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Supporting Information

A Chiral Nonracemic Enolate with Dynamic Axial Chirality: Direct Asymmetric α-Methylation of α-Amino Acid Derivatives

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Compounds **3** ~ **20** and **22** were fully characterized in the racemic form. Enantiomeric purity of the optically active compounds was determined by HPLC analysis. Determination of ee's of solid compounds was performed with un-recrystallized materials. Compound **21** was prepared according to the reported method (Walter, M. W.; Adlimgton, R. M.; Baldwin, J. E.; Chuhan, J.; Schofield, C. J. *Tetrahedron Lett*. **1995**, *36*, 7761).

Preparation of *N*-*tert*-Butoxycarbonyl-*N*-methoxymethylphenylalanine ethyl ester (3) :

Potassium hexamethyldisilazide (KHMDS) (1.05 M in THF, 38.5 mL, 40.4 mmol) was added to a solution of (*S*)-*N*-*tert*-Butoxycarbonylphenylalanine ethyl ester (12.0 g, 41.2 mmol) in THF (165 mL) at −78 °C. After 15 min, chloromethyl methyl ether (15.6 mL, 205 mmol) was added and stirring was continued for 24 h at −78 °C. The mixture was poured into saturated aq NH_4Cl and extracted with ethyl acetate. The organic phase was washed with saturated aq $NaHCO_3$ and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, dioxane:pentane=1:20) to give (*S*)-**3** (>99% *ee*, 10.4 g, 75% yield).

(*S*)-3 (> 99% ee) : Colorless oil. $[\alpha]_D^{20}$ = −106 (*c* 1.0, $CHCl_3$). HPLC conditions: Daicel Chiralpack AD, 2% EtOH / hexane, 1.0 ml/min, t_R = 7.0 min (*S*), t_R = 8.0 min (*R*).

***dl*-3**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.10 (m, 5 H), 4.72 (d, *J* = 11.0 Hz, 4/7 H), 4.59 (d, *J* = 11.4 Hz, 3/7 H), 4.30-4.10 (m, 3 H), 4.01 (d, *J* = 11.4 Hz, 3/7 H), 3.83 (d, *J* = 11.0 Hz, 4/7 H), 3.38 (dd, *J* = 13.7, 5.3 Hz, 1 H), 3.22-3.10 (m, 1 H),

3.21 (s, 12/7 H), 3.14 (s, 9/7 H), 1.48 (s, 9 H), 1.30 (t, *J* =7.0 Hz, 12/7 H), 1.26 (t, *J* = 7.0 Hz, 9/7 H). IR ($CHCl_3$) 3026, 3010, 2981, 1736, 1700 cm^{-1}; MS *m/z* 337 (M^+), 305, 205, 176, 146, 132, 61. Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.08; H, 8.07; N, 4.15%. Found : C, 64.00; H, 8.23; N, 4.08%.

General Procedure for Asymmetric α-Methylation of α-Amino Acid Derivatives:

Each substrate was dried azeotropically with toluene prior to use. A KHMDS solution in THF (0.50 M, 1.1 mL, 0.55 mmol) was diluted with 3 mL of toluene. A solution of substrate (0.5 mmol) in toluene (1.5 mL) was added to the KHMDS solution at –78 °C. After stirring for 30 min (for **3**, **5**, **7**, **9**, and **11**) or 60 min (for **13** and **15**), methyl iodide (0.31 mL, 5.0 mmol) was added. Stirring was continued for 16 ~ 17 h at –78 °C. The mixture was poured into saturated aq NH_4Cl and extracted with ethyl acetate. The organic phase was washed with saturated aq $NaHCO_3$ and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC.

***N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-α-methylphenylalanine ethyl ester (4) :**

(*S*)-4 (81% *ee*): Colorless oil. $[\alpha]_D^{15}$ = –89 (*c* 1.2, $CHCl_3$). HPLC conditions: Daicel Chiralpack AD, 2% *i*-PrOH / hexane, 1.0 mL/min, t_R = 6.9 min (*R*), t_R = 7.6 min (*S*).

***dl*-4**: Colorless oil. ^{1}H NMR (200 MHz, 20 °C , $CDCl_3$) δ 7.32-7.21 (m, 3 H), 7.11-7.02 (m 2 H), 4.91-4.48 (br, 1 H), 4.46-3.98 (br m, 2 H), 3.75-3.42 (br, 1 H), 3.69 (br d, *J* = 11.8 Hz, 1 H), 3.27 (s, 3 H), 3.01 (d, *J* = 13.5 Hz, 1 H), 1.52 (s, 9 H), 1.49 (s, 3 H), 1.28 (br t, *J* = 7.2 Hz, 3 H); (60 °C) δ 7.31-7.21 (m, 3H), 7.11-7.04 (m, 2 H), 4.72 (br d, *J* = 12.0 Hz, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 3.80 (d, *J* = 12.0 Hz, 1 H), 3.58 (br d, *J* = 13.5 Hz, 1 H), 3.26 (s, 3 H), 3.03 (d, *J* = 13.5 Hz, 1 H), 1.51 (s, 9 H), 1.48 (s, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H). IR ($CHCl_3$) 3027, 3010, 2982, 1736, 1700 cm^{-1}; MS *m/z* 351 (M^+), 260, 190, 160, 146; Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.94; H, 8.32; N, 3.98%. Found : C, 64.88; H, 8.46; N, 3.89%.

