

# Supporting Information

## Stereochemical Diversity in Asymmetric Cyclization via Memory of Chirality

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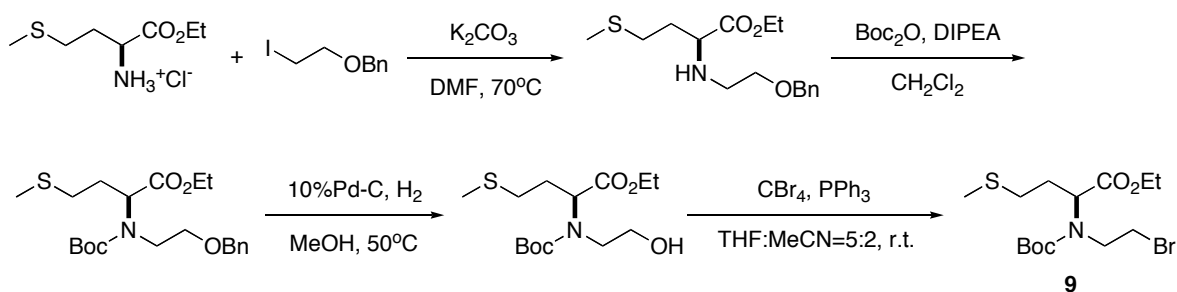
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**RECEIVED DATE (to be automatically inserted after your manuscript is accepted if required according to the journal that you are submitting your paper to)**

Preparation of **1** and the physical data of **2 ~ 8** has been described in Supporting Information of our previous paper (*J. Am. Chem. Soc.*, **2003**, *125*, 13012-13013).

### (*S*)-*N*-(3-Bromoethyl)-*N*-(*tert*-butoxycarbonyl)methionine ethyl ester (**9**)

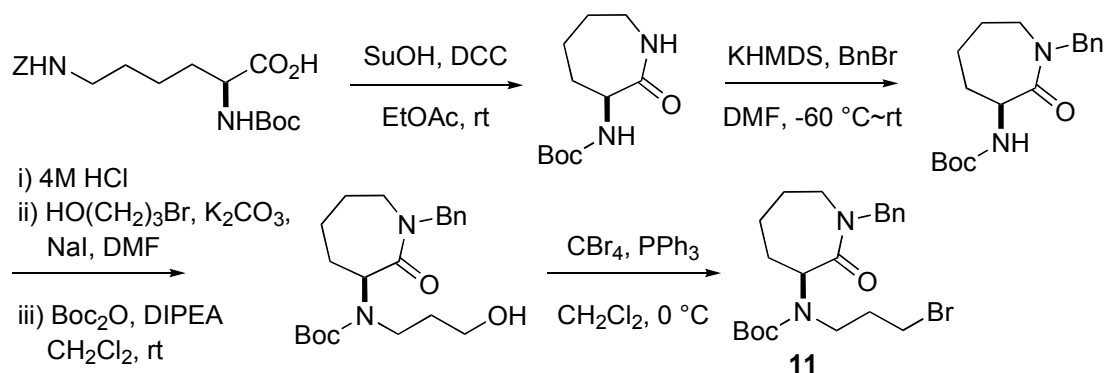


A mixture of methionine ethyl ester hydrochloride (4.0 g, 18.7 mmol),  $K_2CO_3$  (5.2 g, 37.4 mmol), benzyl iodoethyl ether (5.9 g, 22.5 mmol) and DMF (16 mL) was stirred at 70 °C for 2 h. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over  $Na_2SO_4$ , filtered and evaporated *in vacuo*. The residue was purified by column chromatography ( $SiO_2$ , hexane: ethyl acetate=3:1) to give a colorless oil (4.2 g, 69 %). To a solution of this material in dichloromethane (12 mL) were added di-*tert*-butyl dicarbonate (3.54 g, 16.2 mmol) and

diisopropylethylamine (2.6 mL, 14.9 mmol), and the mixture was stirred at room temperature for 24 h. The reaction mixture was poured into saturated aq.  $\text{NH}_4\text{Cl}$  and extracted with dichloromethane. The combined organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated *in vacuo*. The residue was purified by column chromatography ( $\text{SiO}_2$ , hexane: ethyl acetate=5:1) to give a colorless oil (4.5 g, 81 %). This material was dissolved in MeOH (21 mL) and 10% Pd-C (452 mg) was added. The resulting mixture was stirred at under hydrogen atmosphere at  $50^\circ\text{C}$  for 12 h. The reaction mixture was filtered and evaporated *in vacuo*. The residue was purified by column chromatography ( $\text{SiO}_2$ , hexane: ethyl acetate=3:1) to give a colorless oil (3.1 g, 89 %). To a solution of this material in THF (37 mL) were added triphenylphosphine (3.30 g, 12.7 mmol) followed by a solution of carbon tetrabromide (4.2 g, 12.7 mmol) in acetonitrile (14 mL). After stirring for 30 min at room temperature, the reaction mixture was poured into saturated aq.  $\text{NaHCO}_3$  and extracted with dichloromethane. The combined organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated *in vacuo*. The residue was purified by column chromatography ( $\text{SiO}_2$ , hexane:ethyl acetate=10:1) to give **9** (2.60 g, 68 %).

