it is of the same order of magnitude as the unprotonated heterocyclic nitrogen ($\sigma_p \approx 0.9$)[8] and the overall regioselectivity is lower in the latter case.

Compared with alkylation,[9] in which monosubstitution is due to polar deactivation and increased lipophilicity of the alkylated product, monoacylation is favored in a two-phase system by the combination of decreased basicity and increased lipophilicity of the acylated product, with elimination or minimization of the effects of polar activation.

In comparison with the method we had previously[3] developed using aldehydes as the source of acyl radicals, this process must be considered the method of choice for the selective acylation of heteroaromatic bases.

Experimental Section

The heteroaromatic bases and the α-keto acids were commercial products. All reaction products were identified by comparison (GLC, NMR, MS, IR) with authentic samples.[3]

General Acylation Procedure. A mixture of heteroaromatic base (2.5 mmol), α-keto acid (7.5 mmol), $AgNO_3$ (0.2 mmol), $NH_4S_2O_8$, and CF_3COOH or H_2SO_4 in the amounts given in Tables I–V in 25 mL of water and 25 mL of CH_2Cl_2 was stirred for 2 h at 40 °C. The aqueous solution was made basic with NaOH, the organic solvent was separated, and the aqueous solution was further extracted with CH_2Cl_2. The extract was analyzed by GLC by the procedure previously reported.[3] The reaction products were isolated by flash chromatography (eluant hexane:ethyl acetate = 5:1).

The same procedure was used for reactions in the absence in CH_2Cl_2. The results are reported in Tables I–V.

Lepidine, quinaldine, and 4-cyanoquinoline were acylated under the conditions of Table I, entry 9. Conversions were complete, and only the products of monoacylation at positions 2 and 4 were observed by GLC when using pyruvic and benzoylformic acids as sources of acetyl and benzoyl radicals. The products were isolated by flash chromatography (80–90% yield) and identified by comparison with authentic samples.

Acknowledgment. We gratefully acknowledge the financial support of the Progetto Finalizzato Chimica Fine 2, C.N.R.

(8) Jaffé, H. H. *J. Chem. Phys.* **1952**, *20*, 1554.
(9) Fontana, F.; Minisci, F.; Nogueira Barbosa, M. C.; Vismara, E.; *Tetrahedron* **1990**, *46*, 2525.

Selective Transformations of *threo*-2,3-Dihydroxy Esters

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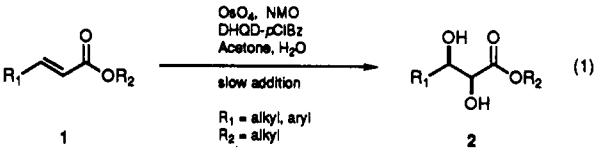
Two highly regio- and stereoselective transformations of *threo*-2,3-dihydroxy esters have been developed. In the first reaction, the α-hydroxy group is converted into a sulfonate group (tosylate or nosylate); the α-tosylates and α-nosylates are then subjected to basic conditions (K_2CO_3/ROH) to give erythro glycidic esters in high yield. The α-nosylates are also suitable electrophiles for azides, giving access to *erythro*-α-azido-β-hydroxy esters. The second reaction involves conversion of the diol esters to acetoxy bromo esters. The β-substituent plays a key role in determining the regiochemistry since cases with β-alkyl substituents afford β-acetoxy-α-bromo esters exclusively, whereas a β-phenyl substituent directs formation of the α-acetoxy-β-bromo ester. The acetoxy bromo esters can subsequently be converted to the threo glycidic esters (via the bromohydrin esters); selective hydrogenolysis of the bromine substituent can also be achieved.

Introduction

The catalytic asymmetric dihydroxylation (ADH) of olefins allows access to a wide variety of vicinal diols of high enantiomeric purity.[1] Efforts in our laboratories have been directed toward the synthetic elaboration of these optically pure diols. Previous work has shown that cyclic sulfates derived from diols are good epoxide-like synthons.[2]

The α,β-unsaturated esters are good substrates for the ADH process, with enantiomeric excesses (ee's) ranging from 67 to 86%.[3] They are easily prepared in high yield by using our catalytic system employing OsO_4, dihydroquinidine *p*-chlorobenzoate (DHQD–*p*ClBz) as the chiral auxiliary and *N*-methylmorpholine *N*-oxide (NMO) as the stoichiometric oxidant (eq 1). As with any synthetic methodology, its value is largely determined by the utility



(1)

of the products. The goal of this study was to determine to what extent the diol esters could be transformed selectively into synthetically advanced and useful intermediates.

Results and Discussion

The first selective reaction attempted was the conversion of one hydroxyl group into a leaving group (sulfonate). Probably because of the difference in acidity of the two hydroxyl groups, selective sulfonylation can be performed; the more acidic α-hydroxyl group reacts preferentially to form the monosulfonate.[4] Diol esters were regioselectively

(1) (a) Lohray, B. B.; Kalantar, T. H.; Kim, B. M.; Park, C. Y.; Shibata, T.; Wai, J. S. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2041. (b) Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G. Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123. (c) Kwong, H.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 2999.
(2) (a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538. (b) Lohray, B. B.; Gao, Y.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2632. (c) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655.
(3) The ee's range from 73 to 91% using potassium ferricyanide as the stoichiometric oxidant (see ref 1c).
(4) (a) The effect of a neighboring carbonyl group on the acidity of an alcohol can be quite dramatic, as α-hydroxy ketones have pK_a values of 11–12 and are readily titrated in water (Masamune S., private communication). (b) An example of this selective sulfonylation has recently been reported by Greene and co-workers. Denis, J.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957. (c) During the preparation of this manuscript another selective sulfonylation appeared in the literature. Watson, K. G.; Fung, Y. M.; Gredley, M.; Bird, G. J.; Jackson, W. R.; Gountzos, H.; Matthews, B. R. *J. Chem. Soc., Chem. Commun.* **1990**, 1018.

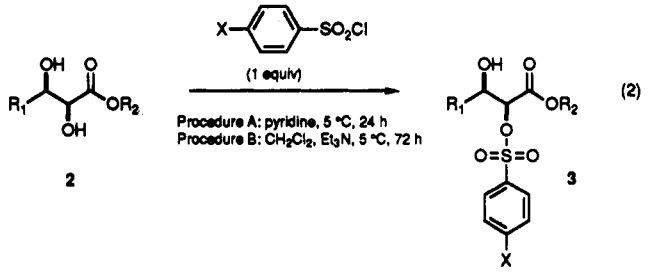
0022-3263/91/1956-2869$02.50/0

Table I. Synthesis of α-(Sulfonyloxy)-β-hydroxy Esters 3

entry	hydroxy sulfonate ester 3	R_1	R_2	X	method[a]	yield[b] (%)
1	**3a**	CH_3	CH_3	CH_3	B	54
2	**3b**	CH_3	CH_3	NO_2	B	58
3	**3c**	n-C_5H_{11}	CH_3	CH_3	A	48
4	**3d**	n-C_5H_{11}	CH_3	NO_2	A	80
5	**3e**	c-C_6H_{11}	C_2H_5	CH_3	B	72
6	**3f**	c-C_6H_{11}	C_2H_5	NO_2	B	91
7	**3g**	Ph	CH_3	CH_3	B	76
8	**3h**	Ph	CH_3	NO_2	B	57
9	**3i**	p-MeOPh	CH_3	CH_3	B	75
10	**3j**	p-MeOPh	CH_3	NO_2	A	74

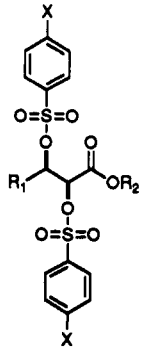
[a] Reactions were performed by procedure A or B as described in the Experimental Section. [b] Isolated yields.

sulfonylated using standard conditions as outlined in eq 2. The monotosylates and mononosylates are readily

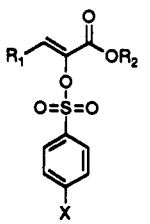


prepared by this method (Table I).

