Catalytic, Asymmetric Mannich-type Reactions of α -Imino Esters Bearing Readily Removable Substituents on Nitrogen

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Supporting Information

Experimental details and physical data of the products.

General. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400, or JNM-LA500 spectrometer. Tetramethylsilane (TMS) served as internal standard ($\delta = 0$) for ^1H NMR, and CDCl_3 was used as internal standard ($\delta = 77.0$) for ^{13}C NMR. Optical rotations were measured with a JASCO P-1010 polarimeter. Mass spectrometry analysis was carried out with JEOL JMS-700. HPLC analyses were carried out using the following apparatuses; Shimadzu LC-10AT (liquid chromatograph), Shimadzu SPD-10A (UV detector), and Shimadzu C-R6A or C-R8A Chromatopac. Column chromatography was conducted on Silica gel 60 (Merck), and preparative thin-layer chromatography was carried out using Wakogel B-5F. All reactions were carried out under argon atmosphere in dried glassware unless otherwise indicated. All reaction solvents were dried or distilled by standard procedures.

The 2-bromoglycine esters **1a-d,f-g** were prepared from the corresponding glycine esters and *N*-bromosuccinimide according to the reported method.¹ *N*-Cbz-2-bromoglycine ethyl ester **1e** was prepared from *N*-Cbz-2-ethoxyglycine ethyl ester and PBr_3 .² Since these 2-bromoglycine esters **1a-g** are sensitive to moisture and unstable at room temperature, **1a-g** were stored in a refrigerator ($-30\text{ }^\circ\text{C}$) and treated under argon atmosphere. The polymer-supported amines **2a,b** (purchased from Novabiochem) were washed with dry THF and dichloromethane, and then dried *in vacuo* at rt. The silyl enol ethers **4a-g** were prepared from the corresponding ketones or a thioester by standard protocols.^{3,4} The methyl vinyl ether **4h** was prepared according to the literature.⁵ The chiral diamine ligands **5a-f** were synthesized by the already reported methods.⁶

Typical procedure for the preparation of *N*-carbamate-protected α -imino esters. To a

¹ (a) Kober, R.; Steglich, W. *Liebigs Ann. Chem.* **1983**, 599. (b) Bretschneider, T.; Miltz, W.; Munster, P.; Steglich, W. *Tetrahedron* **1988**, 44, 5403, and references therein.

² Williams, R. M.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1990**, 55, 4657.

³ Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic: New York, 1988; Chapter 15.1.

⁴ Gennari, C.; Beretta, M. G.; Bernarde, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, 42, 893.

⁵ Gassman, P. G.; Burns, S. J.; Pfister, K. B. *J. Org. Chem.* **1990**, 55, 3114.

solution of 2-bromoglycine ester (0.4 mmol) in dichloromethane (4.0 mL) was added piperidinomethylpolystyrene **2a** (3.7 mmol/g, 216 mg, 0.80 mmol). The reaction mixture was stirred at rt for 10 min, and then the stirring was stopped. The polymer floated on the surface and the clear part of the solution (2.0 mL) was taken by gas-tight syringe. This solution was used immediately for the following Mannich-type reaction. The purity of the α -imino ester was checked by ^1H NMR analysis of the reaction in CD_2Cl_2 . The concentration of the α -imino ester was determined to be 0.92~0.97 mmol/mL after converting to the α -methoxyglycine derivative by addition of methanol.

***N*-tert-Butoxycarbonyl (*N*-Boc)- α -imino methyl ester (**3a**).** A solution of **3a** (0.92 mmol/mL) in dichloromethane was obtained by the standard procedure as mentioned above. To obtain a toluene solution of **3a** (0.82 mmol/mL), **1a** (107.2 mg, 0.40 mmol) and **2a** (1.2 mmol) was stirred in toluene at rt for 30 min. ^1H NMR (CD_2Cl_2) δ = 1.53 (s, 9H), 3.88 (s, 9H), 7.48 (brs, 0.2H, minor rotamer), 7.86 (brs, 0.8H, major rotamer)

***N*-tert-Butoxycarbonyl (*N*-Boc)- α -imino ethyl ester (**3b**).** A solution of **3b** (0.92~0.97 mmol/mL) in dichloromethane was obtained by the standard procedure as mentioned above. ^1H NMR (CD_2Cl_2) δ = 1.35 (t, 3H, J = 7.1 Hz), 1.53 (s, 9H), 4.25-4.40 (m, 2H), 7.47 (brs, 0.2H, minor rotamer), 7.85 (brs, 0.8H, major rotamer).

