Efficient Synthesis of Antihyperglycemic (*S*)-α-Aryloxy-β-phenylpropionic Acid Using a Bifunctional Asymmetric Catalyst

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Received March 1, 2002; accepted May 26, 2002

Antihyperglycemic (*S*)-α-aryloxy-β-phenylpropionic acid was prepared using catalytic asymmetric cyanosilylation as a key reaction to construct α-oxycarboxylic acid moiety.

Key words asymmetric catalysis; antihyperglycemic agent; PPARγ; bifunctional catalyst

Antihyperglycemic thiazolidine-2,4-diones, such as troglitazone,[1] rosiglitazone[2] and pioglitazone,[3] are believed to be ligands for peroxisome proliferator-activated receptor γ (PPARγ) and improve insulin resistance in insulin target organs.[4,5] Recently some research groups revealed that α-oxy-β-phenylpropionic acids, as well as 5-benzylthiazolidine-2,4-diones, possess potent PPARγ agonistic activity and glucose lowering activity.[6,7] According to this knowledge we synthesized novel oxime derivatives having α-oxy-β-phenylpropionic acid moiety, which indicates strong antihyperglycemic activity.[8] In this series, compound **1** (Chart 1) shows potent antihyperglycemic activity compared to rosiglitazone.[9] It is known that enantiomers of α-oxy-β-phenylpropionic acids show different antihyperglycemic activities,[10] however, we are not aware of any practical methods for preparing optically active α-oxy-β-phenylpropionic acids.[10—12] Meanwhile, some of the authors have developed a highly enantioselective catalytic cyanosilylation of aldehydes with broad substrate generality, using a Lewis acid–Lewis base bifunctional catalyst **4** (Chart 2).[13,14] We now describe a practical route to **1** using catalytic asymmetric cyanosilylation as a key step.

Results and Discussion

Although excellent results were obtained from a wide range of aldehydes by the catalytic enantioselective cyanosilylation using **4**, there have been no precedents of using an easily enolizable and unstable aryl acetaldehyde such as **3**[15] as a substrate. Therefore, we were pleased when we found that application of the representative procedure (9 mol% of catalyst **4**, 36 mol% of $Bu_3P(O)$, 1.8 eq of TMSCN [slow addition for 10 h], CH_2Cl_2 solvent at −40 °C for 60 h) gave the product cyanohydrin **2** in 89% yield with 97% ee on a 0.25 mmol scale of **3** (*ca.* 50 mg). However, on a 0.5 mmol scale, the reaction became slow and the ee of the product was decreased to 74% (80% yield for 60 h). A similar problem in scale-up of this reaction was also reported in ref. 14 and which was solved by adding MeOH as an additive. Thus, we tried the cyanosilylation using TMSCN pre-mixed with 10 mol% of MeOH.[16] Then, the reaction rate and the enantioselectivity became satisfactory, and product **2** was obtained in 85% yield with 96% ee on a 0.5 mmol scale of the substrate. Therefore, the addition of proton source is essential for the present reaction (Chart 2).

Based on the previous mechanistic studies, a proposed catalytic cycle and possible role of the proton source are depicted in Chart 3. After the intramolecular transfer of the cyanide through dual activation of the aldehyde and TMSCN by the Lewis acid and the Lewis base (**12**), catalytically inactive species **13** should be generated. If the proton source is not present, the transfer of the silyl cation to the oxide of the product cyanohydrin might be slow. So, before the silyl cation is trapped by the oxide, it could promote a racemic reaction, thus decreasing the ee of the product.[17] On the other hand, if the proton source (HCN) is present, the oxide should be immediately trapped by the proton and the silyl cation should be converted to TMSCN, thus regenerating the active catalyst **10**. The resulting free cyanohydrin was proved to be silylated by TMSCN under the reaction conditions, thus the proton source should be regenerated. Therefore, the proton source should catalytically facilitate the regeneration of the active enantioselective catalyst.[18,19]

