Supporting Information for
Asymmetric Synthesis of β-Amino Acids by Addition of Chiral Enolates to *N*-Acyloxyiminium Ions and Application for Synthesis of Optically Active 5-Substituted 8-Methylindolizidines

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Materials. *N*-Benzylidenebenzylamine *N*-oxide (**9**) and 1-pyrroline *N*-oxide (**16**) were prepared by Na_2WO_4-[1] and SeO_2-catalyzed[2] oxidations of dibenzylamine and pyrrolidine, respectively. (4*R*,5*S*)-4-Methyl-5-phenyl-oxazolidinone was prepared according to the literature proceure.[3]

Addition of Titanium Enolate 11 to Nitrone 9. A solution of titanium enolate **11** was prepared by addition of propiophenone (0.239 mL, 1.8 mmol) to a solution of $TiCl_4$ (0.19 mL, 1.7 mmol) and *i*-Pr_2NEt (0.376 mL, 2.16 mmol) in CH_2Cl_2 (3.0 mL) under argon at –78 °C followed by stirring at 0 °C for 0.5 h.[4] To the solution of titanium enolate **11** was added a solution of *N*-benzoyloxy-*N*-benzylidenebenzylammonium chloride (**10**), which was prepared by the reaction of nitrone **9** (317 mg, 1.5 mmol) and benzoyl chloride (0.191 mL, 1.65 mmol) at –78 °C followed by stirring for 0.5 h. The reaction mixture was stirred at –78 °C for 0.5 h and allowed to warm to room teprerature. To the reaction mixture were added hexane, sat. $NaHCO_3$, and 10 *M* KF, and the mixture was stirred at room temperature for 0.5 h. The mixture was filtered through Celite, and the cake was washed with EtOAc. The organic layer was separated, washed with sat. $NaHCO_3$ and brine, and dried ($MgSO_4$) Evaporation of the filtrate followed by column chromatography on SiO_2 gave 3-(*N*-benzoyloxybenzylamino)-2-methyl-3-phenylpropiophenone (**12**) (532 mg, 79%) as an oil. The ratio of two diastereomers was determined by ^1H NMR analysis to be (2*R**,3*R**)-**12**/(2*R**,3*S**)-**12** =

64:36. **12:** IR (neat) 1744 (OCO), 1682 (CO), 1451 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, mixture of diastereomers (64:36)) δ 0.79 (d, *J* = 7.1 Hz, 3 H x 0.36, CHCH_3 of (2*R**,3*S**)-**12**), 1.61(d, *J* = 6.6 Hz, 3 H x 0.64, CHCH_3 of (2*R**,3*R**)-**12**), 3.84 (d, *J* = 13.7 Hz, 1 H x 0.64, CH_2Ph of (2*R**,3*R**)-**12**), 3.92 (d, *J* = 12.4 Hz, 1 H x 0.36, CH_2Ph of (2*R**,3*S**)-**12**), 4.13 (d, *J* = 13.7 Hz, 1 H x 0.64, CH_2Ph of (2*R**,3*R**)-**12**), 4.16 (d, *J* = 12.7 Hz, 1 H x 0.36, CH_2Ph of (2*R**,3*S**)-**12**), 4.25 (dq, *J* = 7.1 and 9.8 Hz, 1 H x 0.36, C*H*CH_3 of (2*R**,3*S**)-**12**), 4.29 (dq, *J* = 6.6 and 10.5 Hz, 1 H x 0.64, C*H*CH_3 of (2*R**,3*R**)-**12**), 4.39 (d, *J* = 10.5 Hz, 1 H x 0.64, CHN of (2*R**,3*R**)-**12**), 4.74 (d, *J* = 9.8 Hz, 1 H x 0.36, CHN of (2*R**,3*S**)-**12**), 7.05–8.05 (m, 20 H, Ar); ^{13}C NMR ($CDCl_3$, 68 MHz, mixture of diastereomers (64:36)) δ 16.6 and 17.3, 42.9 and 43.7, 59.9 and 61.0, 69.7 and 77.2, 127.3, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.39, 128.4, 128.6, 128.9, 129.0, 129.17, 129.24, 129.3, 129.4, 129.7, 130.1, 132.4, 132.6, 132.8, 133.1, 135.9, 136.0, 136.1, 136.3, 164.9 (OCO), 202.0 and 202.1 (CO); HRMS (FAB), *m/e* calcd for $C_{30}H_{28}NO_3$ 450.2069, found 450.2087.