The best yields obtained approach the 70–90% range. In all cases no ^1H NMR signals corresponding to mono-β-sulfonates were observed. Side product formation occurs to a small extent. The two side products observed in the crude ^1H NMR are the bissulfonate esters **4** and the α-(sulfonyloxy)-α,β-unsaturated ester **5**. The double bond geometry of **5** is tentatively assigned as shown based on ^1H NMR shifts of the β-vinyl proton which appear around 6.7 ppm for the vinyl sulfonates with R_1 = alkyl. It is felt that these products arise from the initially formed α-(sulfonyloxy)-β-hydroxy esters, since no mono-β-sulfonates are observed. The vinyl sulfonate esters **5** presumably arise from elimination of the bissulfonates. The amount of these undesired side products produced can be decreased, but not eliminated, by keeping the reaction mixture dilute. It is best to run the reaction at 0.2–0.3 M or less in diol ester since higher concentrations lead to greater proportions of the side products. The side products **4** and **5** are less polar than **3** and are easily separated from **3** by flash column chromatography. For example, in the monotosylation reaction of (2*S*,3*R*)-(+)-methyl 2,3-dihydroxyoctanoate (entry 3, Table I) the bissulfonate **4a** (R_f = 0.28 in 30% EtOAc/Hex), vinyl sulfonate **5a** (R_f = 0.41 in 30% EtOAc/Hex), and monosulfonate **3c** (R_f = 0.19 in 30% EtOAc/Hex) were isolated in 8, 6, and 48% yield, respectively, by using a gradient of 20–75% EtOAc/Hex as the eluant.[5] In the mononosylation reactions, no bisnosylates are observed in the crude ^1H NMR; the vinyl nosylates are the only side products formed. The mononosylation reaction of (2*S*,3*R*)-(+)-methyl 2,3-dihydroxyoctanoate (entry 4, Table I) gives the corresponding vinyl sulfonate **5b** (R_f = 0.48 in 30% EtOAc/Hex) and monosulfonate **3d** (R_f = 0.22 in 30% EtOAc/Hex) in 11 and 80% yields, respectively, after chromatography using a gradient of 20–75% EtOAc/Hex.[6] Finally, the mono-α-sulfonates **3a** and **3b** appeared to rearrange to a small extent to afford the mono-β-sulfonates when the crude product was stored at 0 °C before chromatographic purification. To insure that rearrangement does not occur, it is best to purify the crude product mixture as soon as possible. In pure form, the α-(sulfonyloxy)-β-hydroxy esters are crystalline compounds that are stable indefinitely at room temperature.



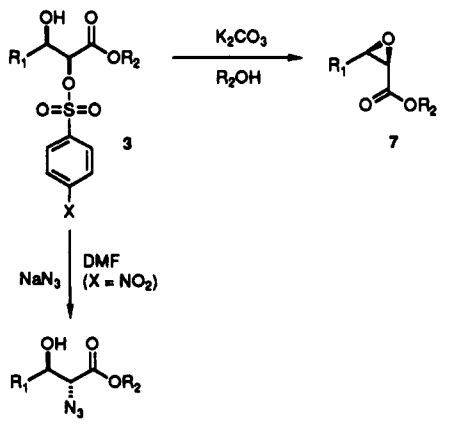
4a: R_1 = n-C_5H_{11}, R_2 = CH_3, X = CH_3



5a: R_1 = n-C_5H_{11}, R_2 = CH_3, X = CH_3

5b: R_1 = n-C_5H_{11}, R_2 = CH_3, X = NO_2

These α-(sulfonyloxy)-β-hydroxy esters show wide utility as synthetic intermediates. They are smoothly converted to the corresponding glycidic esters under basic conditions (K_2CO_3/ROH) in high yield (eq 3). This represents a facile synthesis of enantiomerically enriched erythro glycidic esters.



(3)

For example, monotosylate **3e** was converted to β-cyclohexyl epoxy ester **7** in 86% yield. The nosylates un-

(5) Characteristic ^1H NMR (300 MHz, $CDCl_3$) data for **4a**: δ 4.99 (d, J = 3.5 Hz, H_α), 4.91 (m, 1 H, H_β). **5a**: δ 6.71 (t, J = 7.7 Hz, 1 H, H_β).
(6) Characteristic ^1H NMR (300 MHz, $CDCl_3$) data for **5b**: δ 6.77 (t, J = 7.9 Hz, 1 H, H_β).

Table II. Azide Displacement Reactions[a]

entry	hydroxy sulfonate ester	nucleophile	reaction conditions	yield[b] (%)
1	**3b**	LiN_3	DMF/47 °C/67 h	49
2	**3d**	NaN_3	DMF/50 °C/16 h	77
3	**3f**	NaN_3	DMF/50 °C/21 h	54
4	**3e**	NaN_3	DMF/55 °C/16 h	71[c]

[a] Reactions were performed as described in the Experimental Section. [b] Isolated yields. [c] Afforded a 21:1 (erythro:threo) mixture of diastereomers at C-2.

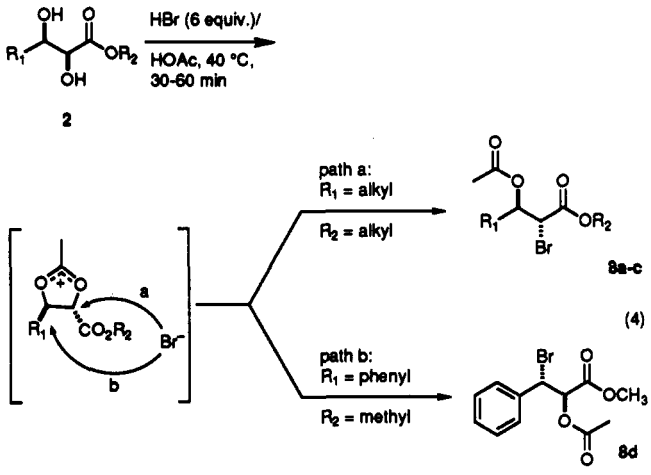
Table III. Synthesis of Acetoxy Bromo Esters[a]

entry	acetoxy bromo ester	R_1	R_2	yield[b] (%)
1	**8a**	CH_3	CH_3	72
2	**8b**	n-C_5H_{11}	CH_3	79
3	**8c**	c-C_6H_{11}	C_2H_5	88
4	**8d**	Ph	CH_3	96

[a] Reactions were performed as described in the Experimental Section. [b] Isolated yields.

dergo displacement with NaN_3 to give the α-azido-β-hydroxy esters, precursors to β-hydroxy amino acids (eq 3).[7] Both reaction sequences are convenient, short (2 steps from the diol esters), and afford useful synthetic intermediates.

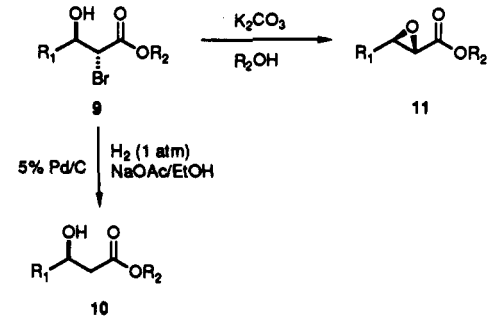
Another way to differentiate the diol esters is by treatment with 30%-by-weight HBr in acetic acid to form the acetoxy bromo esters.[8] This transformation proceeds via a cyclic acetoxonium ion which is opened stereospecifically with inversion by bromide ion. Diol esters possessing β-alkyl substituents produce *erythro*-β-acetoxy-α-bromo esters regioselectively. The carbonyl group must be responsible for the increased reactivity of the α-position in these substrates.[9] Interestingly, if the β-carbon is activated by a phenyl group, the *erythro*-α-acetoxy-β-bromo ester is formed (eq 4). The reaction is



(4)

general for these substrates and the acetoxy bromo esters are formed in good yield (Table III).