***N*-tert-Butoxycarbonyl (*N*-Boc)- α -imino *i*-propyl ester (**3c**).** A solution of **3c** in dichloromethane was obtained by the standard procedure as mentioned above. ^1H NMR (CD_2Cl_2) δ = 1.33 (d, 6H, J = 6.4 Hz), 1.53 (s, 9H), 5.00-5.20 (m, 1H), 7.43 (brs, 0.2H, minor rotamer), 7.83 (major rotamer).

⁶ Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507.

***N*-tert-Butoxycarbonyl (*N*-Boc)- α -imino *t*-butyl ester (**3d**).** A solution of **3d** in dichloromethane was obtained by the standard procedure as mentioned above. ^1H NMR (CD_2Cl_2) δ = 1.52 (s, 9H), 1.53 (s, 9H), 7.37 (brs, 0.2H, minor rotamer), 7.75 (brs, 0.8H, major rotamer).

***N*-Benzyloxycarbonyl (*N*-Boc)- α -imino ethyl ester (**3e**).** A solution of **3e** (0.95 mmol/mL) in dichloromethane was obtained by the standard procedure as mentioned above. ^1H NMR (CD_2Cl_2) δ = 1.34 (t, 3H, J = 6.8Hz), 4.25-4.40 (m, 2H), 5.28 (s, 2H), 7.59 (brs, 0.25H, minor rotamer), 7.94 (brs, 0.75H, major rotamer).

***N*-2,2,2-trichloroethoxycarbonyl (*N*-Troc)- α -imino ethyl ester (**3f**).** A solution of **3f** (0.94 mmol/mL) in dichloromethane was obtained by using morpholinomethylpolystyrene **2b** (3.6 mmol/g, 2 equiv.) instead of **2a**. ^1H NMR (CD_2Cl_2) δ = 1.36 (t, 3H, J = 7.1Hz), 4.30-4.40 (m, 2H), 4.90 (s, 2H), 7.68 (brs, 0.25H, minor rotamer), 8.02 (brs, 0.75H, major rotamer).

***N*-2-trimethylsilylethoxycarbonyl (*N*-Teoc)- α -imino ethyl ester (**3g**).** A solution of **3g** (0.96 mmol/mL) in dichloromethane was obtained by using 3 equivalents of piperidinomethylpolystyrene **2a** and by changing the reaction time to 30 min. ^1H NMR (CD_2Cl_2) δ = 0.06 (s, 9H), 1.10 (t, 2H, J = 8.7 Hz), 1.35 (t, 3H, J = 6.9 Hz), 4.30-4.40 (m, 4H), 7.53 (brs, 0.25H, minor rotamer), 7.91 (brs, 0.75H, major rotamer).

General procedure for Mannich-type reactions using a chiral copper (II) catalyst. $\text{Cu}(\text{OTf})_2$ (6.9 mg, 0.019 mmol) was dried for 2 h under vacuum at 100 °C. Ligand (*R,R*)-**5f** (9.5 mg, 0.021 mmol) in dichloromethane (2.0 mL) was added under argon atmosphere, and then the blue solution was stirred for over 4 h at *ca.* 25 °C until the color changed to green. Dichloromethane (1.0 mL) was added to the catalyst solution, and then the solution was cooled to -20 °C. A silyl enol ether or an alkyl vinyl

ether (0.38 mmol) in CH₂Cl₂ (0.7 mL) was added to this mixture. *N*-Acylimino ester **3** (0.19 mmol) in CH₂Cl₂ (2.0 mL) was then added slowly over 30 min, and the reaction mixture was kept stirred at –20 °C for 1 h. The reaction was quenched by addition of saturated aqueous NaHCO₃, and the reaction mixture was allowed to warm to rt. The mixture was extracted with CH₂Cl₂, and the organic layer was washed with brine, and the solvents were evaporated. The residue was dissolved in THF (3 mL), and then 1M aqueous HCl (0.15 mL) was added to the solution. The mixture was stirred at rt until the N-Si compound was disappeared on TLC (usually 2 h), and then saturated aqueous NaHCO₃ was added. The mixture was extracted with AcOEt, and the organic layers were washed with brine and dried over anhydrous Na₂SO₄. The crude solution was concentrated *in vacuo* and purified by chromatography on silica gel to afford the desired product.

In the case of the reaction with an alkyl vinyl ether, the reaction was quenched by addition of 2M aqueous HCl (0.2 mL) and THF (2 mL), and then the mixture was stirred at rt for 1 h. Saturated NaHCO₃ was added, and the mixture was extracted with CH₂Cl₂, washed with brine, and concentrated *in vacuo* to afford the crude product. Purification was performed as mentioned above.

