Stereoselective Total Synthesis of (±)-Swainsonine Based on Endo Mode Cyclization

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A new stereoselective total synthesis of (±)-swainsonine is described. Successive treatment of *cis*-3,4-epoxy-7-(*p*-toluenesulfonamido)-1-heptyne with dicobalt octacarbonyl, Lewis acid, and cerium(IV) ammonium nitrate effected stereoselective formation of the *trans*-2-ethynyl-3-hydroxypiperidine skeleton with retention of configuration at the propynyl center. The piperidine derivative thus prepared was converted into the title compound efficiently.

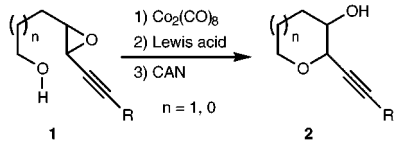
Introduction

In the previous papers,[1] we developed a new procedure for the highly stereoselective construction of tertahydropyran and tetrahydrofuran skeletons **2** possessing the 2-ethynyl-3-hydroxy functionality as a common structural feature by successive treatment of the epoxy alcohols **1** having an acetylenic functionality adjacent to epoxy moiety with dicobalt octacarbonyl ($Co_2(CO)_8$), Lewis acid, and cerium(IV) ammonium nitrate (CAN) (Scheme 1). The most significant point of this method is based on an endo mode cyclization of dicobalt hexacarbonyl complex of the epoxy acetylene derivatives **1** under acidic conditions. The other salient feature of this cyclization must be stereocomplementary formation of **2**. Namely *trans*-**1** afforded *cis*-**2**, while *cis*-**1** gave *trans*-**2** in either a highly stereoselective manner or exclusively.

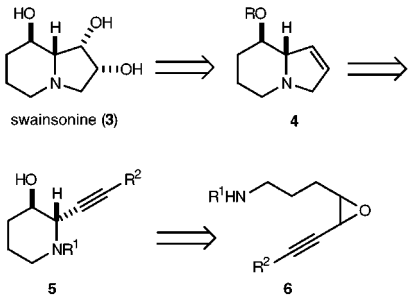
In the course of our program directed toward application of the newly developed endo mode cyclization reaction to the stereoselective synthesis of natural products, we chose an indolizidine alkaloid, (±)-swainsonine (**3**) as our first target natural product. Swainsonine (**3**), isolated from the fungus *Rhizoctonia leguminicola*,[2] *Swainsona canescens*,[3] and *Metarhizium anisopliae*,[4] is a representative indolizidine alkaloid having trihydroxy functionalities. Because of the interesting biological activities[5] of this alkaloid, much effort has so far been dedicated to synthesis of **3** over the past decade.[6]

Our retrosynthetic analysis is outlined in Scheme 2. The *cis*-epoxy amino derivative **6** with a proper protecting group on the nitrogen atom would produce the piperidine derivative **5** possessing *trans*-2-ethynyl-3-hydroxy alignment by consecutive treatment with $Co_2(CO)_8$, Lewis acid, and CAN. Chemical modification of **5** would effected ring closure to give the 1,2-dehydroindolizidine framework **4**. By taking advantage of the protecting group on the C-8 hydroxy functionality of **4**, stereoselective introduction of *cis*-dihydroxy groups would be realized judging from several literature precedents.[6h] This simple analysis

Scheme 1



Scheme 2



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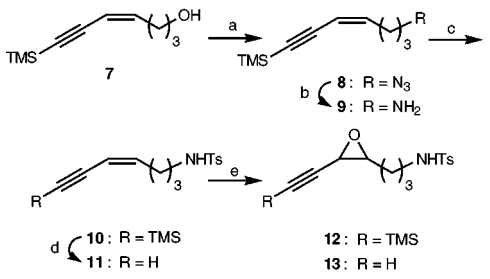
Scheme 3[a]



[a]Reaction conditions : (a) HN_3, DEAD, PPh_3, 99%; (b) PPh_3, H_2O, 99%; (c) TsCl, Et_3N, 81%; (d) TBAF, 96%; (e) *m*CPBA, **10**→**12** (57%), **11**→**13** (58%).

[a] Reaction conditions: (a) HN_3, DEAD, PPh_3, 99%; (b) PPh_3, H_2O, 99%; (c) TsCl, Et_3N, 81%; (d) TBAF, 96%; (e) *m*CPBA, **10** → **12** (57%), **11** → **13** (58%).

prompted us to examine the synthesis of (±)-swainsonine (**3**) in line with the retrosynthetic format. This paper deals with the successful application of the newly developed endo mode cyclization method as a crucial step to stereoselective total synthesis of indolizidine alkaloid, (±)-swainsonine (**3**).

Results and Discussion

The required *cis*-epoxy alkyne derivatives for the endo mode cyclization were prepared by conventional means. The alcohol (*Z*)-**7**[1d] was exposed to Mitsunobu conditions[7] using hydrazoic acid[8] and diethyl azodicarboxylate (DEAD) to give the azido derivative (*Z*)-**8** in 99% yield, which was further treated with triphenylphosphine (PPh_3) in the presence of water affording the corresponding primary amino compound (*Z*)-**9** in 99% yield. The amino group of (*Z*)-**9** was protected with *p*-toluenesulfonyl (Ts) group to provide (*Z*)-**10** in 81% yield, oxidation of which with *m*-chloroperbenzoic acid (*m*CPBA) furnished *cis*-**12** in 57% yield. The terminal trimethylsilyl (TMS) group of (*Z*)-**10** was removed by treatment with tetra-*n*-butylammonium fluoride (TBAF) to give (*Z*)-**11** in 96% yield. The *cis*-epoxide **13** was then obtained in 58% yield from (*Z*)-**11** by similar oxidation with *m*CPBA (Scheme 3).

The pivotal reaction for this synthesis was undertaken under the conditions described in the previous papers.[1] Exposure of *cis*-**13** to $Co_2(CO)_8$ in methylene chloride at 0 °C to give the corresponding cobalt-complexed **13**, which was subsequently treated with a catalytic amount of $BF_3{\cdot}OEt_2$ (0.1 mol %) at −78 °C affording the cyclized products. Decomplexation of cobalt moiety of the resulting piperidine derivatives was carried out by CAN treatment in methanol at 0 °C to afford *trans*-**14** and *cis*-**14** in 85% overall yield in a highly stereoselective manner (*trans*-**14**:*cis*-**14** = 90:10) as expected (Table 1, entry 1). No trace of pyrrolidine compounds resulting from an exo mode cyclization could be detected in the reaction mixture. Similar successive one-pot treatment of the TMS congener **12** also provided *trans*-**15** selectively in 83% yield (*trans*-**15**:*cis*-**15** = 83:17). The *cis*-epoxides **12** and **13** produced the corresponding *trans*-ones with retention of configuration at the propynyl position. This observation is in good agreement with the results[1] obtained in the reaction of compound **1** (see Scheme 1). When the

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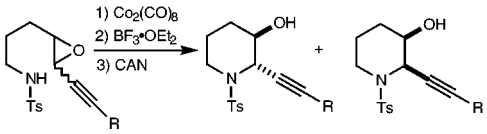
(8) Wolff, H. *Org. React.* **1946**, *3*, 307.

Table 1. Ring Closure of Epoxides 12, 13



13 : R = H
12 : R = TMS

trans-**14** : H
trans-**15** : R = TMS

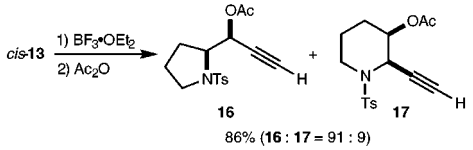
cis-**14** : H
cis-**15** : R = TMS

entry	epoxide	R	product ratio[a]	yield (%)
1	*cis*-**13**	H	*trans*-**14** : *cis*-**14** = 90 : 10	85
2	*cis*-**12**	TMS	*trans*-**15** : *cis*-**15** = 83 : 17	83
3	*trans*-**13**	H	*trans*-**14** : *cis*-**14** = 30 : 70	89

[a] Ratio was determined on the basis of isolated amount of each isomer.

protecting group on the nitrogen atom in **13** was changed from Ts group to Boc or acetyl group, decomposition of the starting material could only be detected leading to an intractable mixture. The desired cyclized products were never isolated from the reaction mixture.

