

Synthesis of Peduncularine

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Peduncularine, the principal alkaloid of the Tasmanian shrub *Aristotelia peduncularis*, was synthesized via the radical cyclization of 7-oxabicyclo[2.2.1]hept-2-en-5-yl ketone oxime **9** forming the 6-azabicyclo[3.2.1]octane skeleton.

Peduncularine (**1**) (Fig. 1) was isolated from the Tasmanian shrub *Aristotelia peduncularis* in 1971 by Bick and co-workers,[1] and the structure was determined in 1979.[2] Peduncularine consists of an unusual 6-azabicyclo[3.2.1]octene core with 3-indolylmethyl group and is reported to show cytotoxic activity towards breast cancer cell lines.[3] The unique structure and the biological feature make this compound an attractive synthetic target.[4] In 1989, Speckamp et al. reported the first synthesis of peduncularine (**1**), showing the synthetic problems of peduncularine: 1) construction of 6-azabicyclo[3.2.1]octene skeleton, and 2) stereoselective introduction of the *exo* indolylmethyl side chain at C(7).[4a] Weinreb et al. reported a formal total synthesis of peduncularine based on the amidyl radical cyclization.[4c] Recently, Woerpel and Roberson reported an efficient synthesis by [3 + 2] annulation of cyclohexenylsilanes and chlorosulfonyl isocyanate as a key step to construct the bicyclic skeleton, and the successive stereoselective installation of the indolylmethyl group at C(7).[4d]

Previously, we reported that γ,δ-unsaturated oxime derivatives are transformed to a variety of 3,4-dihydro-2*H*-pyrrols having 2-bromo-, phenylthio-, and phenylseleno-methyl groups via radical cyclization induced by one-electron reduction.[5] In addition, this radical cyclization was improved to a catalytic process by using copper(I) bromide as a redox catalyst (Scheme 1).[6] Herein, we report the synthesis of peduncularine (**1**) via radical cyclization of oximes as a key step in constructing 6-azabicyclo[3.2.1]octene framework.

Results and Discussion

As shown in Scheme 2, our synthetic plan of peduncularine (**1**) was inspired by an interest to apply the radical cyclization

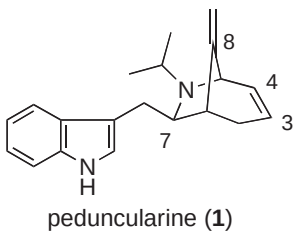
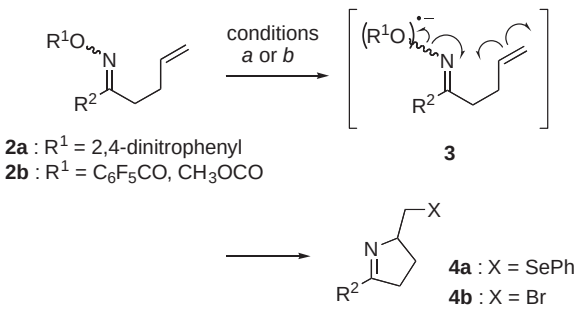


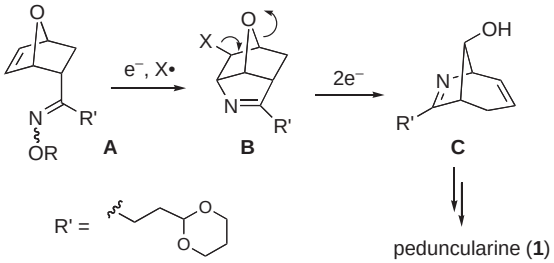
Fig. 1. Structure of peduncularine (**1**).



Scheme 1. Radical cyclization of oximes by one-electron reduction.

of oximes in the construction of 6-azabicyclo[3.2.1]octane framework. That is, 6-azabicyclo[3.2.1]octene **C** is synthesized via radical cyclization of oxime **A**, which has a 7-oxabicyclo[2.2.1]heptene moiety, followed by reductive ring opening of the resulting tricyclic imine **B**.[7] The stereochemistry at C(7) is expected to be arranged when the imine moiety of azabicyclooctene **C** is reduced.[4a]

The synthesis of peduncularine (**1**) was initiated by preparing γ,δ-unsaturated oxime **9** from the known ester **5** (Scheme 3).[8] Ester **5** was reduced to a primary alcohol **6**,[9] which was then oxidized under Swern oxidation conditions[10] to the corresponding aldehyde. Because the aldehyde easily underwent a retro-Diels–Alder reaction, the crude aldehyde was alkylated with 2-(1,3-dioxan-2-yl)ethylmagnesium bro-



Scheme 2. Synthetic strategy for peduncularine (**1**).

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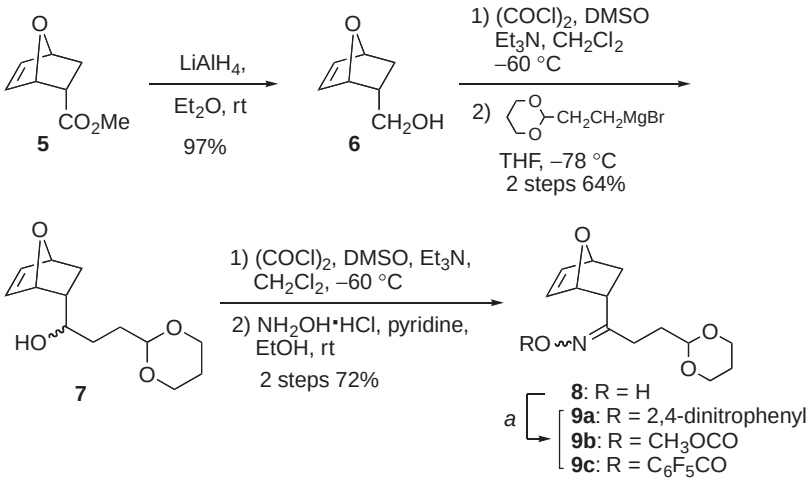


a) **8**→**9a**: 2,4-dinitrofluorobenzene, NaH, DMF, –20 °C (80%);
8→**9b**: MeOCOCl, Et_3N, DMAP, CH_2Cl_2, 0 °C (93%);
8→**9c**: C_6F_5COCl, Et_3N, CH_2Cl_2, 0 °C (95%).

Scheme 3. Preparation of oximes **9a**–**9c**.

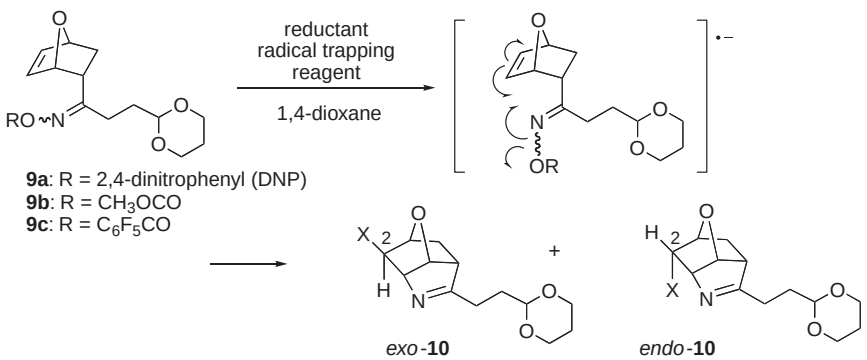
mide[11] to yield the secondary alcohol **7**. Oxidation of the alcohol **7** and successive treatment with $NH_2OH \cdot HCl$ and pyridine afforded oxime **8**. Oxime **8** was then converted into the corresponding *O*-2,4-dinitrophenyloxime **9a**, *O*-methoxycarbonyloxime **9b**, and *O*-pentafluorobenzoyloxime **9c**.[5,6]

Radical cyclization of *O*-2,4-dinitrophenyloxime **9a** (DNP oxime) proceeded smoothly by the treatment with NaH and 3,4-methylenedioxyphenol (sesamol) in the presence of diphenyl diselenide at 50 °C for 2 h, and the expected tricyclic imine *exo*-**10a**, which has a phenylseleno group, was obtained in 77% yield (Table 1, Run 1). The product yield was increased up to 93% yield by performing the reaction at room temperature for 24 h (Run 2). *O*-Methoxycarbonyloxime **9b** was cyclized slowly to form bromotricyclic imine **10b** in moderate yield (65%, *exo*:*endo* = 1:3) by the treatment with an equimolar amount of $CuBr \cdot SMe_2$ (Run 3). Both stoichiometric and catalytic cyclizations of pentafluorobenzoyloxime **9b** with $CuBr \cdot SMe_2$ proceeded smoothly to afford imine **10b** in 98% yield (Run 4) and 75% yield (Run 5), respectively. In the Cu-mediated reaction, the *endo* isomer formed as the major product, possibly via an amino-metallation process.

