Highly Diastereoselective Radical Addition to Oxime Ethers:

Asymmetric Synthesis of β-Amino Acids

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General Procedure for Alkylation of 1. To a solution of **1** (7.7 mmol) in CH_2Cl_2 (190 mL) were added alkyl bromide (8.5 mmol), tetra-*n*-butylammonium bromide (0.77 mmol), and 5*N* NaOH (7.5 mL) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with saturated aqueous NH_4Cl and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by flash column chromatography (AcOEt/hexane 1:4) afforded the alkylated products **2a-c**. The diastereomerically pure products (*R*,*Z*)-**2a-c** were obtained by the recrystallization from hexane/AcOEt.

General Procedure for Ethyl Radical Addition to 2 or 1 at -78 °C. To a solution of **2** or **1** (0.208 mmol) in toluene or CH_2Cl_2 (8 mL) were added $BF_3{\cdot}OEt_2$ (0.625 mmol) and Et_3B (1.0 M in hexane, 0.625 mmol) under a nitrogen atmosphere at -78 °C, and then air was passed into the solution. After being stirred at the same temperature for 3 min, $BF_3{\cdot}OEt_2$ (0.625 mmol) and Et_3B (0.625 mmol) were added twice, and then air was passed into the solution. After being stirred at the same temperature for 3 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (AcOEt/hexane 1:3) afforded the alkylated products **3aA-3dA**.

General Procedure for Alkyl Radical Addition to 2. To a solution of **2** (2.08 mmol) in toluene (15 mL) were added alkyl iodide (62.5 mmol), $BF_3 \cdot OEt_2$ (6.25 mmol), and Et_3B (1.0 M in hexane, 6.25 mmol) at 20 °C. After being stirred at the same temperature for 3 min, $BF_3 \cdot OEt_2$ (6.25 mmol) and Et_3B (6.25 mmol) were added twice. After being stirred at the same temperature for 3 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (AcOEt/hexane 1:4) afforded the alkylated products **3aB-3bB**.

Characterization Data for Compounds 1, 2a-c, 3aA-3bB, and 4

1 (2:3 mixture of *E/Z*-oxime ether) : a colorless oil. $[\alpha]^{32}_D$ -84.5 (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) 2964, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) _ 7.58 (2/5H, t, *J*=5.9 Hz), 7.38-7.25 (5H, m), 7.07 (3/5H, t, *J*=4.7 Hz), 5.13 (6/5H, s), 5.08 (4/5H, s), 3.95-3.75 (11/5H, m), 3.68 (4/5H, d, *J*=5.9 Hz), 3.49 (1H, br d, *J*=13.8 Hz), 3.48 (1H, br d, *J*=13.8 Hz), 2.2-1.8 (5H, m), 1.45-1.30 (2H, m), 1.14 (6/5H, s), 1.12 (9/5H, s), 0.96 (3H, s). ^{13}C NMR ($CDCl_3$) _ 167.3, 167.0, 143.7, 142.6, 137.6, 137.3, 128.3, 128.1, 127.9, 127.8, 127.7, 75.93, 75.86, 65.1, 52.72, 52.66, 48.5, 47.7, 44.51, 44.47, 38.14, 38.08, 36.1, 32.7, 32.5, 26.3, 20.6, 19.7. HRMS: Calcd for $C_{20}H_{26}N_2O_4S$ (M^+) : 390.1612, Found : 390.1624.

