Asymmetric Epoxidation of Homoallylic Alcohols. Synthesis of (−)-γ-Amino-β(*R*)-Hydroxybutyric Acid (GABOB)

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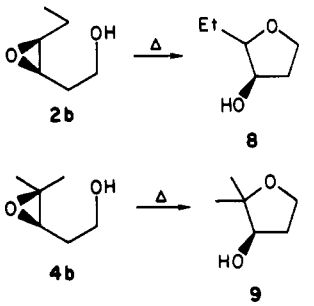
Asymmetric epoxidation of seven homoallylic alcohols using the Ti(O-*i*-Pr)$_4$, (+)- or (−)-diethyl tartrate, and *tert*-butyl hydroperoxide system is described. Enantiomeric purities range from 23% to 55%. Interestingly, the enantiofacial selection is opposite that observed for allylic alcohols. Characteristics of the reaction and product isolation are discussed. Synthetic utility is demonstrated by the synthesis of the title compound in three steps from epoxy alcohol **1b**.

In August of 1980, we reported an efficient method for the asymmetric epoxidation of allylic alcohols using Ti(O-*i*-Pr)$_4$, (+)- or (−)-diethyl tartrate (DET), and *tert*-butyl hydroperoxide (TBHP).[2-4] Since that time this new process has been used to help solve otherwise difficult problems in the synthesis of chiral compounds.[5] Hoping to broaden the scope of this reaction, we attempted the asymmetric epoxidation of various homoallylic alcohols. We now report our results with homoallylic alcohols, and a synthesis of (+)-γ-amino-β(*R*)-hydroxybutyric acid **17** (GABOB), an antiepileptic and hypotensive drug.

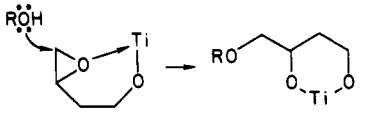
Table I gives the results of the asymmetric epoxidation of seven primary homoallylic alcohols with the Ti(O-*i*-Pr)$_4$/L-(+)-DET/TBHP system described previously.[2] The enantiomeric purities of the products range from 23% to 55%. This is an unfortunate departure from the trend of generally high enantiomeric purities obtained with allylic alcohols. Attempting to increase the enantiomeric excesses by lowering the reaction temperature (much below −20 °C) retards the reaction rate prohibitively. In fact, alcohol **1a** had to be run at 0 °C in order to achieve sufficient reaction. Surprisingly, **1a** also gave the product having the highest enantiomeric excess. Epoxidation of **2a** at 0 °C and at −20 °C illustrates, as expected, that higher enantioselectivity is attained at lower temperatures. Even though the asymmetric induction observed with these substrates is less than desired, it still should be of preparative value in some cases. There may also be special cases where particular structural or electronic features of a substrate will allow more efficient asymmetric induction.[6]

The yields, ranging from 11% to 62%, reflect, in part, the practical problems of isolating water-soluble, low molecular weight products from a complex reaction mixture. Higher molecular weight, more lipophilic epoxy alcohols can probably be isolated in higher yields. Another reason for the relatively low yields in this reaction is the rearrangement of the epoxide to a tetrahydrofuran derivative (Scheme I). At least 20% of **4b** rearranges to such

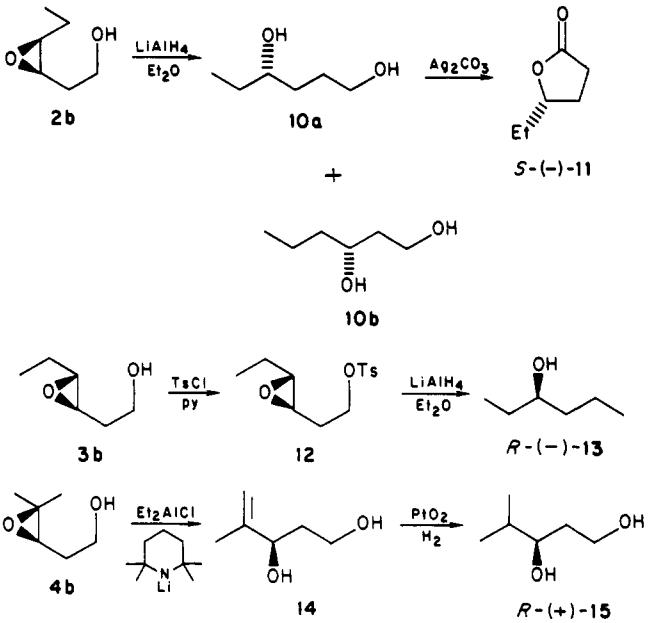
Scheme I



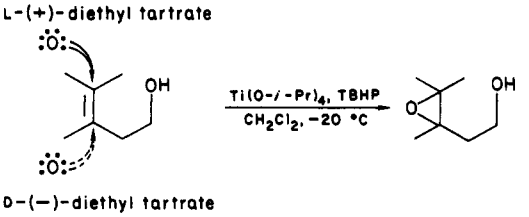
Scheme II



Scheme III. Absolute Configuration Determinations



Scheme IV. Asymmetric Epoxidation of Homoallylic Alcohols



(1) Roche Research Center, Hoffmann-La Roche Inc., Nutley, NJ 07110.