(2*R*)-2-*tert*-Butoxycarbonylamino-4-oxo-4-phenylbutyric acid methyl ester (6a): ¹H NMR (CDCl₃) δ = 1.43 (s, 9H), 3.53 (dd, 1H, *J* = 4.0, 18.2 Hz), 3.73 (dd, 1H, *J* = 4.2, 18.2), 3.74 (s, 3H), , 4.69 (ddd, 1H, *J* = 4.0, 4.2, 8.6 Hz), 5.62 (brd, 1H, *J* = 8.6 Hz), 7.47 (apparent t, 2H, *J* = 7.8 Hz), 7.59 (apparent t, 1H, *J* = 8.1 Hz), 7.94 (apparent d, 2H, *J* = 7.1 Hz); ¹³C NMR (CDCl₃) δ = 28.3, 40.9, 49.6, 52.6, 80.0, 128.1, 128.7, 133.7, 136.1, 155. 6, 172.0, 197.7; HRMS (FAB); Exact mass calcd for C₁₆H₂₁NO₅Na [M+Na]⁺, 330.1317. Found 330.1313; Chiral HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min : *t*_R = 20.7 min (major, *R*), *t*_R = 30.9 min (minor, *S*).

(2R)-2-tert-Butoxycarbonylamino-4-oxo-4-phenylbutyric acid ethyl ester (6b): $[\alpha]^{19}_{\text{D}} -49.8$

(91% ee, c 1.10, CHCl_3); ^1H NMR (CDCl_3) δ = 1.24 (t, 3H, J = 7.2 Hz), 1.44 (s, 9H), 3.53 (dd, 1H, J = 4.1, 18.1 Hz), 3.73 (dd, 1H, J = 4.2, 18.1 Hz), 4.20 (q, 2H, J = 7.2 Hz), 4.67 (ddd, 1H, J = 4.1, 4.2, 8.3 Hz), 5.63 (brd, 1H, J = 8.3 Hz), 7.47 (apparent t, 2H, J = 7.6 Hz), 7.59 (apparent t, 1H, J = 7.3 Hz), 7.95 (apparent d, 2H, J = 7.1 Hz); ^{13}C NMR (CDCl_3) δ = 14.0, 28.3, 40.9, 49.8, 61.6, 79.9, 128.1, 128.7, 133.6, 136.2, 155.6, 171.5, 197.8; HRMS (FAB); Exact mass calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_5\text{Na}$ $[\text{M}+\text{Na}]^+$, 344.1474. Found 344.1465; Chiral HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min : t_{R} = 12.8 min (major, *R*), t_{R} = 18.0 min (minor, *S*).

(2R)-2-tert-Butoxycarbonylamino-4-oxo-4-phenylbutyric acid iso-propyl ester (6c): ^1H NMR

(CDCl_3) δ = 1.17 (d, 3H, J = 6.4 Hz), 1.25 (d, 3H, J = 6.1 Hz), 1.44 (s, 9H), 3.51 (dd, 1H, J = 4.0, 18.0 Hz), 3.72 (dd, 1H, J = 4.1, 18.0 Hz), 4.63 (ddd, 1H, J = 4.0, 4.1, 8.5 Hz), 5.62 (brd, 1H, J = 8.5 Hz), 7.47 (apparent t, 2H, J = 7.8 Hz), 7.59 (apparent t, 1H, J = 6.8 Hz), 7.94 (apparent d, 2H, J = 7.3 Hz); ^{13}C NMR (CDCl_3) δ = 21.5, 21.7, 28.3, 40.9, 49.9, 69.2, 79.8, 128.1, 128.7, 133.5, 136.3, 155.6, 170.9, 197.7; HRMS (FAB); Exact mass calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_5\text{Na}$ $[\text{M}+\text{Na}]^+$, 358.1630. Found 358.1632; Chiral HPLC: Daicel Chiralcel OD, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min; t_{R} = 10.7 min (major, *R*), t_{R} = 14.6 min (minor, *S*).

(2R)-2-tert-Butoxycarbonylamino-4-oxo-4-phenylbutyric acid tert-butyl ester (6d): ^1H NMR

(CDCl_3) δ = 1.416 (s, 9H), 1.423 (s, 9H), 3.45 (dd, 1H, J = 4.1, 17.6 Hz), 3.67 (dd, 1H, J = 4.4, 17.6 Hz), 4.56 (ddd, 1H, J = 4.1, 4.4, 8.3 Hz), 5.59 (brd, 1H, J = 8.3 Hz), 7.46 (apparent t, 2H, J = 7.8 Hz), 7.58 (apparent t, 1H, J = 7.3 Hz), 7.94 (apparent d, 2H, J = 7.3 Hz); ^{13}C NMR (CDCl_3) δ = 27.9, 28.3, 41.0, 50.3, 79.7, 82.0, 128.1, 128.7, 133.5, 136.4, 155.6, 170.4, 197.8; HRMS (FAB); Exact mass calcd

for $C_{19}H_{27}NO_5Na$ $[M+Na]^+$, 372.1787. Found 372.1791; Chiral HPLC Chiral HPLC: Daicel Chiralcel AD, hexane/*i*PrOH = 19/1, flow rate = 1.0 mL/min; t_R = 13.5 min (major, *R*), t_R = 17.9 min (minor, *S*).