Addition of Titanium Enolate 13a to Nitrone 9. To a mixture of Ti(O-*i*-Pr)$_4$ (0.178 mL, 0.60 mmol) and 4A molecular sieves (300 mg) in CH_2Cl_2 (6.0 mL), was added $TiCl_4$ (0.198 mL, 1.80 mmol) at –78 °C under argon, and the solution was allowed to warm to room temperature until it became a clear solution (*ca.* 10 min). (4*R*,5*S*)-4-Methyl-5-phenyl-3-propanoyloxazolidinone (488 mg, 2.09 mmol) and *i*-Pr$_2$NEt (0.437 mL, 2.51 mmol) were added at –78 °C, and the mixture was stirred at 0 °C for 0.5 h. To the solution of titanium enolate **13a**, was added a solution of *N*-acyloxyiminium ion **10**, which was prepared by the reaction of nitrone **9** (587 mg, 2.78 mmol) and benzoyl chloride (0.322 mL, 2.78 mmol) at –78 °C followed by stirring for 0.5 h. The reaction mixture was stirred at –78 °C for 1 h, and allowed to warm to room teprerature. To the reaction mixture were added hexane, sat. $NaHCO_3$, and 10 *M* KF, and the mixture was stirred at room temperature for 0.5 h. The mixture was filtered through Celite, and the cake was washed with EtOAc. The organic layer was separated, washed with sat. $NaHCO_3$ and brine, and dried ($MgSO_4$). Filtration and removal of solvent gave (4*R*,5*S*)-3-[3-(*N*-benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropanoyl]-4-methyl-5-phenyl-2-oxazolidinone (**14**) (745 mg, 65%), of which

diastereomeric ratio were determined by ^{1}H NMR analysis to be (2'*S*,3'*S*)-**14**/(2'*S*,3'*R*)-**14** = 85:15. Column chromatography on SiO_2 (5—10% EtOAc in hexane) afforded pure (2'*S*,3'*S*)-**14** (574 mg, 50%) and (2'*S*,3'*R*)-**14** (108 mg, 9%). (2'*R*,3'*R*)-**14:** $[\alpha]^{24}_D$ +73.4° (*c* 1.02, $CHCl_3$); IR (KBr) 1780, 1744, 1699, 1454, 1383, 1368, 1342, 1256, 1240, 1196, 1055, 1024, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.08 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CHN), 1.58 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CHCO), 3.82 (d, *J* = 12.7 Hz, 1 H, C*H*HPh), 4.18 (d, *J* = 11.2 Hz, 1 H, C*H*Ph), 4.20 (d, *J* = 12.7 Hz, 1 H, C*H*HPh), 4.50 (dq, *J* = 7.3 and 6.6 Hz, 1 H, NC*H*CH$_3$), 4.94 (dq, *J* = 11.0 and 6.6 Hz, 1 H, COC*H*CH$_3$), 5.48 (d, *J* = 7.3 Hz, 1 H, OC*H*), 7.13–7.60 (m, 18 H, Ph), 8.00–8.04 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 ℃) δ 13.2, 16.2, 39.9, 54.2, 59.5, 70.3, 78.3, 125.6, 127.7, 128.0, 128.1, 128.4, 128.5, 128.6, 128.6, 129.3, 129.4, 129.5, 130.6, 133.0, 133.3, 135.8, 136.0, 152.5 (CH_2*C*ON), 165.1 (N*C*OO), 175.2 (O*C*O); Anal. Calcd for $C_{34}H_{32}N_2O_5$: C, 74.42; H, 5.88 N, 5.11. Found: C, 74.70; H, 6.09; N, 5.09. (2'*S*,3'*R*)-**14**: mp 140.5–142.0 °C (MeOH); $[\alpha]^{24}_D$ +20.2° (*c* 1.02, $CHCl_3$); IR (KBr) 1778, 1750, 1698, 1454, 1387, 1370, 1346, 1260, 1234, 1196, 1057, 1024, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.90 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$CHCO), 1.20 (d, *J* = 6.6 Hz, C*H*$_3$CHN), 3.84 (d, *J* = 12.9 Hz, 1 H, N*H*CHPh), 4.00 (d, *J* = 13.2 Hz, 1 H, N*H*CHPh), 4.46 (d, *J* = 11.2 Hz, 1 H, NC*H*Ph), 4.78–4.94 (m, 2 H, NC*H*CHO, COC*H*CH$_3$), 5.63 (d, *J* = 7.8 Hz, 1 H, OC*H*Ph), 7.16–7.58 (m, 18 H, Ph), 7.88–7.93 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 14.4, 15.9, 39.0, 55.2, 60.4, 71.8, 78.7, 126.1, 127.5, 128.0, 128.2, 128.3, 128.6, 128.6, 129.3, 129.4, 129.7, 130.9, 132.7, 133.9, 134.2, 135.9, 153.0 (CH_2*C*ON), 165.0 (N*C*OO), 175.8 (O*C*O); Anal. Calcd for $C_{34}H_{32}N_2O_5$: C, 74.42; H, 5.88; N, 5.11. found: C, 74.60; H, 5.95; N, 5.07.

