The Synthesis of Chiral b^3-Aminoxy Peptides

Dan Yang,[*,†,‡] *Yu-Hui Zhang,*[†] *Bing Li,*[†] *and Dan-Wei Zhang*[‡]

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, China

and Department of Chemistry, Fudan University, Shanghai 200433, China

Supporting Information

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General methods. All reagents and solvents for reactions were of analytical grade and were dried and distilled if necessary. ^{1}H and ^{13}C NMR spectra were recorded at 300 or 400 MHz for protons and at 75.5 or 100.0 MHz for carbons on DPX 300 or 400 Fourier Transform Spectrometers. Infrared spectra were obtained on a FT-IR spectrometer. Melting points were determined with a microscope and were uncorrected. Optical rotations were measured on a polarmeter. Mass spectra were recorded with a mass spectrometer for both low resolution and high-resolution mass spectra.

Compounds **1**–**5** were prepared according to our previous work.[1]

Characterization data for 1. The NMR data is identical to that previously reported.[1]

Characterization data for 2. A white solid; m.p. 62–64 ^{o}C; $[\alpha]^{20}_{D}$ = + 70.9^{o} (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 2H), 4.46 (d, *J* = 7.0 Hz, 2H), 4.33 (dd, *J* = 4.2, 7.4 Hz, 1H), 4.25 (t, *J* = 7.0 Hz, 1H), 1.94–1.84 (m, 1H), 1.74–1.64 (m, 2H), 1.50 (s, 9H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 171.4, 156.8, 143.5, 141.3, 127.8, 127.1, 125.1, 120.0, 82.8, 82.2, 67.6, 46.9, 39.8, 28.1, 24.6, 23.1, 21.8; IR (CH_2Cl_2) 3379 (br, N–H), 1737 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 425 (M^+, 1), 179 (30), 178 (100); HRMS (EI, 20 eV) calcd for $C_{25}H_{31}NO_5$ (M^+) 425.2202, found 425.2202.

Characterization data for 3. A white solid; m.p. 78–80 ^{o}C; $[\alpha]^{20}_{D}$ = + 64.1^{o} (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.37–7.29 (m, 5H), 5.19 (d, *J* = 12.1 Hz, 1H), 5.13 (d, *J* = 12.1 Hz, 1H), 4.31 (dd, *J* = 4.0, 9.6 Hz, 1H), 1.96–1.85 (m, 1H), 1.70–1.52 (m, 2H), 1.47 (s, 9H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 171.4, 156.9, 135.5, 128.6, 128.4, 128.4, 82.8, 82.1, 67.5, 39.8, 28.1, 24.6, 23.1, 21.6; IR (CH_2Cl_2) 3378 (br, N–H), 1755 (C=O), 1735 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 337 (M^+, 6),

107 (20), 106 (16), 91 (100); HRMS (EI, 20 eV) calcd for $C_{18}H_{27}NO_5$ (M^+) 337.1889, found 337.1891.

Characterization data for 4. A colorless liquid; $[\alpha]^{20}_D$ = + 68.9° (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.41–7.33 (m, 5H), 5.22 (d, *J* = 12.1 Hz, 1H), 5.17 (d, *J* = 12.1 Hz, 1H), 4.14 (d, *J* = 9.6 Hz, 1H), 2.21–2.10 (m, 1H), 1.51 (s, 9H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 170.4, 156.9, 135.6, 128.6, 128.4, 128.3, 88.6, 82.0, 67.4, 30.3, 28.1, 18.6, 17.3; IR (CH_2Cl_2) 3380 (br, N–H), 1732 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 324 (M^++1, 27), 314 (36), 268 (81), 224 (13), 106 (27), 91 (100); HRMS (EI, 20 eV) calcd for $C_{17}H_{25}NO_5$ (M^+) 323.1733, found 323.1725.

Characterization data for 5. A colorless oil; $[\alpha]^{20}_D$ = + 100.9 ° (*c* 1.10, CH_2Cl_2); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.00 (s, 1H), 4.25–4.13 (m, 2H), 4.09 (d, *J* = 4.9 Hz, 1H), 2.19–2.07 (m, 1H), 1.50 (s, 9H), 1.28 (t, *J* = 6.9 Hz. 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (67.80 MHz, $CDCl_3$) δ 170.2, 157.2, 88.5, 81.8, 61.7, 30.3, 28.1, 18.6, 17.3, 14.4; IR (CH_2Cl_2) 3382 (br, N–H), 1733 (C=O) cm^{-1}; FABMS 262 (M^+ + 1).

Preparation of 6. A solution of compound **1** (500 mg, 1.50 mmol) in dichloromethane (4 mL) in an ice bath was treated with trifluroacetic acid (4 mL). After stirring at room temperature for 1 h, the reaction mixture was concentrated under vacuum, and azeotroped with toluene. Then dry THF (10 mL) was added and the solution was cooled to –25 °C under N_2. Et_3N (229 μL, 1.65 mmol) and ethyl chloroformate (158 μL, 1.65 mmol) were added subsequently with stirring while the temperature was kept below –20 °C. After 15 min, a freshly prepared diazomethane solution in dry ether was added until the yellow color of the solution persisted. The mixture was allowed to warm up to 0 °C and stirring was continued for 3 h. Acidification with dilute acetic acid or citric acid and addition of an equal volume of ether were followed by washing the

organic layer with water, saturated $NaHCO_3$ and brine. Drying over Na_2SO_4 and evaporation yielded the crude diazoketone, which was further purified by flash chromatography (30% EtOAc in *n*-Hexane) to give a light yellow solid **6** (312 mg, 69% yield). M.p. 70–71 ^oC; $[\alpha]^{20}_D$ = + 113.5^o (c 1.12, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.85–7.68 (m, 4H), 6.44 (s, 1H), 4.84 (dd, *J* = 4.2, 9.1 Hz, 1H), 2.12–2.01 (m, 1H), 1.90–1.80 (m, 1H), 1.70–1.59 (m, 1H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 194.3, 164.0, 135.2, 129.1, 124.1, 89.8, 54.3, 41.6, 24.9, 23.5, 22.2; IR (CH_2Cl_2) 2113 (CH=N_2), 1793 (C=O), 1737 (C=O) cm^{-1}; FABMS 302 (M^+ + 1).

Preparation of 7. Following the procedure for the preparation of **6**, **7** was obtained from **2** as a light yellow solid (63% yield). M.p. 113–114 ^oC; $[\alpha]^{20}_D$ = + 99.3^o (*c* 1.27, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.74 (s, 1H), 7.56 (d, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 5.70 (s, 1H), 4.51 (d, *J* = 6.7 Hz, 2H), 4.31 (dd, *J* = 6.8, 9.7 Hz, 1H), 4.22 (t, *J* = 6.6 Hz, 1H), 1.93–1.84 (m, 1H), 1.64–1.59 (m, 1H), 1.49–1.40 (m, 1H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 194.6, 157.1, 143.3, 141.3, 127.9, 127.2, 124.9, 120.1, 87.8, 67.6, 53.5, 46.9, 40.3, 24.6, 23.2, 21.9; IR (CH_2Cl_2) 3366 (br, N–H), 1758 (C=O), 1733 (C=O) cm^{-1}; FABMS 394 (M^+ + 1).

