Stereoselective S_N2 Reactions of the (*R*)-Pantolactone Ester of Racemic α-Halo Carboxylic Acids with Aryloxides. A Synthesis of (*S*)-2-Aryloxy and (*S*)-2-Hydroxy Acids

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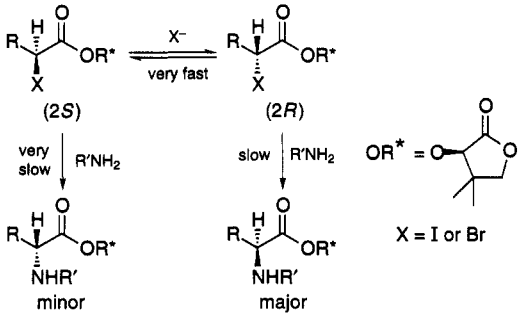
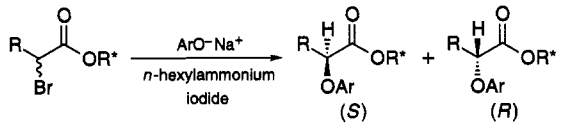
Optically active α-hydroxy acids and esters are important and versatile building blocks in organic synthesis.[1] Various methods have been developed for their preparation. These methods include the reduction of α-oxo esters[2,3] and asymmetric oxygenation of chiral imide enolates.[4] Very recently Corey and Link demonstrated that reduction of α-trichloromethyl ketones by catecholborane in the presence of chiral oxazaborolidine catalyst yielded optically active trichloromethyl carbinols which on treatment with 4-methoxyphenoxide afforded optically active α-aryloxy acids. Treatment of the methyl esters of the α-aryloxy acids with ceric ammonium nitrate (CAN) furnished the desired α-hydroxy esters.[5]

The methodology reported in this paper for the preparation of optically active α-hydroxy acids and α-aryloxy acids make use of the recently discovered reaction of (*R*)-pantolactone esters of racemic α-halo carboxylic acids with amines which furnished predominantly one of the two possible diastereomeric α-amino esters with diastereoselectivity ranging from 88:12 to >95:<5 and in yields up to 80%.[6] The greater than 50% yield of one diastereomer is due to epimerization of the slower reacting (2*S*)-α-halo ester into the faster reacting (2*R*)-isomer by the halide generated in the displacement reaction or added to the reaction mixture.

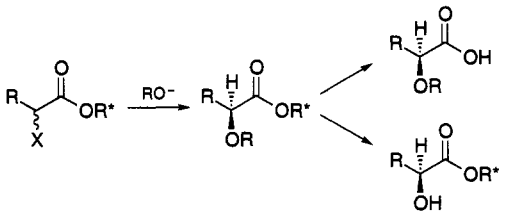


We envisaged that a similar reaction of a suitable oxygen nucleophile with the (*R*)-pantolactone esters of racemic α-halo carboxylic acids could lead to the α-alkoxy esters with comparable diastereomeric ratios. Such compounds should serve as precursors to the corresponding α-hydroxy acids or esters.

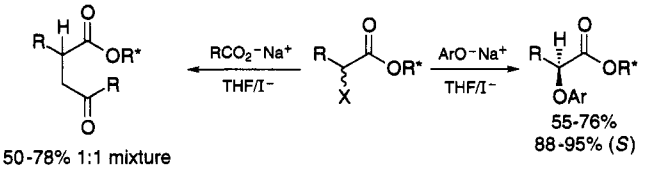
Table 1. Reaction of (*R*)-Pantolactone Esters of α-Bromo Acids with ArO^-Na^+



entries	R	ArOH	ratio (*S*):(*R*)	yield (%)
1	C_2H_5	phenol	89:11	65
2	C_2H_5	2-naphthol	93:7	73
3	C_2H_5	2-methoxyphenol	88:12	74
4	C_2H_5	2-bromophenol	91:9	76
5	C_2H_5	4-methoxyphenol	89:11	70
6	$PhCH_2CH_2$	4-methoxyphenol	88:12	70
7	*i*-C_3H_7	4-methoxyphenol	89:11	55
8	Ph	4-methoxyphenol	95:5	70