***N*(α), *N(t)*-di-*tert*-Butoxycarbonyl-*N*(α)-methoxymethylhistidine ethyl ester (5)** :

(*S*)-**5** (> 99% *ee*) : Colorless oil. $[\alpha]_D^{20}$ = –57 (*c* 1.0, $CHCl_3$). HPLC conditions: Daicel Chiralpack AD, 10% *i*-PrOH / hexane, 1.0 mL/min, t_R = 10 min (*S*), t_R = 14 min (*R*).

***dl*-5**: Colorless oil. ^{1}H NMR (400 MHz, 22 °C, $CDCl_3$) δ 7.99 (d, *J* = 1.2 Hz, 1 H), 7.13, 7.11 (two br s, ratio = 1:2, 1 H), 4.82, 4.73 (two d, *J* = 10.9, 10.9 Hz, ratio = 2:1, 1 H), 4.58-4.07 (m, 3 H), 4.40, 4.30 (two d, *J* = 10.9, 10.9 Hz, ratio = 1:2, 1 H), 3.40-3.02 (m, 2 H), 3.32 3.29 (two s, ratio = 2:1, 3 H), 1.61 (s, 9 H), 1.47 (s, 9 H), 1.30, 1.26 (two t, *J* = 7.3, 7.0 Hz, ratio = 2:1, 3 H); (60 °C) 7.96 (d, *J* = 1.2 HZ, 1 H), 7.11 (s, 1 H), 4.77 (br d, *J* = 10.9 Hz, 1 H), 4.50 (dd, *J* = 9.0, 5.3 Hz, 1 H), 4.42 (br d, *J* = 10.9 Hz, 1 H), 4.19 (br q, *J* = 7.1 Hz, 2 H), 3.36-3.30 (m, 1 H), 3.29 (s, 3 H), 3.18-3.05 (br m, 1 H), 1.60 (s, 9 H), 1.46 (s, 9 H), 1.28 (t, *J* = 7.1 Hz, 3 H). IR ($CHCl_3$) 2982, 2930, 1751, 1700, 1477, 1390, 1370; MS *m/z* 427 (M^+), 412, 380, 339, 266, 212, 166; Anal. Calcd for $C_{20}H_{33}N_3O_7$: C, 56.21; H, 7.73; N, 9.84%. Found : C, 55.94; H, 7.77; N, 9.64%.

_N_(α), _N(t)_-di-_tert_-Butoxycarbonyl-_N_(α)-methoxymethyl-α-methylhistidine ethyl ester (6):

6 (93% *ee*): Colorless oil. $[\alpha]_D^{20}$ = –43 (*c* 1.1, $CHCl_3$). HPLC conditions: Daicel Chiralpack AD, 5% EtOH / hexane, 1.0 mL/min, t_R = 19 min (minor), t_R = 22 min (major).

***dl*-6** : Colorless oil. ^{1}H NMR (400 MHz, 22 °C, $CDCl_3$) δ 7.97 (d, *J* = 1.2 Hz, 1 H), 7.05 (d, *J* = 1.2 Hz, 1 H), 4.95-4.70 (br m, 1 H), 4.33-4.10 (m, 3 H), 3.55-3.40 (br m, 1 H), 3.31 (s, 3 H), 3.05 (d, *J* = 14.3 Hz, 1 H), 1.65 (s, 3 H), 1.61 (s, 9 H), 1.48 (s, 9 H), 1.27 (br t, *J* = 7.1 Hz, 3 H); (60 °C) δ 7.93 (d, *J* = 1.2 Hz, 1 H), 7.05 (s, 1 H), 4.81 (d, *J* = 11.8 Hz, 1 H), 4.32 (d, *J* = 11.8 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.47 (d, *J* = 14.3 Hz, 1 H), 3.30 (s, 3 H), 3.06 (d, *J* = 14.3 Hz, 1 H), 1.64 (s, 3 H), 1.60 (s, 9 H), 1.48 (s, 9 H), 1.26 (t, *J* = 7.1, 3 H). IR ($CHCl_3$) 2982, 2935, 1751, 1739, 1696, 1478,

1391, 1373 cm^{-1}. MS *m/z* 441 (M^+), 409, 394, 353, 280, 226, 180, 160; Anal. Calcd for $C_{21}H_{35}N_3O_7$: C, 57.14; H, 7.94; N, 9.52%. Found : C, 56.85; H, 8.04; N, 9.31%.

***N*-*tert*-Butoxycarbonyl-*N*,*O*-bis(methoxymethyl)tyrosine ethyl ester (7):**

(*S*)-7 (>99% *ee*) : Colorless oil. $[\alpha]_D^{17}$ = −104 (*c* 1.0, $CHCl_3$). HPLC conditions: Daicel Chiralpack AD, 5% EtOH / hexane, 1.0 mL/min, t_R = 8.6 min (*S*), t_R = 9.5 min (*R*).

***dl*-7**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.12-7.07 (m, 2 H), 6.96-6.94 (m, 2 H), 5.14 (s, 2 H), 4.73 (d, *J* = 11.0 Hz, 3/5 H), 4.61 (d, *J* = 11.5 Hz, 2/5 H), 4.25-4.05 (m, 3 H), 4.04 (d, *J* = 11.5 Hz , 2/5 H), 3.90 (d, *J* = 11.0 Hz, 3/5 H), 3.47 (s, 3 H), 3.31 (dd, *J* = 14.2, 5.4 Hz, 1 H), 3.27-319 (br m, 2/5 H), 3.23 (s, 2 H), 3.16 (s, 1 H), 3.10 (dd, *J* = 13.0, 10.0 Hz, 3/5 H), 1.48 (s, 9 H), 1.31-1.23 (m, 3 H). IR ($CHCl_3$) 2981, 1738, 1699, 1612, 1511 cm^{-1}. MS *m/z* 397(M^+), 365, 309, 266, 236, 151. Anal. Calcd for $C_{20}H_{31}NO_7$: C, 60.44; H, 7.86; N, 3.25%. Found : C, 60.58; H, 7.97; N, 3.54%.

