Supporting Information

for Catalytic Asymmetric Synthesis of Nitrogen Analog of Dialkyl Tartrate by Direct Mannich Reaction under Phase–Transfer Conditions

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General Information. Infrared (IR) spectra were recorded on a Shimadzu FT-IR 8200A spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM-FX400 (400 MHz) spectrometer and JMTC-400/54/SS (400 MHz) spectrometer. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using 4.6 mm x 25 cm Daicel Chiralcel AD-H. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel (E. Merck 9385). High resolution mass spectra (HRMS) were performed on Applied Biosystems Mariner API-TOF workstation and JEOL JMS-HX100.

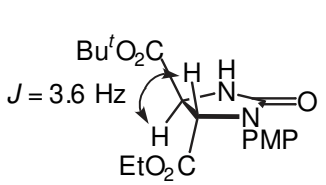
In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were purchased from Kanto Chemical Co. Inc. as "Dehydrated". Benzene and toluene were dried over sodium metal. Dichloromethane (CH_2Cl_2) was stored over 4A molecular sieves. Triethylamine (Et_3N) was stored over potassium hydroxide (KOH) pellet. Other simple chemicals were purchased and used as such.

Enantioselective Direct Mannich Reaction of *tert*-Butyl Glycinate Benzophenone Schiff Base (3) with Ethyl *N*-(4-Methoxyphenylimino)acetate (4) under Phase–Transfer Conditions. To a mixture of **3** (1.48 g, 5.0 mmol) and chiral catalyst (*R*,*R*)-**2b** (91.5 mg, 2 mol%) in mesitylene (50 mL)–17% NaOH aqueous solution (15 mL) was added **4** (2.07 g, 10.0 mmol) dropwise at –20 ℃ under argon atmosphere. The reaction mixture was stirred vigorously at the same temperature for 6 h. The mixture was then poured into saturated NH_4Cl aqueous solution and extracted with ether. The organic extracts were washed with brine and dried over Na_2SO_4. After evaporation of solvents, the residual oil was dissolved in THF (30 mL) and treated with 1 N HCl (15 mL) at 0 ℃ for 2 h. THF was removed under vacuum and the aqueous layer was washed with ether

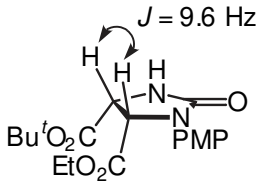
two times, then neutralized with $NaHCO_3$. This mixture was extracted with CH_2Cl_2 three times. The combined extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography on silica gel (ether/CH_2Cl_2/hexane = 1:8:4 then ethyl acetate/hexane = 1:1 as eluants) gave (2*S*,3*S*)-1-*tert*-butyl 4-ethyl 3-*N*-(4-methoxyphenyl)amino aspartate (**5**) as a mixture of diastereomers [1.48 g, 4.38 mmol, 88% yield, *syn*/*anti* = 4.4:1, 91% ee (*syn* isomer), 64% ee (*anti* isomer)]. The diastereomeric ratio was determined by ^{1}H NMR analysis. The enantiomeric excess was determined by HPLC analysis using chiral column [DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time; *anti* isomer: 36.7 min (2*S**,3*R**) and 41.1 min (2*R**,3*S**), *syn* isomer: 45.9 min (2*S*,3*S*) and 60.6 min (2*R*,3*R*)]. The relative configuration was assigned, after conversion to **7**, by ^{1}H NMR analysis, and the absolute configuration of *syn* isomer was established, after preparation of lactam **6**, by Mosher's method and ^{1}H NOE measurement as described later. The absolute configuration of *anti* isomer was not confirmed: *syn* isomer (2*S*,3*S*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (2H, d, *J* = 9.2 Hz, Ar-H), 6.67 (2H, d, *J* = 9.2 Hz, Ar-H), 4.42 (1H, br s, CHCO), 4.28 (1H, br s, Ar-NH), 4.19 (2H, q, *J* = 7.2 Hz, $CH_3C\underline{H}_2$), 3.96 (1H, d, *J* = 2.8 Hz, CHCO), 3.73 (3H, s, OCH_3), 1.64 (2H, br s, NH_2), 1.44 (9H, s, *t*-Bu), 1.25 (3H, t, *J* = 7.2 Hz, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 171.5, 152.9, 141.0, 116.0, 114.6, 82.2, 61.4, 61.4, 56.7, 55.7, 28.1, 14.3 ppm; IR (KBr) 3346, 2974, 2833, 1749, 1728, 1512, 1369, 1271, 1236, 1161, 1091, 1037, 824 cm^{-1}. HRMS (ESI–TOF) Calcd for $C_{17}H_{26}N_2NaO_5$: 361.1734 ([M+Na]$^+$), Found 361.1741 ([M+Na]$^+$). $[\alpha]_D^{27}$ 19.8 ° (*c* 0.40, $CHCl_3$, 91% ee). *anti* isomer (2*S**,3*R**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (2H, d, *J* = 9.2 Hz, Ar-H), 6.69 (2H, d, *J* = 9.2 Hz, Ar-H), 4.40 (2H, br s, Ar-NH and CHCO), 4.18 (2H, q, *J* = 7.2 Hz, $CH_3C\underline{H}_2$), 3.81 (1H, d, *J* = 2.4 Hz, CHCO), 3.74 (3H, s, OCH_3), 1.67 (2H, br, NH_2), 1.51 (9H, s, *t*-Bu), 1.25 (3H, t, *J* = 7.2 Hz, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 170.9, 152.8, 140.5, 115.5, 114.8, 81.9, 61.4, 61.3, 56.6, 55.7, 28.1, 14.3 ppm; IR (KBr) 3385, 2979, 2833, 1737, 1514, 1369, 1238, 1205, 1153, 1035, 823 cm^{-1}. HRMS (ESI–TOF) Calcd for $C_{17}H_{26}N_2NaO_5$: 361.1734 ([M+Na]$^+$), Found 361.1734 ([M+Na]$^+$). $[\alpha]_D^{27}$ –5.3 °(*c* 0.47, $CHCl_3$, 64% ee).