(2*R*)-2-Benzoyloxycarbonylamino-4-oxo-4-phenylbutyric acid ethyl ester (6e): $[\alpha]_D^{19}$ -31.9 (85% ee; c 1.20, $CHCl_3$); 1H NMR ($CDCl_3$) δ = 1.22 (t, 3H, J = 7.2 Hz), 3.55 (dd, 1H, J = 4.2, 18.1 Hz), 3.75 (dd, 1H, J = 4.2, 18.1 Hz), 4.20 (q, 2H, J = 7.2 Hz), 4.74 (ddd, 1H, J = 4.2, 4.2, 8.0 Hz), 5.09 (d, 1H, J = 12.3 Hz), 5.13 (d, 1H, J = 12.3 Hz), 5.89 (brd, 1H, J = 8.0 Hz), 7.25-7.40 (m, 5H), 7.46 (apparent t, 2H, J = 7.8 Hz), 7.58 (apparent t, 1H, J = 7.3 Hz), 7.93 (apparent d, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ = 14.0, 40.8, 50.2, 61.7, 67.0, 128.0, 128.1, 128.5, 128.7, 133.7, 136.1, 136.2, 156.1, 171.0, 197.5; HRMS (FAB); Exact mass calcd for $C_{20}H_{21}NO_5Na$ $[M+Na]^+$, 378.1318. Found 378.1317; Chiral HPLC: Daicel Chiralcel AD-H, hexane/*i*PrOH = 4/1, flow rate = 1.0 mL/min; t_R = 26.0 min (minnor, *S*), t_R = 30.2 min (major, *R*).

(2*R*)-2-(2,2,2-trichloroethoxycarbonylamino)-4-oxo-4-phenylbutyric acid ethyl ester (6f): 1H NMR ($CDCl_3$) δ = 1.25 (t, 3H, J = 7.1 Hz), 3.57 (dd, 1H, J = 4.1, 18.3 Hz), 3.81 (dd, 1H, J = 4.2, 18.3 Hz), 4.23 (q, 2H, J = 7.1 Hz), 4.73 (s, 2H), 4.70-4.80 (m, 1H), 6.14 (brd, 1H, J = 8.6 Hz), 7.48 (apparent t, 2H, J = 7.5 Hz), 7.61 (apparent t, 1H, J = 7.3 Hz), 7.95 (apparent d, 2H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ = 14.0, 40.5, 50.3, 61.9, 74.7, 95.3, 128.1, 128.8, 133.8, 135.9, 154.4, 170.6, 197.5; HRMS (FAB); Exact mass calcd for $C_{15}H_{16}NO_5Cl_3Na$ $[M+Na]^+$, 417.9992. Found 417.9998; Chiral HPLC, Daicel Chiralcel AD, hexane/*i*PrOH = 9/1, flow rate = 1.0 mL/min : t_R = 24.3 min (major, *R*), t_R = 30.6 min (minor, *S*).

(2R)-2-(2-trimethylsilylethoxycarbonylamino)-4-oxo-4-phenylbutyric acid ethyl ester (6g):

^1H NMR (CDCl_3) δ = 0.02 (s, 9H), 0.97 (dd, 2H, J = 6.9, 10.0 Hz), 1.23 (t, 3H, J = 7.1 Hz), 3.54 (dd, 1H, J = 4.2, 18.1 Hz), 3.74 (dd, 1H, J = 4.2, 18.1 Hz), 4.10-4.20 (m, 2H), 4.20 (q, 2H, J = 7.1 Hz), 4.71 (ddd, 1H, J = 4.2, 4.2, 8.4 Hz), 5.73 (brd, 1H, J = 8.3 Hz), 7.47 (apparent t, 2H, J = 7.4 Hz), 7.59 (apparent t, 1H, J = 7.3 Hz), 7.94 (apparent d, 2H, J = 7.1 Hz); ^{13}C NMR (CDCl_3) δ = -1.5, 14.0, 17.6, 40.8, 50.0, 61.7, 63.4, 128.1, 128.7, 133.6, 136.1, 156.4, 171.2, 197.6; HRMS (FAB); Exact mass calcd for $\text{C}_{18}\text{H}_{27}\text{NO}_5\text{SiNa}$ $[\text{M}+\text{Na}]^+$, 388.1556. Found 388.1578; Chiral HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 9/1, flow rate = 1.0 mL/min : t_R = 10.3 min (minor, *S*), t_R = 17.6 min (major, *R*).