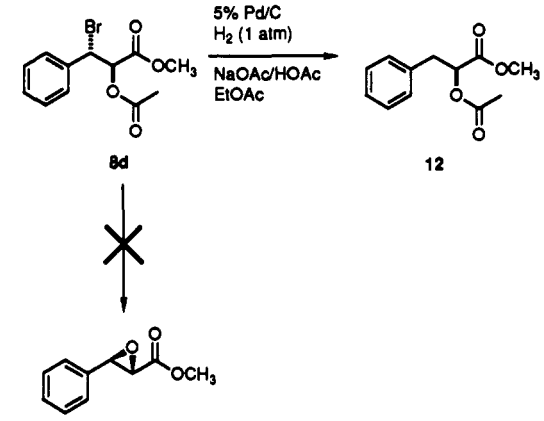
In the alkyl series, the desired synthetic intermediates are the bromohydrins derived from the acetoxy bromides. They are closed under basic conditions (K_2CO_3/ROH) to provide the *threo*-epoxy esters in high yield (eq 5).



(5)

The bromide group, although not a sufficiently active leaving group to be cleanly displaced by nucleophiles, is easily hydrogenolyzed under standard conditions (1 atm of H_2, 5% Pd/C, NaOAc, EtOH) to afford the β-hydroxy ester.[10]

Although the α-acetoxy-β-bromide **6d** is readily hydrogenolyzed, it decomposed upon treatment with acid or base, making the *threo*-β-phenyl epoxy ester inaccessible (eq 6).



(6)

Although the cyclic sulfate, the selective sulfonylation, and the acetoxy bromination methodologies all constitute selective elaborations of the diols, they differ in the stage at which the hydroxyls are differentiated. With sulfonylation, the differing acidities allow one of the two hydroxyls to be converted to a leaving group at the outset. Subsequent steps make use of the difference between the two centers. Likewise, treatment with HBr/HOAc effectively differentiates the two hydroxyl groups. The sulfonylation and HBr/HOAc reactions complement each other as the *erythro*- and *threo*-epoxy esters are available from the same diol ester. Cyclic sulfate formation is not selective, as both hydroxyl groups are incorporated into the sulfate ring; differentiation of the hydroxyls occurs upon attack of a nucleophile (ring opening).

In summary, it has been demonstrated that α,β-dihydroxy esters can be selectively converted into synthetically useful intermediates. The *threo*-β-hydroxy-α-nosylate esters can be converted into *erythro*-α-azido-β-hydroxy esters or ring closed to form the erythro glycidic esters. The former reaction sequence competes well with other methods used to prepare *erythro*-α-amino-β-hydroxy acid precursors and does not require the use of covalently bound chiral auxiliaries.[11] The threo glycidic esters are

(7) (a) For a recent overview see Tetrahedron Symposia-in-Print Number 33, α-Amino Acid Synthesis, O'Donnell, M. J., Ed. In *Tetrahedron* **1988**, *44*, 5253–5605. (b) The α-tosylates are not suitable electrophiles for external nucleophiles; displacement with NaN_3 gave a mixture of epimers at C-2 (Table II, entry 4).

(8) Golding, B. T.; Hall, D. R.; Sakrikar, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1214.

(9) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; p 381 and references cited therein.

(10) Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis*; Wiley-Interscience: New York, 1978; pp 121–123.

obtained easily from the same *threo*-α,β-dihydroxy esters by conversion to the α-bromo-β-hydroxy esters.

The reactions described here further enhance the synthetic utility of the homochiral diol esters now readily available by the ADH process.[12]

Experimental Section

General. Melting points were determined with a Thomas-Hoover capillary melting point apparatus in open glass capillaries; the values are uncorrected. Elemental analyses were performed by Robertson Laboratories, Inc., Madison, NJ. Analytical thin-layer chromatography (TLC) was performed on Merck precoated glass plates (silica gel 60, F-254, 0.25 mm thick). Preparative column chromatography was performed using EM Reagents silica gel 60, 230–400 mesh. High-performance liquid chromatography was carried out on a Perkin-Elmer Series 410 chromatograph equipped with a UV detector using a Pirkle Type I-A preparative column. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.0 MHz) spectra were recorded on a Varian Gemini 300.

All reactions were performed in oven (140 °C) or flame-dried glassware. Pyridine was distilled from CaH_2 and stored over 4-Å molecular sieves; 30%-by-weight HBr/HOAc was obtained from Aldrich Chemical Co. and was used without further purification. All commercially obtained reagents were purified by distillation or recrystallization before use.

Enantiomeric excesses were determined as follows: compounds **3a–j** were analyzed by ^{1}H NMR as a solution in $CDCl_3$ in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) derivative, the bisacetates of *threo*-methyl 2,3-dihydroxy-3-phenylpropionate and *threo*-methyl 2,3-dihydroxy-3-(*p*-methoxyphenyl)propionate were analyzed by HPLC (Pirkle Type I-A preparative column, 10% *i*-PrOH/Hex, 1.0 mL/min), and the bis-Mosher ester of *threo*-methyl 2,3-dihydroxybutanoate was analyzed by HPLC (Chemcopak Chemcosorb 3Si analytical column, 10% EtOAc/Hex, 1.0 mL/min).

General Protocol for the Preparation of Monosulfonate Esters. Procedure A. The diol ester was placed in a screw cap vial (convenient for small to moderate scale reactions), cooled to 0 °C (ice–water bath), and enough dry pyridine was added by syringe to make the solution 0.3 M in diol–ester. After 10 min the arenesulfonyl chloride (1.0 equiv) was added in one portion by means of a solid addition funnel. The vial was then capped and placed in a refrigerator (5 °C) for 24 h. The reaction was quenched by the addition of ice chips followed by cold water. The crude reaction mixture was then transferred to a separatory funnel and extracted three times with Et_2O. The combined organic phases were washed three times with a saturated aqueous $CuSO_4$ solution followed by one water wash. The organic layer was then dried ($MgSO_4$), filtered, and concentrated to afford the crude product mixture, which was purified by flash column chromatography.

Procedure B. To a one-neck round-bottomed flask were added the diol ester, CH_2Cl_2 (enough to make the solution 0.2 M in diol–ester), and Et_3N (1.5 equiv). The flask was placed in an ice–water bath and allowed to equilibrate for 10–30 min, at which time the arenesulfonyl chloride (1.0 equiv) was added in one portion using a solid addition funnel. The flask was fitted with a serum cap and placed in a refrigerator (5 °C) for 72 h. The mixture was then concentrated to afford a paste which was dissolved in either Et_2O or EtOAc. The organic phase was washed three times with a 1 N aqueous HCl solution, once with a saturated aqueous $NaHCO_3$ solution, and once with brine, dried ($MgSO_4$), and concentrated to afford the crude product mixture, which was purified by flash column chromatography.