(4*S*,5*S*)-1-(4-Methoxyphenyl)-2-oxoimidazolidine-4-*tert*-butyl 5-Ethyl Dicarboxylate (*trans*-7). To a solution of **5** (1.48 g, 4.38 mmol, mixture of diastereomers) and triethylamine (1.36 mL, 9.64 mmol) in CH_2Cl_2 (45 mL) was added triphosgene (1.36 g, 4.60 mmol) at 0 ℃ under argon atmosphere. This mixture was stirred at the same temperature for 1 h, and then

poured into saturated $NaHCO_3$ aqueous solution. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:1.2 as eluant) to furnish *trans*-**7** (1.32 g, 3.63 mmol. 79%, 91% ee) and *cis*-**7** (255 mg, 0.70 mmol, 16%, the enantiomeric excess was not determined). The relative configuration was assigned by ^1H NMR analysis (see below). Recrystallization from CH_2Cl_2/hexane gave a optically pure *trans*-**7** (1.04 g, 2.85 mmol, 65% from **5**, >99% ee). The enantiomeric excess was determined by HPLC analysis using chiral column [DAICEL Chiralcel AD-H, hexane/2-propanol = 2:1, flow rate = 0.5 mL/min, retention time; 24.6 min (4*S*,5*S*), 44.2 min (4*R*,5*R*)]: *trans*-**7**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 9.2 Hz, Ar-H), 6.87 (2H, d, *J* = 9.2 Hz, Ar-H), 5.13 (1H, br, CONH), 4.91 (1H, d, *J* = 3.6 Hz, CHCO), 4.21 (1H, d, *J* = 3.6 Hz, CHCO), 4.19 (2H, q, *J* = 7.2 Hz, $CH_3C\underline{H}_2$), 3.78 (3H, s, OCH_3), 1.52 (9H, s, *t*-Bu), 1.20 (3H, t, *J* = 7.2 Hz, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.5, 157.8, 156.9, 130.7, 123.7, 114.2, 83.9, 62.2, 62.0, 55.5, 55.4, 28.0, 14.1 ppm; IR (KBr) 3234, 3112, 2983, 1747, 1717, 1514, 1445, 1410, 1367, 1298, 1244, 1159, 1036, 833 cm^{-1}. HRMS (ESI–TOF) Calcd for $C_{18}H_{24}N_2NaO_6$: 387.1527 ($[M+Na]^+$), Found 387.1528 ($[M+Na]^+$). $[\alpha]_D^{27}$ 44.9 ° (*c* 0.16, $CHCl_3$, >99% ee). *cis*-**7**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, d, *J* = 9.2 Hz, Ar-H), 6.85 (2H, d, *J* = 9.2 Hz, Ar-H), 5.68 (1H, br, CONH), 4.95 (1H, d, *J* = 9.6 Hz, CHCO), 4.53 (1H, d, *J* = 9.6 Hz, CHCO), 4.10 (2H, q, *J* = 7.2 Hz, $CH_3C\underline{H}_2$), 3.77 (3H, s, OCH_3), 1.47 (9H, s, *t*-Bu), 1.13 (3H, t, *J* = 7.2 Hz, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 167.2, 158.4, 156.9, 130.6, 123.6, 114.1, 83.6, 62.1, 61.7, 55.4, 54.1, 27.9, 13.9 ppm; IR (KBr) 3418, 2955, 1749, 1720, 1703, 1518, 1439, 1373, 1298, 1245, 1201, 1165, 1034, 831 cm^{-1}. HRMS (ESI–TOF) Calcd for $C_{18}H_{24}N_2NaO_6$: 387.1527 ($[M+Na]^+$), Found 387.1523 ($[M+Na]^+$).



