Notes

Synthesis of Alkyl (2S,3R)-4-Hydroxy-2,3-epoxybutyrates from Sodium Erythorbate

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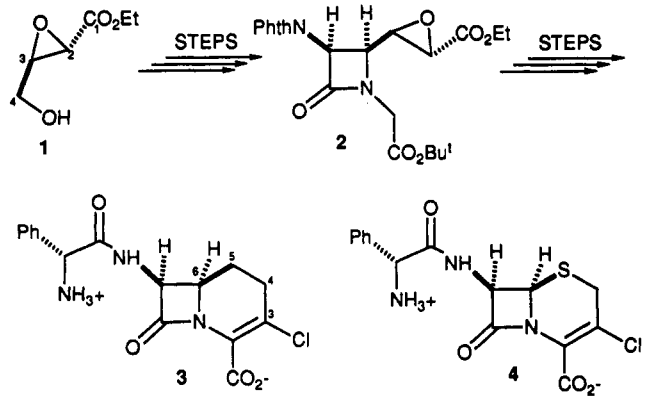
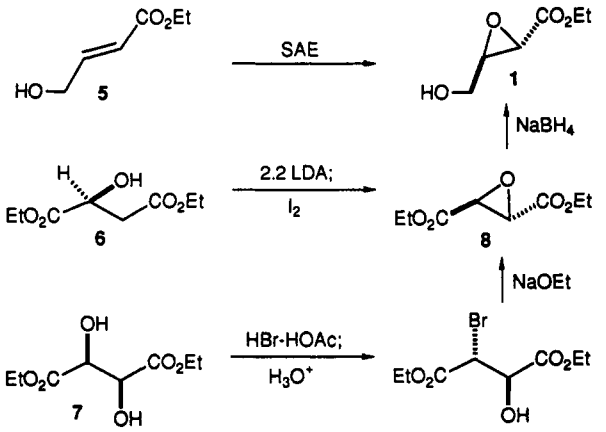
As a segment of a program directed toward the commercial development of the 1-(dethia)-1-carbacephem antibiotics,[1] we have recently disclosed the transformation of ethyl (2S,3R)-4-hydroxy-2,3-epoxybutyrate (1) into the monocyclic β-lactam 2[2] and thence into Lorabid (3, the C-5 analogue of Ceclor, 4). This epoxide[3] provided four of the seven nuclear carbons of 3 (C-1 to C-4 of 1 translate into C-3 to C-6 of 3). Additionally, 1 tactically imparted the required absolute stereochemistry, the desired cis configuration of the β-lactam[4] and the correct oxidation state for a subsequent Dieckmann closure[5] to an enol precursor of 3.



However, the application of this strategy to large-scale production of carbacephems was hampered by lack of a convenient source of the epoxide 1. Our first synthesis of 1[2] was based upon the Sharpless asymmetric epoxidation (AE)[5] of ethyl 4-hydroxycrotonate (5)[6] under noncatalytic conditions (three steps from fumaric acid). Epoxide 1 was also obtained[2] by employing known methods via conversion of diethyl (S)-malate[7] (6) or diethyl (−)-tartrate[8] (7) into the epoxide 8 followed by selective sodium borohydride reduction.[2b,3a]



These routes were adequate for the preparation of hundred-gram quantities but costly for scale-up since they relied upon a number of detailed processing steps or used relatively expensive esters of (−)-tartaric acid (6) or (S)-malic acid (7).

We wish to report an efficient and straightforward synthesis of 1 (and related esters) from the common food preservative sodium erythorbate (9, the sodium salt of D-isoascorbic acid, Scheme I). Our strategy was stimulated by the long-known availability D-erythronolactone (10)[9] from various natural sources (including 9). We rationalized that one route to the required epoxide would involve selective conversion of the C-3 hydroxyl into an appropriate leaving group (retention of configuration) followed by a sequence of reversible lactone ethanolysis and irreversible, kinetically controlled closure to epoxide 1 (Scheme I). Thus, oxidation of sodium erythorbate 9 with alkaline aqueous hydrogen peroxide according to the process of Cohen[10a,b] affords, after the modified isolation,[10c] 10

