

HETEROCYCLES, Vol. 95, No. 2, 2017, pp. 1230-1244. © 2017 The Japan Institute of Heterocyclic Chemistry  
Received, 13th September, 2016, Accepted, 17th October, 2016, Published online, 18th November, 2016  
DOI: 10.3987/COM-16-S(S)74

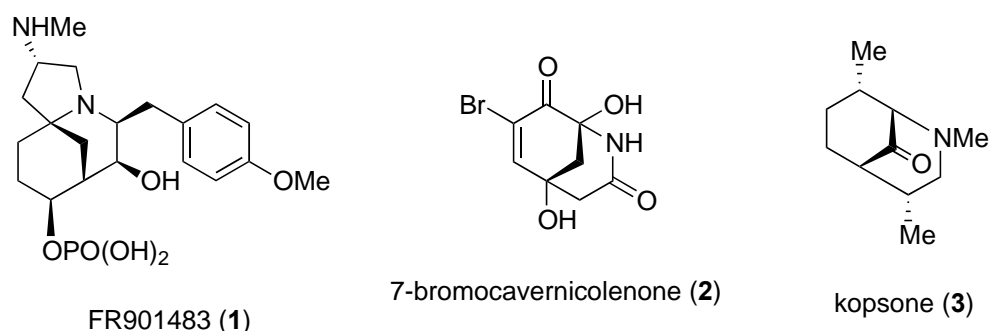
## SYNTHESIS OF A FUNCTIONALIZED MORPHAN SCAFFOLD VIA A PALLADIUM-CATALYZED CYCLOALKENYLATION AND BECKMANN REARRANGEMENT

Natsuko Kagawa,<sup>1</sup> Yutaka Yamamoto,<sup>2</sup> Shuichiro Ono,<sup>2</sup> and Masahiro Toyota\*<sup>2</sup>

<sup>1</sup>) Center for Environment, Health and Field Sciences, Chiba University, 6-2-1 Kashiwa-no-ha, Kashiwa 277-0882, Japan. <sup>2</sup>) Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan.  
E-mail: toyota@c.s.osakafu-u.ac.jp

**Abstract** – Functionalized 2-azabicyclo[3.3.1]nonan-3-ones, potential precursors to morphan, were assembled using a combination of a palladium-catalyzed cycloalkenylation and a Beckmann rearrangement.

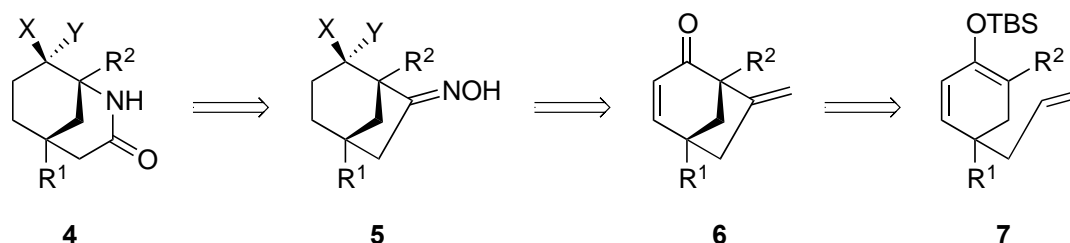
The 2-azabicyclo[3.3.1]nonane (morphan) scaffold is present in a variety of bioactive alkaloids, including FR901483 (**1**),<sup>1</sup> 7-bromocavernicolone (**2**),<sup>2</sup> and kopsone (**3**),<sup>3</sup> as illustrated in Figure 1, and several synthetic methodologies for the construction of this morphan scaffold have been developed.<sup>4</sup>



**Figure 1**

During an effort to demonstrate the utility of the bicyclo[3.2.1]octane ring system, which may be easily obtained *via* a palladium-catalyzed cycloalkenylation,<sup>5</sup> we became interested in assembling 2-azabicyclo[3.3.1]nonan-3-ones, potential precursors to morphan, using a combination of a palladium-catalyzed cycloalkenylation and a Beckmann rearrangement,<sup>6</sup> as depicted in Scheme 1. We

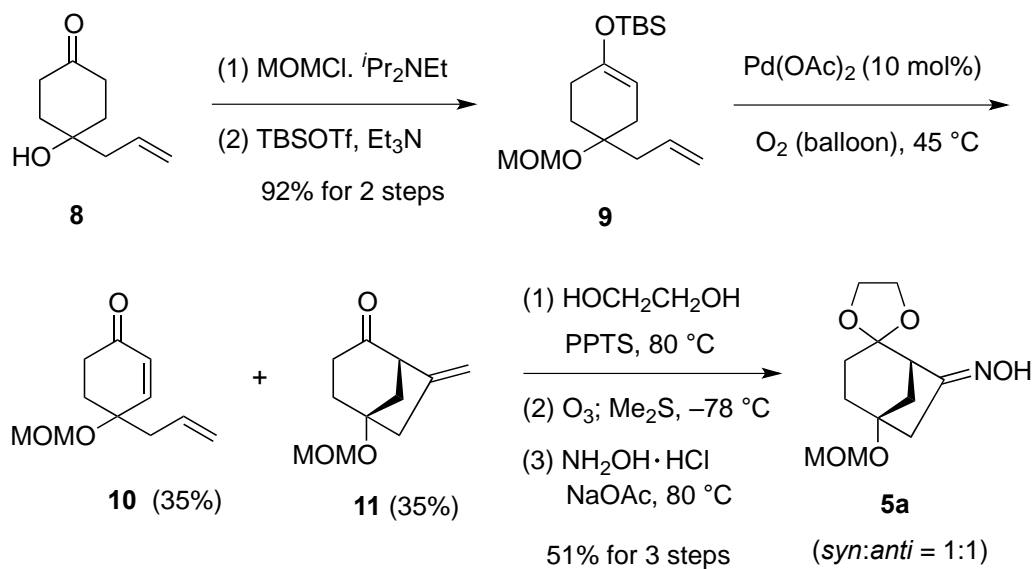
expected that the 2-azabicyclo[3.3.1]nonan-3-ones **4** could be produced by the Beckmann rearrangement of the oximes **5**, which could be synthesized from the *exo*-olefins **6** via functional group manipulations. We anticipated that a variety of bicyclo[3.2.1]octanes **6** could be prepared from the cross-conjugated silyl enol ethers **7** in the presence of a catalytic amount of Pd(OAc)<sub>2</sub>.



**a:** R<sup>1</sup>=OMOM, R<sup>2</sup>=H, X=Y=OCH<sub>2</sub>-; **b:** R<sup>1</sup>=CH<sub>2</sub>OMOM, R<sup>2</sup>=H, X=Y=H; **c:** R<sup>1</sup>=CH<sub>2</sub>OMOM, R<sup>2</sup>=H, X=Y=OCH<sub>2</sub>-; **d:** R<sup>1</sup>=CH<sub>2</sub>OMOM, R<sup>2</sup>=Me, X=Y=OCH<sub>2</sub>-; **e:** R<sup>1</sup>=CH<sub>2</sub>OMOM, R<sup>2</sup>=H, X=H, Y=OMe.