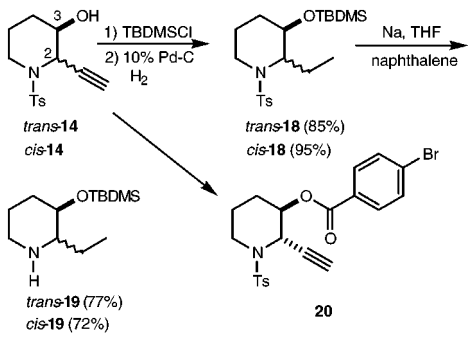
To confirm the stereocomplementarity in this cyclization, we examined the similar ring closure reaction by using *trans*-**13**. The consecutive treatment of *trans*-**13**, prepared from *trans*-**7** according to the procedure described for preparation of *cis*-**13** (see the Experimental Section), with $Co_2(CO)_8$, $BF_3{\cdot}OEt_2$, and CAN furnished *cis*-**14** selectively, although the stereoselectivity (*trans*-**14**: *cis*-**14** = 30:70) was somewhat lower compared with that of *trans*-**13** as shown in Table 1. Thus, it is obvious that this endo mode cyclization proceeds stereocomplementarily. Namely, the *cis*-epoxide provided the *trans*-piperidine derivative, while the *cis*-piperidine derivative was predominatly produced from the corresponding *trans*-epoxide. Control experiment (without formation of cobalt complex) demonstrated that cobalt complexation must be mandatory for this type cyclization. Direct treatment of *cis*-**13** with a catalytic amount of $BF_3{\cdot}OEt_2$ gave, after acetylation, the exo mode product **16** in a highly stereoselective manner along with a small amount of the endo mode product **17**.



86% (**16** : **17** = 91 : 9)

The structure of cyclized products **14** and **15** was determined by careful spectroscopic analysis. ^1H NMR spectrum of *trans*-**14** revealed the H-2 at δ 4.74 as broad singlet. This observation was in sharp contrast to our prediction since we anticipated rather large coupling constant between the H-2 and H-3 due to an axial−axial coupling. In ^1H NMR spectrum of the corresponding *cis*-**14**, the H-2 appeared at δ 4.97 with the small coupling constant (J = 4.4 Hz). In the case of **2** (n = 1, R = TMS), the coupling constant between the H-2 and H-3 of *trans*-**2** was 7.3 Hz, a typical axial−axial coupling, while that of *cis*-**2** showed the smaller one (J = 3.7 Hz) due to an axial−equatorial coupling. Similar smaller coupling constants for both the H-2 of *trans*-**15** (J = 2.9 Hz) and *cis*-**15** (5.4 Hz) were recognized. We assumed that the Ts group on the nitrogen atom might be oriented in a pseudoequatorial position and govern the preference in their conformations. Thus, in the most preferred con-

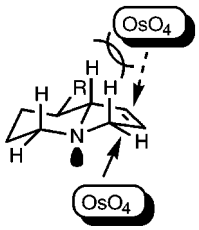
Scheme 4



formation of the *trans*-compounds, the ethynyl moiety at the C-2 position should take an axial site in order to avoid nonbonding interaction with the Ts group, thereby both substituents at the C-2 and C-3 positions on the piperidine skeleton would be in pseudoaxial positions (two protons at the C-2 and C-3 positions, therefore, are in pseudoequatorial positions). On the other hand, the *cis*-products must have the preferred conformer in which two substituents possess pseudoaxial and equatorial positions.

Protection of the secondary hydroxy group of *trans*- and *cis*-**14** with *tert*-butyldimethylsilyl chloride (TBDMSCl) was followed by hydrogenation in the presence of 10% Pd−C to afford *trans*-**18** (85%) and *cis*-**18** (95%), respectively, whose ^{1}H NMR spectra disclosed the similar small coupling constants (2.4 Hz for *trans*-**18** and 4.9 Hz for *cis*-**18**) again (Scheme 4). Treatment of *trans*- and *cis*-**18** with sodium naphthalenide effected ease detosylation to give *trans*-**19** (77%) and *cis*-**19** (72%), respectively. Coupling constant between the H-2 and the H-3 of *trans*-**19** was found to be 8.8 Hz, while that of *cis*-**19** has smaller coupling constant (J = 2.0 Hz) due to axial−axial and axial−equatorial couplings, respectively. This observation strongly supported our conformational analysis as well as assignment of structures. Final and unambiguous confirmation of these structures was made by X-ray crystallographic analysis. The *trans*-piperidine derivative *trans*-**14** was acylated with *p*-bromobenzoyl chloride to give the *p*-bromobenzoate **20**, whose X-ray crystallographic analysis disclosed that **20** has (2*R**,3*S**)-3-((4-bromobenzoyl)oxy)-2-ethynyl-1-(*p*-toluenesulfonyl)-piperidine structure.[9] It should be mentioned that the H-2 signal appears at δ 5.04 as singlet in its ^{1}H NMR spectrum. This is in accordance with the small coupling constants observed in the cases of *trans*-**14** and *trans*-**15**. Thus, we could unambiguously establish the structures of the cyclized products.

With the required *trans*-piperidine compound, *trans*-**14**, for target natural product in hand, we tried to transform it into the desired indolizidine derivative. The secondary hydroxy group of *trans*-**14** was silylated with TBDMSCl to afford **21** in 99% which was successively treated with *n*-butyllithium and paraformaldehyde to provide **22** in 97% yield. Half reduction of **22** in the presence of Lindlar catalyst furnished the (*Z*)-olefin **23** in 99% yield. Indolizidine skeleton formation was realized by two-step sequences. Treatment of **23** with sodium naphthalenide,[10] generated from sodium and naphthalene in THF, at −65 °C gave the detosylated one, which was exposed to carbon tetrabromide and PPh_3 in the presence of Et_3N[6j,11] producing the indolizidine derivative **24** in 57% yield.



24 R = OTBDMS

Figure 1.

The final stage for our synthesis of (±)-swainsonine (**3**) was now faced to stereoselective dihydroxylation of the olefine moiety of the indolizidine framework. IR spectrum of **24** exhibited Bohlmann bands at 2810 and 2790 cm^{-1}, strongly indicating its preferred conformer to be the *trans*-indolizidine skeleton. Therefore, as depicted in Figure 1 on the basis of the literature precedent,[6h] we predicted that dihydroxylation of **24** would predominatly occur from the face opposite to the C-8a hydrogen in order to avoid nonbonding interaction between the dihydroxylating reagent and the pseudoaxial C-8a hydrogen resulting in preferential formation of the desired dihydroxylated product over its stereoisomer.

Introduction of *cis*-dihydroxy functionality was carried out by osmium tetraoxide (OsO_4) to give a mixture of the corresponding diol derivatives.[12] Since these *cis*-dihydroxylated products could not be isolated as a pure form by column chromatography or recrystallization, a mixture of dihydroxylated compounds was converted into the corresponding triacetyl derivatives **25** and **26** by successive treatment with TBAF and acetic anhydride under conventional conditions. Column chromatography of the resulting mixture provided **25** and **26** in 67 and 9% yields, respectively as a pure form (**25**:**26** = 88:12). Comparison of ^{1}H NMR spectra of those triacetate derivatives **25** and **26** with that of the authentic triacetate of swainsonine[2b] allowed us to confirm these structures as depicted in Scheme 5. Thus, dihydroxylation of **24** was shown to occur selectively from the face opposite to the C-8a hydrogen. Finally, base treatment of **25** with potassium carbonate in methanol effected deacetylation to provide (±)-swainsonine (**3**) in 99% yield. Synthetic (±)-swainsonine was identified with natural one by spectral comparison.[2b]

In conclusion, a new synthetic route to (±)-swainsonine was developed that is based on endo mode cyclization as a crucial step where stereoselective construction of *trans*-2-ethynyl-3-hydroxypiperidine skeleton from cobalt-com-

(9) Crystal data: $C_{21}H_{20}BrNO_4S$, M = 462.36, orthorhombic, a = 7.615(2) Å, b = 20.427(3) Å, c = 7.355(1) Å, V = 1016.2(4) Å^3, Z = 2, D_c = 1.511 g/cm^3, space group $P1$ (No. 1), μ(Mo Kα) = 21.25 cm^{-1}. A colorless prisms crystal, ca. 0.4 × 0.4 × 0.1 mm, was mounted on a glass fiber. All measurements were made on a Rigaku AFC5R diffractometer. The cell dimensions and intensities were refined by the least-squares method, using 25 reflections on the diffractometer with Mo Kα radiation with ω-scan mode for 2θ less than 55.0°. The structure was solved by direct method (MITHRIL method). The final cycle of full-matrix least-squares refinement was based on 2525 observed reflections. The final R value was 0.052.