**9**: Colorless oil.  $[\alpha]_{\text{D}}^{21} = -52$  ( $c$  1.0,  $\text{CHCl}_3$ ),  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.39-4.34 (m, 1H), 4.24-4.11 (m, 3H), 3.87-3.79, 3.71-3.66 (two m, ratio=2:1, 1H), 3.59-3.47 (m, 3H), 2.64-2.05 (m, 3H), 2.11 (s, 3H), 1.48, 1.42 (two s, ratio=1:2, 9H), 1.29, 1.27 (two t,  $J=7.1$  Hz, 7.1 Hz, ratio=1:2, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.2, 154.9 and 154.7 (rotamer), 81.3 and 81.1 (rotamer), 62.4 and 61.7 (rotamers), 59.6 and 59.1 (rotamers), 50.7 and 49.8 (rotamers), 30.96 and 30.91 (rotamers), 29.6, 28.92 and 28.86 (rotamers), 28.3 and 28.2 (rotamers), 15.3, 14.2. IR (neat) 2973, 1740, 1702, 1159. MS  $m/z$  (rel intensity) 385 ( $\text{M}^+(\text{}^{81}\text{Br})$ , 10), 383 ( $\text{M}^+(\text{}^{79}\text{Br})$ , 10), 253 (100), 210 (70), 162 (20), 57 (70). HMAS Calcd for  $\text{C}_{14}\text{H}_{26}\text{BrNO}_4\text{S}$ ; 383.0766, Found. 383.0772.

#### ***tert*-butyl (*S*)-1-benzyl-2-oxazepan-3-yl-3-bromopropylcarbamate (**11**)**

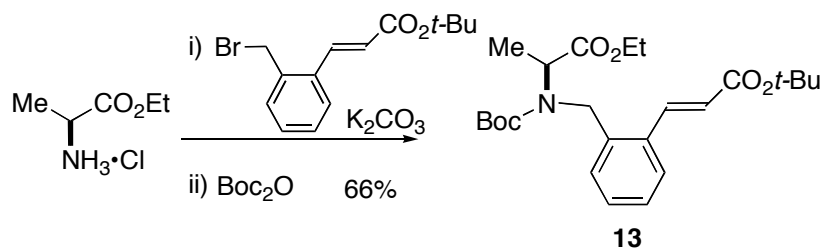


A solution of Boc-Lyz(Z)-OH (10.0 g, 26.3 mmol), *N*-hydroxysuccinimide (3.12 g, 27.1 mmol), and DCC (5.91 g, 28.7 mmol) in ethyl acetate (44 mL) was stirred at room temperature for 5 h. After filtration, the filtrate was concentrated till the volume becomes ca. 10 mL. Ether (90 mL) was added to the residue and the resulting mixture was stirred overnight at room temperature. After filtration, the filtrate was concentrated till the volume becomes ca. 10 mL. *n*-Heptane (90 mL) was added to the residue and the resulting mixture was stirred overnight at room temperature. After filtration, the filtrate was concentrated under the reduced pressure. *n*-Heptane (90 mL) was added again to the residue and the resulting mixture was stirred overnight at room temperature. After filtration, the filtrate was concentrated to dryness. The residue was heated at  $75\sim 80^\circ\text{C}$  *in vacuo* overnight to give white powder (12.7 g). This material was dissolved in ethyl acetate (90 mL), then 10% Pd-C (1.27 g) was added, and the resulting mixture was stirred under hydrogen atmosphere for 8 h. The mixture was filtrated and the filtrate was concentrated *in vacuo*. The residue was purified by  $\text{SiO}_2$  column chromatography (ethyl acetate: hexane

=1:1) to give a lactam (4.40 g, 74%). KHMDS (0.58 M solution in THF, 25.9 mL, 15.0 mmol) was added to a solution of the lactam (4.28g, 18.8 mmol) in DMF (85 mL) at -60 °C. After stirring at -60 °C for 5 min, benzyl bromide (3.34 mL, 28.1 mmol) was added, and the resulting mixture was gradually warmed to room temperature. After stirring at room temperature for 30 min, the mixture was poured into satd. aq. NH<sub>4</sub>Cl and extracted with ether. The combined organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated *in vacuo*. The residue was purified by column chromatography (SiO<sub>2</sub>, hexane : ethyl acetate=10:1) to give a *N*-benzyl lactam (4.47 g, 75 %). 4 M HCl in ethyl acetate (15 mL) was added to the *N*-benzyl lactam (1.68g, 5.28 mmol) and the resulting solution was stirred at room temperature for 1.5 h, and then concentrated *in vacuo*. The residue was dissolved in DMF (26 mL). To the solution were added K<sub>2</sub>CO<sub>3</sub> (1.8 g, 13.2 mmol), NaI (238 mg, 1.58 mmol), and 3-bromopropanol (1.10 g, 7.92 mmol), and the resulting mixture was stirred at 70 °C for 2 h. After filtration, CH<sub>2</sub>Cl<sub>2</sub> (31 mL), di-*tert*-butyl dicarbonate (1.38 g, 6.34 mmol) and diisopropylethylamine (0.81 mL, 5.81 mmol) were added to the filtrate, and the resulting solution was stirred at room temperature for 11 h. The mixture was poured into satd. aq. NH<sub>4</sub>Cl and extracted with ether. The combined organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated *in vacuo*. The residue was purified by column chromatography (SiO<sub>2</sub>, hexane:ethyl acetate=10:1) to give an alcohol (748 mg, 38 %). A solution of the alcohol (512 mg, 1.36 mmol), carbon tetrabromide (588mg, 1.77 mmol), and triphenylphosphine (464 mg, 1.77 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was stirred at 0 °C for 1 h. The mixture was poured into satd. aq. NH<sub>4</sub>Cl and extracted with chloroform. The combined organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated *in vacuo*. The residue was purified by column chromatography (SiO<sub>2</sub>, hexane:ethyl acetate=10:1) to give **11** (459 mg, 77 %).