**Scheme 1**

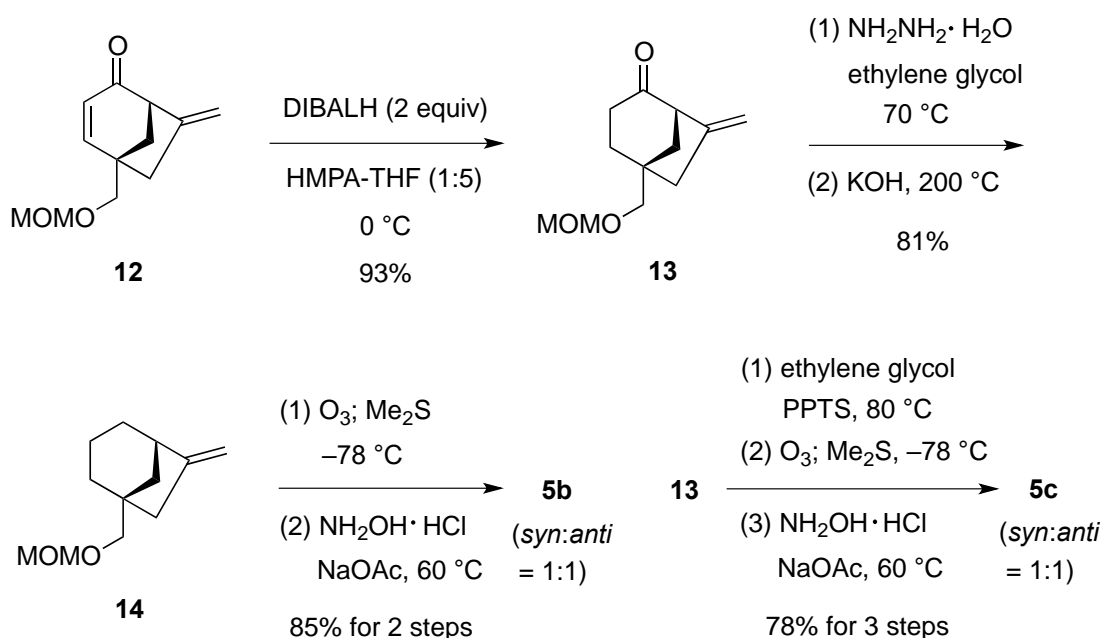
At the outset of the study, five different types of oximes **5a-e** were selected as model substrates for the Beckmann rearrangement. The oxime **5a** was prepared as depicted in Scheme 2. After protection of the tertiary alcohol moiety in **8**<sup>7</sup> with MOMCl in the presence of Hünig's base, followed by silylation using TBSOTf and Et<sub>3</sub>N, the silyl enol ether **9** was isolated in 92% yield over two steps. The bicyclo[3.2.1]octane **11** was constructed in 35% yield through a palladium-catalyzed cycloalkenylation of



**Scheme 2**

**9** in the presence of 10 mol% Pd(OAc)<sub>2</sub> under oxygen (delivered by balloon). At this stage, the enone **10** was also generated in 35% yield. Increasing or decreasing the loading of Pd(OAc)<sub>2</sub> did not improve the yield of product **11**. A diminished chemical yield of **11** was observed at reaction temperatures of room temperature or 80 °C. Fortunately, the desired compound **11** was easily isolated by flash column chromatography. Next, the carbonyl group in **11** was transformed to the corresponding ketal using ethylene glycol and PPTS (pyridinium *p*-toluenesulfonate) at 80 °C. Additionally, the *exo*-olefin part of the ketal compound above was converted into a ketone moiety by ozonolysis, followed by a reductive workup. The desired oxime **5a** was obtained in 51% yield over three steps as a 1:1 mixture of a *syn* isomer and an *anti* isomer *via* condensation with hydroxylamine hydrochloride in the presence of sodium acetate at 80 °C (Scheme 2).

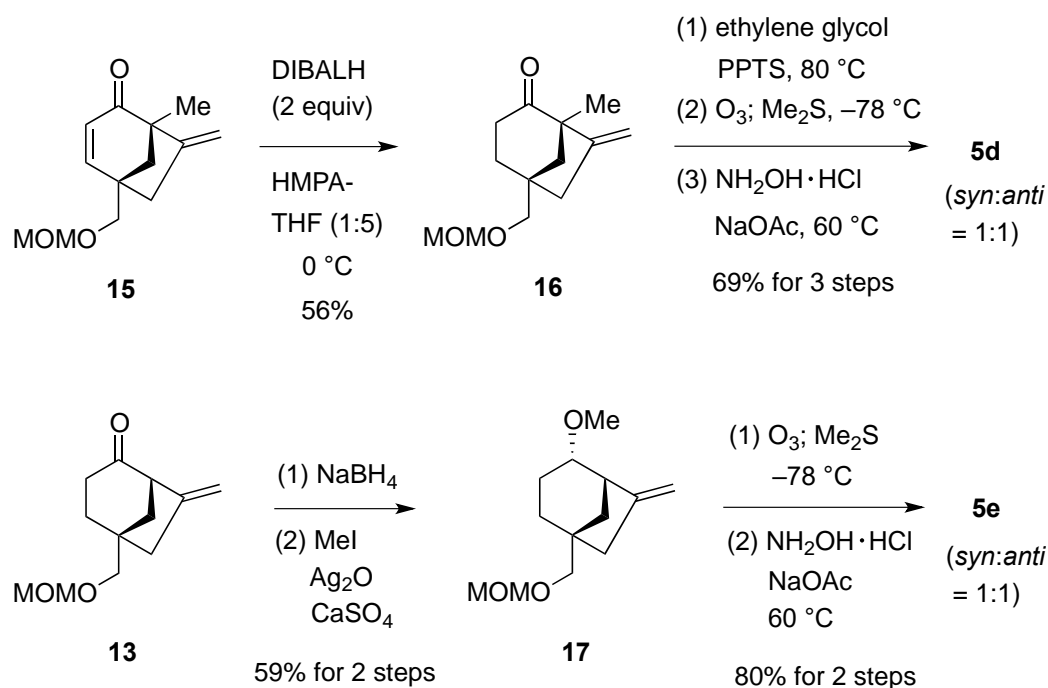
The oximes **5b** and **5c** were synthesized from the bicyclic enone **12**<sup>5d</sup> (Scheme 3). 1,4-Hydride reduction of **12** was performed using two equivalent DIBALH at 0 °C in a 1:5 v/v mixture of HMPA and THF, giving rise to the ketone **13** in 93% yield. The ketone **13** was also obtained in 88% yield from **12** using L-Selectride<sup>®</sup>. The Wolff–Kishner reduction of **13** provided the *exo*-olefin **14** in 81% yield. **14** was then transformed into the desired oxime **5b** in 85% yield over two steps *via* ozonolysis, followed by condensation. On the other hand, the ketone **13** was converted to the oxime **5c** in three steps, as described in Scheme 2.



**Scheme 3**

Two different oximes **5d** and **5e** were constructed as shown in Scheme 4. The conjugate reduction of the enone **15**<sup>5f</sup> with two equivalents of DIBALH furnished the ketone **16** in 56% yield. **16** was then

transformed into the oxime **5d** in 69% yield over three steps. Further, the ketone **13** was subjected to NaBH<sub>4</sub> reduction, followed by methylation<sup>8</sup> of the resulting secondary alcohol moiety with MeI in the presence of Ag<sub>2</sub>O and CaSO<sub>4</sub> to provide **17** in 59% yield over two steps. The relative stereochemistry of **17** was determined using NOE experiments, as depicted in Figure 2. Finally, ozonolysis of **17** and condensation with hydroxylamine afforded the oxime **5e**.



Scheme 4

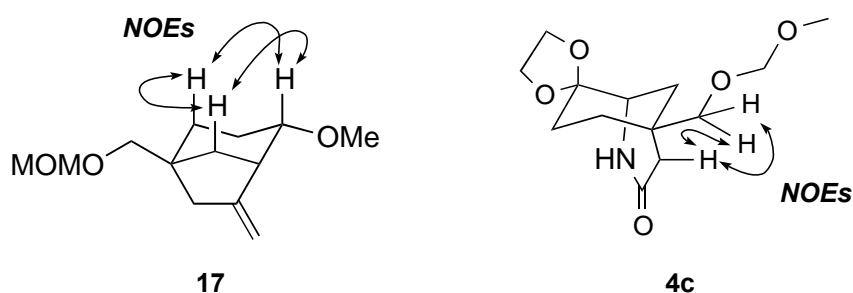
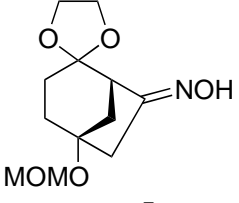
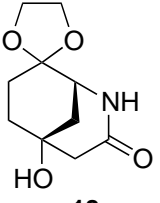
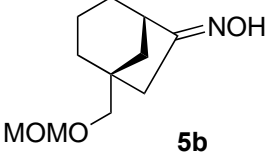
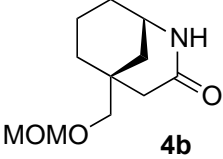
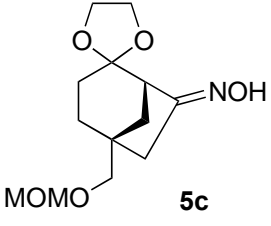
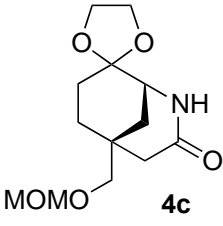
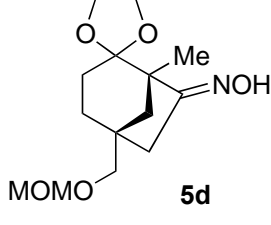
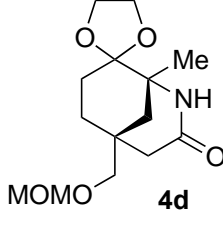
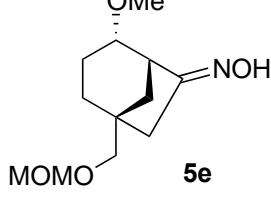
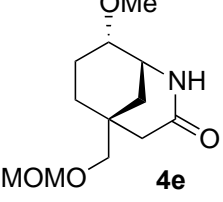