(2*R*,3*R*)-3-(Benzyloxycarbonylamino)-2-methyl-3-phenylpropanoic Acid ((–)-15): mp 169.0–171.0 °C ($CHCl_3$); $[\alpha]^{31}_D$ –36.7° (*c* 1.10, MeOH) ($[\alpha]^{31}_D$ +36.1° (*c* 0.97, MeOH) for (+)-**15**); IR (Nujol) 3358 (NH), 1692, 1532, 1287, 1258, 1019 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 55 °C) δ 1.16 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$CHCO), 2.96 (quint, *J* = 7.1 Hz, 1 H, C*H*CO), 5.01–5.13 (m, 3 H, C*H*Ph and C*H*$_2$Ph), 5.67 (br s, 2 H, CO_2*H* and N*H*), 7.20–7.36 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 55 °C) δ 13.1, 44.8, 57.2, 67.1, 126.9, 127.8, 128.0, 128.1, 128.5, 128.6, 136.4, 139.6, 156.1, 178.0; ^{1}H NMR (CD_3OD,

270 MHz, 35 °C) δ 1.21 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$), 2.88 (dq, *J* = 8.8 and 7.1 Hz, 1 H, C*H*Me), 4.90 (d, *J* = 8.8 Hz, C*H*N), 5.01 (d, *J* = 12.4 Hz, 1 H, C*H*HPh), 5.08 (d, *J* = 12.4 Hz, 1 H, C*H*HPh), 7.12–7.38 (m, 10 H, Ph); ^{13}C NMR (CD_3OD, 68 MHz, 35 °C) δ 15.4, 47.6, 59.5, 68.4, 129.0, 129.2, 129.5, 129.7, 130.1, 130.2, 139.1, 143.3, 159.2, 178.4; Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found: C, 68.69; H, 6.09; N, 4.45.