(1) (a) First enantioselective synthesis of a carbacephem nucleus: Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3787. (b) First disclosure of the synthesis of 3: Hirata, T.; Matsukuma, I.; Mochida, K.; Sato, K. 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, October 4–7, 1987. (c) Recent synthesis of 3: Bodurow, C. C.; Boyer, B. D.; Brennan, J.; Bunnell, C. A.; Burks, J. E.; Carr, M. A.; Doecke, C. W.; Eckrich, T. M.; Fisher, J. W.; Gardner, J. P.; Graves, B. J.; Hines, P.; Hoying, R. C.; Jackson, B. G.; Kinnick, M. D.; Kochert, C. D.; Lewis, J. S.; Luke, W. D.; Moore, L. L.; Morin, J. M. Jr.; Nist, R. L.; Prather, D. E.; Sparks, D. L.; Vladuchick, W. C. *Tetrahedron Lett.* **1989**, *30*, 2321.

(2) (a) Weigel, L. O.; Astleford, B. Presented at the 200th National Meeting of the American Chemical Society, Washington, DC, August 26, 1990; ORGN 51. (b) Aikins, J.; Blanchard, W.; Doecke, C.; Dunigan, J.; Frazier, J.; Gardner, J.; Heath, P.; Jackson, B.; Kennedy, J.; Moore, L.; Pedersen, S.; Rizzo, J.; Staszak, M.; Tao, E.; Ward, J.; Weigel, L. O. Presented at the 201st National Meeting of the American Chemical Society, Atlanta, GA, April 15, 1991; ORGN 107.

(3) (a) In the course of this work the reduction of *ent*-8 into *ent*-1 was reported in an enantioselective synthesis of Carumonam: Manchand, P. S.; Luk, K. C.; Beliica, P. S.; Choudhry, S. C.; Wei, C. C.; Soukup, M. *J. Org. Chem.* **1988**, *53*, 5507. (b) Specific applications of glycidic acids derivable from 1: Sharpless, K. B.; Chong, J. M. *Tetrahedron Lett.* **1985**, *26*, 4683.

(4) Evans, D. A.; Williams, M. J. *Tetrahedron Lett.* **1988**, *29*, 5065.

(5) (a) Hatanaka, M.; Ishimaru, T. *Tetrahedron Lett.* **1983**, *24*, 4837. (b) Jackson, B. G.; Gardner, J. P.; Heath, P. R. *Tetrahedron Lett.* **1990**, *31*, 6317.

(6) Compound 1 is obtained from 5 (*Organic Syntheses*; Kende, A. S., Ed.; John Wiley & Sons; New York, 1986, Vol. 64, p 104) in 85% chromatographed yield (90% ee) utilizing (−)-diisopropyl tartrate (1.2 equiv) with titanium isopropoxide (1 equiv) and *tert*-butyl hydroperoxide (2.5 equiv) in the presence of powdered molecular 3-Å molecular sieves in methylene chloride (0.2 M, −25 °C, 72 h) with a workup involving saturated sodium sulfate according to Sharpless, K. B.; Hanson, R. M. *J. Org. Chem.* **1986**, *51*, 1922. Recrystallization from ether/pentane (−25 °C) provides enantiomerically pure epoxide with identical properties to 1 reported in the Experimental Section.

(7) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *197*, 5.

(8) Mori, K.; Iwasawa, H. *Tetrahedron* **1980**, *36*, 87.

(9) (a) Weidenhagen, R.; Wegner, H. *Chem. Ber.* **1939**, *72*, 2010. (b) Whistler, R. L.; Linke, E. G.; Kazeniac, S. J. *J. Am. Chem. Soc.* **1956**, *78*, 4704. (c) D-Erythronolactone is commercially available from Fluka Chemical Corporation.