(2*S*,3*R*)-(−)-Methyl 3-Hydroxy-2-((*p*-tolylsulfonyl)oxy)butanoate (3a). According to procedure B, enantiomerically enriched (2*S*,3*R*)-(−)-methyl 2,3-dihydroxybutanoate (0.418 g, 3.12 mmol, 63% ee), Et_3N (660 μL, 4.74 mmol), tosyl chloride (0.596 g, 3.13 mmol), and CH_2Cl_2 (16 mL) were combined to afford 0.687 g of a colorless oil. Purification by column chromatography (silica gel, 40% Et_2O/Hex, then Et_2O) afforded **3a** (0.485 g, 1.68 mmol, 54% yield, 62% ee) as white crystals: mp 90–91 °C; $[\alpha]^{23}_D$ −29° (*c* 0.2, absolute EtOH); IR (KBr pellet) 3490, 3246, 2975, 1761, 1596, 1372, and 1138 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 4.74 (d, *J* = 3.9 Hz, 1 H), 4.16 (m, 1 H), 3.65 (s, 3 H), 2.43 (s, 3 H), 2.01 (d, *J* = 8.0 Hz, 1 H), and 1.20 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 167.8, 145.4, 132.7, 129.8, 128.1, 80.8, 67.3, 52.3, 21.2, and 18.3. Anal. Calcd for $C_{12}H_{16}O_6S$: C, 49.99; H, 5.59. Found: C, 49.88; H, 5.42.

(2*S*,3*R*)-(−)-Methyl 3-Hydroxy-2-(((*p*-nitrophenyl)sulfonyl)oxy)butanoate (3b). According to procedure B, enantiomerically enriched (2*S*,3*R*)-(−)-methyl 2,3-dihydroxybutanoate (0.416 g, 3.10 mmol, 63% ee), Et_3N (650 μL, 4.66 mmol), nosyl chloride (0.691 g, 3.11 mmol), and CH_2Cl_2 (16 mL) gave 0.743 g of crude product, which was purified by column chromatography (silica gel, 40% Et_2O/Hex, then Et_2O) to give **3b** (0.578 g, 1.81 mmol, 58% yield, 61% ee) as white crystals: mp 91–92 °C; $[\alpha]^{24}_D$ −15° (*c* 1.0, absolute EtOH); IR (KBr pellet) 3529, 2357, 1735, and 1683 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 9.0 Hz, 2 H), 8.13 (d, *J* = 9.0 Hz, 2 H), 4.86 (d, *J* = 3.4 Hz, 1 H), 4.24 (m, 1 H), 3.65 (s, 3 H), 2.47 (m, 1 H), 1.23 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 167.4, 151.1, 142.0, 129.7, 124.5, 82.0, 67.5, 52.8, and 18.7. Anal. Calcd for $C_{11}H_{13}NO_8S$: C, 41.38; H, 4.10; N, 4.39. Found: C, 41.47; H, 3.99; N, 4.26.

(2*S*,3*R*)-(−)-Methyl 3-Hydroxy-2-((*p*-tolylsulfonyl)oxy)octanoate (3c). Use of procedure A, enantiomerically enriched (2*S*,3*R*)-(+)-methyl 2,3-dihydroxyoctanoate (0.597 g, 3.14 mmol, ee not determined), pyridine (10 mL), and tosyl chloride (0.597 g, 3.13 mmol) gave 0.950 g of crude material which was chromatographed (silica gel, gradient of 20–75% EtOAc/Hex) to afford 0.51 g of **3c** (1.5 mmol, 48% yield, 70% ee) as white crystals: mp 70–71 °C; $[\alpha]^{24}_D$ −4.9° (*c* 1.4, absolute EtOH); IR (KBr pellet) 2950, 1740, 1653, 1560, 1363, and 1291 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2 H), 7.37 (d, *J* = 8.3 Hz, 2 H), 4.82 (d, *J* = 3.2 Hz, 1 H), 3.98 (m, 1 H), 3.68 (s, 3 H), 2.46 (s, 3 H), 2.43 (d, *J* = 8.4 Hz, 1 H), 1.48–1.41 (m, 4 H), 1.40–1.22 (m, 4 H), and 0.87 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 168.1, 145.4, 132.9, 129.8, 128.1, 79.8, 71.4, 52.3, 32.4, 31.1, 24.5, 22.0, 21.2, and 13.5. Compound **3c** gave incorrect analyses; ^{1}H and ^{13}C NMR spectra are provided as supplementary material as evidence of chemical purity.

(2*S*,3*R*)-(−)-Methyl 3-Hydroxy-2-(((*p*-Nitrophenyl)sulfonyl)oxy)octanoate (3d). According to procedure A, enantiomerically enriched (2*S*,3*R*)-(+)-methyl 2,3-dihydroxyoctanoate (0.595 g, 3.13 mmol, ee not determined), pyridine (10 mL), and nosyl chloride (0.691 g, 3.12 mmol) afforded 1.011 g of crude material which was chromatographed (silica gel, gradient of 20–75% EtOAc/Hex) to afford 0.92 g of **3d** (2.5 mmol, 80% yield, 63% ee) as white crystals: mp 72–74 °C; $[\alpha]^{24}_D$ −21.6° (*c* 1.0, absolute EtOH); IR ($CHCl_3$) 3577, 3055, 2957, 1765, 1534, 1405, 1352, 1261, 1189, 896, and 853 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.9 Hz, 2 H), 8.21 (d, *J* = 8.9 Hz, 2 H), 4.99 (d, *J* = 3.1 Hz, 1 H), 4.08 (m, 1 H), 3.70 (s, 3 H), 3.21 (d, *J* = 8.0 Hz, 1 H), 1.60–1.40 (m, 4 H), 1.27–1.23 (m, 4 H), and 0.86 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 167.6, 150.9, 141.9, 129.6, 124.3, 81.0, 71.3, 52.6, 32.5, 31.0, 24.6, 22.0, and 13.5. Anal. Calcd for $C_{15}H_{21}NO_8S$: C, 47.99; H, 5.64; N, 3.73. Found: C, 47.85; H, 5.58; N, 3.63.

(2*S*,3*R*)-(+)-Ethyl 3-Cyclohexyl-3-hydroxy-2-((*p*-tolylsulfonyl)oxy)propionate (3e). According to procedure B, enantiomerically enriched (2*S*,3*R*)-(−)-ethyl 3-cyclohexyl-2,3-dihydroxypropionate (0.682 g, 3.15 mmol, ee not determined), Et_3N (660 μL, 4.74 mmol), tosyl chloride (0.699 g, 3.67 mmol), and CH_2Cl_2 (18 mL) gave 1.160 g of a colorless oil. Column chromatography (silica gel, 40% Et_2O/Hex, then Et_2O) gave 0.844 g of **3e** (2.28 mmol, 72% yield, 71% ee) as white crystals: mp 75–76 °C; $[\alpha]^{24}_D$ +25.8 (*c* 0.6, absolute EtOH); IR (CCl_4) 3591, 2929, 2880, 2854, 1766, 1381, and 1179 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 2 H), 7.36 (d, *J* = 8.2 Hz, 2 H), 4.98 (d, *J* = 2.6 Hz, 1 H), 4.15 (dq, *J* = 1.9, 7.1 Hz, 2 H), 3.65 (ddd, *J* = 2.6, 9.0, 9.0 Hz, 1 H), 2.44 (s, 3 H), 2.36 (d, *J* = 9.0 Hz, 1 H), 2.00–1.90 (m, 1 H), 1.78–1.55 (m, 4 H), 1.48–0.85 (m, 6 H), and 1.21 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 168.0, 145.2, 133.2,

(11) (a) Cardani, S.; Bernardi, A.; Colombo, L.; Gennari, C.; Scolastico, C.; Venturini, I. *Tetrahedron* **1988**, *44*, 5563. (b) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron* **1988**, *44*, 5553. (c) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39 and references therein.

(12) See ref 1.

