

## A NOVEL SYNTHESIS OF CHIRAL DBU/DBN-RELATED MOLECULES FOR USE IN ASYMMETRIC BASE CATALYSIS

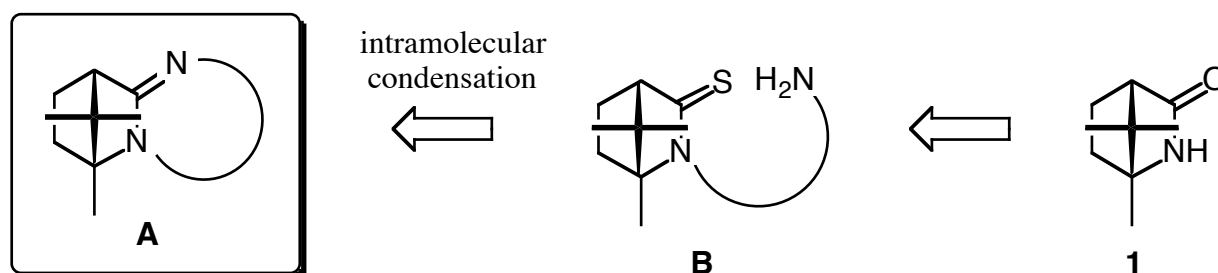
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**Abstract** --- The synthesis of sterically hindered chiral DBU/DBN-related molecules (**6**) from (+)-camphor lactam (**1**) is described. The value of the products as chiral organic base catalysts is exemplified by their use in asymmetric Michael addition reactions of  $\beta$ -keto ester (**7**).

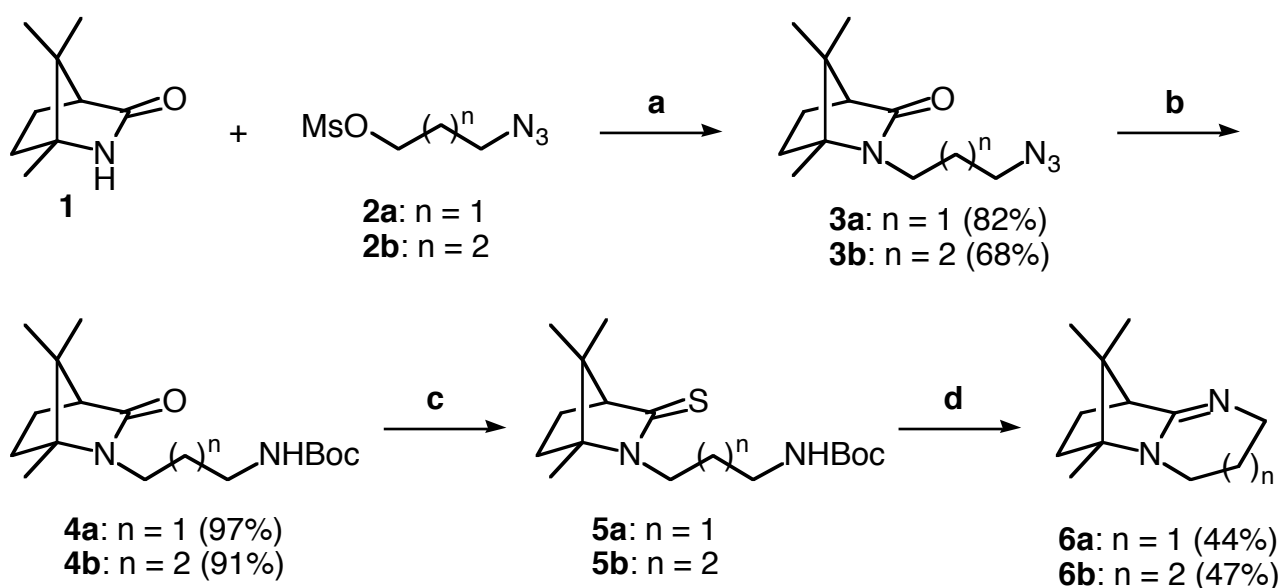
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) have attracted considerable interest due to their importance as non-nucleophilic strong organic bases (*e.g.*,  $pK_a$  values in acetonitrile of 23.79 and 24.31 for DBU and DBN respectively<sup>1</sup>) in promoting several types of organic transformation, such as isomerization, esterification, alkylation, Michael addition, condensation, and protection.<sup>2</sup> Accordingly, it is easy to imagine that the introduction of a chiral center onto the DBU/DBN skeleton could provide an efficient entry to novel enantiopure organic base catalysts. Unfortunately, however, very few examples of the synthesis of chiral DBU/DBN derivatives have been reported so far.<sup>3</sup> In our studies toward this end, we were particularly interested in the conformationally rigid structure of (+)-camphor, since there are numerous examples of the successful use of this chiral framework in asymmetric transformation.<sup>4</sup>