Our synthetic procedure is depicted in Chart 2. Refluxing **2** with 12 N HCl in degassed ethanol gave the α-hydroxyester **5** and undesired hydrolyzed and/or debenzylated compounds. To recover these compounds, esterification and benzylation were performed and **5** was obtained from **2** in a yield of 81% in all. The α-hydroxyester **5** was initially converted to the α-phenoxyester **6** under standard Mitsunobu reaction conditions, *i.e.* a solution of diethyl azodicarboxylate in toluene was added to the solution of **5** and 4-*t*-butylphenol in toluene for 5 min at 0 °C. The chemical yield was 50% and by-product **19**[20] was obtained in 20% yield. A plausible reaction mechanism for generating **19** is depicted in Chart 4. We supposed that α-keto acid **17** is generated to some extent by deprotonation of the intermediate **14** instead of phenol **16**, then

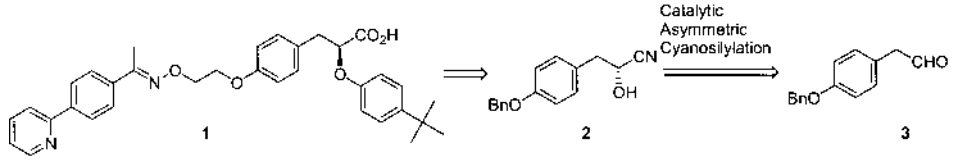

Chart 1

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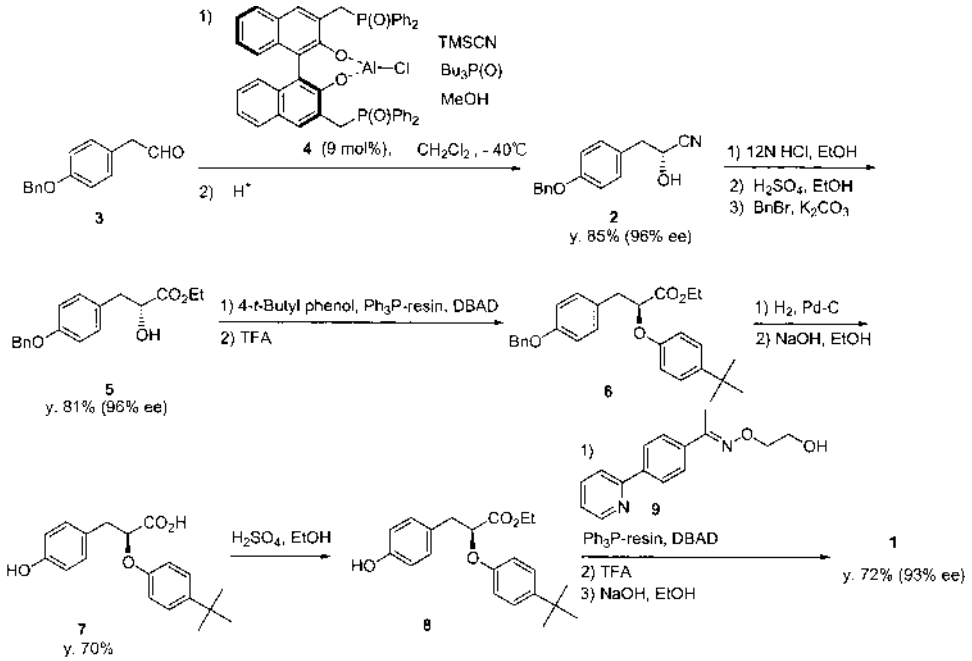