Figure 2

With the oximes **5a-e** in hand, the Beckmann rearrangement of **5a-e** was examined. We found that a combination of TsCl and pyridine (as the solvent) provided the most suitable conditions for this rearrangement. Table 1 summarizes the results. Although the desired rearrangement of **5a** proceeded, the MOM (methoxymethyl) protection group was removed under these reaction conditions. The amide alco-

**Table 1.** Beckmann rearrangement of oximes **5a-e**

entry	oxime	product	time (h)	yield (%)
1	 <b>5a</b>	 <b>18</b>	13	71
2	 <b>5b</b>	 <b>4b</b>	48	82
3	 <b>5c</b>	 <b>4c</b>	86	81
4	 <b>5d</b>	 <b>4d</b>	72	75 (89) <sup>a</sup>
5	 <b>5e</b>	 <b>4e</b>	72	65 (80) <sup>a</sup>

(a) Values in parentheses refer to yield based upon recovered starting materials.

hol **18** was isolated in 71% yield (entry 1). The oxime **5b** gave the best yield (82%) (entry 2). The ketal moiety was compatible with the reaction conditions (entry 3). The oximes **5d** and **5e** gave the desired products, revealing no obvious electronic or steric effects during this transformation (entries 4 and 5). As a result, the Beckmann rearrangement of the oximes **5a-e** proceeded in a regioselective manner, and the

desired 2-azabicyclo[3.3.1]nonan-3-ones **18** and **4b-e** were formed without by-products. The relative stereochemistry of the amide **4c** was established from the NOE correlations (Figure 2).

We calculated the conformational energies of the oxime tosylates **5b-anti** and **5b-syn**, which were derived *in situ* from the oxime **5b**. The calculation was performed at the DFT/B3LYP/6-31\* level using the Spartan program (Spartan '14 for Windows, Wavefunction, Inc., Irvine, CA). The conformation **5b-anti**, which was suitable for the desired Beckmann rearrangement, was 4.2 kJ/mol more stable than the other conformation, **5b-syn**, as shown in Figure 3.

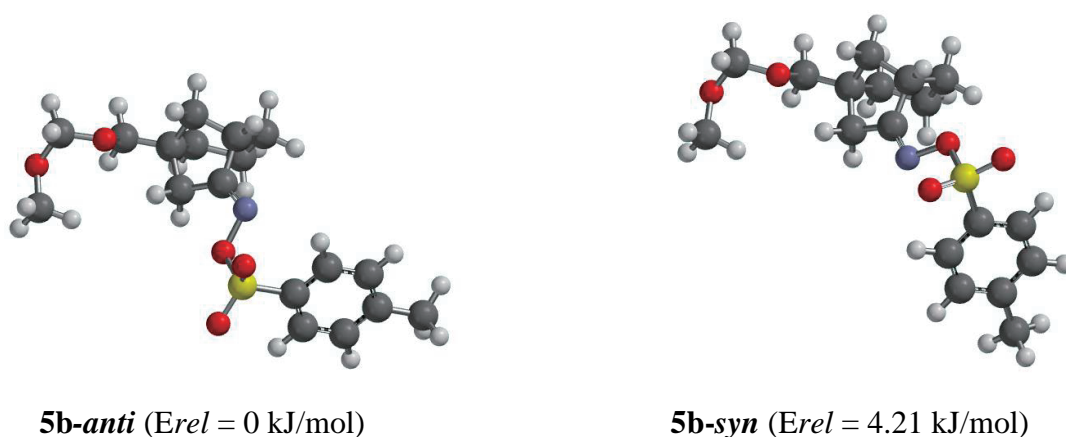


Figure 3

In conclusion, five distinctly functionalized 2-azabicyclo[3.3.1]nonan-6-ones **18** and **4b-e** were synthesized by means of the Beckmann rearrangement of the oximes **5a-e**. The oximes were synthesized using a palladium-catalyzed cyclolakenylation as a key reaction. The methodology developed here should provide access to bioactive natural products, such as **1**, **2** and **3**.

### General Experimental

**Reaction Setup:** All reactions were carried out in heat gun dried glassware under an atmosphere of dry argon unless otherwise indicated.

**Solvents:** Anhydrous THF, Et<sub>2</sub>O, and CH<sub>2</sub>Cl<sub>2</sub> were purchased from Kanto Chemical Co. Inc. DMSO and HMPA were distilled from CaH<sub>2</sub> under reduced pressure. TMSCl, pyridine, Et<sub>3</sub>N, and *i*-Pr<sub>2</sub>NEt were distilled from CaH<sub>2</sub> prior to use. C<sub>6</sub>H<sub>6</sub> was distilled from P<sub>2</sub>O<sub>5</sub>. MOMCl was distilled and used immediately. TsCl was dissolved in Et<sub>2</sub>O, washed with 10% aqueous NaOH solution, dried over MgSO<sub>4</sub> and recrystallized from Et<sub>2</sub>O.

**Chemicals:** Unless otherwise mentioned, materials were obtained from commercial suppliers and used without further purification.

**Flash Column Chromatography:** Flash column chromatography was performed using Cica Silica Gel

60N (40-50 mm particle size/spherical/neutral).

**Spectroscopies:**  $^1\text{H}$  NMR spectra were recorded on Varian 400 MR (400 MHz) or JEOL JX-500 (500 MHz) spectrometers. Chemical shifts were reported relative to residual  $\text{CHCl}_3$  ( $\delta$  7.26 ppm).  $^{13}\text{C}$  NMR spectra were recorded on Varian 400 MR (100 MHz) or JEOL LX-500 (125 MHz) spectrometers. Chemical shifts were reported relative to  $\text{CDCl}_3$  ( $\delta$  77.2 ppm). IR spectra were measured on a SHIMADZU FT-IR 8300 spectrophotometer. Mass spectra were recorded on JEOL JMS-DX 303 and JEOL JMS-AX 700 spectrometers.

**((4-Allyl-4-(methoxymethoxy)cyclohex-1-en-1-yl)oxy)(tert-butyl)dimethylsilane (9).** To a stirred solution of alcohol **8** (1.67 g, 10.8 mmol) in  $\text{CH}_2\text{Cl}_2$  (80 mL) were added successively *i*-Pr<sub>2</sub>NEt (3.0 mL, 17.2 mmol) and MOMCl (1.3 mL, 17.1 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and at rt for 4 h. To the mixture were added an additional *i*-Pr<sub>2</sub>NEt (3.0 mL, 17.2 mmol) and MOMCl (1.3 mL, 17.1 mmol) and the resulting mixture was stirred at rt for 15 h. To the mixture was added water and the resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over  $\text{MgSO}_4$ . Removal of the solvent and column chromatography of the residue with hexane-EtOAc (2.5:1) as an eluent afforded the corresponding ketone (1.99 g, 93%) as a colorless oil.