Preparation of 8. Following the procedure for the preparation of **6**, **8** was obtained from **3** as a light yellow solid (58% yield). M.p. 69–70 ^oC; $[\alpha]^{20}_D$ = + 195.4^o (*c* 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.39–7.33 (m, 5H), 5.76 (s, 1H), 5.17 (s, 2H), 4.32 (dd, *J* = 4.0, 9.7 Hz, 1H), 1.91–1.84 (m, 1H), 1.66–1.58 (m, 1H), 1.48–1.40 (m, 1H), 0.95 (d, *J* = 2.8 Hz, 3H), 0.92 (d, *J* = 2.9 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 194.8, 157.2, 135.2, 128.7, 128.6,

128.4, 87.9, 67.8, 53.2, 40.4, 24.6, 23.1, 21.7; IR (CH_2Cl_2) 3374 (br, N–H), 2112 (CH=N_2), 1757 (C=O) cm^{-1}; FABMS 306 (M^+ + 1).

Preparation of 9. Following the procedure for the preparation of **6**, **9** was obtained from **4** as a light yellow oil (68% yield). $[\alpha]^{20}_D$ = + 86.3° (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.38–7.33 (m, 5H), 5.79 (s, 1H), 5.16 (s, 2H), 4.04 (d, *J* = 5.6 Hz, 1H), 2.08–2.01 (m, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 194.2, 157.2, 135.3,128.6, 128.6, 128.4, 94.1, 67.8, 54.1, 30.8, 18.8, 17.6; IR (CH_2Cl_2) 3367 (br, N–H), 2112 (CH=N_2), 1756 (C=O) cm^{-1}; APCI-MS 291 (M^+).

Preparation of 10. Following the procedure for the preparation of **6**, **10** was obtained from **5** as a light yellow liquid (65% yield). $[\alpha]^{20}_D$ = + 144.4° (*c* 0.99, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (s, 1H), 5.84 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.05 (d, *J* = 5.6 Hz, 1H), 2.09–2.03 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.04 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 194.4, 157.5, 94.0, 62.2, 54.1, 30.8, 18.8, 17.6, 14.4; IR (CH_2Cl_2) 3377 (br, N–H), 2112 (CH=N_2), 1756 (C=O), 1725 (C=O) cm^{-1}.

Preparation of 12. A solution of diazoketone **6** (300 mg, 1.00 mmol) in THF (10 mL) and H_2O (1 mL) at –20 °C was added a solution of CF_3COOAg (24 mg, 0.11 mmol) in Et_3N (402 μL, 2.9 mmol) under N_2 with exclusion of light. After 3 h, ether was added and the mixture was extracted with sat. $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (30% EtOAc in *n*-Hexane) to give **12** as a white solid (169 mg, 69% yield). M.p. 87–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 3.2, 5.5 Hz, 2H), 7.79 (dd, *J* = 3.2, 5.4 Hz, 2H), 7.30 (dt, *J* = 7.5, 15.6 Hz, 1H), 6.08 (d, *J* = 15.7 Hz, 1H), 2.22 (t, *J* = 6.9 Hz, 2H), 1.89–1.80 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75.47 MHz,

$CDCl_3$) δ 161.3, 161.1, 154.0, 133.7, 127.9, 122.9, 115.4, 41.1, 26.7, 21.4; IR (CH_2Cl_2) 1732 (C=O), 1650 (C=C) cm^{-1}; LRMS (EI, 70 eV) *m/z* 247 (M^++2, 2), 163 (12), 111 (100); HRMS (EI, 70 eV) calcd for $C_{14}H_{15}NO_3$ (M^+) 245.1052, found 245.1061.

Preparation of 13. A solution of diazoketone **8** (285 mg, 0.93 mmol) in THF (9 mL) was stirred at −78 °C, then a solution of PhCOOAg (23 mg, 0.10 mmol) in Et_3N (387 μL, 2.79 mmol) was added under N_2 with exclusion of light. After 24 h, ether was added to dilute the solution, which was then extracted with sat. $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (30% EtOAc in *n*−Hexane) to give **13** as a white solid (176 mg, 68% yield). M.p. 79–80 °C; $[\alpha]^{20}_D$ = + 19.1° (*c* 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.33 (m, 5H), 5.34 (s, 2H), 4.65–4.58 (m, 1H), 2.90 (dd, *J* = 6.6, 16.7 Hz, 1H), 2.63 (dd, *J* = 9.8, 16.7 Hz, 1H), 1.84–1.81 (m, 2H), 1.58–1.50 (m, 1H), 0.96 (d, *J* = 6.0 Hz, 3H),), 0.94 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 167.7, 147.8, 134.7, 128.6, 128.5, 78.0, 68.7, 41.9, 39.9, 24.8, 22.7, 22.5; IR (CH_2Cl_2) 1793 (C=O), 1746 (C=O) cm^{-1}; FABMS 278 (M^+ + 1); HRMS (EI, 20 eV) calcd for $C_{15}H_{19}NO_4$ (M^+) 277.1314, found 277.1285.

Preparation of 14. Following the procedure for the preparation of **13**, **14** was obtained from **9** as a white solid (64% yield). M.p. 70–71 °C; $[\alpha]^{20}_D$ = + 21.6° (*c* 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.31 (m, 5H), 5.34 (s, 2H), 4.27 (dt, *J* = 7.2, 10.0 Hz, 1H), 2.82 (dd, *J* = 7.0, 16.8 Hz, 1H), 2.72 (dd, *J* = 10.0, 16.8 Hz, 1H), 2.04–1.93 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 167.7, 147.7, 134.7, 128.6, 128.4, 83.8, 68.7, 37.1, 31.1, 18.2, 17.5; IR (CH_2Cl_2) 1791 (C=O), 1746 (C=O) cm^{-1}; FABMS 264 (M^+ + 1); HRMS (EI, 20 eV) calcd for $C_{14}H_{17}NO_4$ (M^+) 263.1158, found 263.1181.

Preparation of 15. Following the procedure for the preparation of **13**, **15** was obtained from **10** as a colorless liquid (98% yield). $[\alpha]^{20}_D$ = + 14.3° (c 1.50, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (q, *J* = 7.1 Hz, 2H), 4.28 (dt, *J* = 7.2, 10.0 Hz, 1H), 2.84 (dd, *J* = 7.0, 16.8 Hz, 1H), 2.73 (dd, *J* = 10.0, 16.9 Hz, 1H), 2.06–1.94 (m, 1H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (67.80 MHz, $CDCl_3$) δ 167.4, 147.5, 83.6, 63.5, 37.0, 30.9, 18.1, 17.4, 14.2; IR (CH_2Cl_2) 1789 (C=O), 1747 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 201 (M^+, 2), 129 (50), 97 (29), 86 (100); HRMS (EI, 20 eV) calcd for $C_9H_{15}NO_4$ (M^+) 201.1001, found 201.0977.