Initial experiments using the sodium and triethylammonium salts of acetic, pivalic, and benzoic acids gave the expected substitution products but with no diastereoselectivity. The absence of diastereoselectivity in these displacement reactions is not due to epimerization of the products under the reaction conditions. Fortunately, when a variety of sodium aryloxides were used as oxygen nucleophiles, the desired α-aryloxy esters **1–8** were obtained in 55–76% isolated yield with diastereoselectivities ranging from 88:12 to 95:5 (see Table 1). Reactions of aryloxides with the (*R*)-pantolactone esters were carried out by adding a preformed solution of sodium aryloxides via cannula to a cooled THF solution (−5–0 °C) of (*R*)-pantolactone esters of α-halo carboxylic acids[7] containing catalytic amounts of *n*-hexylammonium iodide and stirring at −5–0 °C for 5 h followed by 5 °C for 15 h.[8]



Considerable variation in the R-group is possible without significantly influencing either the overall yield or observed diastereoselectivity. The somewhat higher ratio observed from the reaction of α-bromophenylacetic acid ester (entry 8) is likely due to the relatively large size of the phenyl group and very efficient conversion of the less reactive α-bromo ester into the more reactive isomer. Structural features of the aryloxides appear to have limited influence on the selectivity of the substitution reaction. The sterically more hindered 2-methoxyphenoxide and 2-bromophenoxide neither improve nor erode the diastereoselectivity (entry 1 vs 3 or 4) relative

(1) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, 1983; Chapter 2.
(2) Akiyama, T.; Nishimoto, H.; Ozaki, S. *Tetrahedron Lett.* **1991**, *32*, 1335 and references cited.
(3) For a review on the reduction of α-oxo esters and ketones, see: Singh, V. K. *Synthesis* **1992**, 605.
(4) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.
(5) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 3431.
(6) Durst, T.; Koh, K.; Ben, R. N. *Tetrahedron Lett.* **1993**, *34*, 4476.
(7) (*R*)-Pantolactone esters of α-halo acids were prepared by DCC coupling of commercially available acids.
(8) It is essential to carry out the reactions at temperature ≤5 °C. Reaction at room temperature show lower diastereoselectivity, typically 80:20.

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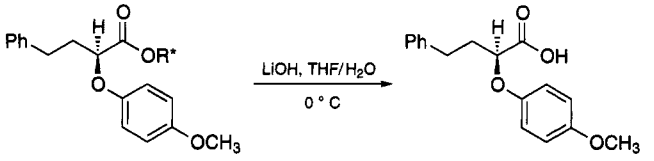
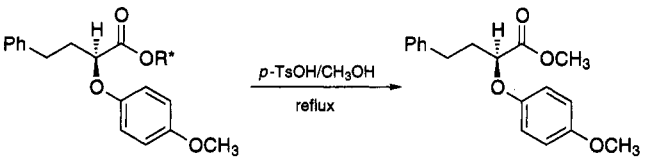
to phenoxides or the 4-substituted phenoxides. Replacement of the sodium counterion with Li^+ or R_3NH^+ resulted in greatly reduced reaction rates and almost complete recovery of the starting α-halo esters after 72 h at 0 °C.

The stereochemistry of the major α-aryloxy esters was elucidated as follows. The product **6** (88:12 mixture) was chosen as a representative case. Saponification of **6** gave the known 2-(*p*-anisyloxy)-4-phenylbutanoic acid **9** in 80% isolated yield, having 75% ee and (*S*)-stereochemistry based on comparison of it's specific rotation with known literature value of optically pure **9**.[5] The (*S*)-stereochemistry is consistent with our previous observations with amines as nucleophiles.[6] The other major products are assumed to have the same (2*S*)-stereochemistry. The (*R*)-



6 **9**

pantolactone auxiliary could also be removed by transesterification. Thus, refluxing product **8** (95:5 mixture) in methanol with catalytic amounts of *p*-toluenesulfonic acid furnished methyl (2*S*)-2-(*p*-anisyloxy)phenylacetate (**10**) in 73% yield. The enantiomeric purity of **10** was assessed to be 89% using the chiral shift reagent Eu(hfc)$_3$.



