 1 H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 52.26 (s), 55.66 (s), 115.18 (s), 116.45 (s), 122.15 (s), 123.62 (2), 132.16 (s), 133.82 (s), 156.14 (s), 165.76 (s); MS, *m/e* (rel intensity) 191 (M^+, 3.8), 176 (18.2), 160 (58.4), 159 (14.8), 149 (10.2), 148 (20.6), 135 (6.5), 120 (57.9), 105 (55.1), 95 (19.5), 92 (100.0), 77 (35.7), 65 (22.4), 64 (56.0), 63 (85.9), 62 (23.6), 51 (21.0), 50 (19.9). Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33; O, 25.11. Found: C, 62.71; H, 4.52; N, 7.27; O, 25.09.

2-[(2'-Carbomethoxyphenoxy)methyl]benzimidazole (5). Under nitrogen, sodium (0.35 g, 15.0 mmol) was added to a stirring solution of **3** (3.0 g, 15.7 mmol) in 50 mL of anhydrous methanol at room temperature. The resulting warm solution was stirred at ambient temperature for 40 min. To this colorless solution was added phenylenediamine dihydrochloride (2.72 g, 15.0 mmol), and the resulting solution turned yellow followed by formation of a precipitate. Stirring was continued for 2 h. The salts that formed were filtered, and the filtrate was treated with decolorizing charcoal. After removal of the charcoal, water (about 70–75 mL) was added to the alcoholic solution until cloudiness developed, and the resulting mixture was allowed to stand at room temperature for several hours. The precipitate that formed was filtered, washed with water, and air dried, giving 3.66 g (88%) of **5** as colorless plates with mp 159–159.5 °C: FTIR (KBr, cm^{-1}) 3300–2200 (br, N–H, H-bonded), 1727 (Ar—C=O, with a shoulder at 1680), 1599, 1588, 1491 (aryl C=C and N heterocycl. combination of C=C and C=N), 1433 (aryl multiple C=C), 1242, 1086, 1045 (alkyl and/or aryl C–O), 761, 752, 741 (Ar–H def.); ^1H NMR (100 MHz, $CDCl_3$, ppm) 3.93 (s, CO_2CH_3, 3 H), 5.47 (s, $ArOCH_2$, 2 H), 6.96–7.91 (m, Ar H, 8 H), 11.54 (br, =NH, 1 H); ^{13}C NMR (50.33 MHz, $CDCl_3$, ppm) 52.29 (s), 65.93 (s), 111.38 (s), 114.56 (s), 119.25 (s), 119.85 (s), 121.73 (s), 122.02 (s), 122.72 (s), 131.95 (s), 133.49 (s), 134.37 (s), 143.65 (s), 150.80 (s), 158.15 (s), 166.46 (s); MS, *m/e* (rel intensity) 282 (M^+, 14.7), 253 (21.7), 131 (100.0), 104 (10.4), 77 (17.5). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.93. Found: C, 68.18; H, 5.00; N, 9.95.

2-[(2'-Carboxyphenoxy)methyl]benzimidazole (1). A suspension of **5** (4.0 g, 14.0 mmol) in 100 mL of 0.5 N HCl was refluxed for 15 h. Cooling to room temperature resulted in formation of a precipitate. The resulting mixture was warmed until complete dissolution of the precipitate, followed by neutralization with concentrated NH_4OH. After being cooled to room temperature, the precipitate that formed was filtered, washed with water, and air dried, giving 3.33 g (85%) of **1** as a white solid with mp 200–203.5 °C. Recrystallization from a mixture of 1:2 water/absolute ethanol gave tan needles with mp 212.5–213 °C. A second recrystallization from 80% aqueous dioxane yielded white solid with mp 201.5–202 °C. A suitable single crystal for X-ray analysis was obtained by slow evaporation from dioxane: FTIR (KBr) 3454 (R_2N–H), 3330–2680 (H-bonded O=C—O—H centered at 3194), 3069 (Ar–H), 1680 (Ar—C=O), 1601, 1489 (aryl C=C and N heterocycl. C=C and C=N), 1452, 1439 (aryl multiple C=C), 1271, 1095, 1049 (alkyl and/or aryl C–O), 735 cm^{-1} (Ar–H def.); ^1H NMR (100 MHz, d_6-DMSO) δ 5.47 (s, $ArOCH_2$, 2 H), 6.99–7.72 (m, Ar H, 8 H); ^{13}C NMR (25.16 MHz) d_6-DMSO, ppm) 64.80 (s), 114.78 (s), 115.03 (s), 121.30 (s), 122.05 (s), 122.61 (s), 130.75 (s), 132.86 (s), 138.14 (s), 150.14 (s), 156.59 (s), 167.17 (s); MS, *m/e* (rel intensity) 268 (M^+, 34.3), 239 (10.2), 223 (11.0), 131 (100.0), 104 (17.5), 92 (10.2), 77 (28.8), 65 (11.8), 64 (12.6), 63 (14.9). Anal. Calcd for $C_{15}H_{12}N_2O_3 \cdot {}^1/_2H_2O$: C, 64.98; H, 4.36; N, 10.10. Found: C, 65.22; H, 4.50; N, 10.16. Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51. Found: C, 66.87; H, 4.49.