Preparation of 16. To a solution of diazoketone **7** (112 mg, 0.29 mmol) and *iso*-butylamine (42.7 μL, 0.43 mmol) in THF (8 mL) at –78 °C were added PhCOOAg (20 mg, 0.09 mmol) and Et_3N (115 μL, 0.83 mmol) under N_2 with exclusion of light. After 3 h, ether was added to dilute the solution, which was then extracted with sat. $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (30% EtOAc in *n*–Hexane) to give **16** as a colorless oil (74 mg, 58% yield). $[\alpha]^{20}_D$ = + 21.2° (*c* 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.68 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.42 (s, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 4.53 (dd, *J* = 6.8, 10.7 Hz, 1H), 4.50 (dd, *J* = 6.7, 10.7 Hz, 1H), 4.23 (t, *J* = 6.6 Hz, 1H), 4.10–4.06 (m, 1H), 3.13 (dt, *J* = 6.7, 13.1 Hz, 1H), 3.04 (dt, *J* = 6.7, 13.0 Hz, 1H), 2.55 (dd, *J* = 2.8, 15.2 Hz, 1H), 2.34 (dd, *J* = 6.7, 15.2 Hz, 1H), 1.84–1.80 (m, 1H), 1.79–1.70 (m, 1H), 1.60–1.55 (m, 1H), 1.38–1.32 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 6H), 0.89 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 170.2, 158.5, 143.4, 143.3, 141.4, 127.9, 127.2, 124.9, 124.9, 120.1, 82.2, 67.7, 47.1, 47.1, 41.1, 40.3, 28.4, 24.8, 22.8, 22.6, 20.2; IR (CH_2Cl_2) 3439 (br, N–H), 3350 (br, N–H),

1660 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 438 (M^+, 1), 184 (34), 179 (19), 178 (100); HRMS (EI, 20 eV) calcd for $C_{26}H_{34}N_2O_4$ (M^+) 438.2519, found 438.2521.

Preparation of 17. A solution of **13** (277 mg, 1 mmol), DMAP (134 mg, 1.1 mmol), and *iso*-butylamine (152 μL, 1.1 mmol) in THF (10 mL) were refluxed for 6 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (40% EtOAc in *n*–Hexane) to afford compound **17** as a colorless oil (287 mg, 82% yield). $[\alpha]^{20}_D$ = + 20.8° (c 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.59 (s, 1H), 7.39–7.31 (m, 5H), 5.17 (s, 2H), 4.12–4.05 (m, 1H), 3.13 (dt, *J* = 6.5, 13.1 Hz, 1H), 3.02 (dt, *J* = 6.4, 13.0 Hz, 1H), 2.58 (dd, *J* = 2.9, 15.2 Hz, 1H), 2.36 (dd, *J* = 6.7, 15.2 Hz, 1H), 1.89–1.81 (m, 1H), 1.79–1.67 (m, 1H), 1.61 (dt, *J* = 7.7, 14.1 Hz, 1H), 1.34 (ddd, *J* = 1.7, 5.7, 7.4 Hz, 1H), 0.92 (d, *J* = 6.7 Hz, 6H), 0.88 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 170.3, 158.5, 135.3, 128.6, 128.6, 128.4, 82.1, 67.9, 47.0, 41.0, 40.2, 28.3, 24.7, 22.8, 22.5, 20.2; IR (CH_2Cl_2) 3448 (br, N–H), 3354 (br, N–H), 1745 (C=O) cm^{-1}; LRMS (EI, 70 eV) *m/z* 350 (M^+, 4), 185 (11), 184 (97), 91 (100); HRMS (EI, 70 eV) calcd for $C_{26}H_{34}N_2O_4$ (M^+) 350.2206, found 350.2202.

Preparation of 18. A solution of **13** (277 mg, 1 mmol), DMAP (134 mg, 1.1 mmol), and *p*-anisidine (135 mg, 1.1 mmol) in THF (10 mL) was refluxed for 24 h. The resulting solution was diluted with ether, and washed with sat. NH_4Cl and NaCl solution, then the organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (30% EtOAc in *n*–Hexane) to afford compound **18** as a light yellow solid (312 mg, 79%). M.p. 86–87 °C; $[\alpha]^{20}_D$ = + 64.7° (*c* 1.03, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.70 (s, 1H), 7.60 (d, *J* = 9.0 Hz, 2H), 7.44–7.30 (m, 5H), 6.86 (d, *J* = 9.0 Hz, 2H), 5.24 (d, *J* = 12.0 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 4.19–4.11 (m, 1H), 3.79 (s, 3H), 2.77 (dd, *J* = 2.5, 15.2 Hz, 1H), 2.45 (dd, *J* = 6.6, 15.1 Hz, 1H), 1.81–1.57 (m, 2H), 1.44–1.35 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H),

0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 168.4, 159.1, 155.9, 135.0, 132.1, 128.8, 128.7, 128.5, 121.5, 113.9, 82.2, 68.2, 55.5, 41.2, 40.7, 24.8, 22.8, 22.5; IR (CH_2Cl_2) 3321 (br, N–H), 1738 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 400 (M^+, 17), 234 (18), 124 (13), 123 (100); HRMS (EI, 20 eV) calcd for $C_{22}H_{28}N_2O_5$ (M^+) 400.1998, found 400.2005.

Preparation of 19. Following the procedure for the preparation of **18**, **19** was obtained from **13** as a white solid (70% yield). M.p. 49–50 °C; $[\alpha]^{20}_D$ = + 52.6° (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.71 (s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.37 (m, 5H), 7.11 (d, J = 8.3 Hz, 2H), 5.25 (d, J = 12.0 Hz, 2H), 5.20 (d, J = 12.0 Hz, 2H), 4.18–4.11 (m, 1H), 2.78 (dd, J = 2.6, 15.0 Hz, 1H), 2.45 (dd, J = 6.4, 15.1 Hz, 1H), 2.31 (s, 3H), 1.85–1.79 (m, 1H), 1.77–1.61 (m, 1H), 1.59–1.35 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 168.5, 159.1, 136.2, 135.1, 133.2, 129.3, 128.7, 128.7, 128.5, 119.9, 82.3, 68.2, 41.3, 40.7, 24.8, 22.8, 22.4, 20.9; IR (CH_2Cl_2) 3321 (br, N–H), 1791 (C=O), 1741 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 384 (M^+, 15), 218 (46), 134 (13), 108 (20), 107 (100); HRMS (EI, 20 eV) calcd for $C_{22}H_{28}N_2O_4$ (M^+) 384.2049, found 384.2052.

Preparation of 20. Following the procedure for the preparation of **18**, **20** was obtained from **14** as a colorless oil (65% yield). $[\alpha]^{20}_D$ = – 16.6° (*c* 0.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.64 (s, 1H), 7.58–7.20 (m, 10H), 5.15 (d, J = 12.0 Hz, 1H), 5.09 (d, J = 12.0 Hz, 1H), 4.52 (dd, J = 6.2, 14.8 Hz, 1H), 4.42 (dd, J = 5.7, 14.8 Hz, 1H), 3.93 (ddd, J = 3.2, 5.4, 8.0 Hz, 1H), 2.50 (dd, J = 3.2, 16.3 Hz, 1H), 2.44 (dd, J = 7.9, 16.3 Hz, 1H), 2.15–2.02 (m, 1H), 0.93 (d, J = 7.4 Hz, 3H), 0.91 (d, J = 7.4 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 170.7, 158.3, 138.9, 135.2, 128.6, 128.5, 128.4, 127.8, 127.0, 87.8, 67.9, 43.4, 35.9, 29.1, 18.6, 16.5; IR (CH_2Cl_2) 3446 (br, N–H), 1750 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 370 (M^+, 15), 279 (31), 204 (100); HRMS (EI, 20 eV) calcd for $C_{21}H_{26}N_2O_4$ (M^+) 370.1893, found 370.1894.

