Supporting Information

Memory of Chirality in Diastereoselective α-Alkylation of Isoleucine and *allo*-Isoleucine Derivatives

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(2*S*, 3*S*)-*N*-*tert*-butoxycarbonyl-*N*-(methoxymethyl)isoleucine ethyl ester (3)

N,N-Diisopropylethylamine (6.97 mL, 40mmol) and di-*tert*-butyl dicarbonate (4.80 g, 22 mmol) were added to a solution of (2*S*, 3*S*)-isoleucine ethyl ester hydrochloride (3.91 g, 20 mmol) in dichloromethane (40 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 20 h, then poured into saturated aq NH_4Cl, and extracted with ethyl acetate. The organic layer was washed with saturated aq $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, ethylÅ@etate:hexane=1:9) to give (2*S*, 3*S*)-*N*-(*tert*-butoxycarbonyl)isoleucine ethyl ester as a colorless oil (5.13 g, 99 % yield). $[\alpha]_D^{19}$ = +16 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (d, *J*=7.8 Hz, 1H), 4.26-4.13 (m, 3H), 1.89-1.80 (m, 1H), 1.48-1.39 (m, 1H), 1.45 (s, 9H), 1.28 (t, *J*=7.2 Hz, 3H), 1.23-1.12 (m, 1H), 0.93 (d, *J*=6.8 Hz, 3H), 0.92 (t, *J*=7.3 Hz, 3H). IR (neat) 3371, 2971, 2935, 1715, 1505, 1456, 1367 cm^{-1}. MS *m/z* 259 (M^+), 244, 214, 203, 186, 158, 147, 130. Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.21; H, 9.72; N, 5.40 %. Found: C, 59.94; H, 9.80; N, 5.34 %.

Potassium hexamethyldisilazide (KHMDS*) (0.46 M in THF, 12.3 mL, 5.7 mmol) was added to a solution of (2*S*, 3*S*)-*N*-(*tert*-butoxycarbonyl)isoleucine ethyl ester

(1.55 g, 6.0 mmol) in THF (5 mL) at –78 °C. After 30 min, chloromethyl methyl ether (1.37 mL, 18 mmol) was added and the mixture was gradually warmed to room temperature during a period of 20 h. The mixture was poured into saturated aq NH_4Cl and extracted with ethyl acetate. The organic layer was washed with saturated aq $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, ether:hexane=1:9) to give **3** as a colorless oil (1.68 g, 93 % yield). $[\alpha]_D^{19}$ = –44 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86-4.67 (m, 2H), 4.33 (br, 1/2 H), 4.21-4.10 (m, 2H), 3.92 (br d, *J*=8.1 Hz, 1/2 H), 3.34 (br s, 3H), 2.14-1.98 (m, 1H), 1.56-1.39 (m, 1H), 1.47 (s, 9H), 1.27 (t, *J*=7.0 Hz, 3H), 1.15-1.01 (m, 1H), 0.97 (d, *J*=6.8 Hz, 3H), 0.90 (t, *J*=7.3 Hz, 3H). IR (neat) 2978, 1742, 1707, 1367, 1300, 1255, 1143, 1083 cm^{-1}. MS *m/z* 303 (M^+), 272, 247, 230, 202, 172, 146, 130. Anal. Calcd for $C_{15}H_{29}NO_5$: C, 59.38; H, 9.63; N, 4.62 %. Found: C, 59.18; H, 9.82; N, 4.61 %.

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(*2R*, 3*S*)-*N*-*tert*-butoxycarbonyl-*allo*-isoleucine ethyl ester

Prepared from (2*R*, 3*S*)-*allo*-isoleucine ethyl ester hydrochloride according to the procedure for (2*S*, 3*S*)-*N*-(*tert*-butoxycarbonyl)isoleucine ethyl ester in 96 % yield. $[\alpha]_D^{19}$ = –17 (*c* 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (d, *J*=9.2 Hz, 1H), 4.34 (dd, *J*=3.6, 9.2 Hz, 1H), 4.25-4.14 (m, 2H), 1.96-1.85 (m, 1H), 1.50-1.40 (m, 1H), 1.45 (s, 9H), 1.28 (t, *J*=7.2 Hz, 3H), 1.23-1.15 (m, 1H), 0.95 (t, *J*=7.3 Hz, 3H), 0.84 (d, *J*=7.0 Hz, 3H). IR (neat) 3373, 2971, 2935, 1716, 1505, 1458, 1367 cm^{-1}. MS *m/z* 259 (M^+), 244, 214, 203, 186, 158, 147, 130. Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.21; H, 9.72; N, 5.40%. Found: C, 60.04; H, 9.88; N, 5.39 %.

