

## Synthesis of the Hexahydroazepine Core of (–)-Balanol

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Protein kinase C (PKC) is involved in a variety of cellular responses. As the activation of PKC is critically related to the progression of a wide range of diseases, chemotherapeutic agents that inhibit PKC have attracted a great deal of attention.

(–)-Balanol (**1**), a metabolite isolated from the fungus *Verticillium balanoides*<sup>1</sup> and *Fusarium merismoides*,<sup>2</sup> exhibits potent activity as a PKC inhibitor (Fig. 1)<sup>3</sup> and hence been an attractive target in numerous synthetic studies.<sup>4</sup> (–)-Balanol is structurally divided into two parts: a hexahydroazepine segment (with 4-hydroxybenzamide) and a benzophenone moiety. The hexahydroazepine core of (–)-balanol has also drawn the attention of the synthetic community, because it can be utilized not only for the synthesis of (–)-balanol but for an example testing a new synthetic route to introduce an amino alcohol moiety.<sup>5</sup>

Because of our interest in natural product synthesis, we attempted to employ *cis*-2,3-bis(hydroxymethyl)aziridine (**3**) as a useful synthetic intermediate for introducing an amino alcohol moiety.<sup>6</sup> Compound **3** can be easily converted into an optically active form by enzymatic desymmetrization.<sup>7</sup> We thought that **3** could be efficiently used for the synthesis of the hexahydroazepine core of (–)-balanol.

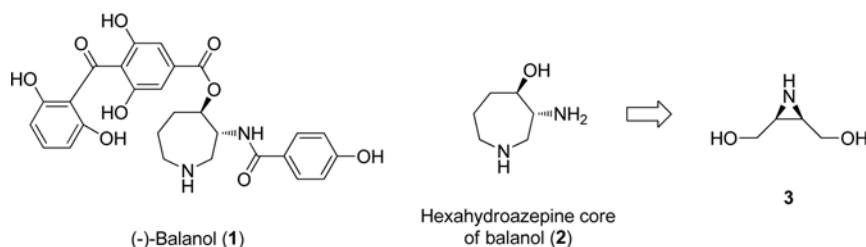
To demonstrate the potential of **3** as a versatile starting material, we decided to investigate the efficient synthetic route to (3*R*,4*R*)-hexahydroazepine core of (–)-balanol. Compound **3** could be readily obtained from *cis*-2-butene-

1,4-diol *via* a well-known synthetic sequence.<sup>6</sup> Retrosynthetic analysis of the (3*R*,4*R*)-hexahydroazepine core of (–)-balanol is summarized in Figure 2. We envisioned that hexahydroazepine core **2** can be derived from intermediate **4**, which can be synthesized from the diene **5** by ring-closing metathesis.<sup>8</sup> Diene **5**, which shows the required stereochemical relationships for the synthesis of **2**, could be prepared by the selective ring opening of aziridine **6**,<sup>9-10</sup> which in turn, could be derived from **3** by the enzymatic desymmetrization.

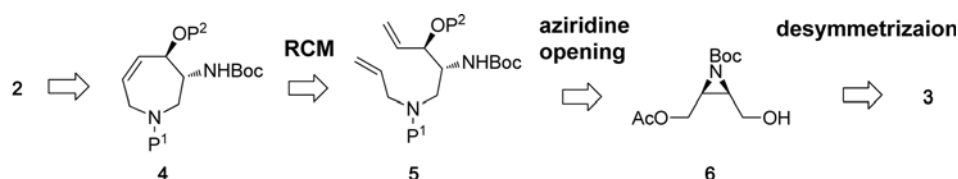
Our synthetic pathway to the (3*R*,4*R*)-hexahydroazepine core (**2**) is summarized in Scheme 1. The entire synthetic sequence is based on the availability of enantiomerically pure chiral *cis*-aziridine derivative **6**. In addition, the stereo- and regioselective ring opening of **6**, and cyclization by ring-closing metathesis to construct the azepine ring, are the two most critical reactions for the success of the synthesis.

