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## DIVERGENT SYNTHESIS OF 2,6-DISUBSTITUTED PIPERIDINE ALKALOID, (+)-SPECTALINE BY PALLADIUM-CATALYZED CYCLIZATION

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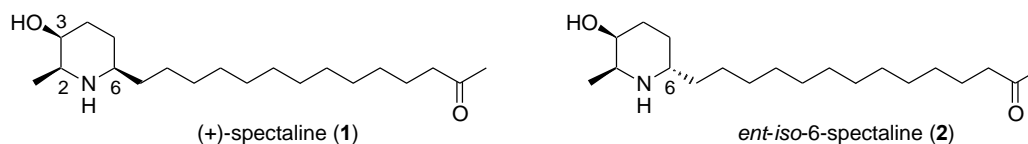
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**Abstract** – Convergent synthesis of 2,6-disubstituted piperidine alkaloid, (+)-spectaline is described. Using substrate-controlled diastereo-selective Pd(II)-catalyzed cyclization, both *cis*-2,6- and *trans*-2,6-disubstituted piperidine backbones were constructed from adequately protected precursors with high selectivity. Synthesis of (+)-spectaline containing *cis*-2,6-disubstituents was accomplished by 10 step reactions with a 31% total yield.

### INTRODUCTION

2,6-Disubstituted piperidin-3-ol is a subclass of hydroxypiperidine alkaloid which shows interesting biological activity including antibiotic and DNA-damaging activities.<sup>1,2</sup> Comparing the biological activities of several natural products with the 2,6-disubstituted piperidine backbone (Figure 1), it has been shown that the configurations of the substituents at the 2- and 6-positions markedly influence biological activity.<sup>3-5</sup> To address this stereostructure-activity relationship, a concise and diastereo-selective construction of the 2,6-disubstituted piperidine backbone would have practical utility. In this paper, we examined an application of Pd(II)-catalyzed cyclization for the construction of *cis*-2,6- and *trans*-2,6-disubstituted piperidine backbones, as well as its application to a total synthesis of (+)-spectaline (**1**). Although (+)-spectaline (**1**), isolated from the leaves of *Cassia spectabilis*, has been stereo-selectively synthesized by several groups,<sup>6-9</sup> further refinement would be desirable regarding the overall steps and/or convergence of the synthetic route. In addition, in our previous syntheses of related

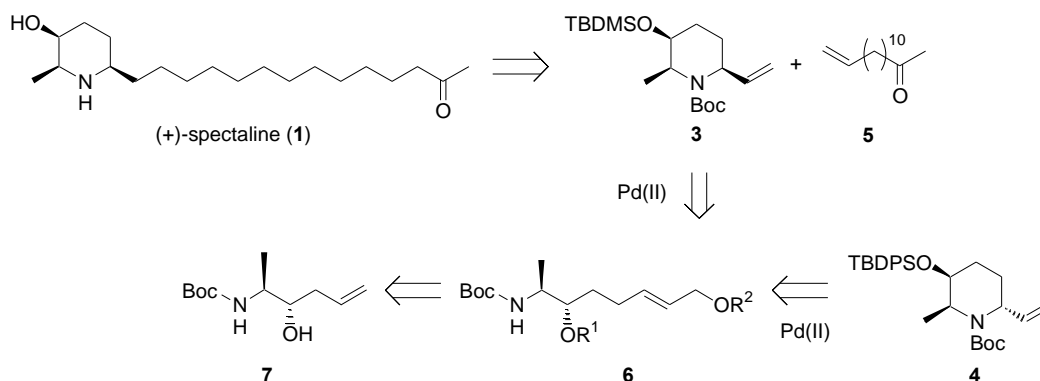
piperidine derivatives, (–)-cassine and (+)-azimine,<sup>10,11</sup> rather long reaction steps were required for the construction of *cis*-2,6-disubstituted piperidin-3-ol backbone (14 steps, 4.5%). Therefore, we applied Pd(II)-catalyzed cyclization<sup>10,11</sup> to a substrate-controlled diastereoselective cyclization for the convergent synthesis of the spectalines.