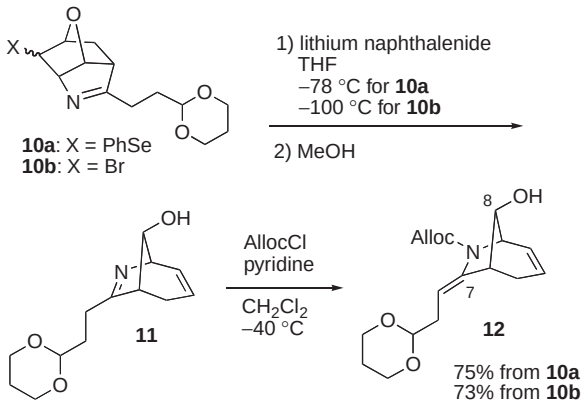
Having synthesized **10a** and **10b**, we turned our attention to the reductive ring opening of cyclic ether **10** to **11**, which possesses the azabicyclo[3.2.1]octene core. Reductive ring opening occurred when **10a** and **10b** were reacted with lithium naphthalenide[12] to afford the desired 6-azabicyclooctene **11** (Scheme 4). Because imine **11** was easily hydrolyzed, it was converted to *N*-Alloc-enamine **12** with allyloxycarbonyl chloride (AllocCl) and pyridine.[13] Enamine **12** was obtained as a single stereoisomer and was stable enough to be purified by silica-gel column chromatography.

Next, we explored the stereo selective reduction of enamine **12**. A preliminary experiment showed that it is difficult to produce the desired stereochemistry at C(7). The reduction of *N*-

Table 1. Radical Cyclization of Oximes **9a**–**9c**

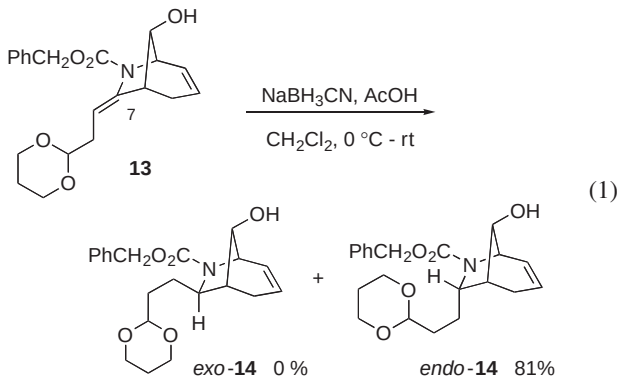


Run	R	9	Reagents	Temp	Time	X	10	Yield (*exo*:*endo*)
1	DNP	**9a**	sesamol, NaH, $(PhSe)_2$	50 °C	2 h	PhSe	**10a**	77% (>99:<1)
2	DNP	**9a**	sesamol, NaH, $(PhSe)_2$	rt	24 h	PhSe	**10a**	93% (>99:<1)
3	CH_3OCO	**9b**	$CuBr \cdot SMe_2$ (1.0), LiBr (4.0)	rt	56 h	Br	**10b**	65% (1:3)
4	C_6F_5CO	**9c**	$CuBr \cdot SMe_2$ (1.0), LiBr (4.0)	rt	2 h	Br	**10b**	98% (1:2.2)
5	C_6F_5CO	**9c**	$CuBr \cdot SMe_2$ (0.2), LiBr (4.0)	40 °C	2 h	Br	**10b**	75% (1:6.5)



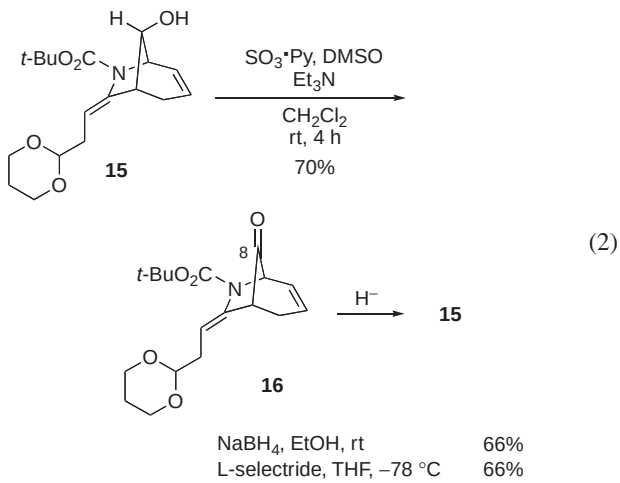
Scheme 4. Synthesis of *N*-Alloc-enamine **12**.

benzyloxycarbonylenamine **13**[14] with $NaBH_3CN$ under acidic conditions[15] afforded only the *endo* isomer of **14**, which does not have the desired stereochemistry at C(7) (Eq. 1).



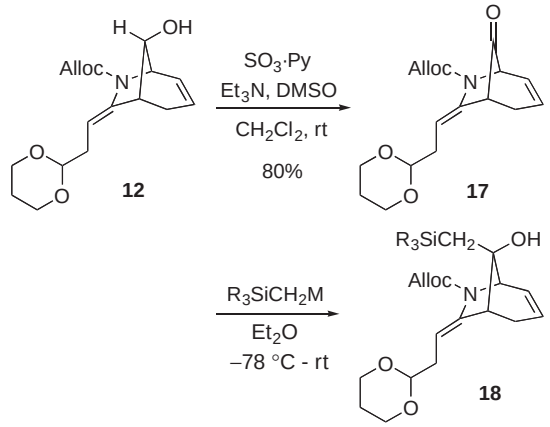
(1)

The following result, however, gave us a clue to control stereochemistry of the reduction of the enamine moiety. Metal-hydrides such as $NaBH_4$ and L-selectride attacked the *Si**-face of the C(8)-carbonyl group in Boc derivative **16** derived from alcohol **15**[14] to regenerate **15** exclusively (Eq. 2),[16,17] which implies that a bulky nucleophile would behave in the same way to convert compound **17** into alkylated product such as compound **18**. The bulky substituent would prevent hydride to attack the *exo* face of the enamine moiety.



(2)

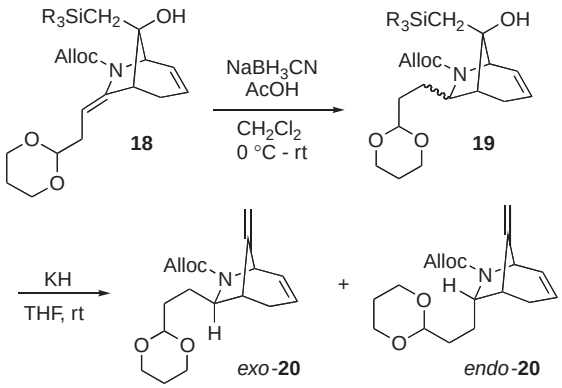
A silylmethyl group was chosen as a substituent because it can be readily converted to a methylene group by Peterson olefination.[18] Alcohol **12** was oxidized[19] and the resulting ketone **17** was treated with various silylmethylmetal reagents to give the corresponding alcohols **18a–18e** as a single product (Scheme 5).[20,21]



R_3SiCH_2M	**18**	yield/%
Me_3SiCH_2MgCl	**18a**	77
Et_3SiCH_2MgCl	**18b**	81
$Me_2PhSiCH_2MgCl$	**18c**	69
Ph_3SiCH_2Li	**18d**	52
i-Pr_3SiCH_2Li	**18e**	23

Scheme 5. Preparation of **18**.

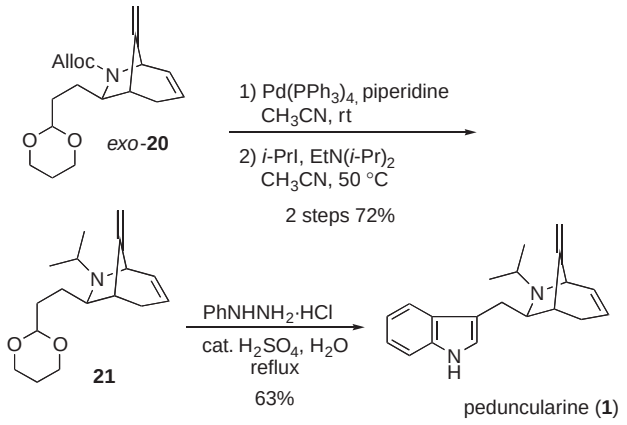
Table 2. Reduction of Enecarbamate **18**



Run	R_3Si	**19**	Yield	**20** Yield (*exo*:*endo*)
1	Me_3Si	**19a**	80%	70% (1:1.1)
2	Et_3Si	**19b**	69% (85%)[a)]	87% (2:1)
3	Me_2PhSi	**19c**	69%	57% (1:1.7)
4	Ph_3Si	**19d**	76%	64% (1:3)
5	*i*-Pr_3Si	**19e**	50%	47% (1:9)

a) Conversion yield.

