Remarkable Chemo-, Regio-, and Enantioselectivity in Lipase-Catalyzed Hydrolysis: Efficient Resolution of (±)-*threo*-Ethyl 3-(4-Methoxyphenyl)-2,3-diacetoxypropionate Leading to Chiral Intermediates of (+)-Diltiazem†

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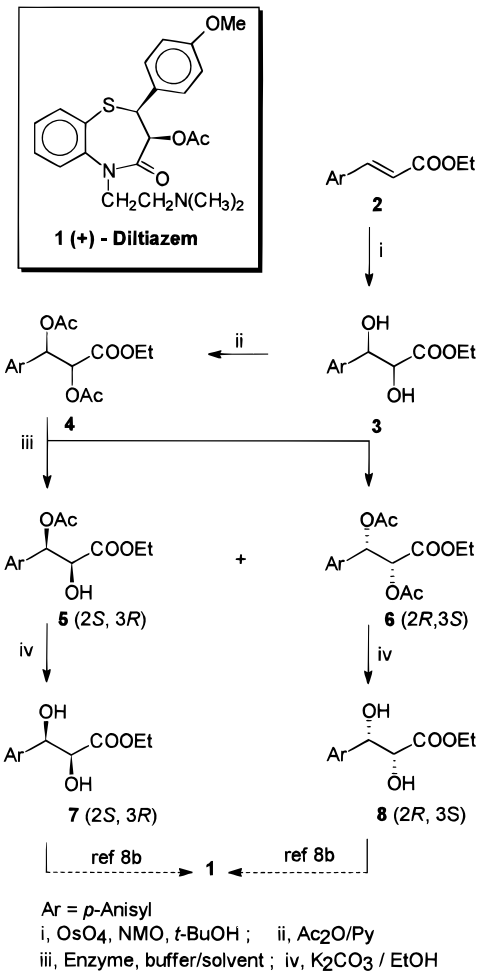
Diltiazem, (+)-*cis*-(2*S*,3*S*)-3-acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (**1**) is one of the most potent calcium channel blockers[1] in clinical use in more than 100 countries. At present the commercially used chemical route consists of condensation of a key intermediate, (±)-*trans*-*p*-methoxyphenylglycidic acid (PGA) methyl ester[2] with *o*-aminothiophenol (*o*-ATP), followed by late stage-resolution.[3] Asymmetric synthesis of (+)-diltiazem involves a diastereoface differentiating nucleophilic addition reaction of *o*-ATP to α-alkoxycinnamic acid derivatives.[4] Stereoselective chemical synthesis of (+)-diltiazem depends on the use of optically active (2*R*,3*S*)-PGA ester derivatives obtainable by asymmetric Darzens condensation,[5] Sharpless asymmetric epoxidation,[6] conventional resolution of PGA salts,[7] or stereospecific synthesis through (2*S*,3*R*)-**7** and (2*R*,3*S*)-**8** vicinal diols.[8] In recent years, enzymatic reactions have been increasingly used for the optical resolution of several functionalized chiral molecules.[9] Kinetic resolution of (±)-PGA ester (epoxy-ester) via lipase-catalyzed hydrolysis or alcoholysis of carbmethoxy function is known,[10] but suffers from the following limitations: (i) the hydrolysis being a subtractive process demands extensive purification of the desired unhydrolyzed isomer and the byproduct ((*p*-methoxyphenyl)acetaldehyde) formed causes enzyme inactivation[10a] and (ii) in alcoholysis, the highest optical purity (92−97% ee) was obtained only when the reactions were arrested much before completion (20−23% yield).[10b] The enzyme-catalyzed hydrolysis of (±)-methyl 2,3-dihydroxy-3-phenylpropionate (diol ester) using lipase from *Serratia marcescens* was slow[10c] whereas with pig liver esterase, very poor enantioselectivity (18−41% ee) was observed.[11]

Scheme 1



We reasoned that if the enzyme reaction is targeted directly on the diol system rather than the terminal carbalkoxy function, it may be possible to obtain a better selectivity. Hence we attempted the enzymatic resolution of (±)-*threo*-diacetate ethyl ester **4** (Scheme 1) and herein, report a highly chemo-, regio-, and enantioselective lipase catalysed hydrolysis of (±)-*threo*-**4** which leads to (+)-diltiazem precursors (2*S*,3*R*)-diol **7** and (2*R*,3*S*)-diol **8** in both high yield and optical purity.