(2*R*, 3*S*)-*N*-*tert*-butoxycarbonyl-*N*-methoxymethyl-*allo*-isoleucine ethyl ester (4)

Prepared from (2*R*, 3*S*)-*N*-*ter*t-butoxycarbonyl-*allo*-isoleucine ethyl ester according to the procedure for **3** in 78 % yield. $[\alpha]_D^{19}$ = +48 (*c* 1.2, $CHCl_3$). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 4.84-4.67 (m, 2H), 4.26 (br d, *J*=8.7 Hz, 1/2 H), 4.20-4.10 (m, 2H), 3.86 (br d, *J*=9.0 Hz, 1/2 H), 3.35, 3.32 (two br s, 3 H), 2.23-2.09 (m, 1H), 1.62-1.51 (m, 1H), 1.46 (s, 9H), 1.27 (br t, *J*=6.3 Hz, , 3H), 1.20-1.07 (m, 1H), 0.93 (t, *J*=7.3 Hz, 3H), 0.88 (d, *J*=7.0 Hz, 3H). IR (neat) 2974, 1745, 1705, 1367, 1295, 1176, 1086 cm^{-1}. MS *m/z* 303 (M^+), 272, 247, 230, 202, 172, 146, 130. Anal. Calcd for $C_{15}H_{29}NO_5$: C, 59.38; H, 9.63; N, 4.62 %. Found: C, 59.33; H, 9.76; N, 4.57 %.

Methylation of 3: (2*S*, 3*S*)- and (2*R*, 3*S*)-*N*-*tert*-butoxycarbonyl-*N*-methoxymethyl-α-methylisoleucine ethyl ester (5) and (6), (2*S*, 3*S*)-*N*-*p*-Nitrobenzoyl-α-methylisoleucine ethyl ester (7)

A solution of **3** (dried azeotropically with toluene prior to use, 152 mg, 0.5 mmol) in THF (4.5 ml) was added to a solution of KHMDS (0.50 M in THF, 1.1 mL, 0.55 mmol) at −78 °C. After 60 min, methyl iodide (0.31 mL, 5.0 mmol) was added and the mixture was stirred at −78 °C for 20 h, then poured into saturated aq NH_4Cl and extracted with ethyl acetate. The organic layer was washed with saturated aq $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, ethyl acetate:hexane=1:12) to give an inseparable mixture (154 mg) of **5**, **6**, and a trace amount (≤4%) of **3**. The combined yield of **5** and **6** and the diastereomeric ratio were determined by 400 MHz ^1H NMR to be 93% and 93:7, respectively. ^1H NMR (400 MHz, $CDCl_3$) δ 5.12, 5.08 (two d, *J*=11.8, 11.7 Hz, ratio=1:<10, 1 H), 4.58, 4.53 (two d, *J*=11.7, 11.8 Hz, ratio=93:7, 1 H), 4.20-4.06 (m, 2 H), 3.36, 3.35 (two s, ratio =93:7, 3 H), 2.37-2.17 (m, 1 H), 1.94-1.76, 1.55-1.42 (two m, ratio=1:>10, 1 H), 1.49 (s, 3 H), 1.45 (s, 9 H), 1.26, 1.25 (two t, *J*=7.3, 7.3 Hz, ratio=>10:1, 3 H), 1.02, 0.84 (two d, *J*=6.6, 6.8 Hz, ratio =93:7, 3H), 1.00-0.85 (m, 1 H). MS *m/z* 317 (M^+), 286, 260, 244, 216, 186, 160, 140, 112. Exact mass calcd for $C_{16}H_{31}NO_5$, 317.2202, found, *m/z* 317.2217. An analytically pure sample of the mixture of **5** and **6** was obtained by removing a trace amount of **3** through selective ester-hydrolysis (10% KOH/dioxane=4:1, Bu_4NI, 50 °C). The diastereomeric ratio of **5** to **6**

did not alter before and after hydrolysis. IR (neat) 2976, 1740, 1702, 1409, 1367, 1299, 1252, 1173, 1104, 1084 cm^{-1}. Anal. Calcd for $C_{16}H_{31}NO_5$: C, 60.54; H, 9.84; N, 4.41 %. Found: C, 60.58; H, 9.99; N, 4.40 %.

