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Facile synthesis of optically pure (*S*)-3-*p*-hydroxyphenyllactic acid derivatives

Short Communication

Q. L. Zeng[1], **H. Q. Wang**[1], **Z. R. Liu**[2], **B. G. Li**[2], and **Y. F. Zhao**[1]

[1] Key Laboratory for Chemical Biology of the Province of Fujian, Department of Chemistry, Xiamen University, Xiamen, China
[2] Institute of Pharmacy, Chengdu Di'ao Pharmaceutical Group, Chengdu, China

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Summary. Optically pure (*S*)-3-*p*-hydroxyphenyllactic acid derivatives are important intermediates of peroxisome proliferator-activated receptor α/γ dual agonists and heteropeptides. Many efforts have been made for synthesis of those intermediates, but there exist some flaws yet. We observed that dielectric constants of organic solvents drastically affected diazotization of *O*-benzyl-L-tyrosine. Optically pure (*S*)-3-*p*-benzyloxyphenyllactic acid was obtained by simple recrystallization when DMF or DMSO of higher dielectric constant was used as a co-solvent in diazotization of *O*-benzyl-L-tyrosine. It was easily turned into various optically pure (*S*)-3-*p*-hydroxyphenyllactic acid derivatives.

Keywords: Solvent effects – Diazotization – *O*-Benzyl-L-tyrosine – (*S*)-3-*p*-Benzyloxyphenylpropionic acid – (*S*)-*p*-Hydroxyphenyllactic acid

Introduction

Optically pure (*S*)-*p*-hydroxyphenyllactic acid derivatives are important intermediates of the peroxisome proliferator-activated receptor α/γ dual agonists, such as SB-219994, SB-236636 (Haigh et al., 1999a, b), Tesaglitazar (Andersson, 1999), carbazole derivatives (Sauerberg et al., 2002), and heteropeptides, such as SF608 (Valls et al., 2002), Aeruginosin 298-A and Aeruginosin 298-B (Ishida et al., 1999; Valls et al., 2001).

There are many processes for the synthesis of optically active *p*-hydroxyphenyllactic acid derivatives. Catalytic hydrogenation of ethyl 2-ethyl-*p*-benzyloxyphenylpropenate with various chiral catalysts gave a product with only low enantiomeric excess (ee) (Deussen et al., 2003). Under severe conditions, cyanosilylation of *p*-benzyloxyphenyl-acetaldehyde and then hydrolyzation gave 3-*p*-benzyloxyphenylpropionic acid with high ee (Takamura et al., 2002). Reduction of *p*-hydroxyphenylpyruvic acid with (+)-*B*-chlorodiisopinocampheylborane gave (*S*)-3-*p*-hydroxyphenyllactic acid with moderate to good ee value (Valls et al., 2001; Wang et al., 1998).

Diazotization of the expensive unnatural *L* form *p*-aminophenylalanine gave (*S*)-3-*p*-hydroxyphenyllactic acid with low yield (Ishida et al., 1999). Diazotization of *O*-benzyl-L-tyrosine with isoamyl nitrite gave 2-AcO-3-*p*-benzyloxyphenylpropionic acid with only 70% ee (Valls et al., 2002).

Recently, chloroform, tetrahydrofuran, 1,4-dioxane, or acetone was adopted as co-solvent in diazotization of *O*-benzylated L-tyrosine (Potlapally et al., 2002). Although the chiral reagent L-tyrosine was used, chiral resolution was still required. The synthetic route needed eight steps and its yield was very low.