0022-3263/91/1956-6225$02.50/0

Scheme I

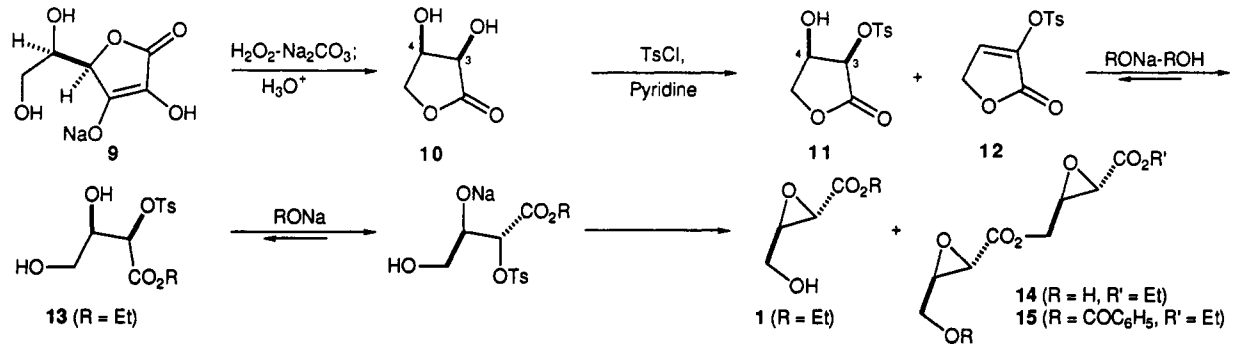
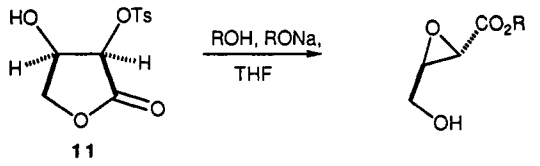


Table I. (2*S*,3*R*)-4-Hydroxyl-2,3-epoxybutyrates from Tosylate 11



R=	Compound number=	Yield =
CH_3	16	94%
$CH_2C_6H_5$	17	90%
$CH_2CH{=}CH_2$	18	93%
$CH_2CH_2CH(CH_3)_2$	19	92%
$CH_2CH_2OCH_3$	20	70%

(87–94% yield). Selective tosylation[11] of **10** at the C-3 OH with 1.06 equiv of *p*-toluenesulfonyl chloride (*p*-TsCl) in pyridine provided tosylate **11** (82-86%). In all systems examined, the primary impurity was lactone **12**. Empirically the corresponding ditosylate of **11** was never isolated. At low conversions the ratio of **11**:**12** appeared to be >95:5, reflecting the possibility that **12** arose from slow tosylation of the C-4 OH of **11** followed by rapid, base-catalyzed elimination of the C-4 tosyloxy group. Treatment of **11** with excess of *p*-TsCl resulted in the formation of **12**, which was consistent with the above pathway. Formation of byproduct **12** was in 10–15% yield under homogeneous reaction conditions but was minimized to <5% by utilization of conditions that allowed direct crystallization of **11** from the reaction medium (see Experimental Section).

In accordance with our expectations, ethanolysis of **11** with catalytic amounts of sodium ethoxide in ethanol[12a] provided the unstable hydroxy ester **13**. This intermediate partially relactonized upon attempted isolation. However, direct addition of 1 equiv of sodium ethoxide provided **1** as a stable, crystalline solid after a nonaqueous workup. Use of more than 1 equiv of ethoxide, relatively concentrated solutions, or prolonged reaction periods led to substantial amounts of dimer **14**[12b] (characterized as the benzoate **15**). A series of related epoxy esters were prepared in good to excellent yield by reaction of **11** with appropriate alkoxides (Table I). Limitations of the rearrangement of **11** into the corresponding epoxide are apparently defined by the pK_a of the reacting alcohol (approximately 16–18), as alcohols of lower pK_a[12a] fail to open the lactone and to close the hydroxy ester at a reasonable rate compared to that of the epoxide.[12]

Methodology presented herein has provided an effective approach to the synthesis of a variety of alkyl (2*S*,3*R*)-4-hydroxy-2,3-epoxybutyrates, which are useful starting materials for the synthesis of carbacephems.