(2R)-2-*tert*-Butoxycarbonylamino-4-oxo-4-(4-methoxyphenyl)butyric acid ethyl ester (7b):

^1H NMR (CDCl_3) δ = 1.22 (t, 3H, J = 7.1 Hz), 1.42 (s, 9H), 3.45 (dd, 1H, J = 4.2, 17.9 Hz), 3.67 (dd, 1H, J = 4.3, 17.9 Hz), 3.86 (s, 3H), 4.18 (q, 2H, J = 7.1 Hz), 4.63 (ddd, 1H, J = 4.2, 4.3, 8.8 Hz), 5.63 (brd, 1H, J = 8.8 Hz), 6.92 (apparent d, 2H, J = 8.8 Hz), 7.91 (apparent d, 2H, J = 8.8 Hz); ^{13}C NMR (CDCl_3) δ = 14.0, 28.3, 40.4, 49.7, 55.5, 61.5, 79.8, 113.8, 129.3, 130.4, 155.6, 163.9, 171.6, 196.2; HRMS (FAB); Exact mass calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_6\text{Na}$ $[\text{M}+\text{Na}]^+$, 374.1579. Found 374.1570; Chiral HPLC, Daicel Chiralcel OD, hexane/*i*PrOH = 9/1, flow rate = 1.0 mL/min : t_R = 11.1 min (major, *R*), t_R = 14.5 min (major, *S*).

(2R)-2-*tert*-Butoxycarbonylamino-4-oxo-4-(4-chlorophenyl)butyric acid ethyl ester (7c):

^1H NMR (CDCl_3) δ = 1.23 (t, 3H, J = 7.1 Hz), 1.43 (s, 9H), 3.49 (dd, 1H, J = 4.2, 18.1 Hz), 3.67 (dd, 1H, J = 4.2, 18.1 Hz), 3.86 (s, 3H), 4.19 (q, 2H, J = 7.1 Hz), 4.65 (dt, 1H, J = 8.6, 4.2 Hz), 5.59 (brd, 1H, J = 8.6 Hz), 7.44 (apparent d, 2H, J = 8.6 Hz), 7.87 (apparent d, 2H, J = 8.5 Hz); ^{13}C NMR (CDCl_3) δ = 14.0, 28.3, 40.8, 49.7, 61.7, 80.0, 129.0, 129.5, 134.5, 140.1, 155.6, 171.3, 196.6; HRMS (FAB);

Exact mass calcd for $C_{17}H_{22}NO_5ClNa$ $[M+Na]^+$, 378.1085. Found 378.1087; HPLC, Daicel Chiralcel OD-H, hexane/*i*PrOH = 19/1, flow rate = 1.0 mL/min : t_R = 12.2 min (major, *R*), t_R = 17.2 min (minor, *S*).

(2*R*)-2-*tert*-Butoxycarbonylamino-4-oxo-4-(naphthalen-2-yl)butyric acid ethyl ester (7d):

1H NMR ($CDCl_3$) δ = 1.25 (t, 3H, J = 7.1 Hz), 1.45 (s, 9H), 3.68 (dd, 1H, J = 3.9, 18.1 Hz), 3.76 (dd, 1H, J = 4.4, 18.1 Hz), 4.22 (q, 2H, J = 7.1 Hz), 4.73 (ddd, 1H, J = 3.9, 4.4, 8.3 Hz), 5.69 (brd, 1H, J = 8.3 Hz), 7.50-7.65 (m, 2H), 7.88 (apparent t, 2H, J = 7.8 Hz), 7.95-8.00 (m, 2H), 8.47 (apparent s, 1H); ^{13}C NMR ($CDCl_3$) δ = 14.0, 28.3, 40.9, 49.8, 61.6, 79.9, 123.5, 126.9, 127.7, 128.5, 128.7, 129.6, 130.1, 132.4, 133.5, 135.7, 155.6, 171.5, 197.7; HRMS (FAB); Exact mass calcd for $C_{21}H_{26}NO_5$ $[M+H]^+$, 371.1811. Found 371.1820; Chiral HPLC: Daicel Chiralcel OD, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min ; t_R = 23.4 min (major, *R*), t_R = 30.7 min (minor, *S*).