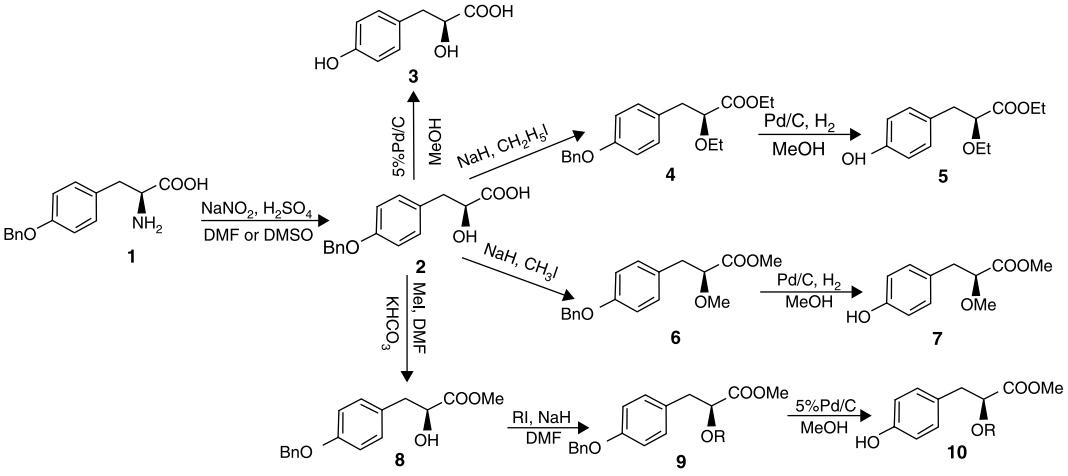
Enantioselective enzyme-catalyzed hydrolysis of racemic ethyl 2-ethyl-*p*-hydroxyphenylpropionate gave *S* form 2-ethyl-*p*-hydroxyphenylpropionic acid with excellent ee value (Deussen et al., 2003). However, racemic substrate should be synthesized in multiple steps and the process has only 50% yield in theory.

Prompted by the difficulty to access the important intermediates and our extensive research on amino acids (Zeng et al., 2002a, b, 2004, 2005a, b; Weng et al., 2004), we successfully tried to improve the process.

Results and discussion

When repeating the literature procedure (Potlapally et al., 2002), we observed that co-solvents significantly affected

the diazotization of *O*-benzyl-L-tyrosine. When chloroform was added in the reaction as a co-solvent, there was hardly any 3-*p*-benzyloxyphenyllactic acid. When THF was added, a little product was observed. When acetone was used, *O*-benzylated L-tyrosine **1** was mostly transformed into the desired compound **2**. But it could not be separated by a simple method, such as recrystallization or extraction. Inspecting the relation of various co-solvents, we