8 **10**

Amongst the aryloxides investigated, *p*-anisyloxide is of particular interest from a synthetic point of view. Corey and Link have recently reported the oxidative removal of the 4-methoxyphenyl group. In particular they show that the optically active methyl ester of **9** could be converted to the corresponding optically active α-hydroxy ester in 90% yield upon treatment with ceric ammonium nitrate.[5] Thus, a variety of both (*S*)-2-aryloxy acids and (*S*)-2-hydroxy esters of ≥75% ee are accessible from racemic α-bromo acids via the methodology described above.

Experimental Section

THF was freshly distilled over sodium/benzophenone. Melting points were measured in open capillary tubes and are uncorrected. Column chromatography was performed on silica gel (230–400 mesh). Optical rotations were measured on a Perkin-Elmer 241 spectrometer.

The preparation of **(*R,S*)-2-bromo-2-phenylacetic acid (*R*)-pantolactone ester** was accomplished by a DCC coupling. An amount of 3.16 g (0.0169 mol) of α-bromophenylacetic acid was dissolved in 60 mL of CH_2Cl_2. To this were added 3.49 g (1.0 equiv) of DCC, 206 mg (0.1 equiv) of DMAP, and 2.20 g (1.0 equiv) of (*R*)-pantolactone. The reaction mixture was stirred at room temperature for 24 h, after which time the precipitate was filtered off and the organic phase was successively with 3 × 30 mL of H_2O and 1 × 20 mL of 10% HCl. The resulting organic phase was then dried with $MgSO_4$ and rotoevaporated to dryness. Purification by column chromatography with 3:1 hexanes:EtOAc furnished 3.81 g (72% yield) of a pale yellow oil which solidified on standing: IR (CH_2Cl_2) 3014, 1800, 1762, 1076, 1136 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88, 1.10, 1.15, 1.23, (all s, total 6H), 3.98 4.05, (both s, total 2H), 5.34, 5.36 (both s, total 1H), 5.48, 5.51, (both s, total 1H), 7.25–7.60 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.1, 20.3, 23.2, 23.4, 40.2 (2), 45.6 (2), 47.3 (2), 77.8 (2), 78.4 (2), 128.5, 128.7, 129.1, 129.6, 130.1, 135.3, 136.1, 167.8, 168.3, 172.1; CIMS *m/z* (relative intensity) 328.9 (33.9), 326.9 (34.6), 283 (8.6), 247 (100), 219 (8.5), 196 (11.7), 169 (17.4). Anal. Calcd for $C_{14}H_{15}O_4Br$: C, 51.40; H, 4.62. Found: C, 51.62; H, 4.77.

The preparation of **(*R,S*)-2-bromobutanoic acid (*R*)-pantolactone ester** was carried out as described above: IR (CH_2Cl_2) 1754, 1802 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95–1.10 (m, 3H), 1.15, 1.25 (both s, 3H each), 1.95–2.25 (m, 2H), 4.05 (s, 2H), 4.20–4.35 (m, 1H), 5.35, 5.85 (both s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 12.3 (2), 20.4 (2), 23.6 (2), 29.1, 41.1, 41.2, 46.9, 47.6, 76.5, 76.8, 76.9, 77.2, 77.7, 78.1, 169.2, 169.7, 172.4; EIMS *m/z* (relative intensity) 281 (2), 279 (2), 151 (94), 149 (99), 123 (100), 121 (100). Anal. Calcd for $C_{10}H_{15}O_4Br$: C, 43.03; H, 5.42. Found: C, 43.31; H, 5.65.