The chiral derivative **6** was prepared from *meso*-aziridine-diol **7** by Amano PS lipase desymmetrization according to the reported procedure.<sup>7,11</sup>

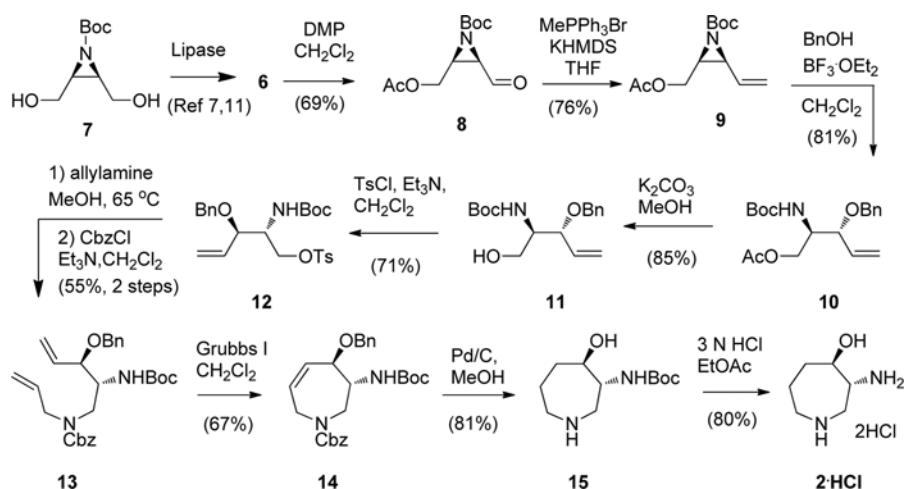
Oxidation of **6** with Dess-Martin periodinane (DMP) afforded aldehyde **8**, which was subsequently subjected to the Wittig reaction. The resulting olefin product **9** underwent regioselective aziridine ring opening.<sup>9,10</sup> Nucleophilic ring opening in the presence of a Lewis acid is useful for the introduction of 1,2-amino alcohol functionality.<sup>9</sup> With benzyl alcohol as the nucleophile, the aziridine ring was success-



**Figure 1.** Balanol and its Hexahydroazepine Core.



**Figure 2.** Retrosynthetic Analysis of the Hexahydroazepine Core of Balanol.



**Scheme 1.** Synthesis of the Hexahydroazepine Core of (–)-Balanol.

fully opened to provide a fully protected amino alcohol **10**. Deprotection and subsequent tosylation set the stage for the introduction of another amino group. After substitution with allylamine followed by protection with a Cbz group, the desired diene product **13** was successfully obtained. Next, ring-closing metathesis with Grubbs catalyst (first generation) was performed to give cyclic product **14** in reasonable yield. Both of **13** and **14** were obtained as 1:1 mixtures of rotamers due to the presence of Cbz groups for protecting amino groups. Hydrogenation of the C=C group and deprotection of the benzyl group were achieved simultaneously. Finally, deprotection of the Boc group under acidic conditions completed the synthesis of **2**. The spectroscopic data ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, optical rotation) of the product **2·HCl** were identical to those reported.<sup>4f</sup>

In conclusion, we have shown that an enantiopure chiral vinylaziridine, which is easily accessible by enzymatic desymmetrization, can be efficiently used for introducing 1,2-amino alcohol functionality. Regio- and stereoselective ring opening of the chiral aziridine in combination with ring-closing metathesis could be an efficient strategy for constructing cyclic compounds bearing vicinal amino alcohol in asymmetric manner. This strategy was successfully applied to the synthesis of the hexahydroazepine core of (–)-balanol.

## Experimental Section

**General Methods.**  $^1\text{H}$  NMR spectra were recorded on either 400 or 500 MHz spectrometer at ambient temperature with  $\text{CDCl}_3$  as the solvent unless otherwise stated.  $^{13}\text{C}$  NMR spectra were recorded on either 100 or 125 MHz spectrometer (with complete proton decoupling) at ambient temperature. High-resolution mass spectrometry (HRMS) was performed using ESI-TOF technique. Flash chromatography was performed using 230–400 mesh silica gel.