Scheme 1. Synthesis of various (*S*)-3-*p*-hydroxyphenyllactic acid derivatives

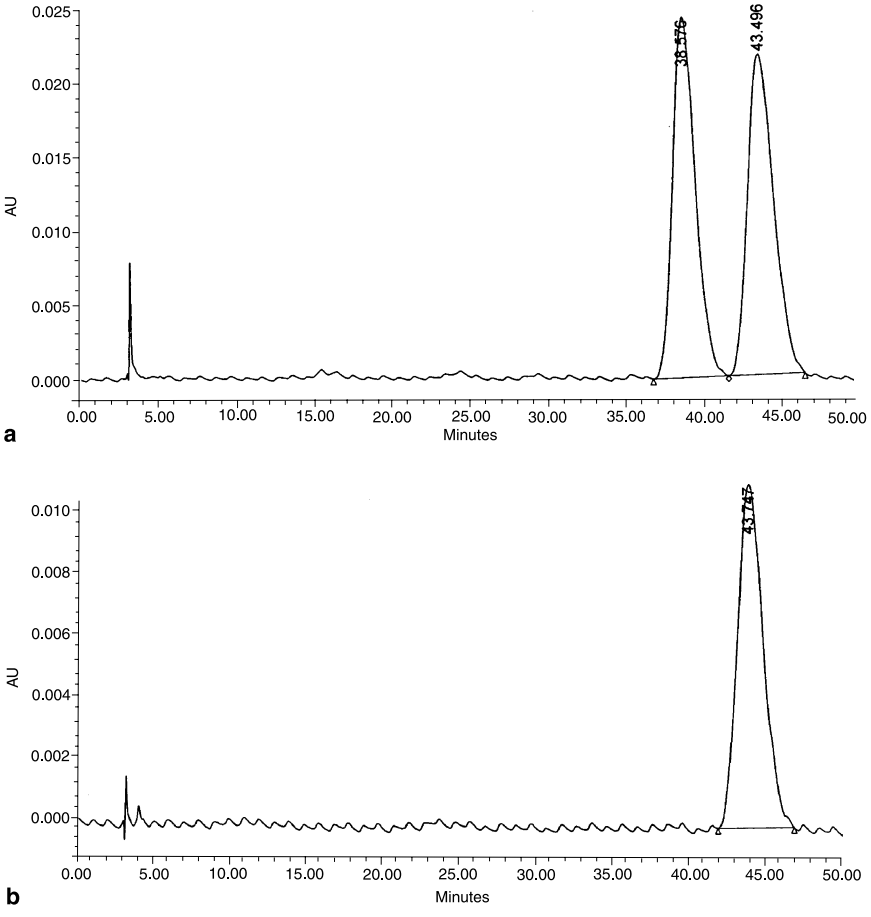


Fig. 1. Racemic (**a**) and optically pure (**b**) methyl (*S*)-2-methoxyl-3-*p*-hydroxyphenylpropionate **7**

found conversions of *O*-benzylated L-tyrosine **1** increased when their dielectric constants increased (the dielectric constants of $CHCl_3$, THF, and CH_3COCH_3 are 4.8 [25 °C], 7.5 [22 °C] and 20.7 [25 °C], respectively) (Dean, 1999).

When a solvent with a larger dielectric constant such as DMF (38.2, 20 °C), DMSO (47.2) (Dean, 1999) was adopted, we surprisingly observed that no *O*-benzylated L-tyrosine **1** was left (Scheme 1). Furthermore, the crude product was pure enough to obtain pale yellow needle crystal **2** with moderate yield by recrystallization.

In order to determine the absolute configuration of 3-*p*-benzyloxyphenyllactic acid **2**, the benzyl group was deprotected by hydrogenolysis in the presence of Pd/C to give 3-*p*-hydroxyphenyllactic acid **3** (Scheme 1). Compared with literature data (Sasaki and Otsuka, 1917), the relative rotation of compound **3** has the same orientation and a similar value (probably the small sample amount resulted in some error). Thus, even if 3-*p*-benzyloxyphenyllactic acid **2** is not 100% *S* form isomer, at least the *S* form isomer is predominant. The ee of (*S*)-3-*p*-benzyloxyphenyllactic acid **2** was not directly determined, but its derivative methyl (*S*)-2-methoxyl-3-*p*-hydroxyphenylpropionate **7** would be analyzed by chiral HPLC.

(*S*)-3-*p*-Benzyloxyphenyllactic acid **2** was facilely turned into its diethyl or dimethyl derivative **4** or **6**, and the latter was further deprotected into ethyl (*S*)-2-ethoxyl-3-*p*-hydroxyphenylpropionate **5** or methyl (*S*)-2-methoxyl-3-*p*-hydroxy-phenylpropionate **7** (Scheme 1).

(*S*)-3-*p*-Benzyloxyphenyllactic acid **2** could also be esterified into various esters **8** (methyl ester), and then the hydroxyl groups of the esters **8** were alkylated into various ethers **9**, and finally the removal of benzyl gave (*S*)-*p*-hydroxyphenyllactic acid derivatives **10** (Scheme 1). Thus, various *p*-hydroxyphenyllactic acid derivatives can be obtained.

In order to test the optical purity of the products, racemic methyl (±)-2-methoxyl-3-*p*-hydroxyphenylpropionate **7** was synthesized according to the procedure for methyl (*S*)-2-methoxyl-3-*p*-hydroxyphenylpropionate **7** when racemic *O*-benzylated DL-tyrosine **1** was used.