(2) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(3) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464.

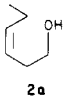
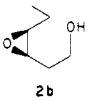
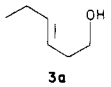
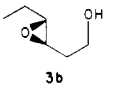
(4) Martin, V. S.; Woodard, S. S.; Katuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(5) (a) Wood, R. D.; Ganem, B. *Tetrahedron Lett.* **1982**, *23*, 707. (b) Yamada, Y.; Seo, C. W.; Olada, H. *Agric. Biol. Chem.* **1981**, *45*, 1741. (c) Isobe, M.; Kitamura, M.; Mio, S.; Goto, T. *Tetrahedron Lett.* **1982**, *23*, 221. (d) Mori, K.; Ebata, T. *Tetrahedron Lett.* **1981**, *22*, 4281. (e) Meyers, A. I.; Hudspeth, J. P. *Tetrahedron Lett.* **1981**, *22*, 3925. (f) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

(6) Mihelich has shown that *cis*-2-methylhomoallylic alcohols are epoxidized with much higher diastereoselectivity than other homoallylic alcohols with V^{+5}/TBHP. Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690.

0022-3263/84/1949-3707$01.50/0

Table I. Asymmetric Epoxidation of Homoallylic Alcohols

homoallylic alcohol	epoxy alcohol	yield, %	ee, %	confign	rotation (solvent)
 1a	 1b	11-25[a]	55	3R	+ (CH_2Cl_2)
 2a	 2b	50[a] 30[b]	36 50	3R,4S 3R,4S	+ ($EtOH_{abs}$) + ($EtOH_{abs}$)
 3a	 3b	34-50[b]	41	3R,4R	+ ($EtOH_{abs}$)
 4a	 4b	41[b,c]	27	3R	+ ($CHCl_3$)
 5a	 5b	60[b]	23		+ ($EtOH_{abs}$)
 6a	 6b	15[b]	*d*		+ ($EtOH_{abs}$)
 7a	 7b	62[b]	48		+ ($EtOH_{abs}$)

[a] Performed at 0 °C. [b] Performed at −20 °C. [c] Isolated as the acetate. [d] Percent ee was not determined for this product.

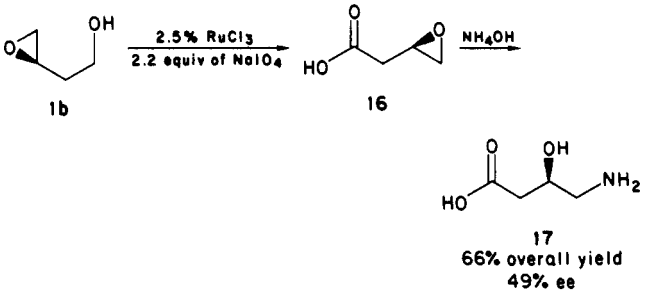
a derivative while other epoxy alcohols rearrange to lesser degrees. In relation to this, attempts to purify **2b** by preparative GLC or **4b** by molecular distillation result in complete isomerization to their respective tetrahydrofuranols.[21]

Another possible problem is titanium-assisted epoxide ring opening to give diols (Scheme II).[7] Byproducts with long retention times were detected by GLC, though never isolated nor fully characterized. An additional problem in obtaining high yields is the lack of substrate reactivity. After a week at 0 °C, substantial quantities of **1a** remain in the reaction mixture.

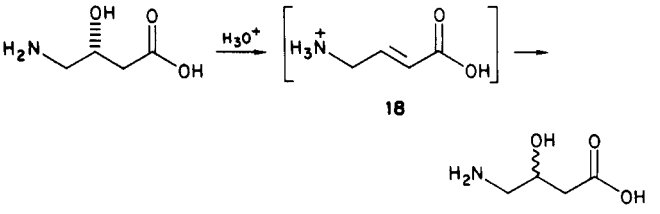
The absolute configurations of **2b–4b** were established as shown in Scheme III. The epoxy alcohol **1b** was correlated previously to (*S*)-malic acid.[8] In each case, epoxidation with L-(+)-DET gives products enriched in the 3*R* enantiomer. In contrast, epoxidation of allylic alcohols with L-(+)-DET gives almost exclusively the 2*S* enantiomer. Thus, epoxidation occurs predominantly on different olefinic faces with allylic and homoallylic alcohols (Scheme IV). The predictability of this reaction, like that with allylic alcohols, is of potential value in structure correlations, as well as rational synthetic planning.

