Enantio- and Diastereoselective, Stereospecific Mannich-type Reactions in Water

Tomoaki Hamada, Kei Manabe, and Shū Kobayashi*

Graduate School of Pharmaceutical Sciences, The University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

Supporting Information

Table of Contents	Pages
Experimental	S-1
Typical Experimental Procedures for the Mannich-type Reactions	S-1
Crystallization of $[\text{ZnCl}_2\text{-1b}\cdot\text{CH}_2\text{Cl}_2]$ complexes	S-4
Determination of the relative configuration of Mannich adduct 5	S-4
Determination of the absolute and relative configurations of Mannich adduct 9	S-7
References	S-13
Ortep drawing of $[\text{ZnCl}_2\text{-1b}\cdot\text{CH}_2\text{Cl}_2]$	S-14
Ortep drawing of 8	S-15

Experimental

General: Melting points were uncorrected. CDCl_3 was used as a solvent for ^1H and ^{13}C NMR spectra unless otherwise noted. Tetramethylsilane (TMS) served as an internal standard ($\delta = 0$) for ^1H NMR and CDCl_3 as an internal standard ($\delta = 77.0$) for ^{13}C NMR. In the case using dimethylsulfoxide- d_6 ($\text{DMSO-}d_6$) as a solvent, the methyl peak of DMSO was served as an internal standard (2.49 ppm in ^1H NMR, 39.5 ppm in ^{13}C NMR). Preparative thin-layer chromatography was carried out using Wakogel B-5F. ZnF_2 was purchased from Soekawa Rikagaku Co., LTD. (1*R*,2*R*)-(+)-1,2-Diphenyl-1,2-ethanediamine was purchased from Kanto Kagaku CO., LTD.

A Typical Experimental Procedure for the Mannich-type Reactions with

Acetophenone-derived Silyl Enol Ether in Water: To a mixture of **1c** (0.0430 mmol) and ZnF_2 (0.430 mmol) in H_2O (2.33 mL) was added a 0.0936 M solution of NaOTf (0.00430 mmol) in H_2O , **2** (0.430 mmol), and acetophenone-derived silyl enol ether (1.29 mmol), and the mixture was stirred vigorously (~1400 rpm) at 0 °C. After 20 h, the reaction was quenched with saturated aqueous NaHCO_3 . The resultant mixture was extracted with dichloromethane (3 times), and the combined organic layers were dried over anhydrous Na_2SO_4 . The solvent was evaporated, and the residue was purified by preparative TLC (silica gel, chloroform/MeOH (39/1), and then hexane/ethyl acetate (1/1)) to give the Mannich adduct (92% yield). The enantiomeric excess of the product was determined by HPLC analysis (96% ee). The spectral data of the product were previously reported.¹

A Typical Experimental Procedure for the Mannich-type Reactions with Propiophenone-derived Silyl Enol Ether in Water: To a mixture of ZnF_2 (0.400 mmol) and **1b** (0.0400 mmol) in H_2O (1.95 mL) was added a 0.0716 M solution of CTAB (0.0200 mmol) in H_2O , **2** (0.400 mmol), and propiophenone-derived silyl enol ether (1.20 mmol), and the mixture was stirred vigorously (~1400 rpm) at 0 °C. After 20 h, the reaction was quenched with saturated aqueous NaHCO_3 . The resultant mixture was extracted with dichloromethane (3 times), and the combined organic layers were dried over anhydrous Na_2SO_4 . The solvent was evaporated, and the residue was purified by preparative TLC (silica gel, hexane/ethyl acetate (2/1), twice) to give the Mannich adduct (94% yield, *syn/anti* = 94/6). The enantiomeric excess of the product was determined by HPLC analysis (97% ee). The spectral data of the product were previously reported.¹

Ethyl 2-(*N'*-benzoylhydrazino)-3-ethyl-4-oxo-4-phenylbutyrate: Diastereomeric ratio of the product was determined from the ratio of integration of each peak on ^1H NMR analysis.

Syn. (*syn/anti* = 99/1, >99.5% ee (*syn*)): mp: 88–91 °C; $[\alpha]_D^{27} +13.2$ (*c* 2.72, CHCl_3); IR (KBr) 3269, 1732, 1682, 1628, 1551, 1194, 706 cm^{-1} ; ^1H NMR (CDCl_3): δ 0.97 (t, 3H, *J* = 7.3 Hz), 1.20 (t, 3H, *J* = 7.1 Hz), 1.75–1.90 (m, 2H), 3.93 (ddd, 1H, *J* = 6.9,