**11** :  $[\alpha]_D^{20} = +12$  (c 0.56, CHCl<sub>3</sub>), <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  7.36-7.23 (m, 5H), 5.00-4.96(m, 1H), 4.72-4.10 (m, 2H), 3.67-3.17 (m, 6H), 2.50-2.30 (m, 1H), 2.20-1.20 (m, 7H), 1.49 (s, 9H). IR (neat) 2932, 1693, 1657, 1405, 1364, 1150 cm<sup>-1</sup>, MS *m/z* (rel intensity) 440 (<sup>81</sup>Br, M<sup>+</sup>, 10), 438 (<sup>79</sup>Br, M<sup>+</sup>, 10), 257 (15), 203 (80), 91 (100), 57 (50). HRMS calcd for C<sub>21</sub>H<sub>31</sub>N<sub>2</sub>O<sub>3</sub><sup>81</sup>Br; 440.1498, found 440.1501. C<sub>21</sub>H<sub>31</sub>N<sub>2</sub>O<sub>3</sub><sup>79</sup>Br; 438.1538, found 438.1529.

**(*S*)-*N*-*tert*-Butoxycarbonyl-*N*-2-(2-*tert*-butoxycarbonylviny)phenylmethyl alanine ethyl ester (**13**):**



A mixture of alanine ethyl ester hydrochloride (153 mg, 1.0 mmol), K<sub>2</sub>CO<sub>3</sub>, (345 mg, 2.5 mmol), 2-bromomethyl *t*-butylcinnamate (446 mg, 1.5 mmol) and DMF (10 mL) was stirred at room temperature for 6 h. The mixture was poured onto ice and then extracted with ether. The combined organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The residual liquid was passed through a short pad of silica gel with elution with hexane/AcOEt (10/1, *R<sub>f</sub>* = 0.3). To a solution of the residue in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) were added Boc<sub>2</sub>O (262 mg, 1.20 mmol) and DIPEA (106  $\mu$ L, 1.10 mmol). The mixture was stirred at room temperature for 40 h. The solution was quenched with cold water and extract with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and

concentrated under reduced pressure. The residual oil was loaded on a silica gel column and eluted with hexane/AcOEt (15/1,  $R_f$  = 0.3) to afford **13** (286 mg, 66% yield).

**13**: viscous oil.  $[\alpha]_D^{20}$  -1.8 (c 1.00,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 2978, 2934, 1741, 1702, 1367, 1320, 1151  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR (400 MHz, toluene- $d_8$ , 90 °C) 8.08 (d,  $J$  = 16.0 Hz, 1H), 7.29 (d,  $J$  = 8.0 Hz, 1H), 7.23 (d,  $J$  = 7.6 Hz, 1H), 7.05–6.90 (m, 2H), 6.25 (d,  $J$  = 16.0 Hz, 1H), 4.58, 4.53 (two ABq,  $\Delta\nu_{AB}$  = 37.7, 31.0 Hz,  $J_{AB}$  = 15.6, 16.0 Hz, ratio = 3:1, 2H), 3.89–3.95 (m, 3H), 1.45 (s, 9H), 1.38 (s, 9H), 1.23 (d,  $J$  = 7.2 Hz, 3H), 1.00 (t,  $J$  = 7.2 Hz, 3H); MS ( $m/z$ ) 433 ( $\text{M}^+$ );  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ) 172.1 and 172.0 (rotamers), 165.9, 155.4 and 154.9 (rotamers), 140.3 and 140.0 (rotamers), 137.6 and 136.7 (rotamers), 133.7 and 132.7 (rotamers), 129.6, 129.0 and 127.7 (rotamers), 127.3 and 127.2 (rotamers), 126.8, 122.4, 80.9 and 80.5 (rotamers), 80.7, 61.1, 55.1 and 54.8 (rotamers), 48.4 and 47.2 (rotamers), 28.2, 15.5 and 15.1 (rotamers), 14.2; HRMS ( $m/z$ ) Calcd. for  $\text{C}_{24}\text{H}_{35}\text{NO}_6$  ( $\text{M}^+$ ) 433.2464, found 433.2449.

## General Procedure for Enantiodivergent Cyclization (Table 2).

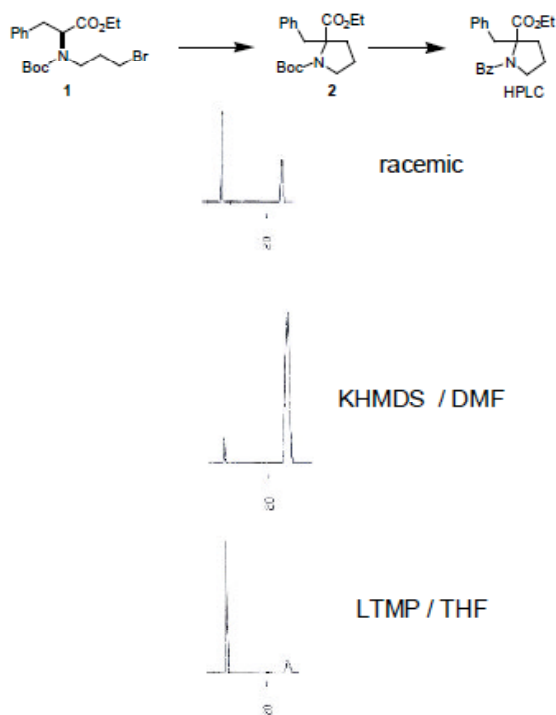
### A: Asymmetric Cyclization with retention of Configuration (entries 1, 3, 5, 7, and 9).