129.7, 128.1, 77.9, 75.9, 61.6, 39.1, 28.4, 28.1, 25.6, 25.2, 21.1, and 13.4. Anal. Calcd for $C_{18}H_{26}O_6S$: C, 58.36; H, 7.07. Found: C, 58.08; H, 7.00.

(2*S*,3*R*)-(+)-Ethyl 3-Cyclohexyl-3-hydroxy-2-(((*p*-nitrophenyl)sulfonyl)oxy)propionate (3f). According to procedure B, enantiomerically enriched (2*S*,3*R*)-(−)-ethyl 3-cyclohexyl-2,3-dihydroxypropionate (0.683 g, 3.16 mmol, ee not determined), Et_3N (660 μL, 4.74 mmol), nosyl chloride (0.716 g, 3.23 mmol), and CH_2Cl_2 (16 mL) gave 1.396 g of crude product. Column chromatography (silica gel, 40% Et_2O/Hex, then Et_2O) gave 1.149 g of **3f** (2.86 mmol, 91% yield, 75% ee) as white crystals: mp 84–85 °C; $[\alpha]^{24}_D$ +14.2° (*c* 1.1, absolute EtOH); IR (KBr pellet) 3469, 2927, 2850, 1734, 1526, 1373, 1187, and 855 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.9 Hz, 2 H), 8.23 (d, *J* = 8.9 Hz, 2 H), 5.21 (d, *J* = 2.6 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 3.78 (ddd, *J* = 2.4, 8.5, 8.5 Hz, 1 H), 2.53 (d, *J* = 8.5 Hz, 1 H), 2.03–1.99 (m, 1 H), 1.77–1.49 (m, 5 H), 1.31–1.01 (m, 5 H), and 1.26 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 167.6, 150.9, 142.1, 129.5, 124.3, 79.2, 75.8, 62.1, 53.3, 39.2, 28.4, 28.2, 25.6, 25.2, and 13.5. Anal. Calcd for $C_{17}H_{23}NO_8S$: C, 50.86; H, 5.78; N, 3.49. Found: C, 50.76; H, 5.77; N, 3.39.

(2*S*,3*R*)-(−)-Methyl 3-Hydroxy-3-phenyl-2-((*p*-tolylsulfonyl)oxy)propionate (3g). According to procedure B, enantiomerically enriched (2*S*,3*R*)-(−)-methyl 2,3-dihydroxy-3-phenylpropionate (0.620 g, 3.16 mmol, 83% ee), Et_3N (660 μL, 4.74 mmol), tosyl chloride (0.604 g, 3.17 mmol), and CH_2Cl_2 (16 mL) gave 1.022 g of a yellow oil. Column chromatography (silica gel, 40% Et_2O/Hex, then Et_2O) gave 0.844 g of **3g** (2.41 mmol, 76% yield, 82% ee) as white crystals: mp 59–61 °C; $[\alpha]^{24}_D$ −56° (*c* 1.5, absolute EtOH); IR (KBr pellet) 3298, 2359, 1772, 1759, 1748, 1595, 1457, 1422, 1371, 1175, 1096, 1071, 870, 766, and 540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.1 Hz, 2 H), 7.28–7.16 (m, 7 H), 5.10 (dd, *J* = 4.4, 4.8 Hz, 1 H), 4.89 (d, *J* = 4.4 Hz, 1 H), 3.59 (s, 3 H), 3.16–3.09 (m, 1 H), and 2.39 (s, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 167.7, 145.1, 137.6, 132.5, 129.7, 128.5, 128.4, 127.9, 126.3, 81.2, 73.5, 52.5, and 21.3. Compound **3g** gave incorrect analyses; ^1H and ^{13}C NMR spectra are provided as supplementary material as evidence of chemical purity.

(2*S*,3*R*)-(−)-Methyl 3-Hydroxy-3-phenyl-2-(((*p*-nitrophenyl)sulfonyl)oxy)propionate (3h). According to procedure B, enantiomerically enriched (2*S*,3*R*)-(−)-methyl 2,3-dihydroxy-3-phenylpropionate (0.629 g, 3.21 mmol, 83% ee), Et_3N (670 μL, 4.8 mmol), nosyl chloride (0.716 g, 3.23 mmol), and CH_2Cl_2 (16 mL) gave 1.043 g of crude product. Column chromatography (silica gel, 30% Et_2O/Hex, then Et_2O) gave 0.702 g of **3h** (1.84 mmol, 57% yield, 85% ee) as white crystals: mp 113–115 °C; $[\alpha]^{24}_D$ −68° (*c* 1.0, absolute EtOH); IR (KBr pellet) 3584, 3116, 1766, 1608, 1529, 1353, 1313, 1188, 1026, 947, 879, and 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.9 Hz, 2 H), 7.81 (d, *J* = 8.9 Hz, 2 H), 7.24 (m, 5 H), 5.25 (dd, *J* = 3.7, 6.1 Hz, 1 H), 5.06 (d, *J* = 3.7 Hz, 1 H), 3.76 (s, 3 H), and 2.59 (d, *J* = 6.1 Hz, 1 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 167.3, 150.7, 141.4, 137.7, 129.1, 128.7, 126.1, 124.3, 111.5, 82.2, 73.3, and 53.0. Anal. Calcd for $C_{16}H_{15}NO_8S$: C, 50.39; H, 3.96; N, 3.67. Found: C, 50.51; H, 3.76; N, 3.53.

(2*S*,3*R*)-(−)-Methyl 3-Hydroxy-3-(*p*-methoxyphenyl)-2-((*p*-tolylsulfonyl)oxy)propionate (3i). According to procedure B, enantiomerically enriched (2*S*,3*R*)-(−)-methyl 2,3-dihydroxy-3-(*p*-methoxyphenyl)propionate (0.846 g, 3.74 mmol, >98% ee), Et_3N (790 μL, 5.7 mmol), tosyl chloride (0.713 g, 3.74 mmol), and CH_2Cl_2 (18 mL) gave 1.349 g of crude product as a brown oil. Column chromatography (silica gel, 40% Et_2O/Hex, then Et_2O) gave 1.070 g of **3i** (2.81 mmol, 75% yield, >98% ee) as cream-colored crystals: mp 83–85 °C; $[\alpha]^{24}_D$ −59° (*c* 1.1, absolute EtOH); IR (KBr pellet) 3513, 3151, 2961, 1740, 1682, 1613, 1517, 1437, 1361, 1307, 1259, 1246, 1170, 1009, 903, 869, 805, 684, and 538 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2 H), 7.19 (d, *J* = 8.3 Hz, 2 H), 7.11 (d, *J* = 8.8 Hz, 2 H), 6.72 (d, *J* = 8.8 Hz, 2 H), 5.04 (dd, *J* = 4.6, 5.4 Hz, 1 H), 4.84 (d, *J* = 4.6 Hz, 1 H), 3.76 (s, 3 H), 3.59 (s, 3 H), 3.11 (d, *J* = 5.4 Hz, 1 H), and 2.40 (s, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 167.7, 159.5, 145.0, 133.0, 129.6, 127.8, 127.4, 113.5, 81.3, 72.9, 54.8, 53.3, 52.3, and 21.1. Anal. Calcd for $C_{18}H_{20}O_7S$: C, 56.83; H, 5.30. Found: C, 56.56; H, 5.13.