To demonstrate the utility of this reaction in organic synthesis, we have prepared (−)-γ-amino-β(*R*)-hydroxybutyric acid in three steps via **1b** (Scheme V). The epoxy alcohol obtained in 55% ee and 15–25% yield is readily oxidized to epoxy acid **16** which can be isolated in ca. 50% yield.[9] The synthesis is simplified, however, by treating the aqueous layer from the oxidation with concentrated NH_4OH. By this method a 66% overall yield of **17** from **1b** is attained. The tan solid has a rotation of −9.76° which indicates an enantiomeric excess of ca. 49% and a 3*R*

Scheme V. Asymmetric Synthesis of GABOB



Scheme VI



stereochemical assignment. The product was recrystallized 4 times from ethanol–water to give a white crystalline material with an optical rotation of −20.11°. The reported literature values ranged from −20.7° to −21.06°, thus indicating that our material is 95–97% ee. The overall yield, assuming an 11% yield in the first step, is ca. 7.3%.

Recently, Jung and Shaw reported the synthesis of (−)-GABOB in ten steps and 10% overall yield from ascorbic acid.[10] Although starting from optically pure ascorbic acid, their synthesis apparently does not produce enantiomerically pure GABOB as one would expect. The reported optical rotation for the product is −7.09° which would indicate ca. 35% ee. We believe that substantial

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(8) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 1208.
(9) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(10) Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304.

racemization occurs in the last step of their synthesis by a reversible dehydration–hydration reaction (Scheme VI). This, in fact, constitutes a method of making racemic GABOB from intermediate **18**, water, and an acidic ion exchange resin.[11] We have subjected enantiomerically pure GABOB to the conditions of the final step in Jung's synthesis and found that complete racemization results. The considerable erosion of stereochemical integrity that occurs in the last step of their GABOB synthesis was apparently not realized by Jung and Shaw.

In summation, a method of making 3,4-epoxy alcohols now exists. Though inefficient, it should prove to be of some value due to its ability to directly, and predictably, furnish a wide variety of chiral products.

Experimental Section

General Procedure for Asymmetric Epoxidation of Homoallylic Alcohols. This procedure is a modification of the original procedure established for asymmetric epoxidation of allylic alcohols.[2] A dry, N_2-purged, 100-mL flask was charged with 10 mmol of the desired homoallylic alcohol, 11 to 12 mmol of L-(+)-diethyl tartrate, and 30 mL of dry CH_2Cl_2. After sealing the flask with a rubber septum and cooling in a dry ice–acetone bath, stirring was initiated. Titanium tetraisopropoxide (3.0 mL, 2.8 g, 10 mmol) was added via syringe to the flask, and after stirring for several minutes anhydrous TBHP in CH_2Cl_2 was added. The reaction mixture was then stored in a freezer (ca. −20 °C) or a refrigerator (ca. 0 °C) for 1 to 4 days and periodically monitored by TLC (silica, diethyl ether). When the reaction appeared to have stopped, the flask was removed from the refrigerator, charged with 50 mL of ether and 10 mL of saturated Na_2SO_4, and stirred vigorously for 1 to 2 h at room temperature. The thick orange mixture was filtered through a cake of Celite and washed with ether. To this solution was added ca. 40 mmol of NaOH as a 1 or 2 N solution, and the mixture was stirred for ca. 15 to 20 min. The aqueous layer was removed and extracted twice with ether. The organic solutions were combined, washed with saturated NaCl solution, dried (Na_2SO_4), and concentrated. The crude product was chromatographed either by flash chromatography or more carefully by MPLC using a Merck Lobar Si 60 column and solvent mixtures ranging from 1:1 ether–hexane to 100% ether. Further purification for combustion analysis and physical characterization was accomplished by additional chromatography and/or molecular distillation at 1 to 28 mmHg. The reaction in many cases was carried out on larger scales by using the same relative proportions of reagents. The enantiomeric excesses of the epoxy alcohols were determined by derivatizing them with MTPA-Cl according to Mosher et al.[13] and analyzing their ^{19}F NMR spectra. For comparison, the racemic epoxy alcohols were also synthesized (V^{+5}/TBHP or MCPBA), derivatized with MTPA-Cl, and analyzed by ^{19}F NMR.