6.9, 7.6 Hz), 4.04 (d, 1H, $J = 7.6$ Hz), 4.08-4.23 (m, 2H), 5.09 (brs, 1H), 7.35-7.51 (m, 5H), 7.53-7.59 (m, 1H), 7.71 (d, 2H, $J = 7.3$ Hz), 7.96 (d, 2H, $J = 7.6$ Hz), 8.20 (s, 1H) ppm; ^{13}C NMR (CDCl_3): δ 11.6, 14.0, 22.7, 48.9, 61.4, 64.8, 126.9, 128.3, 128.5, 128.7, 131.7, 132.6, 133.3, 137.2, 166.6, 172.5, 202.1 ppm; HRMS (FAB) calcd for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$): 369.1814, found: 369.1834; **Anti**: ^1H NMR (CDCl_3): δ 0.93 (t, 3H, $J = 7.3$ Hz), 1.25 (t, 3H, $J = 7.1$ Hz), 1.78-1.92 (m, 1H), 2.01-2.16 (m, 1H), 3.99 (ddd, 1H, $J = 5.0, 5.1, 7.8$ Hz), 4.07 (d, 1H, $J = 5.0$ Hz), 4.17-4.28 (m, 2H), 4.96 (brs, 1H), 7.35-7.57 (m, 6H), 7.62-7.68 (m, 2H), 7.93-8.01 (m, 3H) ppm; ^{13}C NMR (CDCl_3): δ 11.9, 14.0, 21.7, 48.7, 61.5, 63.5, 126.8, 128.4, 128.5, 128.7, 131.8, 132.4, 133.3, 136.5, 166.8, 171.8, 201.7 ppm; HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 4/1, flow rate = 0.70 mL/min) *Syn*: $t_{\text{R}} = 18.3$ min (major), $t_{\text{R}} = 29.4$ min (minor). *Anti*: $t_{\text{R}} = 20.2$ min, $t_{\text{R}} = 25.2$ min.

Ethyl 2-(*N'*-benzoylhydrazino)-3-methyl-4-oxohexanoate: Diastereomeric ratio of the product was determined from the ratio of integration of the 2-methine proton on ^1H NMR analysis.

Syn. (*syn/anti* = 98.5/1.5, >99.5% ee (*syn*)): mp: 117-119 °C; $[\alpha]_{\text{D}}^{25} +8.3$ (*c* 0.25, CHCl_3); IR (KBr) 3251, 1730, 1711, 1626, 1556, 1452, 1205, 694 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.06 (t, 3H, $J = 7.2$ Hz), 1.23 (d, 3H, $J = 7.2$ Hz), 1.26 (t, 3H, $J = 7.2$ Hz), 2.43-2.66 (m, 2H), 3.08 (dq, 1H, $J = 7.2, 7.2$ Hz), 3.87 (d, 1H, $J = 7.2$ Hz), 4.12-4.30 (m, 2H), 4.84 (brs, 1H), 7.37-7.56 (m, 3H), 7.70-7.79 (m, 2H), 8.08 (s, 1H) ppm; ^{13}C NMR (CDCl_3): δ 7.6, 13.5, 14.1, 34.7, 47.1, 61.3, 65.5, 126.9, 128.6, 131.8, 132.6, 166.7, 172.0, 212.2 ppm; HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$): 329.1477, found: 329.1460; **Anti**: ^1H NMR (CDCl_3): δ 1.04 (t, 3H, $J = 7.2$ Hz), 1.25 (d, 3H, $J = 7.2$ Hz), 1.26 (t, 3H, $J = 7.2$ Hz), 2.48-2.70 (m, 2H), 3.11 (dq, 1H, $J = 4.9, 7.2$ Hz), 3.98 (dd, 1H, $J = 4.5, 4.9$ Hz), 4.10-4.29 (m, 2H), 5.35 (dd, 1H, $J = 4.5, 5.5$ Hz), 7.36-7.54 (m, 3H), 7.70-7.78 (m, 2H), 8.18 (brd, 1H, $J = 5.5$ Hz) ppm; ^{13}C NMR (CDCl_3): δ 7.5, 12.4, 14.0, 34.3, 46.9, 61.3, 64.0, 126.8, 128.5, 131.7, 132.4, 166.9, 171.7, 212.3 ppm; HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 9/1, flow rate = 0.80 mL/min) *Syn*: $t_{\text{R}} = 23.9$ min (minor), $t_{\text{R}} = 33.7$ min (major). *Anti*: $t_{\text{R}} = 26.7$ min (minor), $t_{\text{R}} = 44.3$ min (major).

Ethyl 2 - (*N'*-benzoylhydrazino)-4-*tert*-butylthio-3-methyl-4-oxobutanoate:

Diastereomeric ratio of the product was determined from the ratio of integration of the 2-methine proton on ^1H NMR analysis.

Syn: ^1H NMR (CDCl_3): δ 1.28 (t, 3H, $J = 7.2$ Hz), 1.31 (d, 3H, $J = 7.1$ Hz), 1.44 (s, 9H), 3.12 (dq, 1H, $J = 4.3, 7.1$ Hz), 4.00 (dd, 1H, $J = 3.7, 4.3$ Hz), 4.15-4.29 (m, 2H), 5.50 (dd, 1H, $J = 3.7, 6.3$ Hz), 7.38-7.44 (m, 2H), 7.46-7.52 (m, 1H), 7.71-7.77 (m, 2H), 8.08 (brd, 1H, $J = 6.3$ Hz) ppm; ^{13}C NMR (CDCl_3): δ 13.2, 14.0, 29.6, 48.3, 49.5, 61.4, 64.5, 126.9, 128.5, 131.7, 132.5, 166.7, 171.1, 201.8 ppm; **Anti:** IR (neat) (*syn/anti* = 8/92): 3292, 2966, 1738, 1680, 1456, 1211, 964, 696 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.27 (t, 3H, $J = 7.1$ Hz), 1.29 (d, 3H, $J = 7.1$ Hz), 1.47 (s, 9H), 3.10 (dq, 1H, $J = 6.8, 7.1$ Hz), 3.85 (dd, 1H, $J = 6.2, 6.8$ Hz), 4.09-4.35 (m, 2H), 5.32 (dd, 1H, $J = 5.4, 6.2$ Hz), 7.39-7.56 (m, 3H), 7.70-7.79 (m, 2H), 7.94 (brd, 1H, $J = 5.4$ Hz) ppm; ^{13}C NMR (CDCl_3): δ 14.1, 14.5, 29.7, 48.4, 49.4, 61.4, 65.9, 126.9, 128.6, 131.8, 132.6, 166.9, 171.4, 201.4 ppm; HRMS (FAB) calcd for $\text{C}_{18}\text{H}_{27}\text{N}_2\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$): 367.1692, found: 367.1671; HPLC (Daicel Chiralpak AD-H (double), hexane/*i*-PrOH = 4/1, flow rate = 0.50 mL/min) *Syn*: t_R = 34.8 min (minor), t_R = 41.4 min (major). *Anti*: t_R = 28.8 min (minor), t_R = 33.1 min (major).