(2*S*,3*R*)-(−)-Methyl 3-Hydroxy-3-(*p*-methoxyphenyl)-2-(((*p*-nitrophenyl)sulfonyl)oxy)propionate (3j). According to procedure A, enantiomerically enriched (2*S*,3*R*)-(−)-methyl 2,3-dihydroxy-3-(*p*-methoxyphenyl)propionate (0.201 g, 0.89 mmol, >98% ee), nosyl chloride (0.198 g, 0.89 mmol), and pyridine (3.3 mL) gave 0.272 g of **3j** (0.66 mmol, 74% yield, >98% ee) as yellow crystals: mp 123–124.5 °C; $[\alpha]^{24}_D$ −52.2° (*c* 0.5, $CHCl_3$); IR (KBr pellet) 3529, 1739, 1682, 1533, 1514, 1350, 1294, 1259, 1247, 1175, 1008, 906, 874, 855, 753, 743, 611, and 539 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.4 Hz, 2 H), 7.83 (d, *J* = 9.4 Hz, 2 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 6.72 (d, *J* = 8.4 Hz, 2 H), 5.19 (dd, *J* = 4.0, 5.3 Hz, 1 H), 5.00 (d, *J* = 4.0 Hz, 1 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 2.36 (d, *J* = 5.3 Hz, 1 H); ^{13}C NMR (75.0 MHz, CD_2Cl_2) δ 167.7, 160.6, 151.2, 142.0, 130.2, 129.7, 127.9, 124.7, 114.3, 83.1, 73.4, 55.5, and 53.4. Anal. Calcd for $C_{17}H_{17}NO_9S$: C, 49.63; H, 4.17; N, 3.40. Found: C, 49.83; H, 3.91; N, 3.17.

Preparation of Azido Alcohol Esters: General Procedure. The prerequisite hydroxy nosylate ester was placed in a one-neck round-bottomed flask equipped with a magnetic stir bar and reflux condensor. *N*,*N*-Dimethylformamide (DMF) and NaN_3 (6 equiv) were added, and the reaction mixture was heated at 50 °C for 20–24 h under an inert atmosphere. The reaction mixture was diluted with Et_2O and water, and the phases were separated. The aqueous phase was extracted with Et_2O, and the combined organic phases were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to afford the desired product.

(2*R,3*R**)-Methyl 2-Azido-3-hydroxybutanoate (6a).** (2*S**,3*R**)-Methyl 3-hydroxy-2-(((*p*-nitrophenyl)sulfonyl)oxy)-butanoate (0.123 g, 0.39 mmol) was combined with DMF (1 mL) and LiN_3 (0.117 g, 2.4 mmol) as above to yield 0.030 g of **6a** (0.19 mmol, 49% yield) as a colorless oil: IR (thin film) 3446, 2958, 2112, 1742, 1436, 1267, 1235, 1208, and 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (ddt, *J* = 5.5, 6.4, and 6.2 Hz, 1 H), 4.02 (d, *J* = 5.5 Hz, 1 H), 3.88 (s, 3 H), 2.42 (d, *J* = 6.4 Hz, 1 H), and 1.32 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 80.2, 68.1, 67.2, 52.7, and 18.9. Compound **6a** gave incorrect analyses; ^1H and ^{13}C NMR spectra are provided as supplementary material as evidence of chemical purity.

(2*R*,3*R*)-(+)-Methyl 2-Azido-3-hydroxyoctanoate (6b). (2*S*,3*R*)-(−)-Methyl 3-hydroxy-2-(((*p*-nitrophenyl)sulfonyl)oxy)-octanoate (0.201 g, 0.54 mmol, 63% ee) was combined with DMF (5 mL) and NaN_3 (0.202 g, 3.11 mmol) as above to yield 0.106 g of crude product. Column chromatography (silica gel, 40% Et_2O/Hex) afforded 0.090 g of **6b** (0.42 mmol, 77% yield, ee not determined) as a colorless oil: $[\alpha]^{24}_D$ +6.8 (*c* 2.2, absolute EtOH); IR (thin film) 3466, 2952, 2095, 1735, 1437, 1418, 1209, 1119, 1105, 1045, 727, and 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.99–3.85 (m, 2 H), 3.84 (s, 3 H), 2.55 (d, *J* = 5.8 Hz, 1 H), 1.55–1.26 (m, 8 H), 0.90 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 169.8, 71.9, 66.2, 52.5, 32.7, 31.3, 24.8, 22.2, and 13.6. Anal. Calcd for $C_9H_{17}N_3O_3$: C, 50.22; H, 7.96; N, 19.52. Found: C, 50.50; H, 7.68; N, 19.39.

(2*R*,3*R*)-(+)-Ethyl 2-Azido-3-cyclohexyl-3-hydroxypropionoate (6c). (2*S*,3*R*)-(+)-Ethyl 3-cyclohexyl-3-hydroxy-2-(((*p*-nitrophenyl)sulfonyl)oxy)propionate (0.164 g, 0.41 mmol, ee not determined), DMF (7 mL), and NaN_3 (0.166 g, 2.55 mmol) were combined as above to yield, after further purification by filtration (silica gel, 50% Et_2O/Hex), 0.052 g of **6c** (0.22 mmol, 54% yield, ee not determined) as a colorless oil: $[\alpha]^{24}_D$ +6.8° (*c* 1.2, absolute EtOH); IR (thin film) 3495, 2982, 2925, 2853, 2112, 1734, 1450, 1263, 1193, and 1063 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.30 (q, *J* = 7.1 Hz, 2 H), 3.96 (d, *J* = 6.2 Hz, 1 H), 3.69 (q, *J* = 6.0 Hz, 1 H), 2.41 (d, *J* = 6.4 Hz, 1 H), 1.88–1.52 (m, 6 H), 1.38–1.02 (m, 5 H), and 1.34 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 169.9, 76.0, 63.3, 62.0, 39.8, 29.3, 26.9, 26.0, 25.9, 25.6, and 13.9. Anal. Calcd for $C_{11}H_{19}N_3O_3$: C, 54.76; H, 7.94; N, 17.41. Found: C, 55.00; H, 8.04; N, 17.12.

(2*R,3*R**)-Ethyl 2-Azido-3-cyclohexyl-3-hydroxypropionate (6c) and (2*S**,3*R**)-Ethyl 2-Azido-3-cyclohexyl-3-hydroxypropionate (6d), Mixture of Epimers.** (2*S**,3*R**)-Ethyl 3-cyclohexyl-3-hydroxy-2-((*p*-tolylsulfonyl)-oxy)propionate (0.125 g, 0.34 mmol) and NaN_3 (0.137 g, 2.11 mmol) were combined as above to afford 0.057 g of **6c** and **6d** (0.24 mmol, 71% yield) as a 21:1 mixture of epimers at C-2 by ^1H NMR analysis: ^1H NMR (300 MHz, $CDCl_3$) [major(minor)] δ 4.30 (q, *J* = 6.9 Hz, 2 H), (4.01) (d, *J* = 2.9 Hz, 1 H), 3.96 (d, *J* = 6.2 Hz, 1 H), (3.76) (m, 1 H), 3.70 (dd, *J* = 6.0, 6.2 Hz, 1 H), 2.46 (m, 1 H), 1.85–1.53 (m, 6 H), 1.44–1.03 (m, 5 H), and 1.34 (t, *J* = 7.2 Hz, 3 H).

Closure of Hydroxy Sulfonate Esters to Glycidic Esters: (2*R*,3*R*)-(+)-Ethyl 3-Cyclohexyl-2,3-epoxypropionate (7). Into a 25-mL one-neck round-bottomed flask equipped with a magnetic stir bar and drying tube ($CaSO_4$) was placed enantiomerically enriched (2*S*,3*R*)-(+)-ethyl 3-cyclohexyl-3-hydroxy-2-((*p*-tolylsulfonyl)oxy)propionate (0.179 g, 0.48 mmol), EtOH (5 mL), and K_2CO_3 (0.220 g, 1.59 mmol). After being stirred at ambient temperature for 21 h, the reaction mixture was diluted with Et_2O (30 mL) and water (60 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (30 and 20 mL). The combined organic phases were washed with brine (2 × 30 mL), dried ($MgSO_4$), filtered, and concentrated to afford 0.082 g of 7 (0.41 mmol, 86% yield, 74% ee) as a colorless oil. The product was fully characterized by IR and ^1H and ^{13}C NMR analyses, and all the data was in agreement with the literature values:[13] $[\alpha]^{24}_D$ +11.0° (*c* 1.7, EtOH).