**Figure 1.** The structures of (+)-spectaline (1) and *ent*-iso-6-spectaline (2)

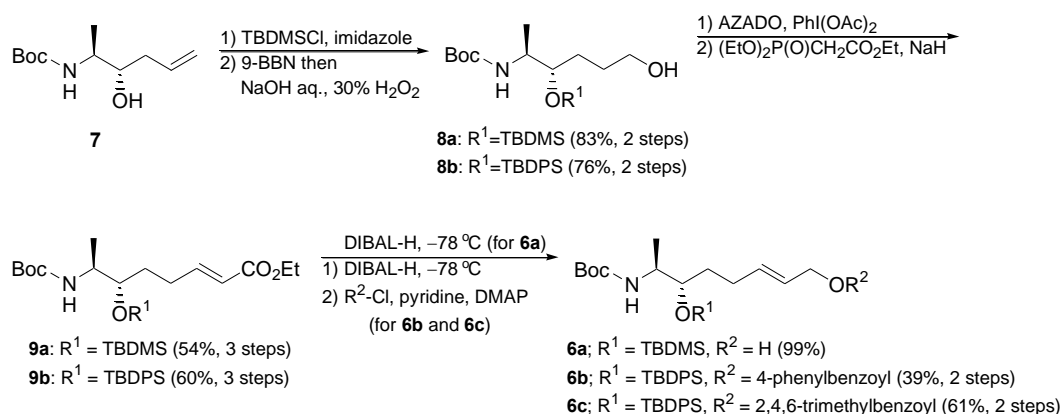
## RESULTS AND DISCUSSION

The retro-synthetic route for (+)-spectaline (1) is shown in Scheme 1. The aliphatic side-chain of **1** was introduced by a cross-metathesis reaction of the key intermediates **3** and **5**. Pd(II)-catalyzed diastereo-selective cyclization gave the necessary key intermediate **3** or **4**, depending on the structure of the cyclization precursor **6** containing a different combination of the protecting groups. Precursor **6** could be synthesized by chain elongation using conventional Horner-Wadsworth-Emmons reaction from a known alcohol **7**.<sup>12</sup>



**Scheme 1.** Synthetic strategy of **1**

The cyclization intermediates **6a** to **6c** were synthesized according to the route shown in Scheme 2. The hydroxy group of a known alcohol **7** was protected with TBDMS or TBDPS group and following hydroboration with 9-BBN gave the primary alcohol **8a** or **8b**. Oxidation of each alcohol with AZADO<sup>13</sup> and  $\text{PhI}(\text{OAc})_2$  followed by Horner-Wadsworth-Emmons reaction yielded the ester **9a** or **9b**. Reduction with DIBAL-H of **9a** gave cyclization precursor **6a**, and reduction of **9b** followed by esterification with 2,4,6-trimethylbenzoyl chloride or 4-phenylbenzoyl chloride gave precursor **6b** and **6c**, respectively.



**Scheme 2.** Syntheses of cyclization precursors **6a**, **6b**, and **6c**

Next, Pd(II)-catalyzed cyclization of the precursors **6a**, **6b**, and **6c** were examined (Table 1). As expected from our previous studies,<sup>10,11</sup> PdCl<sub>2</sub> catalyst gave the *cis*-2,6-disubstituted piperidine backbone as a major product when the unprotected primary alcohol was employed as the precursor (entry 2 to 4), while Pd(0) catalyst [Pd(dba)<sub>2</sub>] was ineffective (entry 1). THF was found to be a superior solvent for the cyclization reaction (entry 4). Use of TBDMS group as a hydroxyl protecting group instead of MOM group, which was used in the previous synthesis of (+)-azimine,<sup>11</sup> improved the yield of the desired cyclized product **3** from 61% to 88%. Relative stereochemistry of the *cis*-products was confirmed by an NOE experiment. In contrast, it was assumed that a *trans*-2,6-disubstituted piperidine backbone could be obtained when the precursor containing a relatively bulky protecting group at the terminal alcohol was used.<sup>14</sup> Cyclization of precursor **6c** gave a 1:1 mixture of *cis*- and *trans*-piperidine products with a 62% yield (entry 5). Cyclization of **6b** gave the *trans*-2,6-piperidine with high selectivity, although the yield was relatively low, probably due to the steric hindrance (entry 6).

**Table 1.** Diastereo-selective cyclization of **6**

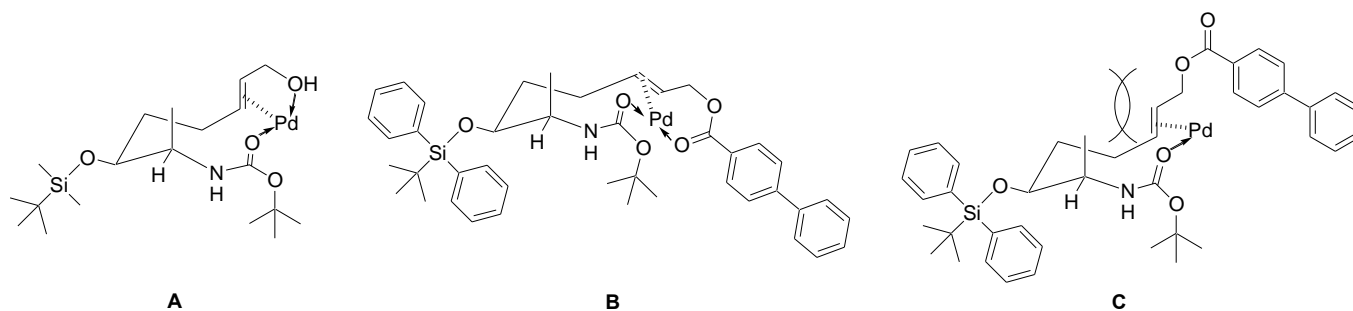
$\text{Boc-NH-CH(CH}_3\text{)-CH}_2\text{-CH}_2\text{-CH=CH-CH}_2\text{-OR}^2 \xrightarrow[\text{solvent}]{\text{catalyst (10 mol\%)}}$  **3** + **4**