Potassium hexamethyldisilazide (KHMDs)\* (0.50 M THF solution, 0.48 mL, 0.24 mmol) was added to a solution of substrate (0.20 mmol) in dry DMF (2.0 mL) at -60 °C. After stirring for 30 min, the reaction mixture was poured into saturated aq  $\text{NH}_4\text{Cl}$  and extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC. *Ee*'s of **2**, **4**, **6**, **8**, and **10** were determined after their conversion to the corresponding *N*-benzoates.

\* Brown, C. A. *J. Org. Chem.* **1974**, 39, 3913.

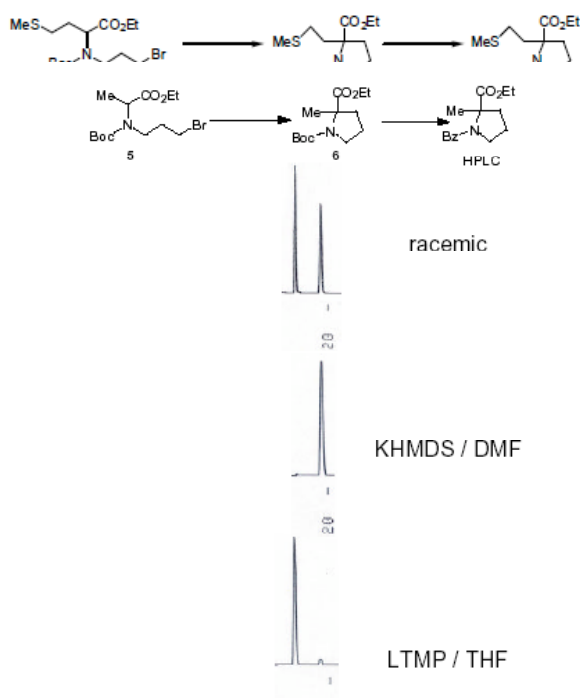
### B: Asymmetric Cyclization with inversion of Configuration (entries 2, 4, 6, 8, and 10).

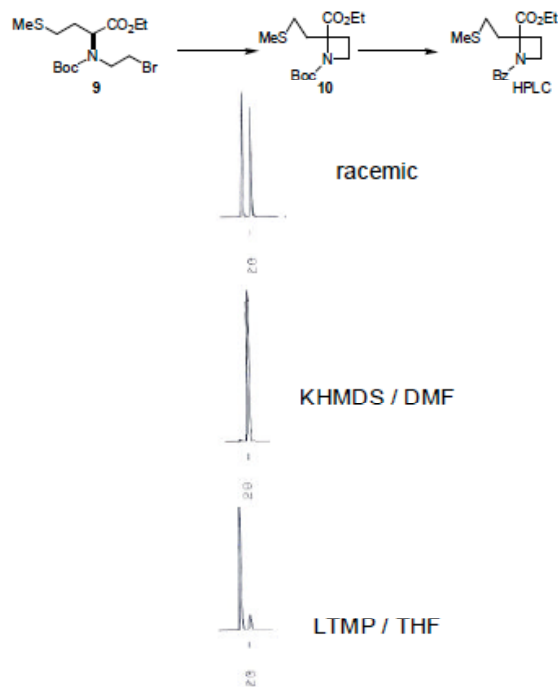
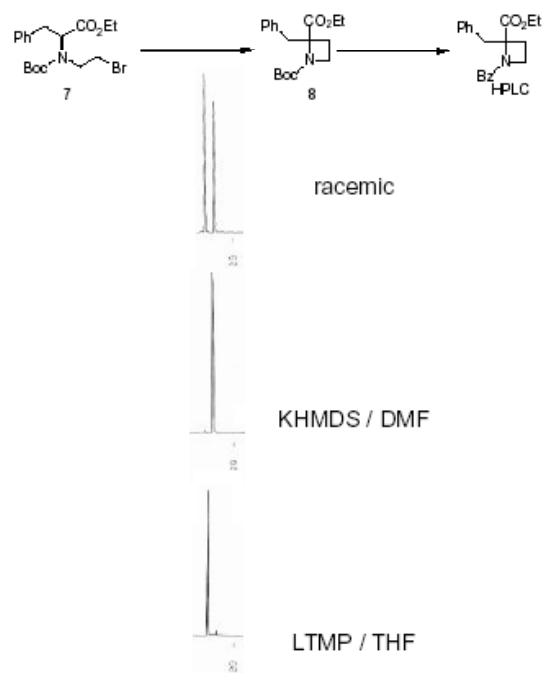
A LTMP solution (0.40 M) was prepared by adding *n*-BuLi (1.52 M in hexane, 0.79 mL, 1.2 mmol) to a stirred solution of TMP (0.20 mL 1.2 mmol) in dry THF (2.0 mL) at 0 °C. The LTMP solution (0.40 M in THF, 0.60 mL, 0.24 mL) was added to a stirred solution of substrate (0.2 mmol) in THF (2.0 mL) at



HPLC conditions (*N*-benzoate derived from **2**): Daicel Chialcel OD, hexane:2-propanol=90:10, flow: 1.0 mL/min,  $t_R$  = 8 (*R*), 27 (*S*) min.

the indicated temperature in Table 2. The reaction mixture was poured into aq  $\text{NH}_4\text{Cl}$  and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC. Ee's of **2**, **4**, **6**, **8**, and **10** were determined after their conversion to the corresponding *N*-benzoates.