***N*-*tert*-Butoxycarbonyl-*N*,*O*-bis(methoxymethyl)-α-methyltyrosine ethyl ester (8):**

(*S*)-8 (79% *ee*) : Colorless oil. $[\alpha]_D^{15}$ = −81 (*c* 1.0, $CHCl_3$). HPLC conditions: Daicel Chiralpack AD, 5% EtOH / hexane, 1.0 mL/min, t_R = 6.1 min (*R*), t_R = 8.8 min (*S*).

***dl*-8**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.05-6.86 (m, 4 H), 5.17 (s, 2 H), 4.95-4.58 (br, 1 H), 4.20 (br, 3 H), 3.75 (br d, *J* = 11.0 Hz, 1 H), 3.50 (s, 3 H), 3.28 (s, 3 H), 2.95 (d, *J* = 11.0 Hz, 1 H), 1.52 (s, 9 H), 1.48 (s, 3 H), 1.27 (br t, *J* = 7.0 Hz, 3 H). IR ($CHCl_3$) 2981, 1731, 1693, 1610, 1510 cm^{-1}. MS *m/z* 411 (M^+), 250, 160 ; Anal. Calcd for $C_{21}H_{33}NO_7$: C, 61.30; H, 8.03; N, 3.41%. Found : C, 61.12; H, 8.14; N, 3.34%.

***N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-(3,4-dimethoxyphenyl)alanine ethyl ester (9)** :

(*S*)-9 (>99% *ee*) : Colorless oil. $[\alpha]_D^{19}$ = −109 (*c* 1.1, $CHCl_3$). HPLC conditions: Daicel Chiralpack AD, 3% EtOH / hexane, 1.0 mL/min, t_R = 11 min (*S*), t_R = 13 min (*R*).

dl-**9**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.84-6.65 (m. 3 H), 4.74 (d, *J* =10.9 , 3/5 H), 4.63 (d, *J* = 11.6 Hz, 2/5 H), 4.28-4.00 (m, 4 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.32 (dd, *J* = 13.8 Hz, 5.0 Hz, 1 H), 3.24 (s, 9/5 H), 3.18 (s, 6/5 H), 3.11 (dd, *J* = 13.8, 12.3 Hz, 1 H), 1.49 (s, 9 H), 1.31 (t, J -7.3 Hz, 9/5 H). IR ($CHCl_3$) 3028, 3012, 2981,

1735, 1699, 1515 cm^{-1}. MS *m/z* 397 (M^+), 264, 236; Anal. Calcd for $C_{20}H_{31}NO_7$: C, 60.44; H, 7.86; N, 3.25%. Found : C, 60.23; H, 7.86; N, 3.60%.

***N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-(3,4-dimethoxyphenyl)-α-methylalanine ethyl ester (10):**

(*S*)-10 (80% *ee*) : Colorless oil. $[\alpha]_D^{19}$ = –96 (*c* 1.0, $CHCl_3$). HPLC conditions: Daicel Chiralpack AD, 5% *i*-PrOH / hexane, 1.0 mL/min, t_R = 11 min (*R*), t_R = 13 min (*S*).

***dl*-10**: Colorless oil. ^{1}H NMR (200 MHz, 20 °C, $CDCl_3$) δ 6.79 (d, *J* = 8.1 Hz , 1 H), 6.64 (dd, *J* = 8.1, 1.9 Hz, 1 H), 6.54 (br s, 1 H), 4.75 (br s, 1 H), 4.38-4.05 (br m, 2 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.83-3.43 (br m, 2 H), 3.29 (s, 3 H), 2.94 (d, *J* = 13.8 Hz, 1 H), 1.52 (s, 9 H), 1.49 (s, 3 H), 1.29 (br t, *J* = 7.1 Hz, 3 H); (60 °C) δ 6.78 (d, *J* = 8.1 Hz, 1 H), 6.64 (dd, *J* = 8.1, 2.0 Hz, 1 H), 6.58 (d, *J* = 2.0 Hz, 1 H), 4.76 (d, *J* = 11.8 Hz, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.83 (d, *J* = 11.8 Hz, 1 H), 3.51 (d, *J* = 13.7 Hz, 1 H), 3.28 (s, 3 H), 2.96 (d, *J* = 13.7 Hz, 1 H), 1.51 (s, 9 H), 1.49 (s, 3 H), 1.28 (*t*, *J* = 7.1 Hz, 3 H). IR ($CHCl_3$) 3027, 3009, 2982, 1733, 1693, 1516 cm^{-1}. MS *m/z* 411 (M^+), 278, 250, 206, 160, 151; Anal. Calcd for $C_{21}H_{33}NO_7$: C, 61.30; H, 8.08; N, 3.40%. Found : C, 60.93; H, 8.12; N, 3.37%.

***N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-(1-methoxymethylindole-3-yl)alanine ethyl ester (11)**:

(*S*)-11 (>99% *ee*) : Pale yellow oil. $[\alpha]_D^{18}$ = –90 (*c* 1.0, $CHCl_3$). HPLC conditions: Daicel Chiralpack AD, 5% EtOH / hexane, 0.5 mL/min, t_R = 17 min (*S*), t_R = 19 min (*R*).