In this paper, we describe a novel synthesis of sterically hindered DBU/DBN-related organic bases. Our synthetic strategy toward the target molecule (**A**) is shown in **Scheme 1**. To construct an amidine functionality as a crucial step we planned to use the intramolecular condensation of  $\omega$ -amino-*N*-alkylated thiolactam **B**, which can be prepared from (+)-camphor lactam (**1**), readily available from (+)-camphoric acid,<sup>5</sup> by straightforward manipulation.



**Scheme 1**

Based on this idea, we proceeded with the synthesis of DBU/DBN-related molecules (**6**) (**Scheme 2**). The reaction of **1** with  $\omega$ -azidoalkyl methanesulfonates (**2**) in the presence of KH in THF gave the  $\omega$ -azido-bearing *N*-alkylated compounds (**3**) in good yields. Reductive transformation of the terminal azido group to the corresponding *N*-(*tert*-butoxycarbonyl)-protected amines (**4**) under catalytic hydrogenation conditions,<sup>6</sup> followed by treatment with Lawesson's reagent<sup>7</sup> in toluene at 100 °C, gave thiolactams (**5**). Finally, treatment of **5** with excess MeI, followed by deprotection of a Boc group with trifluoroacetic acid in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C, afforded the corresponding ammonium salt which, upon exposure to excess 10% aq NaOH, cyclized smoothly to give the desired amidines (**6a**) (44% from **4a**) and (**6b**) (47% from **4b**), respectively:  $[\alpha]_D^{24} +24.8^\circ$  ( $c = 0.73$ , MeOH) for **6a** and  $[\alpha]_D^{26} +98.7^\circ$  ( $c = 0.40$ , MeOH) for **6b**.

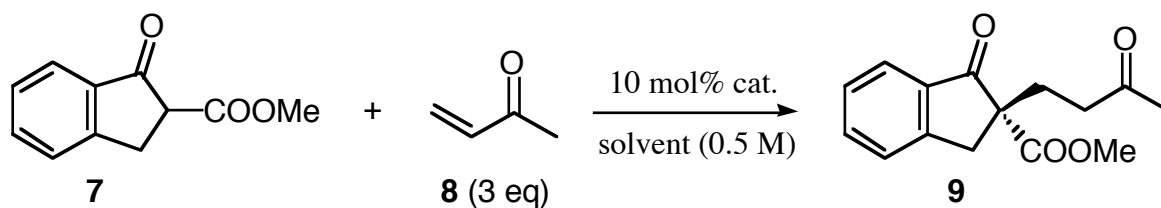


**Scheme 2**

*Reagents and Conditions:* (a) KH, THF, 0 °C  $\rightarrow$  rt; (b) H<sub>2</sub>, 20% Pd(OH)<sub>2</sub> / C, (Boc)<sub>2</sub>O, AcOEt, rt; (c) Lawesson's reagent, toluene, 100 °C; (d) (i) MeI, rt, (ii) CF<sub>3</sub>COOH, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, (iii) 10% aq NaOH.

To evaluate the chemical and stereochemical behavior of **6** for asymmetric catalysis, we examined the well-studied asymmetric Michael addition reactions<sup>8</sup> of  $\beta$ -keto ester (**7**) with methyl vinyl ketone (**8**) in the presence of a catalytic amount of optically active **6a** or **6b**. The results are summarized in Table 1.