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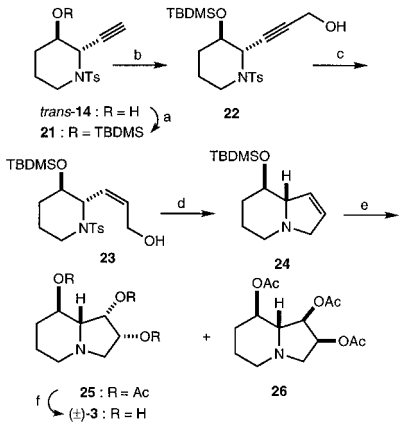
(12) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

Scheme 5[a]



[a]Reaction conditions : (a) TBDMSCl, imidazole, 99%; (b) *n*-BuLi, $(HCHO)_n$, 97%; (c) H_2, Lindlar cat., 99%; (d) (1) Na, naphthalene, (2) CBr_4, PPh_3, Et_3N, 57%; (e) (1) OsO_4, NMO, (2) TBAF, (3) Ac_2O, pyridine, DMAP, 76% (**25** : **26** = 88 : 12); (f) K_2CO_3, MeOH, 99%

[a] Reaction conditions: (a) TBDMSCl, imidazole, 99%; (b) *n*-BuLi, $(HCHO)_n$, 97%; (c) H_2, Lindlar cat., 99%; (d) (1) Na, naphthalene, (2) CBr_4, PPh_3, Et_3N, 57%; (e) (1) OsO_4, NMO, (2) TBAF, (3) Ac_2O, pyridine, DMAP, 76% (**25**:**26** = 88:12); (f) K_2CO_3, MeOH, 99%.

plexed *cis*-3,4-epoxy-7-(*p*-toluenesulfonamido)-1-heptyne was achieved. Studies on further application of the endo mode cyclization to stereoselective total synthesis of natural products are now in progress.

Experimental Section

Melting points are uncorrected. IR spectra were measured in $CHCl_3$ unless otherwise mentioned. ^1H NMR spectra were taken in $CDCl_3$ unless otherwise indicated. $CHCl_3$ (7.26 ppm) was used as an internal standard for silyl compounds. TMS was employed as an internal standard for other compounds. ^{13}C NMR spectra were recorded in $CDCl_3$ with $CHCl_3$ (77.00 ppm) as an internal standard. CH_2Cl_2 was freshly distilled from phosphorus pentoxide, and THF was from sodium diphenyl ketyl, prior to use. All reactions were carried out under nitrogen atmosphere otherwise stated. Silica gel (silica gel 60, 230−400 mesh, Merck) was used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4.

(*Z*)-7-Azido-1-(trimethylsilyl)-3-hepten-1-yne [(*Z*)-8]. To a solution of (*Z*)-**7** (5.50 g, 30.1 mmol) and PPh_3 (8.71 g, 33.2 mmol) in THF (150 mL) was successively added a 4−6% solution of hydrazoic acid in benzene (60 mL), generated from NaN_3 and H_2SO_4, and DEAD (5.20 mL, 33.2 mmol) at 0 °C. After 10 min of stirring at room temperature, the reaction mixture was concentrated to leave the residual oil, which was chromatographed with hexane−AcOEt (40:1) to afford (*Z*)-**8** (6.19 g, 99%) as a colorless oil: FABMS *m*/*z* 208 (M^++1, 1.8), 165 (3.2), 154 (16), 136 (26), 107 (12), 91 (21), 73 (100); IR 2150, 2100 cm^{-1}; ^1H NMR δ 5.92 (dt, 1H, J = 10.9, 7.3 Hz), 5.55 (dt, 1H, J = 10.9, 1.3 Hz), 3.30 (t, 2H, J = 7.3 Hz), 2.42 (qd, 2H, J = 7.3, 1.3 Hz), 1.73 (quint, 2H, J = 7.3 Hz), 0.20 (s, 9H); ^{13}C NMR δ 143.02, 110.66, 101.42, 99.46, 50.82, 27.91, 27.37, −0.09; HRFABMS calcd for $C_{10}H_{17}N_3Si$ 208.1270, found 208.1261.

(*E*)-7-Azido-1-(trimethylsilyl)-3-hepten-1-yne [(*E*)-8]. According to the procedure described for preparation of (*Z*)-**8**, (*E*)-**8** (6.53 g, 99%) was obtained from (*E*)-**7** (6.60 g, 31.8 mmol) as a colorless oil: FABMS *m*/*z* 208 (M^+ + 1, 16), 165 (6.1), 154 (17), 136 (27), 107 (13), 91 (23), 73 (100); IR 2090 cm^{-1}; ^1H NMR δ 6.16 (dt, 1H, J = 15.8, 6.9 Hz), 5.54 (dt, 1H, J = 15.8, 1.3 Hz), 3.28 (t, 2H, J = 6.9 Hz), 2.19 (qd, 2H, J = 6.9, 1.3 Hz), 1.67 (quint, 2H, J = 6.9 Hz), 0.18 (s, 9H); ^{13}C NMR δ 143.83, 111.02, 103.52, 93.39, 50.57, 29.98, 27.84, −0.09; HRFABMS calcd for $C_{10}H_{17}N_3Si$ 208.1270, found 208.1251.

(*Z*)-1-(Trimethylsilyl)-7-(*p*-toluenesulfonamido)-3-hepten-1-yne [(*Z*)-10]. A solution of (*Z*)-**8** (1.17 g, 5.68 mmol) and PPh_3 (1.49 g, 5.68 mmol) in THF (50 mL) was stirred at room temperature for 4 h, and then H_2O (3.0 mL) was added to the reaction mixture which was heated under reflux for 4 h. The reaction mixture was concentrated and passed through a short pad of silica gel with AcOEt−MeOH to give (*Z*)-**9** (1.03 g, 99%). To a solution of (*Z*)-**9** (1.03 g, 5.68 mmol) and Et_3N (1.00 mL) in CH_2Cl_2 (47 mL) was added a solution of TsCl (1.31 g, 6.82 mmol) and *N*,*N*-(dimethylamino)pyridine (DMAP) (71.0 mg, 0.57 mmol) in CH_2Cl_2 (9.5 mL) at 0 °C. The reaction mixture was stirred for 1 h, washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (5:1) afforded (*Z*)-**10** (1.12 g, 81%) as colorless solids, mp 64.5−65.0 °C (hexane−CH_2Cl_2): MS *m*/*z* 335 (M^+, 20), 320 (23), 180 (100), 155 (37), 91 (66); IR 3400, 2140, 1330, 1160 cm^{-1}; ^1H NMR δ 7.74 (d, 2H, J = 8.2 Hz), 7.30 (d, 2H, J = 8.2 Hz), 5.81 (dt, 1H, J = 10.6, 7.6 Hz), 5.50 (d, 1H, J = 10.6 Hz), 4.59 (t, 1H, J = 6.9 Hz), 2.94 (q, 2H, J = 6.9 Hz), 2.42 (s, 3H), 2.34 (q, 2H, J = 6.9 Hz), 1.60 (quint, 2H, J = 6.9 Hz), 0.21 (s, 9H); ^{13}C NMR δ 143.26, 143.06, 137.11, 129.65, 127.05, 110.68, 101.53, 99.72, 42.20, 28.29, 26.94, 21.47, −0.09. Anal. Calcd for $C_{17}H_{25}NO_2SSi$: C, 60.85; H, 7.51; N, 4.17. Found: C, 60.94; H, 7.42; N, 4.28.