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(27) Wormser, H.; Lieu, S. *J. Pharm. Sci.* **1976**, *65*, 397–400.

A Facile and Highly Stereoselective Synthesis of (*R*)- and (*S*)-[2-(Phenylmethoxy)ethyl]oxirane

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In the course of research on stereochemically defined inhibitors of polyamine biosynthesis,[1] we had need for a highly stereoselective synthesis of the *R* and *S* enantiomers of 1,8-dichlorooctan-3-ol.[2] Following unsatisfactory results with an approach based on asymmetric induction,[3] we pursued an enantiomeric synthesis using (*R*)- or (*S*)-malic acid as starting materials. We envisioned using procedures described in the literature[4-6] to afford the desired enantiomerically pure oxiranes **5**, which could then be further elaborated to the desired 1,8-dichlorooctanol.

Conversion of the free malic acids or their dimethyl esters to a 9:1 mixture of the 1,2 and 1,3 cyclic ketals of 1,2,4-butanetriol was done by the procedure described previously.[7] The mixture of cyclic ketals was benzylated at the remaining free hydroxyl group and the ketal removed by mild acid hydrolysis to provide a mixture of the desired 4-benzyloxy diol **1** (Scheme I) and the 1-benzyloxy regioisomer (9:1). Conversion of the primary alcohol of **1** to a good leaving group (e.g., sulfonate ester) followed by treatment with base should result in cyclization to the desired oxirane with retention of configuration at the chiral center of interest. We anticipated that formation of the corresponding oxetane from the 1-benzyloxy regioisomer

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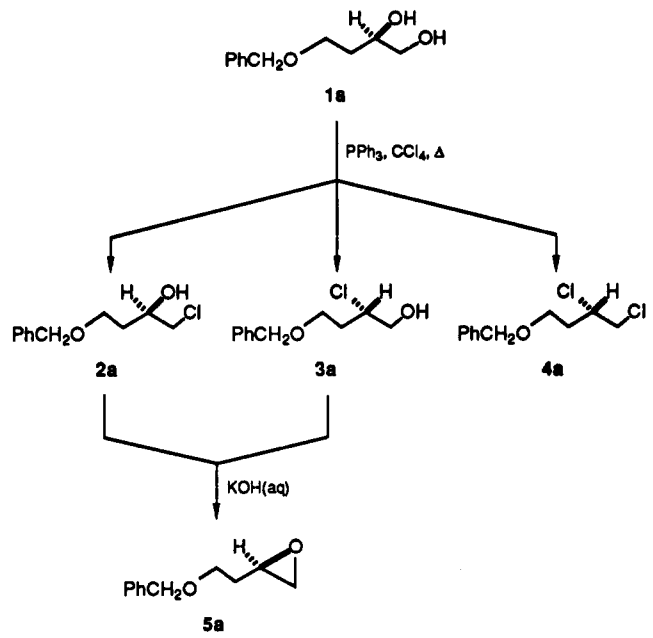
Scheme I[a]



[a] Only the a series derived from (*R*)-malic acid is shown; identical chemistry carried out on **1b** derived from (*S*)-malic acid leads to **5b** (see the Experimental Section).