trans-**7**



cis-**7**

(4*S*,5*S*,1'*S*)-5-(1'-Cyanohydroxymethyl)-1-(4-methoxyphenyl)-2-oxo-imidazolidine-4-*tert*-butyl Carboxylate (8). To a solution of *trans*-**7** (547 mg, 1.50 mmol) in CH_2Cl_2 (4 mL) and ether (12 mL) was added a 2.0 M toluene solution of DIBAH (2.25 mL, 4.50

mmol) dropwise slowly at –78 ℃ under argon atmosphere. After stirring at the same temperature for 1 h, trimethylsilyl cyanide (600 μL, 4.50 mmol) was added and stirring was continued for additional 1 h. Then, this mixture was allowed to warm to 0 ℃ and stirred there for 6 h. The reaction was quenched by addition of 10% citric acid aqueous solution and extracted with ethyl acetate. The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography on silica gel (ethyl acetate/hexane = 1.4:1 as eluant) gave (4*S*,5*S*,1'*S*)-5-(1'-cyanohydroxymethyl)-1-(4-methoxyphenyl)-2-oxoimidazolidine-4-*tert*-butyl carboxylate (**8**) (167 mg, 0.48 mmol, 32%) and (4*S*,5*S*,1'*R*) isomer (***epi*-8**) (250 mg, 0.72 mmol, 48%): **8**: ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.42 (2H, d, *J* = 9.2 Hz, Ar-H), 6.90 (2H, d, *J* = 9.2 Hz, Ar-H), 6.47 (1H, br s, CONH), 5.99 (1H, d, *J* = 6.0 Hz, OH), 4.85 (1H, dd, *J* = 6.0, 3.2 Hz, CHCN), 4.74 (1H, t, *J* = 3.2 Hz, C<u>H</u>CH(OH)CN), 4.35 (1H, dd, *J* = 3.2, 1.2 Hz, C<u>H</u>CO_2*t*-Bu), 3.79 (3H, s, OCH_3), 1.53 (9H, s, *t*-Bu) ppm; ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 170.8, 158.5, 157.6, 131.3, 125.3, 118.7, 114.6, 82.8, 63.1, 60.0, 55.6, 53.5, 28.0 ppm; IR (KBr) 3371, 2932, 1738, 1701, 1516, 1445, 1371, 1294, 1250, 1157, 1105, 1034, 841 cm^{-1}. HRMS (ESI–TOF) Calcd for $C_{17}H_{21}N_3NaO_5$: 370.1373 ([M+Na]$^+$), Found 370.1376 ([M+Na]$^+$). $[\alpha]_D^{27}$ 68.1 ° (*c* 0.24, MeOH). ***epi*-8**: ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.41 (2H, d, *J* = 9.2 Hz, Ar-H), 6.92 (2H, d, *J* = 9.2 Hz, Ar-H), 6.61 (1H, br s, CONH), 6.01 (1H, d, *J* = 5.6 Hz, OH), 4.88 (1H, dd, *J* = 5.6, 4.4 Hz, CHCN), 4.73 (1H, dd, *J* = 4.4, 3.2 Hz, C<u>H</u>CH(OH)CN), 4.33 (1H, dd, *J* = 3.2, 1.2 Hz, C<u>H</u>CO_2*t*-Bu), 3.79 (3H, s, OCH_3), 1.51 (9H, s, *t*-Bu) ppm; ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 170.5, 158.1, 157.7, 131.6, 125.1, 118.3, 114.8, 82.8, 62.2, 61.9, 55.6, 54.3, 28.0 ppm; IR (KBr) 3423, 2968, 1722, 1703, 1518, 1433, 1317, 1256, 1157, 1084, 1031, 833 cm^{-1}. HRMS (ESI–TOF) Calcd for $C_{17}H_{21}N_3NaO_5$: 370.1373 ([M+Na]$^+$), Found 370.1380 ([M+Na]$^+$). $[\alpha]_D^{27}$ 64.5 °(*c* 0.25, MeOH).