Chart 2

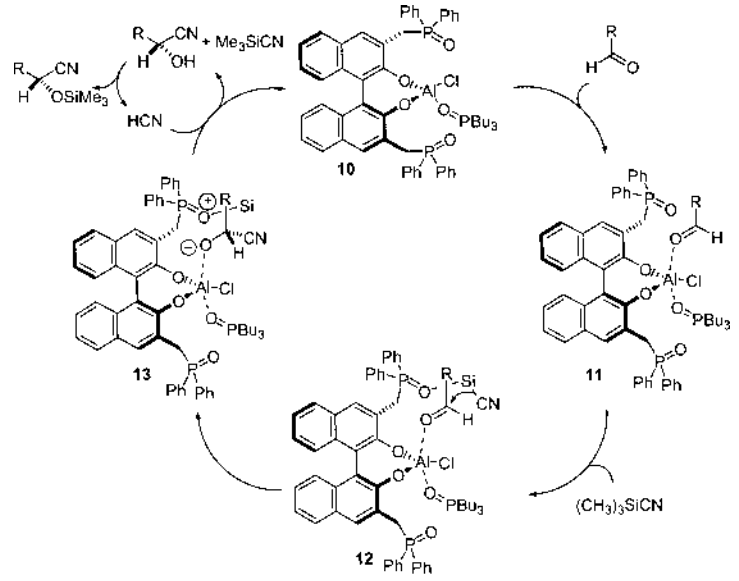

Chart 3

deprotonation of **17** at the β-position gives **18** which reacted with **14** to afford **19**. To avoid the side reaction, we prolonged the addition time of diethyl azodicarboxylate to 10 h so that the yield of **6** was improved to 80% and by-product **19** could not be detected. Next we further optimized the reaction conditions to avoid chromatographic purification after the Mitsunobu reaction. We adopted the modified Mitsunobu reaction developed by Pelletier and Kincaid[21] in which triphenylphosphine resin and di-*t*-butyl azodicarboxlate (DBAD) are employed (a solution of DBAD in toluene was added for 10 h). After treatment of the reaction products with TFA in order to decompose excess DBAD and its hydrazine dicarboxylate, triphenylphosphine resin and its oxide were removed by filtration. Evaporation and aqueous work up gave crude **6**. To avoid chromatographic purification, the obtained crude **6** was converted to easily crystallizable carboxylic acid **7** *via* deprotection of the benzyl group by hydrogenation and subsequent alkaline hydrolysis. After aqueous work up and crystallization, **7** was obtained in 70% yield (3 steps from **5**). Esterification gave the phenol **8**, which was subjected to the modified Mitsunobu reaction with the oximealcohol **9** as mentioned above and subsequent alkaline hydrolysis to afford the desired (*S*)-α-aryloxy-β-phenylpropionic acid **1** without purification by chromatographic technique in 70% yield (2 steps).

In summary, an efficient synthesis of non-thiazolidine-2,4-dione antihyperglycemic agent **1** has been achieved by the use of a bifunctional asymmetric catalyst. We also utilized Pelletier's modified Mitsunobu reaction conditions in which triphenylphosphine resin and di-*t*-butyl azodicarboxylate is

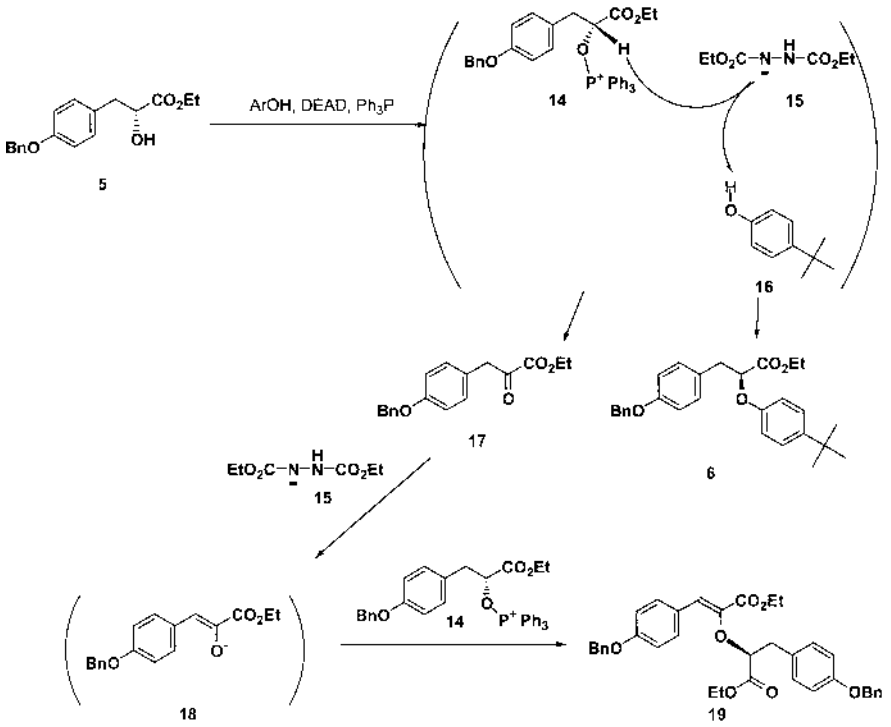

Chart 4

used for avoiding chromatographic purification. This report provides a synthetic method which could be applicable to antihyperglycemic agents having chiral α-oxy-β-phenylpropionic acid moiety. Further extention of this route to large scale synthesis and evaluation of the pharmaceutical use of **1** are currently under investigation.