IR (neat) 1715.4  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  5.87-5.76 (m, 1H), 5.13-5.06 (m, 2H), 4.81 (s, 2H), 3.44 (s, 3H), 2.67 (ddd, 2H,  $J = 6.0, 14.0$  and  $14.2$  Hz), 2.38 (ddd, 2H,  $J = 1.2, 1.2$  and  $7.2$  Hz), 2.25-2.12 (m, 4H) and 1.79-1.71 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  212.0, 133.2, 118.6, 91.2, 75.6, 56.3, 42.9, 37.0 and 34.6. LRMS  $m/z$  198 ( $\text{M}^+$ -MOM); HRMS calcd for  $\text{C}_{11}\text{H}_{18}\text{O}_3$  198.1256, found: 198.1262.

To a stirred solution of the above ketone (1.61g, 8.13 mmol) and  $\text{Et}_3\text{N}$  (2.3 ml, 16.5 mmol) in  $\text{CH}_2\text{Cl}_2$  was added dropwise TBSOTf (2.8 mL, 12.2 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of saturated aqueous  $\text{NaHCO}_3$  solution. The layers were separated, and the aqueous layer was extracted three times with  $\text{Et}_2\text{O}$ . The combined organic layers were washed with brine and dried over  $\text{MgSO}_4$ . Removal of the solvent and column chromatography of the residue with hexane-EtOAc (25:1) as an eluent afforded TBS enol ether **9** (2.58 mg, 99%) as a colorless oil. IR (neat) 1673.0  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 400 MHz)  $\delta$  6.05-5.95 (m, 1H), 5.12-5.03 (m, 2H), 4.82-4.80 (m, 1H), 4.67 (dd, 2H,  $J = 7.6$  and  $10.8$  Hz), 3.27 (s, 3H), 2.42-2.25 (m, 4H), 2.09-1.99 (m, 2H), 1.89-1.82 (m, 1H), 1.63-1.56 (m, 1H), 1.04 (s, 9H) and 0.18 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{C}_6\text{D}_6$ , 100 MHz)  $\delta$  150.0, 134.8, 117.3, 101.0, 91.2, 75.5, 55.4, 42.4, 33.4, 31.8, 27.7, 25.9, 18.3 and -4.3. LRMS  $m/z$  312 ( $\text{M}^+$ ); HRMS calcd for  $\text{C}_{17}\text{H}_{32}\text{O}_3\text{Si}$  312.2121, found: 312.2133.

**4-Allyl-4-(methoxymethoxy)cyclohex-2-en-1-one (10).**

**(1S\*,5S\*)-5-(Methoxymethoxy)-7-methylenebicyclo[3.2.1]octan-2-one (11).** To a stirred solution of

TBS enol ether **9** (157.7 mg, 0.51 mmol) in DMSO (5.0 mL) was added Pd(OAc)<sub>2</sub> (12.2 g, 0.05 mmol) at rt, and the resulting solution was stirred at 45 °C for 87.5 h under oxygen (balloon). The reaction mixture was diluted with Et<sub>2</sub>O and filtered to remove palladium black. H<sub>2</sub>O was added to the filtrate at 0 °C and the layers were separated. The aqueous layer was extracted three times with Et<sub>2</sub>O, and the combined organic layer was washed with saturated aqueous NaHCO<sub>3</sub> solution, brine, and dried over MgSO<sub>4</sub>. Removal of the solvent and column chromatography of the residue with hexane-EtOAc (4:1) as an eluent afforded enone **10** (35.1 mg, 35%) as a colorless oil, along with bicyclo[3.2.1]octanone **11** (35.2 mg, 35%) as a colorless oil. These products were clearly separated by flash column chromatography.

Enone **10**: IR (neat) 1684.5 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 6.84 (d, 1H, *J* = 10.4 Hz), 6.02 (d, 1H, *J* = 10.4 Hz), 5.91-5.81 (m, 1H), 5.18-5.11 (m, 2H), 4.77-4.73 (m, 2H), 3.37 (s, 3H), 3.19-2.54 (m, 2H), 2.49-2.37 (m, 2H), 2.30-2.23 (m, 1H) and 2.11-2.04 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 199.0, 152.3, 132.5, 130.3, 119.1, 91.9, 75.2, 55.6, 43.0, 34.5 and 32.5. LRMS *m/z* 156 (M<sup>+</sup>-MOM); HRMS calcd for C<sub>11</sub>H<sub>16</sub>O<sub>3</sub> 196.1099, found: 196.1066.

Ketone **11**: IR (neat) 1720.2 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 5.01 (d, 2H, *J* = 23.6 Hz), 4.76 (s, 2H), 3.38 (s, 3H), 3.23 (d, 1H, *J* = 5.6 Hz), 2.77 (s, 1H), 2.60-2.51 (m, 1H), 2.33-2.23 (m, 2H) and 2.19-1.99 (m, 4H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 208.2, 145.0, 110.3, 92.5, 81.3, 58.5, 55.6, 41.4, 41.2, 35.2 and 34.4. LRMS *m/z* 196 (M<sup>+</sup>); HRMS calcd for C<sub>11</sub>H<sub>16</sub>O<sub>3</sub> 196.1099, found: 196.1093.

**(1S\*,5S\*)-5-(Methoxymethoxy)spiro[bicyclo[3.2.1]octane-2,2'-[1,3]dioxolan]-7-one oxime (5a)**. A solution of the ketone **11** (105.4 mg, 0.50 mmol), ethylene glycol (0.3 mL, 5.37 mmol) and PPTS (12.6 mg, 0.012 mmol) in C<sub>6</sub>H<sub>6</sub> (5.0 mL) was refluxed at 90 °C for 1 h under a Dean–Stark apparatus. The solution was cooled to rt, and then saturated aqueous NaHCO<sub>3</sub> solution was added. The layers were separated, and the aqueous layer was extracted three times with Et<sub>2</sub>O. The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> solution, brine, and dried over MgSO<sub>4</sub>. Removal of the solvent and column chromatography of the residue with hexane-EtOAc (4:1) as an eluent afforded the desired ketal (99.6 mg, 83%) as a colorless oil. IR (neat) 1077.1 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 5.00 (s, 1H), 4.92 (s, 1H), 4.73 (s, 2H), 4.01-3.87 (m, 4H), 3.36 (s, 3H), 2.58 (d, 1H, *J* = 4.8 Hz), 2.52 (s, 2H), 2.08 (d, 1H, *J* = 11.2 Hz), 1.97-1.75 (m, 4H) and 1.69-1.63 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 147.6, 109.9, 109.2, 92.3, 81.8, 64.7, 64.4, 55.3, 50.9, 40.9, 40.0, 34.1 and 30.4. LRMS *m/z* 240 (M<sup>+</sup>); HRMS calcd for C<sub>13</sub>H<sub>20</sub>O<sub>4</sub> 240.1362, found: 240.1361.

Ozone was bubbled through a stirred solution of the above compound (15.7 mg, 65.0 μmol) in MeOH (5.0 mL) at -78 °C for 0.5 h. After removal of excess ozone, Me<sub>2</sub>S (0.05 mL, 0.68 mmol) was added at -78 °C, and the resulting mixture was stirred at rt for 15 h. Removal of the solvent and column chromatography of the residue with hexane-EtOAc (4:1) as an eluent afforded the corresponding ketone (1.07 g, 83%) as a colorless oil. IR (neat) 1748.2 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 4.73 (s, 2H),

4.00-3.91 (m, 4H), 3.37 (s, 3H), 2.57-2.36 (m, 4H), 2.13-1.96 (m, 3H) and 1.96-1.66 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  212.2, 107.4, 92.2, 79.2, 64.9, 64.7, 57.3, 55.5, 48.3, 38.4, 33.2 and 31.7. LRMS  $m/z$  242 ( $\text{M}^+$ ); HRMS calcd for  $\text{C}_{12}\text{H}_{18}\text{O}_5$  242.1154, found: 242.1159.