(+)-3(*R*),4-Epoxybutan-1-ol (1b). Epoxidation of **1a** was performed at 0 °C over 4 days. The isolation procedure, a modification of the general procedure, consisted of flash chromatographing the crude, concentrating product with ether *before* stirring over base. The product, still containing a residual amount of DET, was dissolved in ether and stirred with a small amount of 2 N NaOH for 0.5 h. The aqueous phase was removed and extracted with ether. The ethereal phases were combined, dried (Na_2SO_4), and concentrated to give a colorless oil which was further purified by MPLC and molecular distillation at 1 mmHg. The isolated yields after chromatography ranged from 11% to 25%: $[\alpha]^{23.5}_D$ +12.48°, $[\alpha]^{23.5}_{578}$ +13.12°, $[\alpha]^{23.5}_{546}$ +14.72°, $[\alpha]^{23.5}_{436}$ +23.6°, $[\alpha]^{23.5}_{365}$ +33.92° (*c* 1.25, CH_2Cl_2) [lit.[8] $[\alpha]^{23}_D$ +23.42° (*c* 5.00, CH_2Cl_2)]; IR (film) ν_{max} 3400, 3050, 1255 (8 μm), 898, 852, 820, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (t, 2, *J* = 6 Hz), 2.8–3.2 (m, 1), 2.7–2.9 (m, 1), 2.45–2.70 (m, 1), 2.35 (br s, 1), 1.6–2.1 (m, 2).

(+)-3(*R*),4(*S*)-Epoxyhexan-1-ol (2b). The reaction leading to **2b** was carried out at 0° C over 5 days with L-(+)-diethyl tartrate on a 10-mmol scale and produced, after chromatography (1:1 Et_2O/petroleum ether) and molecular distillation, 580 mg (56%) of a colorless oil: $[\alpha]^{23}_D$ +5.35°, $[\alpha]^{23}_{578}$ +5.62°, $[\alpha]^{23}_{546}$ +6.32°, $[\alpha]^{23}_{436}$ +10.70°, $[\alpha]^{23}_{365}$ +16.59° (*c* 1.85, $EtOH_{abs}$); IR (film) ν_{max} 3410, 1055, 903, 865, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (t, 2, *J* = 6 Hz), 2.6-3.05 (m, 2), 1.2–1.8 (m, 4), 1.05 (t, 3). Anal. Calcd for $C_6H_{10}O_2$: C, 62.04; H, 10.41. Found: C, 62.16; H, 10.56.

The reaction was also carried out at −20 °C, giving 352 mg (30%) of a colorless oil whose IR, NMR, and GLC characteristics were identical with the above compound.

(+)-3(*R*),4(*R*)-Epoxyhexan-1-ol (3b). The epoxy alcohol **3b** was prepared on a 10-mmol scale and isolated according to the general procedure: $[\alpha]^{24}_D$ +17.69°, $[\alpha]^{24}_{578}$ +18.50°, $[\alpha]^{24}_{546}$ +20.75°, $[\alpha]^{24}_{436}$ +33.06°, $[\alpha]^{24}_{365}$ +47.40° (*c* 1.73, $EtOH_{abs}$); IR (film) ν_{max} 3420, 1240, 1195, 1050, 882, 822, 807, 780, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (t, 2, *J* = 6 Hz), 2.75 (m, 2), 2.45 (br, s, 1, OH) 1.35–1.9 (m, 4), 0.95 (t, 3). Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 61.83; H, 10.54.

(+)-4-Methyl-3(*R*),4-epoxypentan-1-ol Acetate (4c). The epoxy alcohol **4b** was synthesized on a 10-mmol scale according to the general procedure. After saponification of the DET, the solution containing the product was combined with 9 mL of pyridine and 4.5 mL of acetic anhydride. After several hours, the reaction mixture was washed 3 times with saturated $CuSO_4$, dried (Na_2SO_4), concentrated, and chromatographed (1:1, pentane–ether) to give 730 mg (41%) of product which was 90% pure by GLC. The product was further purified by molecular distillation at 28 mmHg to give material ca. 97% pure: $[\alpha]^{25}_D$ +3.70°, $[\alpha]^{25}_{578}$ +3.99°, $[\alpha]^{25}_{546}$ +4.45°, $[\alpha]^{25}_{436}$ +7.02°, $[\alpha]^{D}_{365}$ +9.68° (*c* 2.18, $CHCl_3$); IR (film) ν_{max} 1735, 1238, 1115, 1045, 975, 878, 820, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.16 (t, 2, *J* = 6 Hz), 2.78 (t, 1, *J* = 5.8 Hz), 2.03 (s, 3), 1.6 to 2.1 (m, 2), 1.30 and 1.28 (two s, 6); mass spectrum, *m/z* (relative intensity) 115 (2), 98 (10), 69 (11), 59 (17), 57 (12), 55 (22), 43 (100). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.86; H, 9.20.

