A Novel Chiral Pentamine Ligand for Enantioselective α-Alkylation of Acyclic Lithium Amide Enolates. Optimization of Chiral Ligands for Asymmetric Reactions Using Solid-Phase Organic Synthesis

Jun-ichi Matsuo, Kazunori Odashima, and Shū Kobayashi*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Supporting Information

Experimental Procedures, Physical Data of the Products and Ligands

General: All melting points are uncorrected. IR spectra were recorded on a Jasco FT/IR-610 spectrometer. NMR spectra were recorded on a JEOL JNM-LA-300 FT-NMR system or a JEOL JNM-LA-400 FT-NMR system. Mass spectra (MS) were recorded on a JEOL JMS-DX-300. High resolution mass spectral (HRMS) analyses were done by using a JEOL JMS-SX-102. Optical rotations were measured by a Jasco P-1010 polarimeter. Acyclic propionamides were prepared by using the method of Heathcock and co-workers[1]. Toluene used in enentioselevtive alkylation reactions was distilled from sodium/benzophenone immediately prior to use. Alkyl lithium reagents (*n*-BuLi and MeLi-LiBr) were purchased from Kanto Chemical Co., Inc. A chiral tetradentate amine (**3**)[2] and a chiral pentadentate amine (**4**)[3] were prepared as reported. Trithyl chloride-type resin was prepared from polystyrene (1% DVB, 200~400 mesh, purchased from Advanced Chemtech) by a literature method[4].

N-(polymer supported trithyl)-piperazine

A mixture of trithyl chloride type-resin (62.3 g, 0.88 mmol/g), piperazine (52.0 g, 0.60 mol) and THF (400 mL) was refluxed for 3.5 hours. After cooling to room temperature, the resin was washed with CH_2Cl_2 (200 mL x 2), DMF (100 mL x 3), CH_2Cl_2 (200 mL x 2), and Et_2O (200 mL x 2), and then dried *in vacuo* to give *N*-(polymer supported trithyl)-piperazine (69.0 g, 0.64 mmol/g).

Synthesis of chiral pentadentate amines by solid-phase peptide synthesis (**22**)

To a stirred suspension of *N*-(polymer supported trithyl)-piperazine (1.21 g, 0.64 mmol/g, 0.77 mmol) and CH_2Cl_2 (15 mL), were added PyBOP (528 mg, 1.01 mmol), Fmoc-Leu (355 mg, 1.00 mmol) and DIPEA (0.18 mL, 1.03 mmol), and the mixture was stirred for 10 hours at room temperature. After washing the resin with CH_2Cl_2, to a stirred suspension of the washed resin and CH_2Cl_2 (15 mL), were added PyBOP (525 mg, 1.01 mmol), Fmoc-Leu (356 mg, 1.01 mmol) and DIPEA (0.18 mL, 1.03 mmol), and the mixture was stirred for 4 hours. After the resin was washed with CH_2Cl_2, the resin was suspended with 20% piperidine in DMF solution (5 mL), and the suspension was stirred for 10 min. After the resin was washed with CH_2Cl_2, to a stirred suspension of the washed resin and CH_2Cl_2 (15 mL), were added PyBOP (524 mg, 1.01 mmol), Fmoc-Phe (392 mg, 1.01 mmol) and DIPEA (0.18 mL, 1.03 mmol), and the mixture was stirred for 4 hours. After the resin was washed with CH_2Cl_2, the resin was suspended with 20% piperidine in DMF solution (5

mL), and the suspension was stirred for 10 min. After the resin was washed with CH_2Cl_2, to a stirred suspension of the washed resin and CH_2Cl_2 (15 mL), were added PyBOP (521 mg, 1.00 mmol), Fmoc-Pro (356 mg, 1.10 mmol) and DIPEA (0.18 mL, 1.03 mmol), and the mixture was stirred for 9 hours. After the resin was washed with CH_2Cl_2, the resin was suspended with 20% piperidine in DMF solution (5 mL), and this suspension was stirred for 10 min. After the resin was washed with CH_2Cl_2, to a stirred suspension of the washed resin and CH_2Cl_2 (15 mL), were added PyBOP (528 mg, 1.01 mmol), *N*,*N*-dimethylgrycine hydrochloride (150 mg, 1.07 mmol) and DIPEA (0.36 mL, 2.06 mmol), and the mixture was stirred for 2 hours. After the resin was washed with CH_2Cl_2, the resin was suspended with 20% trifluoroacetic acid in CH_2Cl_2 solution (10 mL), and the mixture was stirred for 2 hours. After filtration, the filtrate was concentrated *in vacuo* to give a yellow oil. A mixture of the residual oil and saturated aqueous $NaHCO_3$ was extracted with $CHCl_3$ (20 mL x 3), and the combined organic extracts were dried with anhydrous K_2CO_3, filtered, and concentrated *in vacuo* to give a pale yellow oil.