To a stirred solution of the above ketone (76.6 mg, 0.32 mmol) and NaOAc (50.2 mg, 0.64 mmol) in THF- $\text{H}_2\text{O}$  (1:1 v/v) (6.0 mL) was added  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (32.1 mg, 0.46 mmol) at 0 °C. The mixture was stirred at 60 °C for 3 h and quenched by addition of saturated aqueous  $\text{NaHCO}_3$  solution. After removal of the solvent, the resulting mixture was extracted three times with EtOAc, and then the combined organic layers were washed with saturated aqueous  $\text{NaHCO}_3$  solution, brine and dried over  $\text{MgSO}_4$ . Removal of the solvent and column chromatography of the residue with hexane-EtOAc (4:1) as an eluent afforded oxime **5a** (56.6 mg, 74%) as a colorless solid. IR (neat) 1075.1, 1652.7 and 3366.1  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  4.76 (s, 2H), 4.03-3.91 (m, 4H), 3.38 (s, 3H), 2.79-2.57 (m, 3H), 2.23-2.16 (m, 1H), 2.04-1.65 (m, 5H), 1.61 (s, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  161.2, 108.7, 92.2, 80.3, 64.9, 64.8, 55.5, 48.5, 39.3, 36.9, 33.6 and 31.0. LRMS  $m/z$  257 ( $\text{M}^+$ ); HRMS calcd for  $\text{C}_{12}\text{H}_{19}\text{O}_5\text{N}$  257.1263, found: 257.1257.

**(1S\*,5S\*)-5-((Methoxymethoxy)methyl)-7-methylenebicyclo[3.2.1]octan-2-one (13).**

(Method A) To a stirred solution of DIBALH (1.02 M in hexane, 0.927 mL, 0.954 mmol) in a mixture of HMPA (2 mL) and THF (19 mL) was added a THF solution (0.1 mL) of enone **12** (98.3 mg, 0.472 mmol) at 0 °C. The reaction was stirred at 0 °C for 2 h, and then carefully quenched by addition of water. The resulting mixture was extracted with EtOAc and the organic layer was washed with saturated aqueous  $\text{NaHCO}_3$  solution, brine, and dried over  $\text{MgSO}_4$ . Removal of the solvent and column chromatography of the residue with hexane-EtOAc (4:1) as an eluent afforded ketone **13**<sup>5d</sup> (92.0 mg, 93%) as an oil.

(Method B) To a stirred solution of enone **12** (2.29 g, 11.0 mmol) in THF (100 mL) was added dropwise L-Selectride<sup>®</sup> (1.0 M in THF, 11.5 mL, 11.5 mmol) at -78 °C. The mixture was stirred at -78 °C for 3 h, and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  solution. After removal of the solvent, the resulting mixture was extracted three times with  $\text{Et}_2\text{O}$ . The combined organic layers were washed with saturated aqueous  $\text{NaHCO}_3$  solution, brine and dried over  $\text{MgSO}_4$ . Removal of the solvent and column chromatography of the residue with hexane-EtOAc (4:1) as an eluent afforded ketone **13** (2.04 g, 88%) as a colorless oil.

**(1S\*,5S\*)-1-((Methoxymethoxy)methyl)-6-methylenebicyclo[3.2.1]octane (14).**

Ketone **13** (34.0 mg, 0.16 mmol) was dissolved in ethylene glycol (3.0 mL), and then  $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$  (160 mg, 3.20 mmol) was added at rt. The mixture was heated at 70 °C for 3 h. After cooling to rt, KOH (50 mg, 0.89 mmol) was added, and then the resulting mixture was heated at 200 °C for 14 h. The mixture was cooled to 0 °C, and then quenched by addition of saturated aqueous  $\text{NH}_4\text{Cl}$  solution. After addition of EtOAc, the layers were separated. The aqueous layer was extracted three times with EtOAc, and then the

combined organic layers were washed with brine and dried over  $\text{MgSO}_4$ . Removal of the solvent and column chromatography of the residue with hexane-EtOAc (10:1) as an eluent furnished **14** (26.0 mg, 81%) as a colorless oil. IR (neat) 1048.1, 1109.8 and 1148.4  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  4.82-4.77 (m, 2H), 3.32 (s, 2H), 2.64 (s, 1H), 2.18 (s, 1H) and 1.65-1.23 (m, 14H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  155.8, 104.0, 96.8, 75.8, 55.1, 44.0, 43.6, 41.9, 39.9, 34.6, 34.0, 29.8 and 19.4. LRMS  $m/z$  196 ( $\text{M}^+$ ); HRMS calcd for  $\text{C}_{12}\text{H}_{20}\text{O}_2$  196.1463, found: 196.1442.

**(1S\*,5S\*)-1-((Methoxymethoxy)methyl)bicyclo[3.2.1]octan-6-one oxime (5b).**

Ozone was bubbled through a stirred solution of the olefin **14** (136.2 mg, 0.75 mmol) in MeOH (10 mL) at  $-78\text{ }^\circ\text{C}$  for 30 min. After removal of excess ozone,  $\text{Me}_2\text{S}$  (0.55 mL, 7.5 mmol) was added at  $-78\text{ }^\circ\text{C}$ , and then the resulting mixture was stirred at rt for 12 h. Removal of the solvent and column chromatography of the residue with hexane-EtOAc (4:1) as an eluent afforded the corresponding ketone (127.5 mg, 93%) as a colorless oil. IR (neat) 1741.4  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  4.62 (s, 2H), 3.42 (s, 2H), 3.34 (s, 3H), 2.20 (d, 1H,  $J = 18.4$  Hz), 2.05 (dd, 1H,  $J = 3.2, 18.4$  Hz), 1.96-1.84 (m, 2H) and 1.74-1.49 (m, 7H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  221.1, 96.7, 74.5, 55.3, 47.6, 46.4, 42.1, 39.2, 33.6, 30.3 and 19.4. LRMS  $m/z$  198 ( $\text{M}^+$ ); HRMS calcd for  $\text{C}_{11}\text{H}_{18}\text{O}_3$  198.1256, found: 198.1249.

To a stirred solution of the above ketone (77.8 mg, 0.42 mmol) and NaOAc (67.7 mg, 0.83 mmol) in THF- $\text{H}_2\text{O}$  (1:1 v/v, 5 mL) was added  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (48.3 mg, 0.70 mmol) at  $0\text{ }^\circ\text{C}$ . The mixture was stirred at  $60\text{ }^\circ\text{C}$  for 3 h, and then quenched by addition of saturated aqueous  $\text{NaHCO}_3$  solution. After removal of the solvent, the resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with saturated aqueous  $\text{NaHCO}_3$  solution, brine and dried over  $\text{MgSO}_4$ . Removal of the solvent and column chromatography of the residue with hexane-EtOAc (4:1) as an eluent afforded oxime **5b** (76.4 mg, 91%) as a colorless solid. IR (neat) 1682.6, 3126.0 and 3235.0  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  4.62 (s, 2H), 3.39 (s, 2H), 3.35 (s, 3H), 2.83 (dd, 1H,  $J = 4.9$  and 4.9 Hz), 2.45-2.23 (m, 2H) and 1.77-1.35 (m, 8H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  168.2, 96.7, 74.8, 55.2, 42.5, 40.8, 40.4, 35.2, 34.0, 32.2 and 19.3. LRMS  $m/z$  213 ( $\text{M}^+$ ); HRMS calcd for  $\text{C}_{11}\text{H}_{19}\text{O}_3\text{N}$  213.1365, found: 213.1406.

**(1S\*,5S\*)-5-((Methoxymethoxy)methyl)spiro[bicyclo[3.2.1]octane-2,2'-[1,3]di-oxolan]-7-one oxime (5c).**

A solution of the crude ketone (90.0 mg, 0.43 mmol), ethylene glycol (0.3 mL, 21.0 mmol) and PPTS (10.8 mg, 0.043 mmol) in  $\text{C}_6\text{H}_6$  (20 mL) was refluxed at  $110\text{ }^\circ\text{C}$  for 1 h under a Dean–Stark apparatus. The solution was cooled to rt, and then saturated aqueous  $\text{NaHCO}_3$  solution was added. The layers were separated, and then the aqueous layer was extracted three times with  $\text{Et}_2\text{O}$ . The combined organic layers were washed with saturated aqueous  $\text{NaHCO}_3$  solution, brine, and dried over  $\text{MgSO}_4$ . Removal of the solvent and column chromatography of the residue with hexane-EtOAc (4:1) as an eluent afforded the corresponding ketal (87.4 mg, 80%) as a colorless oil. IR (neat) 1079.0  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  5.04-4.90 (m, 2H), 4.61 (s, 2H), 4.01-3.88 (m, 4H), 3.40 (dd, 2H,  $J = 9.3$  and 11.7

Hz), 3.34 (s, 3H), 2.58 (d, 1H,  $J = 4.9$  Hz), 2.27-2.25 (m, 2H), 1.85-1.74 (m, 2H) and 1.64-1.57 (m, 4H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  108.1, 96.8, 74.7, 64.7, 64.4, 51.6, 38.3, 32.4 and 29.8. LRMS  $m/z$  254 ( $\text{M}^+$ ); HRMS calcd for  $\text{C}_{14}\text{H}_{22}\text{O}_4$  254.1518, found: 254.1519.