(+)-(*Z*)-3-Methyl-3,4-epoxypentan-1-ol (5b). The reaction, carried out on an 8-mmol scale, yielded 558 mg (4.8 mmol, 60%) after flash chromatography (1:3, pentane–ether): $[\alpha]^{25}_D$ +1.46°, $[\alpha]^{25}_{578}$ +1.50°, $[\alpha]^{25}_{546}$ +1.59°, $[\alpha]^{25}_{436}$ +1.79°, $[\alpha]^{25}_{365}$ +0.71° (*c* 6.08, $EtOH_{abs}$); IR (film) ν_{max} 3410, 1245, 910, 860, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (t, 2, *J* = 6.5 Hz), 2.83 (q, 1, *J* = 6 Hz), 1.80 (t, 2, *J* = 6.5 Hz), 1.32 (s, 3), 1.30 (d, 2, J ≈ 6 Hz), mass spectrum, *m/z* (relative intensity) M^+ 116 (0.9), 98.95 (20.2), 54.95 (27.3), 43.05 (100). Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 61.27; H, 10.62.

(+)-(*E*)-3-Methyl-3,4-epoxypentan-1-ol (6b). The reaction was performed on a 10-mmol scale according to the general procedure, yielding 174 mg (15%) of any oily product: $[\alpha]^{27}_D$ +1.63°, $[\alpha]^{27}_{578}$ +1.71°, $[\alpha]^{27}_{546}$ +1.91°,

(11) Pinza, M.; Pifferi, G. *J. Pharm. Sci.* **1978**, *67*, 120.
(12) Tomita, M.; Sendju, Y. *Hoppe-Seyler's Z. Physiol. Chem.* **1927**, *169*, 270.
(13) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

$[\alpha]^{27}_{436}$ +3.42°, $[\alpha]^{27}_{365}$ +5.57° (c 6.5, $CHCl_3$); IR (film) ν_{max} 3400, 1245, 865, 835, 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (t, 2, J = 6 Hz), 3.0 (q, 1, J = 5.2 Hz), 2.7 (br s, 1, OH), 1.8 (t,2, J = 6 Hz), 1.25 (m, 6). Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 60.60; H, 9.41.

The epoxy alcohol was derivatized to yield the (*tert*-butyldimethyl)silyl ether according to a literature procedure:[14] ^1H NMR ($CDCl_3$) δ 3.57 (t, 2, J = 6 Hz), 2.77 (q, 1, J = 5 Hz), 1.6–1.9 (m, 2), 1.25 (m, 6), 0.87 (s, 9), 0.05 (s, 6); mass spectrum, *m/z* (relative intensity) 172.95 (12), 75.00 (100), 72.90 (24), 58.95 (12), 56.95 (12), 44.95 (18), 42.95 (32), 40.90 (25).

(+)-3,4-Dimethyl-3,4-epoxypentan-1-ol (7b). The reaction was performed on a 3.8-mmol scale from which 300 mg of oily product was obtained (62%): $[\alpha]^{24}_D$ +2.70°, $[\alpha]^{24}_{578}$ +2.50°, $[\alpha]^{24}_{546}$ +3.19°, $[\alpha]^{24}_{436}$ +5.46°, $[\alpha]^{24}_{365}$ +8.53° (c 5.86, $EtOH_{abs}$); IR (film) ν_{max} 3400, 1705 (br w), 1640 (br w), 1240, 930, 880, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (t, 2, J = 8 Hz, 2.10 (t, 2, J = 8 Hz), 1.1–1.4 (m, 9); mass spectrum, *m/z* (relative intensity) 43.95 (100), 43.05 (23).

(−)-2-Ethyl-3(*R*)-tetrahydrofuranol (8).[21] Attempted purification of (+)-**2b** by Prep GLC (10-ft aluminum column with SE-30 phase at 180 °C) resulted in the collection of a colorless oil which was >95% pure by analytical GLC: $[\alpha]^{24}_D$ −15.69°, $[\alpha]^{24}_{578}$ −16.24°, $[\alpha]^{24}_{546}$ −18.20°, $[\alpha]^{24}_{436}$ −28.54°, $[\alpha]^{24}_{365}$ −40.03° (c 2.95, $EtOH_{abs}$) IR (neat) ν_{max} 3400, 1650 (br, w), 920, 878, 845, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.4–4.2 (m, 4), 2.5 (br s, 1), 1.95 (m, 2) 1.2–1.7 (m, 2), 0.97 (t, 3). Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 61.99; H, 10.56.