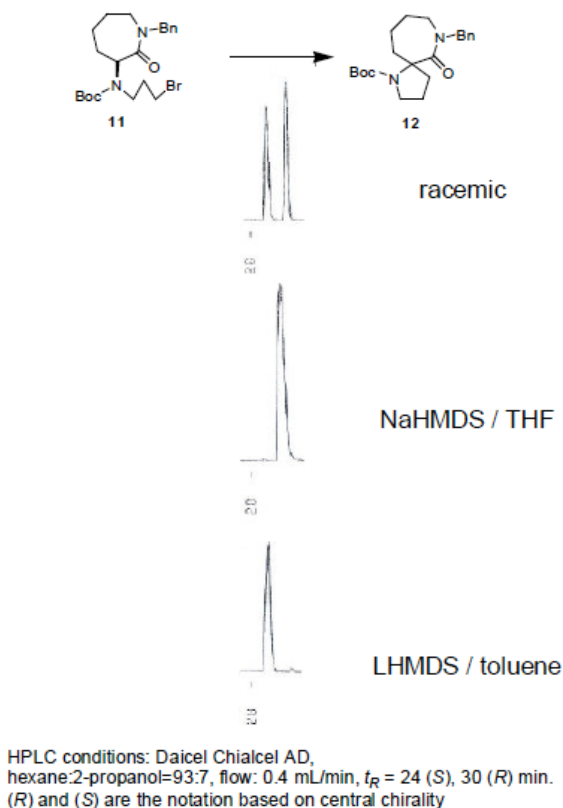


### Transformation of **11** to (*R*)-**12**:

A solution of sodium hexamethyldisilazide (NaHMDS) (1.90 M in THF, 0.19 mL, 0.36 mmol) was added to a solution of **11** (78 mg, 0.18 mmol) in THF (1.4 mL) at 20 °C. After stirring for 30 min, the reaction mixture was poured into saturated aq NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (ethyl acetate:hexane=1:2) to give (*R*)-**12** (46 mg, 72%) in 99% ee.

### Transformation of **11** to (*S*)-**12**:

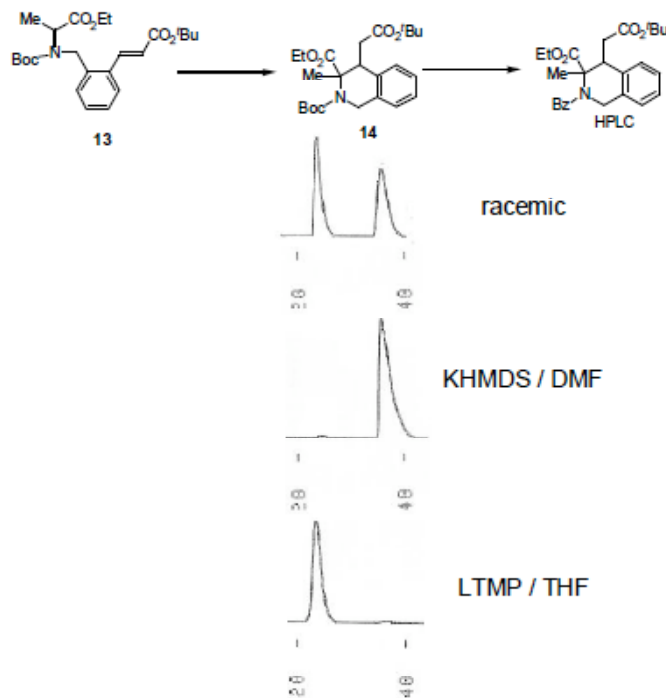
A solution of lithium hexamethyldisilazide (LHMDS) (0.57 M in toluene, 0.61 mL, 0.35 mmol) was added to a solution of **11** (77 mg, 0.18 mmol) in toluene (1.1 mL) at 0 °C. After stirring for 5 h, the reaction mixture was poured into saturated aq NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (ethyl acetate:hexane=1:2) to give (*S*)-**12** (41 mg, 66%) in 94% ee.



### Transformation of **13** to **14**:

A KHMDS solution (0.56 M in THF, 0.98 mL, 0.55 mmol) was diluted with THF-DMF (1:1, 3.5 mL) and cooled to -78 °C. A solution of **13** (216 mg, 0.50 mmol) in THF-DMF (1:1, 1.5 mL) was added to

the solution of KHMDS in THF-DMF over 5 min at  $-78\text{ }^{\circ}\text{C}$ . After 30 min stirring, the reaction mixture was quenched with  $\text{NH}_4\text{Cl}$  and extracted with AcOEt. The combined organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated in *vacuo*. The residual oil was purified by preparative TLC with hexane/AcOEt (5/1,  $R_f = 0.3$ ) to give **14** (204mg, 94%) as a single diastereomer. Ee of **14** was determined after its conversion to *N*-benzoate to be 95% ee.



HPLC conditions (*N*-benzoate derived from **14**): Daicel Chialcel OD, hexane:2-propanol=99:1, flow: 1.5 mL/min,  $t_R = 25, 35$  min.

### Transformation of **13** to *ent*-**14**:

A solution of **13** (43 mg, 0.10 mmol) in THF (0.50 mL) was added to a solution of LTMP (0.24 M in THF, 0.50 mL, 0.12 mmol) over 5 min at  $0^{\circ}\text{C}$ . After 5 min stirring, the reaction mixture was quenched with  $\text{NH}_4\text{Cl}$  and extracted with AcOEt. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated in *vacuo*. The residual oil was purified by preparative TLC (hexane/AcOEt = 5/1,  $R_f = 0.3$ ) to give *ent*-**14** (27mg, 62%) as a single diastereomer. Ee of *ent*-**14** was determined after its conversion to *N*-benzoate to be 91% ee.