After several chiral columns were screened, racemic methyl (±)-2-methoxyl-3-*p*-hydroxyphenylpropionate **7** was baseline-resolved on a Daicel Chiralcel OJ column (Fig. 1a). Under the same condition, the HPLC spectrum of methyl (*S*)-2-methoxyl-3-*p*-hydroxyphenylpropionate **7** showed only one peak and thus demonstrated that methyl (*S*)-2-methoxyl-3-*p*-hydroxyphenylpropionate **7** was 100% ee (Fig. 1b).

Optically pure methyl (*S*)-2-methoxyl-3-*p*-hydroxyphenylpropionate **7** suggests that its precursor (*S*)-3-*p*-benzyloxyphenyllactic acid **2** was 100% ee and no racemization occurred in the next two-step reactions. Synthesized by similar reactions, other derivatives **5** and **10** would also be optically pure as was compound **7**.

In order to further confirm high optically pure (*S*)-3-*p*-benzyloxyphenyllactic acid **2**, a chunk single crystal **2** was picked out and crystal data were collected on a Bruker SMART APEX area-detector diffractometer. Its ORTEP draw shows that the two phenyl groups are essentially coplanar by $\pi-\pi$ interaction and intermolecular O–H···O hydrogen bonds. The ORTEP diagrams are shown in Figs. 2 and 3. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number RM6049 (Wang et al., 2005).

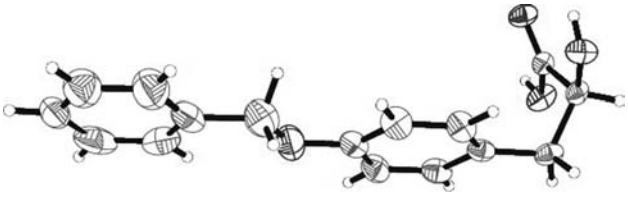


Fig. 2. ORTEP diagram for (*S*)-3-*p*-benzyloxyphenyllactic acid **2**. Thermal ellipsoids are drawn at the 50% probability level

Fig. 3. Stacked ORTEP diagram of (*S*)-3-*p*-benzyloxyphenyllactic acid **2**

Conclusion

We found that dielectric constants of organic solvents hugely influenced the diazotization of *O*-benzyl-L-tyrosine. Optically pure (*S*)-3-*p*-benzyloxyphenyllactic acid was obtained by simple recrystallization when DMF or DMSO was used as co-solvents. It was transformed into various (*S*)-3-*p*-hydroxyphenyllactic acid derivatives without racemization during the reactions. The process is economic, operation-easy and suitable for large-scale production. Besides, a single crystal of (*S*)-3-*p*-benzyloxyphenyllactic acid was cultured.

Experimental

Melting points were measured on an electro-thermal digital melting point apparatus. Optical rotation data were recorded on a Perkin-Elmer Model 341 polarimeter. Electrospray ionization mass (ESI-MS) spectra were recorded using a Bruker Esquire-3000 mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance instrument. Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. Ee values were determined by chiral HPLC analysis on Daicel Chiralcel OJ column.

(S)-3-p-Benzyloxyphenyllactic acid (**2**)