***dl*-11**: Pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.5 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.24 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.15 (dd, *J* = 7.5, 7.0 Hz, 1 H), 7.03 (s, 1/3 H), 7.00 (s, 2/3 H), 5.44 (d, *J* = 11.2 Hz, 1 H), 5.37 (d, *J* = 11.2 Hz, 1 H), 4.73 (d, *J* = 10.8 Hz, 2/3 H), 4.59 (d, *J* = 11.2 Hz, 1/3 H), 4.40-4.12 (m, 3 H), 4.08 (d, *J* = 11.2 Hz, 1/3 H), 4.00 (d, *J* = 10.8 Hz, 2/3 H), 3.60-3.29 (m, 2 H), 3.26 (s, 2 H), 3.20 (s, 3 H), 3.17 (s, 1 H), 1.47 (s, 9 H), 1.31 (t, *J* = 7.1 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 1 H). IR ($CHCl_3$) 3008, 2982, 2932, 1736, 1698, 1465 cm^{-1}. MS *m/z* 420 (M^+), 389, 287, 259, 174. Anal. Calcd for $C_{22}H_{32}N_2O_6$: C, 62.84; H, 7.67; N, 6.66%. Found : C, 62.66; H, 7.67; N, 6.67 %.

***N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-(1-methoxymethylindole-3-yl)-α-methylalanine ethyl ester (12):**

(*S*)-12 (76% *ee*) : Pale yellow oil. $[\alpha]_D^{20}$ = –64 (*c* 0.9, $CHCl_3$). HPLC conditions: Daicel Chiralpack AD, 5% *i*-PrOH / hexane, 0.5 mL/min, t_R = 18 min (minor), t_R = 22 min (major).

***dl*-12**: Pale yellow oil. ^{1}H NMR (200 MHz, 20 °C, $CDCl_3$) δ 7.54 (d, *J* = 7.9 Hz, 1 H), 7.45 (d, *J* = 7.7 Hz, 1 H), 7.26-7.08 (m, 2 H), 6.91 (br s, 1 H), 5.46 (d, *J* = 11.3 Hz, 1 H), 5.39 (d, *J* = 11.3 Hz, 1 H), 5.00-4.45 (br, 1 H), 4.40-4.45 (br, 2 H), 4.00-3.50 (br, 2 H), 3.25 (s, 3 H), 3.21 (s, 3 H), 1.54 (s, 12 H), 1.28 (t, *J* = 7.2 Hz, 3 H); (60 °C) δ 7.54 (ddd, *J* = 7.8, 1.2, 0.7 Hz, 1 H), 7.42 (br d, *J* = 7.8 Hz, 1 H), 7.20 (ddd, *J* = 7.8, 7.0, 1.5 Hz, 1 H), 7.10 (ddd, *J* = 7.8, 7.0, 1.2 Hz, 1 H), 6.90 (s, 1 H), 5.42 (d, *J* = 11.0 Hz, 1 H), 5.36 (d, *J* =11.0 Hz, 1 H), 4.70 (d, *J* = 11.8 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 4.02 (d, *J* = 11.8 Hz, 1 H), 3.69 (d, *J* = 14.7 Hz, 1 H), 3.28 (d, *J* = 14.7 Hz, 1 H), 3.25 (s, 3 H), 3.22 (s, 3 H), 1.54 (s, 3 H), 1,52 (s, 9 H), 1.26 (t, *J* = 7.1 Hz, 3 H). IR ($CHCl_3$) 3009, 2982, 2934, 1732, 1692, 1465 cm^{-1}. MS *m/z* 434 (M^+), 403, 301, 273, 174. Anal. Calcd for $C_{23}H_{34}N_2O_6$: C, 63.58; H, 7.89; N, 6.45%. Found : C, 63.62; H, 7.91; N, 6.48%.

***N*-*tert*-Butoxycarbonyl-*N*-methoxymethylvaline ethyl ester (13):**

(*S*)-13 (>99% *ee*) : Colorless oil. $[\alpha]_D^{20}$ = –50 (*c* 1.0, $CHCl_3$). Ee of **13** was determined after conversion to *N*-benzoyl valine ethyl ester by the following procedure; i) 4 M HCl/EtOAc, rt, 2 h, ii) BzCl/*i*-Pr_2EtN/DMAP/CH_2Cl_2, rt, 2 h (66% yield). HPLC conditions: Daicel Chiralpack AS, 5% *i*-PrOH / hexane, 1.0 mL/min, t_R = 13 min (*S*), t_R = 17 min (*R*).

***dl*-13**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.88-4.62 (br m, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 4.24-4.10 (br, 1/2 H),3.74 (br d, *J* = 10.3 Hz, 1/2 H), 3.35 (br s, 3 H), 2.45-2.25 (br m, 1 H), 1.47 (s, 9 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.92 (d, *J* = 6.8 Hz, 3 H). IR ($CHCl_3$) 2979, 1734, 1697 cm^{-1}; MS *m/z* 289 (M^+), 258, 216, 188, 160, 116, 58. Anal. Calcd for $C_{14}H_{27}NO_5$: C, 58.11; H, 9.40; N, 4.84%. Found : C, 57.74; H, 9.49; N, 4.81%.