(2*S*)-2-*tert*-Butoxycarbonylamino-4-oxo-4-(3-nitrophenyl)butyric acid ethyl ester (7e):

(*S,S*)-Diamine ligand **5f** was used for the Mannich-type reaction. $[\alpha]^{21}_D$ +35.8 (86% ee; c 0.72, $CHCl_3$); 1H NMR ($CDCl_3$) δ = 1.26 (t, 3H, J = 7.2 Hz), 1.44 (s, 9H), 3.61 (dd, 1H, J = 4.2, 18.0 Hz), 3.76 (dd, 1H, J = 4.1, 18.0 Hz), 4.23 (q, 2H, J = 7.2 Hz), 4.72 (ddd, 1H, J = 4.1, 4.2, 8.3 Hz), 5.60 (brd, 1H, J = 8.3 Hz), 7.71 (apparent t, 1H, J = 7.9 Hz), 8.28 (ddd, 1H, J = 1.0, 1.7, 7.8 Hz), 8.45 (ddd, 1H, J = 1.0, 2.2, 8.1 Hz), 8.78 (apparent s, 1H); ^{13}C NMR ($CDCl_3$) δ = 14.0, 28.3, 41.2, 49.7, 61.8, 80.2, 123.0, 127.8, 130.0, 133.6, 137.4, 148.5, 155.5, 171.0, 195.7; HRMS (FAB); Exact mass calcd for $C_{17}H_{23}N_2O_7$ $[M+H]^+$, 367.1506. Found 367.1511; Chiral HPLC: Daicel Chiralcel OD (double column), hexane/*i*PrOH = 9/1, flow rate = 1.0 mL/min : t_R = 33.7 min (minor, *R*), t_R = 38.6 min (major, *S*).

(2S)-2-tert-Butoxycarbonylamino-4-oxo-4-(3,4-dichlorophenyl)butyric acid ethyl ester (7f):

(*S,S*)-Diamine ligand **5f** was used for the Mannich-type reaction. $[\alpha]^{22}_{\text{D}} +39.2$ (91% ee; c 0.82, CHCl_3); ^1H NMR (CDCl_3) δ = 1.23 (t, 3H, J = 7.1 Hz), 1.42 (s, 9H), 3.48 (dd, 1H, J = 4.4, 18.0 Hz), 3.64 (dd, 1H, J = 4.2, 18.0 Hz), 4.19 (q, 2H, J = 7.1 Hz), 4.65 (ddd, 1H, J = 4.2, 4.4, 8.2 Hz), 5.56 (brd, 1H, J = 8.2 Hz), 7.53 (d, 2H, J = 8.3 Hz), 7.75 (dd, 1H, J = 2.0, 8.3 Hz), 8.00 (d, 1H, J = 2.0 Hz); ^{13}C NMR (CDCl_3) δ = 14.0, 28.3, 40.9, 49.7, 61.8, 80.1, 127.1, 130.1, 130.8, 133.5, 135.7, 138.2, 155.5, 171.1, 195.6; HRMS (FAB); Exact mass calcd for $\text{C}_{17}\text{H}_{22}\text{NO}_5\text{Cl}_2$ $[\text{M}+\text{H}]^+$, 390.0875. Found 390.0876; Chiral HPLC: Daicel Chiralcel OD, hexane/*i*PrOH = 40/1; flow rate = 1.0 mL/min : t_{R} = 27.5 min (minor, *R*), t_{R} = 35.3 min (minor, *S*).

(2R, 3R)-3-tert-Butylsulfanylcarbonyl-2-tert-butoxycarbonylamino-butyric acid methyl ester

(7g, *syn/anti* = 73/27): ^1H NMR (CDCl_3) *syn*: δ = 1.19 (d, 3H, J = 7.1 Hz), 1.42 (s, 9H), 1.44 (s, 9H), 2.95-3.10 (m, 1H), 3.73 (s, 3H), 4.58 (dd, 1H, J = 5.0, 8.5 Hz), 5.19 (brd, 1H, J = 8.5 Hz); *anti*: δ = 1.22 (d, 3H, J = 7.1 Hz), 1.43 (s, 9H), 1.44 (s, 9H), 3.24 (dq, J = 4.5, 7.1 Hz, 1H), 3.72 (s, 3H), 4.43 (dd, 1H, J = 4.5, 9.6 Hz), 5.46 (brd, 1H, J = 9.6 Hz); ^{13}C NMR (CDCl_3) *syn*: δ = 13.2, 28.2, 29.6, 48.3, 50.6, 52.4, 55.7, 79.9, 155.0, 171.2, 200.5; *anti*: δ = 14.7, 28.3, 29.7, 48.5, 49.4, 52.3, 55.9, 79.9, 155.9, 171.4, 202.5; HRMS (FAB); Exact mass calcd for $\text{C}_{15}\text{H}_{28}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$, 334.1688. Found 334.1705; Chiral HPLC: Daicel Chiralcel AD-H, hexane/*i*PrOH = 19/1, flow rate = 1.0 mL/min; *syn*, t_{R} = 12.5 min (minor, 2*S*,3*S*), t_{R} = 14.6 min (major, 2*R*,3*R*); *anti*, t_{R} = 7.3 min (major), t_{R} = 9.5 min (minor).