To a solution of H_2SO_4 (1 M, 78 ml) and DMF (38 ml), *O*-benzylated L-tyrosine **1** (6.775 g, 25.0 mmol) was added. The suspensive mixture was stirred to dissolve and then cooled with ice water. A solution of $NaNO_2$ (8.134 g, 117.9 mmol) in H_2O (20 ml) was dropwise added into the resulting solution. After one hour, H_2SO_4 (3.2 M, 20 ml) was added slowly, and the resulting solution was stirred overnight. The reaction mixture was extracted by ethyl acetate (3×100 ml), and organic layer was washed by water (3×40 ml), saturated NaCl solution (1×30 ml), and then dried over anhydrous $MgSO_4$, filtered. After solvent was removed under reduced pressure, yellow liquid was obtained and solidified after a while. The crude product showed a negative result with ninhydrin reactions. The solid was recrystalized with *n*-hexane and ethyl acetate (1/2 ratio) to give the acid **2** (3.457 g) as pale yellow needle crystal or solid. Yield: 50.8%. Mp 150–152 °C (lit. 140–142 °C for >98% ee *R* form [Valls et al., 2001]). $[\alpha]^{20}_D - 11.5°$ (*c* 0.52, EtOH) (lit. +14° [*c* 0.61, MeOH] for >98% ee *R* form [Valls et al., 2001]). ^{1}H NMR (600 MHz, $CDCl_3$). δ 2.60 (br, 2H), 2.96 (dd, 1H, $J_1 = 14.4$ Hz, $J_2 = 7.8$ Hz), 3.17 (dd, 1H, $J_1 = 14.4$ Hz, $J_2 = 4.2$ Hz), 4.49 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 4.2$ Hz), 5.05 (s, 2H), 6.94 (d, 2H, $J = 8.4$ Hz), 7.18 (d, 2H, $J = 8.4$ Hz), 7.33 (t, 1H, $J = 7.2$ Hz), 7.39 (t, 2H, $J = 7.2$ Hz), 7.43 (d, 2H, $J = 7.2$ Hz). ^{13}C NMR (150 MHz, CD_3COCD_3). δ 39.6, 69.7, 71.4, 114.6, 127.6, 127.8, 128.5, 130.1, 130.7, 137.9, 157.8, 174.5. ESI-MS (*m*/*z*): 271 $[M-H]^-$, 543 $[2M-H]^-$. IR (KBr) ν: 3450, 1729, 1614, 1514, 1454, 1383, 1299, 1254, 1180, 1113, 1080, 1044, 1028, 821, 739, 696 cm^{-1}.

(S)-3-p-Hydroxyphenyllactic acid (**3**)

In the presence of 5% Pd/C (30 mg), hydrogen was passed through a methanol (20 ml) solution of (*S*)-benzyloxyphenyllactic acid **2** (96 mg, 0.353 mmol). After 3 h, the reaction was complete. When 5% Pd/C was filtered and solvent was removed, (*S*)-3-*p*-hydroxyphenyllactic acid **3** (56 mg) as white needle crystal was obtained. Yield: 87.2%. Mp 163–165 °C (lit. 164–165 °C [Valls et al., 2001]). $[\alpha]^{20}_D - 17.0°$ (*c* 0.20, H_2O) [lit. $[\alpha]^{15}_D - 19.5°$ [H_2O] [Sasaki and Otsuka, 1917]). ^{1}H NMR (600 MHz, D_2O): δ 2.80 (dd, 1H, $J_1 = 14.1$ Hz, $J_2 = 7.5$ Hz), 2.94 (dd, 1H, $J_1 = 14.1$ Hz, $J_2 = 4.5$ Hz), 4.35 (t, 1H, $J = 6.0$ Hz), 6.73 (d, 2H, $J = 8.4$ Hz), 7.05 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (600 MHz, D_2O). δ 38.9, 71.5, 115.5, 128.8, 131.0, 154.4, 177.4. ESI-MS (*m*/*z*): 205 $[M+Na]^+$, 386 $[2M+Na]^+$. IR (KBr) ν 3479, 3321, 3027, 1723, 1614, 1598, 1514, 1450, 1235, 1107, 1072, 834 cm^{-1}.

Ethyl (S)-2-ethyloxy-3-p-benzyloxyphenylpropionate (**4**)