The reduction of **18a–18e** was performed with $NaBH_3CN$ and acetic acid, and the diastereoselectivity was determined after the product **19** was converted into the methylenated product **20** by Peterson olefination with KH (Table 2).[18] As we expected, the reduction of **18a** having trimethylsilylmethyl group at C(8) gave the desired product *exo*-**20**, as well as a similar



Scheme 6. Synthesis of peduncularine (**1**).

amount of *endo*-**20** was formed (Run 1). The *exo*-**20** was obtained predominantly in a 2:1 ratio of *exo*- and *endo*-**20** from triethylsilyl-substituted **18b** (Run 2). However, reaction with dimethylphenyl, triphenylsilyl, and triisopropylsilyl derivatives afforded the undesired *endo*-**20** predominantly (Runs 3–5).

Synthesis of peduncularine (**1**) was accomplished in the following three steps from *exo*-**20** (Scheme 6). Elimination of the allyloxycarbonyl group under Pd-catalyzed conditions[22] and successive isopropylation of the resulting secondary amine[23] gave cyclic *N*-propylamine **21**, which is an intermediate in Hiemstra and Speckamp's synthesis.[4a] Finally, a 3-indolyl group was constructed by the Fischer method from acetal **21**, leading to peduncularine (**1**) in 63% yield.[4d,24]

Experimental

General. ^{1}H NMR (500 and 270 MHz) spectra were recorded on Bruker DRX-500, Bruker Avance-500, and JEOL AL-270 spectrometers in $CDCl_3$, in which $CHCl_3$ was used as an internal standard ($\delta = 7.24$)] or C_6D_6, in which case C_6HD_5 was used as an internal standard ($\delta = 7.15$). ^{13}C NMR (125 and 67.5 MHz) spectra were recorded on Bruker DRX-500, Bruker Avance-500, and JEOL AL-270 spectrometers in $CDCl_3$, which was used as an internal standard ($\delta = 77.0$) or C_6D_6, which was used as an internal standard ($\delta = 128.0$). IR spectra were recorded on a Horiba FT 300-S by ATR method. High-resolution mass spectra were obtained with a JEOL MS-700M mass spectrometer. Elemental analyses were carried out at The Elemental Analysis Laboratory, Department of Chemistry, Faculty of Science, The University of Tokyo. Flash column chromatography was performed on silica gel [Fuji Silysia silica gel PSQ–100B and Kanto Chemical silica gel 60N (spherical, neutral)], alumina (WAKO) and florisil (WAKO). Preparative thin-layer chromatography (PTLC) was carried out using Wakogel B-5F. *N*,*N*-Dimethylformamide (DMF) was distilled under reduced pressure from P_2O_5 and then from CaH_2, and stored over molecular sieves 4A (MS 4A) under an argon atmosphere. Acetonitrile was distilled from CaH_2, P_2O_5, and CaH_2 again and was stored over MS 4A. Dimethyl sulfoxide (DMSO) was distilled under reduced pressure from CaH_2 and stored over MS 4A. Dichloromethane was distilled from P_2O_5 and then from CaH_2, and was stored over MS 4A. Triethylamine, ethyldiisopropylamine, furan, and pyridine were distilled from CaH_2 and stored over KOH. 1,4-Dioxane was distilled from $LiAlH_4$ and used immediately. MeOH was distilled from Mg and stored with MS 4A. Dry THF and diethyl ether were purchased from Kanto Chemical. 2-Bromoethyl-1,3-dioxane, hydroxylammonium chloride, oxalyl dichloride, methyl acrylate, pentafluorobenzoyl chloride, and 2,4-dinitrofluorobenzene were purchased from Tokyo Chemical Industry and were used without purification. Naphthalene was recrystallized from benzene. Allyloxycarbonyl chloride was distilled from calcium chloride and stored over MS 4A. Lithium wire, copper powder, $CuBr \cdot SMe_2$ and $SO_3 \cdot$ pyridine complex were purchased from Aldrich and were used without purification. Isopropyl iodide was distilled from calcium chloride. $BF_3 \cdot Et_2O$, sodium hydride, lithium aluminum hydride, and sodium cyanoborohydride were purchased from Kanto Chemical and were used without purification. Sesamol was recrystallized from benzene and petroleum ether (P.E.).

***endo*-7-Oxabicyclo[2.2.1]hept-2-ene-5-methanol (6).** To a solution of $LiAlH_4$ (2.48 g, 65.3 mmol) in Et_2O (200 mL) was slowly added ester **5** (8.48 g, 55.0 mmol) in Et_2O (75 mL). After stirring for 2 h at room temperature, to the reaction mixture was added $Na_2SO_4 \cdot 10H_2O$ at 0 °C and was heated to reflux for 15 min. The mixture was dried over anhydrous Na_2SO_4, filtered, and was concentrated in vacuo to yield alcohol **6** (6.73 g, 53.3 mmol) in 97% yield as a colorless oil. The spectral data were in a total agreement with those in Ref. 9.

***endo*-3-(1,3-Dioxan-2-yl)-1-(7-oxabicyclo[2.2.1]hept-2-en-2-yl)propan-1-ol (7).** To a solution of oxalyl dichloride (9.05 mL, 104 mmol) in CH_2Cl_2 (250 mL) at −60 °C was slowly added a solution of DMSO (14.8 mL, 208 mmol) in CH_2Cl_2 (50 mL) and the reaction mixture was stirred for 5 min. Subsequently, alcohol **6** (11.9 g, 94.7 mmol) in CH_2Cl_2 (100 mL) was slowly added over 5 min. After the reaction mixture was stirred for 20 min, triethylamine (65.6 mL, 473 mmol) was slowly added. The reaction mixture was stirred for another 40 min, treated with aq $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo under 10 °C. The residue was dissolved in THF (300 mL) and cooled to −78 °C. To the solution was added 2-(1,3-dioxan-2-yl)ethylmagnesium bromide (1.0 M solution in THF, 97 mL, 97 mmol), and the reaction mixture was allowed to warm to room temperature and stirred for 14 h. The reaction was quenched with aq NH_4Cl, and the mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (SiO_2, $CHCl_3$:MeOH = 25:1) to afford **7** (14.5 g, 64%) as a colorless oil (diastereomer mixture 6:4).

IR (neat) 3438, 3373, 1456, 1379, 1319, 1242, 1146, 1088, 995, 910 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.67 (0.6H, dd, J = 4.1, 11.2 Hz), 1.12 (0.4H, dd, J = 3.9, 11.4 Hz), 1.33 (1H, d, J = 13.6 Hz), 1.44–1.51 (1H, m), 1.62–1.76 (3H, m), 1.92 (0.6H, ddd, J = 4.8, 9.2, 11.2 Hz), 2.03–2.08 (1.4H, m), 2.18–2.23 (1H, m), 2.45 (0.4H, br), 2.92 (0.6H, br), 2.99 (1H, br dd, J = 9.4, 9.4 Hz), 3.75 (2H, dd, J = 12.1, 12.1 Hz), 4.07–4.10 (2H, m), 4.55 (1H, dd, J = 4.4, 4.4 Hz), 4.81 (0.4H, d, J = 4.3 Hz), 4.88 (0.6H, d, J = 4.8 Hz), 4.91 (0.4H, dd, J = 1.5, 4.8 Hz), 5.04 (0.6H, d, J = 4.4 Hz), 6.17 (0.4H, dd, J = 1.2, 5.9 Hz), 6.34 (1.2H, br), 6.40 (0.4H, dd, J = 1.5, 5.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.5, 25.6, 28.5, 28.9, 30.5, 30.8, 31.1, 31.2, 44.9, 45.5, 66.9, 74.3, 75.5, 78.3, 78.7, 78.9, 80.0, 101.9, 102.0, 131.6, 133.0, 136.1, 137.2.

3-(1,3-Dioxan-2-yl)-1-(*endo*-7-oxabicyclo[2.2.1]hept-2-en-5-yl)propan-1-one Oxime (8). To a solution of oxalyl dichloride (9.92 g, 78.1 mmol) in CH_2Cl_2 (220 mL) at −60 °C was slowly added a solution of DMSO (12.2 g, 156 mmol) in CH_2Cl_2 (45 mL), and the reaction mixture was stirred for 5 min. Subsequently, alcohol **7** (17.1 g, 71.0 mmol) in CH_2Cl_2 (88 mL) was slowly added

over 5 min. After the reaction mixture was stirred for 20 min at −60 °C, triethylamine (35.9 mL, 355 mmol) was slowly added. The reaction mixture was stirred for another 40 min, treated with aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in EtOH, and pyridine (16.9 g, 213 mmol) and hydroxylammonium chloride (7.40 g, 107 mmol) were added to the solution at room temperature. After stirring for 24 h, the mixture was diluted with water, and extracted with EtOAc. The combined extracts were dried over anhydrous Na_2SO_4, filtered, successively concentrated in vacuo. The residue was purified by column chromatography (SiO_2) to yield **8** (13.0 g, 72%, *E*:*Z* = 7:2) as colorless crystals.