(*R,Z*)-**2a** : colorless crystals. mp 121-122 °C (AcOEt/hexane); $[\alpha]^{23}_D$ -90.0 (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) 2960, 1691 cm^{-1}; ^1H NMR ($CDCl_3$) _ 7.36-7.12 (10H, m), 6.86 (1H, d, *J*=6.4 Hz), 5.11 (1H, d, *J*=8.1 Hz), 5.10 (1H, d, *J*=8.1 Hz), 4.94 (1H, br m), 3.68 (1H, br m), 3.38 (1H, d, *J*=13.7 Hz), 3.32 (1H, d, *J*=13.7 Hz), 3.12 (1H, dd, *J*=13.2, 8.4 Hz), 3.06 (1H, dd, *J*=13.2, 6.8 Hz), 1.92 (1H, dd, *J*=13.5, 8.0 Hz), 1.84-16.5 (4H, m), 1.26 (2H, br m), 0.87 (3H, s), 0.72 (3H, s). ^{13}C NMR ($CDCl_3$) _ 170.5

147.0, 137.7, 136.8, 129.2, 128.2, 128.1, 127.6, 127.4, 126.7, 75.8, 64.8, 52.8, 48.0, 47.4, 44.8, 44.5, 38.1, 37.1, 32.6, 26.2, 20.4, 19.6. HRMS: Calcd for $C_{27}H_{32}N_2O_4S$ (M^+) : 480.2081, Found : 480.2084. Anal. Calcd for $C_{27}H_{32}N_2O_4S$: C, 67.47; H, 6.71; N, 5.83; S, 6.67. Found: C, 67.65; H, 6.82; N, 5.82; S, 6.84.

(*R*,*Z*)-**2b** : colorless crystals. mp 130-132 °C (AcOEt/hexane); $[\alpha]^{24}_D$ -86.9 (*c* 1.54, $CHCl_3$); IR ($CHCl_3$) 2964, 1690 cm^{-1}; ^1H NMR _ 8.05 (2H, d, *J*=8.4 Hz), 7.40-7.22 (7H, m), 6.87 (1H, d, *J*=6.6 Hz), 5.11 (1H, d, *J*=12.8 Hz), 5.06 (1H, d, *J*=12.8 Hz), 5.08-4.96 (1H, m), 3.82-3.73 (1H, m), 3.43 (1H, d, *J*=14.0 Hz), 3.38 (1H, d, *J*=14.0 Hz), 3.22 (1H, dd, *J*=13.2, 8.3 Hz), 3.12 (1H, dd, *J*=13.2, 6.8 Hz), 2.05-1.68 (5H, m), 1.40-1.22 (2H, m), 0.89 (3H, s), 0.68 (3H, s). ^{13}C NMR ($CDCl_3$) _ 169.9, 146.9, 146.0, 144.5, 137.3, 130.2, 128.2, 127.8, 127.7, 123.4, 76.0, 65.0, 52.8, 48.2, 47.4, 44.4, 44.0, 38.0, 36.6, 32.6, 26.1, 20.1, 19.5. HRMS: Calcd for $C_{27}H_{31}N_3O_6S$ (M^+) : 525.1931, Found : 525.1953. Anal. Calcd for $C_{27}H_{31}N_3O_6S$: C, 61.70; H, 5.94; N, 7.99; S, 6.10. Found: C, 61.75; H, 5.91; N, 8.05; S, 6.21.

(*R*,*Z*)-**2c** : colorless crystals. mp 101-103 °C (AcOEt/hexane); $[\alpha]^{24}_D$ -89.4 (*c* 1.12, $CHCl_3$); IR ($CHCl_3$) 2964, 1697 cm^{-1}; ^1H NMR _ 7.70-7.25 (5H, m), 7.01 (1H, d, *J*=5.9 Hz), 5.14 (2H, s), 4.67 (1H, br q, *J*=6.1 Hz), 3.90-3.83 (1H, m), 3.49 (1H, d, *J*=13.7 Hz), 3.42 (1H, d, *J*=13.7 Hz), 2.84 (1H, ddd, *J*=17.0, 5.6, 2.7 Hz), 2.74 (1H, ddd, *J*=17.0, 6.4, 2.7 Hz), 2.18-1.80 (6H, m), 1.44-1.22 (2H, m), 1.17 (3H, s), 0.96 (3H, s). ^{13}C NMR ($CDCl_3$) _ 169.2, 146.1, 137.5, 128.2, 127.7, 127.6, 79.0, 76.0, 71.4, 65.0, 52.8, 48.4, 47.6, 44.4, 41.2, 38.0, 32.5, 26.3, 20.5, 20.4, 19.7. HRMS: Calcd for $C_{23}H_{28}N_2O_4S$ (M^+) : 428.1768, Found : 428.1740. Anal. Calcd for $C_{23}H_{28}N_2O_4S$: C, 64.46; H, 6.59; N, 6.54; S, 7.48. Found: C, 64.62; H, 6.61; N, 6.58; S, 7.56.