Preparation of 21. Following the procedure for the preparation of **18**, **21** was obtained from **14** as a white solid (59% yield). M.p. 86–87 ^{o}C; $[\alpha]^{20}_{D}$ = + 35.8^{o} (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.79 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.45–7.28 (m, 5H), 7.25 (d, *J* = 8.9 Hz, 2H), 5.24 (d, *J* = 12.0 Hz, 1H), 5.20 (d, *J* = 12.0 Hz, 1H), 3.87 (ddd, *J* = 2.1, 7.3, 8.8 Hz, 1H), 2.68 (dd, *J* = 2.2, 16.1 Hz, 1H), 2.51 (dd, *J* = 7.5, 16.1 Hz, 1H), 2.13–2.04 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 169.0, 158.9, 137.4, 134.9, 128.8, 128.7, 128.7, 128.6, 128.5, 121.4, 88.1, 68.3, 37.4, 29.1, 18.9, 16.9; IR (CH_2Cl_2) 1745 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 390 (M^+, 6), 224 (42), 127 (69), 91 (100); HRMS (EI, 20 eV) calcd for $C_{20}H_{23}N_2O_4Cl$ (M^+) 390.1346, found 390.1346.

Preparation of 22. A solution of **15** (100.5 mg, 0.5 mmol), DMAP (67.1 mg, 055 mmol), and p-toluidine (59 mg, 0.55 mmol) in toluene (8 mL) was refluxed for 24 h. The resulting solution was diluted with ether, and washed with sat. NH_4Cl and NaCl solution. Then the organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (40 % EtOAc in *n*-Hexane) to afford compound **22** as a white solid (149 mg, 97 %). M.p. 96–98 ^{o}C; $[\alpha]^{20}_{D}$ = + 48.7^{o} (c 0.56, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.64 (s, 1H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 4.36–4.26 (m, 2H), 3.93 (ddd, *J* = 2.3, 7.4, 9.0 Hz, 1H), 2.74 (dd, *J* = 2.3, 15.9 Hz, 1H), 2.58 (dd, *J* = 7.5, 15.9 Hz, 1H), 2.36 (s, 3H), 2.21–2.10 (m, 1H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 168.8, 158.9, 136.2, 133.2, 129.2, 120.2, 87.1, 62.6, 37.4, 29.1, 20.8, 18.9, 17.1, 14.4; IR (CH_2Cl_2) 3319 (N–H), 3200 (N–H), 33134 (br, N–H), 1789 (C=O), 1739 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 308 (M^+, 14), 203 (31), 107 (100); HRMS (EI, 20 eV) calcd for $C_{16}H_{24}N_2O_4$ (M^+) 308.1736, found 308.1739.

Preparation of 24. Compound **17** (100 mg, 0.29 mmol) was treated with HBr in acetic acid (40%, 2 mL). After stirring at room temperature for 6 h, the reaction mixture was concentrated under vacuum, and azeotroped with toluene to afford **23** as a colorless oil (57 mg). A solution of **13** (80 mg, 0.29 mmol), DMAP (40 mg, 0.32 mmol), and compound **23** (57 mg, 0.26 mmol) in THF (10 mL) was refluxed for 16 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (50% EtOAc in *n*–Hexane) to afford compound **24** as a colorless oil (107 mg, 72% yield). $[\alpha]^{20}_{D}$ = + 32.9^{o} (c 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.91 (s, 1H), 8.54 (t, *J* = 3.9 Hz, 1H), 7.51 (s, 1H), 7.41–7.34 (m, 5H), 5.22 (d, *J* = 11.9 Hz, 1H), 5.17 (d, *J* = 11.9 Hz, 1H), 4.14–4.05 (m, 2H), 3.17 (dt, *J* = 6.4, 13.1 Hz, 1H), 3.06 (dt, *J* = 6.3, 13.1 Hz, 1H), 2.60 (dd, *J* = 2.5, 15.6 Hz, 2H), 2.38 (dd, *J* = 6.0, 15.5 Hz, 1H), 2.34 (dd, *J* = 7.0, 15.6 Hz, 1H), 1.90–1.81 (m, 2H), 1.78–1.61 (m, 2H), 1.45–1.32 (m, 3H), 0.96 (d, *J* = 7.0 Hz, 6H), 0.93 (d, *J* = 6.7 Hz, 6H), 0.92 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 170.2, 168.7, 159.3, 134.8, 128.9, 128.8, 128.8, 105.1, 81.7, 81.6, 68.5, 47.1, 40.8, 40.3, 37.9, 28.4, 24.8, 24.7, 22.8, 22.6, 22.6, 20.3; IR (CH_2Cl_2) 3442 (br, N–H), 3355 (br, N–H), 3286 (br, N–H), 3233 br, (N–H), 1734 (C=O), 1657 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 493 (M^+, 3), 184 (59), 144 (34), 128 (22), 111 (63), 91 (100); HRMS (EI, 20 eV) calcd for $C_{26}H_{43}N_3O_6$ (M^+) 493.3152, found 493.3188.

Preparation of 27. To a suspension of baker's yeast (50 g) in H_2O (40 mL) and petroleum spirit (300 mL) was added *tert*-butyl acetoacetate (1 mL, 6.03 mmol). After kept stirring for 24 h at room temperature, the mixture was filtered and the baker's yeast was washed with EtOAc. The combined organic layer was washed with brine, dried ($MgSO_4$), concentrated in vacuum and purified by flash column chromatography (10% EtOAc in *n*-Hexane) to give **27** (0.605 g, 63%

yield) as an oil. 93 % ee (determined by HPLC); $[\alpha]^{20}_D$ = + 36.0° (*c* 1.08, $CHCl_3$), Lit.[2] $[\alpha]^{20}_D$ = + 34.0° (*c* 1, $CHCl_3$). The NMR data is identical to that previously reported.[2]

Preparation of 28. The experimental procedure is the same as that previously reported.[3]

Preparation of 29. To the suspension of $LiAlH_4$ (2.384 g, 62.82 mmol) in ether (20 mL) was added a solution of compound **27** (5.000 g, 31.41 mmol) in ether (20 mL) at 0 °C. After kept stirring for 10 h at room temperature, the reaction was quenched with H_2O (1.2 mL), followed by 30% NaOH (1.5 mL) after 10 min, and finally 1.2 mL of water. Then the mixture was kept stirring overnight. The reaction mixture was filtered on a $MgSO_4$ pad. The filtrate was dried with $MgSO_4$, concentrated in vacuum and purified by flash column chromatography (30% EtOAc in CH_2Cl_2) to give **29** (2.517g, 89% yield) as an oil. $[\alpha]^{20}_D$ = + 28.0° (*c* 1.06, EtOH), Lit.[4] $[\alpha]^{21}_D$ = – 28.7° (*c* 3.2, EtOH) for the enantiomer of **29**; the NMR data is identical to that previously reported.[4]

Preparation of 30. Following the procedure for the preparation of **29**, **30** was obtained from **28** as an oil (56%). $[\alpha]^{20}_D$ = + 16.6° (*c* 1.04, EtOH); the NMR data is identical to that previously reported.[5]