***N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-α-methylvaline ethyl ester (14):**

Optically active **14** (87% ee) was obtained as an inseparable mixture of **14** and **13** according to the General Procedure for Asymmetric α-Methylation. Yield was determined based on the ratio observed in ^{1}H-NMR. Standard sample of racemic **14** was obtained by a modified procedure for α-methylation of racemic **13**: Racemic **13** was treated with KHMDS followed by methyl iodide according to the General Procedure for Asymmetric α-Methylation. After addition of methyl iodide, the reaction mixture was gradually warmed 0 °C. Purification by column chromatography (SiO_2, ethyl acetate:hexane = 1:9) gave a mixture of racemic **14** and small amount (~10%) of **13**. Alkaline saponification of the mixture selectively gave **14** as an analytically pure sample. The ee of **14** was determined after its conversion to the *N*-benzoyl derivative (see below).

***dl*-14** : Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.10 (d, *J* = 11.8 Hz, 1 H), 4.59 (d, *J* = 11.8 Hz, 1 H), 4.15 (q, *J* = 7.2 Hz, 1 H), 4.14 (q, *J* = 7.2 Hz, 1 H), 3.36 (s, 3 H), 2.63 (hept, *J* = 6.9 Hz, 1 H), 1.47 (s, 3 H), 1.45 (s, 9 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 0.85 (d, *J* = 6.9 Hz, 3 H). IR ($CHCl_3$) 2980, 1732, 1692 cm^{-1}; MS *m/z* 303 (M^+), 230, 160, 130, 98; Anal. Calcd for $C_{15}H_{29}NO_5$: C,59.38; H, 9.63; N, 4.62%. Found : C, 59.21; H, 9.83; N, 4.70%.

A mixture of optically active **14** and **13** (4.3 : 1 ratio, 38 mg) was dissolved in 4 M HCl in ethyl acetate (2 mL) and the solution was stirred at room temperature for 4 h. After concentration *in vacuo*, the residue was dissolved in dichloromethane (2 mL) and treated with diisopropylethylamine (65 μL, 0.38 mmol), benzoly chloride (30 μL, 0.25 mmol), and DMAP (6 mg, 0.05 mmol) at room temperature for 4 h. Workup followed by purification by preparative TLC (SiO_2, ether:dichlorometane = 1:15) gave *N*-benzoyl-*N*-methoxymethyl-α-methylvaline ethyl ester (24 mg, 90% yield).

(*S*)-*N*-benzoyl-α-methylvaline ethyl ester (87% *ee*) : Colorless oil. $[\alpha]_D^{21}$ = +8.5 (*c* 1.2, $CHCl_3$). HPLC conditions: Daicel Chiralpack AS, 3% *i*-PrOH / hexane, 1.0 mL/min, t_R = 11 min (*R*), t_R = 23 min (*S*).

***dl*-*N*-benzoyl-α-methylvaline ethyl ester**: Colorless needles (*i*-Pr_2O), mp 57-58 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.80-77.4 (m, 2 H), 7.55-7.37 (m, 3 H), 6.86 (br s, 1 H), 4.25 (q, *J* = 7.1 Hz, 1 H), 4.24 (q, *J* = 7.1 Hz, 1 H), 2.45 (qq, *J* = 7.0, 6.8 Hz, 1 H), 1.71 (s, 3 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.06 (d, *J* = 7.0 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H). IR (KBr) 3294, 2973, 1728, 1636, 1529 cm^{-1}; MS *m/z* 263 (M^+), 220, 190, 122,

105, 77. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32%. Found : C, 68.55; H, 8.10; N, 5.26%.

***N-tert*-Butoxycarbony-*N*-methoxymethylleusine ethyl ester (15)**

(*S*)-15 (>99% *ee*) : Colorless oil. $[\alpha]_D^{20} = -29$ (*c* 1.0, $CHCl_3$). Ee of **15** was determined after its conversion to the *N*-benzoyl derivative: HPLC conditions: Daicel Chiralpack AD, 10% *i*-PrOH / hexane, 1.0 mL/min, t_R = 9 min (*S*), t_R = 12 min (*R*).

***dl*-15**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) 4.84 (br t, *J* = 11.9 Hz, 1 H), 4.68 (s, 1/3 H), 4.63 (s, 1/3 H), 4.47 (br t, *J* = 7.5, 1/3 H), 4.17 (q, *J* = 7.0 Hz, 1 H), 4.16 (q, *J* = 7.1 Hz, 1 H), 3.36 (s, 3 H), 1.84-1.51 (m, 4 H), 1.46 (s, 9 H), 1.28 (t, *J* = 7.0 Hz, 3 H), 0.94 (d, *J* = 6.5 Hz, 6 H). IR ($CHCl_3$) 3019, 2960, 1734, 1698 cm^{-1}; MS *m/z* 303 (M^+), 272, 230, 202, 174, 130; Anal. Calcd for $C_{15}H_{29}NO_5$: C, 59.38; H, 9.64; N, 4.62%. Found : C, 59.11; H, 9.68; N, 4.76%.

***N-tert*-Butoxycarbonyl-*N*-methoxymethyl-α-methylleusine ethyl ester (16):**

Optically active **16** (78% ee) was obtained as an inseparable mixture of **16** and **15** according to the General Procedure for Asymmetric α-Methylation. Yield was determined based on the ratio observed in ^{1}H-NMR. Standard sample of racemic **16** was obtained by complete α-methylation of racemic **15**: Racemic **15** was treated with KHMDS followed by methyl iodide according to the General Procedure for Asymmetric α–Methylation. After addition of methyl iodide, the reaction mixture was gradually warmed to room temperature. Purification by column chromatography (SiO_2, ethyl acetate:hexane = 1:10) gave an analytically pure **16**. The ee of **16** was determined after its conversion to the *N*-benzoyl derivative (see below).