| entry | precursor | R <sup>1</sup> | R <sup>2</sup>         | catalyst             | solvent                         | time (d) | yield (%) | 3:4 <sup>a</sup> |
|-------|-----------|----------------|------------------------|----------------------|---------------------------------|----------|-----------|------------------|
| 1     | <b>6a</b> | TBDMS          | H                      | Pd(dba) <sub>2</sub> | THF                             | 0.25     | N.D.      | –                |
| 2     | <b>6a</b> | TBDMS          | H                      | PdCl <sub>2</sub>    | CH <sub>2</sub> Cl <sub>2</sub> | 1        | 30        | >97: 3           |
| 3     | <b>6a</b> | TBDMS          | H                      | PdCl <sub>2</sub>    | DME                             | 1        | 61        | >97: 3           |
| 4     | <b>6a</b> | TBDMS          | H                      | PdCl <sub>2</sub>    | THF                             | 1        | 88        | >97: 3           |
| 5     | <b>6c</b> | TBDPS          | 2,4,6-trimethylbenzoyl | PdCl <sub>2</sub>    | THF                             | 3        | 62        | 50:50            |
| 6     | <b>6b</b> | TBDPS          | 4-phenylbenzoyl        | PdCl <sub>2</sub>    | THF                             | 3        | 27        | < 3:97           |

N.D.: Not detected

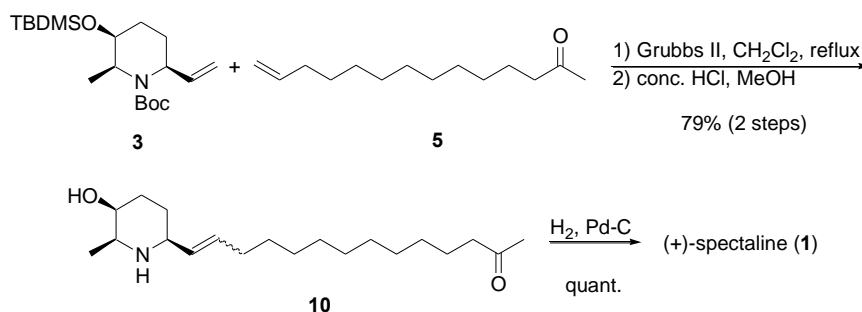
<sup>a</sup>The ratio of **3** and **4** was determined by <sup>1</sup>H NMR analysis.

Construction of *cis*-2,6-disubstituted piperidine backbone described above was assumed to proceed *via* the transition state **A** shown in Figure 2, in which the chelation effect between palladium and allylic hydroxyl group was thought to be crucial as in our previous synthesis of (–)-cassine.<sup>10</sup> In the construction of the *trans*-2,6-disubstituted piperidine backbone, the transition state **B** exhibiting the chelation effect between the palladium and oxygen of the acyl carbonyl would be favorable to transition state **C**, probably due to 1,3-diaxial repulsion.



**Figure 2.** Proposed transition state

Finally, synthesis of **1** was completed according to the route shown in Scheme 3. Cross-metathesis of **3** and tetradec-13-en-2-one **5** using a second generation Grubbs catalyst<sup>15</sup> proceeded under reflux to give **10** as a mixture of *E/Z* isomers (*E:Z* = 10:1). Deprotection of the TBDMS- and Boc-groups by treatment with conc. HCl followed by catalytic hydrogenation yielded (+)-spectaline (**1**) without difficulty. Thus, synthesis of **1** was accomplished by 10 step reactions with a 31% total yield. The optical rotation of synthetic **1** was consistent with those reported for natural and synthetic **1**. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of synthetic **1** were also in good agreement with the reported values.



**Scheme 3.** Synthesis of (+)-spectaline (**1**)

In conclusion, (+)-spectaline (**1**) was synthesized in a convergent way by utilizing substrate-controlled diastereo-selective Pd(II)-catalyzed cyclization by 10 step reactions with a 31% total yield. Syntheses of

analogues containing *cis*- and *trans*-2,6-disubstituents and evaluation of the inhibitory activities against the superoxide production<sup>16</sup> are now underway.

## EXPERIMENTAL

**General Methods.** <sup>1</sup>H NMR spectra were recorded in CDCl<sub>3</sub> on agilent UNITY INOVA 400 NB or Bruker AM-300 spectrometers. Chemical shifts are expressed in ppm relative to tetramethylsilane (0.00 ppm). The coupling constants are given in Hz. <sup>13</sup>C NMR spectra were recorded on the same spectrometers at 100 or 75 MHz, using the central resonance of CDCl<sub>3</sub> (δC 77.0 ppm) as the internal reference. High-resolution mass spectra (HRMS) were obtained on a Shimadzu GC mate II (EI and CI). Optical rotations were determined with a HORIBA SEPA-300 polarimeter.