To the N-unprotected piperazine-tetrapeptide, water (10 mL), formic acid (0.15 mL, 3.98 mmol) and 37% aqueous formaldehyde (0.65 mL) were added, and the mixture was refluxed for 1 hour. The reaction mixture was basified with K_2CO_3 under ice-water cooling, saturated with NaCl, and extracted with $CHCl_3$ (20 mL x 3). The combined organic extracts were dried with anhydrous K_2CO_3, filtered, and concentrated *in vacuo* to give a pale yellow oil. The residual oil was purified by preparative TLC (ether / isopropylamine) to give a corresponding N-methyl-piperazine-tetrapeptide (378 mg, 0.70 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, d, *J* = 6.3 Hz), 0.96 (3H, d, *J* = 6.3 Hz), 1.05 ~ 1.10 (1H, m), 1.18 ~ 1.23 (1H, m), 1.3 ~ 1.7 (3H, m), 1.7 ~ 2.0 (2H, m), 2.1 ~2.4 (4H, m), 2.29 (6H, s), 2.31 (3H, s), 2.9 ~ 3.7 (10H, m), 4.50 ~ 4.57 (1H, m, Pro-aym-H), 4.68 ~ 4.75 (1H, m, Phe-asym-H), 4.87 ~ 4.95 (1H, m, Leu-asym-H), 6.91 (1H, d, *J* = 8.5 Hz), 7.1 ~ 7.3 (5H, m), 7.36 (1H, d, *J* = 8.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, Major rotamer): δ 22.08, 23.31, 24.55, 24.85, 27.15, 37.66, 41.99, 42.46, 45.36, 45.80, 45.99, 46.71, 47.03, 54.01, 54.60, 55.03, 59.89, 62.05, 126.62, 128.29, 129.23, 136.97, 170.15, 170.19, 170.29, 171.26.

Under Ar atmosphere, to a solution of the N-methyl-piperazine-tetrapeptide (378 mg, 0.70 mmol) in THF (10 mL) was added BH_3-THF (1.0 *M*, 13.9 mL, 13.9 mmol), and the mixture was refluxed for 20 hours. The reaction was quenched by adding MeOH (14 mL) under ice-water cooling, and the solvents were evaporated. 5% aqueous HCl (20 mL) was added to the residue, and the mixture was refluxed for 1 hour. The reaction mixture was basified with K_2CO_3, saturated with NaCl, and extracted with $CHCl_3$ (20 mL x 3). The combined organic extracts were dried with anhydrous K_2CO_3, filtered and concentrated *in vacuo* to give a pale yellow oil. This crude product was purified by preparative TLC (hexane / isopropylamine) to give a chiral pentadentate amine (**22**) (254 mg, 0.52 mmol, 74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (3H, d, *J* = 5.3 Hz), 0.86 (3H, d, *J* = 5.5 Hz), 1.0 ~ 1.3 (2H, m), 1.5 ~ 2.0 (5H, m), 2.0 ~ 3.0 (26H, m), 2.23 (6H, s), 2.26 (3H, s), 3.1 (1H, m), 7.1 ~ 7.3 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.77, 22.91, 23.28, 24.84, 29.20, 39.50, 43.02, 45.87, 46.03, 50.11, 51.38, 52.45, 53.64, 54.57, 55.20, 58.76, 60.02, 63.31, 64.93, 125.94, 128.23, 129.29, 139.56.

5; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (6H, s), 2.23 (3H, s), 2.0 ~ 2.8 (30H, m), 7.1 ~ 7.3 (15H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.40, 39.53, 39.69, 44.81, 45.39, 46.02, 50.36, 50.65, 55.22, 56.47, 59.42, 59.74, 62.09, 125.93, 125.99, 128.15, 128.27, 129.20, 129.29, 129.36, 139.34, 139.36, 139.44.

6; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.5 ~ 2.0 (4H, m), 2.12 (6H, s), 2.263 (3H, s), 2.0 ~ 2.78 (29H, m), 2.91 (1H, dd, *J* = 4.7, 13.5 Hz), 3.1 (1H, m), 7.0 ~ 7.3 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.09, 30.27, 39.26, 39.50, 44.66, 45.29, 45.89, 50.13, 53.71, 54.92, 55.27, 59.23, 59.25, 59.73, 59.96, 62.12, 64.03, 125.82, 125.89, 128.12, 128.18, 129.07, 129.29, 139.21, 139.83.

7; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.5 ~ 2.8 (31H, m), 2.09 (6H, s), 2.19 (3H, s), 2.19 (3H, s), 2.96 (1H, dd, *J* = 4.4, 13.8 Hz), 3.1 (1H, m), 7.1 ~ 7.3 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$):

δ 23.23, 29.02, 39.65, 39.73, 45.21, 45.55, 45.94, 52.06, 55.16, 55.26, 56.87, 59.33, 59.52, 59.96, 61.9, 65.04, 125.95, 128.95, 128.17, 128.23, 129.31, 129.39, 139.29, 139.89.

8; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.5 (1H, m), 1.7 ~ 1.8 (3H, m), 2.21 (6H, s), 2.24 (3H, s), 2.1 ~ 3.0 (28H, m), 3.1 (1H, m), 7.1 ~ 7.3 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.75, 28.87, 39.18, 39.45, 45.59, 45.75, 50.04, 50.91, 53.35, 54.30, 54.90, 56.25, 58.40, 59.82, 61.92, 64.64, 125.72, 125.81, 127.95, 128.08, 129.06, 129.15, 139.07, 139.23.

9; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.5 ~ 2.0 (8H, m), 2.0 ~ 2.6 (23H, m), 2.25 (9H, s), 2.7 ~ 2.8 (2H, m), 3.0 (1H, m), 3.1 (2H, m), 7.1 ~ 7.3 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.63, 22.72, 28.49, 29.90, 39.51, 45.73, 45.87, 51.19, 53.71, 54.42, 54.69, 55.06, 56.71, 58.60, 60.39, 61.74, 63.50, 64.89, 125.68, 127.91, 129.20, 139.16.

10; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.4 ~ 1.9 (8H, m), 2.22 (6H, s), 2.26 (3H, s), 2.1 ~ 2.7 (23H, m), 2.8 ~ 2.9 (3H, m), 3.0 ~ 3.1 (2H, m), 7.2 ~ 7.3 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.69, 23.13, 28.96, 30.19, 39.50, 45.76, 45.93, 51.47, 53.37, 53.77, 54.42, 54.97, 55.34, 58.60, 59.23, 59.88, 62.01, 64.10, 64.60, 125.73, 128.04, 129.20, 139.82.

11; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.6 ~ 2.0 (4H, m), 2.24 (6H, s), 2.25 (3H, s), 2.1 ~ 3.0 (27H, m), 3.1 ~ 3.2 (1H, m), 7.1 ~ 7.3 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.86, 28.84, 39.45, 45.66, 45.85, 47.26, 50.06, 53.28, 53.36, 54.50, 55.05, 56.01, 58.58, 61.77, 64.42, 125.72, 127.96, 129.15, 139.07.

12; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (3H, d, J = 6.1 Hz), 1.5 ~ 2.0 (4H, m), 2.24 (6H, s), 2.26 (3H, s), 2.1 ~ 3.0 (26H, m), 3.1 ~ 3.2 (1H, m), 7.1 ~ 7.3 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.53, 22.86, 29.16, 39.44, 45.74, 45.94, 50.44, 53.17, 53.45, 53.93, 54.48, 54.54, 55.17, 55.24, 58.63, 61.80, 64.72, 125.80, 128.01, 129.32, 139.12.

13; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, d, *J* = 6.8 Hz), 0.90 (3H, d, *J* = 6.8 Hz), 1.5 ~ 2.0 (4H, m), 2.23 (6H, s), 2.26 (3H, s), 2.2 ~ 3.0 (27H, m), 3.1 ~ 3.2 (1H, m), 7.1 ~ 7.3 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.30, 18.93, 22.94, 28.97, 29.14, 39.72, 45.82, 45.87, 47.84, 51.60, 55.22, 56.54, 58.78, 62.05, 63.66, 125.86, 128.12, 129.32, 139.38.

14; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, d, *J* = 0.7 Hz), 0.90 (3H, d, *J* = 1.7 Hz), 1.0 ~ 1.5 (2H, m), 1.5 ~ 2.0 (4H, m), 2.24 (6H, s), 2.26 (3H, s), 2.1 ~ 3.0 (27H, m), 3.1 ~ 3.2 (1H, m), 7.1 ~ 7.3 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.07, 23.56, 29.30, 39.74, 42.89, 45.92, 46.09, 50.84, 53.40, 53.72, 54.65, 54.73, 55.29, 55.38, 56.08, 56.59, 58.81, 62.08, 62.64, 64.86, 125.93, 128.18, 129.41, 139.4.

15; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.5 ~ 1.9 (4H, m), 2.23 (6H, s), 2.25 (3H, s), 2.1 ~ 2.9 (28H, m), 3.1 (1H, m), 7.1 ~ 7.3 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.00, 28.83, 39.21, 39.69, 45.80, 46.00, 50.48, 50.94, 53.21, 54.62, 55.17, 56.51, 58.63, 59.66, 62.06, 64.69, 125.87, 125.98, 128.12, 128.27, 129.17, 129.24, 139.17, 139.34.

17; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.4 ~ 1.8 (10H, m), 2.1 ~ 3.0 (32H, m), 2.25 (3H, s), 3.1 (1H, m), 7.1 ~ 7.3 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.91, 24.30, 25.87, 29.11, 39.40, 39.68, 45.99, 50.25, 51.18, 52.86, 54.58, 55.02, .55.17, 56.37, 58.49, 59.89, 62.11, 64.89, 125.85, 125.93, 128.09, 128.22, 129.22, 129.34, 139.30, 139.46.

18; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.4 ~ 1.9 (4H, m), 2.0 ~ 3.0 (29H, m), 2.23 (3H, s), 3.5 ~ 3.7 (4H, m), 7.1 ~ 7.4 (20H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.82, 29.08, 40.10, 46.05, 52.39, 52.65, 53.10, 54.43, 55.21, 55.34, 57.05, 58.74, 58.77, 61.80, 64.75, 125.95, 125.97, 126.77, 128.11, 128.17, 128.25, 128.64, 129.27, 129.35, 129.39, 139.42, 139.73.

19; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.5 ~ 1.9 (4H, m), 2.1 ~ 2.9 (27H, m), 2.23 (6H, s), 2.27 (3H, s), 3.1 (1H, m), 7.1 ~ 7.3 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.82, 29.12, 39.48,

45.84, 45.99, 46.63, 50.96, 52.66, 53.19, 53.53, 54.55, 55.08, 57.93, 58.71, 59.36, 64.95, 125.92, 128.21, 129.18, 139.39.

20; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92, 0.93 (3H, d, *J* = 6.1, 6.1 Hz), 1.5 ~ 1.9 (4H, m), 2.1 ~ 3.0 (22H, m), 2.22, 2.23 (6H, s), 2.25, 2.26 (3H, s), 3.1 (1H, m), 7.1 ~ 7.3 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.81, 22.89, 29.20, 39.48, 45.84, 46.01, 49.56, 49.84, 51.32, 53.63, 54.56, 55.19, 58.72, 59.68, 64.89, 64.93, 125.94, 128.21, 129.28, 139.51.

21; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.8 ~ 0.9 (6H, m), 1.5 ~ 1.6 (1H, m), 1.6 ~ 1.9 (5H, m), 2.0 ~ 3.0 (25H, m), 2.23, 2.24 (6H, s), 2.26, 2.27 (3H, s), 3.1 (1H, m), 7.2 ~ 7.3 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.13, 18.66, 22.94, 28.84, 29.26, 39.64, 45.90, 46.03, 51.20, 51.66, 53.60, 54.59, 55.24, 58.77, 58.86, 59.31, 60.57, 64.94, 125.93, 128.21, 129.33, 139.75.

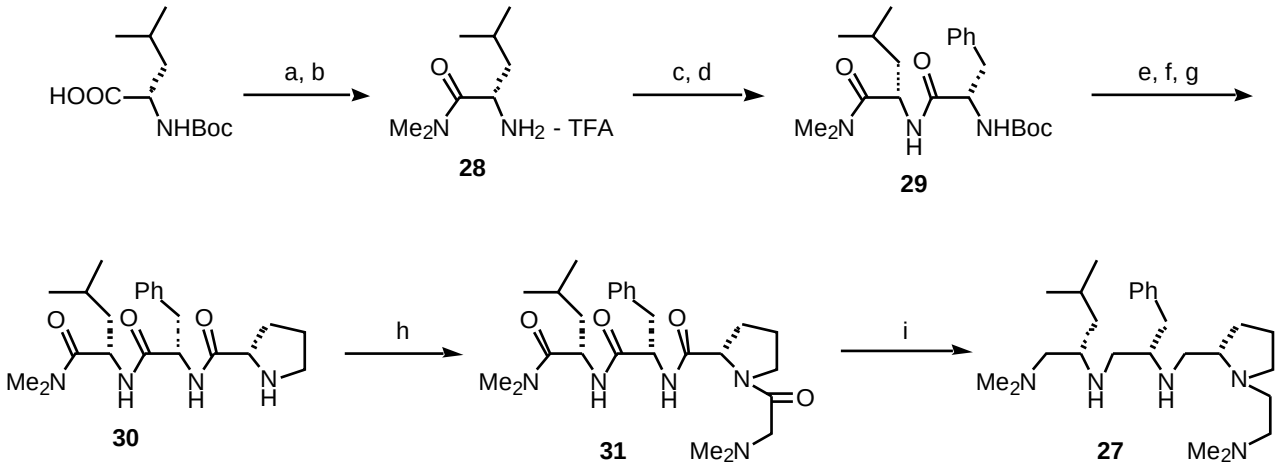
23; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (9H, s), 1.5 ~ 2.0 (4H, m), 2.1 ~ 2.6 (21H, m), 2.23 (9H, s), 2.7 (1H, m), 2.8 ~ 2.9 (4H, m), 3.1 (1H, m), 7.1 ~ 7.3 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.83, 26.89, 29.10, 34.52, 39.52, 45.79, 45.85, 51.71, 53.39, 54.46, 54.98, 55.04, 58.68, 60.03, 61.55, 63.52, 64.78, 125.75, 128.05, 129.15, 139.73.

24; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.4 (1H, m), 1.6 ~ 1.7 (3H, m), 2.0 ~ 2.5 (19H, m), 2.19 (6H, s), 2.26 (3H, s), 2.5 ~ 2.9 (6H, m), 2.9 ~ 3.0 (1H, m), 3.1 (2H, m), 3.22 (1H, dd, *J* = 5.9, 18.8 Hz), 7.0 ~ 7.5 (9H, m), 7.71 (1H, d, *J* = 7.9 Hz), 7.8 (1H, m), 8.1 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.86, 29.12, 37.71, 39.22, 45.79, 45.99, 50.15, 51.04, 53.59, 54.49, 55.23, 56.00, 58.69, 59.73, 62.69, 64.85, 124.04, 125.22, 125.26, 125.55, 125.86, 126.78, 127.41, 128.14, 128.60, 129.11, 132.15, 133.83, 135.79, 139.34.

25; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.5 ~ 2.0 (4H, m), 2.1 ~ 2.9 (25H, m), 2.21 (6H, s), 2.23 (3H, s), 3.1 (1H, m), 3.64 (1H, dd, *J* = 3.2, 11.0 Hz), 7.1 ~ 7.3 (10H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.84, 29.25, 38.99, 45.80, 46.00, 50.71, 53.57, 54.53, 55.17, 55.26, 58.66, 59.07,

60.50, 64.75, 65.02, 65.70, 125.80, 125.84, 126.97, 127.26, 128.12, 128.16, 129.07, 129.25, 139.38, 143.08.

Liquid-phase synthesis of **27**



a) Me_2NH-HCl, DEPC, Et_3N, DMF b) TFA c) OH^- d) Boc-Phe, DEPC, Et_3N, DMF e) TFA then OH^-
f) Boc-Pro, DEPC, Et_3N, DMF g) TFA then OH^- h) $HO_2CCH_2NMe_2$-HCl, DEPC, Et_3N, CH_2Cl_2 i) BH_3-THF

Synthesis of **28**

To a mixture of Boc-Leu-H_2O (5.01 g, 20.1 mmol), dimethylamine hydrochloride (1.84 g, 22.6 mmol) and DMF (30 mL), were added DEPC (90%, 3.7 mL, 22.3 mmol) and triethylamine (6.2 mL, 44.5 mmol) at 0 °C, and the mixture was stirred for 30 min. After stirring for 13 hours at room temperature, the reaction mixture was poured into benzene (100 mL) and AcOEt (200 mL). The organic phase was washed with water (100 mL×4), 10% aqueous citric acid (100 mL×3), water (100 mL), saturated aqueous $NaHCO_3$ (100 mL×2), water (100 mL) and brine, dried with Na_2SO_4, filtered and concentrated *in vacuo* to give a colorless oil (4.96 g).

A mixture of this oil (4.96 g) and TFA (14.6 mL) was stirred for 30 min at room temperature and then TFA was evaporated to give a pale yellow oil, which was crystallized by adding ether. The crystals were collected by filtration and dried to give colorless needles (**28**) (4.82 g, 17.7 mmol). For an analytical sample, **28** was recrystallized from AcOEt. mp 160.5-161.0 °C. $[\alpha]_D^{26}$ + 6.57 (*c* 1.05, MeOH). IR (KBr, cm^{-1}): 3452, 1670, 1597, 1529, 1207, 1182, 1129. MS *m/z*: 159. ^{1}H NMR (300

MHz, D_2O): δ 0.80 (3H, d, *J* = 4.8 Hz), 0.82 (3H, d, *J* = 6.1 Hz), 1.4 ~ 1.6 (3H, m), 2.81 (3H, s), 2.93 (3H, s), 4.3 (1H, m). ^{13}C NMR (75 MHz, D_2O): δ 20.25, 22.22, 23.67, 35.65, 36.75, 38.78, 49.27, 116.27 (^1J = 290 Hz), 162.67 (^2J = 35 Hz), 169.81. Anal. Calcd for $C_{10}H_{19}N_2O_3F_3$: C, 44.1; H, 7.03; N, 10.29. Found: C, 43.97; H, 6.97; N, 10.19.

Synthesis of **29**

28 (4.64 g, 17.0 mmol) was basified with saturated aqueous $NaHCO_3$, and the solution was extracted with $CHCl_3$ (20 mL×9). The combined extracts were dried with anhydrous K_2CO_3, filtered, and concentrated *in vacuo* to give a colorless oil (2.84 g, quant). To a solution of this oil and Boc-Phe (4.96 g, 18.7 mmol) in DMF (20 mL), were added DEPC (90%, 3.1 mL, 18.6 mmol) and triethylamine (2.6 mL, 18.7 mmol) at 0 °C, and the mixture was stirred for 30 min. After stirring for 12 hours at room temperature, the reaction mixture was poured into benzene (60 mL) and AcOEt (120 mL). The organic phase was washed with water (60 mL×4), 10% aqueous citric acid (60 mL×3), water (60 mL), saturated aqueous $NaHCO_3$ (60 mL×2), water (60 mL) and brine, dried with Na_2SO_4, filtered and concentrated *in vacuo* to give a colorless solid. This solid was recrystallized from AcOEt (10 mL)-hexane (50 mL) to give colorless fine needles (5.99 g, 87%). mp 155.5 ~ 156.0 °C. $[\alpha]_D^{26}$ - 11.9 (*c* 1.14, $CHCl_3$). IR (KBr, cm^{-1}): 3284, 3218, 1713, 1636. MS *m/z*: 406 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (3H, d, *J* = 6.4 Hz), 0.98 (3H, d, *J* = 6.4 Hz), 1.2 ~ 1.7 (9H, m), 1.40 (9H, s), 3.1 (2H, m), 3.4 ~ 3.6 (4H, m), 4.4 (1H, m), 4.9 ~ 5.0 (2H, m), 1.40 (9H, s), 1.3 ~ 1.6 (3H, m), 2.93 (3H, s), 3.06 (5H, brs), 4.37 (1H, m), 4.9 ~ 5.0 (2H, m), 6.64 (1H, d, *J* = 7.7 Hz), 7.2 ~ 7.3 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.89, 23.36, 24.51, 28.24, 35.70, 37.01, 38.18, 42.47, 47.24, 55.64, 80.06, 126.84, 128.52, 129.38, 136.55, 155.23, 170.67, 171.79. Anal. Calcd for $C_{22}H_{35}N_3O_4$: C, 65.16; H, 8.70; N, 10.36. Found: C, 64.94; H, 8.77; N, 10.41.