(4*S*,5*S*,1'*R*)-5-(2'-*N*-(4-Methoxybenzyl)amino-1'-hydroxyethyl)-1-(4-methoxyphenyl)-2-oxoimidazolidine-4-*tert*-butyl Carboxylate (10). To a solution of **8** (167 mg, 0.48 mmol) in acetic acid (5 mL) was added platinum oxide (41.8 mg, 25% by weight) at room temperature under argon atmosphere. Then, argon was replaced by H_2, and the reaction mixture was stirred for 2 h. The resulting mixture was filtered to remove the catalyst, and the filtrate was concentrated. The residue was dissolved in water and washed with ethyl acetate two times. The aqueous layer was neutralized with $NaHCO_3$ and saturated with NaCl, then extracted with CH_2Cl_2 six times. The organic extracts were dried over Na_2SO_4 and concentrated to give the crude (4*S*,5*S*,1'*R*)-

5-(2'-amino-1'-hydroxyethyl)-1-(4-methoxyphenyl)-2-oxoimidazolidine-4-*tert*-butyl carboxylate (**9**) (152 mg, 0.43 mmol, 90%) which was directly used for the following reaction without any purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (2H, d, *J* = 9.2 Hz, Ar-H), 6.90 (2H, d, *J* = 9.2 Hz, Ar-H), 5.00 (1H, br s, CONH), 4.37 (1H, dd, *J* = 4.0, 3.2 Hz, C<u>H</u>NPMP), 4.27 (1H, d, *J* = 4.0 Hz, C<u>H</u>CO_2*t*-Bu), 3.80 (3H, s, OCH_3), 3.75 (1H, m, C<u>H</u>OH), 2.77 (1H, dd, *J* = 13.2, 4.4 Hz, C<u>H</u>$_2$$NH_2$), 2.66 (1H, dd, *J* = 13.2, 8.4 Hz, C<u>H</u>$_2$$NH_2$), 1.52 (9H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 158.5, 157.0, 129.9, 125.1, 114.3, 83.1, 69.5, 62.7, 55.4, 52.1, 43.0, 28.0 ppm; IR (KBr) 3420, 2976, 1722, 1699, 1516, 1441, 1296, 1248, 1155, 837 cm^{-1}. HRMS (ESI–TOF) Calcd for $C_{17}H_{25}N_3NaO_5$: 374.1686 ([M+Na]$^+$), Found 374.1685 ([M+Na]$^+$).

To a mixture of the crude **9** (152 mg, 0.43 mmol) and Na_2SO_4 (4.3 g) in CH_2Cl_2 (3 mL) was added *p*-anisaldehyde (62.8 μL, 0.52 mmol) at 0 ℃ under argon atmosphere. This mixture was allowed to warm to room temperature and stirred for 8 h. The resulting mixture was filtered and the filtrate was concentrated. The residue was dissolved in EtOH (2 mL) and sodium borohydride (18.1 mg, 0.43 mmol) was added to this solution at 0 ℃. This mixture was stirred at the same temperature for 1 h and poured into water, then extracted with ethyl acetate. The organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:10 as eluant) gave (4*S*,5*S*,1'*R*)-5-(2'-*N*-(4-methoxybenzyl)amino-1'-hydroxyethyl)-1-(4-methoxyphenyl)-2-oxoimidazolidine-4-*tert*-butyl carboxylate (**10**) (144 mg, 0.31 mmol, 71%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 9.2 Hz, Ar-H), 7.13 (2H, d, *J* = 9.2 Hz, Ar-H), 6.88 (2H, d, *J* = 9.2 Hz, Ar-H), 6.82 (2H, d, *J* = 9.2 Hz, Ar-H), 4.99 (1H, br s, CONH), 4.32 (1H, dd, *J* = 4.0, 2.8 Hz, C<u>H</u>NPMP), 4.24 (1H, d, *J* = 4.0 Hz, C<u>H</u>CO_2*t*-Bu), 3.85 (1H, m, C<u>H</u>OH), 3.79 (6H, s, 2(OCH_3)), 3.69 (1H, d, *J* = 13.2 Hz, $ArCH_2$), 3.64 (1H, d, *J* = 13.2 Hz, $ArCH_2$), 2.66 (1H, dd, *J* = 12.4, 4.0 Hz, C<u>H</u>$_2$NHPMB), 2.57 (1H, dd, *J* = 12.4, 9.2 Hz, C<u>H</u>$_2$NHPMB), 1.51 (9H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 158.6, 158.6, 157.0, 131.4, 130.1, 129.2, 125.0, 114.3, 113.8, 83.0, 67.5, 63.1, 55.5, 55.3, 53.2, 52.2, 50.5, 28.0 ppm; IR (KBr) 3337, 2980, 2932, 2837, 1736, 1707, 1514, 1445, 1246, 1157, 1034, 831 cm^{-1}. HRMS (ESI–TOF) Calcd for $C_{25}H_{34}N_3O_6$: 472.2442 ([M+H]$^+$), Found 472.2439 ([M+H]$^+$). $[\alpha]_D^{27}$ 37.8 °(*c* 0.17, $CHCl_3$, >99% ee).