(2R)-2-amino-4-oxo-4-phenylbutyric acid ethyl ester hydrochloride (8) (Deprotection of 6a):

To a solution of **6a** (44.0 mg, 0.137 mmol) in 1,4-dioxane (1.5 mL) was added a 4M solution of

hydrogen chloride in 1,4-dioxane (1.5 mL) at rt, and the mixture was kept stirred for 3 h at rt. The mixture was concentrated *in vacuo*, and the solid residue was washed with diethyl ether (3mL) and dried *in vacuo* to give the desired product **8** (34.6 mg, 98% yield). **8**: $[\alpha]_D^{18} - 21.8$ (91% ee; c 0.128, H₂O), *cf.* lit. $[\alpha]_D + 5.5$ (c 0.010, D₂O, *S*-isomer)⁷; ¹H NMR (D₂O) $\delta = 1.19$ (t, 3H, *J* = 7.1 Hz) 3.85 (dd, 1H, *J* = 3.9, 19.1 Hz), 3.95 (dd, 1H, *J* = 5.8, 19.1 Hz), 4.26 (q, *J* = 7.1 Hz, 2H), 4.54 (dd, 1H, *J* = 3.9, 5.8 Hz), 7.54 (apparent t, 2H, *J* = 7.8 Hz), 7.70 (apparent t, 1H, *J* = 7.3 Hz), 7.97 (apparent d, 2H, *J* = 7.7 Hz); ¹³C NMR (D₂O) $\delta = 13.9, 39.0, 49.8, 64.6, 129.2, 129.9, 135.7, 135.7, 170.6, 200.0$; HRMS (FAB); Exact mass calcd for C₁₂H₁₆NO₃ [M+H]⁺, 222.1131. Found 222.1133; Chiral HPLC: Daicel Chiralcel OD, hexane/*i*PrOH = 9/1.; flow rate = 1.0 mL/min : *t*_R = 14.8 min (minor, *S*), *t*_R = 17.5 min (major, *R*)

Determination of the absolute configuration of the Mannich adduct: The deprotected product **8** was treated with dodecanoyl chloride and triethylamine to afford a known compound, 2-dodecanoylamino-4-oxo-4-phenyl-butyric acid ethyl ester. The absolute configuration of **6a** was determined to be *2R* by comparison of the optical rotation of the dodecanoyled product with the reported value: $[\alpha]_D^{19} - 54.2$ (c 0.48, CHCl₃, 91% ee), *cf.* lit. $[\alpha]_D^{23} - 58.5$ (c 1.02, CHCl₃, *2R*, 94% ee).⁶ Absolute configuration of **6b-g**, **7b-d**, **7g** were tentatively assigned to be *2R* by analogy. Absolute configurations of **7f** was determined to be *2S* by converting to FCE-28833 (*vide infra*). Absolute configuration of **7e** was also tentatively assigned to be *2S* by analogy.

Synthesis of *L-m*-Nitrobenzoylalanine hydrochloride (*m*-NBA) (9e**):** To a solution of **7e** (62.0 mg, 0.169 mmol) in 1,4-dioxane (1.5 mL) was added 2M hydrochloric acid (3.0 mL) at rt, and the mixture was refluxed for 6 h. The mixture was cooled to rt and concentrated *in vacuo*. The solid

⁷ Ferraris, D.; Young, B.; Dudding, T.; Drury, W. J., III; Lectka, T. *Tetrahedron* **1999**, 55, 8869.

residue was triturated with acetone (2 mL) for 1h, and the mixture was filtered to give *L-m*-nitrobenzoylalanine hydrochloride **9e** (45.3 mg, 97% yield). $[\alpha]^{24}_{\text{D}} +26.1$ (c 0.5, 1M HCl), *cf.* lit. $[\alpha]^{22}_{\text{D}} +13.21$ (c 1, H₂O, *S*-isomer);⁸ ¹H NMR (D₂O): δ = 3.90-3.95 (m, 2H), 4.45-4.55 (m, 1H), 7.76 (t, 1H, *J* = 8.0 Hz), 8.34 (apparent d, 1H, *J* = 7.9 Hz), 8.48 (apparent dt, 1H, *J* = 8.2, 1.1 Hz), 8.76 (apparent s, 1H); ¹³C NMR (D₂O) δ = 39.4, 49.8, 124.0, 129.5, 131.3, 135.2, 137.0, 149.0, 172.6, 198.1; HRMS (FAB); Exact mass calcd for C₁₀H₁₁N₂O₅ [M+H]⁺, 239.0668. Found 239.0682.