**(2*S*,3*R*)-tert-Butyl 2-(acetoxymethyl)-3-formylaziridine-1-carboxylate (8).** (2*S*,3*R*)-tert-Butyl 2-(acetoxymethyl)-3-(hydroxymethyl)aziridine-1-carboxylate (**6**) (480 mg, 1.96 mmol) prepared according to the reported procedure<sup>7,11</sup> was

dissolved in  $\text{CH}_2\text{Cl}_2$  (15 mL). To this solution was added Dess-Martin periodinane (DMP) (1.66 g, 3.92 mmol). The resulting solution was stirred for 2 h at room temperature. After the reaction was completed, aqueous saturated  $\text{NaHCO}_3$  (15 mL) and aqueous saturated  $\text{Na}_2\text{S}_2\text{O}_3$  (10 mL) were added. The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 15$  mL). The organic layer was separated, dried ( $\text{MgSO}_4$ ), and concentrated. Purification by flash chromatography (hexane:EtOAc = 4:1) offered the desired aldehyde **8** (330 mg, 69%) as a colorless oil:  $[\alpha]_D^{26} +48.5$  ( $c$  1.25,  $\text{CHCl}_3$ ); IR (film) 2979, 2936, 1714, 1516, 1367, 1245, 1167, 1048  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.41 (s, 9H), 2.02 (s, 3H), 3.04 (m, 2H), 4.14 (dd,  $J = 5.6, 12.3$  Hz, 1H), 4.29 (dd,  $J = 5.5, 12.2$  Hz, 1H), 9.32 (d,  $J = 4.8$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  195.9, 170.0, 159.3, 82.5, 60.8, 44.4, 41.1, 27.4, 20.2; HRMS-ESI ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{11}\text{H}_{17}\text{NNaO}_5$ , 266.0999; found, 266.1001.

**(2*S*,3*S*)-tert-Butyl 2-(acetoxymethyl)-3-vinylaziridine-1-carboxylate (9).** To a solution of methyltriphenylphosphonium bromide (971 mg, 2.72 mmol) in THF (10 mL) was added potassium bis(trimethylsilyl)amide (KHMDS) [5.44 mL (0.5 M in toluene), 2.72 mmol]. The resulting mixture was stirred for 30 min at  $-20$  °C. After dropwise addition of aldehyde **8** (330 mg, 1.36 mmol) dissolved in THF (2 mL) to the above solution *via* cannula, the reaction mixture was stirred for 3 h at  $-20$  °C. After the reaction was completed, aqueous saturated  $\text{NH}_4\text{Cl}$  (15 mL) was added. The mixture was extracted with ether ( $3 \times 10$  mL). The organic layer was separated, dried ( $\text{MgSO}_4$ ), and concentrated. Purification by flash chromatography (hexane:EtOAc = 7:1) offered the desired vinylaziridine **9** (249 mg, 76%) as a colorless oil:  $[\alpha]_D^{28} +50.9$  ( $c$  1.44,  $\text{CHCl}_3$ ); IR (film) 2979, 1725, 1448, 1370, 1300, 1231, 1160, 1040, 984  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.38 (s, 9H), 2.00 (s, 3H), 2.76 (q,  $J = 6.6$  Hz, 1H), 2.99 (t,  $J = 6.3$  Hz, 1H), 4.00 (m, 2H), 5.24 (m, 1H), 5.39 (td,  $J = 1.1, 17.1$  Hz, 1H), 5.61 (ddd,  $J = 6.1, 10.4, 16.9$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.5, 162.4, 131.7, 120.7, 81.8, 62.3, 42.3, 40.6, 27.8, 20.7; HRMS-ESI ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{12}\text{H}_{19}\text{NNaO}_4$ , 264.1206;

found, 264.1205.