(4*S*,5*S*,1'*S*)-5-(2'-Amino-1'-hydroxyethyl)-1-(4-methoxyphenyl)-2-oxo-imidazolidine-4-*tert*-butyl Carboxylate (*epi*-9). This compound was prepared from ***epi*-8** in a similar manner to that described above and directly used for the following reaction without any purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 9.2 Hz, Ar-H), 6.88 (2H, d, *J* = 9.2 Hz, Ar-H), 5.15 (1H, br s, CONH), 4.65 (1H, dd, *J* = 4.0, 3.2 Hz, C<u>H</u>NPMP), 4.16 (1H, d, *J* = 3.2 Hz, C<u>H</u>CO_2*t*-Bu), 3.79 (3H, s, OCH_3), 3.76 (1H, m, C<u>H</u>OH), 2.81 (1H, d, *J* = 12.4 Hz, C<u>H_2</u>NH_2), 2.61 (1H, dd, *J* = 12.4, 8.8 Hz, C<u>H_2</u>NH_2), 1.51 (9H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 158.7, 156.8, 130.8, 124.2, 114.3, 83.1, 70.4, 62.1, 55.4, 53.3, 41.9, 28.0 ppm; IR (KBr) 3420, 2978, 2934, 1695, 1514, 1443, 1294, 1246, 1155, 835 cm^{-1}. HRMS (ESI–TOF) Calcd for $C_{17}H_{25}N_3NaO_5$: 374.1686 ([M+Na]$^+$), Found 374.1680 ([M+Na]$^+$).

(4*S*,5*S*,1'*S*)-5-(2'-*N*-(4-Methoxybenzyl)amino-1'-hydroxyethyl)-1-(4-methoxy-phenyl)-2-oxoimidazolidine-4-*tert*-butyl Carboxylate (*epi*-10). Reductive amination of the crude ***epi*-9** was performed as described before. The residual crude product was purified by column chromatography on silica gel (MeOH/CH_2Cl_2 = 1/10 as eluant) to afford (4*S*,5*S*, 1'*S*)-5-(2'-*N*-(4-methoxybenzyl)amino-1'-hydroxyethyl)-1-(4-methoxyphenyl)-2-oxoimidazolidine-4-*tert*-butyl carboxylate (***epi*-10**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 9.2 Hz, Ar-H), 7.09 (2H, d, *J* = 8.4 Hz, Ar-H), 6.86 (2H, d, *J* = 9.2 Hz, Ar-H), 6.81 (2H, d, *J* = 8.4 Hz, Ar-H), 5.34 (1H, br, CONH), 4.63 (1H, dd, *J* = 3.6, 2.8 Hz, C<u>H</u>NPMP), 4.24 (1H, d, *J* = 2.8 Hz, C<u>H</u>CO_2*t*-Bu), 3.87 (1H, m, C<u>H</u>OH), 3.79 (6H, s, 2(OCH_3)), 3.65 (1H, d, *J* = 12.8 Hz, $ArCH_2$), 3.58 (1H, d, *J* = 12.8 Hz, $ArCH_2$), 2.68 (1H, dd, *J* = 12.4, 3.6 Hz, C<u>H_2</u>NH), 2.54 (1H, dd, *J* = 12.4, 10.0 Hz, C<u>H_2</u>NH), 1.49 (9H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 158.7, 158.7, 156.8, 130.8, 129.3, 129.2, 124.3, 114.3, 113.8, 83.1, 68.3, 61.9, 55.5, 55.3, 53.2, 52.8, 48.9, 28.0 ppm; IR (KBr) 3258, 2934, 2837, 1736, 1701, 1514, 1443, 1248, 1155, 1036, 829 cm^{-1}. HRMS (ESI–TOF) Calcd for $C_{25}H_{34}N_3O_6$: 472.2442 ([M+H]$^+$), Found 472.2443 ([M+H]$^+$). $[\alpha]_D^{27}$ 14.1 °(*c* 0.25, $CHCl_3$, >99% ee).

(4*S*,5*S*,1'*R*)-5-(2'-*N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxybenzyl)amino-1'-hydroxyethyl)-1-(4-methoxyphenyl)-2-oxoimidazolidine-4-*tert*-butyl Carboxylate (11). To a solution of ***epi*-10** (75.4 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) was added triethylamine (29.3 μL, 0.21 mmol) and $(Boc)_2O$ (45.5 μL, 0.19 mmol) at 0 ℃. The mixture was stirred at the same temperature for 5 h and then poured into water. The organic layer was separated and aqueous layer was extracted with CH_2Cl_2. The organic extracts were washed with brine and dried over Na_2SO_4.