Synthesis of FCE28833 (9f): The reaction was carried out according to the same procedure as the synthesis of *m*-NBA. FCE28833 (hydrochloride salt, 46.0 mg, 98% yield) was obtained from **7f** (61.6 mg). $[\alpha]^{23}_{\text{D}} +33.5$ (c 0.25, 1M HCl), *cf.* lit. $[\alpha]_{\text{D}} + 32.7$ (c 0.1, *aq.* HCl, *S*-isomer);⁹ ¹H NMR (D₂O+CD₃OD): δ = 3.80 (d, 2H, *J* = 5.1 Hz), 4.44 (t, 1H, *J* = 5.1 Hz), 7.69 (d, 1H, *J* = 8.4 Hz), 7.89 (dd, 1H, *J* = 2.0, 8.4 Hz), 8.13 (d, 1H, *J* = 2.0 Hz); ¹³C NMR (D₂O+CD₃OD): δ = 39.0, 49.5, 128.5, 130.8, 131.9, 133.8, 135.7, 139.2, 171.8, 197.1; HRMS (FAB); Exact mass calcd for C₁₀H₁₀NO₃Cl₂ [M+H]⁺ 262.0038. Found 262.0036.

Determination of the Relative stereochemistry of **7g**:

(2R,3S)-2-tert-butoxycarbonylamino-3-methylbutane-1,4-diol (10): To a solution of **7g** (42.0 mg, 0.126 mmol, *syn/anti* = 73/27) in THF (2.5 mL) was added a 1M solution of LiBEt₃H (0.94 mL, 0.94 mmol) at 0 °C, and the mixture was kept stirred for 0.5 h at the same temperature. The reaction was quenched by careful addition of water, 30 % aqueous H₂O₂, and 1M HCl. The mixture was extracted with AcOEt three times, and the combined organic layer was washed with saturated aqueous NaHCO₃, saturated aqueous Na₂S₂O₃, and brine. The organic layer was dried over anhydrous Na₂SO₄,

⁸ Natalini, B.; Mattoli, L.; Pellicciari, R. *BioMed. Chem. Lett.* **1995**, 5, 1451.

⁹ Giordani, A.; Corti, L.; Cini, M.; Bormetti, R.; Marconi, M.; Veneroni, O.; Speciale, C.; Varasi, M. *Adv. Exp. Med. Biol.*

evaporated, and purified by column chromatography on silica gel to give the desired product **10** (23.5 mg, 85% yield, *syn/anti* = 75/25). The relative stereochemistry of the major diastereomer of **7g** was assigned to be *syn* by ¹H NMR analysis as compared with the reported value.¹⁰: ¹H NMR (CDCl₃) *syn*: δ = 0.82 (d, 3H, *J* = 6.9 Hz), 1.45 (s, 9H), 1.90-2.05 (m, 1H), 3.11 (brs, 2H), 3.37 (dd, 1H, *J* = 9.3, 11.6 Hz), 3.55 (dd, 1H, *J* = 3.9, 11.6 Hz), 3.64 (dd, 1H, *J* = 5.1, 11.3 Hz), 3.70 (dd, 1H, *J* = 5.6, 11.3 Hz), 3.75-3.90 (m, 1H), 4.90-5.10 (brs, 1H).; Distinguishable peaks of *anti* isomer as follows; ¹H NMR (CDCl₃) *anti*: δ = 1.02 (d, 3H, *J* = 6.9 Hz), 1.75-1.85 (m, 1H), 3.48 (dd, 1H, *J* = 4.6, 11.7 Hz); ¹³C NMR (CDCl₃) *syn*: δ = 11.6, 28.3, 37.3, 53.0, 63.2, 64.3, 80.0, 157.0.; HRMS (FAB); Exact mass calcd for C₁₀H₂₁NO₄Na [M+Na]⁺, 242.1368. Found 242.1355.

(Recent Advances in Tryptophan Research) **1996**, 398, 531.

¹⁰ For ¹H NMR data for the *anti*-isomer of **10**, see: (a) Yoshida, T.; Takeshita, M.; Orita, H.; Kado, N.; Yasuda, S.; Kato, H.; Itoh, Y. *Chem. Pharm. Bull.* **1996**, 44, 1128. For ¹H NMR data for the diastereomeric mixture of **10**, see: (b) Hirabayashi, S.; Ike, K.; Zanka, A.; Kawakami, T.; Ichihara, M. World Intellectual Property Organization Patent WO9220652, 1992.