Experimental

Melting points (mp) were determined with a Yanaco melting point apparatus and are not corrected. Infrared (IR) spectra were measured with a Nic 5SXCFT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Mercury 400 or 500 spectrometer. Chemical shifts were expressed in δ ppm from the internal standard tetramethylsilane (TMS). MS or high-resolution mass spectra (HR-MS) were obtained on a JEOL JMS-D 300 mass spectrometer. Optical rotations ($[\alpha]_D$) were determined on a Jasco DIP-360 polarimeter. HPLC was performed on a. Shimadzu HPLC system consisting of the following: pump, LC-10Advp; detector, SPD-M10Avp, measured at 254 nm. Column chromatography was performed with silica gel Merck 60 (230—400 mesh ASTM). In general, reactions were carried out in dry solvents under an argon atmosphere, unless noted otherwise. Dichloromethane was distilled from calcium hydride.

(*R*)-3-(4-Benzyloxyphenyl)-2-hydroxypropionitrile (2) To a stirred solution of well-dried $Bu_3P(O)$ (37 mg, 0.17 mmol) in CH_2Cl_2 (0.25 ml) was added Et_2AlCl (44 μl, 41 μmol, 0.93 M in hexane) at room temperature, followed by the addition of the chiral ligand (31 mg, 44 μmol) in CH_2Cl_2 (1.0 ml). The resulting mixture was stirred for 1 h at room temperature and cooled to -40 °C. After the addition of the aldehyde **3** (105 mg, 0.46 mmol), TMSCN (0.12 ml, 0.84 mmol) and MeOH (1.67 μl) in CH_2Cl_2 (0.12 ml) were slowly added over 20 h, and then the mixture was stirred for 44 h. To the reaction mixture were added 1 N HCl (1.0 ml) and THF (5 ml) in order to hydrolyze the trimethylsilyl ether moiety of the product. The mixture was stirred for 30 min and the organic layer was separated and washed with water. The aqueous layer was extracted with ethyl acetate (30 ml×2). The combined organic layer was washed with brine and dried over Na_2SO_4. The crude cyanohydrin was purified by chromatography on silica gel (EtOAc/hexane, 3/7) to give **2** (100 mg, 85%, 96% ee) as colorless crystals.

mp: 124—125 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.43 (1H, d, J=7.0 Hz), 3.07 (2H, d, J=6.0 Hz), 4.62 (1H, dd, J=6.5, 13.0 Hz), 5.06 (2H, s), 6.97 (2H, d, J=8.5 Hz), 7.22 (2H, d, 8.5 Hz), 7.30—7.44 (5H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 40.48, 62.24, 70.06, 115.30, 119.33, 125.89, 127.48, 128.05, 128.62, 130.84, 136.78, 158.48. IR (KBr) cm^{-1}: 3393, 2262, 1513, 1250, 1070, 740. HR-MS *m/z*: 253.1104 (Calcd for $C_{16}H_{15}NO_2$: 253.1103). The enantiomeric excess was determined by HPLC analysis using Chiralpak OD (2-propanol/hexane, 1/100) after conversion to the corresponding TBDMS ether. The absolute configuration of **2** was determined to be *R* by the comparison of the optical rotation with the reported value[22] after the conversion to 3-(4-hydroxyphenyl)lactic acid. $[\alpha]_D^{25}$ +17.5° (c=1.04, H_2O) (lit. $[\alpha]_D^{19}$ +19.8° [c=1.45, H_2O] for *R* enantiomer).

(*R*)-Ethyl-3-(4-benzyloxyphenyl)-2-hydroxyphenylpropionate (5) To a solution of **2** (507 mg, 2.0 mmol) in degassed EtOH (8.0 ml) was added 12 N HCl (2.0 ml) and the mixture was gently refluxed for 48 h. The solvent was removed and the residue was extracted with EtOAc (30 ml×2). The combined organic layer was washed with water and brine. The solvent was dried over Na_2SO_4 and removed to give the crude mixture of **5**, ethyl (*R*)-3-(4-hydroxyphenyl)lactate, (*R*)-3-(4-benzyloxyphenyl)lactic acid and (*R*)-3-(4-hydroxyphenyl)lactic acid.