The (±)-*threo*-diol ester **3** was prepared in 88% yield by dihydroxylation of (*E*)-ethyl 3-(4-methoxyphenyl)-propeonate (**2**) with catalytic amount of osmium tetraoxide[12] in presence of NMO in *t*-BuOH. Treatment of (±)-*threo*-diol ester **3** with acetic anhydride/pyridine at rt gave (±)-*threo*-diacetate **4** in 92% yield. For enzymatic hydrolysis of (±)-*threo*-diacetate **4**, we screened several

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(1) Abe, K.; Inoue, H.; Nagao, T. *Yakugaku Zasshi*. **1988**, *108*, 716.
(2) Hashiama ,T.; Inoue, H.; Takeda, M.; Aoe, K.; Kotera, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 421.
(3) (a) Senuma, M.; Shibazaki, M.; Nishimoto, S.; Shibata, K.; Okamura, K.; Date, T. *Chem. Pharm. Bull.* **1989**, *37*, 3204. (b) For late stage enzymatic resolution, see; Akita, H.; Enoti, Y.; Yamada, H.; Oishi, T. *Chem. Pharm. Bull.* **1989**, *37*, 2876 and 10b.
(4) (a) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T. *Tetrahedron Lett.* **1991**, *32*, 3519. (b) Miyata, O.; Shinada, T.; Naito, T.; Ninomiya, I.; Date, T.; Okamura, K. *Tetrahedron* **1993**, *49*, 8119.
(5) (a) Schwartz, A.; Madan, P. B.; Mohacsi, E.; O'Brien, J. P.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1992**, *57*, 851. (b) Sanada, K.; Inamoto, Y.; Kawai, S.; Endo, T. Jap. Pat. 61/268663 A2 [86268663], 1986.
(6) (a) Shionogi and Co. Ltd. U.S. Patent 4,552, 695, 1985. (b) Igarashi, H.; Konma, T. Ger. Pat. 3,415,035, 1984.
(7) Sawai Pharmaceuticals, Jap. Pat. 61-145173, 61-145174, 1986.
(8) (a) Lohray, B. B.; Jayachandran, B.; Bhushan, V.; Nandan, E.; Ravindranathan, T. *J. Org. Chem.* **1995**, *60*, 5983. (b) 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. (c) Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123. (d) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
(9) (a) Theil, F. *Chem. Rev.* **1995**, *95*, 2203. (b) Mori, K. *Synlett* **1995**, 1097.
(10) (a) Gentile, A.; Giordano, C.; Fuganti, C.; Ghirotto, L.; Servi, S. *J. Org. Chem.* **1992**, *57*, 6635. (b) Kanerva, L. T.; Sundholm, O. *J. Chem. Soc., Perkin Trans 1* **1993**, 1385. (c) Matsumae, H.; Shibatani, T. J. *Ferment. Bioeng.* **1994**, *77*, 152. (d) Dodds, D. R.; Lopez, J. L.; Zepp, C. M.; Brandt, S.; Rossi, R. F. PCT Int. Pat. 90/04643 A1, 1990. (e) Hulshof, I. A.; Roskam, J. H. Eur. Pat. 0343714 A1, 1989.
(11) Du, J. F.; Zhou, J.; Huang, L. *Chin. Chem. Lett.* **1992**, *3*, 95.
(12) Crispina, G. A.; Jeong, K. S.; Kolb, H. C.; Wang, Z. M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.