***dl*-16**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.01 (d, *J* = 11.0 Hz, 1 H), 4.76 (d, *J* = 11.8 Hz, 2/3 H), 4.65 (d, *J* = 11.8 Hz, 1/3 H), 4.20-4.09 (q, *J* = 6.6 Hz, 2H), 3.36 (s, 3 H), 2.07-1.95 (m, 1 H), 1.61-1.81 (m, 2 H), 1.55 (s, 3H), 1.45 (s, 9 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 0.96-0.89 (m, 6 H). IR ($CHCl_3$) 2985, 2961, 1732, 1693 cm^{-1}. MS *m/z* 317 (M^+), 245, 216, 184, 160; Anal. Calcd for $C_{16}H_{31}NO_5$: C, 60.60; H, 9.78; N, 4.42%. Found : C, 60.44; H, 9.77; N, 4.54%.

A mixture of optically active **16** and **15** (3.4 : 1 ratio, 20 mg) was dissolved in 4 M HCl in ethyl acetate (2 mL) and the solution was stirred at room temperature for 4 h.

After concentration *in vacuo*, the residue was dissolved in dichloromethane (2 mL) and treated with diisopropylethylamine (33 μL, 0.19 mmol), benzoly chloride (16 μL, 0.14 mmol), and DMAP (4 mg, 0.03 mmol) at room temperature for 4 h. Workup followed by purification by preparative TLC (SiO_2, ether:dichlorometane = 1:15) gave *N*-benzoyl-α-methylleusine ethyl ester (12 mg, 82% yield).

(*S*)-*N*-benzoyl-α-methylleusine ethyl ester (78% *ee*) : Pale yellow oil. $[\alpha]_D^{20}$ = +20 (*c* 0.5, $CHCl_3$). HPLC conditions: Daicel Chiralpack AD, 1% *i*-PrOH / hexane, t_R = 17 min (*R*), t_R = 20 min (*S*).

***dl*-*N*-benzoyl-α-methylleusine ethyl ester** : ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.82-7.78 (m, 2 H), 7.52-7.27 (m, 4 H), 427 (q, *J* = 7.0 Hz, 2 H), 2.59 (dd, *J* =14.2, 5.1 Hz, 1 H), 1.85-1.52 (m, 2 H) 1.73 (s, 3 H), 1.33 (t, *J* =7.3 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.82 (d, *J* = 6.5 Hz, 3 H). IR ($CHCl_3$) 3411, 2961, 1721, 1662, 1519 cm^{-1}; MS *m/z* 277 (M^+), 204, 105, ; Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05%. Found : C, 69.25; H, 8.23; N, 4.79%.

(*Z*)-2-(*tert*-Butoxycarbonyl-methoxymethyl)amino-1-ethoxy-3-phenyl-1-silyloxy-1-propene (17) and its *E*-isomer 18:

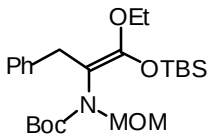
A KHMDS solution in THF (0.50 M, 1.1 mL, 0.55 mmol) was diluted with 3 mL of toluene. A solution of **3** (azeotropically dried with toluene, 0.5 mmol) in toluene (1.5 mL) was added to the KHMDS solution at -78 °C. After stirring for 30 min, *t*-butyldimethylsilyl triflate (0.13 mL, 0.55 mmol) was added and stirring was continued for additional 30 min. The mixture was poured into saturated aq $NaHCO_3$ and extracted with ether. The organic phase was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flush column chromatography (SiO_2, ether:hexane:triethylamine=12:87:1) to give **17** (126 mg, 56% yield) and **18** (60 mg, 27% yield). The geometry of the double bond was determined by a NOESY spectrum (400 MHz, $CDCl_3$, 20 °C) of **17** (see below).