would be much less facile[4] and would not constitute a problem in the isolation of the desired oxirane. Unfortunately, our attempts to convert the diol **1** to oxirane **5** via the intermediate sulfonate ester (MsCl,[8-10] TsCl[5]) or via Mitsunobu chemistry (Ph_3P, DEAD)[11] led to oxirane **5** with only ca. 80% ee as determined by NMR spectroscopy in the presence of a chiral shift reagent (see the Experimental Section). This approach has been used previously in the synthesis of racemic[8] and (*R*)-[9] and (*S*)-[5,10] oxirane. However, only optical rotation data were provided as evidence for the enantiomeric purity of the oxirane **5**.[5,9,10] An alternate synthesis of (*R*)- and (*S*)-**5** described by Golding and colleagues[4,12] involves the oxidative bromination (NBS) of the 1,2-benzylidene derivative of **1a**[12] or its enantiomer[4] and subsequent basic hydrolysis of the intermediate bromo ester. These authors reported optical purity in excess of 98% based on NMR shift reagent experiments.

An investigation of the regioselective reaction of **1** with MsCl or TsCl showed that the desired 1-alkyl- or arylsulfonate derivative of **1** could be separated from the 2-sulfonate regioisomer and the 1,2-disulfonate by careful chromatography on silica gel (2–5% EtOAc in cyclohexane). In the case of the tosylates, effective separation of the two regioisomers resulted in a low yield (37%) of the desired 1-*O*-tosyl derivative. Base-mediated cyclization of the purified 1-*O*-tosyl derivative to **5** could be effected in 75% yield to give a product of high stereochemical purity (ee >98%). This chromatographic method, although useful in providing pure 1-*O*-tosyl derivative for establishing the stereochemical integrity of the cyclization reaction on a small scale, proved to be tedious and much less effective on larger scale reactions.[13] Therefore, we sought a method that would permit a direct conversion of **1** to **5** without loss of stereochemical purity. Use of Ph_3P and CCl_4 proved to be effective in this regard. Reaction of **1** (together with ca. 10% of the 1-benzyloxy 2,4-diol regioisomer; not shown in Scheme I) and Ph_3P/CCl_4 resulted in formation of a mixture of two monochloro alcohols, **2** and **3** (63%), and the dichloro derivative **4** (17%). Inversion of configuration at the chiral carbon of **1a** to give **3a** is assumed, based on an understanding of the reaction mechanism.[14] Plug filtration on silica gel provided a rapid method for removing **4**, following which cyclization of the mixture, **2** and **3**, under basic conditions provided **5** in 85% purified yield. Examination of the ^1H NMR spectra of **5** in the presence of the chiral shift reagent Eu(hfc)$_3$ demonstrated that the stereochemical integrity at the chiral center was maintained through the synthesis of **5** from (*R*)- or (*S*)-malic acid. These spectral data (Figure 1, supplementary material) demonstrate that the facile synthetic route described here provides the enantiomeric oxiranes **5a** and **5b** of high stereochemical purity (>96% ee). Optically active (*R*)- and (*S*)-[2-(phenylmethoxy)ethyl]oxiranes (**5a** and **5b**) have been widely used as a key intermediate for enantioselective synthesis of bioactive compounds, such as Milbemycin β_3,[15] Compactin,[10] and Mevinolin.[10] Our methodology provides an efficient and highly stereoselective route for preparing these key intermediates and could find extensive application in synthesis that requires this type of epoxide functionality with high isomeric purity.

Experimental Section

All experiments were carried out in oven-dried or flame-dried glassware, and reaction solutions were magnetically stirred. Reactions involving air- or moisture-sensitive material were carried out under a positive pressure of dry nitrogen.

^1H NMR spectra were recorded at 300 or 360 MHz. ^{13}C NMR spectra were recorded at 75 or 90 MHz. Analytical thin-layer chromatography (TLC) was done on silica gel plates (EM Science, 5554-7) with 254-nm fluorescent indicator and were visualized under a UV lamp and/or phosphomolybdic acid solution. Flash chromatography refers to liquid chromatography on silica gel according to the method of Still et al.[16] Optical rotations were measured with a 1-dm path length in a constant-temperature jacket. Mass spectra were obtained on a GC/MS instrument.