**(2*S*,3*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-3-(*tert*-butyldimethylsilyloxy)hex-5-ene:** To a solution of **7** (1.42 g, 6.62 mmol) in DMF (30 mL) was added TBDMSCl (1.10 g, 7.28 mmol) and imidazole (451 mg, 9.93 mmol). The mixture was stirred for 16 h at room temperature and quenched with saturated aqueous NH<sub>4</sub>Cl. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to give silyl ether as a colorless oil (2.12 g, 97%). <sup>1</sup>H NMR (400 MHz, 10:1 mixture of two diastereomers,<sup>17</sup> major isomer) δ: 0.07 (6H, s), 0.91 (9H, s), 1.10 (3H, d, *J* = 6.8 Hz), 1.45 (9H, s), 2.14-2.21 (1H, m), 2.23-2.30 (1H, m), 3.57-3.60 (1H, m), 3.73-3.76 (1H, m), 4.47 (1H, brd, *J* = 8.8 Hz), 5.04-5.09 (2H, m), 5.72-5.83 (1H, m); <sup>13</sup>C NMR (100 MHz) δ: -4.7, -4.2, 18.1, 18.8, 25.9, 28.4, 39.2, 48.3, 74.9, 78.9, 117.6, 134.3, 155.5; HRCIMS [M+H]<sup>+</sup>: Found, 330.2467. Calcd. for C<sub>17</sub>H<sub>36</sub>NO<sub>3</sub>Si: 330.2465.

**(2*S*,3*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-3-(*tert*-butyldiphenylsilyloxy)hex-5-ene:** 3.88 g (99%) of TBDPS ether was obtained from 1.86 g (8.64 mmol) of **7** as described above. <sup>1</sup>H NMR (300 MHz, 10:1 mixture of two diastereomers, major isomer) δ: 1.08 (9H, s), 1.11 (3H, d, *J* = 6.8 Hz), 1.46 (9H, s), 2.04-2.12 (1H, m), 2.20-2.30 (1H, m), 3.57-3.60 (1H, m), 3.74-3.79 (1H, m), 4.76-4.91 (3H, m), 5.50-5.59 (1H, m), 7.35-7.46 (6H, m), 7.67-7.71 (4H, m); <sup>13</sup>C NMR (75 MHz) δ: 19.2, 19.5, 27.1, 28.4, 38.9, 48.0, 76.4, 78.9, 117.8, 127.5, 127.66, 129.67, 129.8, 133.1, 133.7, 134.1, 135.87, 135.93, 155.5; HRCIMS [M+H]<sup>+</sup>: Found, 454.2775. Calcd. for C<sub>27</sub>H<sub>40</sub>NO<sub>3</sub>Si: 454.2778.

**(2*S*,3*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-3-(*tert*-butyldimethylsilyloxy)hexan-6-ol (**8a**):** To a solution of above ether (2.12 g, 6.42 mmol) in THF (30 mL) was added 9-BBN (0.5 mol/L in THF, 25.7

mL, 12.8 mmol) at 0 °C under an argon gas atmosphere. The mixture was stirred for 6 h at room temperature and quenched with 3 mol/L NaOH (40 mL). Aqueous H<sub>2</sub>O<sub>2</sub> (30%, 15 mL) was added at 0 °C and the mixture was stirred for 14 h at room temperature. The resultant mixture was diluted with H<sub>2</sub>O and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give **8a** as a colorless oil (1.92 g, 86%). <sup>1</sup>H NMR (400 MHz, 10:1 mixture of two diastereomers, major isomer) δ: 0.08 (6H, s), 0.90 (9H, s), 1.12 (3H, d, *J* = 6.8 Hz), 1.45 (9H, s), 1.57-1.61 (4H, m), 3.55-3.68 (4H, m), 3.75-3.79 (1H, m), 4.65 (1H, brd, *J* = 9.2 Hz); <sup>13</sup>C NMR (100 MHz) δ: -4.7, -4.3, 18.0, 18.6, 25.9, 28.4, 28.7, 30.3, 48.3, 62.6, 74.9, 79.1, 155.8; HRCIMS [M+H]<sup>+</sup>: Found, 348.2574. Calcd. for C<sub>17</sub>H<sub>38</sub>NO<sub>4</sub>Si: 348.2570.