Preparation of Acetoxy Bromo Esters: General Procedure. The acetoxy bromo esters were prepared using a slightly modified approach to that reported by Golding et al.[14] The diol ester was placed in a one-neck round-bottomed flask equipped with a magnetic stirring bar. The flask was cooled (ice–water bath), and 30%-by-weight HBr in HOAc was added by pipette (6 equiv of HBr). The flask was fitted with a serum cap, and the reaction mixture was heated (45 °C) with stirring under an inert atmosphere for 30–60 min. The reaction mixture was quenched by slowly pouring into a cooled (ice–water bath) saturated aqueous $NaHCO_3$ solution. The mixture was then extracted three times with Et_2O. The combined organic phases were washed once with water and twice with brine. Drying ($MgSO_4$), filtration, and concentration afforded the acetoxy bromo ester.

(2*R,3*R**)-Methyl 3-Acetoxy-2-bromobutanoate (8a).** (2*S**,3*R**)-Methyl 2,3-dihydroxybutanoate (0.241 g, 1.80 mmol) was placed in a 25-mL one-neck round-bottomed flask followed by 2.3 mL of 30%-by-weight HBr/HOAc (11 mmol HBr, 6.1 equiv), and the reaction mixture was heated at 45 °C for 30 min. Workup afforded 0.310 g of 8a as a colorless oil (1.30 mmol, 72% yield). The product was fully characterized by IR and ^1H and ^{13}C NMR analyses, and all the data was in agreement with reported literature values.[15]

(2*R,3*R**)-Methyl 3-Acetoxy-2-bromooctanoate (8b).** (2*S**,3*R**)-Methyl 2,3-dihydroxyoctanoate (0.628 g, 3.30 mmol) was placed in a 25-mL one-neck round-bottomed flask followed by 4.2 mL of 30%-by-weight HBr/HOAc (19.7 mmol HBr, 6.0 equiv), and the reaction mixture was heated at 45 °C for 30 min. Workup afforded 0.859 g of crude product as yellow oil. Bulb-to-bulb distillation afforded 8b as a colorless oil (0.768 g, 2.60 mmol, 79% yield): bp 165 °C (0.20 mmHg); IR (thin film) 3479, 2956, 2932, 2862, 1757, 1436, 1374, 1272, 1225, 1151, 1090, 1020, and 955 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.27 (dt, *J* = 3.4, 7.2 Hz, 1 H), 4.41 (d, *J* = 7.2 Hz, 1 H), 3.79 (s, 3 H), 2.07 (s, 3 H), 1.90–1.69 (m, 2 H), 1.40–1.20 (m, 6 H), 0.91–0.87 (m, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 170.0, 168.2, 73.0, 52.9, 46.7, 31.2, 30.9, 24.1, 22.1, 20.5, and 13.6. Anal. Calcd for $C_{11}H_{19}O_4Br$: C, 44.76; H, 6.49; Br, 27.07. Found: C, 44.57; H, 6.40; Br, 26.70.

(2*R,3*R**)-Ethyl 3-Acetoxy-2-bromo-3-cyclohexylpropionate (8c).** (2*S**,3*R**)-Ethyl 3-cyclohexyl-2,3-dihydroxypropionate (0.209 g, 0.97 mmol) was placed in a 25-mL one-neck round-bottomed flask followed by 1.4 mL of 30%-by-weight HBr/HOAc (6.6 mmol HBr, 6.8 equiv), and the reaction mixture was heated at 45 °C for 60 min. Workup gave 0.274 g of 8c as a colorless oil (0.85 mmol, 88% yield): IR (thin film) 3644, 3479, 2982, 2929, 2855, 1752, 1464, 1450, 1369, 1308, 1219, 1174, and 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.22 (dd, *J* = 4.1, 8.8 Hz, 1 H), 4.26 (d, *J* = 8.8 Hz, 1 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 1.96 (s, 3 H), 1.95–1.82 (m, 1 H), 1.75–1.53 (m, 5 H), 1.28–0.83 (m, 5 H), and 1.19 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 169.3, 167.6, 75.7, 61.7, 43.8, 38.3, 29.4, 25.6, 25.4, 20.0, and 13.4. Compound 8c gave incorrect analyses; ^1H and ^{13}C NMR spectra are provided as supplementary material as evidence of chemical purity.

(2*R,3*S**)-Methyl 2-Acetoxy-3-bromo-3-phenylpropionate (8d).** (2*S**,3*R**)-Methyl 2,3-dihydroxy-3-phenylpropionate (0.184 g, 0.94 mmol) was placed in a 25-mL one-neck round-bottomed flask followed by 1.4 mL of 30%-by-weight HBr/HOAc (6.6 mmol HBr, 7.0 equiv), and the reaction mixture was heated at 45 °C for 30 min. Workup gave 0.270 g of 8d as white crystals (0.90 mmol, 96% yield): mp 57–59 °C; IR (KBr pellet) 2964, 1748, 1652, 1560, 1450, 1377, 1219, 1090, and 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.30 (m, 5 H), 5.65 (d, *J* = 6.4 Hz, 1 H), 5.36 (d, *J* = 6.4 Hz, 1 H), 3.68 (s, 3 H), and 2.09 (s, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 169.6, 167.6, 137.0, 129.3, 128.8, 128.7, 75.3, 52.5, 49.1, and 20.1. Anal. Calcd for $C_{12}H_{13}O_4Br$: C, 47.9; H, 4.4; Br, 26.5. Found: C, 47.83; H, 4.14; Br, 26.10.

(2*R,3*R**)-Methyl 2-Bromo-3-hydroxyoctanoate (9).** (2*S**,3*R**)-Methyl 2,3-dihydroxyoctanoate (1.022 g, 5.37 mmol) was placed in a 25-mL one-neck round-bottomed flask followed by 6.9 mL of 30% wt HBr/HOAc (32.3 mmol HBr, 6.0 equiv), and the reaction mixture was heated at 45 °C for 30 min. The reaction mixture was allowed to cool to room temperature for 1 h after which the flask was charged with MeOH (10 mL) and the reaction mixture was heated at 45 °C for 24 h. The same workup procedure as that used for the acetoxy bromo esters gave 1.242 g of a pale yellow oil. Bulb-to-bulb distillation gave 0.982 g of 9 (3.88 mmol, 72% yield) as a colorless oil which solidified to a waxy white solid upon standing at 25 °C: bp 175–180 °C (0.20 mmHg; IR (thin film) 3850, 3818, 3798, 3746, 3742, 3685, 3672, 3644, 1738, 1732, 1699, 1634, 1435, 1284, and 723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.20 (d, *J* = 7.7 Hz, 1 H), 4.05 (m, 1 H), 3.86 (s, 3 H), 3.05 (m, 1 H), 1.95–1.82 (m, 1 H), 1.66–1.28 (m, 7 H), and 0.95 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 170.1, 72.3, 52.8, 47.9, 33.1, 31.3, 24.6, 22.2, and 13.6. Anal. Calcd for $C_9H_{17}O_3Br$: C, 42.7; H, 6.8; Br, 31.6. Found: C, 42.65; H, 6.77; Br, 31.57.