All chemical reagents used in this work were commercially available, generally >98% purity, and were used without further purification. CCl_4 was distilled from CaH_2. The racemic[8] and (*R*)- (**1a**)[9] and (*S*)-4-(phenylmethoxy)-butane-1,2-diol (**1b**),[10] in addition to racemic 2-[(phenylmethoxy)ethyl]oxirane,[8] were prepared according to the procedures described previously with minor modifications. The stereochemical purities of **1a** and **1b** were determined to be >99% ee by ^1H NMR spectroscopy of the

(1) Coward, J. K. In *Design of Enzyme Inhibitors as Drugs*; Sandler, M., Smith, H. J., Eds.; Oxford University Press: New York, 1988; Chapter 21.
(2) Tang, K.-C.; Mariuzza, R.; Coward, J. K. *J. Med. Chem.* **1981**, *24*, 1277.
(3) Meyers, A. I.; Williams, D. R.; Druelinger, M. *J. Am. Chem. Soc.* **1976**, *98*, 3032. Liu, C.; Coward, J. K. Unpublished results.
(4) 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.
(5) Mulzer, J.; deLasalle, P. *J. Chem. Res., Synop.* **1983**, 10.
(6) Asymmetric epoxidation of homoallylic alcohols under Sharpless conditions proceeds in only modest yield and low enantiomeric excess; e.g., 3-butene-1-ol conversion to the alcohol corresponding to **5a**: 11–25% yield, 55% ee. Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3707–3711.
(7) Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1982**, 4883.
(8) Martin, J. C.; Smee, D. F.; Verheyden, J. P. H. *J. Org. Chem.* **1985**, *50*, 755.
(9) Van der Eycken, E.; DeWilde, H.; Deprez, L.; Vandewalle, M. *Tetrahedron Lett.* **1987**, *28*, 4759.
(10) Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Tetrahedron Lett.* **1984**, *25*, 2101.
(11) Takano, S.; Seya, K.; Goto, E.; Hirama, M.; Ogasawara, K. *Synthesis* **1983**, 116.
(12) Brookes, M. H.; Golding, B. T.; Hudson, A. T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 9.
(13) Takano, S.; Akiyama, M.; Ogasawara, K. *Synthesis* **1985**, 503.
(14) Slagle, J. D.; Huang, T. T.-S.; Franzus, B. *J. Org. Chem.* **1981**, *46*, 3526.
(15) Kocienski, P. J.; Street, S. D. A.; Yeates, C.; Campbell, S. F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2171.
(16) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

1,2-di-*O*-methylmandelates:[17] **1a**, δ 5.22 (m, 1 H); **1b**, δ 5.31 (m, 1 H).