Crystallization of $[\text{ZnCl}_2\text{-1b}\cdot\text{CH}_2\text{Cl}_2]$ complexes

Crystallization of $[\text{ZnCl}_2\text{-1b}\cdot\text{CH}_2\text{Cl}_2]$ was carried out as follows: To a suspension of ZnCl_2 (0.039 mmol) in CH_2Cl_2 (0.81 mL) was added a solution of **1b** (0.032 mmol) in CH_2Cl_2 (0.81 mL), and the mixture was stirred for 16 h at rt. The resulting clear solution was filtered, and the filtrate was allowed to stand at 5 $^\circ\text{C}$ under hexane vapor to give the colorless crystals.

Determination of the relative configuration of Mannich adduct **5**

The relative configuration of **5** obtained in Table 3, entry 1 was determined to be *syn* by the X-ray analysis, after conversion to lactone **8** (eq. 1). Mannich adduct **5** was used after increasing both the diastereo- and enantiomerically excess by one recrystallization (*syn/anti* = 98.5/1.5, >99.5% ee (*syn*)).

6: To a solution of **5** (0.103 mmol) in 1,4-dioxane (0.18 mL) were added a solution of *i*-Pr₂NEt (0.144 mmol) and di-*tert*-butyl dicarbonate (0.129 mmol) in 1,4-dioxane (1.50 mL) and 4-(dimethylamino)pyridine (0.012 mmol) at rt. After stirring for 13 h, a solution of *i*-Pr₂NEt (0.149 mmol) and di-*tert*-butyl dicarbonate (0.132 mmol) in 1,4-dioxane (1.20 mL) was added to the mixture. After stirring for 2 h, the reaction was quenched with water. The resultant mixture was extracted with CH₂Cl₂ (3 times), and the combined organic layers were dried over anhydrous Na₂SO₄. The solvents were evaporated, and the residue was purified by preparative TLC (silica gel, hexane/ethyl acetate (3/1)) to give **6** (87% yield).

[α]_D²⁴ −60.0 (*c* 1.49, CHCl₃); IR (neat): 3325, 2979, 1716, 1477, 1369, 1277, 1153, 756 cm^{−1}; ¹H NMR (DMSO-*d*₆, 110 °C): δ 0.92 (t, 3H, *J* = 7.2 Hz), 1.10 (d, 3H, *J* = 7.3 Hz), 1.21 (t, 3H, *J* = 7.1 Hz), 1.39 (s, 9H), 2.53 (q, 2H, *J* = 7.2 Hz), 3.12 (dq, 1H, *J* = 7.2, 7.5 Hz), 4.13 (q, 2H, *J* = 7.1 Hz), 5.02 (d, 1H, *J* = 7.5 Hz), 7.43–7.50 (m, 2H), 7.51–7.59 (m, 1H), 7.76–7.82 (m, 2H), 9.76 (s, 1H) ppm; ¹³C NMR (DMSO-*d*₆, 110 °C): δ 6.8, 12.7, 13.2, 27.3, 32.5, 44.5, 60.0, 61.1, 80.4, 126.9, 127.7, 131.0, 132.4, 153.3, 166.4, 168.1, 209.0 ppm; HRMS (FAB) calcd for C₂₁H₃₁N₂O₆ ([M+H]⁺): 407.2182, found: 407.2193.

7: NaBH₄ (0.410 mmol) was added to a solution of **6** (0.0900 mmol) in EtOH (3.4 mL) at rt. After stirring for 40 min at rt, the reaction was quenched with water (10 mL). The resultant mixture was extracted with ethyl acetate (30 mL, 3 times), and the combined organic layers were dried over anhydrous Na₂SO₄. The solvents were

evaporated, and the residue was purified by preparative TLC (silica gel, hexane/ethyl acetate (3/1)) to give **7** (80% yield, 3,4-*cis*/3,4-*trans* = 78/22). Diastereomeric ratio of the product was determined from the ratio of integration of the methyl proton at C3 on ¹H NMR analysis.