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Table 1. Biphasic Enzymatic Hydrolysis of (±)-Diacetate 4[e]

				(2*S*,3*R*)-hydroxy acetate **5**		(2*R*,3*S*)-diacetate **6**	
no.	enzyme	solvent (2:1)	time (h)	% conversion	% ee	% conversion	% ee
1	PPL	petroleum ether/benzene	140	12 (10)	92[a]	88 (83)	*d*
2	PLAP	petroleum ether/benzene	140	36 (35)	88[b]	64 (61)	51[c]
3	PLAP	diethyl ether	144	37 (32)	70[b]	62 (59)	*d*
4	PLAP	isooctane/benzene	156	20 (17)	96[a]	79 (77)	*d*
5	Amano PS	petroleum ether/benzene	100	40 (39)	98[b]	60 (57)	72[c]
6	Amano PS	isooctane/benzene	180	44 (42)	96−98[a−c]	56 (51)	86[c]

[a] By chiral shift reagent. [b] By ^{1}H NMR of MTPA-derivative of hydroxyacetate **5**. [c] By ^{1}H NMR of bis-MTPA-derivative of corresponding diol. [d] Not determined. [e] For entries 1−4, the reactions were carried out at 35 °C in 5 mM sodium phosphate buffer at pH 8.0, and for entries 5 and 6, reactions were done at 25 °C in 5 mM sodium phosphate buffer at pH 7.0. % Conversion refers to estimation by GC (HP-I, 3 m megabore column), and figures in bracket indicate isolated yield.

enzymes from microbial and animal sources, and the results obtained are summarized in Table 1. The biphasic enzymatic hydrolysis was selective to the (2*S*,3*R*)-isomer from (±)-*threo*-diacetate **4** with enzymes Amano PS, pig liver acetone powder (PLAP), and pig pancreatic lipase (PPL) while the enzymes bovine liver acetone powder (BLAP), Novozym-435, and Bioprotease-alk were ineffective in reaction. In control reactions without enzymes, the (±)-*threo*-diacetate ester **4** remained unreacted, proving absence of any accompanying chemical hydrolysis under the reaction conditions. The (±)-*threo*-diacetate **4**, with the enzyme Amano PS in phosphate buffer at pH 7.0 and isooctane:benzene (2:1) solvent system at 25 °C showed highest conversion (44%) of (2*S*,3*R*)-diacetate to (2*S*,3*R*)-hydroxyacetate **5** in 180 h as monitored by GC. The retention of both groups, ethyl ester and 3-acetoxy, in the hydrolysis product was indicated by the PMR spectrum of product mixture of **5** and **6**. A large upfield shift ($\Delta\delta$, 0.93) noticed for chemical shift of C-2 proton of the diacetate ester **4** upon the formation of hydroxyacetate **5**, relative to a minor difference observed for the C-3 proton ($\Delta\delta$, 0.18), gives the direct proof for the assigned structure for **5**. Thus the enzymatic hydrolysis was operative only on the C-2 acetoxy group of one isomer, amounting to a complete chemo- and regioselectivity.[13] The hydrolysis products were separated on a silica gel column to give (2*S*,3*R*)-hydroxyacetate **5** in 42% and (2*R*,3*S*)-diacetate **6** in 51% isolated yields. The optical purity of (2*S*,3*R*)-hydroxyacetate **5** was determined by PMR of its (i) complex with the chiral shift reagent, tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III) and (ii) derivatization to corresponding MTPA ester with (*S*)-(+)-MTPA-Cl,[14] and both methods concorded to a 96% ee. The (2*S*,3*R*)-hydroxyacetate **5** and (2*R*,3*S*)-diacetate **6** (obtained from Amano PS reaction in isooctane−benzene) were individually hydrolyzed with potassium carbonate (catalytic amount) in dry ethanol to the corresponding (2*S*,3*R*)-diol **7** and (2*R*,3*S*)-diol **8**, respectively, in 83−85% yield. The optical purity of both diols, as checked by PMR of their bis-MTPA derivatives, corresponded to 98% ee for **7** and 86% ee for **8**. Thus in three steps from (±)-**3**, overall yields of optically pure diols **7** and **8** were 33% and 39%, respectively. The conversion of both the diols **7** and **8** to (+)-diltiazem (**1**) is known in literature.[8b]

In summary, we have demonstrated a convenient and efficient enzymatic strategy for resolution of racemic (±)-*threo*-ethyl 3-(4-methoxyphenyl)-2,3-diacetoxypropionate via enantioselective hydrolysis of one of the vicinal diacetates (2*S*) rather than the terminal ester (carbethoxy) function. The specificity in hydrolysis is remarkable since it is not only chemoselective (acetate rather than terminal ester), but also accompanied by regio- (C-2 acetate is hydrolyzed and not C-3 acetate) and high enantioselectivity (hydrolysis of only 2*S* acetate). Given a multiple choice of ester functions in a single molecule, the enzyme prefers to hydrolyze a specific one; the selective hydrolysis of the central (C-2) acetate appears to be favored by electronic assistance from the oxygens of the neighboring ester groups. Enzymatic resolution as reported here, followed by solvolysis, enables access to enantiomerically pure diols (**7** and **8**), both of which can be processed by partially separate routes to obtain (+)-diltiazem.[8b]