To this crude mixture was added EtOH (5.0 ml) and H_2SO_4 (0.2 ml), and the reaction mixture was stirred for 16 h at room temperature. The solvent was removed and the residue was extracted with EtOAc (30 ml×2). The combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1/3) to give **5** (157 mg, 26%) and ethyl (*R*)-3-(4-hydroxyphenyl)lactate (247 mg, 59%) as a colorless oil.

To a solution of ethyl (*R*)-3-(4-hydroxyphenyl)lactate (247 mg, 1.17 mmol) in DMF (2.5 ml) were added BnBr (167 μl, 1.40 mmol) and K_2CO_3 (303 mg, 2.19 mmol), and the mixture was stirred at 60 °C for 4 h. To the reaction mixture was added H_2O and extracted with EtOAc (30 ml×2). The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane, 3/7) to give **5** (279 mg, 93% from ethyl (*R*)-3-(4-hydroxyphenyl)lactate, 96% ee) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, t, J=7.0 Hz), 2.71 (1H, d, J=6.0 Hz), 2.92 (1H, dd, J=6.5, 14.0 Hz), 3.07 (1H, dd, J=4.5, 14.0 Hz), 4.22 (2H, q, J=7.0 Hz), 4.37—4.22 (1H, m), 5.04 (2H, s), 6.91 (2H, d, J=8.5 Hz), 7.14 (2H, d, J=8.5 Hz), 7.30—7.44 (5H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.04, 39.51, 61.45, 69.80, 71.21, 114.59, 127.29, 127.74, 128.39, 128.55, 130.40, 136.93, 157.62, 174.15. IR (liquid film) cm^{-1}: 3489, 1734, 1512, 1242, 1177, 1026. HR-MS *m/z*: 323.1257 (Calcd for $C_{18}H_{20}O_4Na$ 323.1260). The enantiomeric excess was determined by HPLC analysis using Chiralpak AD-RH (CH_3CN/pH 2.2 buffer solution of phosphoric acid and Et_3N, 7/3).

(*R*)-2-(4-*t*-Butylphenoxy)-3-(4-hydroxyphenyl)propioic Acid (7) To a solution of **5** (896 mg, 2.90 mmol) in toluene (9.0 ml) were added 4-*t*-butylphenol (671 mg, 4.47 mmol) and triphenylphosphine-resin (3 mmol/g, 1.99 g, 5.97 mmol), and the mixture was stirred magnetically. To the stirred reaction mixture, a solution of DBAD (1.03 g, 4.47 mmol) in toluene (9.0 ml) was slowly added over 10 h at 0 °C, and the mixture was stirred for another 16 h. After completion of the reaction, TFA (5 ml) was added. After 1 h, the reaction mixture was filtered (Celite®) and the residue was washed with EtOAc and H_2O. The combined filtrate was separated and the organic layer was washed with H_2O and brine, and dried over Na_2SO_4. The solvent was removed and 1.5 g of the crude **6** was obtained as a colorless oil.

To a solution of crude **6** (1.50 g) in EtOH (10 ml), 5% Pd–C (0.1 g) was added, and the mixture was stirred under H_2 atmosphere at 50 °C for 2 h. The solvent was removed, and the residue was solved in EtOH (30 ml). 1 N NaOH (6 ml) was added to the solution at 0 °C and the reaction mixture was stirred at room temperature for 16 h. The solvent was removed and the residue was washed with EtOAc. After the addition of 1 N HCl to pH 4, the mixture was extracted with EtOAc and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, and the solvent was removed. The crystals were collected by filtration using isopropyl ether to give the title compound **7** (659 mg, 70%) as colorless crystals.

mp: 170—171 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.22 (9H, s), 3.00—3.08 (2H, m), 4.72—4.76 (1H, m), 6.66 (2H, d, J=8.5 Hz), 6.74 (2H, d, J=8.5 Hz), 7.09 (2H, d, J=8.5 Hz), 7.25 (2H, d, J=8.5 Hz). ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 31.19, 33.66, 37.30, 76.83, 114.18, 114.87, 125.95, 126.81, 130.15, 143.09, 155.28, 155.91, 172.16. IR (KBr pellet) cm^{-1}: 3234, 2964, 1717, 1513, 1238, 1207, 1187. HR-MS *m/z*: 314.1503 (Calcd for $C_{19}H_{22}O_4$ 314.1518). *Anal.* Calcd for $C_{19}H_{22}O_4 \cdot$l/10H_2O: C, 72.10; H, 7.05; Found: C, 71.99; H, 7.04.