(*E*)-1-(Trimethylsilyl)-7-(*p*-toluenesulfonamido)-3-hepten-1-yne [(*E*)-10]. According to the procedure described for preparation of (*Z*)-**10**, (*E*)-**10** (1.72 g, 81% overall yield) was obtained from (*E*)-**8** (1.30 g, 6.28 mmol) as colorless solids, mp 96.0−97.0 °C (hexane−CH_2Cl_2): MS *m*/*z* 335 (M^+, 30), 320 (41), 180 (100), 155 (48), 91 (70); IR 3400, 2130, 1330, 1160 cm^{-1}; ^1H NMR δ 7.73 (d, 2H, J = 8.2 Hz), 7.31 (d, 2H, J = 8.2 Hz), 6.06 (dt, 1H, J = 15.8, 7.3 Hz), 5.43 (dt, 1H, J = 15.8, 1.3 Hz), 4.41 (t, 1H, J = 7.3 Hz), 2.94 (q, 2H, J = 7.3 Hz), 2.42 (s, 3H), 2.09 (qd, 2H, J 7.3, 1.3 Hz), 1.55 (quint, 2H, J = 7.3 Hz), 0.17 (s, 9H); ^{13}C NMR δ 143.93, 143.44, 136.88, 129.73, 127.05, 110.80, 103.56, 93.29, 42.42, 29.84, 28.53, 21.49, −0.09. Anal. Calcd for $C_{17}H_{25}NO_2SSi$: C, 60.85; H, 7.51; N, 4.17. Found: C, 60.86; H, 7.53; N, 4.13.

(*Z*)-7-(*p*-Toluenesulfonamido)-3-hepten-1-yne [(*Z*)-11]. To a solution of (*Z*)-**10** (319 mg, 0.95 mmol) in THF (10 mL) was added a solution of TBAF (1.0 M THF solution, 1.14 mL, 1.14 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 30 min and diluted with Et_2O. The ether solution was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (5:1) afforded (*Z*)-**11** (241 mg, 96%) as a colorless oil: MS *m*/*z* 263 (M^+, 6.4), 184 (52), 155 (90), 91 (100); IR 3400, 3325, 1330, 1160 cm^{-1}; ^1H NMR δ 7.74 (d, 2H, J = 8.2 Hz), 7.30 (d, 2H, J = 8.2 Hz), 5.90 (dt, 1H, J = 10.9, 7.6 Hz), 5.46 (ddt, 1H, J = 10.9, 2.3, 1.0 Hz), 4.66 (t, 1H, J = 6.6 Hz), 3.12 (d, 1H, J = 2.3 Hz), 2.95 (q, 2H, J = 6.6 Hz), 2.42 (s, 3H), 2.34 (qd, 2H, J = 7.6, 1.0 Hz), 1.60 (m, 2H); ^{13}C NMR δ 143.95, 143.17, 136.80, 129.54, 126.92, 109.14, 82.04, 80.01, 42.29, 28.25, 26.94, 21.34. Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.51; H, 6.50; N, 5.13.

(*E*)-7-(*p*-Toluenesulfonamido)-3-hepten-1-yne [(*E*)-11]. According to the procedure described for preparation of (*Z*)-**11**, (*E*)-**11** (677 mg, 99%) was obtained from (*E*)-**10** (874 mg, 2.60 mmol) as colorless solids, mp 88.0−89.0 °C (hexane−CH_2Cl_2): MS *m*/*z* 263 (M^+, 6.8), 184 (53), 155 (83), 108 (30), 91 (100); IR 3400, 3320, 1330, 1160 cm^{-1}; ^1H NMR δ 7.73 (d, 2H, J = 8.2 Hz), 7.31 (d, 2H, J = 8.2 Hz), 6.11 (dt, 1H, J = 15.8, 7.3 Hz), 5.40 (dd, 1H, J = 15.8, 2.0 Hz), 4.37 (t, 1H, J = 5.9 Hz), 2.98−2.91 (m, 2H), 2.79 (d, 1H, J = 2.0 Hz), 2.43 (s, 3H), 2.11 (q, 2H, J = 7.3, 1.0 Hz), 1.57 (quint, 2H, J = 7.3 Hz); ^{13}C NMR δ 144.65, 143.45, 136.80, 129.72, 127.03, 109.67, 82.03, 76.19, 42.34, 29.74, 28.41, 21.48. Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.96; H, 6.62; N, 5.32.

***(3R*,4S*)*-3,4-Epoxy-1-trimethylsilyl-7-(*p*-toluenesulfonamido)-1-heptyne (*cis*-12).** To a solution of (*Z*)-**10** (500 mg, 1.49 mmol) in CH_2Cl_2 (25 mL) were added Na_2HPO_4 (2.13 g, 15.0 mmol) and *m*CPBA (80% purity, 971 mg, 4.59 mmol) at room temperature. The suspension was stirred at room temperature for 24 h and filtered. The filtrate was washed with saturated Na_2SO_3 solution, water, and brine,

dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (5:1) afforded *cis*-**12** (298 mg, 57%) as a colorless oil: MS *m*/*z* 351 (M^+, 1.2), 224 (100), 196 (45), 180 (48), 155 (61), 91 (96); IR 3400, 2160, 1330, 1160 cm^{-1}; ^1H NMR δ 7.75 (d, 2H, J = 8.3 Hz), 7.31 (d, 2H, J = 8.3 Hz), 4.53 (t, 1H, J = 6.3 Hz), 3.40 (d, 1H, J = 3.9 Hz), 3.03 (q, 2H, J = 6.8 Hz), 2.97 (td, 1H, J = 6.8, 3.9 Hz), 2.43 (s, 3H), 1.77−1.66 (m, 4H), 0.18 (s, 9H); ^{13}C NMR δ 143.40, 137.02, 129.72, 127.06, 99.86, 77.22, 57.40, 45.32, 42.64, 26.26, 21.49, −0.34. Anal. Calcd for $C_{17}H_{25}NO_3SSi$: C, 58.08; H, 7.17; N, 3.98. Found: C, 57.84; H, 7.19; N, 3.95.

(3*R,4*S**)-3,4-Epoxy-7-(*p*-toluenesulfonamido)-1-heptyne (*cis*-13).** According to the procedure described for preparation of *cis*-**12**, *cis*-**13** (182 mg, 58%) was obtained from (*Z*)-**11** (297 mg, 1.13 mmol) as a colorless oil: MS *m*/*z* 279 (M^+, 0.4), 224 (67), 155 (76), 91 (100); IR 3400, 3320, 1330, 1160 cm^{-1}; ^1H NMR δ 7.75 (d, 2H, J = 8.3 Hz), 7.31 (d, 2H, J = 8.3 Hz), 4.54 (t, 1H, J = 6.3 Hz), 3.41 (dd, 1H, J = 3.9, 1.9 Hz), 3.03 (q, 2H, J = 6.3 Hz), 3.00 (td, 1H, J = 6.8, 3.9 Hz), 2.43 (s, 3H), 2.36 (d, 1H, J = 1.9 Hz), 1.80−1.65 (m, 4H); ^{13}C NMR δ 143.25, 136.76, 129.58, 126.90, 78.43, 73.95, 56.95, 44.61, 42.55, 26.19, 25.89, 21.34. Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.06; H, 6.16; N, 4.96.