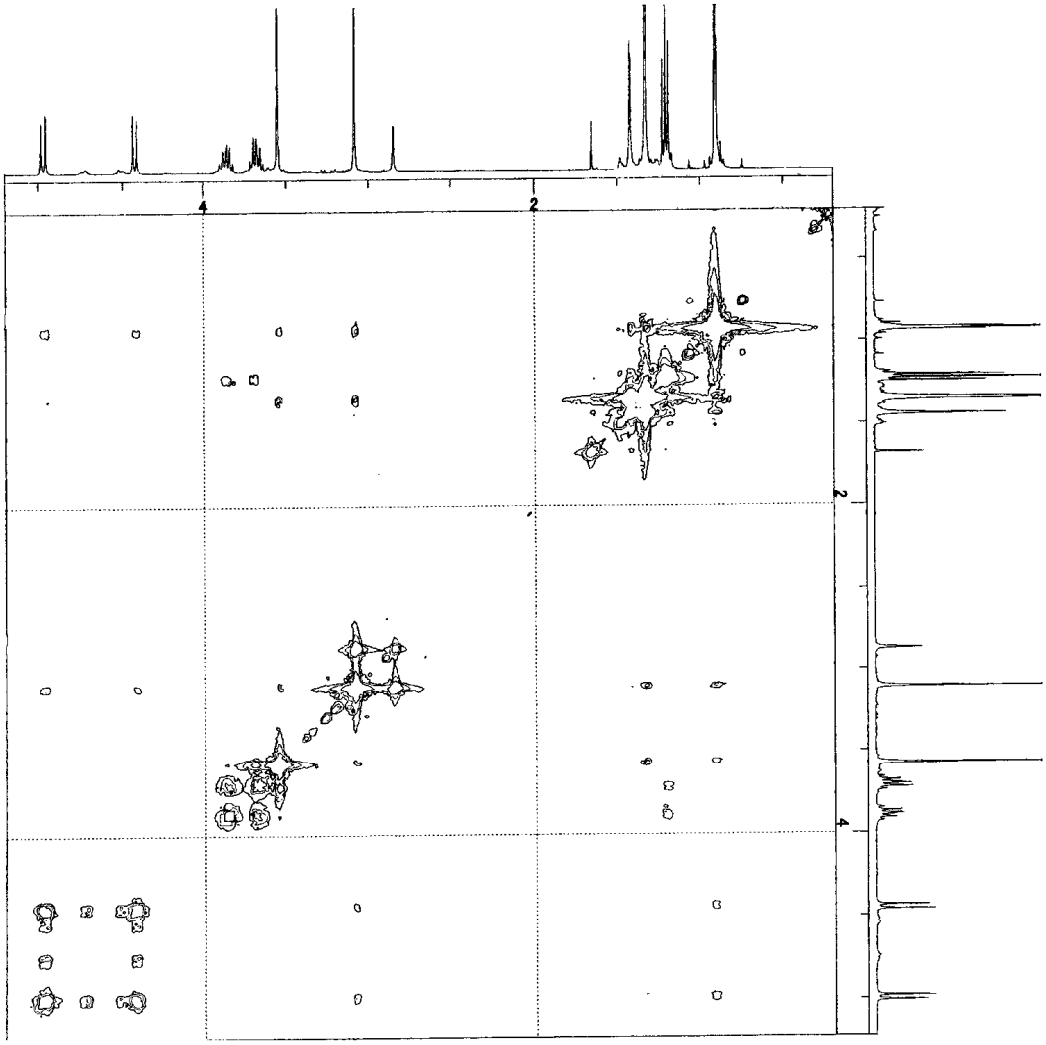
17 : Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.14 (m, 5 H), 4.97 (d, *J* = 10.2 Hz, 4/5 H), 4.73 (br d, *J* = 10.8 Hz, 1/5 H), 4.51 (br d, *J* = 10.8 Hz, 1/5 H), 4.43 (d, *J* = 10.2 Hz, 4/5 H), 3.87 (dq, *J* = 9.5, 7.1 Hz, 1 H), 3.68 (dq, *J* = 9.5, 7.1 Hz, 1 H), 3.56 (s, 2H), 3.03 (s, 3H), 1.43 (s, 9/5 H), 1.34 (s, 36/5 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 0.92 (s, 9 H), 0.18 (s, 3 H), 0.17 (s, 3 H). ^{1}H NMR (400 MHz, d_8-toluene) δ 7.40 (d, *J* = 7.5 Hz, 2 H), 7.20-7.05 (m, 3H), 4.88 (ABq, J_{AB}= 9.9 Hz, $\Delta\nu_{AB}$ = 228.4 Hz, 8/5 H), 4.80-4.60

(br, 2/5 H), 3.86-3.48 (m, 4H), 3.16 (s, 12/5 H), 2.87 (s, 3/5 H), 1.37, 1.33 (two s, ratio = 1:4, 9H), 1.03 (t, *J* = 7.2 Hz, 3 H), 0.93, 0.92 (two s, ratio = 1:4, 9H) 0.16 (s, 3H), 0.13 (s, 3H). IR (neat) 2931, 1704 cm^{-1}; MS *m/z* 451 (M^+), 395, 262, 204, 73. Anal. Calcd for $C_{24}H_{41}NO_5Si$: C, 63.82; H, 9.15; N, 3.10%. Found : C, 63.79; H, 9.27; N, 3.16%.

18: Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.13 (m, 5 H), 4.61 (d, *J* = 10.3 Hz, 1 H), 4.53 (d, *J* = 10.3 Hz, 1 H), 3.89 (br q, *J* = 7.2 Hz, 1 H), 3.83 (br d, *J* = 7.2 Hz, 1 H), 3.55 (d, *J* = 14.4 Hz, 1 H), 3.38 (d, *J* = 14.4 Hz, 1 H), 3.23, 3.05 (two s, ratio = 5:1, 3 H), 1.41, 1.27 (two s, ratio = 1:5, 9 H), 1.22 (t, *J* = 7.2 Hz, 3 H), 0.98, 0.95 (two s, ratio = 5:1, 9 H), 0.24 (s, 6 H). IR (neat) 2932, 1703 cm^{-1}; MS *m/z* 451 (M^+), 395, 262, 204, 73. Anal. Calcd for $C_{24}H_{41}NO_5Si$: C, 63.82; H, 9.15; N, 3.10%. Found : C, 63.82; H, 9.19; N, 3.11%.

NOESY spectrum of **17**





***N, N*-Bis(*tert*-butoxycarbonyl)phenylalanine ethyl ester (19) :**

A mixture of (*S*)-*N*-*tert*-butoxycarbonylphenylalanine ethyl ester (293 mg, 1.0 mmol), DMAP (24 mg, 0.2 mmol), and di-*tert*-butyldicarbonate (436 mg, 1.0 mmol) in acetonitrile (4 mL) was heated under reflux for 1 h. After cooling to room temperature, the mixture was diluted with ethyl acetate and washed with 0.2 M HCl, saturated aq $NaHCO_3$, and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flush column chromatography (SiO_2, ethyl acetate:hexane =2:11) to give **19** (326 mg, 83% yield). The optical purity of **19** was

determined after its conversion to *N*-benzoyl-*N*-methylphenylalanine ethyl ester, see: T. Kawabata, T. Wirth, K. Yahiro, K. Fuji, *J. Am. Chem. Soc.*, **1994**, *116*, 10809.