**(2*S*,3*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-3-(*tert*-butyldiphenylsilyloxy)hexan-6-ol (8b):** 3.11 g (77%) of **8b** was obtained from 3.88 g (8.56 mmol) of above TBDPS ether. <sup>1</sup>H NMR (400 MHz, 10:1 mixture of two diastereomers, major isomer) δ: 1.07 (9H, s), 1.14 (3H, d, *J* = 6.8 Hz), 1.22-1.39 (3H, m), 1.46 (9H, s), 1.54-1.61 (2H, m), 3.31 (1H, m), 3.56-3.58 (1H, m), 3.79 (1H, m), 4.77 (1H, brd, *J* = 9.6 Hz), 7.27-7.46 (6H, m), 7.67-7.69 (4H, m); <sup>13</sup>C NMR (100 MHz) δ: 19.2, 19.6, 27.1, 28.37, 28.43, 30.2, 48.2, 62.3, 76.5, 79.2, 127.5, 127.6, 127.7, 129.7, 129.9, 133.2, 134.3, 135.89, 135.94, 156.0; HRCIMS [M+H]<sup>+</sup>: Found, 472.2876. Calcd. for C<sub>27</sub>H<sub>42</sub>NO<sub>4</sub>Si: 472.2883.

**(6*S*,7*S*)-Ethyl 7-[*N*-(*tert*-butoxycarbonyl)amino]-6-(*tert*-butyldimethylsilyloxy)oct-2-enonate (9a):** A solution of **8a** (1.92 g, 5.51 mmol) and AZADO (8.4 mg, 0.055 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added PhI(OAc)<sub>2</sub> (2.66 g, 8.27 mmol). The mixture was stirred for 1 h at room temperature and the reaction mixture was diluted with ether and quenched with saturated aqueous NaHCO<sub>3</sub>, followed by a saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was roughly purified by silica gel column chromatography (hexane/EtOAc = 10:1). The product was used for the next step without further purification. Triethyl phosphonoacetate (1.3 mL, 6.1 mmol) was added to a suspension of NaH (264 mg, 6.61 mmol) in THF (20 mL) at 0 °C under an argon gas atmosphere. After stirring for 30 min, a solution of the product obtained above was dissolved in THF (10 mL). The mixture was stirred for 2 h at the same temperature, and the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to give **9a** as a colorless oil (1.26 g, 55%, 2 steps). <sup>1</sup>H NMR (400 MHz, 10:1 mixture of two diastereomers, major isomer) δ: 0.07 (3H, s), 0.08 (3H, s), 0.90 (9H, s), 1.11

(3H, d,  $J = 6.8$  Hz), 1.28 (3H, t,  $J = 7.2$  Hz), 1.45 (9H, s), 1.50-1.59 (2H, m), 2.17-2.24 (2H, m), 3.59 (1H, m), 3.75 (1H, m), 4.18 (2H, q,  $J = 7.2$  Hz), 4.60 (1H, brd,  $J = 10.0$  Hz), 5.82 (1H, dt,  $J = 15.7, 1.6$  Hz), 6.93 (1H, dt,  $J = 15.5, 6.9$  Hz);  $^{13}\text{C}$  NMR (100 MHz)  $\delta$ : -4.6, -4.3, 14.2, 18.0, 18.3, 25.8, 28.1, 28.4, 32.3, 48.4, 60.1, 74.1, 79.0, 121.4, 148.5, 155.5, 166.5; HRCIMS  $[\text{M}+\text{H}]^+$ : Found, 416.2834. Calcd. for  $\text{C}_{21}\text{H}_{42}\text{NO}_5\text{Si}$ : 416.2832.

**(6S,7S)-Ethyl 7-[N-(tert-butoxycarbonyl)amino]-6-(tert-butyldiphenylsilyloxy)oct-2-enonate (9b):** 2.17 g (61%, 2 steps) of **9b** was obtained from 3.11 g (6.59 mmol) of **8b**.  $^1\text{H}$  NMR (400 MHz, 10:1 mixture of two diastereomers, major isomer)  $\delta$ : 1.06 (9H, s), 1.12 (3H, d,  $J = 6.8$  Hz), 1.27 (3H, t,  $J = 7.0$  Hz), 1.39-1.45 (1H, m), 1.45 (9H, s), 1.61-1.64 (1H, m), 1.88-1.90 (1H, m), 2.06 (1H, m), 3.56 (1H, m), 3.75 (1H, m), 4.14 (2H, q,  $J = 7.1$  Hz), 4.71 (1H, brd,  $J = 8.8$  Hz), 5.55 (1H, d,  $J = 16.0$  Hz), 6.61 (1H, td,  $J = 15.1, 7.4$  Hz), 7.39-7.45 (6H, m), 7.66-7.68 (4H, m);  $^{13}\text{C}$  NMR (100 MHz)  $\delta$ : 14.2, 19.0, 19.5, 27.0, 27.1, 28.3, 28.4, 32.4, 48.2, 60.1, 75.8, 79.1, 121.3, 127.57, 127.64, 127.7, 129.8, 129.9, 132.9, 134.0, 135.8, 135.9, 148.1, 155.6, 166.5; HRCIMS  $[\text{M}+\text{H}]^+$ : Found, 540.3149. Calcd. for  $\text{C}_{31}\text{H}_{46}\text{NO}_5\text{Si}$ : 540.3145.