Preparation of 31. To the solution of compound **29** (1.353 g, 15.02 mmol) in DMF (12 mL) were added triphenylmethyl chloride (4.653 g, 16.53 mmol), 4-dimethylaminopyridine (0.185 g, 1.50 mmol), and Et_3N (3.14 mL, 22.53 mmol) at 0 °C. Then the solution was warmed to room temperature and kept stirring for 14 h. The reaction mixture was poured into ice water, extracted with CH_2Cl_2 3 times. The combined organic layer was washed successively with sat. NH_4Cl, water, and brine, then dried ($MgSO_4$), concentrated in vacuum and purified by flash column chromatography (10% EtOAc in *n*-Hexane) to give **31** (4.590 g, 92% yield) as a solid. M.p. 63–64 °C; $[\alpha]^{20}_D$ = + 2.3° (*c* 2.30, EtOH), Lit.[6] $[\alpha]^{22}_D$ = – 2.5° (*c* 1.12, EtOH) for the enantiomer

of **31**; LRMS (EI, 20 eV) *m/z* 332 (M^+, 5), 259 (41), 243 (95), 241 (100); HRMS (EI, 20 eV) calcd for $C_{23}H_{24}O_2$ (M^+) 332.1776, found 332.1779. The NMR data is identical to that previously reported.[6]

Preparation of 32. Following the procedure for the preparation of **31**, **32** was obtained from **30** as an oil (97% yield): $[\alpha]^{20}_D = -9.6^o$ (*c* 0.78, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) d 7.51–7.16 (m, 15H), 3.68–3.64 (m, 1H), 3.41–3.35 (m, 1H), 3.26–3.19 (m, 1H), 2.86 (d, *J* = 2.9 Hz, 1H), 1.79–1.67 (m, 2H), 1.51–1.37 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) d 143.8, 128.5, 127.8, 126.9, 87.2, 72.6, 62.6, 36.2, 30.1, 9.9; IR (CH_2Cl_2) 3525 (br, O–H) cm^{-1}; LRMS (EI, 20 eV) *m/z* 346 (M^+, 4), 259 (34), 242 (100), 165 (30); HRMS (EI, 20 eV) calcd for $C_{24}H_{26}O_2$ (M^+) 346.1933, found 346.1940.

Preparation of 33. To the solution of compound **31** (0.205 g, 0.617 mmol), N-hydroxyphthalimide (0.109 g, 0.648 mmol), and PPh_3 (0.178 g, 0.678 mmol) in THF (5 mL) was added diisopropylazodicarboxylate (0.126 mL, 0.646 mmol) at 0 ^{o}C. After 1 h, the reaction was warmed to room temperature and kept stirring overnight, then concentrated in vacuum and purified by flash column chromatography directly (10% EtOAc in *n*-Hexane) to give **33** (0.277 g, 94% yield) as a solid. M.p. 98–99 ^{o}C; $[\alpha]^{20}_D = +9.6^o$ (*c* 0.84, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.84–7.79 (m, 2H), 7.75–7.71 (m, 2H), 7.44–7.18 (m, 15H), 4.62–4.54 (m, 1H), 3.34 (dt, *J* = 6.2, 9.5 Hz, 1H), 3.20 (dt, *J* = 6.2, 9.5 Hz, 1H), 2.22–2.14 (m, 1H), 1.87–1.79 (m, 1H), 1.29 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 164.2, 144.1, 134.3, 128.9, 128.6, 127.7, 126.8, 123.4, 86.6, 82.3, 60.0, 35.4, 18.9; IR (CH_2Cl_2) 1790 (C=O), 1734 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 243 (78), 241 (100), 237 (11), 234 (M^+–Tr, 23); HRMS (EI, 20 eV) calcd for $C_{12}H_{12}O_4$ (M^+–Tr) 234.0766, found 234.0760.

Preparation of 34. Following the procedure for the preparation of **33**, **34** was obtained from **32** as a solid (74% yield). M.p. 56–57 ^{o}C; $[\alpha]^{20}_{D}$ = + 7.0^{o} (*c* 0.73, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.83–7.79 (m, 2H), 7.75–7.70 (m, 2H), 7.47–7.40 (m, 6H), 7.27–7.17 (m, 9H), 4.37–4.31 (m, 1H), 3.32 (dt, *J* = 6.5, 9.4 Hz, 1H), 3.25 (dt, *J* = 6.6, 9.4 Hz, 1H), 2.11–2.02 (m, 1H), 1.95–1.87 (m, 1H), 1.71–1.62 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.1, 144.1, 134.2, 128.9, 128.5, 127.6, 126.8, 123.2, 86.9, 86.6, 60.2, 32.7, 25.6, 9.1; IR (CH_2Cl_2) 1791 (C=O), 1734 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 248 (M^+–Tr, 21), 243 (100), 165 (27); HRMS (EI, 20 eV) calcd for $C_{13}H_{14}O_4$ (M^+–Tr) 248.0923, found 248.0919.

Preparation of 35. To the solution of compound **33** (5.621 g, 11.78 mmol) in CH_2Cl_2 (20 mL) was added HCOOH (20 mL). After kept stirring for 14 min at room temperature, the reaction was quenched with brine, and diluted with CH_2Cl_2. The organic layer was washed with brine, sat. $NaHCO_3$, and brine again until pH 7, dried ($MgSO_4$), concentrated in vacuum and purified by flash column chromatography (50% EtOAc in *n*-Hexane) to give **35** (2.022g, 73% yield) as a solid. M.p.71–72 ^{o}C; $[\alpha]^{20}_{D}$ = – 35.7^{o} (*c* 0.93, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) d 7.88–7.80 (m, 2H), 7.80–7.74 (m, 2H), 4.55–4.44 (m, 1H), 4.13–4.03 (m, 1H), 3.91–3.75 (m, 1H), 3.08 (t, *J* = 6.6 Hz, 1H), 1.97–1.86 (m, 2H), 1.41 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) d 164.5, 134.6, 128.8, 123.6, 82.6, 58.7, 37.6, 19.7; IR (CH_2Cl_2) 3507 (br, O–H), 1790 (C=O), 1731 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 236 (M^++1, 0.7), 164 (12), 163 (100), 147 (7); HRMS (EI, 20 eV) calcd for $C_{12}H_{13}O_4$ (M^+) 235.0845, found 235.0846.

Preparation of 36. Following the procedure for the preparation of **35**, **36** was obtained from **34** as a solid (75% yield). M.p. 45–46 ^{o}C; $[\alpha]^{20}_{D}$ = – 34.2^{o} (*c* 0.73, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.87–7.82 (m, 2H), 7.79–7.74 (m, 2H), 4.35–4.29 (m, 1H), 4.13–4.06 (m, 1H), 3.84–3.80 (m, 1H), 3.25 (s, 1H), 1.93–1.76 (m, 4H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100

MHz, $CDCl_3$) d 164.7, 134.6, 128.8, 123.6, 87.2, 58.7, 34.2, 26.1, 8.7; IR (CH_2Cl_2) 3513 (br, O–H), 1790 (C=O), 1730 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 250 (M^++1, 2), 163 (100), 162 (70), 132 (6); HRMS (EI, 20 eV) calcd for $C_{13}H_{15}O_4$ (M^+) 249.1001, found 249.1004.

Preparation of 39. To the solution of compound **35** (1.911 g, 8.13 mmol) in 6.43 mL of the solvent ($CH_3CN/CCl_4/H_2O$/actone=1/1/1.4/0.3) were added $NaIO_4$ (3.476 g, 16.25 mmol) and $RuO_2 \cdot xH_2O$ (0.216 g, 1.62 mmol) at room temperature. After kept stirring for 5 h, the reaction was diluted with CH_2Cl_2 and filtered on celite, dried ($MgSO_4$) and concentrated in vacuum. The crude product **37** was used directly in next step without further purification.