(*R,S*)-4-Phenyl-2-bromobutanoic acid (*R*)-pantolactone ester was prepared via a DCC coupling as described previously in 41% yield after column chromatography using 1:1 hexanes:EtOAc: IR (CH_2Cl_2) 1797, 1753, cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.15 (s, 3H), 2.20–2.45 (both m, 2H), 2.60–2.85 (m, 2H), 3.95 (s, 2H), 4.10–4.25 (m, 1H), 5.30 (s, 1H), 7.05–7.28 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 19.7, 19.8, 32.9, 33.1, 35.9, 36.4, 40.7, 40.6, 43.9, 44.5, 75.8, 75.9, 76.1, 76.1, 126.4, 128.5, 128.6, 139.5, 139.6, 168.4, 169.0, 171.4, 171.7; CIMS *m/z* (relative intensity) 357 (93.1), 355 (93.1), 275 (46.0). Anal. Calcd for $C_{16}H_{19}O_4Br$: C, 54.09; H, 5.40. Found: C, 53.94; H, 5.47.

(*S*)-2-Iodo-3-methylbutanoic acid (*R*)-pantolactone ester was prepared using the procedure described in a previous paper:[9] mp 28–30 °C; IR (CH_2Cl_2) 1744, 1830 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (t, 6H, *J* = 7.05 Hz), 1.17 (s, 3H), 1.23 (s, 3H), 1.90–2.20 (m, 1H), 4.03 (ABq, 2H, *J* = 9.20 Hz), 4.15 (d, 1H, *J* = 9.01 Hz), 5.36 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 19.8, 19.9, 22.5, 22.9, 31.2, 32.6, 40.5, 75.5, 76.1, 169.6, 171.6; EIMS *m/z* (relative intensity) 340 (0.5), 213 (6), 182 (19), 131 (17), 113 (23), 83 (100); HRMS calcd for $C_{11}H_{17}O_4I$: 340.0172, found 340.0160.

2-Acetoxybutanoic Acid (*R*)-Pantolactone Ester. To a stirred mixture of 2-bromobutanoic acid (*R*)-pantolactone ester (260 mg, 0.93 mmol), *n*-hexylammonium iodide (90 mg, 0.19 mmol), and glacial acetic acid (0.16 mL, 2.80 mmol) in THF (20 mL) was added triethylamine (0.40 mL, 2.80 mmol). After 72 h, the mixture was filtered and the solvent evaporated. ^{1}H NMR (200 MHz) of the crude reaction mixture shows that the expected substitution product was present as a 1:1 mixture of diastereomers. Chromatography of the crude mixture (hexanes/ethyl acetate 10:1) gave 188 mg (78%) of product as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95–1.10 (m, 9H), 1.13 (s, 3H), 1.18 (s, 3H), 1.21 (s, 3H), 1.80–2.05 (m, 4H), 2.13 (s, 3H), 2.14 (s, 3H), 4.02 (m, 4H), 4.91 (dd, 1H, *J* = 5.05, 7.00 Hz), 5.05 (dd, 1H, *J* = 5.74, 6.59 Hz), 5.37 (s, 2H); IR (CH_2Cl_2) 1760, 1784, 1807 cm^{-1}.

General Procedure for the Substitution Reactions of Aryl Oxides. Sodium aryloxides were performed by adding a THF solutions (5–10 mL) of phenols via cannula to a stirred suspension of sodium hydride at room temperature under nitrogen. Stirring continued until evolution of hydrogen ceased. The resulting solution was then added dropwise via cannula to a well-stirred THF solution (20–30 mL) of (*R*)-pantolactone esters of racemic α-halo acids with *n*-hexylammonium iodide (0.2 equiv) at −5–0 °C under nitrogen. The mixture was stirred at −5–0 °C for 5 h followed by 5 °C for 17 h (unless stated otherwise). The reaction mixture was quenched with water (10 mL) and saturated with sodium chloride. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (15 mL). The combined organic phase was dried ($MgSO_4$) and concentrated. Diastereoselectivities were determined by examining the ^{1}H NMR (500 MHz) of the crude reaction mixture. The crude product was then purified by chromatography on silica gel using hexanes/ethyl acetate as eluant. The major isomer could be isolated via chromatography and was characterized. Chemical yields refer to the total yield of both isomers.