**(2R,3R)-3-(Benzyloxy)-2-((tert-butoxycarbonyl)amino)-pent-4-en-1-yl acetate (10).** Vinylaziridine **9** (249 mg, 1.03 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at -20 °C. To this solution were added benzyl alcohol (1.13 mL, 10.30 mmol) and catalytic amount of BF<sub>3</sub>·OEt<sub>2</sub> (3 drops). The reaction mixture was stirred for 1 h at -20 °C. After the reaction was completed, aqueous saturated NaHCO<sub>3</sub> (15 mL) was added. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 mL). The organic layer was separated, dried (MgSO<sub>4</sub>), and concentrated. Purification by flash chromatography (hexane:EtOAc = 4:1) offered the desired benzyl ether **10** (292 mg, 81%) as a colorless oil: [ $\alpha$ ]<sub>D</sub><sup>30</sup> -7.6 (*c* 1.56, CHCl<sub>3</sub>); IR (film) 3401, 3030, 2871, 1695, 1496, 1454, 1366, 1244, 1167, 1022, 739 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.42 (s, 9H), 1.95 (s, 3H), 3.93 (m, 2H), 4.10 (m, 2H), 4.30 (d, *J* = 11.8 Hz, 1H), 4.60 (d, *J* = 11.8 Hz, 1H), 4.89 (bd, *J* = 9.1 Hz, 1H), 5.31 (m, 2H), 5.81 (ddd, *J* = 7.4, 10.6, 17.4 Hz, 1H), 7.31 (m, 5H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  170.6, 155.6, 137.7, 134.6, 128.3, 127.9, 127.7, 119.2, 77.6, 70.3, 63.4, 60.3, 52.6, 28.2, 20.7; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>19</sub>H<sub>27</sub>NNaO<sub>5</sub>, 372.1781; found, 372.1783.

**tert-Butyl ((2R,3R)-3-(benzyloxy)-1-hydroxypent-4-en-2-yl)carbamate (11).** To a solution of benzylether **10** (280 mg, 0.80 mmol) in methanol (7 mL) was added potassium carbonate (K<sub>2</sub>CO<sub>3</sub>) (133 mg, 0.96 mmol) at room temperature. The resulting solution was stirred for 3 h at room temperature. After reaction was completed, aqueous saturated NH<sub>4</sub>Cl solution (10 mL) was added. The mixture was extracted with ether (3 × 15 mL). The organic layer was separated, dried (MgSO<sub>4</sub>), and concentrated. Purification by flash chromatography (hexane:EtOAc = 4:1) offered the desired alcohol **11** (210 mg, 85%) as a colorless oil: [ $\alpha$ ]<sub>D</sub><sup>31</sup> -8.4 (*c* 1.42, CHCl<sub>3</sub>); IR (film) 3442, 2977, 1695, 1501, 1393, 1365, 1248, 1170, 1055, 930, 856 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.43 (s, 9H), 3.18 (bs, 1H), 3.70 (m, 3H), 4.06 (d, *J* = 4.7 Hz, 1H), 4.34 (d, *J* = 11.6 Hz, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 5.12 (bd, *J* = 7.0 Hz, 1H), 5.34 (m, 2H), 5.83 (ddd, *J* = 7.4, 10.7, 17.3 Hz, 1H), 7.31 (m, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  156.2, 137.8, 135.0, 128.3, 127.7, 127.6, 118.8, 79.4, 79.2, 70.5, 63.0, 55.4, 28.2; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>17</sub>H<sub>25</sub>NNaO<sub>4</sub>, 330.1676; found, 330.1676.