Reaction of Titanium Enolate 13b with Nitrone 16. To a mixture of (4*R*,5*S*)-3-propanoyl-4-methyl-5-phenyl-2-oxazolidinone (515 mg, 2.20 mmol) and 4A molecular sieves (300 mg) in CH_2Cl_2 (5 mL) were added $TiCl_4$ (0.277 mL, 2.53 mmol) and *i*-Pr_2NEt (0.460 mL, 2.64 mmol) at –78 °C under argon. The mixture was stirred at 0 °C for 0.5 h and cooled to –78 °C, and a mixture of benzoic acid (322 mg, 2.64 mmol), *i*-Pr_2NEt (0.479 mL, 2.75 mmol), and 4A molecular sieves (200 mg) in CH_2Cl_2 (3.0 mL) was added to the cooled mixture. After the mixture was stirred at 0 °C for 0.5 h, was added a solution of *N*-acyloxyiminium ion **17**, which was prepared from nitrone **16** (639 mg, 3.00 mmol) and (±)-*O*-acetylmandelyl chloride (0.348 mL, 3.00 mmol), dropwise at –78 °C under argon. The mixture was stirred at the same temperature for 1 h. To the reaction mixture were added hexane, sat. $NaHCO_3$, and 10 *M* KF, and the mixture was stirred at room temperature for 0.5 h. The mixture was filtered through Celite and the cake was washed with EtOAc. The organic layer was separated, washed with sat. $NaHCO_3$ and brine, and dried ($MgSO_4$). Filtration and removal of the solvent gave a mixture of (4*R*,5*S*)-3-{(2*S*)-2-{(2*S*)-*N*-[(2*R*)-2-acetoxyphenylacetoxy]pyrrolidin-2-yl}propanoyl}-4-methyl-5-phenyl-2-oxazolidinone ((2'*S*,2"*S*,2"'*R*)-**18**), (2'*S*,2"*S*,2"'*S*)-**18**, (2'*R*,2"*S*,2"'*R*)-**18**, and (2'*R*,2"*S*,2"'*S*)-**18** (84%), of which diastereomeric ratio were determined by ^{1}H NMR analysis to be (2'*S*,2"*S*,2"'*R*)-**18**/(2'*S*,2"*S*,2"'*S*)-**18**/(2'*R*,2"*S*,2"'*R*)-**18**/(2'*R*,2"*S*,2"'*S*)-**18** = 49:49:1:1. (2'*S*,2"*S*,2"'*R*)-**18**: IR (KBr) 2976, 1784, 1761, 1703, 1456, 1346, 1228, 1149, 766, 704 cm^{-1} ; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.85 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$CHN), 1.15 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CHCO), 1.44–2.21 (m, 4 H, C*H*$_2$C*H*$_2$), 2.18 (s, 3 H, C*H*$_3$CO), 3.06 (ddd, *J* = 7.3, 7.5 and 13.0 Hz, 1 H, C*H*HN), 3.14–3.30 (m, 1 H, CH*H*N), 3.54 (q, *J* = 8.4 Hz, 1 H, NC*H*CH$_2$), 4.01 (br, 1 H, CH$_3$C*H*CO), 4.73 (dq, *J* = 7.0 and 6.7 Hz, 1 H, C*H*CHPh), 5.62

(d, *J* = 7.6 Hz, 1 H, PhC*H*CH), 5.93 (s, 1 H, C*H*O$_2$CCH$_3$), 7.02–7.54 (m, 10 H , Ph); ^{13}C NMR (CDCl$_3$, 68 MHz) δ 14.3, 20.7, 22.2, 25.8, 39.2, 54.9, 57.7, 70.8, 73.6, 78.8, 125.9, 127.5, 128.5, 128.6, 128.7, 129.0, 133.6, 133.8, 152.7(CH$_2$*C*ON), 166.9 (N*C*OO), 170.0 (CH$_3$*C*O$_2$), 174.9 (O*C*O); HRMS (FAB) Calcd for $C_{27}H_{31}N_2O_7$ (M+H$^+$) 495.2131, found 495.2136. (2'*S*,2"*S*,2"'*S*)-**18**: IR (Nujol) 1780, 1745, 1701, 1350, 1237, 1042, 763, 728, 700 cm^{-1} ; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 0.84 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CHN), 1.19 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CHCO), 1.48–2.04 (m, 4 H, C*H*$_2$C*H*$_2$), 2.15 (s, 3 H, C*H*$_3$CO), 2.89 (ddd, *J* = 6.6, 6.8 and 12.7 Hz, 1 H, C*H*HN), 3.28 (ddd, *J* = 6.4, 7.0 and 12.2 Hz, 1 H, CH*H*N), 3.67 (q, *J* = 8.2 Hz, 1 H, NC*H*CH$_2$), 3.96 (dq, *J* = 8.2 and 7.0 Hz, 1 H, CH$_3$C*H*CO), 4.75 (dq, *J* = 6.8 and 6.6 Hz, 1 H, C*H*CHPh), 5.61 (d, *J* = 6.8 Hz, 1 H, PhC*H*CH), 5.91 (s, 1 H, C*H*O$_2$CCH$_3$), 7.20–7.54 (m, 10 H , Ph); ^{13}C NMR (CDCl$_3$, 68 MHz) δ 14.3, 20.6, 22.1, 25.3, 39.7, 54.9, 57.1, 70.4, 73.8, 78.8, 125.8, 127.7, 128.5, 128.6, 128.7, 129.1, 133.6, 133.9, 152.6(CH$_2$*C*ON), 166.8 (N*C*OO), 170.0 (CH$_3$*C*O), 174.8 (O*C*O); HRMS (FAB) Calcd for $C_{27}H_{31}N_2O_7$ (M+H$^+$) 495.2131, found 495.2119.