Methyl 3-Hydroxyoctanoate (10). (2*R**,3*R**)-Methyl 2-bromo-3-hydroxyoctanoate (0.161 g, 0.64 mmol) was placed in a 10-mL two-necked round-bottomed flask equipped with a magnetic stir bar. To this was added EtOH (3 mL), NaOAc (0.057 g, 0.69 mmol), and 5% Pd/C (0.016 g). The flask was fitted with serum caps, and the system was alternately evacuated and charged with hydrogen (4 cycles). After 2 h the reaction mixture was diluted with Et_2O and filtered through Celite. This afforded a gray solution which was then dried ($MgSO_4$), filtered, and concentrated to give 10 as a colorless oil (0.098 g, 0.56 mmol, 88% yield). The product was fully characterized by IR and ^1H and ^{13}C NMR analyses, and all the data was in agreement with the literature values.[16]

(2*S,3*R**)-Methyl 2,3-Epoxyoctanoate (11).** (2*R**,3*R**)-Methyl 2-bromo-3-hydroxyoctanoate (0.036 g, 0.14 mmol) was placed in a 25-mL one-neck round-bottomed flask equipped with a magnetic stir bar and drying tube ($CaSO_4$). The flask was charged with MeOH (5 mL) and K_2CO_3 (0.029 g, 0.21 mmol). After 20 min the reaction mixture was diluted with Et_2O (50 mL) and water (50 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic phases were washed with brine (2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated to afford 11 (0.023 g, 0.13 mmol, 93% yield). The product was fully characterized by IR and ^1H and ^{13}C NMR analyses, and the data was in agreement with the literature values.[17]

Methyl 2-Acetoxy-3-phenylpropionate (12). (2*R**,3*S**)-Methyl 2-acetoxy-3-bromo-3-phenylpropionate (0.141 g, 0.468 mmol) was placed in a 10-mL two-necked round-bottomed flask equipped with a magnetic stir bar. EtOAc (1.2 mL), acetic acid (130 μL), NaOAc (0.132 g, 1.61 mmol), and 5% Pd/C (0.015 g) were then added, and the system was alternately evacuated and charged with hydrogen (4 cycles). After 15 h the reaction mixture was diluted with Et_2O and filtered through Celite. Drying ($MgSO_4$), filtration, and concentration gave 12 (0.083 g, 0.37 mmol, 79% yield) as a colorless oil: IR (thin film) 3064, 3051, 3031, 2982, 1732, 1634, 1605, 1435, 1373, 1217, 1082, and 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.22 (m, 5 H), 5.23 (dd, *J* = 4.6, 8.8 Hz, 1 H), 3.73 (s, 3 H), 3.13 (m, 2 H), and 2.09 (s, 3 H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 170.5, 170.4, 136.2, 129.4, 128.6, 127.2, 72.9, 52.1,

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37.2, and 20.2. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.4. Found: C, 64.62; H, 6.18.

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Registry No. **2**(R_1 = R_2 = CH_3), 38410-83-2; (±)-**2**(R_1 = R_2 = CH_3), 96613-68-2; **2**(R_1 = n-C_5H_{11}, R_2 = CH_3), 132486-46-5; (±)-**2**(R_1 = n-C_5H_{11}, R_2 = CH_3), 132377-81-2; **2**(R_1 = C_6H_{11}, R_2 = C_2H_5), 132486-47-6; (±)-**2**(R_1 = C_6H_{11}, R_2 = C_2H_5), 132377-82-3; **2**(R_1 = Ph, R_2 = CH_3), 124649-67-8; (±)-**2**(R_1 = Ph, R_2 = CH_3), 81691-59-0; **2**(R_1 = p-MeOPh, R_2 = CH_3), 122517-80-0; **3a**, 132377-61-8; **3b**, 132377-62-9; (±)-**3b**, 132486-48-7; **3c**, 132377-63-0; **3d**, 132377-64-1; **3e**, 132377-65-2; (±)-**3e**, 132486-49-8; **3f**, 132377-66-3; **3g**, 124605-43-2; **3h**, 132377-67-4; **3i**, 132377-68-5; **3j**, 132377-69-6; **4a**, 132377-78-7; **5a**, 132377-79-8; **5b**, 132377-80-1; **6a**, 132377-70-9; **6b**, 132377-71-0; **6c**, 132377-72-1; (±)-**6c**, 132486-50-1; **6d**, 132486-44-3; **7**, 132486-45-4; **8a**, 132377-73-2; **8b**, 132377-74-3; **8c**, 132377-75-4; **8d**, 132377-76-5; **9**, 132377-77-6; **10**, 85549-54-8; **11**, 100939-32-0; **12**, 55528-54-6; nosyl chloride, 98-74-8; tosyl chloride, 98-59-9.

Supplementary Material Available: ^1H and ^{13}C NMR of compounds **3c**, **3g**, **6a**, and **8c** (8 pages). Ordering information is given on any current masthead page.

Highly Diastereoselective Michael Addition of Lithiated Camphor Imines of Glycine Esters to α,β-Unsaturated Esters. Synthesis of Optically Pure 5-Oxo-2,4-pyrrolidinedicarboxylates of Unnatural Stereochemistry

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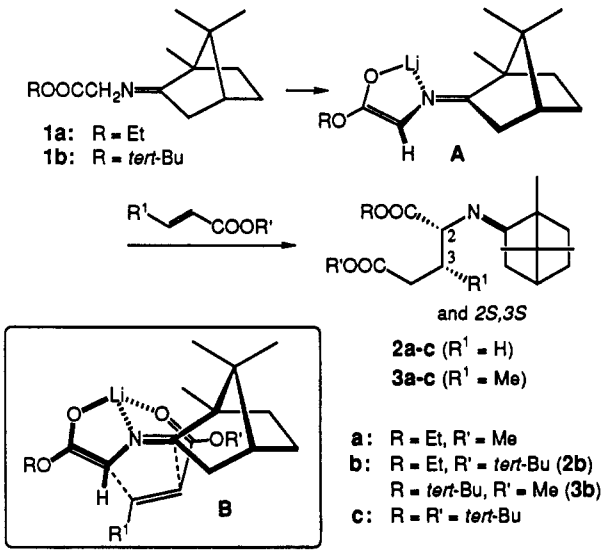
The lithium enolates of camphor imines of glycine esters underwent highly diastereoselective Michael additions to α,β-unsaturated esters. The tightly chelated structure of the *Z,E* enolates and the selective approach of the α,β-unsaturated esters to the *re* face of the enolates were responsible for the high diastereoselectivity observed. The use of alkylidenemalonate acceptors led to the diastereospecific formation of Michael adducts. Removal of the camphor auxiliary of the adducts and concomitant cyclization led to optically pure enantiomeric 5-oxo-2,4-pyrrolidinedicarboxylates of unnatural stereochemistry.

Introduction

Enhanced reactivity and high stereoselectivity were recently observed in the cycloaddition of ester-stabilized N-metalated azomethine ylides to α,β-unsaturated carbonyl compounds.[1,2] The high stereoselectivity arose from a combination of two kinds of attractive interactions operating in the transition state: a frontier orbital interaction between the dipole and the dipolarophile and chelation of the metal ion by the carbonyl oxygen atoms of the ylide and the dipolarophile.[3,4] This type of frontier orbital controlled and chelation-controlled transition state was also apparently involved in the highly stereoselective Michael addition of metalated imines of α-amino esters.[5]

Although several chiral nucleophilic glycine equivalents have been developed and have been widely utilized for the asymmetric synthesis of α-amino acids and their derivatives,[6,7] reports of Michael additions that employ such reagents are few.[8] Most of these reported that a satisfactory level of diastereoselectivity was obtained with respect to the diastereotopic face of the nucleophile. Few, however, discussed the stereoselectivity displayed in the formation of the new carbon–carbon bond.[9]

Scheme I



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