In the presence of 10 mol% of **6a**,  $\beta$ -keto ester (**7**) reacted quite smoothly with **8** in EtOH as a solvent at room temperature to give the adduct (**9**), but with no enantioselectivity (Entry 1). Switching from EtOH solvent to CH<sub>2</sub>Cl<sub>2</sub> did not affect ee (Entry 2). However, the use of a less polar solvent such as CCl<sub>4</sub> and toluene appeared to be favorable in terms of enantioselectivity: **9** was obtained in a quantitative yield and with 8 and 7% ee, respectively, in favor of its *R*-isomer (Entries 3 and 4). The reaction at 0 °C gave no significant increase in enantioselectivity (Entry 5). Quite similar results were obtained for **6b**, albeit with less catalytic activity (Entries 7 and 8, 5 and 6% ee, respectively).

**Table 1.** Asymmetric Michael addition reactions of  $\beta$ -keto ester (**7**) with MVK (**8**)

| Entry | Catalyst  | Conditions                                 | Yield (%) <sup>a</sup> | ee (%) <sup>b</sup> | Abs. Configuration <sup>c</sup> |
|-------|-----------|--------------------------------------------|------------------------|---------------------|---------------------------------|
| 1     | <b>6a</b> | EtOH, rt, 1.5 h                            | 100                    | 0                   | --                              |
| 2     | <b>6a</b> | CH <sub>2</sub> Cl <sub>2</sub> , rt, 19 h | 97                     | 0                   | --                              |
| 3     | <b>6a</b> | CCl <sub>4</sub> , rt, 11 h                | 100                    | 8                   | <i>R</i>                        |
| 4     | <b>6a</b> | toluene, rt, 2 h                           | 100                    | 7                   | <i>R</i>                        |
| 5     | <b>6a</b> | toluene, 0 °C, 2.5 h                       | 100                    | 8                   | <i>R</i>                        |
| 6     | <b>6a</b> | no solvent, rt, 1.5 h                      | 100                    | 0                   | --                              |
| 7     | <b>6b</b> | toluene, rt, 19 h                          | 100                    | 5                   | <i>R</i>                        |
| 8     | <b>6b</b> | toluene, 0 °C, 70 h                        | 93                     | 6                   | <i>R</i>                        |

a) Isolated yields. b) Determined by HPLC (DAICEL Chiralpak AD). c) Determined by optical rotation:  $[\alpha]_{578}^{\text{rt}} -77^\circ$  ( $c = 2$ , benzene) for enantiomerically pure (*S*)-**9**. See ref. 8.

This unexpectedly disappointing result may be ascribed to the severe steric shielding of both the upper and lower sides of the amidine base face in **6** by a bulky bornane skeleton.<sup>9</sup> The pronounced solvent effect of EtOH undoubtedly indicates its great tendency to solvate the transient intermediates, making the interaction between the reactants and our chiral base catalysts much less severe.

In conclusion, the synthesis of a family of new sterically hindered DBU/DBN-related chiral derivatives (**6**) was accomplished in a four-step sequence starting from (+)-camphor lactam (**1**) as a convenient chiral source. Unfortunately, all of these compounds are still unsatisfactory for achieving a high level of asymmetric induction in Michael addition reactions. Further studies on modification of the ligand design and its application to asymmetric synthesis are now underway.

## EXPERIMENTAL

All melting points are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a JEOL LA-400 (400 MHz for <sup>1</sup>H NMR and 100 MHz for <sup>13</sup>C NMR analysis) spectrometer. All NMR spectra were taken in CDCl<sub>3</sub> solutions and are reported in parts per million ( $\delta$ ) downfield from TMS as an internal standard. The FT-IR spectra (cm<sup>-1</sup>) were measured with a JASCO Model FT/IR-5300 Fourier transform infrared spectrophotometer. Optical rotations were measured on a JASCO DIP-370 polarimeter. HPLC analyses were carried out using a Hitachi L-6200 HPLC system. Elemental analyses (C, H, N) were performed on

a Perkin Elmer-2400 elemental analyzer. TLC was performed using Merck precoated Kieselgel 60F-254 plates (0.25 mm). Preparative TLC was carried out on 2 mm-thick Merck Kieselgel 60PF-254. Column chromatography was done on Wakogel C-300 (silica gel) or Merck activated neutral alumina 90 (alumina).