IR (KBr): 3307, 2978, 1780, 1712, 1365, 1302, 1147, 960 cm⁻¹; ¹H NMR (DMSO-*d*₆, 70 °C) 3,4-*Cis* isomer: δ 0.92 (t, 3H, *J* = 7.3 Hz), 1.13 (d, 3H, *J* = 7.0 Hz), 1.37 (s, 9H), 1.45-1.57 (m, 1H), 1.57-1.66 (m, 1H), 2.70-2.84 (m, 1H), 4.44 (ddd, 1H, *J* = 3.7, 8.2, 10.1 Hz), 4.48-4.64 (m, 1H), 7.43-7.49 (m, 2H), 7.52-7.58 (m, 1H), 7.76-7.86 (m, 2H), 10.38 (brs, 1H) ppm; Detectable peaks of 3,4-*trans* isomer: δ 1.18 (d, 3H, *J* = 6.4 Hz), 1.69-1.79 (m, 1H), 3.96-4.06 (m, 1H) ppm; ¹³C NMR (DMSO-*d*₆, 70 °C) Detectable peaks of 3,4-*cis* isomer: δ 10.1, 12.3, 22.9, 27.7, 82.1, 127.5, 128.3, 131.8, 132.3, 172.3 ppm; HRMS (FAB) calcd for C₁₉H₂₇N₂O₅ ([M+H]⁺): 363.1920, found: 363.1909.

8: A 0.1 M solution of SmI₂ in THF (3.8 mL, 0.38 mmol) was added to a degassed solution of **7** (0.0720 mmol) in MeOH (0.77 mL) at 0 °C. After stirring for 30 min, the reaction was quenched with water. The resultant mixture was extracted with ethyl acetate (3 times), and the combined organic layers were dried over anhydrous Na₂SO₄. The solvents were evaporated, and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate (3/1)) to give **8** (94% yield, 3,4-*cis*/3,4-*trans* = 77/23). Diastereomeric ratio of the product was determined from the ratio of integration of the 4-methine proton on ¹H NMR analysis.

¹H NMR (CDCl₃, 45 °C) 3,4-*Cis* isomer: δ 1.05 (t, 3H, *J* = 7.4 Hz), 1.17 (d, 3H, *J* = 7.0 Hz), 1.46 (s, 9H), 1.41-1.64 (m, 1H), 1.68 (ddq, 1H, *J* = 3.4, 7.4, 14.7 Hz), 2.48-2.58 (m, 1H), 4.05-4.22 (m, 1H), 4.40 (ddd, 1H, *J* = 3.4, 7.7, 10.7 Hz), 4.83 (brs, 1H) ppm; Detectable peaks of 3,4-*trans* isomer: δ 1.21 (d, 3H, *J* = 6.4 Hz), 1.82 (ddq, 1H, *J* = 3.5, 7.4, 14.8 Hz), 2.00-2.12 (m, 1H), 3.89-3.95 (m, 1H), 4.89 (brs, 1H) ppm.

The almost pure 3,4-*cis*-**8** was obtained from one recrystallization (EtOH-hexane) to yield 6.9 mg (39% yield) of colorless needles suitable for X-ray analysis. mp: 121-123 °C; [α]_D²⁶ -84.7 (*c* 0.32, CHCl₃); IR (KBr) 3373, 2976, 1784, 1695, 1529, 1373, 1342, 1294, 1167 cm⁻¹; ¹H NMR (CDCl₃): δ 1.06 (t, 3H, *J* = 7.3 Hz), 1.17 (d, 3H, *J* = 6.8 Hz), 1.46 (s, 9H), 1.42-1.58 (m, 1H), 1.68 (ddq, 1H, *J* = 3.3, 7.3, 14.6 Hz), 2.46-2.60 (m, 1H), 4.10-4.25 (m, 1H), 4.41 (ddd, 1H, *J* = 3.3, 7.8, 10.9 Hz), 4.82 (brs, 1H) ppm; ¹³C NMR (CDCl₃): δ 10.4, 12.5, 23.3, 28.2, 40.8, 55.1, 80.5, 82.7,

155.7, 174.9 ppm; HRMS (ESI-TOF) calcd for C₁₂H₂₁NO₄Na ([M+Na]⁺): 266.1368, found: 266.1354.

Determination of the absolute and relative configurations of Mannich adduct **9**

The relative configuration of **9** obtained in the reaction with **4Z** was determined to be *syn*, comparing ¹H NMR spectrum of **10** with the reported one² (eq. 2).

On the other hand, the absolute configurations of **9** obtained in the reactions with both **4E** and **4Z** were determined to be (2*R*)-form, comparing the retention time of HPLC charts of **12** with those of (2*R*,3*S*)-**12** and (2*R*,3*R*)-**12** obtained via Rapoport-type aspartate alkylation³ of **13**⁴ (eq. 2, 3).

In eq. 2, N-N bond cleavage mediated by SmI₂ (25 min) gave low yield (18% yield). However, another set of the reactions (15 min) from **9** (syn/anti = 97/3, 87% ee (*syn*), 27% ee (*anti*)) gave **10** (syn/anti = 96/4, 87% ee (*syn*), 9% ee (*anti*)) in 45% yield.