(*S*)-19 (> 99% *ee*): Colorless oil. $[\alpha]_D^{21} = -79$ (*c* 1.0, $CHCl_3$). HPLC conditions for *N*-benzoyl-*N*-methylphenylalanine ethyl ester: Daicel Chiralpack AS, 3% EtOH / hexane, 1.0 mL/min, t_R = 33 min (*R*), t_R = 37 min (*S*).

***dl*-19**: Colorless needles (*i*-Pr_2O), mp 87-89 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32-7.15 (m, 5 H), 5.13 (dd, *J* = 10.3, 5.0 Hz, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 3.44 (dd, *J* = 14.0, 5.0 Hz, 1 H), 3.21 (dd, *J* = 14.0, 10.3 Hz, 1 H), 1.39 (s, 9 H), 1.28 (t, *J* = 7.2 Hz, 3 H). IR (KBr) 2980, 1755, 1735, 1712, 1367 cm^{-1}; MS *m/z* 393 (M^+), 337, 281, 220, 176; Anal. Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56%. Found : C, 64.06; H, 7.98; N, 3.60%.

***N*, *N*-Bis(*tert*-Butoxycarbonyl)-α-methylphenylalanine ethyl ester (20):**

Ee of **20** was determine after its conversion to *N*-benzoyl-α-methylphenylalanine ethyl ester. HPLC conditions: Daicel Chiralpack AS, 3% *i*-PrOH / hexane, 1.0 mL/min, t_R = 12 min (*R*), t_R = 14 min (*S*).

***dl*-20**: Colorless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31-7.19 (m, 3 H), 7.19-7.15 (m, 2 H), 4.18 (q, *J* = 7.2 Hz, 1 H), 4.17 (q, *J* =7.1 Hz, 1 H), 3.53 (d, *J* = 13.3 Hz, 1 H), 3.10 (d, *J* = 13.3 Hz, 1 H), 1.47 (s, 3 H), 1.42 (s, 9 H), 1.27 (t, *J* = 7.2 Hz, 3 H). IR (neat) 2979, 1746, 1712, 1351 cm^{-1}; MS *m/z* 407 (M^+), 351, 316, 250, 160, 146. Anal. Calcd for $C_{22}H_{33}NO_6$: C, 64.84; H, 8.16; N, 3.44%. Found : C, 64.80; H, 8.18; N, 3.44%.

HPLC conditions for 4-Benzyl-3-*tert*-Butoxycarbonyloxazolidine-5-one (21):

Ee of **21** was determined after its conversion to *N*-benzoyl-*N*-methylphenylalanine ethyl ester: Daicel Chiralpack AS, 3% EtOH / hexane, 1.0 mL/min, t_R = 33 min (*R*), t_R = 37 min (*S*).

4-Benzyl-3-*tert*-Butoxycarbonyl-4-methyloxazolidine-5-one (22):

HPLC conditions: Daicel Chiralpack AD, 2% EtOH / hexane, 1.0 mL/min, t_R = 5.6 min, t_R = 6.3 min.

dl-**4**: Colorless prisms (*i*-Pr_2O), mp 109-111 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35-7.28 (m, 3 H), 7.23-7.08 (m 2 H), 5.08 (d, *J* = 4.0 Hz, 2/5 H), 4.95 (d, *J* = 3.7 Hz, 3/5 H), 4.16 (d, *J* = 4.0 Hz, 2/5 H), 3.97 (d, *J* = 3.7 Hz, 3/5 H), 3.57 (d, *J* = 13.5 Hz, 3/5

H), 3.32 (d, *J* = 13.6 Hz, 2/5 H), 3.04 (d, *J* = 13.5 Hz, 1 H), 1.75 (s, 9/5 H), 1.71 (s, 6/5 H), 1.63 (s, 18/5 H), 1.50 (s, 27/5 H). IR (KBr) 2972, 1789, 1701, 1686, 1413, 1400. MS *m/z* 291(M^+), 200, 91, 57 ; Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81%. Found : C, 65.83; H, 7.26; N, 4.83%.

Experiments of Figure 1:

A KHMDS solution in THF (0.50 M, 0.55 mL, 0.28 mmol) was diluted with 1.5 mL of toluene. A solution of **3** (azeotropically dried with toluene, 85 mg, 0.25 mmol) in toluene (0.75 mL) was added to the KHMDS solution at −78 °C. After stirring for 5 min, methyl iodide (0.16 mL, 2.5 mmol) was added and stirring was continued for 30 min at −78 °C. The mixture was poured into saturated aq NH_4Cl and extracted with ethyl acetate. The organic phase was washed with saturated aq $NaHCO_3$ and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (SiO_2, ethyl acetate:hexane=1:5) to give **4** (80% *ee*, 39% yield). This ee value was employed as ee^0.

Six different batches of enolate solution of **3** were independently prepared by the same procedure as above. Before treating with methyl iodide, the enolate solutions were stirred at -78 °C for 30 min, 1.5 h, 3 h, 7 h, 12 h, and 24 h, respectively. The same workup procedure as above was followed. *Ee*'s and yields of **4** were as follows: 30 min-stirring (79% *ee*, 39% yield), 1.5 h-stirring (76% *ee*, 46% yield), 3 h-stirring (74% *ee*, 46% yield), 7 h-stirring (63% *ee*, 37% yield), 12 h-stirring (56% *ee*, 41% yield), 24 h-stirring (37% *ee*, 35% yield).