(9) Durst, T.; Koh, K. *Tetrahedron Lett.* **1992**, *33*, 6799–6802.

2(S)-Phenoxybutanoic Acid (R)-Pantolactone Ester (1). The reaction was performed with 2-bromobutanoic acid (*R*)-pantolactone ester (221 mg, 0.80 mmol), *n*-hexylammonium iodide (76 mg, 0.16 mmol), phenol (89 mg, 0.95 mmol), and NaH (21 mg, 0.87 mmol). Chromatography of the crude product (hexanes/ethyl acetate 10:1) gave 133 mg (65%) of colorless oil. The major isomer has the following physical properties: $[\alpha]^{22}_D$ −37.1° (*c* 0.65, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (s, 3H), 0.96 (s, 3H), 1.12 (t, 3H, *J* = 7.44 Hz), 1.90−2.20 (m, 2H), 3.94 (s, 2H), 4.72 (t, 1H, *J* = 6.16 Hz), 5.35 (s, 1H), 6.80−7.00 (m, 3H), 7.20−7.35 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.4, 171.4, 158.3, 130.2 (2), 122.2, 115.4 (2), 77.6, 76.6, 75.9, 40.7, 26.9, 23.1, 20.2, 10.1; IR (CH_2Cl_2) 1765, 1802 cm^{-1}; EIMS *m/z* (relative intensity) 292 (18), 135 (100), 119 (32), 107 (15), 94 (63), 86 (43), 77 (48); HRMS calcd for $C_{16}H_{20}O_5$: 292.1311, found 292.1316.

2(S)-Naphthoxybutanoic Acid (R)-Pantolactone Ester (2). The reaction was performed with 2-bromobutanoic acid (*R*)-pantolactone ester (150 mg, 0.54 mmol), *n*-hexylammonium iodide (58 mg, 0.11 mmol), 2-naphthol (93 mg, 0.65 mmol), and NaH (15 mg, 0.59 mmol). Chromatography of the crude product (hexanes/ethyl acetate 10:1) gave 133 mg (73%) of colorless oil. The major isomer has the following physical properties: $[\alpha]^{22}_D$ −56.2° (*c* 0.79, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (s, 3H), 0.93 (s, 3H), 1.17 (t, 3H, *J* = 7.18 Hz), 2.05−2.20 (m, 2H), 3.95 (s, 2H), 4.86 (t, 1H, *J* = 6.23 Hz), 5.41 (s, 1H), 7.00−7.50 (m, 4H), 7.60−8.80 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.4, 171.4, 156.1, 134.9, 130.4, 129.9, 128.1, 127.6, 127.1, 124.7, 119.3, 108.0, 77.9, 76.7, 75.9, 40.7, 26.9, 23.1, 20.3, 10.2; IR (CH_2Cl_2) 1763, 1804 cm^{-1}; EIMS *m/z* (relative intensity) 342 (36), 185 (14), 144 (69), 127 (14), 115 (18), 86 (23), 77 (11), 71 (100), 69 (83); HRMS calcd for $C_{20}H_{22}O_5$ 342.1467, found 342.1477.

2(S)-(o-Anisyloxy)butanoic Acid (R)-Pantolactone Ester (3). The reaction was performed with 2-bromobutanoic acid (*R*)-pantolactone ester (181 mg, 0.65 mmol), *n*-hexylammonium iodide (70 mg, 0.13 mmol), 2-methoxyphenol (96 mg, 0.78 mmol), and NaH (17 mg, 0.72 mmol). Chromatography of the crude product (hexanes/ethyl acetate 10:1) gave 155 mg (74%) of colorless oil. The major isomer has the following physical properties: $[\alpha]^{22}_D$ −30.5° (*c* 1.58, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.05 (s, 3H), 1.14 (t, 3H, *J* = 7.44 Hz), 2.10−2.20 (m, 2H), 3.83 (s, 3H), 3.98 (s, 2H), 4.74 (t, 1H, *J* = 6.21 Hz), 5.38 (s, 1H), 6.80−7.00 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.4, 171.4, 150.5, 147.8, 123.3, 121.5, 116.6, 113.2, 79.4, 76.7, 75.8, 56.6, 40.8, 27.0, 23.3, 20.3, 10.2; IR (CH_2Cl_2) 1765, 1802 cm^{-1}; EIMS *m/z* (relative intensity) 322 (49), 165 (16), 124 (100), 109 (18), 100 (11), 95 (14), 77 (25); HRMS calcd for $C_{17}H_{22}O_6$ 322.1416, found 322.1417.