Mp 75–76 °C (Et_2O); IR (KBr) 3305, 2954, 2856, 1666, 1651, 1568, 1471, 1240, 1128, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35^E (br d, $J = 13.6$ Hz) and 1.39^Z (dd, $J = 4.1$, 11.6 Hz) (1H); 1.50^E (dd, $J = 4.4$, 12.6 Hz), 1.66–$2.14^{E,Z}$ (m), 2.33^E (ddd, $J =$ 6.6, 9.7, 13.0 Hz) and 2.46^E (ddd, $J = 6.5$, 9.5, 13.0 Hz) (5H); 3.02^E (ddd, $J = 4.3$, 4.4, 8.9 Hz) and 3.46^Z (ddd, $J = 4.1$, 4.3, 9.0 Hz) (1H); 3.71–$3.79^{E,Z}$ (m, 2H); 4.06–$4.15^{E,Z}$ (m, 2H); 4.51^Z (dd, $J = 5.0$, 5.0 Hz) and 4.56^E (dd, $J = 4.9$, 4.9 Hz) (1H); 4.99^E (dd, $J = 1.4$, 4.7 Hz) and 5.02^Z (dd, $J = 1.1$, 4.4 Hz) (1H); 5.12^E (dd, $J = 1.0$, 4.3 Hz) and 5.49^Z (d, $J = 4.3$ Hz) (1H); 6.16^E (dd, $J = 1.0$, 5.8 Hz) and 6.18^Z (dd, $J = 1.5$, 5.8 Hz) (1H); 6.39^E (dd, $J = 1.4$, 5.8 Hz) and 6.41^Z (dd, $J = 1.1$, 5.8 Hz) (1H); 7.83^E (br) and 8.25^Z (br) (1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.4, 25.7, 27.5, 27.5, 27.7, 30.9, 31.4, 37.2, 42.6, 66.8, 66.8, 78.4, 78.9, 79.0, 79.6, 132.4, 133.2, 136.0, 136.1, 158.9, 160.0; Anal. Found: C, 61.37; H, 7.52; N, 5.49%. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53%.

3-(1,3-Dioxan-2-yl)-1-(*endo*-7-oxabicyclo[2.2.1]hept-2-en-5-yl)propan-1-one *O*-2,4-Dinitrophenyloxime (9a). A solution of oxime **8** (603 mg, 2.38 mmol) in DMF (24 mL) was added to NaH (55.7 mg, 3.57 mmol, washed with P.E.) in a three necked flask at 0 °C. After the solution was stirred for 1 h, to this solution was added a solution of 2,4-dinitrofluorobenzene (487 mg, 2.62 mmol), and the mixture was stirred for 24 h at room temperature. The reaction was quenched with ice water, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography (SiO_2; hexane:EtOAc = 2:1) to give 784 mg (80%) of **9a** as colorless crystals.

E isomer: mp 97–98 °C (hexane–Et_2O); IR (KBr) 1604, 1529, 1348, 1273, 1146, 899 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (1H, d, $J = 13.6$ Hz), 1.68 (1H, dd, $J = 4.3$, 11.4 Hz), 1.87–1.96 (2H, m), 2.07 (1H, ddddd, $J = 5.0$, 5.0, 12.0, 12.0, 13.6 Hz), 2.15 (1H, ddd, $J = 4.8$, 8.9, 11.4 Hz), 2.58 (1H, ddd, $J = 7.0$, 8.9, 12.9 Hz), 2.69 (1H, ddd, $J = 6.7$, 9.0, 12.9 Hz), 3.26 (1H, ddd, $J = 4.3$, 4.4, 8.9 Hz), 3.78 (2H, dd, $J = 10.0$, 12.0 Hz), 4.11 (2H, d, $J = 10.0$ Hz), 4.65 (1H, dd, $J = 4.8$, 4.8 Hz), 5.08 (1H, d, $J =$ 4.8 Hz), 5.25 (1H, dd, $J = 1.0$, 4.4 Hz), 6.22 (1H, dd, $J = 1.0$, 5.8 Hz), 6.47 (1H, dd, $J = 1.4$, 5.8 Hz), 7.77 (1H, d, $J = 9.3$ Hz), 8.38 (1H, dd, $J = 2.8$, 9.4 Hz), 8.88 (1H, d, $J = 2.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 25.7, 27.6, 31.2, 43.1, 66.8, 79.0, 79.5, 100.9, 117.1, 122.1, 129.3, 132.2, 136.0, 136.6, 140.6, 157.3, 169.4; Anal. Found: C, 54.31; H, 4.99; N, 10.04%. Calcd for $C_{19}H_{21}N_3O_8$: C, 54.41; H, 5.05; N, 10.02%.

3-(1,3-Dioxan-2-yl)-1-(*endo*-7-oxabicyclo[2.2.1]hept-2-en-5-yl)propan-1-one *O*-Methoxycarbonyloxime (9b). To a solution of oxime **8** (199 mg, 0.79 mmol) in 1.2-dichloroethane (10 mL) at 0 °C was added triethylamine (0.29 mL, 2.0 mmol), 4-dimethylaminopyridine (11.7 mg, 0.096 mmol), and methoxycarbonylchloride (0.070 mL, 1.2 mmol). The solution was stirred at 0 °C for 3 h. To this solution was added pyridine (0.30 mL, 3.8 mmol) and methoxycarbonyl chloride (0.23 mL, 3.9 mmol). The reaction mixture was stirred for 24 h at room temperature, and the reaction was quenched with aq $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, evaporated. The residue was purified by column chromatography (SiO_2; hexane: acetone = 2:1) to afford 211 mg of **9b** in 93% yield as a colorless oil (*E*:*Z* = 7.7:2.3 mixture).

IR(neat) 2956, 2852, 2360, 1772, 1653, 1506, 1437, 1228, 1128, 1026, 893, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.31 (1H, dd, $J = 1.0$, 13.5 Hz), 1.38 (0.23H, dd, $J = 4.0$, 11.8 Hz), 1.58 (0.77H, dd, $J = 4.4$, 11.4 Hz), 1.71–1.80 (2H, m), 1.97–2.20 (2.46H, m), 2.34–2.45 (1.54H, m), 3.07–3.11 (0.77H, m), 3.41–3.45 (0.23H, m), 3.71 (2H, dd, $J = 10.8$, 13.5 Hz), 3.80 (2.31H, s), 3.85 (0.69H, s), 4.00–4.10 (2H, m), 4.50 (1H, t, $J = 4.8$ Hz), 4.97 (0.77H, d, $J = 4.6$ Hz), 5.00 (0.23H, d, $J = 4.5$ Hz), 5.15 (0.77H, d, $J = 4.2$ Hz), 5.34 (0.23H, d, $J = 4.5$ Hz), 6.14 (0.23H, d, $J = 5.8$ Hz), 6.19 (0.77H, dd, $J = 1.1$, 5.8 Hz), 6.37 (0.77H, dd, $J = 1.5$, 5.8 Hz), 6.42 (0.23H, dd, $J = 1.5$, 5.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6, 25.5, 25.6, 27.3, 27.6, 27.7, 31.1, 31.3, 38.5, 42.8, 55.0, 55.1, 66.8, 78.5, 78.9, 79.3, 79.4, 100.7, 132.5, 132.6, 136.2, 136.8, 154.3, 167.1, 167.7.

3-(1,3-Dioxan-2-yl)-1-(*endo*-7-oxabicyclo[2.2.1]hept-2-en-5-yl)propan-1-one *O*-Pentafluorobenzoyloxime (9c). To a solution of oxime **8** (2.74 g, 10.8 mmol) in CH_2Cl_2 at 0 °C was added triethylamine (2.95 mL, 21.3 mmol) and pentafluorobenzoyl chloride (1.95 mL, 14.4 mmol). After stirring for 10 min at 0 °C, the reaction was quenched with aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (SiO_2) to afford **9c** (4.60 g, 95%) as colorless crystals.