Ozone was bubbled through a stirred solution of the above compound (1.07 g, 4.20 mmol) in MeOH (40 mL) at  $-78$  °C for 30 min. After removal of excess ozone,  $\text{Me}_2\text{S}$  (3.1 mL, 42.3 mmol) was added at  $-78$  °C, and the resulting mixture was stirred at rt for 7 h. Removal of the solvent and column chromatography of the residue with hexane-EtOAc (4:1) as an eluent afforded ketone (1.07 g, 99%) as a colorless oil. IR (neat)  $1745.3\text{ cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  4.61 (s, 2H), 4.02-3.88 (m, 4H), 3.46 (dd, 2H,  $J = 9.6$  and  $11.6$  Hz), 3.34 (s, 3H), 2.49 (d, 1H,  $J = 5.2$  Hz), 2.26-2.15 (m, 2H), 2.01 (dd, 1H,  $J = 2.8$  and  $12.0$  Hz), 1.89 (ddd, 1H,  $J = 2.0$ ,  $5.2$  and  $12.0$  Hz) and 1.85-1.67 (m, 4H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  215.5, 108.2, 96.7, 73.6, 64.8, 64.6, 56.2, 55.3, 45.3, 41.5, 35.7, 31.5 and 31.0. LRMS  $m/z$  256 ( $\text{M}^+$ ); HRMS calcd for  $\text{C}_{13}\text{H}_{20}\text{O}_5$  256.1311, found: 256.1292.

To a stirred solution of the above ketone (343.3 mg, 1.34 mmol) and NaOAc (227.7 mg, 2.78 mmol) in THF- $\text{H}_2\text{O}$  (1:1 v/v, 24 mL) was added  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (143.3 mg, 2.06 mmol) at 0 °C. The mixture was stirred at 60 °C for 7 h, and then quenched by addition of saturated aqueous  $\text{NaHCO}_3$  solution. After removal of the solvent, the resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with saturated aqueous  $\text{NaHCO}_3$  solution, brine and dried over  $\text{MgSO}_4$ . Removal of the solvent and column chromatography of the residue with hexane-EtOAc (4:1) as an eluent afforded oxime **5c** (356.5 mg, 98%) as a colorless solid. IR (neat)  $1677.8$  and  $3359.4\text{ cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  4.62 (s, 2H), 4.04-3.90 (m, 4H), 3.44 (dd, 2H,  $J = 9.6$  and  $11.2$  Hz), 3.35 (s, 3H), 2.75 (d, 1H,  $J = 5.2$  Hz), 2.43-2.38 (m, 2H), 1.90 (dd, 1H,  $J = 2.0$  and  $12.0$  Hz) and 1.75-1.60 (m, 5H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  164.3, 109.4, 96.7, 73.7, 64.9, 64.7, 55.3, 48.7, 41.8, 37.1, 34.3, 31.7 and 30.2. LRMS  $m/z$  271 ( $\text{M}^+$ ); HRMS calcd for  $\text{C}_{13}\text{H}_{21}\text{O}_5\text{N}$  271.1420, found: 271.1430.

**(1S\*,5R\*)-5-((Methoxymethoxy)methyl)-1-methyl-7-methylenebicyclo[3.2.1]octan-2-one (16)**. To a stirred solution of enone **15** (126.0 mg, 0.567 mmol) in HMPA-THF (1:5 v/v, 18 mL) was added dropwise DIBALH (1.02 M in hexane, 1.1 mL, 0.944 mmol) at  $-78$  °C. The mixture was stirred at 0 °C for 2 h, and then quenched by successive addition of 1 mL of water and 1 mL of aqueous HCl solution at 0 °C. The resulting mixture was extracted three times with EtOAc, and then the combined organic layers were washed with saturated aqueous  $\text{NaHCO}_3$  solution, brine and dried over  $\text{MgSO}_4$ . Removal of the solvent and column chromatography of the residue with hexane-EtOAc (6:1) as an eluent afforded ketone **16** (71.0 mg, 56%) as a colorless oil. IR (neat)  $1712.5\text{ cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.96 (br s, 1H), 4.87 (dd, 1H,  $J = 2.4$  and  $2.4$  Hz), 4.63 (s, 2H), 3.47 (s, 2H), 3.36 (s, 3H), 2.70-2.51 (m, 3H), 2.30 (dd, 1H,  $J = 16.6$  and  $6.0$  Hz), 1.93-1.76 (m, 3H), 1.69 (dd, 1H,  $J = 12.4$  and  $2.0$  Hz) and 1.20 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  210.5, 153.0, 107.6, 96.7, 73.9, 58.3, 55.3, 47.5, 41.9, 40.6, 35.0, 34.4 and 17.3.

LRMS  $m/z$  224 ( $M^+$ ); HRMS calcd for  $C_{13}H_{20}O_3$  224.1412, found: 224.1416.

**(1S\*,5S\*)-5-((Methoxymethoxy)methyl)-1-methylspiro[bicyclo[3.2.1]octane-2,2'-[1,3]dioxolan]-7-one oxime (5d)**. A solution of ketone **16** (47.4 mg, 0.21 mmol), ethylene glycol (1.0 mL, 17.9 mmol) and PPTS (5.3 mg, 0.021 mmol) in  $C_6H_6$  (20 mL) was refluxed at 110 °C for 1.5 h under a Dean–Stark apparatus. The solution was cooled to rt, and then quenched with saturated aqueous  $NaHCO_3$  solution. The layers were separated. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were washed with saturated aqueous  $NaHCO_3$  solution, brine and dried over  $MgSO_4$ . Removal of the solvent and flash column chromatography of the residue with hexane-EtOAc (4:1) as an eluent afforded the corresponding ketal (47.4 mg, 72%) as a colorless oil. IR (neat)  $1656.5\text{ cm}^{-1}$ .  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  4.95-4.86 (m, 2H), 4.60 (s, 2H), 4.03-3.84 (m, 4H), 3.39 (d, 1H,  $J = 9.2$ , Hz), 3.36 (d, 1H,  $J = 9.2$  Hz), 3.34 (s, 3H), 2.41-2.30 (m, 2H), 1.82 (dd, 1H,  $J = 11.4$  and 2.2 Hz), 1.68-1.54 (m, 5H), 1.46 (dd, 1H,  $J = 11.2$  and 1.4 Hz) and 1.06 (s, 3H).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  155.1, 112.2, 106.7, 96.7, 74.6, 65.8, 65.1, 55.2, 52.5, 45.8, 40.2, 32.6, 30.8 and 16.9.

Ozone was bubbled through a stirred solution of the above compound (40.4 mg, 0.15 mmol) in MeOH (10 mL) at  $-78$  °C for 30 min. After removal of excess ozone,  $Me_2S$  (0.1 mL, 1.18 mmol) was added at  $-78$  °C, and then the resulting mixture was stirred at rt for 4 h. Removal of the solvent and flash column chromatography of the residue with hexane-EtOAc (1:1) as an eluent afforded the corresponding ketone (40.1 mg, 99%) as a colorless oil. IR (neat)  $1742.4\text{ cm}^{-1}$ .  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  4.62 (s, 2H), 4.05-3.86 (m, 4H), 3.47 (dd, 1H,  $J = 9.2$  and 9.5 Hz), 3.44 (d, 1H,  $J = 9.6$  Hz), 3.35 (s, 3H), 2.33-2.23 (m, 2H), 2.11 (dd, 1H,  $J = 13.0$  and 2.2 Hz), 1.84 (ddd, 1H,  $J = 8.0$ , 5.2 and 1.6 Hz), 1.73-1.51 (m, 4H) and 1.03 (s, 3H).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  217.6, 109.6, 96.6, 73.6, 66.2, 64.8, 57.7, 55.3, 45.8, 43.0, 39.6, 31.8, 31.5 and 13.6.