(3*R,4*R**)-3,4-Epoxy-7-(*p*-toluenesulfonamido)-1-heptyne (*trans*-13).** According to the procedure described for preparation of *cis*-**12**, *trans*-**13** (336 mg, 51%) was obtained from (*E*)-**11** (615 mg, 2.34 mmol) as a colorless oil: MS *m*/*z* 279 (M^+, 10), 224 (53), 184 (40), 155 (100), 124 (50), 91 (95); IR 3400, 3320, 1325, 1155 cm^{-1}; ^1H NMR δ 7.74 (d, 2H, J = 8.8 Hz), 7.31 (d, 2H, J = 8.8 Hz), 4.55 (t, 1H, J = 6.3 Hz), 3.08−2.96 (m, 4H), 2.43 (s, 3H), 2.31 (d, 1H, J = 1.7 Hz), 1.81−1.60 (m, 3H), 1.41 (m, 1H); ^{13}C NMR δ 143.45, 136.84, 129.72, 127.01, 80.00, 72.04, 59.53, 44.78, 42.50, 28.48, 25.81, 21.48. Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 59.85; H, 6.19; N, 4.90.

(2*R,3*S**)- and (2*R**,3*R**)-2-Ethynyl-3-hydroxy-1-(*p*-toluenesulfonyl)piperidine (*trans*-14 and *cis*-14).** To a solution of *cis*-**13** (28.0 mg, 0.10 mmol) in CH_2Cl_2 (3.0 mL) was added $Co_2(CO)_8$ (40 mg, 0.11 mmol) at room temperature. After 15 min of stirring, the reaction mixture was cooled to −78 °C and held at the same temperature for 30 min. A solution of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (0.1 M solution, 0.10 mL, 0.01 mmol) was added to the reaction mixture, which was further stirred for 10 min, quenched by addition of water, and gradually warmed to 0 °C. The CH_2Cl_2 layer was separated, washed with brine, dried, and concentrated to dryness. To a solution of the residual oil in MeOH (3.0 mL) was added CAN (219 mg, 0.40 mmol) at 0 °C. After 30 min of stirring, the reaction mixture was concentrated, diluted with water, and extracted with AcOEt. The extract was washed with water and brine, dried, and conentrated to dryness. Chromatography of the residue with hexane−AcOEt (5:1) afforded *trans*-**14** (21.4 mg, 76%) and *cis*-**14** (2.4 mg, 9%). *trans*-**14** was obtained as colorless solids, mp 132−133 °C (hexane-CH_2Cl_2): MS *m*/*z* 279 (M^+, 0.2), 155 (3.7), 139 (3.8), 124 (100), 91 (36); IR 3600, 3320, 1345, 1160 cm^{-1}; ^1H NMR δ 7.72 (d, 2H, J = 8.3 Hz), 7.28 (d, 2H, J = 8.3 Hz), 4.74 (bs, 1H), 3.96 (qd, 1H, J = 9.3, 2.4 Hz), 3.69 (m, 1H), 2.86 (dt, 1H, J = 11.7, 3.4 Hz), 2.44 (d, 1H, J = 9.3 Hz), 2.42 (s, 3H), 2.10 (d, 1H, J = 2.0 Hz), 1.97−1.84 (m, 2H), 1.72 (m, 1H), 1.56 (m, 1H); ^{13}C NMR δ 143.64, 134.90, 129.27, 128.03, 76.83, 76.41, 67.76, 51.85, 41.64, 25.63, 21.49, 19.14. Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.30; H, 6.08; N, 4.97. *cis*-**14** was obtained as colorless solids, mp 128−129 °C (hexane−CH_2Cl_2): MS *m*/*z* 279 (M^+, 0.4), 155 (8.4), 139 (11), 124 (100), 91 (67); IR 3600, 3320, 1345, 1160 cm^{-1}; ^1H NMR δ 7.71 (d, 2H, J = 8.3 Hz), 7.28 (d, 2H, J = 8.3 Hz), 4.97 (dd, 1H, J = 4.4, 2.0 Hz), 3.77 (m, 1H), 3.63 (m, 1H), 2.70 (dt, 1H, J = 12.2, 2.9 Hz), 2.42 (s, 3H), 2.08 (d, 1H, J = 2.0 Hz), 1.94−1.48 (m, 5H), 1.72 (m, 1H); ^{13}C NMR δ 143.56, 134.97, 129.24, 127.87, 76.96, 75.90, 68.41, 51.72, 40.77, 28.45, 23.51, 21.42. Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.14; H, 6.21; N, 4.95. *trans*-**13** (29.1 mg, 0.10 mmol) provided *trans*-**14** (7.8 mg, 27%) and *cis*-**14** (18.1 mg, 62%) under the same conditions described for ring closure of *cis*-**13**.

(2*R,3*S**)- and (2*R**,3*R**)-3-Hydroxy-2-[(2′-trimethylsilyl)ethynyl]-1-(*p*-toluenesulfonyl)piperidine (*trans*-15 and *cis*-15).** According to the procedure described for preparation of **14**, *trans*-**15** (24.8 mg, 69%) and *cis*-**15** (5.1 mg, 14%) were obtained from *cis*-**12** (36.0 mg, 0.10 mmol). *trans*-**15** was obtained as colorless solids, mp 154−155 °C (hexane−CH_2Cl_2): MS *m*/*z* 351 (M^+, 0.2), 336 (2.3), 196 (100), 139 (6.2), 126 (14), 91 (29); IR 3600, 2160, 1345, 1160 cm^{-1}; ^1H NMR δ 7.70 (d, 2H, J = 8.3 Hz), 7.28 (d, 2H, J = 8.3 Hz), 4.69 (d, J = 2.9 Hz, 1H), 3.93 (qd, 1H, J = 9.8, 2.9 Hz), 3.71 (m, 1H), 2.85 (dt, 1H, J = 11.7, 2.9 Hz), 2.42 (s, 3H), 2.40 (d, 1H, J = 9.8 Hz), 1.94−1.83 (m, 2H), 1.71 (m, 1H), 1.56 (m, 1H), −0.04 (s, 9H); ^{13}C NMR δ 143.42, 134.98, 129.36, 128.02, 97.94, 93.77, 67.92, 52.83, 41.65, 25.64, 21.49, 19.31, −0.53. Anal. Calcd for $C_{17}H_{25}NO_3SSi$: C, 58.08; H, 7.17; N, 3.98. Found: C, 58.00; H, 7.14; N, 3.98. *cis*-**15** was obtained as colorless solids, mp 127−128 °C (hexane−CH_2Cl_2): MS *m*/*z* 351 (M^+, 3.4), 196 (100), 126 (32), 91 (73); IR 3600, 2150, 1345, 1160 cm^{-1}; ^1H NMR δ 7.71 (d, 2H, J = 8.3 Hz), 7.28 (d, 2H, J = 8.3 Hz), 4.93 (d, 1H, J = 5.4 Hz), 3.75 (dt, 1H, J = 10.7, 5.4 Hz), 3.69 (m, 1H), 2.67 (dt, 1H, J = 12.2, 2.9 Hz), 2.42 (s, 3H), 1.99 (m, 1H), 1.71−1.62 (m, 2H), 1.67 (d, 1H, J = 10.7 Hz), 1.47 (dq, 1H, J = 12.2, 4.4 Hz), −0.04 (s, 9H); ^{13}C NMR δ 143.36, 135.17, 129.36, 127.92, 96.87, 94.83, 68.41, 52.63, 40.81, 28.86, 23.65, 21.48, −0.43. Anal. Calcd for $C_{17}H_{25}NO_3SSi$: C, 58.08; H, 7.17; N, 3.98. Found: C, 57.99; H, 7.18; N, 3.93.