3aA : colorless crystals. mp 136-137 °C (AcOEt/hexane); $[\alpha]^{28}$ _ -6.8 (*c* 1.07, $CHCl_3$);

IR ($CHCl_3$) 2965, 1679 cm^{-1}; ^1H NMR _ 7.40-7.20 (10H, m), 6.32 (1H, br m), 4.730 (1H, d, *J*=12.0 Hz), 4.725 (1H, d, *J*=12.0 Hz), 3.65 (2H, m), 3.29 (2H, br s), 3.11 (1H, dd, *J*=13.4, 4.4 Hz), 3.09 (1H, m), 2.95 (1H, dd, *J*=13.4, 10.7 Hz), 2.00-1.50 (7H, m), 1.29-1.16 (2H, m), 1.01 (3H, t, *J*=7.4 Hz), 0.81 (3H, s), 0.43 (3H, s). ^{13}C NMR ($CDCl_3$) _ 174.0, 138.3, 138.0, 129.5, 128.2, 128.1, 127.5, 126.3, 76.5, 65.0, 62.8, 52.9, 48.3, 47.6, 47.3, 44.5, 38.3, 35.2, 32.7, 26.2, 23.1, 20.2, 19.6, 11.0. HRMS: Calcd for $C_{29}H_{38}N_2O_4S$ (M^+) : 510.2550, Found : 510.2522. Anal. Calcd for $C_{29}H_{38}N_2O_4S$: C, 68.21; H, 7.50; N, 5.49; S, 6.28. Found: C, 67.99; H, 7.48; N, 5.35; S, 6.50.

3bA : a colorless oil. $[\alpha]^{28}_D$ -3.3 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 2966, 1680 cm^{-1}; ^1H NMR _ 8.06 (2H, br d, *J*=8.8 Hz), 7.40-7.22 (7H, m), 6.22 (1H, br m), 4.72 (2H, br s), 3.80-3.62 (2H, m), 3.31 (2H, s), 3.23 (1H, dd, *J*=13.4, 4.6 Hz), 3.14-2.98 (2H, m), 2.14-1.40 (7H, m), 1.32-1.10 (2H, m), 1.01 (3H, t, *J*=7.4 Hz), 0.80 (3H, s), 0.32 (3H, s). ^{13}C NMR ($CDCl_3$) _ 173.2, 146.7, 146.4, 137.8, 130.5, 128.2, 127.6, 123.3, 76.5, 65.2, 63.0, 52.9, 48.1, 47.7, 47.2, 44.3, 38.3, 35.5, 32.7, 26.1, 23.1, 19.7, 19.4, 11.0. HRMS: Calcd for $C_{29}H_{37}N_3O_6S$ (M^+) : 555.2401, Found : 555.2402.