Experimental Section

Stereochemical assignments are based on the optical rotation of the known compounds.[8a,b] Melting points are uncorrected. The term usual aqueous workup refers to pouring the reaction mixture in water, extraction with ethyl acetate, washing with water, aqueous bicarbonate, water, and brine, drying of organic layer over Na_2SO_4, and concentration under vacuo. Column chromatographic separations were done on ACME silica gel (100−200 mesh). Chiral shift reagent (Aldrich) and (+)-MTPA (Sigma) were used for NMR estimation of % ee. The enzymes used were PPL-35 U (Sigma), Amano PS-1420 U (Amano Pharmaceuticals), Novozym-435-18 U (Novo Nordisk Fermentation Ltd.), Bioprotease-alk (Biocon India Ltd.), PLAP-152 U, and BLAP-120 U. The activity of lipase powder used is expressed in terms of units, 1 unit corresponding to micromoles of butyric acid (estimation by GC) liberated from glyceryl tributyrate per minute per milligram of enzyme powder.[15]

(±)-*threo*-Ethyl 3-(4-Methoxyphenyl)-2,3-dihydroxypropionate (3). To a stirred solution of **2** (2.06 g, 10 mmol) in *tert*-butyl alcohol (25 mL) was added 60% aqueous NMO (15 mL) solution, and the reaction mixture was cooled to 0 °C. To this mixture, was added dropwise a solution of OsO_4 (40 mg, 0.02 mmol) in *tert*-butyl alcohol (1 mL). The reaction mixture was stirred at rt for 24 h, a fresh lot of NMO solution (10 mL) was added and stirred at rt for further 24 h, and reaction was quenched with an aqueous solution of sodium sulfite (25 mL, 20%). The mixture was stirred at rt for 1 h, filtered through Celite, concentrated in vacuo, and extracted with ethyl acetate (50 mL × 3). The organic layer upon usual workup gave a residue which was chromatographed on silica gel to obtain pure diol **3**: 2.1 g (88% yield); mp 67−69 °C; ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.25 (t, J = 7.3 Hz, 3H), 3.05 (bs, 1H), 3.35 (bs, 1H), 3.85 (s, 3H), 4.15−4.30 (q, J = 7.3 Hz, 2H), 4.33 (bs, 1H), 4.95 (bs, 1H), 6.90 (d, J = 9.8 Hz, 2H), 7.34 (d, J = 9.8 Hz, 2H). IR (Nujol) ν_{max} 3460, 1700, 1610 cm^{-1}.

(13) Amano PS-catalyzed acylation of **3** with vinyl acetate [petroleum ether:benzene (2:1), 25 °C, 96 h] at 45% conversion gave a mixture of diacetate, 2-acetoxy-3-hydroxy, and 2-hydroxy-3-acetoxy derivatives in 5.2, 30.2, and 10.2%, respectively, as seen by PMR, indicating a poor regioselectivity.

(14) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(15) Dupus, C.; Corre, C.; Boyaval, P. *Appl. Environ. Microbiol.* **1993**, *59*, 4004.

(±)-*threo*-Ethyl 3-(4-Methoxyphenyl)-2,3-diacetoxypropionate (4). To a stirred solution of diol **3** (1.92 g, 8 mmol) in pyridine (20 mL) was added acetic anhydride (15 mL), and the reaction mixture was kept in dark for 48 h at rt. On usual aqueous workup, ether extraction followed by concentration and column purification gave pure diacetate **4**: 2.38 g (92% yield): mp 56−58 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, J = 7.3 Hz, 3H), 2.10 (s, 3H), 2.14 (s, 3H), 3.80 (s, 3H), 4.15 (q, J = 4.8 Hz, 2H), 5.30 (d, J = 4.8 Hz, 1H), 6.23 (d, J = 4.8 Hz, 1H), 6.88 (d, J = 9.8 Hz, 2H), 7.42 (d, J = 9.8 Hz, 2H); ^{13}C NMR δ ($CDCl_3$, 50 MHz) 13.7, 20.0, 20.4, 54.9, 61.4, 73.3, 74.1, 113.6, 127.4, 128.2, 159.7, 166.8, 169.0, 169.5; MS (*m/e*) 324, 264, 222, 206, 193, 179, 161, 150, 137, 121, 109, 91, 77; IR (Nujol) ν_{max} 1740, 1730, 1720, 1610 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.10; H, 6.46.