Preparation of (4*R*,5*S*)-3-[(2*S*)-2-{(2*S*)-*N*-Benzyloxycarbonyl-pyrrolidin-2-yl}propanoyl]-4-methyl-5-phenyl-2-oxazolidinone (22). A mimxture of **18** (4.35 g, 8.8 mmol) and zinc powder (11.7 g, 176 mmol) in MeOH—4 M HCl (3:2, 50 mL) was stirred at 60 °C for 0.5 h. Cooling to room temperature, filtration, and evaporation gave an oil. To a solution of the oil in THF—water (1:1, 45 mL) were added KHCO$_3$ (2.00 g, 14.5 mmol) to adjust pH to 8 and benzyl chloroformate (2.51 mL, 17.6 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with EtOAc, washed with brine, and dried (MgSO$_4$). Evaporation of the filtrate and purification by column chromatography on SiO$_2$ (15–20% EtOAc in hexane) afforded (4*R*,5*S*,2'*S*,2"*S*)-**22** (3.40 g, 7.78 mmol, 88%) as a colorless oil: [α]$^{24}_D$ +21.1° (*c* 1.01, CH$_2$Cl$_2$); IR (neat) 1779, 1705, 1499, 1456, 1410, 1200, 1148, 1030, 988, 959, 767, 736, 699 cm^{-1}; ^{1}H NMR (CDCl$_3$, 270 MHz, 50 °C) δ 0.81 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$), 1.15 (br s, 3 H, C*H*$_3$), 1.74–2.08 (m, 4 H, C*H*$_2$C*H*$_2$), 3.28–3.70 (m, 2 H), 4.20–4.39 (m, 2 H), 4.77 (quint, *J* = 6.6 Hz, 1 H, CH$_3$C*H*CO), 5.08 (br, 2 H, C*H*$_2$Ph), 5.61 (d, *J* = 7.4 Hz, 1 H, PhC*H*O) 7.12–7.54 (m, 10 H, Ph); ^{13}C NMR (CDCl$_3$, 68 MHz, 50 °C) δ 14.4, 23.8, 28.2,

40.5, 47.2, 47.3, 54.9, 66.7, 77.2, 78.8, 125.8, 127.8, 127.9, 128.4, 128.6, 128.7, 133.7, 137.1, 152.2, 155.1, 174.9; HRMS(FAB) calcd for $C_{25}H_{29}N_2O_5$ ($M+H^+$) 437.2076, found 437.2075.