(−)-2,2-Dimethyl-3(*R*)-tetrahydrofuranol (9). Attempted purification of (+)-**4b** by molecular distillation (~100 °C, 26 mmHg), gave a colorless oil which was >97% pure by GLC: $[\alpha]^{26}_D$ −4.17° (c 3.38, $EtOH_{abs}$); ^1H NMR ($CDCl_3$) δ 3.7 to 4.1 (m, 3), 2.82 (br s, 1, OH), 1.6–2.5 (m, 3), 1.20 and 1.27 (two s, 6, $C(CH_3)_2$).

(−)-4(*S*)-Hydroxyhexanoic Acid Lactone (11). A. A 50-mL flask was charged with 150 mg of lithium aluminum hydride (3.75 mmol) and 35 mL of ether. The mixture was stirred for 1 h at room temperature and then cooled in a dry ice/acetone bath. (+)-**2b** (19% ee as determined by ^{19}F NMR of MTPA derivative) was dissolved in 10 mL of ether, chilled to ca. −40 to −50 °C, and added slowly to the vigorously stirring reaction mixture. Gradual warming to 10 °C over several hours was allowed, followed by quenching of the reaction (slow sequential addition of 150 μL of H_2O, 150 μL 15% NaOH, and 450 μL H_2O). Filtration and concentration afforded 140 mg of a colorless oil (70%). Capillary GLC analysis indicated the presence of two products with very similar retention times in the ratio of 15:85 with the minor component emerging first. It was assumed, but not proven, that the predominant compound was the 1,4-hexanediol. Without further purification, this product was carried on in the next step; ^1H NMR ($CDCl_3$) δ 3.4–3.9 (m, 3), 1.1–1.8 (m, 6), 0.7–1.1 (t, 3); the presence of exchangeable protons was indicated by addition of D_2O.

B. A 50-mL flask with a stirring bar and fitted with a reflux condenser was charged with 6.2 g of Ag_2CO_3 on Celite[15] (11 mequiv) and 30 mL of $CHCl_3$. Stirring and refluxing were initiated. The diols from LAH reduction of **2b**, dissolved in 3 mL of Et_2O, were added to the reaction mixture. After 6 h of refluxing the reaction mixture was filtered through a pad of Celite and the Celite was washed with a small amount of ether. GLC analysis indicated the presence of several products, one of which corresponded to the desired lactone as shown by comparison of GLC retention times with that of authentic material.[16] The reaction mixture was concentrated by slow distillation first with a 10-cm Vigreaux column and then with a short-path distillation head. The product was isolated by preparative GLC and shown to be ca. 75–80% pure by capillary GLC analysis. The product and authentic material have identical GLC retention times as demonstrated by coinjection on an SE-30 liquid phase as well as on a Carbowax 20M capillary column. Proof of the absolute configuration of the lactone was obtained by taking the NMR spectrum of the lactone in the presence of excess (+)-2,2,2-trifluoro-1-(9-anthryl)ethanol. In so doing, the methyl triplet was split into a doublet of triplets. The major triplet was displaced downfield from the minor, indicating the *S* configuration.[17] Integration of the two peaks revealed the % ee to be ca. 23%: $[\alpha]^{22}_D$ −10.0° (c 0.38, MeOH) [lit.[18] $[\alpha]^{20}_D$ −46.3° (c 0.05, MeOH); IR (CCl_4) ν_{max} 1780 (γ-lactone C=O), 1180, 1163 cm^{-1}; ^1H NMR (CCl_4/C_6D_6) δ 3.80–3.91 (m, 1), 1.88–2.10 (m, 2), 1.56–1.68 (m, 1), 1.35–1.50 (m, 1), 1.14–1.35 (m, 2), 0.79 (t, 3).