Lipase-Catalyzed Hydrolysis of (±)-*threo*-Ethyl 3-(4-Methoxyphenyl)-2,3-diacetoxypropionate (4). A solution of (±)-diacetate **4** (324 mg, 1 mmol) in isooctane:benzene (2:1) mixture (20 mL) was added to a suspension of Amano PS lipase (275 mg) in 5 mM aqueous sodium phosphate (10 mL) at pH 7.0. The reaction mixture was stirred at 25 °C for 180 h after which it was filtered through Celite and extracted with ethyl acetate (25 mL × 3). The combined organic layer after usual workup and concentration in vacuo gave an oily residue which was subjected to column chromatography. Elution with 12% ethyl acetate:petroleum ether gave ethyl (2*R*,3*S*)-3-(4-methoxyphenyl)-2,3-diacetoxypropionate (**6**), 165 mg (51% yield): $[\alpha]^{25}_D$ = +26.4° (*c* 2.0, $CHCl_3$) (^{1}H NMR and IR spectral data identical with compound **4**) and with 18% ethyl acetate:petroleum ether gave ethyl (2*S*,3*R*)-3-(4-methoxyphenyl)-2-hydroxy-3-acetoxypropionate (**5**) 118 mg (42% yield): mp 48−50 °C, $[\alpha]^{25}_D$ = −37.1° (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30 (t, J = 8.1 Hz, 3H), 2.12 (s, 3H), 3.02 (bs, 1H), 3.85 (s, 3H), 4.25 (q, J = 8.1 Hz, 2H), 4.37 (bs, 1H), 6.05 (d, J = 2.7 Hz, 1H), 6.90 (d, J = 10.8 Hz, 2H), 7.35 (d, J = 10.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.2, 21.0, 55.4, 62.3, 73.8, 75.5, 114.0, 128.5−129.0 (2-carbons), 159.9, 169.9, 172.1. MS (*m/e*) 282, 223, 206, 179, 161, 149, 137, 121, 109, 104, 94, 77, 65. IR (Nujol) ν_{max} 3420, 1730, 1720, 1610 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 5.00. Found: C, 59.76; H, 5.16.

Hydrolyses reactions with other enzymes were similarly carried out on (±)-diacetate **4** (1 mmol) in organic solvent (20 mL) and buffer solution (10 mL) using PPL (500 mg), PLAP (500 mg), Amano PS (275 mg), Novozym-435 (300 mg), BLAP (500 mg), and Bioprotease-alk (275 mg). For details see Table 1.

MTPA-Ester of (2*S*,3*R*)-Hydroxyacetate 5. To a solution of hydroxyacetate **5** (14 mg, 0.05 mmol) in pyridine (0.1 mL) was added 0.5 M solution of (*S*)-(+)-MTPA-Cl[14] in EDC (0.2 mL) at 0 °C, and the reaction mixture was stirred at rt for 12 h. On usual aqueous workup, ether extraction and concentration in vacuo furnished MTPA-derivative of **5** as thick oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22 (t, J = 7.3 Hz, 3H), 2.10 (s, 3H), 3.48 (s, 3H), 3.83 (s, 3H), 4.20 (q, J = 7.3 Hz, 2H), 5.35 (d, J = 4.6 Hz), 5.43 (d, J = 4.2 Hz), 6.23 (d, J = 4.6 Hz), 6.33 (d, J = 4.2 Hz), 6.88 (d, J = 9.8 Hz, 2H), 7.28 (d, J = 9.8 Hz, 2H), 7.35−7.45 (m, 5H). On expansion, the signals at δ 6.23 and 6.33 were in a ratio of 0.02:0.98, indicating 96% ee. The ^{1}H NMR spectrum of (2*S*,3*R*)-hydroxyacetate **5** (10 mg) in $CDCl_3$ (0.5 mL) with chiralshiftreagent,tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III) (10 mg) in $CDCl_3$ (0.2 mL) indicated 96% ee [as seen by signal ratio (0.02 :0.98) for benzylic protons at δ 6.67 and 6.77, respectively].