**(2R,3R)-3-(Benzyloxy)-2-((tert-butoxycarbonyl)amino)-pent-4-en-1-yl-4-methylbenzenesulfonate (12).** To a stirred solution of alcohol **11** (198 mg, 0.64 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) were added triethylamine (134  $\mu$ L, 0.96 mmol) and 4-toluenesulfonyl chloride (TsCl) (147 mg, 0.77 mmol) at 0 °C. The reaction mixture was stirred for 8 h at 0 °C. After reaction was completed, the mixture was then concentrated. The residue was dissolved with EtOAc (20 mL) and washed with water (15 mL) and brine (15 mL). The organic layer was dried (MgSO<sub>4</sub>), and concentrated. Purification by flash chromatography (hexane:EtOAc = 5:1) offered the tosylated product **12** (209 mg, 71%) as a colorless oil: [ $\alpha$ ]<sub>D</sub><sup>29</sup> -4.9 (*c* 0.82, CHCl<sub>3</sub>); IR (film) 3411, 3027, 2925, 1744, 1600, 1496, 1365, 1175, 1125, 1036, 1011 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.39 (s, 9H), 2.41 (s, 3H), 3.93 (m, 1H), 4.02 (m,

2H), 4.11 (m, 1H), 4.24 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 11.3 Hz, 1H), 4.83 (bd, *J* = 8.6 Hz, 1H), 5.33 (m, 2H), 5.77 (ddd, *J* = 7.6, 9.5, 17.5 Hz, 1H), 7.24 (d, *J* = 7.0 Hz, 2H), 7.31 (m, 5H), 7.78 (d, *J* = 8.3 Hz, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  155.2, 144.9, 137.6, 134.1, 132.6, 129.8, 128.3, 127.9, 127.8, 127.7, 119.6, 79.7, 77.4, 70.8, 67.8, 52.4, 28.2, 21.5; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>24</sub>H<sub>31</sub>NNaO<sub>6</sub>S, 484.1764; found, 484.1765.

**Benzyl N-allyl-N-((2R,3R)-3-(benzyloxy)-2-((tert-butoxycarbonyl)amino)pent-4-en-1-yl)carbamate (13).** To a stirred solution of the tosylated product **12** (200 mg, 0.43 mmol) in methanol (5 mL) was added allylamine (5 mL) at room temperature. The reaction solution was stirred for 18 h at 65 °C in a sealed tube. The reaction mixture was concentrated and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at 0 °C. To this solution were added triethylamine (1 mL, 6.77 mmol) and benzyl chloroformate (CbzCl) (121  $\mu$ L, 0.86 mmol). The solution was stirred for 4 h at 0 °C. After reaction was completed, and mixture was diluted with EtOAc (20 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was dried (MgSO<sub>4</sub>), and concentrated. Purification by flash chromatography (hexane:EtOAc = 4:1) offered the product **13** (114 mg, 55%) as a colorless oil: [ $\alpha$ ]<sub>D</sub><sup>28</sup> +5.0 (*c* 0.79, CHCl<sub>3</sub>); IR (film) 3444, 3066, 3032, 2977, 2929, 1711, 1499, 1417, 1368, 1240, 1168, 1067 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>), (mixture of rotamers)  $\delta$  1.41 (s, 9H), 3.44 (m, 2H), 3.97 (m, 4H), 4.30 (m, 1H), 4.56 (dd, *J* = 11.4, 23.6 Hz, 1H), 4.93 (m, 1H), 5.13 (m, 4H), 5.29 (m, 2H), 5.80 (m, 2H), 7.29 (m, 10H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>), (mixture of rotamers)  $\delta$  156.8, 156.1, 155.9, 155.7, 138.2, 136.7, 134.9, 133.5, 133.4, 128.3, 127.9, 127.6, 119.0, 118.8, 117.2, 116.7, 79.2, 79.1, 70.7, 70.4, 67.3, 67.2, 52.6, 50.0, 49.6, 47.7, 47.3, 28.3; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>28</sub>H<sub>36</sub>N<sub>2</sub>NaO<sub>5</sub>, 503.2516; found, 503.2516.