(+)-3(*R*),4(*R*)-Epoxyhexanol *p*-Toluenesulfonate (12). A 50-mL flask was charged with 24 mL of CH_2Cl_2, 464.6 mg of **3b** (4.0 mmol), and 10 mL of dry pyridine. After cooling to 0 °C, 1.0 g of *p*-toluenesulfonyl chloride (5.2 mmol) was added to the stirred reaction mixture. Upon disappearance of starting material, as monitored by TLC (1:1, ether–hexane), the reaction was quenched with H_2O, diluted with ether, and washed 3 times with saturated $CuSO_4$ and once with saturated NaCl. After drying (Na_2SO_4) and concentration, the product was flash chromatographed (9:1, hexane–ether), giving 544 mg (2.0 mmol) of a colorless oil (53%): $[\alpha]^{24}_D$ +10.68° (c 13.6, CCl_4); IR (film) ν_{max} 1595, 1355, 1188, 1175, 970, 912, 888, 835, 812, 785, 760, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 and 7.2 (two sets of mirror image doublets, 4, J = 8 Hz), 4.05 (t, 2, ^1J = 6 Hz), 2.6 (m, 2), 2.35 (s, 3), 1.6–2.0 (m, 2), 1.2–1.6 (m, 2), 0.87 (t, 3).

(−)-3(*R*)-Hexanol (13). A 50-mL flask was charged with 320 mg of lithium aluminum hydride (8 mmol) and 25 mL of diethyl ether. After stirring for several minutes at room temperature, 540 mg (2 mmol) of (+)-**12** dissolved in 10 mL of ether was added dropwise to the reaction mixture followed by continued stirring at room temperature for 3 h. The reaction mixture was quenched by dropwise addition of 320 μL of H_2O and then filtered through a Celite pad, dried ($MgSO_4$), and concentrated. Portions of the product were purified by preparative GLC. The purified product was 98% pure by analytical GLC (10-ft 10% Carbowax 20M) and gave a single peak when coinjected with authentic *dl*-3-hexanol: $[\alpha]^{22}_D$ −3.33° (c 1.29, $EtOH_{abs}$) [lit.[19] $[\alpha]^{20}_D$ −8.21° (c 11.5, $EtOH_{abs}$); ^1H NMR ($CDCl_3$) δ 3.5 (m, 1), 1.2–1.8 (m, 7), 0.80–1.20 (m, 6).

(+)-4-Methyl-1,3(*R*)-pentanediol (15). A 25-mL flask with stirring bar was charged with 15 mL of THF, 1 mL of MeOH, ca. 20 mg of NaOMe, and 100 μL of acetate **4c**. After stirring for ca. 1 h the methanolysis was quenched by addition of ca. 50 mg of NH_4Cl. The product was filtered, concentrated, and dissolved in 5 mL of benzene.

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TLC analysis indicated the presence of the desired epoxy alcohol **4b**.

A dry, N_2-purged flask was charged with 5 mL of benzene, 0.675 mL of tetramethylpiperidine (4 mmol), cooled to 0 °C, and charged with 2.5 mL of *n*-BuLi (4 mmol, 1.6 M solution in hexane). After stirring for 30 min at 0 °C, 4 mL of diethyl aluminum chloride (4 mmol, 1 M solution in hexane) was added to the flask via syringe, and stirring was continued for an additional 30 min. The benzene solution of **4b** was added to the cold reaction mixture via syringe, and stirring was continued for 4 h. The reaction was quenched with 2.5 mL of saturated NH_4Cl, and the organic phase dried (Na_2SO_4), concentrated, and flash chromatographed with ether to give a colorless oil. In addition to the desired olefinic diol, NMR analysis showed the presence of residual tetramethylpiperidine: NMR ($CDCl_3$) δ 4.9 (d, 2), 4.25 (t, 1, J = 6 Hz), 3.78 (t, 2, ^1J = 6 Hz), 1.5–2.0 (singlet superimposed on a multiplet, 5). This enediol **14** was added to a flask containing 25 mL of MeOH, ca. 20 mg of PtO_2, and a stirring bar. The mixture was placed under 1 atm of H_2, vigorously stirred for 1 h, and then filtered and concentrated to give a colorless oil. This oil was taken up in 20 mL of ether and stirred over 0.5 mL of saturated $CuSO_4$ to remove residual tetramethylpiperidine. After drying (Na_2SO_4) and concentration of the organic phase, the oily product was purified by preparative GLC to give a colorless oil which was 98% pure by analytical GLC. This product and authentic (*S*)-(−)-4-methyl-1,3-pentanediol[20] had identical capillary GLC retention times as demonstrated by conjection: $[\alpha]^{22}_D$ +6.67° (*c* 1.29, $CHCl_3$) [lit.[20] $[\alpha]^{27}_D$ −6.9° (*c* 2.84, $CHCl_3$)]; IR (CCl_4) ν_{max} 3610, 3360, 1380, 1345, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (t, 2, J = 6 Hz), 3.52 (t, 1, ^1J = 6Hz), 2.5 (br s, 2), 2.65 (m,3), 0.92 (d, 6).