To the stirred solution of compound **37** (8.13 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.026 g, 10.57 mmol) and 1-hydroxy-7-azabenzotriazole (1.438 g, 10.57 mmol) in CH_2Cl_2 (40 mL) was added cyclohexylamine (1.12 mL, 9.76 mmol) at room temperature. After kept stirring overnight, the reaction was diluted with CH_2Cl_2. The organic layer was washed with 5% $NaHCO_3$ solution and brine, then dried ($MgSO_4$), concentrated in vacuum and purified by flash column chromatography (25% EtOAc in CH_2Cl_2) to give **39** (1.638g, 61% yield) as a solid. M.p. 182–183 ^oC; $[\alpha]^{20}_D$ = + 85.8^o (*c* 0.80, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) d 7.88–7.84 (m, 2H), 7.81–7.77 (m, 2H), 7.03 (d, *J* = 7.3 Hz, 1H), 4.74–4.65 (m, 1H), 3.85–3.74 (m, 1H), 2.58 (d, *J* = 5.1 Hz, 2H), 1.93–1.92 (m, 2H), 1.75–1.71 (m, 2H), 1.63–1.52 (m, 1H), 1.45 (d, *J* = 6.4 Hz, 3H), 1.39–1.09 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) d 168.0, 164.5, 134.7, 128.8, 123.7, 81.6, 48.3, 42.1, 32.9, 32.8, 25.5, 24.8, 18.3; IR (CH_2Cl_2) 3428 (br, N–H), 3367 (br, N–H), 1791 (C=O), 1734 (C=O), 1662 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 330 (M^+, 19), 168 (100), 152 (67), 139 (50); HRMS (EI, 20 eV) calcd for $C_{18}H_{22}N_2O_4$ (M^+) 330.1580, found 330.1584.

Preparation of 40. Following the procedure for the preparation of **39**, **40** was obtained from **38** as a solid. A small part of crude product was purified by crystallization in CH_2Cl_2/hexane. Others were used in the next step without further purification. M.p. 153–154 °C; $[\alpha]^{20}_D$ = + 94.9° (*c* 0.62, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.88–7.83 (m, 2H), 7.80–7.77 (m, 2H), 7.10 (d, *J* = 7.4 Hz, 1H), 4.48–4.42 (m, 1H), 3.82–3.73 (m, 1H), 2.62 (dd, *J* = 3.1, 15.5 Hz, 1H), 2.55 (dd, *J* = 6.2, 15.5 Hz, 1H), 1.93–1.91 (m, 2H), 1.87–1.70 (m, 4H), 1.64–1.58 (m, 1H), 1.38–1.22 (m, 5H), 1.13 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 168.2, 164.6, 134.7, 128.8, 123.7, 86.8, 48.3, 40.1, 32.9, 32.8, 25.6, 25.4, 24.9, 9.8; IR (CH_2Cl_2) 3428 (br, N–H), 3357 (br, N–H), 1790 (C=O), 1734 (C=O), 1657 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 344 (M^+, 5), 182 (100), 168 (27), 147 (23); HRMS (EI, 20 eV) calcd for $C_{19}H_{24}N_2O_4$ (M^+) 344.1736, found 344.1733.

Preparation of 43. To a stirred solution of compound **39** (0.300 g, 0.91 mmol) in CH_3OH (2 mL) and CH_2Cl_2 (2 mL) was added $NH_2NH_2 \cdot H_2O$ (0.132 mL, 2.73 mmol). After kept stirring at room temperature for 1.5 h, the reaction was diluted with CH_2Cl_2, washed with 5% $NaHCO_3$ and brine, then dried ($MgSO_4$) and concentrated to give **41**, which was used directly in the next step.

To the stirred solution of *iso*-butyric acid (0.093 mL, 0.999 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.226 g, 1.18 mmol) and 1-hydroxy-7-azabenzotriazole (0.161 g, 1.18 mmol) in CH_2Cl_2 (5 mL) was added a solution of compound **41** in CH_2Cl_2 (3 mL) at room temperature. After kept stirring overnight, the reaction was diluted with CH_2Cl_2. The organic layer was washed with 5% $NaHCO_3$ and brine, then dried ($MgSO_4$), concentrated in vacuum and purified by flash column chromatography (50% EtOAc in CH_2Cl_2) to give **43** (0.125g, 51% yield) as a solid. M.p. 166–167 °C; $[a]_D^{20}$ = + 5.8° (c 0.99, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) d 9.24 (s, 1H), 8.02 (d, *J* = 6.8 Hz, 1H), 4.24–4.21 (m, 1H), 3.79–3.71 (m, 1H), 2.48 (dd, *J* = 2.4, 15.8 Hz, 1H), 2.40–2.31 (m, 2H), 1.90–1.88 (m, 2H), 1.75–1.68 (m,

2H), 1.62–1.59 (m, 1H), 1.42–1.12 (m, 5H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 176.1, 169.2, 78.4, 48.6, 41.9, 32.8, 32.7, 32.5, 25.5, 25.1, 19.4, 19.2, 18.3; IR (CH_2Cl_2, 2 mM) 3428 (br, N–H), 3391 (br, N–H), 3302 (br, N–H), 1694 (C=O), 1652 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 270 (M^+, 13), 168 (79), 152 (100), 104 (64); HRMS (EI, 20 eV) calcd for $C_{14}H_{26}N_2O_3$ (M^+) 270.1943, found 270.1932.

Preparation of 44. Following the procedure for the preparation of **43**, **44** was obtained from **40** as a solid (39% overall yield for four steps from compound **36**). M.p. 164–165 ^oC; $[a]_D^{20}$ = + 5.7^o (c 1.04, CH_2Cl_2): ^{1}H NMR (400 MHz, $CDCl_3$) d 9.75 (s, 1H), 8.32 (d, *J* = 7.5 Hz, 1H), 3.97–3.94 (m, 1H), 3.74–3.70 (m, 1H), 2.51 (dd, *J* = 2.3, 5.7 Hz, 1H), 2.43–2.28 (m, 2H), 1.89–1.87 (m, 2H), 1.75–1.52 (m, 5H), 1.39–1.11 (m, 5H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 176.2, 169.4, 83.5, 48.6, 39.5, 32.7, 32.6, 32.4, 25.4, 25.0, 19.4, 19.2, 9.6; IR (CH_2Cl_2, 2 mM) 3426 (br, N–H), 3389 (br, N–H), 3302 (br, N–H), 1693 (C=O), 1651 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 284 (M^+, 8), 182 (100), 152 (74), 116 (39); HRMS (EI, 20 eV) calcd for $C_{15}H_{28}N_2O_3$ (M^+) 284.2100, found 284.2091.