### 3-Azido-1-propyl Methanesulfonate (**2a**).

1,3-Propanediol mono-THP ether<sup>10</sup> (5 g, 31.2 mmol) was converted into the corresponding mesylate (6.93 g, 93%) by the usual method. A solution of this mesylate and NaN<sub>3</sub> (2.27 g, 35 mmol) in dry DMF (45 mL) was stirred at 70 °C overnight. After conventional work-up, the crude product was purified by silica gel column chromatography (hexane / AcOEt = 4 : 1) to give the corresponding THP-azido (5.22 g, 97%) as a pale yellow oil. Deprotection of a THP group (MeOH, Amberlyst H-15, 45 °C, 3 h) followed by mesylation gave **2a** (1.54 g, 98%) as a pale yellow oil: FTIR (neat)  $\nu$  2101, 1352, 1173; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.01 (2H, quintet,  $J$  = 6.1 Hz), 3.04 (3H, s), 3.49 (2H, t,  $J$  = 6.1 Hz), 4.33 (2H, t,  $J$  = 6.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  28.7, 37.3, 47.3, 66.5.

In a similar manner, 4-azido-1-butyl methanesulfonate (**2b**) was prepared from 1,4-butanediol mono-THP ether<sup>10</sup>: FTIR (neat)  $\nu$  2101, 1352, 1173; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.70-1.77 (2H, m), 1.83-1.89 (2H, m), 3.03 (3H, s), 3.36 (2H, t,  $J$  = 6.6 Hz), 4.27 (2H, t,  $J$  = 6.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  25.0, 26.4, 37.4, 50.7, 69.1.

### (1*S*,4*R*)-3-(3-Azidopropyl)-3-aza-4,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**3a**).

To a suspension of KH (35% suspension in oil; 1.35 g, 13.2 mmol) in THF (100 mL) at 0 °C was added dropwise a solution of (+)-camphor lactam (**1**) (1.69 g, 11.0 mmol) in THF (50 mL), and the mixture was stirred under Ar for 1 h at rt. A solution of 3-azidopropyl mesylate (**2a**) (1.97 g, 11.0 mmol) in THF (50 mL) was then added dropwise at 0 °C, and the mixture was stirred for 24 h at rt. After quenching by adding water, the mixture was concentrated *in vacuo* and extracted with AcOEt. The extracts were washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The crude product was purified by silica gel column chromatography (hexane / acetone = 4 : 1) to give **3a** (2.12 g, 82%) as a light yellow oil:  $R_f$  0.40 (hexane / acetone = 2 : 1);  $[\alpha]_D^{26} +32.2^\circ$  ( $c$  = 0.78, CHCl<sub>3</sub>); FTIR (neat)  $\nu$  2097, 1698; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.89, 0.96, 1.21 (each 3H, s), 1.50 (2H, m), 1.74-1.84 (3H, m), 1.93-2.00 (1H, m), 2.30 (1H, d,  $J$  = 4.1 Hz), 3.08 (1H, dt,  $J$  = 14.1, 7.1 Hz), 3.26 (1H, dt,  $J$  = 14.1, 7.1 Hz), 3.34 (2H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  12.2, 18.1, 18.5, 23.5, 29.3, 33.6, 36.1, 49.3, 49.7, 55.0, 70.7, 178.6; MS  $m/z$  (rel. intensity) 237 ( $M^+$  + 1, 100), 208 (32), 194 (59), 180 (31), 166 (23), 153 (13), 109 (36), 56 (16). HRMS calcd for C<sub>12</sub>H<sub>20</sub>N<sub>4</sub>O + H, 237.1715, found 237.1694.

In a similar manner, **3b** (1.56 g, 68%) was prepared from **1** (1.40 g, 9.14 mmol) and **2b** (1.77 g, 9.16 mmol) as a light yellow oil:  $R_f$  0.35 (hexane / acetone = 2 : 1);  $[\alpha]_D^{23} +30.5^\circ$  ( $c$  = 0.98, CHCl<sub>3</sub>); FTIR (neat)  $\nu$  2097, 1696; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.88 (3H, s), 0.96 (3H, s), 1.21 (each 3H, s), 1.44-1.66 (6H, m), 1.79 (1H, dt,  $J$  = 12.2, 3.9 Hz), 1.95 (1H, m), 2.29 (1H, d,  $J$  = 4.1 Hz), 3.07 (1H, dt,  $J$  = 14.0, 6.8 Hz), 3.19 (1H, dt,  $J$  = 14.0, 6.8 Hz), 3.32 (2H, t,  $J$  = 6.3 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  12.2, 18.1, 18.5,