Synthesis of **30**

A mixture of **29** (5.93 g, 14.6 mmol) and TFA (1.0 mL) was stirred for 30 min at room temperature and TFA was evaporated to give a colorless oil. This oil was basified with saturated aqueous $NaHCO_3$, and the solution was extracted with $CHCl_3$. The combined extracts were dried

with anhydrous K_2CO_3, filtered, and concentrated *in vacuo* to give a colorless oil. To a solution of this oil and Boc-Pro (3.46 g, 16.1 mmol) in DMF (20 mL), were added DEPC (90%, 2.7 mL, 16.2 mmol) and triethylamine (2.3 mL, 16.5 mmol) at 0 °C, and stirred for 30 min. After stirring for 48 hours at room temperature, the reaction mixture was poured into benzene (60 mL) and AcOEt (120 mL). The organic phase was washed with water (60 mL×4), 10% aqueous citric acid (60 mL×3), water (60 mL), saturated aqueous $NaHCO_3$ (60 mL×2), water (60 mL) and brine, dried with Na_2SO_4, filtered and concentrated *in vacuo* to give a pale yellow amorphous (8.01 g).

After TFA (11.0 mL) was added to the amorphous, the mixture was stirred for 30 min at room temperature and then TFA was evaporated to give a pale yellow oil. This oil was basified with saturated aqueous $NaHCO_3$, and the solution was extracted with $CHCl_3$. The combined extracts were dried with anhydrous K_2CO_3, filtered, and concentrated *in vacuo* to give a pale yellow solid. This solid was recrystallized from acetonitrile (5 mL) to give colorless fine needles (4.28 g, 75%). mp 129.5 ~ 130.0 °C. $[\alpha]_D^{26}$ - 39.7 (*c* 1.04, $CHCl_3$). IR (KBr, cm^{-1}): 3332, 1641, 1513. MS *m/z*: 403 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (3H, d, *J* = 6.4 Hz), 0.97 (3H, d, *J* = 6.4 Hz), 1.3 ~ 1.7 (6H, m), 1.9 ~ 2.0 (2H, m), 2.68 (1H, m), 2.91 (1H, m), 2.94 (3H, s), 2.99 (1H, dd, *J* = 8.6, 13.8 Hz), 3.07 (3H, s), 3.17 (1H, dd, *J* = 5.5, 14.0 Hz), 3.4 ~ 3.6 (4H, m), 3.69 (1H, dd, *J* = 4.9, 9.3 Hz), 4.67 (1H, dt, *J* = 5.5, 8.5 Hz), 4.92 (1H, dt, *J* = 4.8, 8.6 Hz), 6.85 (1H, d, *J* = 8.4 Hz), 7.1 ~ 7.3 (5H, m), 8.08 (1H, d, *J* = 8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.98, 23.31, 24.59, 25.92, 30.53, 35.73, 36.98, 37.86, 42.32, 47.10, 47.34, 53.53, 60.24, 126.75, 128.36, 129.24, 136.68, 170.58, 171.85, 175.35. Anal. Calcd for $C_{22}H_{34}N_4O_3$: C, 65.64; H, 8.51; N, 13.92. Found: C, 65.66; H, 8.53; N, 13.92.

Synthesis of **31**

To a stirred suspension of **30** (4.08 g, 10.5 mmol) and *N*,*N*-dimethylglycine hydrochloride (1.60 g, 11.5 mmol) in CH_2Cl_2 (40 mL), were added DEPC (90%, 1.90 mL, 11.4 mmol) and triethylamine (3.20 mL, 23.0 mmol) at 0 °C, and the mixture was stirred for 30 min. After stirring for 13 hours at room temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (50 mL), and extracted with CH_2Cl_2 (40 mL×3). The combined organic extracts were dried with K_2CO_3, filtered and concentrated *in vacuo* to give a pale yellow oil. This oil was purified by column

chromatography (silica gel, ether / isopropylamine) to give a colorless amorphous (4.85 g, 95%). $[\alpha]_D^{26}$ - 80.2 (*c* 1.34, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (3H, d, *J* = 6.6 Hz), 0.97 (3H, d, *J* = 6.2 Hz), 1.3 ~ 1.6 (3H, m), 1.7 ~ 1.9 (2H, m), 2.30 (6H, s), 2.1 ~ 2.4 (2H, m), 2.93 (3H, s), 2.98 (2H, s), 3.06 (3H, s), 3.0 ~ 3.5 (4H, m), 4.6 (1H, m), 4.7 (1H, m), 4.9 (1H, m), 6.85 (1H, d, *J* = 8.3 Hz), 7.1 ~ 7.3 (5H, m), 7.38 (1H, d, *J* = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, for major rotamer): δ 21.95, 23.35, 24.57, 24.85, 27.14, 35.75, 37.01, 37.73, 42.30, 45.82, 46.70, 47.29, 54.03, 59.88, 62.02, 126.60, 128.27, 129.24, 137.00, 170.24, 170.27, 171.28, 171.83. IR (film, cm^{-1}): 3294, 1637. MS *m/z*: 487 (M^+). HRMS Calcd for $C_{26}H_{41}N_5O_4$: 487.3159. Found: 487.3203.