(2*R,3*R**)-2-(1′-Acetoxy-2′-propyn-1′-yl)-1-(*p*-toluenesulfonyl)amido]pyrrolidine (16) and (2*R**,3*R**)-3-Acetoxy-2-ethynyl-1-(*p*-toluenesulfonyl)piperidine (17).** A solution of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (0.1 M solution, 0.10 mL, 0.01 mmol) was added to a solution of *cis*-**13** (28.0 mg, 0.10 mmol) in CH_2Cl_2 (3.0 mL) at −78 °C. The reaction mixture was stirred at the same temperature for 10 min, gradually warmed to 0 °C, and then quenched by addition of water. The CH_2Cl_2 layer was separated, washed with brine, dried, and concentrated to dryness. The residue was dissolved in CH_2Cl_2 (1.0 mL) to which acetic anhydride (0.01 mL, 0.11 mmol), Et_3N (0.02 mL, 0.14 mmol), and DMAP (92.0 mg, 0.02 mmol) were added. The reaction mixture was allowed to stand for 1 h, diluted with CH_2Cl_2, which was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (3:1) afforded **16** (25.4 mg, 79%) and **17** (2.4 mg, 7%). Compound **16** was obtained as colorless solids, mp 110−111 °C (hexane−AcOEt): MS *m*/*z* 321 (M^+, 1.4), 278 (6.4), 261 (11), 166 (100), 139 (14), 124 (36), 91 (53), 43 (63); IR 3330, 2120, 1745, 1350, 1160 cm^{-1}; ^1H NMR δ 7.74 (d, 2H, J = 8.8 Hz), 7.31 (d, 2H, J = 8.8 Hz), 5.72 (dd, 1H, J = 5.9, 2.4 Hz), 3.84 (ddd, 1H, J = 8.3, 5.4, 4.4 Hz), 3.43 (dt, 1H, J = 10.7, 7.3 Hz), 3.29 (dt, 1H, J = 10.7, 7.3 Hz), 2.43 (s, 3H), 2.42 (d, 1H, J = 2.4 Hz), 2.08 (m, 1H), 2.11 (s, 3H), 1.98 (m, 1H), 1.72 (m, 1H), 1.49 (m, 1H); ^{13}C NMR δ 169.32, 143.68, 134.43, 129.74, 127.57, 78.83, 74.97, 65.79, 60.65, 49.51, 27.62, 24.25, 21.49, 20.84. Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.79; H, 5.96; N, 4.36. Found: C, 60.00; H, 6.04; N, 4.33. Compound **17** was obtained as colorless solids, mp 108−110 °C (hexane−AcOEt): MS *m*/*z* 321 (M^+, 0.2), 279 (0.3), 262 (1.3), 224 (100), 155 (83), 91 (100), 43 (31); IR 3330, 2110, 1745, 1350, 1160 cm^{-1}; ^1H NMR δ 7.70 (d, 2H, J = 8.3 Hz), 7.28 (d, 2H, J = 8.3 Hz), 5.10 (dd, 1H, J = 4.9, 2.0 Hz), 4.79 (td, 1H, J = 11.2, 4.9 Hz), 3.65 (m, 1H), 2.80 (dt, 1H, J = 12.2, 2.4 Hz), 2.42 (s, 3H), 2.07 (s, 3H), 2.04 (d, 1H, J = 2.0 Hz), 1.77−1.64 (m, 3H), 1.87 (m, 1H); ^{13}C NMR δ 169.79, 143.63, 135.29, 129.31, 127.98, 76.04, 75.74, 69.99, 48.70, 40.92, 25.00, 23.36, 21.51, 20.97. Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.79; H, 5.96; N, 4.36. Found: C, 59.89; H, 6.03; N, 4.37.

(2*R,3*S**)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-ethynyl-1-(*p*-toluenesulfonyl)piperidine (21).** To a solution of *trans*-**14** (121 mg, 0.43 mmol) in *N*,*N*-dimethylformamide (0.5 mL) was added imidazole (64.0 mg, 0.95 mmol) and *tert*-butyldimethylsilyl chloride (TBDMSCl) (72.0 mg, 0.47 mmol). The reaction mixture was heated at 70 °C for 1 h, cooled to room temperature, and diluted with Et_2O. The Et_2O layer was washed with water several times, brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (20:1) afforded **21** (166 mg, 97%) as colorless

solids, mp 112−113 °C (hexane−AcOEt): MS *m/z* 378 (M^+ − Me, 3.8), 336 (100), 238 (85), 185 (16), 73 (31); IR 3330, 1345, 1160 cm^{-1}; ^1H NMR δ 7.74 (d, 2H, J = 8.3 Hz), 7.24 (d, 2H, J = 8.3 Hz), 4.69 (bs, 1H), 3.97 (q, 1H, J = 2.9 Hz), 3.56 (m, 1H), 2.90 (dt, 1H, J = 12.2, 2.9 Hz), 2.40 (s, 3H), 2.18 (d, 1H, J = 2.4 Hz), 1.99 (m, 1H), 1.86 (m, 1H), 1.59 (m, 1H), 1.39 (m, 1H), 0.93 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR δ 143.00, 136.42, 129.15, 127.84, 78.26, 75.53, 68.39, 51.47, 41.49, 26.99, 25.72, 21.48, 19.14, 18.08, −4.96, −5.00. Anal. Calcd for $C_{20}H_{31}NO_3SSi$: C, 61.03; H, 7.94; N, 3.56. Found: C, 61.12; H, 8.02; N, 3.70.

(2*R,3*S**)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-ethyl-1-(*p*-toluenesulfonyl)piperidine (*trans*-18).** A solution of **21** (166 mg, 0.42 mmol) in AcOEt (3.0 mL) was hydrogenated for 4 h at room temperature under hydrogen atmosphere in the presence of 10% Pd−C (12.0 mg). The catalyst was filtered off, and the filtrate was concentrated to leave the residue, which was chromatographed with hexane−AcOEt (20:1) to give *trans*-**18** (103 mg, 88%, 85% overall yield from *trans*-**14**) as colorless solids, mp 75.5−76.0 °C (hexane): MS *m/z* 396 (M^+ − H, 0.5), 340 (100), 242 (18), 73 (31); IR 1345, 1160 cm^{-1}; ^1H NMR δ 7.89 (d, 2H, J = 8.3 Hz), 7.23 (d, 2H, J = 8.3 Hz), 3.95 (td, 1H, J = 7.3, 2.4 Hz), 3.84 (q, 1H, J = 2.4 Hz), 3.32 (m, 1H), 2.93 (dt, 1H, J = 13.2, 2.5 Hz), 2.40 (s, 3H), 1.75 (m, 1H), 1.69−1.53 (m, 4H), 1.23 (m, 1H), 1.00 (t, 3H, J = 7.3 Hz), 0.92 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ 142.44, 138.72, 129.16, 127.64, 67.21, 61.12, 40.02, 26.63, 25.88, 22.79, 21.42, 18.40, 18.31, 11.11, −4.89. Anal. Calcd for $C_{20}H_{35}NO_3SSi$: C, 60.41; H, 8.87; N, 3.52. Found: C, 60.45; H, 8.87; N, 3.46.

(2*R,3*R**)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-ethyl-1-(*p*-toluenesulfonyl)piperidine (*cis*-18).** According to the procedure described for preparation of *trans*-**18**, *cis*-**14** (85.0 mg, 0.30 mmol) was successively treated with TBDMSCl and hydrogenated to give *cis*-**18** (114 mg, 95% overall yield) as colorless solids, mp 66.0−67.5 °C (hexane): MS *m/z* 396 (M^+ − H, 0.2), 340 (100), 242 (69), 73 (36); IR 1345, 1150 cm^{-1}; ^1H NMR δ 7.72 (d, 2H, J = 8.3 Hz), 7.27 (d, 2H, J = 8.3 Hz), 3.81 (td, 1H J = 10.4, 4.9 Hz), 3.72 (dd, 1H, J = 13.2, 4.4 Hz), 3.48 (td, 1H, J = 10.2, 4.9 Hz), 2.83 (dt, 1H, J = 13.2, 2.4 Hz), 2.42 (s, 3H), 1.69 (m, 1H), 1.52−1.41 (m, 4H), 1.33 (m, 1H), 0.86 (t, 3H, J = 7.3 Hz), 0.85 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR δ 142.80, 139.12, 129.54, 126.90, 68.95, 59.75, 39.14, 28.23, 25.70, 23.99, 21.40, 17.92, 15.80, 10.78, −4.80. Anal. Calcd for $C_{20}H_{35}NO_3SSi$: C, 60.41; H, 8.87; N, 3.52. Found: C, 60.45; H, 8.81; N, 3.64.