The mixture (120 mg) was dissolved in 4 M HCl in ethyl acetate (3 mL) and the solution was stirred at room temperature for 1 h. After concentration *in vacuo*, the residue was dissolved in dichloromethane (2 mL) and treated with *N*,*N*-diisopropylethylamine (0.20 mL, 1.1 mmol) and *p*-nitrobenzoyl chloride (140 mg, 0.76 mmol) at room temperature for 4 h. Work-up followed by purification by flash column chromatography ($CHCl_3$:acetone = 60:1) gave a mixture of **7** and **8** (110 mg, 94 % yield). Recrystallization from ether-hexane gave diastereomerically and analytically pure **7**. Colorless needles (ether-hexane), mp 135-136 °C. $[\alpha]_D^{18}$ = +14 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.30 (d, *J*=8.7 Hz, 2H), 8.05 (d, *J*=8.7 Hz, 2H), 7.96 (br s, 1H), 4.15 (q of ABq, J_{AB}=10.7 Hz, J_{AX}=7.0 Hz, $\Delta\nu_{AB}$=15.9 Hz, 2H), 1.98-1.83 (m, 2H), 1.56 (s, 3H), 1.22 (t, *J*=7.0 Hz, 3H), 1.18-1.10 (m, 1H), 0.96 (t, *J*=7.2 Hz, 3H), 0.94 (d, *J*=6.8 Hz, 3H). IR (KBr) 3439, 2971, 1728, 1663, 1603, 1525, 1510, 1482 cm^{-1}. MS *m*/*z* 322 (M^+), 293, 277, 265, 249, 219, 167, 150, 134, 104, 92, 76. Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.62; H, 6.88; N, 8.69 %. Found: C, 59.60; H, 6.99; N, 8.66 %.

Methylation of 4: (2*R*, 3*S*)-*N*-*p*-nitrobenzoyl-α-methyl-*allo*-isoleucine ethyl ester (8)

Methylation of **4** was performed according to the procedure for methylation of **3**. The reaction residue was purified by flash column chromatography (SiO_2, ethyl acetate:hexane=1:12) to give an inseparable mixture (154 mg) of **5**, **6**, and a trace amount (≤6%) of **4**. The combined yield of **5** and **6** and the diastereomeric ratio were determined by 400 MHz ^{1}H NMR to be 91% and 14:86, respectively. The mixture (129 mg) was treated with 4 M HCl in ethyl acetate followed by *p*-nitrobenzoyl chloride to give a mixture of **7** and **8** (118 mg, 90 % yield). Recrystallization from ether-hexane gave diastereomerically and analytically pure **8**. Colorless prisms (ether-hexane), mp 129-130

°C. $[\alpha]_D^{18}$ = −17 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.30 (d, *J*=8.7 Hz, 2H), 8.06 (d, *J*=8.7 Hz, 2H), 7.88 (s, 1H), 4.15 (q of ABq, J_{AB}=10.7 Hz, J_{AX}=7.0 Hz, $\Delta\nu_{AB}$=7.6 Hz, 2H), 2.04-1.97 (m, 1H), 1.68-1.61 (m, 1H), 1.58 (s, 3H), 1.22 (t, *J*=7.0 Hz, 3H), 1.13-1.09 (m, 1H), 1.07 (d, *J*=6.8 Hz, 3H), 0.92 (t, *J*=7.2 Hz, 3H). IR (KBr) 3437, 2973, 1727, 1663, 1523, 1482 cm^{-1}. MS *m/z* 322 (M^+), 293, 277, 265, 249, 219, 167, 150, 134, 104, 92, 76. Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.62; H, 6.88; N, 8.69 %. Found: C, 59.50; H, 6.96; N, 8.44 %.