23.5, 26.4, 27.1, 33.7, 38.0, 49.8, 51.0, 55.0, 70.6, 178.4; MS  $m/z$  (rel. intensity) 251 ( $M^+ + 1$ , 100), 222 (22), 208 (42), 194 (40), 179 (20), 166 (14), 154 (13), 109 (22), 70 (49). HRMS calcd for  $C_{13}H_{22}N_4O + H$ , 251.1872, found 251.1867.

**(1*S*,4*R*)-3-{3-(*N*-*tert*-Butoxycarbonyl)aminopropyl}-3-aza-4,7,7-trimethylbicyclo-[2.2.1]heptan-2-one (4a).**

A mixture of azidolactam (**3a**) (680 mg, 2.9 mmol), Boc<sub>2</sub>O (1.14 g, 5.2 mmol), and a catalytic amount of 20% Pd(OH)<sub>2</sub>/C in AcOEt (10 mL) was stirred under H<sub>2</sub> for 36 h at rt. The inorganic catalyst was removed by filtration through Celite, and the filtrate was concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (AcOEt) to give **4a** (870 mg, 97%) as a colorless oil:  $R_f$  0.47 (AcOEt);  $[\alpha]_D^{26} +5.1^\circ$  ( $c = 0.98$ , CHCl<sub>3</sub>); FTIR (neat)  $\nu$  3349, 1711, 1688; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.89, 0.96, 1.19 (each 3H, s), 1.43 (9H, s), 1.40-1.60 (3H, m), 1.60-1.70 (1H, m), 1.74-1.83 (1H, m), 1.94-2.02 (1H, m), 2.31 (1H, d,  $J = 4.1$  Hz), 3.02-3.22 (3H, m), 3.25 (1H, ddd,  $J = 14.6, 8.8, 5.9$  Hz), 5.75 (1H, br); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  12.1, 18.1, 18.5, 23.6, 28.4 ( $\times 3$ ), 29.9, 33.6, 35.6, 37.2, 50.0, 55.0, 70.8, 78.7, 156.2, 179.4; MS  $m/z$  (rel. intensity) 311 ( $M^+ + 1$ , 27), 255 (36), 237 (39), 211 (100), 194 (15), 167 (19), 83 (12). *Anal.* Calcd for C<sub>17</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>: C, 65.77; H, 9.74; N, 9.02. Found: C, 65.59; H, 9.97; N, 8.94.

In a similar manner, **4b** (240 mg, 91%) was prepared from **3b** (200 mg, 0.8 mmol) and Boc<sub>2</sub>O (320 mg, 1.4 mmol) as a colorless oil:  $R_f$  0.28 (AcOEt);  $[\alpha]_D^{23} +21.5^\circ$  ( $c = 0.98$ , CHCl<sub>3</sub>); FTIR (neat)  $\nu$  3339, 1686; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.87, 0.95, 1.19 (each 3H, s), 1.44 (9H, s), 1.40-1.60 (6H, m), 1.77 (1H, dt,  $J = 12.2, 3.9$  Hz), 1.95 (1H, m), 2.28 (1H, d,  $J = 4.1$  Hz), 3.05-3.20 (4H, m), 4.66 (1H, br); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  12.1, 18.1, 18.5, 23.5, 27.2, 27.6, 28.4 ( $\times 3$ ), 33.7, 38.3, 40.1, 49.8, 55.0, 70.6, 79.0, 156.0, 178.3; MS  $m/z$  (rel. intensity) 324 ( $M^+$ , 3), 251 (7), 220 (18), 205 (11), 192 (37), 177 (71), 166 (11), 138 (16), 110 (19), 70 (19), 56 (100). *Anal.* Calcd for C<sub>18</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>: C, 66.63; H, 9.94; N, 8.63. Found: C, 66.51; H, 10.16; N, 8.73.