Preparation of (2*S*)-2-{(2*S*)-*N*-Benzyloxycarbonylpyrrolidin-2-yl}propanol (19). To a solution of β-amino acid derivative **22** (273 mg, 0.63 mmol) in THF—H_2O (2:1, 10.5 mL), $NaBH_4$ (95 mg, 2.5 mmol) was added at 0 °C, and the mixture was stirred at 5 °C for 15 h. To the mixture was added 1.6 M aqueous NaH_2PO_4 dropwise. After removal of THF, the mixture was extracted with EtOAc, washed with brine, and dried ($MgSO_4$). After filtration and removal of the solvent, the residue was purified by column chromatography on SiO_2 (30–50% EtOAc in hexane), affording **19** (146 mg, 88%) as a colorless oil along with (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone (97 mg, 82%). **19:** $[\alpha]^{23}_D$ –37.3° (*c* 1.43, MeOH); IR (neat) 3424 (OH), 2969, 2880, 1678 (NCOO), 1455, 1416, 1358, 1339, 1101, 769 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 50 °C) δ 1.03 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$), 1.49 (br, 1 H, C*H*CH_3), 1.75–1.98 (m, 4 H, (C*H*$_2$)$_2$), 3.24–3.47 (m, 2 H), 3.47–3.71 (m, 2 H), 3.72–3.95 (m, 2 H), 5.14 (d, *J* = 12.0 Hz, 1 H, *H*CHPh), 5.17 (d, *J* = 12.0 Hz, 1 H, *H*CHPh), 7.28–7.38 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 50 °C) δ 14.7, 23.6, 28.6, 39.0, 46.3, 59.6, 64.0, 67.2, 127.8, 128.0, 128.5, 136.7, 157.0; HRMS(EI) calcd for $C_{15}H_{21}NO_3$ (M^+) 263.1521, found 263.1494.

Preparation of (2*S*)-*N*-Benzyloxycarbonyl-2-{(2*S*)-1-bromo-2-propyl}pyrrolidine (23). To a solution of alcohol **19** (397 mg, 1.50 mmol) in dry THF (8 mL), were added PPh_3 (590 mg, 2.25 mmol) and CBr_4 (746 mg, 2.25 mmol) at 0 °C, and the mixture was warmed up to room temperature. The mixture was stirred for 10 min then quenched with sat. aq. $NaHCO_3$. After extraction with EtOAc, the extracts were washed with brine and dried ($MgSO_4$). After filtration and removal of solvent, the resulting oil was purified by column chromatography on SiO_2 (15% EtOAc in hexane) to afford **23** (471 mg, 96%) as a colorless oil: $[\alpha]^{25}_D$ –39.4° (*c* 1.26, $CHCl_3$); IR (neat) 2970, 1699, 1499, 1456, 1410, 1356, 1103, 770, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 55 °C) δ 0.97 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$), 1.73–1.98 (m, 4 H, (-C*H*$_2$-)$_2$), 2.38 (septet, *J* = 6.6 Hz, 1 H, CH_3C*H*), 3.12–3,45 (m, 3 H), 3.53–3.70 (m, 1 H), 3.93–4.04 (m, 1 H), 5.11 (d, *J* = 12.5 Hz, 1 H of C*H*$_2$Ph), 5.15 (d, *J* =

12.5 Hz, C*H*HPh), 7.15–7.42 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 55 °C) δ 14.4, 24.0, 26.9, 37.3, 38.8, 46.9, 60.8, 66.9, 127.8, 127.9, 128.5, 137.0, 155.4; HRMS (FAB) calcd for $C_{15}H_{20}NO_2Br$ ($M+H^+$) 325.0677, found 325.0707.