Reaction of (*R*)-4-(Phenylmethoxy)butane-1,2-diol (1a) with CCl_4/Ph_3P. To a well-stirred solution of triphenylphosphine (421 mg, 1.61 mmol) in 10 mL of dry CCl_4 was added **1a** (300 mg, 1.53 mmol) in one portion at room temperature. The reaction mixture was allowed to stir at reflux temperature for 16 h and then cooled to room temperature. *n*-Pentane (5 mL) was added, and the resultant precipitate of triphenylphosphine oxide was separated by filtration. After evaporation of the filtrate under reduced pressure, the residual liquid was plug filtered (10% EtOAc in hexane) through a short silica gel column to give 62 mg (17% yield) of **4a** (R_f = 0.63, hexane:EtOAc = 5:3) and 205 mg (63% yield) mixture of **2a** and **3a** (2:1) as a colorless liquid (R_f = 0.40 (**2a**) and 0.32 (**3a**), hexane:EtOAc = 5:3). **4a**: IR (neat) 1255, 1020, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.24 (m, 5 H), 4.52 (s, 2 H), 4.32 (m, 1 H), 3.81–3.71 (dd, *J* = 8.4, 5.9 Hz, 2 H), 3.70–3.64 (m, 2 H), 2.36–2.27 (ddt, *J* = 3.7, 14.6, 7.1 Hz, 1 H), 1.98–1.89 (ddt, *J* = 4.7, 14.0, 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 138.25, 128.42, 127.63, 73.22, 66.41, 58.28, 48.70, 35.61; MS, *m/e* 232 (M^+), 125, 107, 91 (100), 79, 65, 51, 39. Anal. Calcd for $C_{11}H_{14}Cl_2O$: C, 56.67; H, 6.05. Found: C, 56.93; H, 6.17. Small portions of **2a** and **3a** were separated in order to obtain the spectral data as follows. **2a**: IR (neat) 3420 (OH), 1080, 742, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.25 (m, 5 H), 4.52 (s, 2 H), 4.02 (m, 1 H), 3.75–3.61 (m, 2 H), 3.57 (dd, *J* = 5.0, 11.2 Hz, 1 H), 3.51 (dd, *J* = 6.1, 11.1 Hz, 1 H), 3.15 (d, *J* = 3.9 Hz, 1 H, OH exchangeable), 1.87 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 137.79, 128.42, 127.74, 127.62, 73.24, 70.38, 67.66, 49.32, 33.72; MS, *m/e* 214, 107, 91 (100), 79, 65, 51, 39; HRMS for $C_{11}H_{15}O_2Cl$, calcd *m/e* 214.0760, obsd 214.0751. **3a**: IR (neat) 3400 (OH), 1080, 735, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.27 (m, 5 H), 4.52 (s, 2 H), 3.81–3.6 (m, 4 H), 2.70 (t, *J* = 6.7 Hz, 1 H, OH exchangeable), 2.15–2.02 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 137.79, 128.42, 127.74, 73.24, 66.67, 66.47, 61.35, 34.68; MS, m/e 214, 107, 91 (100), 79, 65, 51, 41; HRMS for $C_{11}H_{15}O_2Cl$, calcd *m/e* 214.0760, obsd 214.0757. Anal. Calcd for $C_{11}H_{15}ClO_2 \cdot 0.15H_2O$ (mixture of **2a** and **3a**): C, 60.78; H, 7.09. Found: C, 60.50; H, 6.98.

Reaction of (*S*)-4-(Phenylmethoxy)butane-1,2-diol (1b) with CCl_4/Ph_3P. The reaction was carried out with 1.0 g (5.1 mmol) of **1b** exactly as described above for the *R* enantiomer, **1a**, to give 159 mg (13%) of the corresponding dichloro derivative, **4b**, and 711 mg (65%) of a mixture of the monochloro alcohols, **2b** and **3b**. All spectral data (IR, ^1H NMR, ^{13}C NMR) for **2b–4b** were as reported above for **2a–4a**.

(*R*)-[2-(Phenylmethoxy)ethyl]oxirane (5a). The mixture (181 mg, 0.84 mmol) of monochloro alcohols **2a** and **3a** was dissolved in 4 mL of mixed solvent (H_2O:DMSO = 3:1), and 71 mg (1.27 mmol) of KOH was added into the reaction mixture. The reaction mixture was stirred at 60 °C and monitored by TLC until all the starting material was consumed (about 45 min). The reaction mixture was then poured into ice water (10 mL) and extracted with ether. The combined ether phase was washed with brine, dried (Na_2SO_4), and evaporated. The residue was applied to a silica gel column, and the desired oxirane was obtained by elution with 3% EtOAc in hexane to give 127 mg (85% yield) of **5a** as a colorless liquid: IR (neat) 1258, 1026, 738, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.25 (m, 5 H), 4.53 (s, 2 H), 3.64 (t, 2 H), 3.07 (m, 1 H), 2.79 (dd, *J* = 4.3, 4.9 Hz, 1 H), 2.52 (dd, *J* = 5.0, 2.7 Hz, 1 H), 1.98–1.76 (ddt, *J* = 4.7, 14.1, 6.5 Hz), 1.75–1.65 (ddt, *J* = 6.4, 14.1, 5.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 138.31, 128.36, 127.57, 73.1, 67.06, 50.04, 47.05, 33.0; $[\alpha]_D$ = +16.9 (*c* 2.51, $CHCl_3$); HRMS for $C_{11}H_{14}O_2$ ($M - H^+$), calcd *m/e* 177.0915, obsd 177.0915. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.12; H, 7.91. Found: C, 73.95; H, 7.90.