**(1*S*,4*R*)-3-{3-(*N*-*tert*-Butoxycarbonyl)aminopropyl}-3-aza-4,7,7-trimethylbicyclo-[2.2.1]heptane-2-thione (5a).**

A solution of *N*-Boc-lactam (**4a**) (100 mg, 0.3 mmol) and Lawesson's reagent (78 mg, 0.2 mmol) in dry toluene (2 mL) was stirred at 100 °C for 3 h under N<sub>2</sub>. The mixture was concentrated *in vacuo* to give a brownish oil which was purified by preparative TLC (hexane / AcOEt = 1 : 1) to give thiolactam (**5a**) (70 mg, 67%) as a white solid:  $R_f$  0.22 (hexane / AcOEt = 2 : 1); FTIR (KBr)  $\nu$  3314, 1680, 1513; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.89, 0.91, 1.29 (each 3H, s), 1.44 (9H, s), 1.40-1.58 (4H, m), 1.76 (2H, tt,  $J = 6.8, 6.1$  Hz), 1.86 (1H, ddd,  $J = 12.9, 9.5, 3.4$  Hz), 1.98-2.05 (1H, m), 2.89 (1H, d,  $J = 4.1$  Hz), 3.14 (2H, q,  $J = 6.1$  Hz), 3.68 (2H, t,  $J = 6.8$  Hz), 5.54 (1H, br); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  12.2, 18.1, 18.6, 25.2, 28.4 ( $\times 3$ ), 28.7, 34.0, 37.5, 40.9, 52.5, 66.0, 76.5, 79.0, 156.0, 205.8. *Anal.* Calcd for C<sub>17</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>S: C, 62.54; H, 9.26; N, 8.58. Found: C, 62.41; H, 9.29; N, 8.53. This sample was used immediately for the next reaction.

In a similar manner, **5b** (160 mg, 74%) was prepared from **4b** (205 mg, 0.63 mmol) and Lawesson's reagent (170 mg, 0.42 mmol) as a white solid: *R*<sub>f</sub> 0.25 (hexane / AcOEt = 2 : 1); FTIR (KBr)  $\nu$  3291, 1681, 1476; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.88, 0.90, 1.29 (each 3H, s), 1.44 (9H, s), 1.40-1.62 (4H, m), 1.69 (2H, br), 1.85 (1H, ddd, *J* = 12.9, 9.3, 3.7 Hz), 2.00 (1H, ddd, *J* = 16.6, 9.8, 3.9 Hz), 2.86 (1H, d, *J* = 4.1 Hz), 3.18 (2H, br d, *J* = 6.1 Hz), 3.52-3.67 (2H, m), 4.74 (1H, br); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  12.2, 18.1, 18.5, 24.8, 25.1, 27.5, 28.4 ( $\times$  3), 34.0, 39.7, 43.1, 52.4, 65.9, 76.3, 79.1, 156.0, 204.6. *Anal.* Calcd for C<sub>18</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>S: C, 63.49; H, 9.47; N, 8.23. Found: C, 63.46; H, 9.63; N, 8.11.

**(1*R*,8*S*)-2,6-Diaza-1,11,11-trimethyltricyclo[6.2.1.0<2,7>]undec-6-ene (6a).**

A solution of thiolactam (**5a**) (181 mg, 0.55 mmol) in MeI (1 mL, 16 mmol) was stirred under N<sub>2</sub> for 15 h at rt in the dark. After concentration *in vacuo*, the crude product was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (4 mL), and trifluoroacetic acid (0.4 mL, 5.2 mmol) at 0 °C was added. After stirring at 0 °C for 4 h, the mixture was quenched by adding ice and 10% NaOH. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined extracts were washed with brine, dried (K<sub>2</sub>CO<sub>3</sub>), and concentrated. The residue was purified by alumina column chromatography (AcOEt / MeOH = 9 : 1) to give chiral amidine (**6a**) (42 mg, 44% from **4a**) as a pale yellow solid: mp ~30 °C; [ $\alpha$ ]<sub>D</sub><sup>24</sup> +24.8° (*c* = 0.73, MeOH); FTIR (KBr)  $\nu$  1672, 1574, 1318; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.94, 0.97, 1.26 (each 3H, s), 1.58 (2H, m), 1.84-1.95 (2H, m), 2.04-2.14 (1H, m), 2.16-2.25 (1H, m), 3.28 (2H, t, *J* = 6.0 Hz), 3.44 (1H, ddd, *J* = 13.9, 7.1, 4.4 Hz), 3.47 (1H, d, *J* = 3.9 Hz), 3.53 (1H, ddd, *J* = 13.9, 6.8, 4.9 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  10.7, 17.9, 18.0, 19.4, 24.8, 32.5, 37.1, 38.0, 51.5, 52.2, 74.4, 168.2; MS *m/z* (rel. intensity) 193 (*M*<sup>+</sup> + 1, 100), 177 (18), 164 (10), 149 (37). HRMS calcd for C<sub>12</sub>H<sub>20</sub>N<sub>2</sub> + H, 193.1706, found 193.1685.