To a stirred solution of the above ketone (40.1 mg, 0.15 mmol) and NaOAc (60 mg, 0.73 mmol) in MeOH- $H_2O$  (1:1 v/v, 4 mL) was added  $NH_2OH \cdot HCl$  (50.0 mg, 0.71 mmol) at rt. The mixture was stirred at 60 °C for 6 h and quenched by addition of saturated aqueous  $NaHCO_3$  solution. After removal of the solvent, the resulting mixture was extracted three times with EtOAc, and then the combined organic layers were washed with saturated aqueous  $NaHCO_3$  solution, brine and dried over  $MgSO_4$ . Removal of the solvent and flash column chromatography of the residue with hexane-EtOAc (1:2) as an eluent afforded oxime **5d** (41.2 mg, 97%) as a colorless oil. IR (neat)  $3380.6\text{ cm}^{-1}$ .  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.80 (br s, 1H), 4.61 (s, 2H), 4.04-3.87 (m, 4H), 3.40 (dd, 2H,  $J = 10.4$  and 10.4 Hz), 3.34 (s, 3H), 2.74 (d, 1H,  $J = 5.5$  Hz), 2.45 (dd, 2H,  $J = 19.6$  and 19.6 Hz), 1.92 (d, 1H,  $J = 11.2$  Hz) and 1.76-1.52 (m, 5H) and 1.13 (s, 3H).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  166.3, 111.0, 96.7, 73.8, 66.1, 65.2, 55.3, 52.5, 44.9, 40.8, 35.2, 32.0, 30.9 and 15.6. LRMS  $m/z$  285 ( $M^+$ ); HRMS calcd for  $C_{14}H_{23}NO_5$  285.1576, found: 285.1575.

**(1S\*,4S\*,5S\*)-4-Methoxy-1-((methoxymethoxy)methyl)-6-methylenebicyclo[3.2.1]octane (17).** A solution of ketone **13** (31 mg, 0.15 mmol) in MeOH (7 mL) was added NaBH<sub>4</sub> (17.0 mg, 0.45 mmol) at 0 °C and the mixture was stirred for 2 h. The solution was quenched by addition of H<sub>2</sub>O. After removal of the solvent, the residue was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over MgSO<sub>4</sub>. Removal of the solvent and the residue was dissolved into MeI (5 mL), and then Ag<sub>2</sub>O (347.5 mg, 1.50 mmol) and CaSO<sub>4</sub> (500 mg, 3.67 mmol) were added. The resulting mixture was stirred at rt in a sealed tube for 40 h. The solution was filtered through Celite. Removal of the solvent and flash column chromatography of the residue with hexane-EtOAc (4:1) as an eluent afforded ether **17** (20.0 mg, 59%) as a colorless oil. IR (neat) 1660.0 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.15 (br s, 1H), 5.05 (br s, 1H), 4.46 (s, 2H), 3.22 (s, 2H), 3.16 (s, 3H), 3.15 (s, 3H), 3.03 (ddd, 1H, *J* = 10.8, 5.6 and 2.8 Hz), 2.83 (d, 1H, *J* = 6.0 Hz), 2.26-2.18 (m, 1H), 2.05 (dd, 1H, *J* = 16.6 and 2.2 Hz), 1.80-1.71 (m, 1H), 1.63 (ddd, 1H, *J* = 13.2, 6.0 and 3.2 Hz), 1.53-1.46 (m, 1H), 1.42-1.38 (m, 1H), 1.28 (ddt, 1H, *J* = 13.2, 5.6 and 1.6 Hz) and 1.08 (dd, 1H, *J* = 11.4 and 2.6 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 150.4, 107.3, 96.7, 81.8, 74.8, 55.9, 55.1, 45.6, 43.6, 39.7, 39.6 and 32.8.

**(1S\*,4S\*,5S\*)-4-Methoxy-1-((methoxymethoxy)methyl)bicyclo[3.2.1]octan-6-one oxime (5e).** Ozone was bubbled through a stirred solution of ketal **17** (20.0 mg, 0.09 mmol) in MeOH (10 mL) at -78 °C for 0.5 h. After removal of excess ozone, Me<sub>2</sub>S (0.1 mL, 1.18 mmol) was added at -78 °C and the solution was stirred at rt for 6 h. Removal of the solvent and flash column chromatography of the residue with hexane-EtOAc (1:1) as an eluent afforded the corresponding ketone (18.0 mg, 89%) as a colorless oil. IR (neat) 1742.4 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.37 (s, 2H), 3.15 (s, 3H), 3.05 (s, 3H), 2.97 (ddd, 1H, *J* = 6.0, 3.6 and 2.4 Hz), 2.56 (dd, 1H, *J* = 5.6 and 3.6 Hz), 1.96 (d, 1H, *J* = 18.4 Hz), 1.78-1.69 (m, 1H), 1.65 (dd, 1H, *J* = 11.8 and 1.8 Hz), 1.53-1.46 (m, 1H), 1.44-1.38 (m, 1H) and 1.26-1.21 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 213.7, 96.6, 81.0, 73.7, 55.7, 54.8, 49.8, 45.9, 41.4, 36.7, 32.0 and 27.1.

To a stirred solution of the above ketone (18.0 mg, 0.09 mmol) and NaOAc (20.0 mg, 0.25 mmol) in MeOH-H<sub>2</sub>O (1:1 v/v, 8 mL) was added NH<sub>2</sub>OH·HCl (30.0 mg, 0.42 mmol) at rt. The mixture was stirred at 60 °C for 23 h, and then quenched by addition of saturated aqueous NaHCO<sub>3</sub> solution. After removal of the solvent, the resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> solution, brine and dried over MgSO<sub>4</sub>. Removal of the solvent and flash column chromatography of the residue with hexane-EtOAc (1:2) as an eluent afforded oxime **5e** (17.0 mg, 90%) as a colorless oil. IR (neat) 3287.1 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.52 (br s, 1H), 4.60 (s, 2H), 3.40 (s, 2H), 3.36 (s, 3H), 3.31-3.26 (m, 4H), 3.00 (dd, 1H, *J* = 5.8 and 2.2 Hz), 2.38 (d, 1H, *J* = 18.0 Hz), 2.32 (dd, 1H, *J* = 18.6 and 2.6 Hz), 1.99-1.87 (m, 1H), 1.48 (dt, 1H, *J* = 12.8 and 5.2 Hz) and 1.32-1.27 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 163.2, 96.8, 81.4, 74.2, 56.0, 55.0, 43.1, 42.4, 38.5, 35.8, 32.6 and 26.7. LRMS *m/z* 243 (M<sup>+</sup>); HRMS calcd for C<sub>12</sub>H<sub>21</sub>NO<sub>4</sub> 243.1471, found: 243.1498.

**Typical procedure for the Beckmann rearrangement.**

**(1*R*\*,5*S*\*)-5-((Methoxymethoxy)methyl)-2-azabicyclo[3.3.1]nonan-3-one (4b) (Table 1, entry 2).** To a stirred solution of the oxime **5b** (76.3 mg, 0.35 mmol) in pyridine (6.0 mL) was added TsCl (79.6 mg, 0.42 mmol) at 0 °C. The mixture was stirred at rt for 3 h. The solvent was removed under reduced pressure, and then the residue was diluted with EtOAc. The mixture was washed with aqueous saturated NaHCO<sub>3</sub> solution, brine, and dried over MgSO<sub>4</sub>. Removal of the solvent and column chromatography of the residue with EtOAc-MeOH (20:1) as an eluent afforded the lactam **4b** (64.4 mg, 82%) as a white solid. IR (neat) 1656.5 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 6.61 (br s, 1H), 4.58 (s, 2H), 3.69 (dd, 1H, *J* = 3.2 and 3.2 Hz), 3.32 (s, 3H), 3.17 (dd, 2H, *J* = 9.2 and 14.8 Hz), 2.44 (dd, 1H, *J* = 1.6 and 18.4 Hz), 2.14 (dd, 1H, *J* = 2.4 and 18.4 Hz), 1.84-1.79 (m, 1H) and 1.71-1.36 (m, 7H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 174.4, 96.8, 77.7, 55.5, 47.8, 39.6, 35.0, 34.7, 33.9, 32.1 and 17.1. HRMS (FAB<sup>+</sup>) calcd for C<sub>11</sub>H<sub>19</sub>NO<sub>3</sub> 213.1365, found: 213.1366.