Preparation of Diethyl (2*R*)-2-{(2*S*)-*N*-benzyloxycarbonylpyrrolidin–2–yl}propylmalonate (24). A solution of diethyl malonate (8.95 mL, 59 mmol) in of DME (20 mL) was added to the suspension of NaH (53.6 mmol, secured from 2.14 g of 60% mineral oil dispersion through hexane washing) in DME (20 mL). A solution of **23** (1.75 g, 5.36 mmol) in DME (20 mL) was added to the solition of sodiomalonate over a period of 20 min, and the mixture was stirred at 60 °C for 20 h. Ethereal acetic acid was added to neutralize the excess sodiomalonate, and the product was extracted with EtOAc and washed with brine. The extracts were dried ($MgSO_4$) and evaporated. The resulting oil was purified by column chromatography on SiO_2 (10—20% EtOAc in hexane), to give **24** (1.87 g, 86%) as a colorless oil: $[\alpha]^{23}_D$ –13.6° (*c* 1.71, $CHCl_3$); IR (neat) 2995, 1751, 1732, 1701, 1410, 1030, 769, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 50 °C) δ 0.81 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$), 1.16–1.29 (m, 6 H, CH$_2$C*H*$_3$), 1.62–2.29 (m, 7 H), 3.23–3.34 (m, 1 H), 3.39 (br t, *J* = 6.4 Hz, 1 H, C*H*(CO$_2$)$_2$), 3.61 (br, 1 H), 3.86 (br q, *J* = 5.0 Hz, 1 H, C*H*N), 4.02–4.27 (m, 4 H, C*H*$_2$CH$_3$), 5.12 (s, 2 H, C*H*$_2$Ph), 7.26–7.37 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 50 °C) δ 13.8, 14.0, 24.1, 26.2, 32.7, 33.5, 39.9, 47.3, 50.5, 61.2, 61.3, 62.7, 66.6, 127.7, 128.4, 137.2, 155.2, 169.3, 169.6; HRMS (FAB) calcd for $C_{22}H_{32}NO_6$ ($M+H^+$) 406.2230, found 406.2196.

Preparation of Ethyl (4*R*)-4-{(2*S*)-*N*-Benzyloxycarbonylpyrrolidin-2-yl}pentanoate (20). A mixture of malonate **24** (1.85 g, 4.6 mmol), NaCl (539 mg, 9.22 mmol), and water (0.33 mL, 18.4 mmol) in DMSO (25 mL) was stirred under argon at 170 °C for 10 h, and then water was added. After extraction with EtOAc—Et_2O (3:1), the extracts were washed with brine and dried ($MgSO_4$). After filtration and the removal of the solvent, the resulting oil was purified by column chromatography on SiO_2 (15% EtOAc in hexane), to afford **20** (1.22 g, 80%) as a pale yellow oil: $[\alpha]^{25}_D$ –26.9° (*c* 1.05, $CHCl_3$); IR (neat) 2973, 1732, 1703, 1456, 1412, 1183, 1100, 1028, 770, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 50 °C) δ 0.79 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$), 1.23 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$), 1.34–1.52 (m, 1

H), 1.57–1.93 (m, 5 H), 1.93–2.49 (m, 3 H), 3.23–3.36 (m, 1 H), 3.62 (br, 1 H), 3.79–3.91 (m, 1 H), 4.10 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 5.10 (d, *J* = 12.5 Hz, C*H*HPh), 5.15 (d, *J* = 12.5 Hz, C*H*HPh), 7.24–7.39 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 50 °C) δ 13.7, 14.2, 24.2, 25.9, 29.0, 32.6, 34.7, 47.2, 60.2, 61.5, 66.7, 127.7, 127.8, 128.4, 137.2, 155.2, 173.6; HRMS (FAB) calcd for $C_{19}H_{28}NO_4$ (M+H$^+$) 334.2019, found 334.2000.