Synthesis of **27**

Under Ar atmosphere, BH_3-THF (1.0 *M*, 116 mL, 116 mmol) was added to **31** (4.72 g, 9.68 mmol), and the solution was refluxed for 10 hours. The reaction was quenched by adding MeOH (120 mL) under ice-water cooling, and then the solvents were evaporated. 5% aqueous HCl (60 mL) was added to the residue and the mixture was refluxed for 1 hour. The reaction mixture was basified with K_2CO_3, saturated with NaCl, and extracted with $CHCl_3$ (20 mL x 3). The combined organic extracts were dried with anhydrous K_2CO_3, filtered and concentrated *in vacuo* to give a colorless oil. This crude product was purified by column chromatography (hexane / isopropylamine) to give a colorless oil (**27**) (2.48 g, 59%). $[\alpha]_D^{26}$ -4.33 (*c* 1.13, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (3H, d, *J* = 6.1 Hz), 0.87 (3H, d, *J* = 5.4 Hz), 1.12 ~ 1.17 (1H, m), 1.24 ~ 1.28 (1H, m), 1.5 ~ 2.0 (7H, m), 2.0 ~ 3.0 (16H, m), 2.16 (6H, s), 2.23 (6H, s), 3.1 (1H, m), 7.2 ~ 7.3 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.81, 22.89, 23.18, 24.81, 29.12, 39.59, 42.92, 45.85, 45.89, 50.11, 51.45, 53.27, 53.57, 54.57, 58.74, 60.03, 64.62, 64.95, 125.89, 128.19, 129.26, 139.56. MS *m/z*: 432 (M^+). IR (neat, cm^{-1}): 3178, 1460. HRMS Calcd for $C_{29}H_{53}N_5$: 431.3988. Found: 431.3989.

Physical data of products (**2a** – **2g**)

(S)-**2a** (46% ee): Daicel Chiralcel OD-H®, hexane/2-propanol = 30/1, 0.5 mL/min, 254 nm) 25.8 min (*S*-isomer), 31.2 min (*R*-isomer). $[\alpha]_D^{24}$ +32.8 (*c* 1.01, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (3H, d, *J* = 6.8 Hz), 1.6 ~ 1.8 (4H, m), 2.64 (1H, dd, *J* = 6.2, 12.8 Hz), 2.7 ~ 2.8 (1H, m), 2.9 ~ 3.0 (2H, m), 3.2 ~ 3.4 (3H, m), 7.1 ~ 7.3 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.25, 24.09, 25.83, 40.37, 40.50, 45.51, 46.20, 126.05, 128.12, 128.87, 140.08, 174.32. IR (nujol, cm^{-1}): 1633. MS *m/z*: 217 (M^+). HRMS Calcd for $C_{14}H_{19}NO$: 217.1467. Found: 217.1472.

2b: see the text.

2c (81% ee): Chiralcel OD-H® (Hexane / 2-propanol / diethylamine = 180 / 6 / 0.19, 0.5 mL/min, 254 nm) 29.8 min (minor), 36.3 min (major). $[\alpha]_D^{24}$ –32.2 (*c* 0.30, $CHCl_3$). ^{1}H-NMR (400 MHz / $CDCl_3$); δ 1.16 (3H, d, *J* = 6.1 Hz), 1.80 ~ 1.85 (1H, m), 2.1 ~ 2.4 (3H, m), 2.20 (3H, s), 2.6 ~ 2.7 (1H, m), 2.9 ~ 3.0 (2H, m), 3.3 (1H, m), 3.4 (1H, m), 3.5 (1H, m), 7.1 ~ 7.3 (5H, m). ^{13}C-NMR (100 MHz / $CDCl_3$); δ 17.90, 37.34, 40.64, 41.53, 45.30, 45.84, 54.59, 54.84, 126.23, 128.35, 129.05, 140.00, 174.23. IR (neat, cm^{-1}) 1629. MS *m/z*: 246 (M^+). HRMS Calcd for $C_{15}H_{22}N_2O$: 246.1732. Found: 246.1727.

2d (79% ee): Chiralcel OD-H® (Hexane / 2-propanol = 9 / 1, 0.5 mL/min, 254 nm) 18.2 min (minor), 23.0 min (major). $[\alpha]_D^{24}$ –48.0 (*c* 0.66, $CHCl_3$). ^{1}H-NMR (400 MHz / $CDCl_3$); δ 1.18 (3H, d, *J* = 6.1 Hz), 2.70 (1H, m), 2.9 ~ 3.1 (3H, m), 3.1 ~ 3.2 (1H, m), 3.2 ~ 3.3 (1H, m), 3.4 ~ 3.5 (3H, m), 3.5 ~ 3.7 (2H, m), 7.1 ~ 7.3 (5H, m). ^{13}C-NMR (100 MHz / $CDCl_3$); δ 17.97, 37.23, 40.76, 41.99, 45.93, 66.33, 66.76, 126.35, 128.37, 129.00, 139.84, 174.38. IR (neat, cm^{-1}) 1638. MS *m/z*: 233 (M^+), 218. HRMS Calcd for $C_{14}H_{19}NO_2$: 233.1416. Found: 233.1414.