(2*R,3*S**)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-ethylpiperidine (*trans*-19).** To a solution of *trans*-**18** (100 mg, 0.25 mmol) in THF (2.5 mL) was added a solution of sodium naphthalenide in THF (0.2 M solution, 3.7 mL, 0.75 mmol) at −60 °C. The reaction mixture was stirred for 20 min at the same temperature, quenched by addition of saturated NH_4Cl solution, diluted with water, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with $CHCl_3$−MeOH (10:1) afforded *trans*-**19** (47 mg, 77%) as colorless crystals, mp 172−173 °C (hexane−$CHCl_3$): MS *m/z* 243 (M^+, 13), 214 (72), 186 (65), 112 (27), 72 (100); IR 3150 cm^{-1}; ^1H NMR δ 3.79 (dt, 1H J = 8.8, 3.9 Hz), 3.39 (m, 1H), 2.82 (dt, 1H, J = 12.2, 3.4 Hz), 2.75 (dt, 1H, J = 8.8, 3.9 Hz), 2.08−1.95 (m, 3H), 1.90 (m, 1H), 1.83 (m, 1H), 1.45 (m, 1H), 1.15 (t, 3H, J = 7.3 Hz), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ 71.70, 64.13, 45.52, 33.95, 25.75, 24.17, 24.14, 17.94, 9.99, −4.08, −4.80; HRMS calcd for $C_{13}H_{29}NOSi$ 243.2018, found 243.2040.

(2*R,3*R**)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-ethylpiperidine (*cis*-19).** According to the procedure described for preparation of *trans*-**19**, *cis*-**19** (20 mg, 72%) was obtained from *cis*-**18** (45 mg, 0.11 mmol) as colorless solids, mp 181−182 °C (hexane−$CHCl_3$): MS *m/z* 243 (M^+, 12), 214 (61), 186 (67), 112 (26), 72 (100); IR 3350 cm^{-1}; ^1H NMR δ 4.06 (t, 1H J = 2.0 Hz), 3.47 (dt, 1H, J = 12.7, 2.0 Hz), 2.89 (dt, 1H, J = 12.7, 3.4 Hz), 2.86 (m, 1H), 2.15(m, 1H), 1.97 (m, 1H), 1.91 (m, 1H), 1.74 (m, 1H), 1.64 (m, 1H), 1.55 (m, 1H), 1.00 (t, 3H, J = 7.3 Hz), 0.95 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR δ 64.34, 61.42, 44.48, 30.44, 25.72, 22.48, 18.03, 17.29, 9.76, −4.45, −5.05; HRMS calcd for $C_{13}H_{29}NOSi$ 243.2018, found 243.2041.

(2*R,3*S**)-3-[(4′-Bromobenzoyl)oxy]-2-ethynyl-1-(*p*-toluenesulfonyl)piperidine (20).** To a solution of *trans*-**14** (30.0 mg, 0.11 mmol) and Et_3N (0.02 mL, 0.17 mmol) in CH_2Cl_2 (1.1 mL) were added *p*-bromobenzoyl chloride (26.0 mg, 0.12 mmol) and DMAP (3.0 mg, 0.02 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 30 min, quenched by addition of saturated NH_4Cl solution, and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (7:1) afforded **20** (47.0 mg, 94%) as colorless crystals, mp 170.5−171.5 °C (Et_2O): MS *m/z* 308 (M^+ − Ts, 38), 306 (M^+ − Ts, 39), 278 (31), 261 (100), 185 (83), 183 (85), 155 (54), 91 (77); IR 3300, 1720, 1345, 1165 cm^{-1}; ^1H NMR δ 7.93 (dd, 2H, J = 8.8, 2.0 Hz), 7.68 (d, 2H, J = 8.3 Hz), 7.60 (dd, 2H, J = 8.8, 2.0 Hz), 7.22 (d, 2H, J = 8.3 Hz), 5.17 (dd, 1H, J = 2.9, 2.4 Hz), 5.04 (bs, 1H), 3.79 (m, 1H), 3.02 (dt, 1H, J = 12.2, 2.4 Hz), 2.39 (s, 3H), 2.22 (d, 1H, J = 2.4 Hz), 2.08−1.95 (m, 3H), 1.63 (m, 1H); ^{13}C NMR δ 164.87, 143.38, 135.96, 131.78, 131.36, 129.33, 128.73, 128.42, 127.59, 76.44, 76.36, 69.78, 48.71, 41.28, 23.78, 21.51, 20.17. Anal. Calcd for $C_{21}H_{20}BrNO_4S$: C, 54.55; H, 4.36; N, 3.03. Found: C, 54.93; H, 4.52; N, 2.89.

(2*R,3*S**)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-(3′-hydroxy-1′-propynyl)-1-(*p*-toluenesulfonyl)piperidine (22).** To a solution of **21** (535 mg, 1.34 mmol) in THF (15 mL) was added a solution of *n*-BuLi (1.59 M hexane solution, 0.94 mL, 1.49 mmol) at −78 °C, and the reaction mixture was stirred for 1 h. Paraformaldehyde (85.0 mg, 2.83 mmol) was added to the reaction mixture, which was then stirred at room temperature for 1 h. The reaction was quenched by addition of saturated NH_4Cl solution and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (3:1) afforded **22** (557 mg, 97%) as a colorless oil: MS *m/z* 423 (M^+, 0.2), 408 (9.9), 366 (100), 292 (3.1), 268 (99), 185 (28), 120 (11), 91 (57); IR 3600, 3500, 1340, 1210 cm^{-1}; ^1H NMR δ 7.74 (d, 2H, J = 8.3 Hz), 7.27 (d, 2H, J = 8.3 Hz), 4.67 (m, 1H), 3.98 (dd, 2H, J = 6.3, 2.0 Hz), 3.94 (q, 1H, J = 2.4 Hz), 3.57 (m, 1H), 2.85 (dt, 1H, J = 12.2, 2.4 Hz), 2.41 (s, 3H), 1.99 (m, 1H), 1.80 (m, 1H), 1.56 (m, 1H), 1.41 (m, 1H), 1.32 (t, 1H, J = 6.3 Hz), 0.92 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ 143.10, 136.34, 129.07, 128.03, 85.56, 80.01, 68.28, 51.80, 50.78, 41.70, 27.10, 25.71, 21.46, 19.14, 18.06, −4.95, −4.99. Anal. Calcd for $C_{21}H_{33}NO_4SSi$: C, 59.54; H, 7.85; N, 3.31. Found: C, 59.37; H, 8.07; N, 3.20.

(2*R,3*S**)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[(*Z*)-3′-hydroxy-1′-propen-1′-yl]-1-(*p*-toluenesulfonyl)piperidine (23).** A solution of **22** (557 mg, 1.31 mmol) in AcOEt (7.0 mL) was hydrogenated for 30 min under hydrogen atmosphere in the presence of Lindlar catalyst (280 mg). The catalyst was filtered off, and the filtrate was concentrated to dryness. Chromatography of the residue with hexane−AcOEt (3:1) afforded **23** (554 mg, 99%) as colorless solids, mp 92.0−93.0 ($CHCl_3$−MeOH): MS *m/z* 425 (M^+, 0.1), 410 (11), 368 (98), 352 (3.9), 270 (86), 213 (28), 185 (17), 155 (29), 138 (100), 120 (24), 91 (99); IR 3500, 3420, 1340, 1160 cm^{-1}; ^1H NMR δ 7.75 (d, 2H, J = 8.3 Hz), 7.24 (d, 2H, J = 8.3 Hz), 5.76 (dddd, 1H, J = 11.2, 8.3, 5.9, 1.0 Hz), 5.66 (dd, 1H, J = 11.2, 9.8 Hz), 4.69 (dd, 1H, J = 9.8, 2.9 Hz), 4.41 (m, 1H), 4.07 (m, 1H), 3.70 (m, 1H), 3.35 (dt, 1H, J = 12.7, 3.9 Hz), 3.06 (dt, 1H, J = 12.7, 2.9 Hz), 2.40 (s, 3H), 2.23 (dd, 1H, J = 7.8, 4.4 Hz), 1.94 (m, 1H), 1.68−1.56 (m, 2H), 1.42 (m, 1H), 0.90 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR δ 143.01, 137.30, 131.64, 129.30, 127.55, 126.32, 68.99, 58.14, 56.88, 41.22, 27.24, 25.76, 21.46, 18.86, 18.06, −4.75, −5.01. Anal. Calcd for $C_{21}H_{35}NO_4SSi$: C, 59.26; H, 8.29; N, 3.29. Found: C, 59.29; H, 8.44; N, 3.21.