(*E*:*Z* = 7.7:2.3) IR(neat) 2954, 2852, 1757, 1653, 1523, 1506, 1325, 1198, 1147, 1003, 893, 868 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.31 (1H, brd, $J = 12.3$ Hz), 1.42 (0.23H, dd, $J = 4.0$, 11.9 Hz), 1.58 (0.77H, dd, $J = 4.4$, 12.2 Hz), 1.76–1.83 (2H, m), 1.97–2.04 (1H, m), 2.05–2.13 (1H, m), 2.17–2.28 (0.46H, m), 2.40–2.51 (1.54H, m), 3.15–3.19 (0.77H, m), 3.48–3.52 (0.23H, m), 3.71 (2H, dd, $J = 10.8$, 12.3 Hz), 4.04 (2H, dd, $J = 4.9$, 10.8 Hz), 4.51 (0.77H, t, $J = 4.7$ Hz), 4.55 (0.23H, t, $J = 4.8$ Hz), 5.00 (0.77H, d, $J = 4.5$ Hz), 5.03 (0.23H, d, $J = 3.7$ Hz), 5.19 (0.77H, d, $J = 4.1$ Hz), 5.24 (0.23H, d, $J = 4.4$ Hz), 6.18 (0.23H, dd, $J =$ 1.3, 5.8 Hz), 6.23 (0.77H, dd, $J = 1.2$, 5.8 Hz), 6.41 (0.77H, dd, $J = 1.5$, 5.8 Hz), 6.47 (0.23H, dd, $J = 1.5$, 5.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.0, 25.4, 25.5, 27.4, 27.6, 27.7, 30.9, 31.0, 38.7, 42.9, 66.7, 78.6, 78.9, 79.2, 79.3, 100.4, 100.5, 107.0, 132.1, 132.4, 136.3, 136.6, 137.1, 138.6, 142.2, 144.2, 146.2, 156.3, 169.6, 170.5; Anal. Found: C, 53.57; H, 4.15; N, 2.99%. Calcd. for $C_{20}H_{18}F_5NO_5$: C, 53.70; H, 4.06; N, 3.13%.

5-[2-(1,3-Dioxan-2-yl)ethyl]-2-phenylseleno-8-oxa-4-azatricyclo[4.2.1.$0^{3,7}$]non-4-ene (10a). To a solution of sodium hydride (1.39 g, 5.77 mmol, washed with P.E. three times) in 1,4-dioxane (10 mL) at room temperature was added a solution of sesamol (0.811 g, 5.87 mmol) in 1.4-dioxane (10 mL), a solution of diphenyl diselenide (5.27 g, 16.9 mmol) in 1,4-dioxane (18 mL), and *O*-2,4-dinitrophenyloxime **9a** (2.42 g, 5.77 mmol) in 1,4-dioxane (10 mL). After stirring for 24 h at room temperature, ice water was added to the reaction mixture. The mixture was extracted with Et_2O, and the combined organic extracts were washed with brine,

dried over anhydrous Na_2SO_4, filtered, and evaporated. Purification by column chromatography (SiO_2) gave **10a** (1.78 g, 93%) as pale yellow crystals.

Mp 71–72 °C (hexane–Et_2O); IR (KBr) 1626, 1377, 1136, 1022, 964, 879, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (1H, ddd, $J = 0.8$, 1.8, 13.5 Hz), 1.65 (1H, dd, $J = 1.2$, 12.5 Hz), 1.84–1.96 (3H, m), 2.05 (1H, ddddd, $J = 4.9$, 4.9, 12.6, 12.6, 13.5 Hz), 2.34–2.59 (2H, m), 2.65 (1H, dd, $J = 4.6$, 9.5 Hz), 3.14 (1H, s), 3.75 (2H, ddd, $J = 1.8$, 10.9, 12.6 Hz), 4.08 (2H, ddd, $J = 0.8$, 4.9, 10.9 Hz), 4.17 (1H, d, $J = 4.5$ Hz), 4.59 (1H, dd, $J = 4.8$, 4.8 Hz), 4.64 (1H, d, $J = 5.1$ Hz), 5.42 (1H, dd, $J = 4.6$, 5.1 Hz), 7.25–7.30 (3H, m), 7.51–7.55 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 28.4, 30.8, 36.7, 46.7, 49.5, 66.8, 66.8, 76.7, 84.0, 89.5, 101.1, 127.3, 129.2, 129.9, 133.4, 185.8; Anal. Found: C, 58.11; H, 5.87; N, 3.57%. Calcd for $C_{19}H_{23}NO_3Se$: C, 58.16; H, 5.91; N, 3.57%.

2-Bromo-5-[2-(1,3-dioxan-2-yl)ethyl]-8-oxa-4-azatricyclo-[4.2.1.0^{3,7}]non-4-ene (10b). To a solution of *O*-pentafluorobenzoyloxime **9c** (145 mg, 0.324 mmol) and lithium bromide (110 mg, 1.27 mmol) in 1,4-dioxane (7 mL) at room temperature was added $CuBr \cdot SMe_2$ (66.2 mg, 0.322 mmol). After the reaction mixture was stirred for 2 h at room temperature, brine and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine was added. The mixture was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (florisil; hexane:acetone = 4:1) to give **10b** (100 mg, 98%, *exo*:*endo* = 1:2.2) as a colorless oil. *O*-Methoxycarbonyloxime **9b** also gave **10b** in 65% (*exo*:*endo* = 1:3 mixture) in a similar manner as **9c**.

exo Isomer: IR (neat) 2964, 2852, 1699, 1622, 1377, 1144, 1082, 1043, 1001, 883, 850, 793 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.32 (1H, dd, $J = 1.0$, 13.5 Hz), 1.67 (1H, d, $J = 12.6$ Hz), 1.83–1.91 (3H, m), 1.98–2.14 (1H, m), 2.37–2.48 (2H, m), 2.63 (1H, dd, $J = 4.6$, 9.9 Hz), 3.67 (1H, s), 3.72 (2H, dd, $J = 11.9$, 13.5 Hz), 4.06 (2H, brd, $J = 11.9$ Hz), 4.36 (1H, d, $J = 4.5$ Hz), 4.57 (1H, t, $J = 4.8$ Hz), 4.73 (1H, d, $J = 5.2$ Hz), 5.42 (1H, dd, $J = 4.5$, 4.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 28.3, 30.5, 36.5, 46.2, 51.9, 66.8, 66.84, 79.4, 86.1, 89.1, 101.0, 186.8; HRMS (FAB^+) Found: m/z 316.0530, Calcd for $C_{13}H_{19}BrNO_3$: $(M + H)^+$, 316.0548.

endo Isomer: IR (neat) 2962, 2852, 1699, 1628, 1442, 1377, 1242, 1144, 1028, 1001, 955, 874, 777 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.62 (1H, brd, $J = 13.2$ Hz), 1.65 (1H, ddd, $J = 4.5$, 9.2, 10.4 Hz), 1.73–1.84 (1H, m), 1.88 (1H, dd, $J = 1.6$, 9.2 Hz), 1.94 (1H, dd, $J = 4.9$, 10.4 Hz), 2.09–2.17 (1H, m), 2.20–2.26 (1H, m), 2.28–2.35 (1H, m), 2.43–2.49 (1H, m), 3.34–3.42 (2H, m), 3.67–3.83 (4H, m), 4.10 (1H, dd, $J = 4.5$, 4.5 Hz), 4.69 (1H, t, $J = 5.0$ Hz), 4.79 (1H, dd, $J = 4.6$, 4.9 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 25.7, 28.5, 30.2, 30.6, 47.9, 48.6, 66.8, 66.9, 82.0, 90.3, 100.9, 186.8; HRMS (FAB^+) Found: m/z 316.0533, Calcd for $C_{13}H_{19}BrNO_3$: $(M + H)^+$, 316.0548.

6-Allyloxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethylidene]-6-azabicyclo[3.2.1]oct-3-ene-8-ol (12). To a solution of the selenide **10a** (211 mg, 0.537 mmol) in THF (8 mL) at −78 °C was slowly added lithium naphthalenide (0.1 M solution in THF, 3 mL, 1.5 mmol). The mixture was stirred for 25 min at −78 °C, and the reaction was quenched with MeOH. The mixture was evaporated, and the residue was diluted in CH_2Cl_2 (8 mL). The resulting suspension was filtered through a celite pad and the filtrate was evaporated. To a solution of the residue in CH_2Cl_2 (8 mL) at −20 °C was added pyridine (0.057 mL, 7.1 mmol) and AllocCl (0.063 mL, 6.0 mmol). The mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched with aq $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2; hexane:acetone = 2:1) to afford enecarbamate **12** (129 mg, 75%) as a colorless oil. Compound **12** was also prepared from imine **10b** in a similar manner as **10a**, in 73%.