2e (78% ee): Chiralcel AD® (Hexane / 2-propanol = 10 / 1, 1.0 mL/min, 254 nm) 8.0 min (minor), 8.7 min (major). $[\alpha]_D^{24}$ –62.0 (*c* 1.17, $CHCl_3$). ^{1}H-NMR (300 MHz / $CDCl_3$); δ 1.14 (3H, d, *J* = 6.4 Hz), 2.64 (1H, dd, *J* = 9.8, 16.2 Hz), 2.79 (3H, s), 2.89 (3H, s), 2.95 ~ 3.05 (2H, m), 7.1 ~

7.3 (5H, m). ^{13}C-NMR (75 MHz / $CDCl_3$); δ 17.42, 35.51, 36.94, 37.80, 40.41, 126.09, 128.19, 128.91, 140.12, 175.78. IR (neat, cm^{-1}) 1641, 1495, 1454, 1398, 702. MS *m/z*: 191 (M^+), 176, 91. HRMS Calcd for $C_{12}H_{17}NO$: 191.1310. Found: 191.1294.

2f (79% ee): Chiralcel AD® (Hexane / 2-propanol = 100 / 1, 0.5 mL/min, 254 nm) 28.5 min (minor), 29.5 min (major). $[\alpha]_D^{24}$ –65.3 (*c* 0.83, $CHCl_3$). ^{1}H-NMR (300 MHz / $CDCl_3$); δ 0.96 (3H, t, *J* = 7.1 Hz), 1.02 (3H, t, *J* = 7.1 Hz), 1.16 (3H, d, *J* = 6.6 Hz), 2.63 (1H, dd, *J* = 5.9, 12.8 Hz), 2.8 ~ 2.9 (1H, m), 2.9 ~ 3.1 (1H, m), 3.1 ~ 3.3 (1H, m), 3.3 ~ 3.5 (1H, m), 7.1 ~ 7.3 (5H, m). ^{13}C-NMR (75 MHz / $CDCl_3$); δ 12.96, 14.61, 18.23, 38.12, 40.42, 40.79, 41.64, 126.09, 128.19, 129.06, 140.26, 175.11. IR (neat, cm^{-1}) 1635, 1452, 701. MS *m/z*: 219 (M^+), 204. HRMS Calcd for $C_{14}H_{21}NO$: 219.1623. Found: 219.1602.

2g (59% ee): Chiralcel OJ® (Hexane / 2-propanol = 100 / 1, 0.5 mL/min, 254 nm) 23.5 min (major), 25.8 min (minor). ^{1}H-NMR (300 MHz / $CDCl_3$); δ 0.90 (3H, t, *J* = 7.4 Hz), 1.5 ~ 1.8 (6H, m), 2.6 ~ 2.8 (3H, m), 2.91 (1H, dd, *J* = 9.5, 12.7 Hz), 3.2 ~ 3.5 (3H, m), 7.1 ~ 7.3 (5H, m). ^{13}C-NMR (75 MHz / $CDCl_3$); δ 12.11, 24.16, 25.79, 25.84, 39.36, 45.39, 46.34, 48.41, 126.05, 128.12, 128.86, 140.18, 173.73. IR (neat, cm^{-1}) 1635, 1449, 702. MS *m/z*: 231 (M^+), 202. HRMS Calcd for $C_{15}H_{21}NO$: 231.1623. Found: 231.1629.

Absolute configuration determination of **2a**

A mixture of (+)-**2a** (46% ee, $[\alpha]_D^{24}$ +31.8 (*c* 1.01, $CHCl_3$), 25 mg, 0.12 mmol) and 5 *N* aqueous HCl was refluxed for 11 hours. After cooling to room temperature, the reaction mixture was basified with 15% aqueous NaOH, and then washed with ether (10 mL x 2). The aqueous layer was acidified with 10% aqueous HCl, and then extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were washed with H_2O, dried with Na_2SO_4, filtered and concentrated *in vacuo* to give α-benzyl-propionic acid (13 mg, 68%, $[\alpha]_D^{24}$ +8.6 (*c* 0.64, $CHCl_3$)). Compared with the reported value[5], the absolute configuration of (+)-**2a** was determined to *S*.

References

1) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132-157.

2) Shirai, R.; Aoki, K.; Sato, D.; Kim, H.-D.; Murakata, M.; Yasukata, T.; Koga, K. *Chem. Pharm. Bull.* **1994**, *42*, 690-693.

3) Yasuda, K. *Ph.D Thesis*; The University of Tokyo, 1997.

4) Fréchet, J. M. J.; Nuyens, L. J. *Can. J. Chem.* **1976**, *54*, 926-934.

5) Schrecker, A. W. *J. Org. Chem.* **1957**, *22*, 33-35.