2(S)-(o-Bromophenoxy)butanoic Acid (R)-Pantolactone Ester (4). The reaction was performed with 2-bromobutanoic acid (*R*)-pantolactone ester (183 mg, 0.66 mmol), *n*-hexylammonium iodide (63 mg, 0.13 mmol), 2-bromophemol (125 mg, 0.79 mmol), and NaH (16 mg, 0.73 mmol). Chromatography of the crude product (hexanes/ethyl acetate 10:1) gave 150 mg (76%) of colorless oil. The major isomer has the following physical properties: $[\alpha]^{22}_D$ −6.5° (*c* 0.58, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (s, 3H), 0.97 (s, 3H), 1.16 (t, 3H, *J* = 7.42 Hz), 2.00−2.30 (m, 2H), 3.97 (s, 2H), 4.77 (t, 1H, *J* = 6.02 Hz), 5.34 (s, 1H), 6.70−6.90 (m, 2H), 7.10−7.20 (m, 1H), 7.52 (dd, 1H, *J* = 1.52, 7.97 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.2, 170.6, 154.6, 134.3, 129.1, 123.3, 114.0, 112.9, 78.4, 76.7, 76.0, 40.6, 26.8, 23.2, 20.3, 10.0; IR (CH_2Cl_2) 1765, 1803 cm^{-1}; EIMS *m/z* (relative intensity) 372 (13), 370 (13), 215 (23), 213 (21), 174 (31), 172 (30), 134 (17), 113 (23), 71 (23), 69 (100); HRMS calcd for $C_{16}H_{19}O_5{}^{79}Br$ 370.0416, found 370.0437.

2(S)-(p-Anisyloxy)butanoic Acid (R)-Pantolactone Ester (5). The reaction was performed with 2-bromobutanoic acid (*R*)-pantolactone ester (161 mg, 0.58 mmol), *n*-hexylammonium iodide (56 mg, 0.12 mmol), 4-methoxyphenol (87 mg, 0.70 mmol), and NaH (15 mg, 0.64 mmol). Chromatography of the crude product (hexanes/ethyl acetate 10:1) gave 131 mg (70%) of colorless oil. The major isomer has the following physical properties: $[\alpha]^{22}_D$ −30.8° (*c* 1.65, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.02 (s, 3H), 1.11 (t, 3H, *J* = 7.27 Hz), 1.90−2.15 (m, 2H), 3.72 (s, 3H), 3.79 (s, 2H), 4.64 (t, 1H, *J* = 6.21 Hz), 5.36 (s, 1H), 6.80−6.90 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.4, 171.6, 155.1, 152.4, 116.5 (2), 115.3 (2), 78.5, 76.7, 75.9, 56.3, 40.7, 26.9, 23.3, 20.3, 10.2; IR (CH_2Cl_2) 1765, 1802 cm^{-1}; EIMS *m/z* (relative intensity) 322 (48), 165 (18), 124 (80), 123 (100), 109 (15), 69 (17); HRMS calcd for $C_{17}H_{22}O_6$ 322.1416, found 322.1389.