**(6S,7S)-7-[N-(tert-Butoxycarbonyl)amino]-6-(tert-butyldimethylsilyloxy)oct-2-en-1-ol (6a):** To a solution of **9a** (1.26 g, 3.02 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 mL) was added DIBAL-H (1.0 mol/L in hexane, 6.6 mL, 6.6 mmol) at  $-78$  °C under an argon gas atmosphere. After stirring for 15 min, the reaction was quenched with MeOH. The mixture was warmed to room temperature and filtered through celite and silica gel layer, and the filtrate was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford **6a** (1.12 g, 99%) as a colorless oil,  $^1\text{H}$  NMR (400 MHz, 10:1 mixture of two diastereomers, major isomer)  $\delta$ : 0.07 (6H, s), 0.90 (9H, s), 1.10 (3H, d,  $J = 6.8$  Hz), 1.45 (9H, s), 1.50-1.66 (3H, m), 2.01-2.13 (2H, m), 3.54-3.58 (1H, m), 3.75-3.78 (1H, m), 4.02-4.10 (2H, m), 4.67 (1H, brd,  $J = 8.8$  Hz), 5.58-5.69 (2H, m);  $^{13}\text{C}$  NMR (100 MHz)  $\delta$ : -4.6, -4.3, 18.1, 18.6, 25.9, 28.2, 28.4, 33.3, 48.3, 63.5, 74.8, 79.1, 129.5, 132.6, 155.6; HREIMS  $[\text{M}]^+$ : Found, 373.2640. Calcd. for  $\text{C}_{19}\text{H}_{39}\text{NO}_4\text{Si}$ : 373.2648.

**(6S,7S)-7-[N-(tert-Butoxycarbonyl)amino]-6-(tert-butyldiphenylsilyloxy)-1-(4-phenylbenzoyloxy)oct-2-ene (6b):** 1.96 g (98%) of alcohol as above was obtained from 2.17 g (4.02 mmol) of **9b** as described above.  $^1\text{H}$  NMR (300 MHz, 10:1 mixture of two diastereomers, major isomer)  $\delta$ : 1.06 (9H, s), 1.12 (3H, d,  $J = 6.4$  Hz), 1.46 (9H, s), 1.55-1.60 (3H, m), 1.80-1.84 (2H, m), 3.52-3.55 (1H, m), 3.77 (1H, m), 3.91 (2H, d,  $J = 5.4$  Hz), 4.80 (1H, brd,  $J = 9.3$  Hz), 5.23-5.31 (1H, m), 5.35-5.42 (1H, m), 7.39-7.45 (6H, m),

7.66-7.69 (4H, m);  $^{13}\text{C}$  NMR (75 MHz)  $\delta$ : 19.2, 19.6, 27.1, 27.9, 28.4, 33.2, 48.2, 63.5, 76.3, 79.2, 127.5, 127.7, 129.4, 129.7, 129.8, 132.2, 133.1, 135.9, 136.0, 155.7; HRCIMS  $[\text{M}+\text{H}]^+$ : Found, 498.3032. Calcd. for  $\text{C}_{29}\text{H}_{44}\text{NO}_4\text{Si}$ : 498.3040. To a solution of the alcohol (1.96 g, 3.95 mmol) in pyridine (15 mL) were added 4-phenylbenzoyl chloride (1.28 g, 5.93 mmol) and DMAP (965 mg, 7.90 mmol) at 0 °C. The mixture was stirred for 16 h at room temperature and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$ . The mixture was extracted with EtOAc and the organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to give **6b** as a colorless oil (1.07 g, 40%).  $^1\text{H}$  NMR (300 MHz, 10:1 mixture of two diastereomers, major isomer)  $\delta$ : 1.06 (9H, s), 1.13 (3H, d,  $J = 7.2$  Hz), 1.39-1.50 (1H, m), 1.46 (9H, s), 1.60-1.63 (1H, m), 1.84 (1H, m), 1.94 (1H, m), 3.58 (1H, m), 3.76 (1H, m), 4.61 (2H, d,  $J = 3.2$  Hz), 4.75 (1H, brd,  $J = 9.6$  Hz), 5.41-5.43 (2H, m), 7.35-7.49 (9H, m), 7.62-7.68 (8H, m), 8.08-8.10 (2H, m);  $^{13}\text{C}$  NMR (75 MHz)  $\delta$ : 19.1, 19.6, 27.1, 27.9, 28.4, 33.1, 48.2, 65.5, 75.8, 79.0, 124.1, 127.0, 127.3, 127.5, 127.7, 128.1, 128.9, 129.1, 129.7, 129.9, 130.1, 133.1, 135.2, 135.9, 136.0, 140.0, 145.6, 155.7, 166.2; HRCIMS  $[\text{M}+\text{H}]^+$ : Found, 678.3607. Calcd. for  $\text{C}_{42}\text{H}_{52}\text{NO}_5\text{Si}$ : 678.3615.