In a similar manner, **6b** (270 mg, 47% from **4b**) was prepared from **5b** (870 mg, 2.55 mmol) as a pale yellow oil: [ $\alpha$ ]<sub>D</sub><sup>26</sup> +98.7° (*c* = 0.40, MeOH); FTIR (neat)  $\nu$  1670; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.95 (6H, s), 1.26 (3H, s), 1.56-1.89 (4H, m), 1.96-2.11 (2H, m), 2.15-2.22 (1H, m), 3.09 (1H, ddd, *J* = 13.2, 10.2, 2.9 Hz), 3.35-3.46 (2H, m), 3.54 (1H, d, *J* = 3.9 Hz), 3.75 (1H, ddd, *J* = 14.4, 5.9, 3.2 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  12.1, 17.8, 18.1, 24.6, 26.5, 26.7, 31.7, 44.1, 45.7, 51.1, 53.5, 76.9, 173.0; MS *m/z* (rel. intensity) 207 (*M*<sup>+</sup> + 1, 100), 191 (48), 178 (7), 163 (17), 143 (6). HRMS calcd for C<sub>13</sub>H<sub>22</sub>N<sub>2</sub> + H, 207.1861, found 207.1849.

**Typical Procedure for the Asymmetric Michael Addition Reaction of  $\beta$ -Keto Ester (7) with Methyl Vinyl Ketone (8).**

To a solution of  $\beta$ -keto ester (**7**) (40 mg, 0.20 mmol) and chiral amidine (**6a**) (4 mg, 0.021 mmol) in dry toluene (0.4 mL) at rt was added methyl vinyl ketone (**8**) (44 mg, 0.60 mmol), and the mixture was stirred under Ar for 2 h at rt. After concentration *in vacuo*, the crude product was purified by preparative TLC (hexane / AcOEt = 2 : 1) to yield the adduct (**9**) (55 mg, 100 %) as a white solid. The enantiomeric excess (ee) of this product was determined by HPLC analysis (254 nm, flow rate: 0.5 mL/min) carried out with Chiralpak AD (eluent: hexane / 2-propanol = 90 : 10, *t*<sub>R</sub> 21.9 min for the *S*-isomer and *t*<sub>R</sub> 24.3 min for the *R*-isomer): *R*<sub>f</sub> 0.19 (hexane / AcOEt = 2 : 1); [ $\alpha$ ]<sub>D</sub><sup>25</sup> +4.18° (*c* = 0.96, C<sub>6</sub>H<sub>6</sub>) (7% ee by HPLC analysis);

FTIR (KBr) 1734, 1713, 1607;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.13 (3H, s), 2.24 (2H, m), 2.48-2.68 (2H, m), 3.05 (1H, d,  $J = 17.3$  Hz), 3.67 (1H, d,  $J = 17.3$  Hz), 3.70 (3H, s), 7.42 (1H, t,  $J = 7.6$  Hz), 7.48 (1H, d,  $J = 7.6$  Hz), 7.64 (1H, t,  $J = 7.6$  Hz), 7.78 (1H, d,  $J = 7.6$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  28.6, 29.9, 37.9, 38.8, 52.7, 59.1, 124.9, 126.4, 128.0, 135.0, 135.5, 152.5, 171.6, 202.3, 207.5.

## ACKNOWLEDGMENT

The authors are grateful to Prof. Y. Fukuyama of Tokushima Bunri University for MS/HRMS measurements. This work was supported in part by a Grant-in-Aid for Special Scientific Research from Kochi University.

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