(*S*)-Benzyloxyphenyllactic acid **2** (136 mg, 0.50 mmol) was dissolved in dry DMF (10 ml) with a dry tube filled with anhydrous $CaCl_2$. To the resulting solution, NaH (44 mg, 1.83 mmol) was added. After 30 min, iodoethane (0.3 ml) was added. The resulting mixture was stirred overnight. The mixture was poured into water and extracted with ethyl acetate (2×15 ml), washed with water (3×10 ml) and saturated NaCl solution (10 ml). Then the organic layer was dried over anhydrous $MgSO_4$ and filtered. After solvent was removed, red liquid was obtained and purified on a silica gel chromatograph (petroleum ether/AcOEt [10/1, 5/1]) to give the ester **4** (101 mg) as colorless oil. Yield: 47.4%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.18 (t, 3H, $J = 7.2$ Hz), 1.23 (t, 3H, $J = 7.2$ Hz), 2.97 (d, 2H, $J = 7.2$ Hz), 3.34–3.39 (m, 1H), 3.59–3.64 (m, 1H), 3.98 (t, 1H, $J = 6.6$ Hz), 4.17 (q, 2H, $J = 7.2$ Hz), 5.05 (s, 2H), 6.91 (d, 2H, $J = 8.4$ Hz), 7.17 (d, 2H, $J = 8.4$ Hz), 7.32 (t, 1H, $J = 7.2$ Hz), 7.39 (t, 2H, $J = 7.2$ Hz), 7.44 (d, 2H, $J = 7.2$ Hz). ESI-MS (*m*/*z*): 351 $[M+Na]^+$, 657 $[2M+H]^+$. IR (neat) ν: 1749, 1612, 1512, 1456, 1377, 1243, 1176, 1119, 1026 cm^{-1}.

Methyl (S)-2-methoxyl-3-p-benzyloxyphenylpropionate (**6**)

With a procedure similar to the synthesis of ethyl (*S*)-2-ethyloxy-3-*p*-benzyloxyphenylpropionate **4**, 200 mg of (*S*)-benzyloxyphenyllactic acid **2** gave the ester **6** (192 mg) as colorless, transparent oil. Yield: 87.0%. $[\alpha]^{20}_D - 9.6$ (*c* 0.46, EtOH). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.97 (m, 2H), 3.36 (s, 3H), 3.72 (s, 3H), 3.95 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 5.4$ Hz), 5.05 (s, 2H), 6.91 (d, 2H, $J = 8.4$ Hz), 7.15 (d, 2H, $J = 8.4$ Hz), 7.33 (t, 1H, $J = 7.2$ Hz), 7.39 (t, 2H, $J = 7.2$ Hz), 7.44 (d, 2H, $J = 7.2$ Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 38.5, 52.0, 58.5, 70.2, 82.1, 114.9, 127.6, 128.1, 128.7, 129.4, 130.5, 137.3, 157.8, 172.8. ESI-MS (*m*/*z*): 323 $[M+Na]^+$. IR (neat) ν: 1750, 1611, 1584, 1512, 1454, 1243, 1200, 1177, 1118, 1024 cm^{-1}.

Ethyl (S)-2-ethoxyl-3-p-hydroxyphenylpropionate (**5**)

(*S*)-Benzyloxyphenyllactic acid **2** (136 mg, 0.5 mmol) was transformed into ethyl (*S*)-2-ethyloxy-3-*p*-benzyloxyphenylpropionate **4** according to the procedure for compound **4**. Hydrogen was passed through the crude product in methanol in the presence of 5% Pd/C (50 mg). After 5 h, Pd/C was filtered and solvent was removed. The resulting residue was purified on a silica gel column chromatograph (petroleum ether/AcOEt [10/1]) to give the ester **5** (56 mg) as yellow oil. Yield: 48.7% in two steps. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (t, 3H, $J = 7.2$ Hz), 1.23 (t, 3H, $J = 7.2$ Hz), 2.96 (d, 2H, $J = 7.2$ Hz), 3.31–3.41 (m, 1H), 3.55–3.65 (m, 1H), 3.98 (t, 1H, $J = 6.6$ Hz), 4.17 (q, 2H, $J = 7.2$ Hz), 5.25 (br, 1H), 6.74 (d, 2H, $J = 8.4$ Hz), 7.10 (d, 2H, $J = 8.4$ Hz), 7.10 (d, 2H, $J = 8.4$ Hz). ESI-MS (*m*/*z*): 239 $[M+H]^+$, 261 $[M+Na]^+$. IR (neat) ν: 3400, 2979, 1730, 1614, 1596, 1517, 1446, 1370, 1267, 1222, 1115, 1029, 835 cm^{-1}.