Experimental Section[15]

Dihydro-3(*R*),4(*R*)-dihydroxy-2(3*H*)-furanone (10). According to the procedure of Cohen,[10a] D-isoascorbic acid (704 g) in water (10 L, 4 °C) was sequentially treated with sodium carbonate (848 g over 30 min; conversion to **9**), hydrogen peroxide (CAUTION,[10b] 30%, 880 mL over 1 h; exotherm from 5 to 35 °C; warmed to 40 °C for 30 min), and Darco G-60 (160 g in portions, 0–4 °C, then 25 °C). After observing a negative peroxide test, the mixture was filtered through Celite (2-L boiling water wash), treated with 6 N hydrochloric acid (2.1 L, pH 1.5), and concentrated to dryness under vacuum (45–50 °C). The solid was extracted with boiling ethyl acetate (5 × 3 L portions). These combined extracts were concentrated in vacuo, treated with diethyl ether[10c] (2 L), filtered, affording D-erythronolactone[10d] (436g, 94%), which was suitable for further use: mp 101–103 °C (lit.[10a] mp 97.5–99 °C; lit.[9a] mp 104–105 °C); $[\alpha]^{25}_D$ −73° (*c* 1.00, H_2O) (lit.[9a] $[\alpha]^{25}_D$ −73.2° (*c* 0.533, H_2O)).

Dihydro-3(*R*)-[[(4-methylphenyl)sulfonyl]oxy]-4(*R*)-hydroxy-2(3*H*)-furanone (11). Diol **10** (50.0 g, 0.42 mol) was treated with *p*-TsCl (85.5g, 0.445 mol) in pyridine (210 mL, −26 °C, 28 h) after which **11** was filtered from the reaction and the filtrate returned to the cooling bath (−26 °C, 48 h). Isolated **11** from above was carefully washed with water (300 mL) and dried (80.8 g). The first-crop filtrate was concentrated (<25 °C, 5 mm) to 90 mL, diluted with water (1.5 L, 0 °C), and filtered. This dried material (26.1 g) was recrystallized from ethyl acetate (260 mL), affording additional **11** (14.6 g; combined yield 84%): mp 181–184

(10) (a) Cohen, N.; Banner, B. L.; Lopresti, R. J.; Wong, F.; Rosenberger, M.; Liu, Y. Y.; Thom, E.; Liebman, A. A. *J. Am. Chem. Soc.* **1983**, *105*, 3661. (b) This procedure is a minor variation of the full account by N. Cohen, B. L. Banner, A. J. Laurenzano, and L. Carozza; CAUTION statements should be observed. See: *Organic Syntheses*; Saucy, G., Ed.; John Wiley & Sons: 1985; Vol. 63, p 127. (c) We acknowledge Mr. Jeff Ward for this process modification.

(11) After submission of this paper, an account noting similar observations with acyclic *threo*-2,3-dihydroxy esters appeared: Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869 and references therein.

(12) (a) Unpublished work with Mr. Jeff Ward suggests that trifluoroethanol, trichloroethanol, phenol, and thiophenol failed to provide the expected epoxide under the conditions described herein. (b) We especially thank Mr. Ward for preparing **1** containing these impurities. (c) The use of ethanol denatured with methanol must be avoided because of facile transesterification of **1**.

(13) The enantiomeric excess can be determined on 1-naphthyl carbamate derivatives (obtained by reaction of the epoxides with 1-naphthyl isocyanate catalyzed by dibutyltin diacetate) by HPLC analysis on a 25-cm Chiralcel OD column with 40% hexane in isopropyl alcohol as eluent at 290 nm, 25 °C with a flow rate of 1 mL/min. Weigel, L. O.; Kennedy, J. H. *Chirality*. Submitted for publication.

(14) For large-scale preparations, sodium erythorbate can be converted into **1** without isolation or purification of the diol or tosylate.