**(1*R*\*,5*S*\*)-5-Hydroxy-8-azaspiro[bicyclo[3.3.1]nonane-2,2'-[1,3]dioxolan]-7-one (18) (Table 1, entry 1).** IR (neat) 1645.0 and 3326.6 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 6.11 (s, 1H), 4.00-3.87 (m, 4H), 3.27 (s, 1H), 2.58 (s, 1H), 2.21 (d, 1H, *J* = 12.0 Hz) and 1.96-1.63 (m, 6H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 172.0, 108.1, 76.8, 67.6, 65.4, 64.8, 54.3, 54.2, 45.6 and 36.6. LRMS *m/z* 213 (M<sup>+</sup>); HRMS calcd for C<sub>10</sub>H<sub>15</sub>O<sub>4</sub>N 213.1001, found: 213.0984.

**(1*R*\*,5*S*\*)-5-((Methoxymethoxy)methyl)-8-azaspiro[bicyclo[3.3.1]nonane-2,2'-[1,3]dioxolan]-7-one (4c) (Table 1, entry 3).** IR (neat) 1649.8 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 6.18 (br s, 1H), 4.59 (s, 2H), 4.02-3.85 (m, 4H), 3.33 (s, 3H), 3.26-3.21 (m, 3H), 2.51 (d, 1H, *J* = 18.0 Hz), 2.16 (dd, 1H, *J* = 2.0 and 18.4 Hz), 1.91-1.80 (m, 3H) and 1.65-1.51 (m, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 173.7, 109.5, 97.2, 76.3, 65.9, 65.2, 55.9, 54.1, 39.8, 34.3, 32.8, 31.5 and 27.4. LRMS *m/z* 271 (M<sup>+</sup>). Anal. Calcd for C<sub>13</sub>H<sub>21</sub>O<sub>5</sub>N: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.56; H, 8.09; N, 5.13.

**(1*R*\*,5*S*\*)-5-((Methoxymethoxy)methyl)-1-methyl-8-azaspiro[bicyclo[3.3.1]nonane-2,2'-[1,3]dioxolan]-7-one (4d) (Table 1, entry 4).** IR (neat) 1650.8 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.73 (br s, 1H), 4.60 (s, 2H), 4.04-3.85 (m, 4H), 3.34 (s, 3H), 3.23 (d, 1H, *J* = 9.2 Hz), 3.20 (d, 1H, *J* = 9.2 Hz), 2.47 (dd, 1H, *J* = 18.0 and 1.2 Hz), 2.13 (dd, 1H, *J* = 18.2 and 2.2 Hz), 1.88-1.75 (m, 2H) 1.64-1.47 (m, 4H) and 1.14 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 173.2, 110.5, 96.7, 75.7, 65.8, 65.7, 57.7, 55.4, 38.6, 38.4, 34.7, 32.3, 27.8 and 21.2. HRMS (FAB<sup>+</sup>) calcd for C<sub>14</sub>H<sub>23</sub>NO<sub>5</sub> 285.1576, found 285.578.

**(1*R*\*,5*S*\*,8*S*\*)-8-Methoxy-5-((methoxymethoxy)methyl)-2-azabicyclo[3.3.1]nonan-3-one (4e) (Table 1, entry 5).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.88 (br s, 1H), 4.60 (s, 2H), 3.70 (br s, 1H), 3.34 (s, 3H), 3.23 (s, 3H), 3.21 (d, 1H, *J* = 1.2 Hz), 2.47 (dd, 1H, *J* = 18.4 and 1.2 Hz), 2.15 (dd, 1H, *J* = 18.2 and 1.2 Hz), 2.00-1.91 (m, 2H) and 1.62-1.37 (m, 5H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 173.3, 96.6, 80.3, 63.6, 55.9, 55.5, 50.5, 42.5, 35.6, 32.3 and 22.3. HRMS (FAB<sup>+</sup>) calcd for C<sub>12</sub>H<sub>21</sub>NO<sub>4</sub> 243.1471, found: 243.1473.

## REFERENCES

1. K. Sakamoto, E. Tsujii, F. Abe, T. Nakanishi, M. Yamashita, N. Shigematsu, S. Izumi, and M. Okuhara, *J. Antibiot.*, 1996, **49**, 37.
2. M. D'Ambrosio, C. Mealli, A. Guerriero, and F. Pietra, *Helv. Chim. Acta*, 1985, **68**, 1453.
3. C. Kan-fan, T. Sevenet, H. A. Hadi, M. Bonin, J.-C. Quirion, and H.-P. Husson, *Nat. Prod. Lett.*, 1995, **7**, 283.
4. *A selected review*: J. Bonjoch, F. Diaba, and B. Bradshaw, *Synthesis*, 2011, 993; *Recent synthetic examples*: (a) R.-R. Liu, B.-L. Li, J. Lu, C. Shen, J.-R. Gao, and Y.-X. Jia, *J. Am. Chem. Soc.*, 2016, **138**, 5198; (b) T. Hiro, T. Ukegawa, S. Yokoshima, and T. Fukuyama, *Angew. Chem. Int. Ed.*, 2015, **54**, 7367; (c) F. Diaba, C. Pujol-grau, A. Martínez-Laporta, I. Fernandez, and J. Bonjoch, *Org. Lett.*, 2015, **17**, 568; (d) F. Diaba, A. Martínez-Laporta, and J. Bonjoch, *J. Org. Chem.*, 2014, **79**, 9365; (e) F. Diaba, A. Martínez-Laporta, and J. Bonjoch, *Eur. J. Org. Chem.*, 2014, 2371; (f) B. Bradshaw, C. Parra, and J. Bonjoch, *Org. Lett.*, 2013, **15**, 2458; (g) N. M. Garrido, C. T. Nieto, and D. Diez, *Synlett*, 2013, **24**, 169.
5. *Reviews*: (a) M. Toyota, *Procedia Chem.*, 2014, **13**, 3; (b) M. Toyota and M. Ihara, *Synlett*, 2002, 1211; *Applications to natural product synthesis*: (a) Y. Komori, A. Kozen, and M. Toyota, *Heterocycles*, 2016, **93**, 792; (b) A. Ishihata, M. Saeki, M. Watanabe, M. Ihara, and M. Toyota, *Heterocycles*, 2010, **80**, 903; (c) M. Toyota, T. Asano, and M. Ihara, *Org. Lett.*, 2005, **7**, 3929; (d) M. Toyota, M. Sasaki, and M. Ihara, *Org. Lett.*, 2003, **5**, 1193; (e) M. Toyota, A. Ilangova, R. Okamoto, T. Masaki, M. Arakawa, and M. Ihara, *Org. Lett.*, 2002, **4**, 4293; (f) M. Toyota, M. Rudyanto, and M. Ihara, *J. Org. Chem.*, 2002, **67**, 3374; (g) M. Toyota, T. Odashima, T. Wada, and M. Ihara, *J. Am. Chem. Soc.*, 2000, **122**, 9036; (h) M. Toyota, T. Wada, and M. Ihara, *J. Org. Chem.*, 2000, **65**, 4565; (i) M. Toyota, T. Wada, K. Fukumoto, and M. Ihara, *J. Am. Chem. Soc.*, 1998, **120**, 4916.
6. *A selected review*: R. E. Gawley, *Org. React.*, 1988, **35**, 1; *A similar example*: P. A. Hunt, C. J. Moody, A. M. Z. Slawin, D. J. Williams, P. L. Myers, and C. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1992, 831.
7. M. M. Kayser and C. M. Clouthier, *J. Org. Chem.*, 2006, **71**, 8424.
8. G. Stork, P. C. Tang, M. Casey, B. Goodman, and M. Toyota, *J. Am. Chem. Soc.*, 2005, **127**, 16255.