IR (neat) 3435, 1711, 1402, 1333, 1277, 1240, 1138, 1014 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (1H, d, $J = 13.4$ Hz), 1.98–2.08 (1H, m), 2.16–2.20 (1H, m), 2.18 (1H, d, $J = 18.6$ Hz), 2.24–2.34 (2H, m), 2.49 (1H, dd, $J = 4.5$, 18.6 Hz), 3.04 (1H, br), 3.71 (2H, dt, $J = 2.3$, 12.1 Hz), 4.03–4.06 (2H, m), 4.22–4.26 (2H, m), 4.50 (1H, t, $J = 5.3$ Hz), 4.58 (2H, br), 5.18 (1H, d, $J = 10.4$ Hz), 5.27 (1H, d, $J = 17.2$ Hz), 5.85–5.94 (3H, m), 6.04 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 28.4, 35.1, 38.9, 54.9, 65.7, 66.9, 67.9, 101.9, 102.9, 117.5, 125.4, 131.7, 132.6, 142.3, 152.0; Anal. Found: C, 63.35; H, 7.38; N, 4.08%. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36%.

6-Benzyloxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethylidene]-6-azabicyclo[3.2.1]oct-3-en-8-ol (13). IR (neat) 3413, 1711, 1664, 1402, 1277, 1136, 1014 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (1H, ddd, $J = 0.6$, 2.3, 13.5 Hz), 1.94–2.09 (2H, m), 2.20 (1H, d, $J = 18.8$ Hz), 2.25–2.35 (2H, m), 2.50 (1H, dd, $J = 4.6$, 18.8 Hz), 3.05 (1H, m), 3.71 (2H, ddd, $J = 2.3$, 12.1, 11.7 Hz), 4.06 (2H, ddd, $J = 0.6$, 4.4, 11.7 Hz), 4.23–4.27 (1H, m), 4.29 (1H, br), 4.50 (1H, br), 5.13 (2H, br), 5.94 (1H, br), 6.08 (1H, br), 7.27–7.37 (5H, m).

6-Benzyloxycarbonyl-7-[*endo*-2-(1,3-dioxan-2-yl)ethyl]-6-azabicyclo[3.2.1]oct-3-en-8-ol (*endo*-14). IR (neat) 3417, 1693, 1415, 1136, 1088 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 323 K) δ 1.28 (1H, d, $J = 13.3$ Hz), 1.47–1.52 (3H, br), 1.90 (1H, br d, $J = 9.0$ Hz), 2.03 (1H, ddddd, $J = 4.8$, 4.8, 12.6, 12.6, 13.3 Hz), 2.25 (1H, br d, $J = 18.4$ Hz), 2.39–2.43 (3H, br m), 3.69 (2H, br), 3.88 (1H, br), 4.04 (2H, dd, $J = 4.8$, 10.8 Hz), 4.13 (1H, ddd, $J = 4.5$, 4.5, 9.0 Hz), 4.21 (1H, br), 4.47 (1H, br), 5.07 (1H, d, $J = 12.4$ Hz), 5.12 (1H, d, $J = 12.4$ Hz), 5.89–5.93 (1H, br m), 7.26–7.33 (5H, m).

6-*t*-Butoxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethylidene)-6-azabicyclo[3.2.1]oct-3-en-8-ol (15). IR (neat) 3442, 1707, 1390, 1138, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (1H, d, $J = 13.4$ Hz), 1.46 (9H, s), 1.92 (1H, d, $J = 10.0$ Hz), 2.05 (1H, ddddd, $J = 4.1$, 4.1, 12.7, 12.7, 13.4 Hz), 2.19 (1H, d, $J = 18.7$ Hz), 2.25–2.35 (2H, m), 3.04 (1H, br), 3.72 (2H, ddd, $J = 1.8$, 11.4, 12.7 Hz), 4.06 (2H, dd, $J = 4.1$, 11.4 Hz), 4.19 (1H, br), 4.23 (1H, br quin), 4.52 (1H, dd, $J = 5.3$, 5.3 Hz), 5.94 (3H, br).

6-*t*-Butoxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethylidene]-6-azabicyclo[3.2.1]oct-3-ene-8-one (16). IR (neat) 1782, 1711, 1383, 1136, 1014, 862 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (1H, d, $J = 13.4$ Hz), 1.46 (9H, s), 2.02 (1H, ddddd, $J = 4.7$, 4.7, 12.7, 12.7, 13.4 Hz), 2.25 (2H, dd, $J = 5.2$, 7.7 Hz), 2.84 (1H, d, $J = 17.6$ Hz), 2.92 (1H, dddd, $J = 2.3$, 3.2, 4.6, 17.6 Hz), 3.31 (1H, br), 3.71 (2H, dddd, $J = 2.6$, 2.6, 11.1, 12.7 Hz), 4.04 (2H, dd, $J = 4.7$, 11.1 Hz), 4.18 (1H, br), 4.51 (1H, dd, $J = 5.2$, 5.2 Hz), 5.78 (1H, ddd, $J = 3.2$, 3.2, 8.9 Hz), 6.13 (2H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 28.3, 35.0, 39.9, 47.3, 58.9, 66.9, 81.3, 101.6, 102.8, 130.8, 131.1, 139.2, 151.3, 206.5.

6-Allyloxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethylidene]-6-azabicyclo[3.2.1]oct-3-ene-8-one (17). To a solution of enecarbamate **12** (95.2 mg, 0.296 mmol) in CH_2Cl_2 (1 mL) and DMSO (1 mL) was added triethylamine (195 mg, 1.93 mmol), a solution of $SO_3 \cdot$pyridine (142 mg, 0.888 mmol) in DMSO (1 mL) and

CH_2Cl_2 (1 mL). After the mixture was stirred for 17 h at room temperature, the reaction was quenched by adding water. The mixture was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by PTLC (SiO_2; hexane:EtOAc = 1:1) gave 78.0 mg (82%) of **17** as a colorless oil.

IR (neat) 1780, 1716, 1396, 1281, 1236, 1138, 1014 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 323 K) δ 1.28 (1H, dm, J_d = 13.3 Hz), 2.03 (1H, dm, J_d = 13.3 Hz), 2.26 (2H, dd, J = 5.1, 7.8 Hz), 2.86 (1H, dm, J_d = 17.6 Hz), 2.94 (1H, dm, J_d = 17.6 Hz), 3.32–3.34 (1H, m), 3.68–3.73 (2H, m), 4.03–4.06 (2H, m), 4.26 (1H, dd, J = 1.4, 6.0 Hz), 4.51 (1H, t, J = 5.1 Hz), 4.62 (2H, d, J = 5.5 Hz), 5.19–5.22 (1H, m), 5.27–5.31 (1H, m), 5.80 (1H, dm, J_d = 9.0 Hz), 5.91 (1H, dm, J_d = 5.5 Hz), 6.13–6.16 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$, 323 K) δ 25.7, 35.0, 40.0, 47.1, 58.7, 66.1, 66.9, 101.6, 103.8, 117.9, 130.6, 131.4, 132.4, 138.9, 151.9, 205.7; HRMS (FAB$^+$) Found: m/z 320.1941, Calcd for $C_{17}H_{22}NO_5$: $(M + H)^+$, 320.1498.

6-Allyloxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethylidene]-8-*anti*-trimethylsilylmethyl-6-azabicyclo[3.2.1]oct-3-en-8-ol (18a). Compound **18a** was prepared from **17** in a similar manner as **18b** in 80% (conv. 84%) as a colorless oil.

IR (neat) 3487, 1712, 1398, 1304, 1246, 1140, 1018, 845 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 323 K) δ 0.06 (9H, s), 1.28 (1H, dd, J = 1.8, 13.4 Hz), 2.05 (1H, dtm, J_d = 13.4, J_t = 5.0 Hz), 2.24–2.35 (3H, m), 2.24 (1H, s), 2.25–2.35 (2H, m), 2.54 (1H, dm, J_d = 18.8 Hz), 2.81–2.82 (1H, m), 3.72 (2H, dm, J_d = 1.8 Hz), 4.05 (2H, dd, J = 5.0, 10.9 Hz), 4.04–4.07 (1H, m), 4.50 (1H, t, J = 5.2 Hz), 4.60 (2H, d, J = 4.9 Hz), 5.19 (1H, d, J = 10.6 Hz), 5.28 (1H, d, J = 17.2 Hz), 5.88–6.02 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$, 323 K) δ 0.2, 25.7, 25.8, 30.8, 35.2, 45.3, 61.5, 65.6, 66.8, 66.8, 74.5, 102.0, 103.5, 117.3, 127.8, 131.4, 132.8, 143.3, 152.3.

6-Allyloxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethylidene]-8-*anti*-triethylsilylmethyl-6-azabicyclo[3.2.1]oct-3-en-8-ol (18b). To a solution of ketone **17** (86.2 mg, 0.27 mmol) in Et_2O (3.5 mL) at −78 °C was added triethylsilylmethylmagnesium bromide (0.5 M solution in Et_2O, 1.2 mL, 0.66 mmol). The reaction mixture was stirred for 1 h at room temperature and was treated with aq NH_4Cl. The mixture was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (SiO_2; hexane:EtOAc = 3:1) to give **18b** (75.8 mg, 62%, conv. 81%) as a colorless oil.