(15) Unless noted otherwise physical data were gathered under the following conditions: $^1H/^{13}C$ NMR QE300 at 300/75.5 MHz, respectively (only characteristic proton data) (*J* values are in hertz); melting points (uncorrected), Thomas Hoover Uni-melt; HPLC, Hatachi L6200 with L4000 Detector and D2500 Chromato-Integrator at 230 nm on a Zorbax RX column at 1.0 mL/min with methanol/triethylamine/water/ammonium acetate (40:40:1:1, v/v/wt/wt then pH to 7 with acetic acid); FTIR, Nicolet 510P; optical rotations, Perkin Elmer 241 (10 mg/mL); FD mass spectra, Varian Matt 731; TLC, silica gel 60 F_{254} (0.25 mm) using ethyl acetate–hexane–methanol (5:5:1) with a Shimadzu CS-930 Scanner (255 or 520 nm with development using phosphomolybdic acid); elemental analysis, CEC 440; reaction solvents employed were dry (<0.05% water by KF titration). Sodium alkoxide solutions were prepared in a safe manner (−78 °C to 25 °C under nitrogen) from the alcohol, using 60% sodium hydride (CAUTION) and were titrated before use.

°C; R_f 0.36; $[\alpha]^{25}_D$ −13.2° (c 1.00, pyridine); IR (KBr) 1782, 1773; MS, 272 (M^+); ^1H NMR (DMSO-d_6) 7.79 (2 H, d, J = 9), 7.50 (2 H, d, J = 9), 5.96 (1 H, br, D_2O exchanges), 5.51 (1 H, d, J = 4.5), 4.39 (1 H, dd, J = 2.5, 8), 4.31 (1 H, dd, J = 2.5, 4.5), 4.13 (1 H, d, J = 8), 2.43 (3 H, s); ^{13}C (DMSO-d_6) 170.3, 145.3, 132,5, 130.0, 127.8, 75.1, 72.9, 67.1, 21.0. Anal. Calcd for $C_{11}H_{12}O_6S$: C, 48.52; H, 4.44; S, 11.78. Found: C, 48.74; H, 4.51; S, 12.00.

Chromatography of the mother liquors from **11** on silica gel (ethyl acetate–hexane) and recrystallization from ethyl acetate afforded **12**: mp 119–122 °C; R_f 0.46; IR 1781; MS 255 (M^+ + 1); ^1H NMR 7.82 (2 H, d, J = 7), 7.39 (2 H, d, J = 7), 7.24 (1 H, dd), 4,86 (2 H, dd), 2.43 (3 H, s); ^{13}C NMR 165.9, 146.6, 137.3, 132.0, 130.18, 128.6, 67.5, 21.8. Anal. Calcd for $C_{11}H_{10}O_6S$; C, 51.96; H, 3.96; S, 12.61. Found: C, 52.04; H, 3.93, S, 12.38.

Ethyl 4-Hydroxy-2(*S*),3(*R*)-epoxybutyrate (1). As a slurry, tosylate **11** (25.0g) in absolute ethanol[12c] and tetrahydrofuran (430 mL/75 mL, respectively) was treated with sodium ethoxide (12.2 mL of 0.82 N in ethanol, 0 °C, over 2 h) after which the solution became homogeneous and TLC indicated the presence of **13** (R_f 0.21). Additional ethoxide solution (101 mL over 30 min, −30 °C) was added. After 2 h the reaction was quenched with acetic acid (0.7 mL, pH = 7). All volatiles were evaporated (<25 °C, 5 mm) and the solids treated with ethyl acetate–hexane (2:1, 200 mL). Gravity filtration of one-half of this mixture thru silica (100 g, 230–400 mesh) using hexane and then ethyl acetate–hexane as eluent afforded chromatographically pure **1** (6.43 g, 95%). Alternatively, the remaining half was filtered, volatiles were removed under vacuum, and the material was recrystallized from ether–hexane, affording pure **1** (6.16 g, 91%): R_f 0.35; mp 47–49 °C (lit.[3a] mp *ent*-**1**, 45–46 °C); $[\alpha]^{25}_D$ +33.1° (c 1.00, ethanol) (lit.[3a] *ent*-**1**, $[\alpha]^{20}_D$ −33.8° (c 1.00, ethanol)); IR 1743, 1210; MS, 147 (M^+ +1); HPLC analysis[13] >99% ee; ^1H NMR ($CDCl_3$–D_2O) 4.24 (2 H, m), 3.96 (1 H, dd, J = 2, 12), 3.73 (1 H, dd, J = 4, 12), 3.54 (1 H, d, J = 1), 3.38 (1 H, ddd, J = 1, 2, 4); ^{13}C NMR 14.1, 50.3, 58.0, 60.2, 61.8, 169.08. Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.23; H, 6.85.