(*R*)-Ethyl-2-(4-*t*-butylphenoxy)-3-(4-hydroxyphenyl)propionate (8) To a solution of **7** (1.89 g, 6.0 mmol) in EtOH (20 ml), was added H_2SO_4 (0.5 ml) and the mixture was stirred at room temperature for 16 h. The solvent was removed, and the residue was extracted with EtOAc (30 ml×2). The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed and the title compound **8** was obtained as a colorless oil (2.05 g, quant.).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz) 1.26 (9H, s), 3.14—3.17 (2H, m), 4.15—4.21 (2H, m), 4.68—4.71 (1H, m), 6.73—6.78 (4H, m), 7.16 (2H, d, J=8.5 Hz), 7.24 (2H, d, J=8.5 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.11, 31.46, 34.09, 38.29, 61.30, 78.28, 114.80, 115.26, 126.29, 128.50, 130.68, 144.39, 154.57, 155.51, 171.59. IR (Liquid film) cm^{-1}: 3421, 2963, 1731, 1514, 1238, 1187. HR-MS: 365.1739 (Calcd for $C_{21}H_{26}O_4Na$ 365.1729).

(*S*)-2-(4-*t*-Butylphenoxy)-3-[4-[2-[1-(4-pyridine-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionic Acid (1) To a solution of **8** (2.05 g, 6.0 mmol) in toluene (40 ml), were added oximealcohol **9** (2.31 g, 9.0 mmol) and triphenylphosphine resin (3 mmol/g, 4.0 g, 12.0 mmol), and the mixture was stirred magnetically. To the stirred reaction mixture, a solution of DBAD (2.76 g, 12.0 mmol) in toluene (30 ml) was slowly added over 1 h at 0 °C, and the mixture was stirred for another 16 h at room temperature. After completion of the reaction, TFA (12 ml) was added. After 1 h, the reaction mixture was filtered (Celite®), and the residue was washed with EtOAc and H_2O. The combined filtrate was washed with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was removed and to the obtained crude oil (4 g) were added EtOH (25 ml), THF (25 ml) and 1 N NaOH (12 ml) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The organic solvent was removed and the residue was washed with Et_2O. After the addition of 1 N HCl to pH 4, the mixture was extracted with EtOAc (80 ml×3) and washed with H_2O and brine. The obtained organic layer was dried over Na_2SO_4, and the solvent was removed. The solids were collected by filtration using isopropylether and hexane to give the title compound **1** (2.4 g, 72%, 93% ee.) as a colorless solid.

mp: 148—150 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.30 (9H, s), 2.31 (3H, s), 3.26 (2H, d, J=6.0 Hz), 4.34 (2H, t, J=5.0 Hz), 4.59 (2H, t, J=5.0 Hz), 4.84 (1H, t, J=6.0 Hz), 6.86 (2H, d, J=9.0 Hz), 6.93 (2H, d, J=8.5 Hz), 7.25—7.35 (5H, m), 7.74—7.88 (4H, m), 7.95 (2H, d, J=8.5 Hz), 8.76 (1H, d, J=4.5 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 12.79, 31.45, 34.05, 38.10, 66.60, 72.61, 77.99, 114.63, 114.76, 121.56, 122.63, 126.26, 126.51, 127.26, 128.98, 130.54, 137.23, 137.78, 138.92, 144.25, 148.91, 154.86, 155.49, 156.63, 157.79, 174.74. IR (KBr pellet) cm^{-1}: 2960, 1512, 1242, 1185, 1071, 783. HR-MS *m/z*: 553.2698 (Calcd for $C_{34}H_{36}N_2O_5$ 553.2703). *Anal.* Calcd for $C_{34}H_{36}N_2O_5$: C, 73.89; H, 6.57; N, 5.07; Found: C, 74.02; H, 6.57; N, 4.99. The enantiomeric exess was determined by HPLC analysis using Chiralpak OJ-R (CH_3CN/pH 2.2 buffer solution of phosphoric acid and Et_3N, 7/3).

Acknowledgements Financial support was provided by JSPS's Research for the Future Program.

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