IR(neat) 2962, 2848, 1780, 1716, 1647, 1398, 1340, 1281, 1236, 1138, 1016, 787, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.56 (6H, q, J = 8.0 Hz), 0.90 (9H, t, J = 8.0 Hz), 1.05 (2H, s), 1.30 (1H, d, J = 13.0 Hz), 2.03 (1H, dtt, J = 4.6, 12.2, 13.0 Hz), 2.23–2.35 (4H, m), 2.53 (1H, brd, J = 18.9 Hz), 2.78 (1H, brs), 3.72 (2H, dd, J = 11.3, 13.0 Hz), 4.01 (1H, brs), 4.05 (2H, dd, J = 4.6, 11.3 Hz), 4.50 (1H, t, J = 5.3 Hz), 4.58 (2H, brs), 5.19 (1H, d, J = 10.4 Hz), 5.28 (1H, d, J = 17.2 Hz), 5.88–6.08 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.6, 7.5, 20.6, 25.7, 30.9, 35.2, 45.2, 61.6, 65.5, 66.9, 74.4, 102.0, 103.4, 117.4, 127.8, 131.5, 132.7, 143.4, 152.2; Anal. Found: C, 63.93; H, 8.68; N, 3.00%. Calcd for $C_{24}H_{39}NO_5Si$: C, 64.11; H, 8.74; N, 3.11%.

6-Allyloxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethylidene]-8-*anti*-dimethyl(phenyl)silylmethyl-6-azabicyclo[3.2.1]oct-3-en-8-ol (18c). Compound **18c** was prepared from **17** in a similar manner as **18b** in 69% as a colorless oil.

IR(neat) 2954, 2850, 1701, 1525, 1398, 1303, 1244, 1140, 1113, 1016, 831, 723, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.36 (6H, s), 1.29 (3H, m), 2.00–2.05 (1H, m), 2.17–2.25 (4H, m), 2.46 (1H, d, J = 18.8 Hz), 2.72 (1H, brs), 3.71 (2H, dd, J = 11.6, 13.4 Hz), 3.92 (1H, brs), 4.02–4.10 (2H, m), 4.47 (1H, t, J = 5.2 Hz), 4.49–4.55 (2H, m), 5.18 (1H, d, J = 10.1 Hz), 5.24 (1H, d, J = 17.0 Hz), 5.87–6.05 (4H, m), 7.51–7.54 (3H, m), 7.67 (2H, brs).

6-Allyloxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethylidene]-8-*anti*-triphenylsilylmethyl-6-azabicyclo[3.2.1]oct-3-en-8-ol (18d). To a solution of tributyl(triphenylsilylmethyl)tin (234 mg, 0.415 mmol, prepared from triphenylsilylmethyl chloride and tributyltinlithium) at 0 °C was slowly added butyllithium (1.63 M solution in hexane, 0.26 mL, 0.42 mmol). After the reaction mixture was stirred for 30 min at 0 °C, it was cooled to −78 °C. To this solution was slowly added ketone **17** (57.6 mg, 0.180 mmol) in THF (2 mL). The reaction mixture was stirred for 1 h at −78 °C and was treated with aq NH_4Cl. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by PTLC (SiO_2; hexane:EtOAc = 1:1) to yield **18d** (62.4 mg, 60%, conv. 82%) as a colorless oil.

^1H NMR (270 MHz, $CDCl_3$) δ 1.26 (1H, d, J = 11.6 Hz), 1.99–2.09 (6H, m), 2.29 (1H, d, J = 13.1 Hz), 2.61 (1H, brs), 3.62–3.73 (2H, m), 3.94–4.07 (3H, m), 4.44 (1H, t, J = 5.4 Hz), 4.46–4.60 (2H, m), 5.15–5.25 (2H, m), 5.81–6.06 (4H, m), 7.29–7.39 (9H, m), 7.58–7.61 (6H, m).

6-Allyloxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethylidene]-8-*anti*-triisopropylsilylmethyl-6-azabicyclo[3.2.1]oct-3-en-8-ol (18e). Compound **18e** was prepared from **17** in a similar manner as **18b** in 23% as a colorless oil.

^1H NMR (270 MHz, $CDCl_3$) δ 0.99–1.12 (21H, m), 1.13 (2H, s), 1.30 (1H, d, J = 13.5 Hz), 1.97–2.04 (1H, m), 2.24–2.33 (4H, m), 2.54 (1H, brd, J = 13.5 Hz), 2.84 (1H, brs), 3.71 (2H, dd, J = 11.2, 13.5 Hz), 4.05 (3H, dd, J = 4.9, 11.2 Hz), 4.50 (1H, t, J = 5.1 Hz), 4.60 (2H, brs), 5.19 (1H, dd, J = 0.4, 13.9 Hz), 5.28 (1H, d, J = 13.9 Hz), 5.86–6.06 (4H, m).

6-Allyloxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethyl]-8-*anti*-triethylsilylmethyl-6-azabicyclo[3.2.1]oct-3-en-8-ol (19b). To a solution of **18b** (41.8 mg, 0.093 mmol) in CH_2Cl_2 (2 mL) at room temperature was added an excess amount of sodium cyanoborohydride and acetic acid (0.11 mL). The reaction mixture was stirred for 48 h at room temperature, poured into aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by PTLC (SiO_2; hexane:EtOAc = 3:1) to yield 29.1 mg (69%, conv. 85%) of **19b** as a colorless oil.

6-Allyloxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethyl]-8-methylene-6-azabicyclo[3.2.1]oct-3-en (20). To a solution of alcohol **19b** (61.0 mg, 0.135 mmol) in THF (3 mL) at room temperature was added excess amount of KH. The mixture was stirred for 30 min, and the reaction was quenched with ice water. The mixture was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (SiO_2) to yield **20** (37.3 mg, 87%) as a mixture of *exo*/*endo* isomers (*exo*:*endo* = 2:1). The ratio of *endo*- and *exo*-**20** was determined by ^1H NMR. The mixture was separated by column chromatography (SiO_2; benzene:EtOAc = 6:1). Since the low polar material could be transformed to peduncularine, the compound was assigned as the *exo* isomer and the high polar material was assigned as the *endo* isomer. Compound **20** was also derived from compounds **19a** (70%), **19c** (57%), **19d** (64%), **19e** (47%) in a similar manner as **19b**.

exo-**20**: IR(neat) 2956, 2850, 1697, 1653, 1558, 1506, 1456, 1396, 1254, 1140, 1093, 995 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (1H, d, $J = 12.8$ Hz), 1.39–1.49 (1H, m), 1.51–1.64 (2H, m), 1.75–1.84 (1H, m), 1.98–2.09 (1H, m), 2.32 (1H, d, $J = 18.1$ Hz), 2.55–2.68 (2H, m), 3.61–3.75 (3H, m), 4.04–4.08 (2H, m), 4.30 (1H, dd, $J = 5.7$, 13.9 Hz), 4.58–4.60 (3H, m), 4.82 (1H, d, $J = 4.4$ Hz), 4.87 (1H, d, $J = 11.8$ Hz), 5.17 (1H, d, $J = 10.5$ Hz), 5.28 (1H, dd, $J = 1.4$, 17.3 Hz), 5.53 (1H, m), 5.86–5.98 (1H, m), 6.12–6.33 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8, 28.4, 32.0, 38.5, 44.5, 56.8, 65.4, 65.5, 66.8, 102.3, 102.4, 116.9, 127.8, 132.7, 133.2, 147.8, 154.7; HRMS (FAB^+) Found: m/z 320.1857; Calcd for $C_{18}H_{26}NO_4$: $(M + H)^+$ 320.1862.

endo-**20**: ^1H NMR (500 MHz, $CDCl_3$, 323 K) δ 1.29 (1H, d, $J = 13.3$ Hz), 1.46–1.55 (4H, m), 2.05 (1H, tm, $J = 5.0$ Hz), 2.41 (1H, dm, $J = 18.3$ Hz), 2.49 (1H, d, $J = 18.3$ Hz), 2.80–2.81 (1H, m), 3.69–3.75 (2H, m), 3.79–3.80 (1H, m), 4.06 (2H, dm, $J = 5.0$ Hz), 4.47–4.59 (1H, m), 4.51 (1H, t, $J = 4.6$ Hz), 4.55 (2H, ddd, $J = 1.2$, 1.3, 5.4 Hz), 4.75 (1H, s), 5.17 (1H, dd, $J = 1.3$, 10.5 Hz), 5.27 (1H, dd, $J = 1.2$, 17.2 Hz), 5.61 (1H, dm, $J = 9.1$ Hz), 5.88–5.96 (1H, m), 6.05–6.07 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$, 323 K) δ 25.9, 32.1, 32.6, 57.0, 61.5, 65.5, 66.9, 100.3, 102.3, 116.9, 128.7, 131.8, 133.4, 148.8.