(*S*)-[2-(Phenylmethoxy)ethyl]oxirane (5b). The reaction was carried out with 636 mg (2.96 mmol) of the (*S*)-monochloro alcohols, **2b** and **3b**, exactly as described above for the *R* enantiomer to give 423 mg (80%) of **5b** as a colorless liquid: $[\alpha]_D$ = −14.5 (*c* 2.51, $CHCl_3$); HRMS for $C_{11}H_{14}O_2$ ($M - H^+$), calcd *m/e* 177.0915, obsd 177.0916. All spectral data (IR, ^1H NMR, ^{13}C NMR) for **5b** were as reported for **5a**.

(17) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

Determination of Percent Enantiomeric Excess of (*R*)- and (*S*)-Oxiranes by Shift Reagent ($Eu(hfc)_3$). A measured amount of the epoxide to be analyzed (2–4 mg) was transferred to a high-quality 5-mm NMR tube. One drop of deuteriochloroform containing 1% TMS was then added, followed by sufficient $CDCl_3$ (dried over 4A molecular sieves) to bring the total volume in the tube to 0.5 mL. A fresh solution of $Eu(hfc)_3$ was made up by transferring the sublimed $Eu(hfc)_3$ (65 mg) to a 1.0-mL volumetric flask. The material was then dissolved in sufficient CCl_4 to bring the solvent level to the mark. Shift reagent titration was carried out by transfer of the $Eu(hfc)_3$ solution (via a 25-μL syringe) to the oxirane sample solution in the NMR tube. Addition of the shift reagent was repeated until the desired separation of the signals due to the benzylic protons (Figure 1) was optimal.

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Supplementary Material Available: Figure 1, a portion of each of the ^1H NMR spectra obtained for the racemic (*R,S*)-oxirane, the *R* isomer (**5a**), and the *S* isomer (**5b**) (1 page). Ordering information is given on any current masthead page.

Oxovanadium(V)-Induced Oxidative Transformations of Cyclobutanones

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Transition-metal compounds can often act as catalysts or even reagents in organic reactions that involve electron transfer.[1] Some versatile synthetic methods based on one-electron transfer have been recently developed.[2] Vanadium(V) compounds, in which vanadium is in a high oxidation state, are known to promote one-electron oxidation reactions.[3] The utilization of such compounds is, however, limited because the reactions are usually performed in acidic aqueous media.[3b] In previous papers, we reported that $VO(OR)Cl_2$ works well as a Lewis acid with oxidative capability in organic solvents.[4]

Cyclobutanones are regarded as important sources of four-carbon synthetic building blocks via ring opening.[5]

(1) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981.

(2) (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Curran, D. P. *Synthesis* **1989**, 417, 489. (c) Heiba, E. I.; Dessau, R. M. *J. Org. Chem.* **1974**, *39*, 3456. (d) Corey, E. J.; Kang, M.-C. *J. Am. Chem. Soc.* **1984**, *106*, 5384. (e) Yang, F. Z.; Trost, M. K.; Fristad, W. E. *Tetrahedron Lett.* **1987**, *28*, 1493. (f) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152, 6551. (g) RajanBabu, T. V.; Nugent, W. A. *Ibid.* **1989**, *111*, 4525. (h) Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *Ibid.* **1989**, *111*, 8014.

(3) (a) Schwartz, M. A.; Holton, R. A.; Scott, S. W. *J. Am. Chem. Soc.* **1969**, *91*, 2800; **1970**, *92*, 1090. (b) Freeman, F. In *Organic Syntheses by Oxidation with Metal Compounds*; Mijs, W. J., de Jonge, C. R. H. I., Ed.; Plenum Press: New York, 1986; pp 1–39. (c) The imido derivative of $VOCl_3$ was reported to be useful for oxidative decarboxylations in organic solvents. See: Meier, I. K.; Schwartz, J. *J. Am. Chem. Soc.* **1989**, *111*, 3069.

(4) Hirao, T.; Mori, M.; Ohshiro, Y. (a) *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2399; (b) *J. Org. Chem.* **1990**, *55*, 358. (c) Hirao, T.; Ohshiro, Y. *Tetrahedron Lett.* **1990**, *31*, 3917. (d) Hirao, T.; Mikami, S.; Mori, M.; Ohshiro, Y. *Tetrahedron Lett.* In press.

0022-3263/91/1956-2264$02.50/0