(8*R,8a*R**)-8-[(*tert*-Butyldimethylsilyl)oxy]-1,2-dehydroindolizidine (24).** To a solution of **23** (530 mg, 1.25 mmol) in THF (12 mL) was added sodium naphthalenide (0.20 M THF solution, 18.8 mL, 3.76 mmol) at −78 °C. After 20 min of stirring at the same temperature, the reaction was quenched by addition of water and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to

dryness. The residue was passed through a short pad of silica gel with $CHCl_3$−MeOH (10:1) to give the secondary amine derivative (304 mg, 1.12 mmol), which was dissolved in CH_2Cl_2 (11 mL). Carbon tetrabromide (482 mg, 1.46 mmol) and PPh_3 (440 mg, 1.68 mmol) was added to the CH_2Cl_2 solution at 0 °C. The reaction mixture was stirred at the same temperature for 10 min and then Et_3N (3.1 mL, 22.4 mmol) was added. After 30 min of stirring at room temperature, the reaction was quenched by addition of water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (1:1) afford **24** (179 mg, 57% overall yield) as a colorless oil: MS *m*/*z* 253 (M^+, 6.0), 238 (2.2), 196 (100), 154 (36), 120 (86), 75 (20); IR 2860, 2790, 2715 cm^{-1}; ^1H NMR δ 6.05 (m, 1H), 5.89 (m, 1H), 3.64 (dddd, 1H, J = 12.7, 3.9, 2.4, 1.5 Hz), 3.46 (ddd, 1H, J = 10.3, 9.3, 4.4 Hz), 3.23 (dddd, 1H, J = 12.7, 6.4, 2.4, 1.5 Hz), 2.92 (m, 1H), 2.86 (m, 1H), 2.39 (m, 1H), 1.93 (m, 1H), 1.68−1.63 (m, 2H), 1.26 (m, 1H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ 131.51, 128.46, 73.95, 71.93, 57.89, 48.84, 34.29, 25.79, 24.35, 18.03, −4.28, −4.70; HRMS calcd for $C_{14}H_{27}NOSi$ 253.1861, found 253.1868.

(1*R,2*S**,8*S**,8a*S**)- and (1*R**,2*S**,8*R**,8a*R**)-1,2-Diacetoxy-8-[(*tert*-butyldimethylsily)oxy]indolizidines (25 and 26).** To a solution of **24** (130 mg, 0.51 mmol) and NMO (120 mg, 1.03 mmol) in a combined solution of acetone (2.1 mL) and H_2O (0.7 mL) was added 4% aqueous solution of OsO_4 (0.26 mL, 0.05 mmol) at room temperature. The reaction was stirred at room temperature for 3 h, quenched by addition of saturated $NaHSO_3$, and stirred for an additional 30 min. The reaction mixture was extracted with AcOEt, which was washed with brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with $CHCl_3$−MeOH (10:1) to give a mixture of crude dihydroxylated products. To a solution of the crude dihydroxylated compounds in THF (2.0 mL) was added a solution of TBAF (1.0 M THF solution, 0.52 mL, 0.52 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h and concentrated to leave the residue which was taken up in CH_2Cl_2 (2.0 mL). Pyridine (0.2 mL, 2.47 mmol), DMAP (10 mg, 0.08 mmol), and acetic anhydride (0.14 mL, 1.48 mmol) were added to the CH_2Cl_2 solution. After 1 h of stirring at room temperature, the reaction mixture was diluted with MeOH and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (2:1) afforded **25** (102 mg, 67%) and **26** (14.0 mg, 9%). Compound **25** was a colorless oil: MS *m*/*z* 299 (M^+, 0.1), 256 (3.1), 239 (70), 180 (82), 154 (30), 137 (51), 120 (100), 96 (15); IR 2810, 2740, 1740 cm^{-1}; ^1H NMR δ 5.52 (dd, 1H, J = 6.4, 3.9 Hz), 5.22 (ddd, 1H, J = 7.8, 6.4, 2.0 Hz), 4.96 (ddd, 1H, J = 11.2, 9.8, 4.9 Hz), 3.17 (dd, 1H, J = 11.2, 2.0 Hz), 3.06 (dt, 1H, J = 11.2, 2.9 Hz), 2.58 (dd, 1H, J = 11.2, 7.8 Hz), 2.16−2.12 (m, 2H), 2.09 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), 1.93 (dt, 1H, J = 11.2, 3.9 Hz), 1.81−1.72 (m, 2H), 1.24 (m, 1H); ^{13}C NMR δ 170.18, 169.94, 169.90, 70.15, 69.74, 69.18, 68.00, 59.21, 51.72, 29.73, 23.22, 20.99, 20.58, 20.45. Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.14; H, 7.12; N, 4.58. Compound **26** had mp 117−118 °C (colorless solids from $CHCl_3$−MeOH): MS *m*/*z* 299 (M^+, 0.1), 256 (3.0), 239 (69), 180 (80), 154 (29), 137 (51), 120 (100), 96 (15); IR 2810, 2760, 1750 cm^{-1}; ^1H NMR δ 5.20 (td, 1H, J = 7.3, 5.4 Hz), 5.01 (t, 1H, J = 7.3 Hz), 4.69 (ddd, 1H, J = 11.2, 7.3, 4.9 Hz), 3.57 (dd, 1H, J = 9.8, 7.3 Hz), 2.93 (m, 1H), 2.33 (dd, 1H, J = 9.8, 5.4 Hz), 2.29 (t, 1H, J = 7.3 Hz), 2.13−2.06 (m, 2H), 2.04 (s, 6H), 2.00 (s, 3H), 1.72 (m, 1H), 1.63 (m, 1H), 1.24 (m, 1H); ^{13}C NMR δ 170.01, 169.86, 169.14, 73.88, 72.91, 68.36, 67.41, 58.53, 51.19, 30.05, 23.58, 20.99, 20.64, 20.38. Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.14; H, 7.13; N, 4.56.

(1*R,2*S**,8*S**,8a*S**)-1,2,8-trihydroxyindolizidine [(±)-Swainsonine (3)].** To a solution of **25** (87.0 mg, 0.29 mmol) in MeOH (3.0 mL) was added K_2CO_3 (20.0 mg, 0.15 mmol). The reaction mixture was stirred at room temperature for 1.5 h and concentrated to dryness. Chromatography of the residue with $CHCl_3$−MeOH (5:1) afforded (±)-swainsonine (**3**)(50.0 mg, 99%) as colorless solids, mp 143−144 °C ($CHCl_3$−Et_2O): MS *m*/*z* 173 (M^+, 28), 155 (30), 138 (13), 129 (6.6), 113 (100), 96 (75), 84 (15), 72 (35); IR(KBr) 3430, 3370, 2810, 2730 cm^{-1}; ^1H NMR δ (in D_2O; sodium 3-(trimethylsilyl)propanesulfonate was used as an internal standard) 4.35 (ddd, 1H, J = 7.8, 5.9, 2.5 Hz), 4.26 (dd, 1H, J = 5.9, 3.9 Hz), 3.81 (ddd, 1H, J = 10.8, 9.8, 4.4 Hz), 2.91 (m, 1H), 2.89 (dd, 1H, J = 11.2, 2.5 Hz), 2.55 (dd, 1H, J = 11.2, 7.8 Hz), 2.07 (m, 1H), 1.96 (dt, 1H, J = 12.2, 2.9 Hz), 1.92 (dd, 1H, J = 9.8, 3.9 Hz), 1.72(m, 1H), 1.52 (m, 1H), 1.24 (m, 1H); ^{13}C NMR δ (in D_2O; CH_3OH was used as an internal reference) 73.40, 70.24, 69.60, 66.95, 61.22, 52.24, 33.08, 23.78. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.13; H, 8.66; N, 8.01.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds (*E*)-**8**, (*Z*)-**8**, and **24** and X-ray analysis data and ORTEP drawing of compound **20** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microform version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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