6-Allyloxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethyl]-8-*anti*-trimethylsilylmethyl-6-azabicyclo[3.2.1]oct-3-en-8-ol (19a). Compound **19a** was prepared from **18a** in a similar manner as **19b** in 74% (conv. 78%) as a colorless oil.

^1H NMR (500 MHz, $CDCl_3$, 323 K) δ 0.05–0.08 (9H, m), 0.90–1.60 (6H, m), 2.00–2.29 (5H, m), 2.41–2.61 (1H, m), 3.36–4.12 (6H, m), 4.48–4.58 (3H, m), 5.15–5.30 (2H, m), 5.86–5.92 (3H, m).

6-Allyloxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethyl]-8-*anti*-dimethyl(phenyl)silylmethyl-6-azabicyclo[3.2.1]oct-3-en-8-ol (19c). Compound **19c** was prepared from **18c** in a similar manner as **19b** in 69% as a colorless oil.

^1H NMR (270 MHz) δ 0.34–0.39 (6H, m), 1.55–1.58 (5H, m), 1.98–2.03 (3H, m), 2.10–2.65 (3H, m), 3.30–3.73 (3H, m), 3.82–3.95 (1H, m), 4.02–4.06 (2H, m), 4.44–4.52 (3H, m), 5.16 (1H, dd, $J = 1.4$, 11.0 Hz), 5.26 (1H, d, $J = 11.0$ Hz), 5.84–5.90 (3H, m), 7.30–7.33 (3H, m), 7.50–7.56 (2H, m).

6-Allyloxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethyl]-8-*anti*-triphenylsilylmethyl-6-azabicyclo[3.2.1]oct-3-en-8-ol (19d). Compound **19d** was prepared from **18d** in a similar manner as **19b** in 76% as a colorless oil.

^1H NMR (270 MHz, $CDCl_3$) δ 1.21–1.50 (2H, m), 1.73–1.85 (3H, m), 1.86–2.17 (3H, m), 2.18–2.45 (3H, m), 3.63–3.90 (4H, m), 4.03 (2H, d, $J = 11.6$ Hz), 4.11–4.57 (3H, m), 5.11–5.32 (2H, m), 5.69–5.91 (3H, m), 7.32–7.37 (9H, m), 7.49–7.66 (6H, m).

6-Allyloxycarbonyl-7-[2-(1,3-dioxan-2-yl)ethyl]-8-*anti*-triisopropylsilylmethyl-6-azabicyclo[3.2.1]oct-3-en-8-ol (19e). Compound **19e** was prepared from **18e** in a similar manner as **18b** in 69% as a colorless oil.

^1H NMR (270 MHz, $CDCl_3$) δ 0.88–1.21 (21H, m), 1.28 (1H, d, $J = 15.9$ Hz), 1.33–1.56 (3H, m), 2.01–2.19 (3H, m), 2.20–2.32 (3H, m), 2.33–2.48 (1H, m), 3.68–3.92 (4H, m), 4.05 (2H, dd, $J = 5.9$, 11.6 Hz), 4.48–4.60 (3H, m), 5.16 (1H, d, $J = 10.5$ Hz), 5.25 (1H, d, $J = 16.5$ Hz), 5.84–5.96 (3H, m).

7-*exo*-[2-(1,3-Dioxan-2-yl)ethyl]-6-isopropyl-8-methylene-6-azabicyclo[3.2.1]oct-3-ene (21). To a solution of **20** (25.2 mg, 0.0794 mmol) and piperidine (35 µL, 0.42 mmol) in CH_3CN (3 mL) at room temperature was added tetrakis(triphenylphosphine)-palladium (9.6 mg, 0.0083 mmol). After stirring for 2 h at room temperature, the reaction mixture was diluted with Et_2O, filtered through a celite pad, and concentrated in vacuo. The residue was dissolved in CH_3CN (4 mL). To this solution at room temperature was added ethyldiisopropylamine (1.7 mL, 0.007 mmol), isopropyl iodide (0.7 mL, 0.07 mmol), and the mixture was stirred at 50 °C for 7 h. The mixture was treated with brine containing 10% NaOH and was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (alumina; EtOAc:hexane = 1:8) to afford **21** (15.8 mg, 72%) as a colorless oil.

IR(neat) 2964, 2926, 2850, 1734, 1684, 1558, 1507, 1457, 1374, 1146, 996, 755, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (3H, d, $J = 5.4$ Hz), 1.07 (3H, d, $J = 5.4$ Hz), 1.22–1.38 (3H, m), 1.50–1.60 (2H, m), 1.99–2.08 (1H, m), 2.18 (1H, brd, $J = 17.6$ Hz), 2.34 (2H, brs), 2.53 (1H, brd, $J = 17.6$ Hz), 2.83 (1H, septet, $J = 5.4$ Hz), 3.69–3.73 (3H, m), 4.06 (2H, dd, $J = 4.8$, 11.1 Hz), 4.46 (1H, t, $J = 5.1$ Hz), 4.75 (1H, s), 4.85 (1H, s), 5.67 (1H, brd, $J = 9.2$ Hz), 5.87–5.89 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 23.3, 25.8, 32.9, 33.1, 40.1, 46.1, 50.8, 60.1, 66.8, 66.9, 69.5, 101.0, 102.3, 130.6, 132.9, 150.1; HRMS (FAB^+) Found: m/z 278.2124, Calcd for $C_{17}H_{28}NO_2$: $(M + H)^+$, 278.2120.

Peduncularine (1). A solution of 4% aqueous sulfuric acid (1.4 mL) was heated to 50 °C for 30 min. An excess amount of phenylhydrazine hydrochloride (20.0 mg) was added to the heated solution and the solid was allowed to dissolve over 10 min. The hot solution was transferred to a flask containing **21** (4.8 mg, 0.017 mmol) and H_2O (0.1 mL). After stirring for 40 min at reflux, the reaction mixture was cooled to room temperature. To the mixture was added saturated aqueous $NaHCO_3$ and brine, and then the mixture was extracted CH_2Cl_2. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated. Purification by column chromatography (alumina, hexane:EtOAc = 6:1) gave peduncularine as a white foam (3.2 mg, 63%).

IR (neat) 2964, 2926, 2850, 1734, 1684, 1558, 1507, 1457, 1374, 1146, 996, 755, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (3H, d, $J = 6.2$ Hz), 1.29 (3H, d, $J = 6.3$ Hz), 2.05 (1H, ddt, $J = 1.7$, 3.2, 17.6 Hz), 2.44 (1H, ddt, $J = 2.3$, 4.7, 17.6 Hz), 2.49 (1H, br d, $J = 4.3$ Hz), 2.69 (1H, dd, $J = 11.4$, 14.7 Hz), 2.87 (1H, br d, $J = 11.4$ Hz), 2.93 (1H, br d, $J = 15.0$ Hz), 2.98 (1H, septet, $J = 6.3$ Hz), 3.83 (1H, d, $J = 4.9$ Hz), 4.80 (1H, s), 4.94 (1H, s), 5.67 (1H, br d, $J = 9.2$ Hz), 5.93 (1H, ddt, $J = 2.0$, 5.3, 9.2 Hz), 6.97 (1H, s), 7.11 (1H, t, $J = 7.4$ Hz), 7.18 (1H, t, $J = 7.4$ Hz), 7.35 (1H, d, $J = 8.1$ Hz), 7.59 (1H, d, $J = 7.9$ Hz), 7.99 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7, 23.6, 34.2, 40.1, 45.8, 50.9, 60.4, 69.8, 101.4, 111.0, 115.1, 119.1, 119.3, 121.3, 122.0, 127.8, 128.5, 130.6, 136.1, 150.0; HRMS (FAB^+) Found: m/z 278.2124, Calcd for $C_{17}H_{28}NO_2$: $(M + H)^+$ 278.2120.

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14 *N*-Benzyloxycarbonyl (Cbz) enamine **13** and *N*-*t*-butoxycarbonyl (Boc) enamine **15** could be derived from imine **11** by the treatment of benzyloxycarbony chloride or Boc_2O, respectively, instead of AllocCl.

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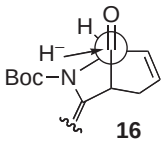
16 Although all the compounds are racemic, *Si**-*Re** notation is temporary employed in the formula **16**.

17 Hydride attack to carbonyl group in **16** would be occurred from the side of low torsional strain.



16

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