Preparation of (2*S*)-1-Benzyloxycarbonyl-2-[(2*R*)-5,5-dimethoxypent-2-yl]pyrrolidine (25). To a solution of ester **20** (157.2 mg, 0.47 mmol) in CH_2Cl_2 (15 mL), was added dropwise a 1.0 *M* hexane solution of DIBALH (0.54 mL, 0.54 mmol) at –78 °C. The mixture was stirred for 30 min at the same temperature, then were added Na_2SO_4•10H_2O and hexane. After the mixture was allowed to warm to room temperature, evaporation of the filtrate gave crude aldehyde. A solution of the aldehyde and catalytic amount of TsOH•H_2O in MeOH (12 mL) was stirred at reflux for 3 h. After addition of sat. $NaHCO_3$, the solution was extracted with ether, and the combined extracts were washed with brine and dried ($MgSO_4$). After filtration and removal of the solvent, the crude acetal was purified by column chromatography on SiO_2 (20% EtOAc in hexane), to afford acetal **25** (101 mg, 64%) as a colorless oil: [α]$^{22}_D$ –26.7° (*c* 1.39, CHCl3); IR (neat) 2955, 1699, 1408, 1190, 1100, 698 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$, 50 °C) δ 0.78 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$), 1.05–2.30 (m, 9 H), 3.29 (s, 6 H, OC*H*$_3$), 3.15–3.38 (m, 1 H), 3.62 (br, 1 H), 3.86 (m, 1 H), 4.30 (br, 1 H), 5.10 (d, *J* = 12.5 Hz, 1 H, HC*H*Ph), 5.15 (d, *J* = 12.5 Hz, 1 H, HC*H*Ph), 7.26–7.38 (m, 5 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 50 °C) δ 13.8, 24.2, 25.7, 28.7, 30.7, 34.5, 47.3, 52.7, 61.8, 66.5, 104.8, 127.7, 128.0, 128.4, 137.2, 155.2.

Preparation of (2*S*)-2-[(2*R*)-5,5-Dimethoxypent-2-yl]pyrrolidine (21).[5] A mixture of acetal **25** (490 mg, 1.46 mmol) and 10% Pd on carbon (160 mg) in MeOH (8 mL) was stirred under H_2 (1 atm) at room temperature for 90 min. Filtration and removal of the solvent gave **21** (253 mg, 86%): [α]$^{23}_D$ +7.8° (*c* 1.12 CH_2Cl_2), (lit.[5] [α]$_D$ + 7.4° (*c* 1.1 CH_2Cl_2)); IR (neat) 3347, 2957, 1460, 1383, 1192, 1127, 1059 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$, 35 °C) δ 0.88 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$), 1.08-1-88 (m, 10 H), 2.74 (m, 1 H), 2.82 (m, 1 H), 2.99 (m, 1 H), 3.31 (s, 6 H, OC*H*$_3$), 4.33 (t, *J* = 5.5 Hz, 1 H, C*H*(OCH$_3$)$_2$); ^{13}C NMR (68 MHz, $CDCl_3$, 50 °C) δ 16.2, 25.5, 29.3, 29.4, 30.1, 38.5, 46.8, 52.7, 64.4,

105.1; HRMS(EI) calcd for $C_{11}H_{23}NO_2$ (M^+) 201.1729, found 201.1735.

Preparation of (5*R*,8*R*,8a*R*)-(–)-5-Cyano-8-methylindolizidine (7). To a solution of amino acetal **21** (240 mg, 1.19 mmol) in CH_2Cl_2—H_2O (15 mL each), KCN (932 mg, 14.3 mmol) was added. The pH value of the solution was adjusted to 3 with conc. HCl, and the mixture was stirred for 10 h. After the solution was made alkaline with 2 *M* NaOH, it was extraction with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to afford (–)-**7** as an oil (191 mg, containing 7% of a diastereomer, 98%): $[\alpha]^{24}_D$ –25.8° (*c* 1.64, CH_2Cl_2), (lit.[5] $[\alpha]_D$ –18.8° (*c* 1, CH_2Cl_2)); IR (neat) 2953, 2224, 1460, 1167 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 50 °C) δ 0.92 (d, *J* = 6.5 Hz, 3 H, C*H*$_3$), 1.20–1.47 (m, 3 H), 1.61–2.06 (m, 7 H), 2.49 (q, *J* = 8.8 Hz, 1 H, C_3-*H*), 2.95 (dt, *J* = 3.0 and 8.5 Hz, C_3-*H*), 4.03 (t, *J* = 3.4 Hz, 1 H, C_5-*H*); ^{13}C NMR (68 MHz, $CDCl_3$, 50 °C) δ 18.3, 20.3, 28.7, 28.9, 29.4, 36.7, 51.3, 51.4, 64.8, 116.6; HRMS (EI) calcd for $C_{10}H_{16}N_2$ (M^+) 164.1313, found 164.1288.

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