Preparation of 45. Following the procedure for the preparation of **43**, **45** was obtained from **39** as a solid (54% yield). M.p. 148–149 ^oC; $[\alpha]^{20}_D$ = + 74.8^o (*c* 0.80, CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) d 10.57 (s, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 7.88–7.84 (m, 2H), 7.83–7.79 (m, 2H), 4.72–4.66 (m, 1H), 4.34–4.27 (m, 1H), 3.77–3.75 (m, 1H), 2.66 (dd, *J* = 6.4, 15.5 Hz, 1H), 2.60 (dd, *J* = 4.2, 15.5 Hz, 1H), 2.51 (dd, *J* = 3.5, 16.4 Hz, 1H), 2.45 (dd, *J* = 7.2, 16.4 Hz, 1H),1.89–1.88 (m, 2H), 1.72–1.69 (m, 2H), 1.60–1.57 (m, 1H), 1.49 (d, *J* = 6.4 Hz, 3H), 1.38–1.16 (m, 5H), 1.33 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 169.0, 167.7, 164.6, 134.9, 128.5, 123.8, 81.2, 78.3, 48.4, 41.8, 39.4, 32.6, 32.6, 25.4, 25.0, 18.5, 18.3; IR (CH_2Cl_2)

3294 (br, N–H), 1791 (C=O), 1732 (C=O), 1678 (C=O), 1651 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 431 (M^+, 2), 168 (69), 163 (100), 152 (41); HRMS (EI, 20 eV) calcd for $C_{22}H_{29}N_3O_6$ (M^+) 431.2056, found 431.2067.

Preparation of 46. Following the procedure for the preparation of **43**, **46** was obtained from **45** as a solid (50% yield). M.p. 189–190 ^oC; $[\alpha]^{20}_D = -5.26^o$ (*c* 0.60, EtOH); ^1H NMR (400 MHz, $CDCl_3$) d 11.89 (s, 1H), 9.19 (s, 1H), 8.39 (d, *J* = 7.5 Hz, 1H), 4.32–4.25 (m, 1H), 4.22–4.15 (m, 1H), 3.77–3.75 (m, 1H), 2.54–2.32 (m, 5H), 1.91–1.89 (m, 2H), 1.74–1.70 (m, 2H), 1.61–1.58 (m, 1H), 1.38–1.13 (m, 5H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 177.4, 169.4, 167.9, 78.2, 77.9, 48.5, 41.8, 39.8, 32.8, 32.8, 32.4, 25.5, 25.2, 19.3, 19.2, 18.5, 18.3; IR (CH_2Cl_2) 3386 (br, N–H), 3288 (br, N–H), 3189 (br, N–H), 1667 (C=O), 1658 (C=O), 1649 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 371 (M^+, 4), 200 (67), 168 (100), 152 (68); HRMS (EI, 20 eV) calcd for $C_{18}H_{33}N_3O_5$ (M^+) 371.2420, found 371.2411.

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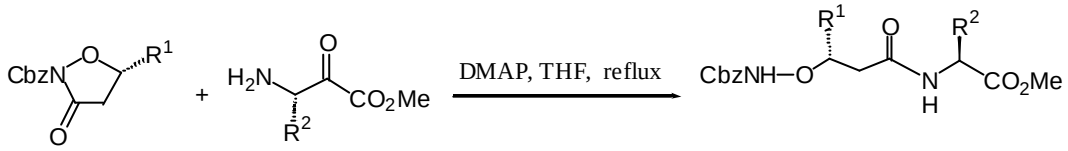
Determination of optical purity of 13 and 14 by ^{1}H NMR spectroscopy

Since the racemic diamides **16** and **17** of β^3-aminoxy acids cannot be base-line separated by HPLC columns (Chiracel OD and (*R*, *R*) Whelk-O 1), we resorted to derivatize β^3-aminoxy acids with suitable chiral reagents, and the diastereoisomeric excess of the corresponding diamides was examined by ^{1}H NMR spectroscopy. For this purpose, (*S*)-leucine methyl ester and (*S*)-phenylglycine methyl ester reacted with the lactams **13** and **14** to give the diastereomers **48** and **49**, respectively (Scheme 1), and the de % value was determined by the integration of α-protons of the (*S*)-amino acids or methylene protons of Cbz group of the crude products. The results are shown in Table 1.

Scheme 1



$R^1 = CH_2CH(CH_3)_2$ **13**
$R^1 = CH(CH_3)_2$ **14**

$R^1 = CH_2CH(CH_3)_2$, $R^2 = Ph$ **48**
$R^1 = CH(CH_3)_2$, $R^2 = CH_2CH(CH_3)_2$ **49**

The Cbz regions of the ^{1}H NMR (500 MHz) spectra of (*R*/*S*, *S*)-**48** and (*R*, *S*)-**48** are showed in Figure 1. And the α-CH (*L*-Leu) regions of the ^{1}H NMR (500 MHz) spectra of (*R*/*S*, *S*)-**49** and (*R*, *S*)-**49** are shown in Figure 2.

The ^{1}H NMR spectra of (*R*/*S*, *S*)-**48** showed two well-separated AB quartet peaks of different patterns at 5.17 ppm and 5.10 ppm, respectively, and the integration ratio of these two signals was almost 1:1. These two signals were assigned to the protons of Cbz group. The integration ratio of these two signals in the ^{1}H NMR spectra of (*R*, *S*)-**48** was about 1:39.3.

The ^{1}H NMR spectra of (*R*/*S*, *S*)-**49** contained two well-separated ddd peaks at 3.92 ppm and 3.86 ppm, respectively, and the integration ratio of these two signals was almost 1:1. These two signals were assigned to the α-CH's of *L*-Leu residue. The integration ratio of these two signals in the ^{1}H NMR spectra of (*R*, *S*)-48 was about 1:34.8.

Table 1. Diastereomeric excess determination of β^3-aminoxy diamides **47** and **48**

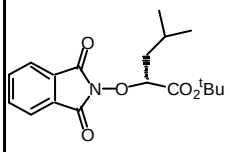
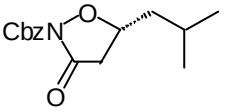
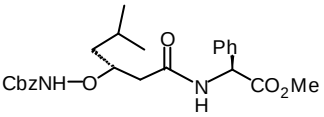
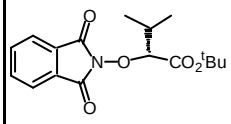
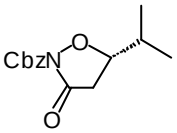
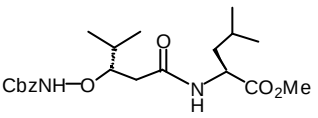
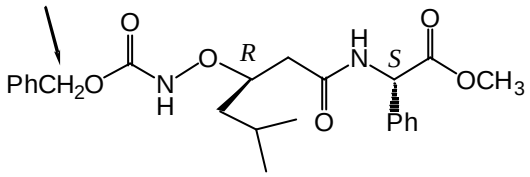
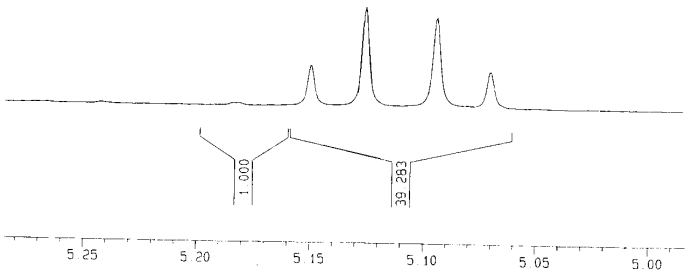
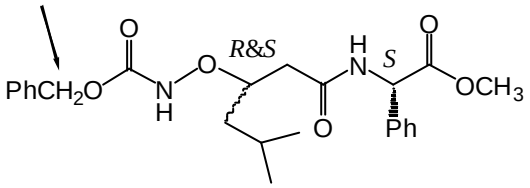
α-aminoxy acid	lactam	diastereomer	ee % of α-aminoxy acid (by HPLC)	de % of β^3-aminoxy acid (by ^{1}H NMR)
	 **13**	 **48**	98.6	98.6
	 **14**	 **49**	95.8	95.8

Figure 1. Cbz regions of the ^{1}H NMR (500 MHz) spectra of (*R, S*)-**48** and (*R*/*S, S*)-**48**.