After evaporation of solvents, the residual crude products were purified by column chromatography on silica gel (ethyl acetate/hexane = 3:1 as eluant) to afford (4*S*,5*S*,1'*R*)-5-(2'-*N*-(*tert*-butoxycarbonyl)-*N*-(4-methoxybenzyl)amino-1'-hydroxyethyl)-1-(4-methoxyphenyl)-2-oxoimidazolidine-4-*tert*-butyl carboxylate (***epi*-11**) (89.6 mg, 0.16 mmol, 98%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.8 Hz, Ar-H), 6.95 (2H, br, Ar-H), 6.86 (2H, d, *J* = 8.8 Hz, Ar-H), 6.76 (2H, d, *J* = 8.8 Hz, Ar-H), 4.99 (1H, br, CONH), 4.64 (1H, br s, OH), 4.63 (1H, dd, *J* = 3.6, 3.6 Hz, C<u>H</u>NPMP), 4.26 (1H, br d, *J* = 15.6 Hz, $ArCH_2$), 4.09-4.13 (2H, br, C<u>H</u>CO_2*t*-Bu and $ArCH_2$), 3.98 (1H, br, C<u>H</u>OH), 3.81 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.60 (1H, br, CH_2N), 2.54 (1H, br d, *J* = 14.8 Hz, CH_2N), 1.49 (9H, s, *t*-Bu), 1.45 (9H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 158.7, 158.1, 156.6, 130.4, 129.0, 128.5, 123.5, 114.3, 113.8, 83.0, 81.3, 70.5, 61.6, 55.4, 55.1, 52.5, 51.9, 48.8, 28.3, 27.9 ppm; IR (KBr) 3373, 2976, 2932, 1701, 1514, 1441, 1414, 1367, 1248, 1159, 1036, 833 cm^{-1}. HRMS (ESI–TOF) Calcd for $C_{30}H_{41}N_3NaO_8$: 594.2786 ($[M+Na]^+$), Found 594.2784 ($[M+Na]^+$). $[\alpha]_D^{27}$ 52.3 °(*c* 0.17, $CHCl_3$, >99% ee).

To a solution of oxalyl chloride (29.4 μL, 0.32 mmol) in CH_2Cl_2 (1 mL) was added DMSO (45.4 mL, 0.64 mmol) dropwise at –78 ℃ under argon atmosphere. After stirring for 15 min, a solution of ***epi*-11** (89.6 mg, 0.16 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The mixture was stirred for 1 h and then treated with *N*,*N*-diisopropylethylamine (287 μL, 1.6 mmol) at the same temperature. The reaction mixture was stirred for 3 h and quenched by addition of water. Extractive workup was performed with CH_2Cl_2 and the combined organic extracts were washed with brine, and then dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (ethyl acetate/hexane = 2:1 as eluant) gave (4*S*,5*S*)-5-(2'-*N*-(*tert*-butoxycarbonyl)-*N*-(4-methoxybenzyl)aminoacetyl)-1-(4-methoxyphenyl)-2-oxoimidazolidine-4-*tert*-butyl carboxylate (**12**) (87.5 mg, 0.15 mmol, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) 1.2:1 ratio of rotamers: δ 7.24 (1.1H, d, *J* = 9.2 Hz, Ar-H), 7.21 (0.9H, d, *J* = 9.2 Hz, Ar-H), 6.98 (0.9H, d, *J* = 8.8 Hz, Ar-H), 6.95 (1.1H, d, *J* = 8.8 Hz, Ar-H), 6.82-6.85 (2H, m, Ar-H), 6.75-6.79 (2H, m, Ar-H), 5.46 (0.45H, br, CONH), 5.39 (0.55H, br, CONH), 4.93 (0.55H, d, *J* = 3.6, Hz, CHCO), 4.80 (0.45H, d, *J* = 3.6, Hz, CHCO), 4.39 (0.45H, d, *J* = 14.4 Hz, $ArCH_2$), 4.35 (0.55H, d, *J* = 14.8 Hz, $ArCH_2$), 4.24 (0.45H, d, *J* = 14.4 Hz, $ArCH_2$), 4.23 (0.55H, d, *J* = 14.8 Hz, $ArCH_2$), 4.18 (0.55H, d, *J* = 3.6 Hz, C<u>H</u>CO_2*t*-Bu), 4.10 (0.55H, d, *J* = 18.4 Hz, NCH_2CO), 4.03 (0.45H, d, *J* = 19.6 Hz, NCH_2CO), 3.87 (0.45H, d, *J* = 19.6 Hz, NCH_2CO), 3.82 (0.55H, d, *J* = 18.4 Hz, NCH_2CO), 3.79