Ethyl 2-(N'-benzoyl-N-tert-butoxycarbonylhydrazino)-4-tert-butylthio-3-methyl-4-oxobutanoate: To a solution of **9** (syn/anti = 92/8, 62% ee (*syn*), 56% ee (*anti*))

(0.473 mmol) in 1,4-dioxane (0.85 mL) were added a solution of *i*-Pr₂NEt (1.73 mmol) in 1,4-dioxane (2.3 mL), a solution of di-*tert*-butyl dicarbonate (1.69 mmol) in 1,4-dioxane (2.3 mL), and 4-(dimethylamino)pyridine (0.142 mmol) at rt. After stirring for 13 h, a solution of *i*-Pr₂NEt (0.687 mmol) and di-*tert*-butyl dicarbonate (0.672 mmol) in 1,4-dioxane (2.3 mL) was added to the mixture. After stirring for 1 h, the reaction was quenched with water. The resultant mixture was extracted with CH₂Cl₂ (3 times), and the combined organic layers were dried over anhydrous Na₂SO₄. The solvents were evaporated, and the residue was purified by preparative TLC (silica gel, hexane/ethyl acetate (4/1)) to give the desired compound (52% yield). IR (neat) 3313, 2974, 1721, 1468, 1375, 1281, 1164, 1026, 974, 723 cm⁻¹; ¹H NMR (DMSO-*d*₆, 110 °C) *Syn* isomer: δ 1.19 (t, 3H, *J* = 7.2 Hz), 1.32 (d, 3H, *J* = 7.0 Hz), 1.40 (s, 9H), 1.42 (s, 9H), 3.12 (dq, 1H, *J* = 7.0, 9.8 Hz), 4.01-4.16 (m, 2H), 4.88 (brd, 1H, *J* = 9.8 Hz), 7.42-7.51 (m, 2H), 7.53-7.60 (m, 1H), 7.71-7.84 (m, 2H), 9.89 (s, 1H) ppm; Detectable peaks of *anti* isomer: δ 5.00 (brd, 1H, *J* = 7.0 Hz), 9.72 (s, 1H) ppm; ¹³C NMR (DMSO-*d*₆, 110 °C): δ 13.1, 15.5, 27.3, 29.0, 47.1, 47.5, 60.2, 64.2, 80.6, 127.0, 127.7, 131.0, 132.5, 153.3, 166.4, 167.4, 201.0 ppm; HRMS (FAB) calcd for C₂₃H₃₅N₂O₆S ([M+H]⁺): 467.2216, found: 467.2233.

10: A 0.1 M solution of SmI₂ in THF (8.2 mL, 0.82 mmol) was added to a degassed solution of ethyl 2-(*N'*-benzoyl-*N*-*tert*-butoxycarbonylhydrazino)-4-*tert*-butylthio-3-methyl-4-oxobutanoate (0.247 mmol) in EtOH (2.62 mL) at -10 °C. After stirring for 25 min, the reaction was quenched with water. The resultant mixture was extracted with CH₂Cl₂ (5 times), and the combined organic layers were dried over anhydrous Na₂SO₄. The solvents were evaporated, and the residue was purified by preparative TLC (silica gel, hexane/ethyl acetate (4/1)) to give **10** (18% yield).

Diastereomeric ratio of the product was determined from the ratio of integration of the amide proton on ¹H NMR analysis (*syn/anti* = 73/27). The enantiomeric excess of the product was determined by HPLC analysis (62% ee (*syn*), 49% ee (*anti*)).

¹H NMR (CDCl₃) *Syn* isomer: δ 1.21 (d, 3H, *J* = 6.9 Hz), 1.29 (t, 3H, *J* = 7.2 Hz), 1.44 (s, 9H), 1.46 (s, 9H), 3.07 (dq, 1H, *J* = 4.9, 6.9 Hz), 4.21 (q, 2H, *J* = 7.2 Hz), 4.57 (dd, 1H, *J* = 4.9, 8.5 Hz), 5.21 (brd, 1H, *J* = 8.5 Hz) ppm; Detectable peaks of *anti* isomer: δ 5.49 (brd, 1H, *J* = 10.0 Hz) ppm; HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 19/1, flow rate = 1.0 mL/min) *Syn*: *t*_R = 11.1 min (minor), *t*_R = 14.6 min (major). *Anti*: *t*_R = 7.3 min (major), *t*_R = 9.0 min (minor).

11: This compound was prepared according to the known method from methyl 2-*tert*-butoxycarbonylamino-4-*tert*-butylthio-3-methyl-4-oxobutanoate² (73% yield). Diastereomeric ratio of the product was determined from the ratio of integration of the methyl proton on ¹H NMR analysis (CDCl₃) (*syn/anti* = 76/24).

12: To a solution of **11** (0.032 mmol) in CH₂Cl₂ (0.22 mL) were added a solution of benzoyl chloride (0.128 mmol) in CH₂Cl₂ (0.42 mL) and pyridine (0.33 mmol) at rt. After stirring for 18 h, the reaction was quenched with water. The resultant mixture was extracted with CH₂Cl₂ (twice), and the combined organic layers were washed with brine, and dried over anhydrous Na₂SO₄. The solvent was evaporated, and the residue was purified by preparative TLC (silica gel, hexane/ethyl acetate (3/1)) to give **12** (86% yield). Diastereomeric ratio of the product was determined from the ratio of integration of the methyl proton on ¹H NMR analysis (CDCl₃) (*syn/anti* = 76/24). The enantiomeric excess of the product was determined by HPLC analysis (62% ee (*syn*), 49% ee (*anti*)).