(*R, S*)-**48**





(*R*/*S, S*)-**48**

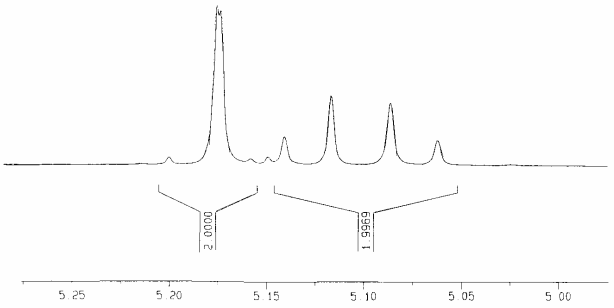
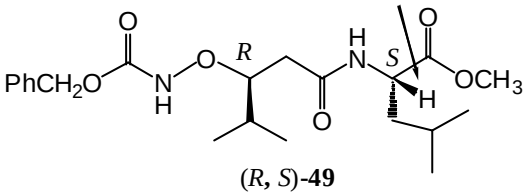
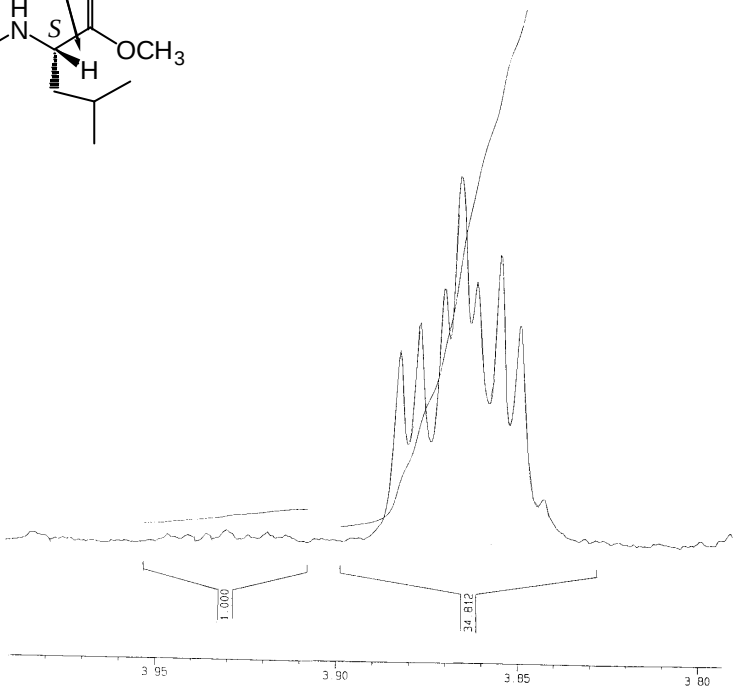
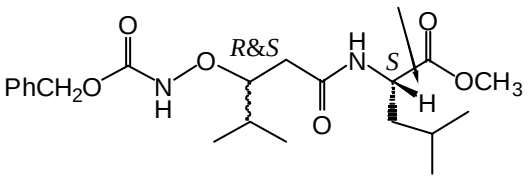


Figure 2. α-CH regions of the ^{1}H NMR spectra (500 MHz) of (*R, S*)-**49** and (*R*/*S, S*)-**49.**

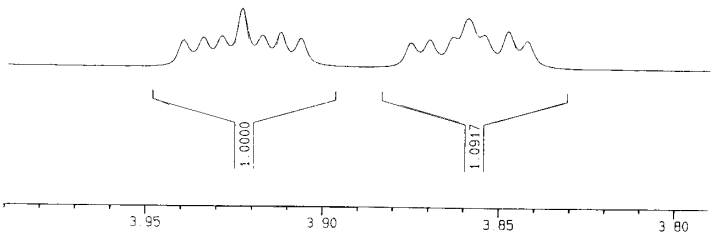


(*R, S*)-**49**



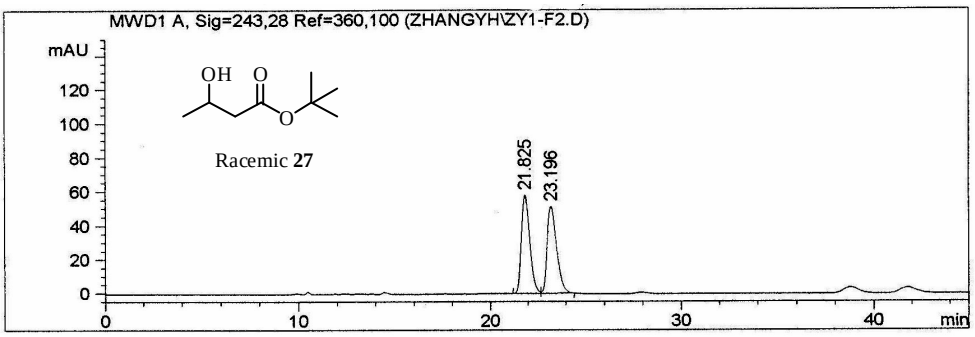


(*R*/*S*, *S*)-**49**

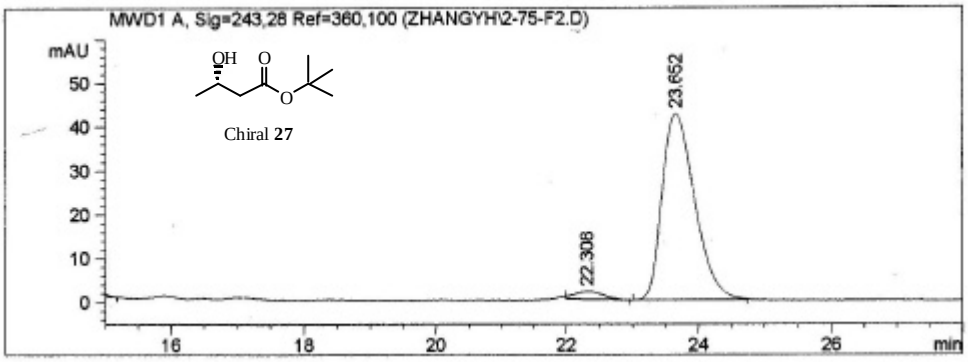


Determination of enantiomeric excess of compound 27 by HPLC

HPLC Conditions:
Column: Chiral OD (Column No. OD00CE-AH045)
Solvents: *n*-Hexane/*i*-PrOH (98.0/2.0)
Flow rate: 0.3 mL/min
Detection: UV 243 nm



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.825	BV	0.4734	1801.41882	58.15118	50.0003
2	23.196	VB	0.5356	1801.40063	51.56609	49.9997
Totals :				3602.81946	109.71727	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.898	PB	0.3397	32.83032	1.43060	2.0108
2	12.654	BB	0.2984	27.98365	1.36962	1.7140
3	14.649	BB	0.3330	60.67344	2.71176	3.7162
4	22.308	BB	0.4442	56.56086	1.81194	3.4643
5	23.652	PB	0.5366	1454.61401	42.36550	89.0946
Totals :				1632.66228	49.68943	