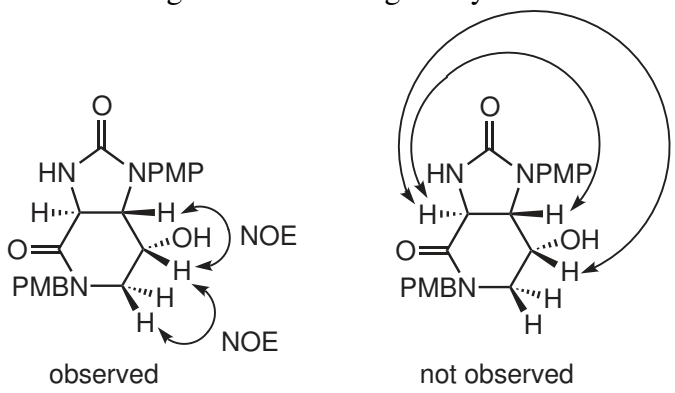
(6H, s, 2(OCH_3)), 3.74 (0.45H, d, J = 3.6 Hz, C<u>H</u>CO_2*t*-Bu), 1.49 (9H, s, *t*-Bu), 1.47 (4.95H, s, *t*-Bu), 1.37 (4.05H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 201.6, 168.4, 168.2, 158.8, 158.8, 157.5, 156.5, 156.4, 155.3, 155.0, 130.7, 130.4, 129.7, 128.9, 128.7, 128.4, 122.0, 121.9, 114.4, 114.3, 113.7, 113.7, 84.1, 83.8, 80.6, 80.4, 65.3, 55.4, 55.3, 55.2, 55.1, 53.9, 53.6, 53.6, 52.4, 52.2, 51.1, 50.2, 28.3, 28.1, 27.8 ppm; IR (KBr) 3402, 2970, 1751, 1706, 1690, 1518, 1437, 1369, 1308, 1246, 1159, 1132, 1034, 827 cm^{-1}. HRMS (ESI–TOF) Calcd for $C_{30}H_{39}N_3NaO_8$: 592.2629 ([M+Na]$^+$), Found 592.2632 ([M+Na]$^+$). $[\alpha]_D^{27}$ 45.9 ° (*c* 0.15, $CHCl_3$, >99% ee).

To a solution of **12** (87.5 mg, 0.15 mmol) in THF (0.4 mL) and toluene (1.6 mL) was added freshly prepared 0.5 M ether solution of $Zn(BH_4)_2$ (900 μL, 0.45 mmol) at –78 ℃ under argon atmosphere. The mixture was stirred at the same temperature for 6 h and then quenched with 10% citric acid. The aqueous phase was extracted with ethyl acetate. The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 3:1 as eluant) to afford (4*S*,5*S*,1'*R*)-5-(2'-*N*-(*tert*-butoxycarbonyl)-*N*-(4-methoxybenzyl)amino-1'-hydroxyethyl)-1-(4-methoxy-phenyl)-2-oxoimidazolidine-4-*tert*-butyl carboxylate (**11**) (45.8 mg, 0.080 mmol, 53%) and ***epi*-11** (37.7 mg, 0.066 mmol, 44%): **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (2H, d, J = 8.8 Hz, Ar-H), 7.05 (2H, br, Ar-H), 6.85 (2H, d, J = 8.8 Hz, Ar-H), 6.80 (2H, d, J = 8.8 Hz, Ar-H), 5.06 (1H, br s, CONH), 4.30 (2H, br), 4.21 (3H, br), 3.79 (8H, br), 3.45 (1H, br, C<u>H</u>$_2$N), 2.99 (1H, br d, J = 14.8 Hz, C<u>H</u>$_2$N), 1.46 (18H, s, 2(*t*-Bu)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 158.8, 158.3, 157.7, 156.9, 129.9, 129.2, 128.6, 125.0, 114.3, 113.8, 83.0, 81.1, 70.0, 63.0, 55.4, 55.1, 52.2, 51.7, 50.2, 28.3, 27.9 ppm; IR (KBr) 3431, 2976, 2932, 1697, 1514, 1456, 1414, 1367, 1248, 1159, 1036 cm^{-1}. HRMS (ESI–TOF) Calcd for $C_{30}H_{41}N_3NaO_8$: 594.2786 ([M+Na]$^+$), Found 594.2786 ([M+Na]$^+$). $[\alpha]_D^{27}$ 23.5 ° (*c* 0.16, $CHCl_3$, >99% ee).