3cA : colorless crystals. mp 101-102 °C (AcOEt/hexane); $[\alpha]^{23}_D$ -149.5 (*c* 0.24, $CHCl_3$); IR ($CHCl_3$) 2965, 1694 cm^{-1}; ^1H NMR _ 7.40-7.20 (5H, m), 5.95 (1H, br m), 4.67 (2H, s), 3.90 (1H, dd, *J*=7.6, 5.1 Hz), 3.49 (1H, d, *J*=13.7 Hz), 3.45 (1H, d, *J*=13.7 Hz), 3.50-3.40 (1H, m), 3.15 (1H, td, *J*=8.5, 4.4 Hz), 2.80 (1H, ddd, *J*=17.3, 7.2, 2.7 Hz), 2.69 (1H, ddd, *J*=17.3, 4.4, 2.7 Hz), 2.20-1.32 (10H, m), 1.19 (3H, s), 0.97 (3H, s), 0.96 (3H, t, *J*=7.4 Hz). ^{13}C NMR ($CDCl_3$) _ 172.5, 137.9, 128.2, 127.6, 80.4, 77.1, 76.4, 70.9, 65.2, 61.0, 53.1, 48.2, 47.7, 45.9, 44.5, 38.3, 32.7, 26.4, 23.0, 20.7, 19.8, 19.0, 10.8. HRMS: Calcd for $C_{25}H_{34}N_2O_4S$ (M^+) : 458.2237, Found : 458.2209. Anal. Calcd for C, H, N, O, S: C, 65.47; H, 7.47; N, 6.11; S, 6.99. Found:

C, 65.18; H, 7.43; N, 6.00; S, 7.08.

3dA (9:10 mermixture of diastereomer) : a colorless oil. $[\alpha]^{31}_{D}$ -63.1 (*c* 3.39, $CHCl_3$); IR ($CHCl_3$) 2964, 1693 cm^{-1}; ^1H NMR _ 7.40-7.20 (5H, m), 5.83 (1H, br m), 4.68 (18/19H, s), 4.66 (20/19H, s),3.89-3.78 (1H, m), 3.53-3.30 (3H, m), 3.05-2.70 (2H, m), 2.18-1.25 (9H, m), 1.13 (27/19H, s), 1.11 (30/19H, s), 0.950 (27/19H, s), 0.945 (30/19H, s), 0.933 (30/19H, t, *J*=6.4 Hz), 0.930 (27/19H, t, *J*=6.4 Hz). ^{13}C NMR ($CDCl_3$) _ 170.72, 170.67, 137.90, 137.86, 128.24, 128.18, 128.1, 127.5, 76.20, 76.15, 65.0, 58.7, 58.6, 52.84, 52.77, 48.2, 47.5, 44.5, 38.3, 38.2, 37.61, 37.56, 32.7, 26.3, 24.8, 24.7, 20.7, 20.6, 19.7, 10.3, 10.2. HRMS: Calcd for $C_{22}H_{32}N_2O_4S$ (M^+) : 420.2081, Found : 420.2107.

3aB : a colorless oil. $[\alpha]^{27}_{D}$ +1.7 (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) 2964, 1679 cm^{-1}; ^1H NMR _ 7.39-7.09 (10H, m), 6.55 (1H, br m), 4.76 (1H, d, *J*=11.5 Hz), 4.72 (1H, d, *J*=11.5 Hz), 3.76-3.67 (2H, m), 3.30 (1H, d, *J*=13.5 Hz), 3.28 (1H, d, *J*=13.5 Hz), 3.12-3.05 (3H, m), 2.18-2.11 (1H, m), 1.88 (1H, dd, *J*=13.5, 7.5 Hz), 1.83-1.73 (1H, m), 1.67-1.55 (3H, m), 1.30-1.20 (2H, m), 1.28 (6H, t, *J*=5.5 Hz), 0.81 (3H, s), 0.38 (3H, s). ^{13}C NMR ($CDCl_3$) _ 174.0, 138.8, 138.1, 129.5, 128.3, 128.2, 128.1, 127.5, 126.3, 75.7, 65.5, 65.2, 53.0, 47.8, 47.7, 47.4, 44.5, 38.3, 34.6, 32.8, 29.2, 26.4, 20.5, 20.3, 20.2, 19.7. HRMS: Calcd for $C_{30}H_{40}N_2O_4S$ (M^+) : 524.2706, Found : 524.2721.