14: (2*R*,3*S*)-**14** and (2*R*,3*R*)-**14** were prepared according to the known method.⁴ (2*R*,3*S*)-**14**.⁴ ¹H NMR (CDCl₃): δ 0.61 (d, 3H, *J* = 7.1 Hz), 2.57 (dq, 1H, *J* = 7.1, 11.2 Hz), 2.89 (s, 3H), 3.53 (s, 3H), 3.79 (d, 1H, *J* = 11.2 Hz), 4.35 (d, 1H, *J* = 14.3 Hz), 4.69 (d, 1H, *J* = 14.3 Hz), 7.10-7.36 (m, 9H), 7.40 (t, 1H, *J* = 7.4 Hz), 7.52-7.77 (m, 7H), 7.96-8.02 (m, 1H) ppm; ¹³C NMR (CDCl₃): δ 15.8, 40.9, 50.6, 50.9, 51.3, 62.6, 80.4, 119.3, 119.9, 126.7, 126.7, 127.3, 127.4, 127.5, 127.5, 127.7, 127.9, 128.1, 128.2, 128.5, 129.2, 139.2, 141.5, 142.3, 144.4, 144.7, 147.3, 171.3, 174.3 ppm.

(2*R*,3*R*)-**14**.⁴ ¹H NMR (CDCl₃): δ 1.14 (d, 3H, *J* = 7.2 Hz), 2.27 (dq, 1H, *J* = 7.2, 11.6 Hz), 2.95 (s, 3H), 3.34 (s, 3H), 3.54 (d, 1H, *J* = 11.6 Hz), 4.16 (d, 1H, *J* = 13.5 Hz), 4.40 (d, 1H, *J* = 13.5 Hz), 7.17-7.38 (m, 10H), 7.43 (t, 1H, *J* = 7.4 Hz), 7.52-7.90 (m, 7H) ppm; ¹³C NMR (CDCl₃): δ 15.3, 40.8, 51.1, 51.4, 52.7, 62.2, 80.0, 120.2, 120.2, 126.4, 126.8, 126.8, 127.2, 127.4, 127.5, 127.6, 127.9, 128.4, 128.5, 129.7, 139.8, 140.1, 141.8, 144.8, 145.5, 147.1, 171.9, 175.5 ppm.

15: (2*R*,3*S*)-**15** was prepared according to the known method.⁵ (2*R*,3*R*)-**15** was prepared according to a modified procedure of the known method⁵.

(2*R*,3*S*)-**15**.⁵ ¹H NMR (CDCl₃): δ 0.52 (d, 3H, *J* = 7.1 Hz), 1.50-1.61 (m, 1H), 1.83 (brs, 2H), 2.58-2.66 (m, 1H), 2.85 (dd, 1H, *J* = 5.4, 10.5 Hz), 3.04 (dd, 1H, *J* = 6.6, 11.0 Hz), 3.13 (dd, 1H, *J* = 4.6, 10.5 Hz), 3.25 (dd, 1H, *J* = 6.0, 11.0 Hz), 4.16 (d, 1H, *J* = 15.0 Hz), 4.28 (d, 1H, *J* = 15.0 Hz), 7.16-7.48 (m, 10H), 7.50-7.62 (m, 2H), 7.64-7.82 (m, 6H) ppm; ¹³C NMR (CDCl₃): δ 12.9, 36.8, 51.2, 61.6, 61.9, 67.8, 80.2, 120.2, 120.3, 126.3, 126.8, 127.0, 127.0, 127.5, 127.5, 127.9, 128.1, 128.2, 128.4, 128.6, 128.6, 139.9, 140.7, 141.2, 143.7, 147.6, 148.1 ppm.

(2*R*,3*R*)-**15**: To a solution of (2*R*,3*R*)-**14** (0.225 mmol) in THF (3.88 mL) was added LiAlH₄ (0.788 mmol) at 0 °C. The reaction mixture was stirred for 5 min at 0 °C, and stirred for 8 h at rt. The reaction was quenched with water (0.20 mL), and stirred for 2 h at rt. To the mixture was added 15% aqueous NaOH (0.10 mL). After stirring for 44 h at rt, the resultant mixture was filtered. After washing with THF and ethyl acetate, the filtrate was concentrated, and the residue was purified by preparative TLC (silica gel, hexane/ethyl acetate (1/1)) to give (2*R*,3*R*)-**15** (79% yield).

mp: 91–97 °C; [α]_D²⁷ +266.2 (*c* 0.39, ethyl acetate); IR (KBr): 3375, 2939, 1448, 1032, 739, 700 cm⁻¹; ¹H NMR (CDCl₃): δ 0.78 (d, 3H, *J* = 6.8 Hz), 1.11-1.22 (m, 1H),

2.30 (ddd, 1H, $J = 3.2, 5.6, 9.0$ Hz), 2.45 (brs, 2H), 2.90 (dd, 1H, $J = 5.6, 11.2$ Hz), 3.09 (dd, 1H, $J = 3.2, 11.2$ Hz), 3.16 (d, 2H, $J = 4.4$ Hz), 4.09 (d, 1H, $J = 13.9$ Hz), 4.26 (d, 1H, $J = 13.9$ Hz), 7.17-7.45 (m, 10H), 7.52-7.85 (m, 8H) ppm; ^{13}C NMR (CDCl_3): δ 17.0, 37.8, 51.8, 63.0, 63.4, 65.9, 79.9, 119.8, 120.4, 126.8, 126.9, 127.1, 127.3, 127.4, 127.9, 128.2, 128.3, 128.5, 128.8, 139.8, 140.7, 141.2, 144.3, 147.2, 148.2 ppm; HRMS (FAB) calcd for $\text{C}_{31}\text{H}_{32}\text{NO}_2$ ($[\text{M}+\text{H}]^+$): 450.2433, found: 450.2441.