2(S)-(p-Anisyloxy)-4-phenylbutanoic Acid (R)-Pantolactone Ester (6). The reaction was performed with 2-bromo-4-phenylbutanoic acid (*R*)-pantolactone ester (569 mg, 1.60 mmol), *n*-hexylammonium iodide (154 mg, 0.32 mmol), 4-methoxyphenol (238 mg, 1.92 mmol), and NaH (42 mg, 1.76 mmol). Chromatography of the crude product (hexanes/ethyl acetate 10:1) gave 470 mg (74%) of colorless oil. The major isomer has the following physical properties: $[\alpha]^{22}_D$ −36.0° (*c* 1.20, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.02 (s, 3H), 2.20−2.45 (m, 2H), 2.80−3.00 (m, 2H), 3.74 (s, 3H), 3.98 (s, 2H), 4.68 (dd, 1H, *J* = 4.96, 7.87 Hz), 5.36 (s, 1H), 6.80−6.90 (m, 4H), 7.10−7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.3, 171.6, 155.1, 152.3, 141.1, 129.2 (4), 126.9, 116.5 (2), 115.4 (2), 76.7, 76.5, 76.0, 56.3 40.7, 35.3, 31.9, 23.3, 20.4; IR (CH_2Cl_2) 1764, 1803 cm^{-1}; EIMS *m/z* (relative intensity) 398 (48), 155 (10), 143 (12), 124 (54), 117 (35), 109 (12), 100 (57), 91 (100); HRMS calcd for $C_{23}H_{26}O_6$ 398.1729, found 398.1754.

2(S)-(p-Anisyloxy)-3-methylbutanoic Acid (R)-Pantolactone Ester (7). The reaction was performed with 2-iodo-3-methylbutanoic acid (*R*)-pantolactone ester (259 mg, 0.58 mmol), *n*-hexylammonium iodide (74 mg, 0.12 mmol), 4-methoxyphenol (114 mg, 0.70 mmol), and NaH (20 mg, 0.64 mmol). The reaction was carried out at −5−0 °C for 5 h followed by 5 °C for 72 h. Chromatography of the crude product (hexanes/ethyl acetate 10:1) gave 50 mg of starting ester and 113 mg (55%) of the expected product as colorless oil. The major isomer has the following physical properties: $[\alpha]^{22}_D$ −48.4° (*c* 1.86, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.00 (s, 3H), 1.10 (d, 3H, *J* = 6.81 Hz), 1.11 (d, 3H, *J* = 6.82 Hz), 2.20−2.40 (m, 1H), 3.73 (s, 3H), 3.97 (s, 2H), 4.45 (d, 1H, *J* = 5.35 Hz), 5.38 (s, 1H), 6.70−6.90 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.4, 171.2, 155.0, 152.7, 116.5 (2), 115.3 (2), 82.4, 76.7, 75.8, 56.3, 40.7, 32.3, 23.2, 20.4, 19.3, 18.2; IR (CH_2Cl_2) 1766, 1804 cm^{-1}; EIMS *m/z* (relative intensity) 336 (19), 124 (10), 109 (21), 93 (14), 83 (11); HRMS calcd for $C_{18}H_{24}O_6$ 336.1573, found 336.1554.

2(S)-(p-Anisyloxy)phenylacetatic Acid (R)-Pantolactone Ester (8). The reaction was performed with 2-bromophenylacetic acid (*R*)-pantolactone ester (257 mg, 0.79 mmol), *n*-hexylammonium iodide (76 mg, 0.16 mmol), 4-methoxyphenol (103 mg, 0.95 mmol), and NaH (19 mg, 0.87 mmol). The reaction was complete after 6 h at −5−0 °C. Chromatography of the crude product (hexanes/ethyl acetate 10:1) gave 202 mg (70%) of colorless oil. The major isomer has the following physical properties: $[\alpha]^{22}_D$ +61.9° (*c* 0.63, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 0.69 (s, 3H), 0.90 (s, 3H), 3.72 (s, 3H), 3.92 (s, 2H), 5.37 (s, 1H), 5.67 (s, 1H), 6.79 (d, 2H, *J* = 9.34 Hz), 6.92 (d, 2H, *J* = 9.34 Hz), 7.30−7.45 (m, 3H), 7.50−7.70 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.4, 169.9, 155.3, 151.7, 135.0, 130.0, 129.5 (2), 128.1 (2), 117.2 (2), 115.3 (2), 79.5, 76.6, 76.1, 56.3, 41.0, 23.2, 19.9; IR (CH_2Cl_2) 1763, 1807 cm^{-1}; EIMS *m/z* (relative intensity) 370 (21), 247 (16), 213 (15), 155 (10), 135 (20), 124 (14), 123 (100), 118 (16), 77 (27); HRMS calcd for $C_{21}H_{22}O_6$ 370.1416, found 398.1387.