4-Amino-3(*R*)-hydroxybutyric Acid (17). A 100-mL round-bottomed flask with a Teflon-coated stir bar was charged with 639 mg of $NaIO_4$, 1 mL of H_2O, and 6 μL of CCl_4. Stirring was initiated, and 100 mg of crude **1b** (1.1 mmol) was added. After several minutes 15 mg of $RuCl_3 \cdot (H_2O)_n$ was added and stirring was continued for 2 h. The heterogenous mixture was filtered and the aqueous and organic phases partitioned. The aqueous phase was extracted several times with THF and the organic phases were combined. The organic extracts were treated with excess concentrated NH_4OH and warmed on a steam bath for 24 h. The reaction mixture was then concentrated to give ca. 86 mg of a tan solid (66%): $[\alpha]^{25}_D$ −9.76° (*c* 1.67, H_2O) (lit.[12] $[\alpha]^{25}_D$ −20.7° (*c* 1.83, H_2O)]; ^1H NMR (D_2O) δ 4.5–4.0 (1, m), 3.15 (2, m), 2.45 (2, d); mp 212 °C dec (lit.[12] mp 216–217 °C dec).

This solid was recrystallized 4 times from ethanol–water to give a white crystalline solid: $[\alpha]^{25}_D$ −20.11° (*c* 1.0, H_2O). About 20 mg of purified **17** was dissolved in 1 mL of concentrated H_2SO_4, warmed on a steamed bath for ca. 10 min, and diluted with 10 mL of water. After continued warming on a stream bath for 2 h the reaction was treated with lead carbonate, filtered, and concentrated. Treatment with EtOH gave a white crystalline solid with spectral characteristics identical with authentic GABOB: $[\alpha]^{25}_D$ 0.00° (*c* 1.0, H_2O). In addition ^1H NMR analysis showed evidence of vinylic protons which we believe to correspond to the vinylic protons of **18** (δ 6.96 m, 6.16 d).

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Registry No. **1a**, 627-27-0; (+)-(*R*)-**1b**, 76282-48-9; (*Z*)-**2a**, 928-96-1; (+)-(3*R*,4*S*)-**2b**, 91603-21-3; (*E*)-**3a**, 928-97-2; (+)-(3*R*,4*R*)-**3b**, 91603-22-4; **4a**, 763-89-3; (*R*)-**4b**, 91523-66-9; (*Z*)-**5a**, 51446-29-8; (+)-(*Z*)-**5b**, 91523-67-0; (*E*)-**6a**, 1594-24-7; (+)-(*E*)-**6b**, 91523-68-1; **7a**, 74126-47-9; (+)-**7b**, 91523-69-2; (−)-**8**, 75809-18-6; (−)-(*R*)-**9**, 91523-70-5; (−)-(*S*)-**11**, 41035-07-8; (+)-(3*R*,4*R*)-**12**, 91603-23-5; (−)-(*R*)-**13**, 13471-42-6; (*R*)-**14**, 91523-71-6; (+)-(*R*)-**15**, 16451-48-2; (*R*)-**17**, 7013-07-2; **18**, 91523-72-7; TBHP, 75-91-2; Ti(*i*-PrO)$_4$, 546-68-9; 1,4-hexanediol, 16432-53-4; L-(+)-diethyl tartarate, 87-91-2.

(20) We thank Prof. Büchi for a generous sample of (*S*)-(−)-4-methyl-1,3-pentanediol: Büchi, G.; Crombie, L.; Godin, P. J.; Kaltenbram, J. S.; Siddalingaiah, K. S.; Whiting, D. A. *J. Chem. Soc.* **1961**, 2843.

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Electroorganic Chemistry. 81. Anodic Oxidation of Sulfonamides and Amidophosphates

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Oxidation peak potentials of sulfonamides and amidophosphates were measured in acetonitrile and compared with the corresponding amides and carbamates. The results showed that the order of easiness of oxidation was amides > carbamates > amidophosphates > sulfonamides. Furthermore, the reaction of silyl enol ethers or trimethyl phosphite with anodically α-methoxylated sulfonamides or amidophosphates has clearly shown that the α-methoxylated compounds are useful starting materials in organic synthesis. For example, optically active L-tryptophan was synthesized from α-methoxylated *N*-(*p*-tolylsulfonyl)-L-proline ester.

We have already reported that the anodic oxidation of cyclic (**1**, R,R′ = −$(CH_2)_n$−) and acyclic (**1**, R,R′ = higher alkyl groups) amides **1a** and carbamates **1b** in methanol is a convenient method to introduce a methoxyl group to the position α to the nitrogen atom of **1a** and **1b** and also suggested that the initiation step of the oxidation involves

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