If an excess of ethoxide was employed compound **14** was isolated (>5%) by silica gel chromatography (R_f 0.30) and was characterized by benzoylation (1 equiv of benzoyl chloride in dry methylene chloride with 1.2 equiv of pyridine), affording **15**: mp 99–102 °C; R_f 0.87; $[\alpha]^{25}_D$ +63° (c 1.00, MeOH); IR 1748, 1726; MS 350 (M^+); ^1H NMR 3.58 (1 H, d, J = 1.5), 3.43 (2 H, d, J = 1.5), 1.31 (3 H, t, J = 7); ^{13}C NMR 167.84, 165.95, 133.47, 119.80, 129.26, 128.53, 63.89, 62.82, 64.00, 55.40, 54.44, 50.83, 50.59, 14.07. Anal. Calcd for $C_{17}H_{18}O_8$: C, 58.28; H, 5.18. Found: C, 58.49; H, 5.31.

Methyl 4-hydroxy-2(*S*),2(*R*)-epoxybutyrate (16) was prepared from **11** (10 g in 1:4 tetrahydrofuran–methanol, 150 mL, −10 to −25 °C), using sodium methoxide in methanol (8.0 mL, 25% wt, Aldrich), affording **16** (4.88g, 91%) after silica gel filtration as above: mp 19–20 °C; R_f 0.29; $[\alpha]^{25}_D$ +36.9° (c 1, MeOH); IR 1748; MS 132 (M^+); ^1H NMR (MeOH-d_4) 3.82 (1 H, dd, J = 4, 12), 3.76 (3 H, s), 3.62 (1 H, dd, J = 4,12), 3.51 (1 H, d, J = 1), 3.27 (1 H, m); ^{13}C NMR 169.41, 60.08, 58.00, 52.59, 50.07. Anal. Calcd for $C_5H_8O_4$; C, 45.46; H, 6.10. Found: C, 45.57; H, 6.14.

Benzyl 4-hydroxy-2(*S*),3(*R*)-epoxybutyrate (17) was prepared from 31.5 g of **11** in benzyl alcohol (312 g) and THF (500 mL) as above, affording **17** (90%) after chromatography (Waters Prep 500): mp: 39–42 °C; R_f 0.42; $[\alpha]^{25}_D$ +22.4° (c 1.00, $CHCl_3$); IR 3599 (nonbonded), 1748; UV 258 (230), 208 (7900); MS 208 (M^+); ^1H NMR 7.36 (5 H, s), 3.56 (1 H, d, J = 1); ^{13}C NMR 168.84, 135.00, 128.63; 128.48, 67.38, 60.04, 58.07, 50.16. Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45: H, 5.81. Found: C, 62.23; H, 5.73.

Allyl 4-hydroxy-2(*S*),3(*R*)-epoxybutyrate (18) was prepared from **11** (2.30 g) in allyl alcohol (58 g) and THF (50 mL, −25 °C) with sodium allyloxide (68.2 mL, 0.124 M), affording **18** (1.24 g, 93%) after silica gel filtration: R_f 0.38; $[\alpha]^{25}_D$ +27.4° (c 1, $CHCl_3$); IR 1748, 1197; ^1H NMR 5.91 and 5.32 (3 H, m), 4.68 (2 H, m), 3.98 (1 H, dd, J = 2, 11). 3.68 (1 H, J = 4, 11), 3.77 (2 H, J = 2), 3.42 (1 H, m); ^{13}C NMR 168.5, 131.3, 119.3, 66.2, 60.1, 57.9, 50.1. Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.78; H, 6.18.