**(6*S*,7*S*)-7-[*N*-(*tert*-Butoxycarbonyl)amino]-6-(*tert*-butyldiphenylsilyloxy)-1-(2',4',6'-trimethylbenzyloxy)oct-2-ene (6c)**: Yield; 69 mg (62%).  $^1\text{H}$  NMR (300 MHz, 10:1 mixture of two diastereomers, major isomer)  $\delta$ : 1.06 (9H, s), 1.12 (3H, d,  $J = 6.6$  Hz), 1.45 (9H, s), 1.57 (1H, m), 1.80-1.89 (3H, m), 2.24 (6H, s), 2.27 (3H, s), 3.55 (1H, m), 3.74 (1H, m), 4.58 (2H, d,  $J = 4.8$  Hz), 4.73 (1H, brd,  $J = 9.3$  Hz), 5.39-5.41 (2H, m), 6.83 (2H, s), 7.35-7.46 (6H, m), 7.65-7.68 (4H, m);  $^{13}\text{C}$  NMR (75 MHz)  $\delta$ : 19.2, 19.6, 19.7, 21.1, 27.1, 27.9, 28.37, 28.42, 29.7, 33.2, 48.1, 65.3, 70.6, 75.9, 79.0, 123.9, 127.5, 127.6, 127.7, 128.3, 129.7, 129.9, 130.9, 133.1, 134.2, 135.1, 135.9, 136.0, 139.2, 155.7, 169.8; HREIMS  $[\text{M}]^+$ : Found, 643.3700. Calcd. for  $\text{C}_{39}\text{H}_{53}\text{NO}_5\text{Si}$ : 643.3693.

**(2*S*,3*S*,6*S*)-*N*-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)-2-methyl-6-vinylpiperidine (3)**: A solution of **6a** (129 mg, 0.345 mmol) in THF (5 mL) was treated with  $\text{PdCl}_2$  (5.4 mg, 0.030 mmol) at 0 °C under an argon gas atmosphere. After stirring for 1 day at room temperature, the reaction mixture was filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) gave **3** (108 mg, 88%) as a colorless oil.  $[\alpha]_D^{25} -37$  ( $c$  0.70,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz)  $\delta$ : 0.06 (6H, s), 0.88 (9H, s), 1.09 (3H, d,  $J = 6.8$  Hz), 1.43-1.52 (1H, m), 1.46 (9H, s), 1.65-1.78 (2H, m), 1.89-1.92 (1H, m), 3.68-3.74 (1H, m), 4.27-4.32 (1H, m), 4.61 (1H, brs), 5.06 (1H, ddd,  $J = 10.6, 1.8, 1.2$  Hz), 5.12 (1H, td,  $J = 17.4, 1.6$  Hz), 5.90 (1H, ddd,  $J = 17.4, 10.6, 5.4$  Hz);  $^{13}\text{C}$  NMR (75 MHz)  $\delta$ : -4.9, -4.7, 13.7, 18.1, 24.0, 25.8, 26.2, 28.5, 50.1, 51.7, 70.3, 79.5, 114.4, 140.1, 155.2; HRCIMS  $[\text{M}+\text{H}]^+$ :



Found, 356.2626. Calcd. for  $C_{19}H_{38}NO_3Si$ : 356.2621. NOE correlation was observed between methyl group at C-2 position and methine proton of vinyl group at C-6 position.

**(2*S*,3*S*,6*R*)-*N*-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldiphenylsilyloxy)-2-methyl-6-vinylpiperidine (4):**

Treatment of **6b** (58 mg, 0.085 mmol) with  $PdCl_2$  (1.5 mg, 0.0085 mmol) gave 11 mg (27%) of **4** as a colorless oil.  $^1H$  NMR (300 MHz)  $\delta$ : 1.06 (9H, s), 1.22 (3H, d,  $J = 6.9$  Hz), 1.41 (9H, s), 1.57-1.62 (2H, m), 1.67-1.81 (2H, m), 3.70-3.77 (1H, m), 4.31 (1H, m), 4.51 (1H, brs), 5.03-5.06 (1H, m), 5.07-5.12 (1H, m), 5.88 (1H, ddd,  $J = 17.4, 10.5, 5.1$  Hz), 7.34-7.46 (6H, m), 7.64-7.69 (4H, m);  $^{13}C$  NMR (75 MHz)  $\delta$ : 14.0, 19.2, 23.6, 25.9, 26.9, 28.4, 29.7, 50.3, 51.4, 71.2, 79.4, 114.4, 127.5, 127.7, 129.6, 129.7, 133.8, 134.5, 135.70, 135.74, 140.1, 155.1; HREIMS  $[M]^+$ : Found, 479.2851. Calcd. for  $C_{29}H_{41}NO_3Si$ : 479.2856.