3aC : a colorless oil. $[\alpha]^{28}_{D}$ -10.1 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2930, 1679 cm^{-1}; ^1H NMR _ 7.38-7.09 (10H, m), 6.55 (1H, br m), 4.75 (1H, d, *J*=11.5 Hz), 4.70 (1H, d, *J*=11.5 Hz), 3.77-3.66 (2H, m), 3.30 (1H, d, *J*=13.5 Hz), 3.27 (1H, d, *J*=13.5 Hz), 3.14 (1H, dd, *J*=3.5, 7.5 Hz), 3.06 (2H, d, *J*=8.0 Hz), 2.11-2.04 (1H, m), 1.92-1.56 (10H, m), 1.32-1.10 (7H, m), 0.81 (3H, s), 0.39 (3H, s). ^{13}C NMR ($CDCl_3$) _ 174.1, 138.8, 138.1, 129.4, 128.3, 128.2, 127.5, 126.3, 75.7, 65.2, 64.8, 53.0, 47.8, 47.4, 47.3, 44.5, 38.9, 38.3, 34.6, 32.8, 30.53, 30.46, 26.7, 26.51, 26.48, 26.38, 20.2, 19.7.

HRMS: Calcd for $C_{33}H_{44}N_2O_4S$ (M^+) : 564.3020, Found : 564.3002.

3aD : a colorless oil. $[\alpha]^{28}_D$ -12.2 (*c* 1.36, $CHCl_3$); IR ($CHCl_3$) 2960, 1679 cm^{-1}; ^1H NMR _ 7.39-7.10 (10H, m), 6.70 (1H, br m), 4.77 (1H, d, *J*=11.5 Hz), 4.72 (1H, d, *J*=11.5 Hz), 3.73-3.66 (2H, m), 3.30 (1H, d, *J*=13.5 Hz), 3.27 (1H, d, *J*=13.5 Hz), 3.18 (1H, dd, *J*=2.5, 9.5 Hz), 3.15-3.07 (2H, m), 2.36-2.26 (1H, m), 2.05-1.97 (1H, m), 1.92-1.84 (2H, m), 1.82-1.20 (12H, m), 0.81 (3H, s), 0.37 (3H, s). ^{13}C NMR ($CDCl_3$) _ 173.8, 138.9, 138.2, 129.5, 128.3, 128.2, 128.1, 127.5, 126.3, 75.9, 65.2, 64.8, 53.1, 49.3, 47.9, 47.4, 44.5, 41.8, 38.3, 34.2, 32.8, 31.4, 30.1, 26.4, 25.2, 25.0, 20.2, 19.7. HRMS: Calcd for $C_{32}H_{42}N_2O_4S$ (M^+) : 550,2863, Found : 550.2885.

3aE (1:1 mixture of diastereomer) : a colorless oil. $[\alpha]^{26}_D$ -4.1 (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 2964, 1681 cm^{-1}; ^1H NMR _ 7.38-7.09 (10H, m), 6.45 (1H, br m), 4.73 (1/2H, d, *J*=11.5 Hz), 4.716 (1/2H, d, *J*=11.5 Hz), 4.715 (1/2H, d, *J*=11.0 Hz), 4.712 (1/2H, d, *J*=11.0 Hz), 3.75-3.64 (2H, m), 3.33-3.28 (2H, m), 3.26 (1/2H, t, *J*=5.5 Hz), 3.20 (1/2H, dd, *J*=8.0, 3.5 Hz), 3.13 (1/2H, dd, *J*=8.0, 3.5 Hz), 3.09-2.99 (3/2H, m), 1.96-1.56 (7H, m), 1.35-1.20 (3H, m), 1.10 (3/2H, d, *J*=7.0 Hz), 1.05 (3/2H, d, *J*=6.5 Hz), 0.95 (3H, br t, *J*=7.5 Hz), 0.81 (3H, br s), 0.40 (3/2H, s), 0.38 (3/2H, s). ^{13}C NMR ($CDCl_3$) _ 174.1, 138.9, 138.6, 138.15, 138.13, 129.5, 129.4, 128.3, 128.19, 128.16, 128.11, 127.52, 127.48, 126.4, 126.3, 75.8, 75.7, 65.3, 65.2, 64,2, 64.0, 53.06, 53.04, 48.1, 47.84, 47.81, 47.76, 47.6, 47.4, 44.51, 44.48, 38.29, 38.28, 36.4, 35.7, 35.3, 34.6, 32.8, 27.1, 26.4, 26.0, 20.2, 19.7, 16.2, 15.8, 12.1, 11.4. HRMS: Calcd for $C_{31}H_{42}N_2O_4S$ (M^+) : 538.2863, Found : 538.2861.