11: These compounds were prepared according to a modified procedure of the known method.⁵ To a solution of (2*R*,3*S*)-**15** (0.206 mmol) in MeOH (3.45 mL) was added 5% Pd-C (wet) (48.4 mg). The reaction mixture was stirred for 11 h under H_2 (11 atm) at 40°C. The resultant mixture was filtered, and washed with MeOH thoroughly. The filtrate was evaporated, and the residue was filtered. After washing with *i*-PrNH₂, the filtrate was evaporated. The residue was dissolved in *i*-PrOH, and the insoluble materials were filtered out. After the filtrate was concentrated, *i*-PrOH (1.82 mL) was added. To the solution was added a solution of di-*tert*-butyl dicarbonate (0.417 mmol) in *i*-PrOH (1.82 mL). After stirring for 38 h at rt, the reaction mixture was concentrated, and the residue was purified by column chromatography (silica gel, ethyl acetate) to give (2*R*,3*S*)-**11** (70% yield).

(**2*R*,3*S*)-11**).⁵ $[\alpha]_{\text{D}}^{27} +12.6$ (*c* 0.15, CHCl_3). (lit⁶; $[\alpha]_{\text{D}}^{20} -10.4$ (*c* 1, CHCl_3) ((2*S*,3*R*)-**11**)); IR (neat): 3415, 2947, 1687, 1522, 1379, 1257, 1169, 1063 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.04 (d, 3H, $J = 7.1$ Hz), 1.46 (s, 9H), 1.72-1.85 (m, 1H), 2.44 (brs, 2H), 3.49 (dd, 1H, $J = 4.0, 11.6$ Hz), 3.61 (dddd, 1H, $J = 4.0, 4.6, 8.1, 8.1$ Hz), 3.67-3.82 (m, 3H), 5.22 (brd, 1H, $J = 4.6$ Hz) ppm; ^1H NMR (CDCl_3 , 45 °C): δ 1.03 (d, 3H, $J = 7.1$ Hz), 1.45 (s, 9H), 1.73-1.85 (m, 1H), 2.21 (brs, 2H), 3.50 (dd, 1H, $J = 4.5, 11.6$ Hz), 3.57-3.65 (m, 1H), 3.70 (dd, 1H, $J = 3.3, 11.6$ Hz), 3.75 (d, 2H, $J = 4.2$ Hz), 5.13 (brs, 1H) ppm; ^{13}C NMR (CDCl_3 , 45 °C): δ 14.8, 28.4, 37.2, 54.3, 63.9, 64.6, 79.9, 157.1 ppm; HRMS (ESI-TOF) calcd for $\text{C}_{10}\text{H}_{21}\text{NNaO}_4$ ($[\text{M}+\text{Na}]^+$): 242.1368, found: 242.1359.

(**2*R*,3*R*)-11**). $[\alpha]_{\text{D}}^{26} -8.4$ (*c* 0.68, CHCl_3); IR (neat): 3361, 2976, 1687, 1525, 1367, 1261, 1165, 1032 cm^{-1} ; ^1H NMR (CDCl_3): δ 0.83 (d, 3H, $J = 6.8$ Hz), 1.45 (s, 9H), 1.91-2.03 (m, 1H), 2.75 (brs, 2H), 3.32-3.43 (m, 1H), 3.44-3.89 (m, 4H), 4.97 (brd, 1H, $J = 8.5$ Hz) ppm; ^1H NMR (CDCl_3 , 45 °C): δ 0.85 (d, 3H, $J = 6.8$ Hz), 1.45 (s, 9H), 1.89-2.02 (m, 1H), 2.79 (brs, 2H), 3.40 (dd, 1H, $J = 8.9, 11.2$ Hz), 3.56 (dd, 1H, $J = 4.1, 11.2$ Hz), 3.65 (dd, 1H, $J = 4.8, 11.3$ Hz), 3.71 (dd, 1H, $J = 5.2, 11.3$ Hz),

3.74-3.86 (m, 1H), 4.95 (brs, 1H) ppm; ^{13}C NMR (CDCl_3 , 45 °C): δ 11.8, 28.4, 37.5, 53.3, 63.3, 64.5, 80.0, 157.0 ppm; HRMS (ESI-TOF) calcd for $\text{C}_{10}\text{H}_{21}\text{NNaO}_4$ ($[\text{M}+\text{Na}]^+$): 242.1368, found: 242.1372.

12: These compounds were prepared in a similar manner to that described in eq. 2.