### 1-*tert*-Butyl 2-ethyl 2-{2-(methylthio)ethyl}azetidine-1,2-dicarboxylate (**10**)

Colorless oil. HPLC conditions (*N*-benzoate derived from **10**): Daicel Chialcel OD, hexane:2-propanol=95:5, flow: 1.0 mL/min,  $t_R = 18$  (*R*), 21 (*S*) min.  $[\alpha]_D^{21}$  (*S*, 99% ee) =  $-8.5$  ( $c$  1.0,  $\text{CHCl}_3$ ),  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.31-4.16 (m, 2H), 4.03-3.92 (m, 1H), 3.77-3.72 (m, 1H), 2.70 (td,  $J=5.1$  Hz, 12.7 Hz, 1H), 2.59 (td,  $J=4.4$  Hz, 12.7 Hz, 1H), 2.28-2.15 (m, 4H), 2.15 (s, 3H), 1.44, 1.41 (two s,



ratio=1:3, 9H), 1.32 (t,  $J=7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.1, 155.4 and 155.3 (rotamer), 80.2 and 79.8 (rotamer), 70.5 and 70.2 (rotamer), 61.4, 46.5 and 45.0 (rotamer), 35.6 and 34.9 (rotamer), 28.8 and 28.6 (rotamer), 28.4, 25.7 and 25.2 (rotamer), 15.6, 14.2. IR (neat) 2975, 1738, 1707, 1369, 1151. MS  $m/z$  (rel intensity) 303 ( $\text{M}^+$ , 10), 247 (10), 203 (10), 173 (100), 157 (50), 130 (40), 127 (40), 82 (10), 57 (30). HRMS Calcd for  $\text{C}_{14}\text{H}_{25}\text{NO}_4\text{S}$ ; 303.1504, Found, 303.1498. Anal. Calcd for  $\text{C}_{14}\text{H}_{25}\text{NO}_4\text{S}$ : C, 55.42; H, 8.30; N, 4.62 %. Found: C, 55.34; H, 8.30; N, 4.64 %.

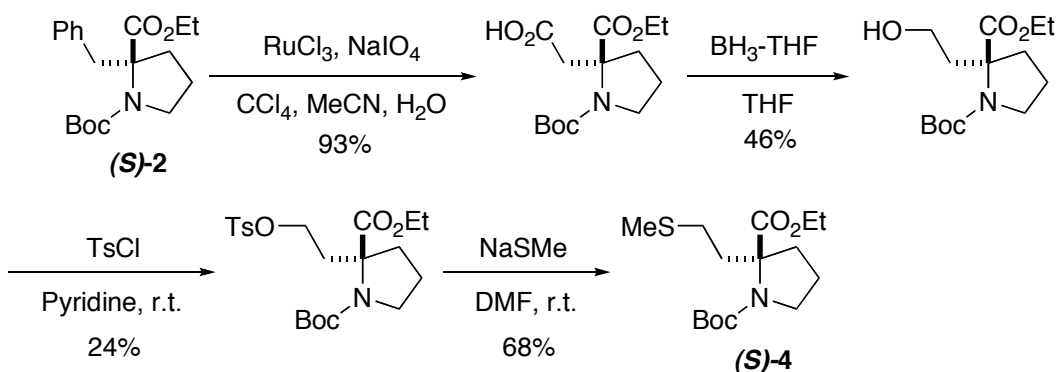
#### 7-Benzyl-1-*tert*-butoxycarbonyl-1,7-diaza-spiro[4,6]undec-6-one (12):

HPLC condition; Dical Chiralpak AD, hexane : 2-propanol=93:7, flow: 0.4 mL/min,  $t_R$  = 24 (*S*), 30 (*R*) min.  $[\alpha]_{\text{D}}^{20}$  (*R*, 97% ee) = +39 ( $c$  0.9,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29-7.25 (m, 5H), 4.63, 4.61 (ABq and s,  $\Delta\nu_{\text{AB}}$  = 133.2 Hz,  $J_{\text{AB}}$  = 14.6 Hz, ratio = 2:1, 2H), 3.80-3.17 (m, 4H), 2.84-1.40 (m, 10H), 1.49, 1.45 (two s, ratio=2:1, 9H). IR (neat) 2971, 1685, 1637, 1388, 1168  $\text{cm}^{-1}$ . MS  $m/z$  (rel intensity) 358 ( $\text{M}^+$ , 70), 285 (30), 257 (80), 167 (70), 110 (50), 91 (100), 57 (50). HRMS Calcd for  $\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_3$ : 358.2256, found, 358.2267.

#### 4-*tert*-Butoxycarbonylmethyl-3-methyl-3,4-dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-*tert*-butyl ester 3-ethyl ester (14):