3aF : a colorless oil. $[\alpha]^{29}_D$ -17.3 (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 2960, 1682 cm^{-1}; ^1H NMR _ 7.38-7.09 (10H, m), 6.21 (1H, br m), 4.71 (2H, s), 3.64 (1H, br m), 3.32-3.23 (3H, m), 3.12 (1H, dd, *J*=13.5, 5.0 Hz), 2.97 (1H, dd, *J*=13.5, 10.5 Hz), 1.91-1.46 (7H, m), 1.33-1.18 (3H, m), 0.95 (3H, d, *J*=6.0 Hz), 0.89 (3H, d, *J*=6.5 Hz), 0.81 (3H

s), 0.92-0.77 (1H, m), 0.44 (3H, br s). ^{13}C NMR ($CDCl_3$) _ 174.0, 138.4, 138.2, 129.6, 128.3, 128.24, 128.18, 127.6, 126.4, 76.5, 65.2, 59.3, 53.0, 49.4, 47.7, 47.4, 44.6, 39.7, 38.4, 35.8, 32.8, 26.4, 24.9, 23.3, 22.3, 20.4, 19.8. HRMS: Calcd for $C_{31}H_{42}N_2O_4S$ (M^+) : 538.2863, Found : 538.2855.

3bB : a yellow oil. $[\alpha]^{27}_D$ +10.5 (*c* 0.57, $CHCl_3$); IR ($CHCl_3$) 2964, 1681 cm^{-1}; ^{1}H NMR _ 8.06 (2H, d, *J*=8.5 Hz), 7.42-7.20 (7H, m), 6.36 (1H, br m), 4.73 (2H, s), 3.80-3.68 (2H, m), 3.31 (3H, s), 3.30-3.07 (3H, m), 2.20-2.15 (1H, m), 1.97-0.68 (6H, m), 1.12 (3H, d, *J*=6.6 Hz), 1.11 (3H, d, *J*=6.9 Hz), 0.80 (3H, s), 0.33 (3H, br s). ^{13}C NMR ($CDCl_3$) _ 173.2, 146.9, 146.7, 137.9, 130.3, 128.2, 128.0, 127.5, 123.3, 75.7, 65.4, 65.2, 52.9, 47.9, 47.3, 44.3, 38.2, 34.7, 32.6, 28.8, 26.2, 20.4, 19.9, 19.6, 19.5. HRMS: Calcd for $C_{30}H_{39}N_3O_6S$ (M^+) : 569.2557, Found : 569.2580.

4 : a white powder. $[\alpha]^{25}_D$ -23.7 (*c* 1.18, $CHCl_3$); IR ($CHCl_3$) 2969, 1716 cm^{-1}; ^{1}H NMR _ 7.45-7.13 (10H, m), 5.12 (1H, d, *J*=12.4 Hz), 5.06 (1H, d, *J*=12.4 Hz), 4.94 (1H, br d, *J*=10.0 Hz), 3.87 (1H, m), 3.10-2.75 (4H, m), 1.68 (1H, m), 1.42 (1H, m), 0.95 (3H, t, *J*=7.1 Hz). ^{13}C NMR ($CDCl_3$) _ 177.3, 156.2, 138.6, 136.3, 128.6, 128.4, 128.1, 128.0, 126.4, 77.1, 66.8, 54.0, 51.6, 34.4, 24.9, 10.6. HRMS: Calcd for $C_{20}H_{23}NO_4$ (M^+) : 341.1626, Found : 341.1630.