**(1'*EZ*,2*S*,3*S*,6*S*)-3-Hydroxy-2-methyl-6-(13'-oxotetradec-1'-en-1'-yl)piperidine (10):** To a solution of **3** (36 mg, 0.10 mmol) and tetradec-13-en-2-one (129 mg, 0.613 mmol) in  $CH_2Cl_2$  (5.0 mL) was added Grubbs 2<sup>nd</sup> catalyst (17 mg, 0.020 mmol). After stirring for 1 day under reflux, an additional solution of Grubbs 2<sup>nd</sup> catalyst in  $CH_2Cl_2$  (17 mg, 0.020 mmol) was added. After stirring for 1 day under reflux, the solvent was removed and the residue was roughly purified by silica gel column chromatography (hexane/EtOAc = 20:1). The product was used for next step without further purification. The product was dissolved in MeOH (5 mL) and 12 mol/L HCl (0.5 mL) was added. After stirring for 12 h, the reaction was quenched with saturated aqueous  $NaHCO_3$ . The mixture was extracted with EtOAc, washed with brine, dried over  $Na_2SO_4$ , filtered, and concentrated. The residue was purified by preparative TLC ( $CHCl_3/MeOH = 5:1$ ) to give **10** (33 mg, 79%, 2 steps,  $E:Z = 10:1$ ) as a yellowish oil.  $^1H$  NMR (400 MHz, major isomer)  $\delta$ : 1.14 (3H, d,  $J = 6.4$  Hz), 1.26-1.39 (10H, m), 1.43-1.56 (9H, m), 1.89-1.93 (1H, m), 1.96-2.01 (2H, m), 2.14 (3H, s), 2.42 (2H, t,  $J = 7.6$  Hz), 2.79 (1H, qd,  $J = 6.6, 1.6$  Hz), 3.07-3.12 (1H, m), 3.53 (1H, brs), 5.39 (1H, dd,  $J = 15.4, 7.4$  Hz), 5.54-5.61 (1H, m);  $^{13}C$  NMR (100 MHz)  $\delta$ : 18.6, 23.8, 26.4, 29.1, 29.2, 29.3, 29.36, 29.43, 29.5, 29.9, 31.8, 32.3, 43.8, 55.6, 59.5, 67.4, 131.4, 132.7, 209.4; HREIMS  $[M]^+$ : Found, 323.2828. Calcd. for  $C_{20}H_{37}NNO_2$ : 323.2824.

**(+)-Spectraline (1).** Pd-C (3.3 mg) was added to a solution of **10** (33 mg, 0.10 mmol) in  $CH_2Cl_2$  (0.2 mL) and then MeOH (1 mL) was added under hydrogen gas atmosphere. After being stirred for 30 min, the mixture was filtered and concentrated to afford **1** (33 mg, quant.) as a yellowish oil,  $[\alpha]_D^{26} +11$  ( $c$  0.45,  $CHCl_3$ ), {natural (+)-spectaline,<sup>5</sup>  $[\alpha]_D^{25} +8.0$  ( $c$  0.27,  $CHCl_3$ )};  $^1H$  NMR (400 MHz)  $\delta$ : 1.10 (3H, d,  $J = 6.4$  Hz), 1.26-1.32 (20H, m), 1.45-1.58 (5H, m), 1.87-1.92 (1H, m), 2.14 (3H, s), 2.42 (2H, d,  $J = 7.4$  Hz),

2.51-2.55 (1H, m), 2.76 (1H, qd,  $J = 6.4, 1.4$  Hz), 3.55 (1H, brs);  $^{13}\text{C}$  NMR (100 MHz)  $\delta$ : 18.4, 23.8, 25.8, 25.9, 29.2, 29.4, 29.4, 29.5, 29.6, 29.8, 29.8, 32.0, 36.7, 43.8, 55.8, 57.2, 67.9, 209.5; HREIMS  $[\text{M}]^+$ : Found, 325.2984. Calcd. for  $\text{C}_{20}\text{H}_{39}\text{NO}_2$ : 325.2981.

## SUPPORTING INFORMATION

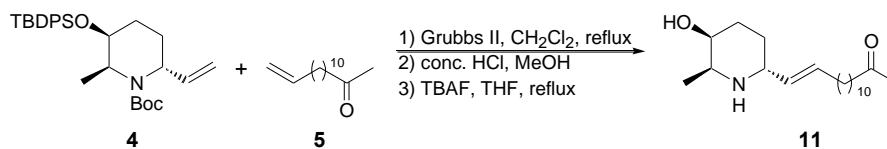
Synthetic procedure of **11** and  $^1\text{H}$  NMR data of **10** and **11**.

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14. Since the estimated *trans*-configuration of **4** could not be definitely confirmed by NOE experiments, the cyclized product **4** was converted to **11** to compare the  $^1\text{H}$  NMR spectrum with that of the intermediate **10** for (+)-spectaline (**1**). Synthesis of **11** and its  $^1\text{H}$  NMR data were included as supporting information.



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17. The diastereomers were derived from the hydroxyl group of compound 7. Although a desired single diastereomer was obtained by using Brown's chiral (–)-*B*-allyldiisopinocampheylborane in toluene prepared according to the published procedure,<sup>12</sup> small amount of an undesired diastereomer was produced when a commercially available (–)-*B*-allyldiisopinocampheylborane in hexane was used.