(2R,3S)-12. $[\alpha]_{\text{D}}^{27} +28.3$ (*c* 1.54, CHCl_3); IR (neat): 3363, 2976, 1722, 1522, 1281, 1173, 1115, 714 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.18 (d, 3H, $J = 6.8$ Hz), 1.39 (s, 9H), 2.22-2.34 (m, 1H), 4.07-4.18 (m, 1H), 4.31 (dd, 1H, $J = 5.7, 11.3$ Hz), 4.35-4.56 (m, 3H), 4.92 (brd, 1H, $J = 9.8$ Hz), 7.39-7.47 (m, 4H), 7.53-7.60 (m, 2H), 8.01-8.09 (m, 4H) ppm; ^1H NMR ($\text{DMSO}-d_6$, 80 °C): δ 1.09 (d, 3H, $J = 6.8$ Hz), 1.32 (s, 9H), 2.16-2.29 (m, 1H), 3.91-4.01 (m, 1H), 4.23-4.37 (m, 3H), 4.45 (dd, 1H, $J = 4.1, 11.2$ Hz), 6.79 (brs, 1H), 7.44-7.54 (m, 4H), 7.59-7.67 (m, 2H), 7.92-8.04 (m, 4H) ppm; ^{13}C NMR ($\text{DMSO}-d_6$, 80 °C): δ 13.8, 27.7, 33.9, 51.3, 64.9, 66.2, 77.5, 128.0, 128.1, 128.7, 128.8, 129.6, 129.7, 132.6, 132.7, 155.1, 165.3, 165.3 ppm; HRMS (FAB) calcd for $\text{C}_{24}\text{H}_{30}\text{NO}_6$ ($[\text{M}+\text{H}]^+$): 428.2073, found: 428.2049.

(2R,3R)-12. $[\alpha]_{\text{D}}^{25} +25.3$ (*c* 0.555, CHCl_3); IR (neat): 3377, 2976, 1724, 1520, 1281, 1173, 1115, 714 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.13 (d, 3H, $J = 7.1$ Hz), 1.40 (s, 9H), 2.27-2.39 (m, 1H), 4.17-4.48 (m, 5H), 4.76 (brd, 1H, $J = 9.8$ Hz), 7.39-7.47 (m, 4H), 7.52-7.59 (m, 2H), 7.99-8.08 (m, 4H) ppm; ^1H NMR ($\text{DMSO}-d_6$, 80 °C): δ 1.03 (d, 3H, $J = 7.1$ Hz), 1.34 (s, 9H), 2.18-2.35 (m, 1H), 4.06 (dddd, 1H, $J = 5.1, 5.1, 7.7, 9.4$ Hz), 4.20 (dd, 1H, $J = 5.7, 11.1$ Hz), 4.27 (dd, 1H, $J = 5.1, 11.2$ Hz), 4.29 (dd, 1H, $J = 3.5, 11.1$ Hz), 4.40 (dd, 1H, $J = 5.1, 11.2$ Hz), 6.71 (brs, 1H), 7.44-7.54 (m, 4H), 7.58-7.66 (m, 2H), 7.93-8.00 (m, 4H) ppm; ^{13}C NMR ($\text{DMSO}-d_6$, 80 °C): δ 12.0, 27.8, 33.7, 50.6, 64.9, 66.3, 77.6, 128.1, 128.2, 128.7, 128.8, 129.5, 129.7, 132.7, 132.7, 155.3, 165.3, 165.3 ppm; HRMS (FAB) calcd for $\text{C}_{24}\text{H}_{30}\text{NO}_6$ ($[\text{M}+\text{H}]^+$): 428.2073, found: 428.2092.

HPLC (Chiralcel OD, hexane/*i*-PrOH = 19/1, flow rate = 0.70 mL/min) (2*S*,3*R*): t_{R} = 14.5 min. (2*S*,3*S*): t_{R} = 16.0 min. (2*R*,3*R*): t_{R} = 18.0 min. (2*R*,3*S*): t_{R} = 20.1 min.

The relative configuration of the product of the reaction with propiophenone-derived silyl enol ether was assumed to be *syn*.¹ The absolute configuration was assumed to be (2*R*)-form by analogy to Mannich-adducts from acetophenone-derived silyl enol ether, **4E** and **4Z**.

The stereochemistry of the product of the reaction with butyrophenone-derived silyl enol ether was assumed to be (2*R*,3*R*) by analogy to that of propiophenone-derived silyl enol ether.

The absolute configuration of **5** was assumed to be (2*R*)-form by analogy to the products of the reactions with acetophenone-derived silyl enol ether, **4E**, and **4Z**.

References

- 1) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640.
- 2) Nakamura, Y.; Matsubara, R.; Kiyohara, H.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 2481.
- 3) Wolf, J. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3164.
- 4) Humphrey, J. M.; Bridges, R. J.; Hart, J. A.; Chamberlin, A. R. *J. Org. Chem.* **1994**, *59*, 2467.
- 5) Yoshida, T.; Takeshita, M.; Orita, H.; Kado, N.; Yasuda, S.; Kato, H.; Itoh, Y. *Chem. Pharm. Bull.* **1996**, *44*, 1128.

X-Ray Structure of $\text{ZnCl}_2 \cdot 1\text{b} \cdot \text{CH}_2\text{Cl}_2$

X-Ray Structure of 8