3-Methylbutyl 4-hydroxy-2(*S*),2(*R*)-epoxybutyrate (19) was prepared from **11** (20.0 g) isoamyl alcohol–THF (38:62, w/w) at −9 to −17 °C with sodium isoamylate (0.34 M, 205 mL), affording **19** (12.64 g, 92%): R_f 0.48; $[\alpha]^{25}_D$ = +22.4° (c 1.00, MeOH); IR, 1743; MS, 189 (M^+ + 1); ^1H NMR ($CDCl_3$ + D_2O) δ 3.96 (1 H, dd, J = 2,12), 3.80 (1 H, dd, J = 4, 12); ^{13}C NMR δ 169.18, 64.56, 60.22, 58.08, 50.29, 37.21, 25.08, 22.51, 22.48. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43, H, 8.57. Found: C, 57.64, H, 8.46.

2-Methoxyethyl 4-hydroxy-2(*S*),3(*R*)-epoxybutyrate (20) was prepared from **11** (13 g) in 2-methoxyethanol (400 mL), using sodium 2-methoxyethanolate (0.65 M, 74 mL, −20 °C), affording **20** (5.89 g, 70%) after flash chromatography: R_f 0.30; $[\alpha]^{25}_D$ +27.1° (c 1.00 $CHCl_3$); IR 1750, 1227; MS 177 (M^+ + 1); ^1H NMR ($CDCl_3$ + D_2O) 3.96 (1 H, dd, J = 4, 12), 3.74 (1 H, dd, J = 4, 12), 3.40 (3 H, s); ^{13}C NMR 168.9, 70.1, 64.6, 60.1, 59.0, 58.1, 50.1. Anal. Calcd for $C_7H_{12}O_5$: C, 47.73; H, 6.87. Found: C, 47.51; H, 6.71.

Acknowledgment. We thank Prof K. B. Sharpless for helpful suggestions and comments in advance of publication of his work. We also thank co-workers mentioned in refs 1c and 2b for gainful insights and the Molecular Structure Division of Eli Lilly and Company.

Fine-Tuned Remote Control of Electrophilic Additions to Substituted Norbornenes

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The chemistry of bicyclo[2.2.1]heptane derivatives continues to attract considerable attention both from mechanistic[1] and synthetic standpoints.[2] Recent developments in the preparation of optically pure norbornenes by asymmetric Diels–Alder processes[3] as well as by enzymatic protocols[4] should render these intermediates even more ubiquitous in organic synthesis, especially if new regio- and stereocontrolled functionalizations are developed. While the outcome of the electrophilic additions of sulfur and selenium halides to ketone **1** and its cyanoacetoxy precursor **2** have been thoroughly studied.[5,6] other simple norbornenic substrates such as compounds **3–10** (Scheme I) have not be examined. In connection with our involvement in the chemistry of bicyclic compounds, particularly oxanorbornenic derivatives[7] we undertook the research described here in parallel to a previous report.[7c]

Readily available norbornenic substrates **3–10**[8] (Scheme I) were selected for this study. Based upon previous knowledge on these processes,[5–7,9] we anticipated that endo-substituted systems **3–5** and **10** would allow for complete steric control producing exclusively adducts arising from endo attack of the nucleophile on C-5 (A, Table I). Alternatively, exo-substituted substrates **6** and **7** were expected to display some regioselectivity in favor of the opposite isomers **B** possibly due to electronic reasons.[10] Hydroxymethyl derivatives **8** and **9**, on the other hand, were expected to show a small selectivity in favor of isomers A.[7c] However, we guessed that the substitution of an oxygen bridge for a methylene could alter the selectivity of these processes, especially for exo-substituted substrates free of strong endo steric requirements, and therefore governed by a delicate interplay of steric and electronic effects. Table I gathers the results obtained in the course of this study.

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