(S)-2-(p-Anisyloxy)-4-phenylbutanoic Acid (9). To a stirred mixture of 2(*S*)-(*p*-anisyloxy)-4-phenylbutanoic acid (*R*)-pantolactone ester (272 mg, 0.68 mmol) and THF/H_2O (3:1, 12 mL) at 0 °C was added LiOH (57 mg, 1.36 mmol in 5 mL of H_2O). The mixture was stirred for 45 min and most of the THF was rotoevaporated. The residue was acidified to pH = 1 (10% HCl), extracted with Et_2O/CH_2Cl_2 (9:1, 4 × 10 mL), dried ($MgSO_4$), and concentrated to give 209 mg of crude product. Chromatography (hexanes/ethyl acetate/acetic acid 5:1:0.2) gave 156 mg (80%) of colorless solid: mp 82−83 °C, lit.[5] mp 81.5−82.5 °C; $[\alpha]^{22}_D$ −23.9° (*c* 0.53, $CHCl_3$), ee 75%, lit.[5] $[\alpha]^{22}_D$ −31.9° (*c* 1.6, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 2.20−2.50 (m, 2H), 2.70−3.10 (m, 2H), 3.77 (s, 3H), 4.56 (dd, 1H, *J* = 5.57, 7.08 Hz), 6.85 (s, 4H), 7.10−7.30 (m, 5H), 9.85 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.5, 155.3, 152.3, 141.0, 129.2, 129.2 (3), 126.9, 117.1 (2), 115.4 (2), 76.7, 56.3, 34.9, 31.9; IR (CH_2Cl_2) 3500−3000, 1725, 1502 cm^{-1}; EIMS *m/z* (relative intensity) 286 (54), 124 (91), 123 (59), 117 (22), 109 (23), 91 (100), 77 (11); HRMS calcd for $C_{17}H_{18}O_4$ 286.1205, found 286.1203.

(S)-Methyl 2-(p-anisyloxy)phenylacetate (10). (*S*)-2-(*p*-Anisyloxy)phenylacetic acid (*R*)-pantolactone ester (165 mg, 0.45 mmol) and *p*-toluenesulfonic acid (5 mg) in methanol (25 mL)

were refluxed for 72 h. The solvent was evaporated and chromatography of the residue (hexanes/ethyl acetate 10:1) afforded 89 mg (73%) of a colorless solid. The ee of the product was determined to be 89% using the chiral shift reagent Eu(hfc)$_3$: mp 78–79 °C; $[\alpha]^{22}_D$ +75.9° (*c* 0.75, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.73 (s, 3H), 5.54 (s, 1H), 6.78 (d, 2H, J = 9.43 Hz), 6.88 (d, 2H, J = 9.36 Hz), 7.30–7.45 (m, 3H), 7.50–7.60 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.2, 155.2, 152.0, 136.2, 130.0, 129.4 (2), 127.7 (2), 117.5 (2), 115.3 (2), 80.2, 56.2, 53.2; IR (CH_2Cl_2) 1756, 1509, 1212 cm^{-1}; EIMS *m/z* (relative intensity) 272 (37), 240 (7), 213 (12), 149 (45), 123 (100), 121 (41), 77 (14); HRMS calcd for $C_{16}H_{16}O_4$ 272.1048, found 272.1046.

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Supplementary Material Available: Copies of ^{1}H and ^{13}C NMR spectra (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.