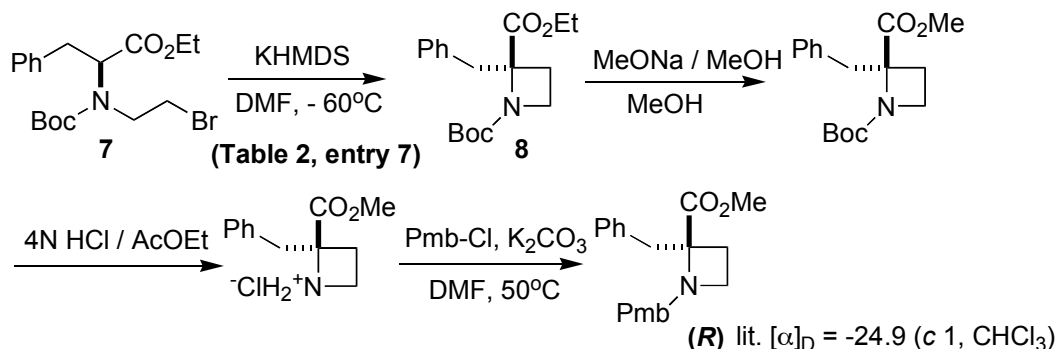
HPLC condition (*N*-benzoate derived from **14**); Dical Chiralcel OD, hexane : 2-propanol=99:1, flow: 1.5 mL/min,  $t_R$  = 25, 35 min.  $[\alpha]_{\text{D}}^{20}$  (95% ee) = +66 ( $c$  1.2,  $\text{CHCl}_3$ , 95% ee determined after benzylation); IR ( $\text{CHCl}_3$ ) 2950, 1737, 1696, 1387, 1151  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ ) 7.15–7.30 (m, 4H), 5.03–3.90 (m, 4H), 3.65, 3.37 (two dd,  $J$  = 10.8, 2.6 Hz, 10.8, 4.4 Hz, ratio = 4:1, 1H), 2.75 (dd,  $J$  = 10.8, 16.4 Hz, 1H), 2.39-2.54 (m, 1H), 1.43 (br s, 18H), 1.29 (br t,  $J$  = 7.2 Hz, 3H), 1.08 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.8, 171.0, 154.1, 136.7 and 136.3 (rotamers), 135.4 and 135.1 (rotamers), 127.6, 127.4, 126.3, 124.4, 81.1 and 80.9 (rotamers), 77.2, 64.5 and 63.6 (rotamers), 61.3 and 60.9 (rotamers), 45.8 and 44.4 (rotamers), 42.3 and 41.6 (rotamers), 33.4, 28.4, 28.0, 18.5 and 17.6 (rotamers), 14.2 and 14.0 (rotamers); MS  $m/z$  (rel intensity) 433 ( $\text{M}^+$ , 1), 360 (20), 332 (30), 276 (60), 248 (90), 204 (100), 144 (40); HRMS ( $m/z$ ) Calcd. for  $\text{C}_{24}\text{H}_{35}\text{NO}_6$  ( $\text{M}^+$ ) 433.2464, found 433.2449.

#### Determination of the Absolute Configuration of 4:



The absolute configuration of **2** has already been determined (Kawabata, T.; Kawakami, S.; Swapan, M. *J. Am. Chem. Soc.*, **2003**, 125, 13012-13013). (*S*)-**2** (98% ee) was transformed into (*S*)-**4** according to the following scheme. (*S*)-**4** thus obtained showed the optical rotation,  $[\alpha]_{\text{D}}^{21}$  = -25 ( $c$  1.1,  $\text{CHCl}_3$ ). On the other hand, **4** (97% ee) obtained by the reaction with  $\text{KHMDS}/\text{DMF}/-60^\circ\text{C}$  (entry 3 in Table2) showed the optical rotation,  $[\alpha]_{\text{D}}^{21}$  -26 ( $c$  0.9,  $\text{CHCl}_3$ ).

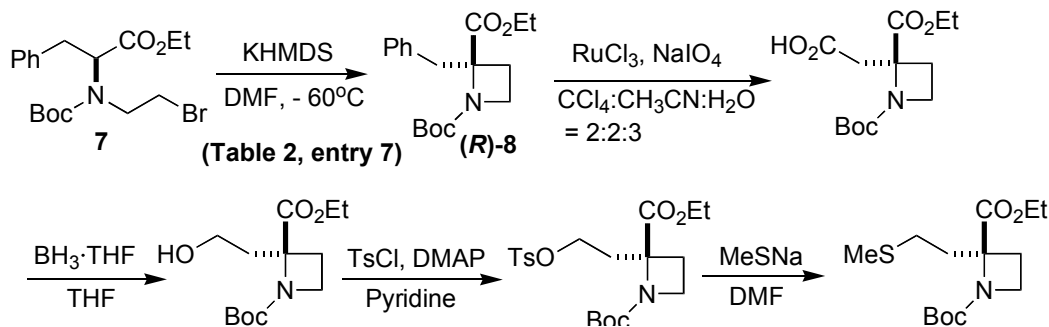
### Determination of the Absolute Configuration of 8:



Compound **8** (704 mg, 2.21 mmol, 97% ee) obtained by the reaction of Table 2, entry 7 was dissolved in MeOH (20 mL). Sodium methoxide (28% MeOH solution, 641 mg, 3.32 mmol) was added to the solution and the resulting mixture was stirred at room temperature for 13 h. The reaction mixture was poured onto saturated aq  $\text{NH}_4\text{Cl}$  and extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The residue was purified by column chromatography ( $\text{SiO}_2$ , EtOAc:hexane=1:2) to give a methyl ester (608 mg, 90% yield). A solution of the methyl ester (583 mg) in 4 M HCl in EtOAc (20 mL) was stirred at room temperature for 2 h. The reaction mixture was evaporated *in vacuo*, and residual solids were washed with  $\text{Et}_2\text{O}$  to give an azetidine hydrochloride (403 mg, 87% yield). A mixture of the azetidine hydrochloride (200 mg, 0.83 mmol),  $\text{K}_2\text{CO}_3$  (343 mg, 2.48 mmol), 4-methoxybenzyl chloride (225  $\mu\text{L}$ , 1.66 mmol) and DMF (2 mL) was stirred at 50  $^\circ\text{C}$  for 10 h. The reaction mixture was quenched with saturated aq  $\text{NH}_4\text{Cl}$  and extracted with  $\text{Et}_2\text{O}$ . The organic phase was washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC ( $\text{SiO}_2$ , EtOAc:hexane=1:5) to give a *N*-Pmb azetidine derivative (150 mg, 56% yield) whose spectral data and optical rotation ( $[\alpha]_D^{20} = -24.7$  ( $c$  2.6,  $\text{CHCl}_3$ )) were identical with those reported for (*R*)-methyl 1-(4-methoxybenzyl)-2-benzylazetidine-2-carboxylate (lit\*  $[\alpha]_D = -24.9$  ( $c$  1,  $\text{CHCl}_3$ )).