(2*S*, 3*S*)-*N*, *N*-Bis(*tert*-butoxycarbonyl)isoleucine ethyl ester (9)

Potassium hexamethyldisilazide (KHMDS) (0.51 M in THF, 5.56 mL, 2.8 mmol) was added to a solution of (2*S*, 3*S*)-*N*-(*ter*t-butoxycarbonyl)isoleucine ethyl ester (777 mg, 3.0 mmol) in THF (20 mL) at –78 °C. After 30 min, di-*tert*-butyl dicarbonate (1.31 g, 6.0 mmol) was added and the mixture was gradually warmed to room temperature during a period of 20 h. The reaction mixture was poured into saturated aq NH_4Cl and extracted with ethyl acetate. The organic layer was washed with saturated aq $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, ether:hexane=1:15) to give **9** as a colorless oil (710 mg, 66 % yield). $[\alpha]_D^{19}$ = −43 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (d, *J*=9.5 Hz, 1H), 4.15 (q of ABq, J_{AB}=10.7 Hz, J_{AX}=7.0 Hz, $\Delta\nu_{AB}$=14.4 Hz, 2H), 2.29-2.22 (m, 1H), 1.49 (s, 18 H), 1.48-1.38 (m, 1H), 1.25 (t, *J*=7.0 Hz, 3H), 1.10 (d, *J*=6.5 Hz, 3H), 1.07-0.99 (m, 1H), 0.88 (t, *J*=7.4 Hz, 3H). ^{1}H NMR (400 MHz, C_6D_6) δ 4.87 (d, *J*=9.4 Hz, 1H), 3.96 (q of ABq, J_{AB}=10.9 Hz, J_{AX}=7.0 Hz, $\Delta\nu_{AB}$=23.8 Hz, 2H), 2.58-2.51 (m, 1H), 1.67-1.59 (m, 1H), 1.40 (s, 18 H), 1.27-1.22 (m, 1H), 1.20 (d, *J*=6.5 Hz, 3H), 0.96 (t, *J*=7.0 Hz, 3H), 0.88 (t, *J*=7.3 Hz, 3H). IR (neat) 2979, 1748, 1705, 1456, 1368, 1311, 1237, 1130 cm^{-1}. MS *m/z* 359 (M^+), 303, 286, 258, 247, 202, 186, 147, 130. Anal. Calcd for $C_{18}H_{33}NO_6$: C, 60.14; H, 9.25; N, 3.90 %. Found: C, 59.94; H, 9.37; N, 3.90 %.

(2*R*, 3*S*)-*N*, *N*-Bis(tert-butoxycarbonyl)-*allo*-isoleucine ethyl ester (10)

Prepared from (2*R*, 3*S*)-*N*-(*tert*-butoxycarbonyl)-*allo*-isoleucine ethyl ester according to the procedure for **9** in 85 % yield. $[\alpha]_D^{19}$ = +41 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (d, *J*=9.2 Hz, 1H), 4.15 (q of ABq, J_{AB}=10.9 Hz, J_{AX}=7.1 Hz, $\Delta\nu_{AB}$=14.2 Hz, 2H), 2.33-2.26 (m, 1H), 1.82-1.72 (m, 1H), 1.49 (s, 18 H), 1.25 (t, *J*=7.1 Hz, 3H), 1.21-1.16 (m, 1H), 0.95 (t, *J*=7.5 Hz, 3H), 0.84 (d, *J*=7.0 Hz, 3H). ^{1}H NMR (400 MHz, C_6D_6) δ 4.88 (d, *J*=9.0 Hz, 1H), 3.97 (q of ABq, J_{AB}=10.9 Hz, J_{AX}=7.2 Hz, $\Delta\nu_{AB}$=26.2 Hz, 2H), 2.61-2.54 (m, 1H), 1.96-1.87 (m, 1H), 1.39 (s, 18 H), 1.36-1.23 (m, 1H), 0.98 (d, *J*=7.0 Hz, 3H), 0.97 (t, *J*=7.2 Hz, 3H), 0.96 (t, *J*=7.5 Hz, 3H). IR (neat) 2979, 1747, 1456, 1368, 1314, 1235, 1132 cm^{-1}. MS *m/z* 359 (M^+), 303, 286, 258, 247, 202, 186, 147, 130. Anal. Calcd for $C_{18}H_{33}NO_6$: C, 60.14; H, 9.25; N, 3.90 %. Found: C, 59.98; H, 9.38; N, 4.01 %.