**(3R,4R)-Benzyl 4-(benzyloxy)-3-((tert-butoxycarbonyl)amino)-2,3,4,7-tetrahydro-1H-azepine-1-carboxylate (14).** To a stirred solution of product **13** (78 mg, 0.16 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL) at room temperature was added Grubbs catalyst (first generation) (13 mg, 0.016 mmol). The resulting light brown solution was stirred for 18 h at 40 °C. After the solution was then concentrated, purification by flash chromatography (hexane:EtOAc = 4:1) offered the desired tetrahydroazepine core **14** (48 mg, 67%) as a brown oil: [ $\alpha$ ]<sub>D</sub><sup>29</sup> -41.3 (*c* 1.65, CHCl<sub>3</sub>); IR (film) 3365, 3031, 2928, 1698, 1500, 1459, 1367, 1243, 1168, 1108, 866 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), (mixture of rotamers)  $\delta$  1.43 (s, 9H), 3.65 (m, 2H), 3.92 (m, 1H), 4.11 (m, 2H), 4.52 (m, 3H), 5.12 (s, 2H), 5.83 (m, 2H), 7.32 (m, 10H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>), (mixture of rotamers)  $\delta$  156.4, 155.8, 155.2, 138.1, 138.0, 136.4, 131.6, 131.0, 130.6, 128.8, 128.5, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 79.4, 79.2, 76.2, 71.5, 71.1, 67.5, 67.4, 53.3, 52.1, 49.8, 48.8, 47.8, 47.2, 28.3; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>26</sub>H<sub>32</sub>N<sub>2</sub>NaO<sub>5</sub>, 475.2203; found, 475.2208.

**tert-Butyl ((3R,4R)-4-hydroxyazepan-3-yl)carbamate (15).** To a solution of tetrahydroazepine core **14** (31 mg,

0.069 mmol) in methanol (8 mL) was treated with palladium, 5 wt % on activated carbon (62 mg) under an atmosphere of hydrogen for 18 h at room temperature. After filtration through a pad of Celite with methanol (3 × 10 mL), the solution was concentrated. Purification by flash chromatography (EtOAc:methanol = 10:1) offered the desired product **15** (13 mg, 81%) as a brown oil:  $[\alpha]_D^{27} +11.11$  (*c* 0.82, CHCl<sub>3</sub>); IR (film) 3321, 2927, 1702, 1526, 1367, 1248, 1169, 1015 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.45 (s, 9H), 1.57 (m, 1H), 1.70 (m, 1H), 1.85 (m, 2H), 2.37 (m, 2H), 2.49 (m, 1H), 2.76 (m, 2H), 2.72 (m, 1H), 2.88 (d, *J* = 13.9 Hz, 1H), 3.55 (m, 1H), 3.80 (m, 1H), 5.54 (bs, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 156.3, 79.6, 75.2, 59.0, 56.4, 48.1, 30.7, 28.4, 22.7; HRMS-ESI (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub>, 231.1703; found, 231.1701.

**(3R,4R)-3-aminoazepan-4-ol dihydrochloride (2·HCl).** The product **15** (11 mg, 0.048 mmol) in EtOAc (3 mL) was added 3 N HCl (2 mL) at room temperature. The resulting solution was stirred for 3 h at room temperature. After the reaction was completed, and the solution was then concentrated *in vacuo*. The residue was taken up into water (5 mL) and washed with CH<sub>2</sub>Cl<sub>2</sub> (2 × 5 mL), and concentrated to provide the desired product (**2·HCl**, 7.0 mg, 80%) as a white salt: mp 176–178 °C;  $[\alpha]_D^{27} -19.1$  (*c* 0.38, MeOH); IR (film) 3400, 1626, 1458, 1055 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ 1.76 (m, 1H), 1.87 (m, 1H), 2.05 (m, 1H), 2.25 (m, 1H), 3.33 (m, 2H), 3.40 (m, 1H), 3.59 (m, 2H), 3.87 (ddd, *J* = 4, 6, 9.5, 9.5 Hz, 1H); <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O) δ 71.2, 53.3, 46.0, 42.1, 31.8, 18.5; HRMS-ESI (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>6</sub>H<sub>15</sub>N<sub>2</sub>O, 131.1179; found, 131.1178.

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