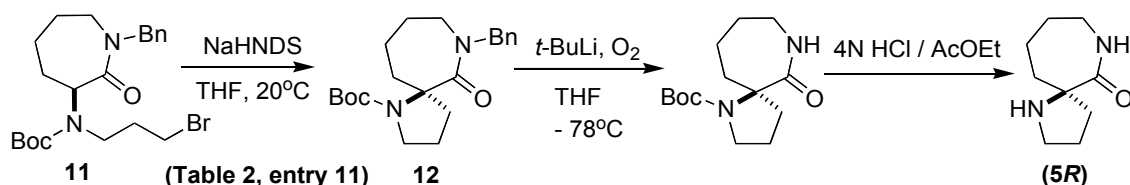
\*C. Cativiela, R. González-Muñiz, *et al.*, *Tetrahedron Lett.*, **2004**, 45, 2193-2196

### Determination of the Absolute Configuration of 10:



To a solution of (*R*)-**8** (380 mg, 1.19 mmol, 95% ee, product of entry 7 in Table 2) in CCl<sub>4</sub> (2.4 mL), CH<sub>3</sub>CN (2.4 mL), and H<sub>2</sub>O (3.6 mL) were added NaIO<sub>4</sub> (3.82 g, 17.9 mmol) followed by RuCl<sub>3</sub>·*n*H<sub>2</sub>O (5.4 mg, ~0.026 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 5 min and then at room temperature for 15 h. After cooling at 0 °C, *i*-PrOH was added to the mixture. The mixture was passed through a short pad of SiO<sub>2</sub> and washed with EtOAc. The combined filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC (AcOEt : hexane = 1:1) to give a carboxylic acid (135 mg, 40% yield). A solution of BH<sub>3</sub>·THF (1.03 M in THF, 0.46 mL, 0.47 mmol) was added to a solution of the carboxylic acid (135 mg, 0.47 mmol) in THF (2.1 mL) at – 18 °C. After stirring at – 18 °C for 10 h, the mixture was warmed to room temperature and stirred for additional 26 h. The mixture was quenched with satd. aqueous NaHCO<sub>3</sub> and extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (SiO<sub>2</sub>, EtOAc:hexane=1:1) to give an alcohol (96 mg, 75% yield). A solution of the alcohol (96 mg, 0.35 mmol), *p*-toluenesulfonyl chloride (188mg, 0.99 mmol), DMAP (8 mg) in Pyridine (3.5 mL) was stirred at 0 °C then at room temperature for additional 19 h. The mixture was quenched with water and extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (SiO<sub>2</sub>, EtOAc : hexane = 1:1) to give a tosylate (106mg, 69% yield). Sodium methanethiolate (15% aq. solution, 112 mg, 0.24 mmol) was added to a solution of the tosylate (106 mg, 0.24 mmol) in DMF (2.4 mL) at room temperature. After stirring for 30 min, the mixture was quenched with satd. aqueous NH<sub>4</sub>Cl and extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (SiO<sub>2</sub>, EtOAc : hexane = 1:2) to give (*S*)-**10** (41 mg, 56% yield).  $[\alpha]_D^{20} = -8.0$  (*c* 2.0, CHCl<sub>3</sub>). Compound **10** obtained by the reaction of entry 9 in Table 2 was determined to have *S* configuration because it showed the optical rotation,  $[\alpha]_D^{21} = -8.5$  (*c* 1.0, CHCl<sub>3</sub>).

### Determination of the Absolute Configuration of **12**:



*t*-BuLi (1.46 M solution in pentane, 0.49 mL, 0.72 mmol) was added dropwise to a solution of **12** obtained by the reaction of entry 11 in Table 2 (128mg, 0.36 mmol, 99% ee) in THF (3.3 mL) cooled to – 78 °C. After stirring for 5 min, a stream of dry oxygen was introduced into the solution for 10 min. A few drops of Me<sub>2</sub>S, 80 mg of NH<sub>4</sub>Cl, a drop of water were successively added. The resulting mixture was allowed to warm to room temperature. After filtration, the mixture was concentrated under reduced pressure and the residue was purified by preparative TLC (SiO<sub>2</sub>, EtOAc : hexane = 1:1) to give an oily material (49 mg). 4 M HCl in EtOAc (15 mL) was added to this residue, and the resulting solution was stirred at room temperature for 1.5 h. The reaction mixture was concentrated *in vacuo*. Saturated aq NaHCO<sub>3</sub> was added to the residue and it was extracted with EtOAc. The organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (SiO<sub>2</sub>, CHCl<sub>3</sub>:MeOH:Et<sub>3</sub>N=100:10:1) to give 1,7-diaza-spiro[4,6]undec-6-one (30 mg, 96% yield).  $[\alpha]_D^{20} = 58$  (*c* 1.2, CHCl<sub>3</sub>) [lit\*  $[\alpha]_D^{25} = -45.9$  (*c* 1.36, CHCl<sub>3</sub>) for (*S*)-isomer].

\*P. Ahlberg, *et al.*, *Tetrahedron Asymmetry* **2005**, 16, 2075-2080.