Lactam 6. Route A (from 10). A solution of **10** (144 mg, 0.31 mmol) in formic acid (1.5 mL) was heated to 60 ℃ and stirred for 8 h under argon atmosphere. The solvents were removed under reduced pressure, and the residue was evaporated with toluene twice to remove the residual formic acid completely. The resulting solid was dissolved in DMF (3 mL) and triethylamine (109 μL, 0.78 mmol) and DPPA (87.7 μL, 0.40 mmol) were added at 0 ℃ under argon atmosphere. The mixture was allowed to warm to room temperature and stirred for 20 h. The resulting solution was poured into water and extracted with ethyl acetate. The organic extracts were washed with brine and

dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (ethyl acetate/hexane = 6:1 as eluant) gave **6** (80.1 mg, 0.20 mmol, 65%).

Route B (from 11). Preparation of **6** from **11** was performed in a similar manner to that described above (Route A) (61%): **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (2H, d, *J* = 9.2 Hz, Ar-H), 7.16 (2H, d, *J* = 9.2 Hz, Ar-H), 6.90 (2H, d, *J* = 8.8 Hz, Ar-H), 6.86 (2H, d, *J* = 8.8 Hz, Ar-H), 5.24 (1H, br s, CONH), 4.69 (1H, d, *J* = 14.8 Hz, $ArCH_2$), 4.51 (1H, dd, *J* = 12.8, 1.2 Hz, CHC=O), 4.43 (1H, br m, C<u>H</u>OH), 4.29 (1H, d, *J* = 14.8 Hz, $ArCH_2$), 3.86 (1H, dd, *J* = 12.8, 2.4 Hz, C<u>H</u>NPMP), 3.80 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.54 (1H, dd, *J* = 14.0, 5.6 Hz, CH(OH)C<u>H</u>$_2$N), 3.35 (1H, d, *J* = 14.0 Hz, CH(OH)C<u>H</u>$_2$N), 2.17 (1H, br s, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 160.8, 159.0, 157.7, 130.0, 129.4, 127.9, 124.8, 114.5, 114.0, 62.4, 61.1, 55.5, 55.2, 53.2, 50.1, 49.5 ppm; IR (KBr) 3425, 3287, 2932, 1717, 1641, 1514, 1300, 1244, 1177, 1030, 826 cm^{-1}. HRMS (ESI–TOF) Calcd for $C_{21}H_{24}N_3O_5$: 398.1711 ($[M+H]^+$), Found 398.1709 ($[M+H]^+$). $[\alpha]_D^{27}$ –87.0 ° (*c* 0.20, MeOH, >99% ee). The absolute configuration was determined, after protection of hydroxyl moiety [(*R*)- and (*S*)-MTPA-Cl, triethylamine, DMAP, CH_2Cl_2], by Mosher's method. The relative configuration was assigned by ^{1}H NOE measurement as shown below.



(*R*)-MTPA-lactam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.45 (5H, m, Ph), 7.13 (2H, d, *J* = 8.8 Hz, Ar-H), 7.06 (2H, d, *J* = 9.2 Hz, Ar-H), 6.90 (2H, d, *J* = 9.2 Hz, Ar-H), 6.85 (2H, d, *J* = 8.8 Hz, Ar-H), 5.67 (1H, br m, C<u>H</u>OMTPA), 5.22 (1H, br s, CONH), 4.56 (1H, d, *J* = 14.8 Hz, $ArCH_2$), 4.39 (1H, d, *J* = 14.8 Hz, $ArCH_2$), 4.25 (1H, dd, *J* = 13.2, 1.2 Hz, CHC=O), 4.06 (1H, dd, *J* = 13.2, 2.4 Hz, C<u>H</u>CH(OMTPA)), 3.81 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.67 (1H, dd, *J* = 15.2, 5.6 Hz, CH_2N), 3.37 (3H, s, OCH_3), 3.35 (1H, d, *J* = 15.2 Hz, CH_2N) ppm.

(*S*)-MTPA-lactam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.44 (5H, m, Ph-H), 7.16 (2H, d, *J* = 8.8 Hz, Ar-H), 6.94 (2H, d, *J* = 9.2 Hz, Ar-H), 6.86 (2H, d, *J* = 8.8 Hz, Ar-H), 6.85 (2H, d, *J* = 9.2 Hz, Ar-H), 5.59 (1H, br m, C<u>H</u>OMTPA), 5.16 (1H, br s, CONH), 4.53 (1H, d, *J* = 14.8 Hz,

$ArCH_2$), 4.46 (1H, d, J = 14.8 Hz, $ArCH_2$), 4.23 (1H, dd, J = 13.2, 1.6 Hz, CHC=O), 4.01 (1H, dd, J = 13.2, 2.4 Hz, C<u>H</u>CH(OMTPA)), 3.80 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.68 (1H, dd, J = 15.2, 5.2 Hz, CH_2N), 3.43 (1H, d, J = 15.2 Hz, CH_2N), 3.37 (3H, s, OCH_3) ppm.