Methyl (S)-2-methoxyl-3-p-hydroxyphenylpropionate (**7**)

With a procedure similar to the synthesis of ethyl (*S*)-2-ethoxyl-3-*p*-hydroxyphenylpropionate **5**, 191 mg of methyl (*S*)-2-methoxyl-3-*p*-benzyloxyphenylpropionate **6** gave the ester **7** (109 mg) as pale yellow oil. Yield: 81.5%. $[\alpha]^{20}_D - 11.1$ (*c* 0.44, EtOH). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.19 (s, 1H), 2.91–2.99 (m, 2H), 3.35 (s, 3H), 3.72 (s, 3H), 3.95 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 5.4$ Hz), 6.73 (d, 2H, $J = 8.4$ Hz), 7.06 (d, 2H, $J = 8.4$ Hz). ^{13}C

NMR (150 MHz, $CDCl_3$): δ 38.4, 52.1, 58.5, 82.1, 115.5, 128.8, 130.6, 154.8, 173.0. ESI-MS (m/z): 233 $[M+Na]^+$, 443 $[2M+Na]^+$. IR (neat) ν: 3391, 1738, 1662, 1615, 1596, 1517, 1455, 1370, 1207, 1116, 1022, 949 cm^{-1}.

Chiral HPLC analysis (Daicel Chiralcel OJ column [250 × 4.6 m], *i*-PrOH/*n*-hexane [10:90, v/v], 1.0 ml/min^{-1}, 25 °C, UV 254 nm): t_1 = 38.5 min (*R*), t_2 = 43.5 min (*S*). There is only one peak in the HPLC spectra of the product **7**, retention time of which is 43.7 min, which testifies product **7** being optically pure, that is, 100% ee.

(S)-3-(4-Benzyloxy-phenyl)-2-hydroxy-propionic acid methyl ester (**8**)

(*S*)-Benzyloxyphenyllactic acid **2** (319 mg, 1.173 mmol), dry DMF (15 ml), and $KHCO_3$ (400 mg) were added into a flask (50 ml) with a stirrer. Then the flask was capped with rubber stopper and cooled with ice water bath. CH_3I (0.2 ml) was injected into the flask. After stirring overnight, the resulting mixture was quenched by addition of water (30 ml) and extracted with ethyl acetate (3 × 20 ml), washed with water (3 × 10 ml) and saturated NaCl solution (10 ml). The organic layer was dried over $MgSO_4$, filtered, and condensed under reduced pressure. The crude product was purified by a column chromatograph (petroleum ether/AcOEt [10/1, 5/1]) to give the ester **8** (288 mg) as pale yellow solid. Yield: 85.8%. Mp 59–60 °C. $[\alpha]^{20}_D$ + 5.9 (*c* 0.44, EtOH). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.37 (br, 1H), 2.92 (dd, 1H, J_1 = 14.4 Hz, J_2 = 6.6 Hz), 3.08 (dd, 1H, J_1 = 14.4 Hz, J_2 = 4.2 Hz), 3.78 (s, 3H), 4.43 (t, 1H, J = 5.4 Hz), 5.05 (s, 2H), 6.92 (d, 2H, J = 8.4 Hz), 7.33 (t, 1H, J = 7.2 Hz), 7.39 (t, 2H, J = 7.2 Hz), 7.44 (d, 2H, J = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 39.8, 52.6, 70.2, 71.5, 115.0, 127.6, 128.1, 128.7, 130.7, 137.2, 158.0, 174.8. ESI-MS (m/z): 309 $[M+Na]^+$, 594 $[2M+Na]^+$. IR (neat) ν: 3487, 3033, 1738, 1610, 1583, 1512, 1454, 1243, 1176, 1113, 1025 cm^{-1}.

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Authors' address: Prof. Qing-Le Zeng, Department of Chemical Engineering and Pharmaceutics, Chengdu University of Technology, Chengdu 610059, People's Republic of China,
Fax: +86-28-84077066, E-mail: qlzeng@cdut.edu.cn