Ethyl (2*S*,3*R*)-2,3-Dihydroxy-3-(4-methoxyphenyl)propionate (7). To an ice-cold solution of hydroxyacetate **5** (100 mg) in dry ethanol (2mL) was added anhyd K_2CO_3 (5 mg), and the reaction mixture was stirred at rt for 3 h after which it was filtered through Celite and washed with ethanol. The combined ethanol solution on concentration in vacuo gave a thick oil which was dissolved in ethyl acetate (15 mL), washed successively with water and brine, and dried over Na_2SO_4. Removal of ethyl acetate in vacuo followed by silica gel column chromatographic purification gave (2*S*,3*R*) diol **7**, 73 mg (86% yield): mp 87−89 °C; $[\alpha]^{25}_D$ = −4.8° (*c* 2.0, $CHCl_3$) (^{1}H NMR and IR identical to that of **3**).

Ethyl (2*R*,3*S*)-2,3-Dihydroxy-3-(4-methoxyphenyl)propionate (8). The reaction of diacetate **6** (100 mg) with anhyd K_2CO_3 (5 mg) in dry ethanol (2mL) for 16 h similarly furnished (2*R*,3*S*) diol **8**, 62 mg (84% yield): mp 88−90 °C, (lit.[8a] 68−70 °C); $[\alpha]^{25}_D$ = +4.3° (*c* 2.0, $CHCl_3$) [lit.[8a] +5.0° (*c* 1.08, $CHCl_3$)] (^{1}H NMR and IR identical to that of **3** and **7**).

Bis-MTPA-Esters of (±)-Diol 3, (2*S*,3*R*)-Diol 7, and (2*R*,3*S*)-Diol 8. To a solution of diol (12 mg, 0.05 mmol) in pyridine (0.1 mL) was added 0.5 M solution of (*S*)-(+)-MTPA-Cl[14] in EDC (0.3 mL) at 0 °C, and the reaction mixture was further stirred for 8 h at 0 °C. Usual workup furnished corresponding bis-MTPA-derivatives as thick oil, for analysis by ^{1}H NMR.

Bis-MTPA-esters of (±)-diol 3: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.16−1.30 (m, 6H), 3.40 (bs, 6H), 3.62 (bs, 6H), 3.82 (s, 3H), 3.87 (s, 3H), 4.12−4.25 (m, 4H), 5.41 (d, J = 2.9 Hz, 1H), 5.47 (d, J = 3.5 Hz, 1H), 6.48 (d, J = 2.9 Hz, 1H), 6.52 (d, J = 3.5 Hz, 1H), 6.62 (d, J = 9.7 Hz, 2H), 6.84 (d, J = 9.7 Hz, 2H), 7.11 (d, J = 9.7 Hz, 2H), 7.21 (d, J = 9.7 Hz, 2H), 7.30−7.52 (m, 20H).

Bis-MTPA-ester of (2*S*,3*R*)-diol 7: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3(*S*)-H, 6.47 (d, J = 2.9 Hz), 3(*R*)-H, 6.52 (d, J = 3.5 Hz), the integral ratios of these protons indicated 98% ee of (2*S*,3*R*)-diol **7**.

Bis-MTPA-ester of (2*R*,3*S*)-diol 8: ^{1}H NMR ($CDCl_3$, 200 MHz), δ 2(*R*)-H 5.40 (d, J = 2.9 Hz), 2(*S*)-H 5.48 (d, J = 3.5 Hz), the integral ratios correspond to 86% ee of (2*R*,3*S*)-diol **8**.

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Supporting Information Available: ^{1}H NMR spectra of **4**, **5**, MTPA derivative of **5**, and bis-MTPA derivatives of **3** and **7** (10 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 the ACS; see any current masthead page for ordering information.

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