New Chiral Route to (−)-Swainsonine via an Aqueous Acylnitroso Cycloaddition Approach

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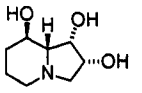
A new noncarbohydrate-based enantioselective approach to (−)-swainsonine (1) is described, in which the aqueous intramolecular Diels–Alder reaction of a chiral acylnitroso diene has been employed as a key reaction. The intramolecular cycloaddition of the chiral hydroxamic acid **9**, available from D-malic acid in 10 steps, with Pr_4NIO_4 was conducted under the conventional nonaqueous conditions using $CHCl_3$ as a solvent, whereupon intermediacy acylnitroso compound **10** cyclized spontaneously to give the *trans*- and *cis*-1,2-oxazinolactams **11** and **12** with a low diastereoselction of 1.3:1 in 76% combined yield. When the corresponding reaction was performed in water, it led to significant enhancements of trans selectivity of 4.1:1 as well as combined yield (89%). The trans adduct **11** was subjected to reductive N–O bond cleavage followed by diastereoselective hydroxylation with OsO_4 to provide the 1,2-glycol **21**, which was then converted to the amino alcohol **25**. Intramolecular cyclodehydration of **25** with $CBr_4/PPh_3/Et_3N$ and subsequent deprotection furnished (−)-swainsonine (**1**).

Swainsonine (**1**), a naturally occurring trihydroxyindolizidine, was first isolated from the fungus *Rhizoctonia leguminicola*[1] and later found in the plants *Swainsona canescens*[2] and *Astragalus lentiginosus*[3] and also in the fungus *Metarhizium anisopliae*.[4] In addition to its use in the study of α-mannosidase inhibitors, this alkaloid has been shown to be a potent inhibitor of Golgi α-mannosidase II[5] and, perhaps as a consequence of this, has been found to exhibit immunomodulatory[4,6] and antimetastatic activities.[6,7] Its interesting activities have prompted extensive synthetic efforts which have culminated in numerous syntheses of **1** over the past decade.[8] Owing to the structural features of **1** involving the three-hydroxy alignment and four contiguous chiral centers, most of the reported approaches to **1** have utilized D-mannose as the chiral precursor. We have for some time been interested



(−)-swainsonine (**1**)

in hetero Diels–Alder reactions of acylnitroso compounds as a synthetic tool for the preparation of natural products[9] and developed the synthetic entries to bioactive alkaloids utilizing the nonchiral[10] and chiral[11] intramolecular acylnitroso cycloadditions. In this paper, we describe a new noncarbohydrate-based approach to (−)-swainsonine (**1**) utilizing as a key feature the intramolecular hetero Diels–Alder reaction of a chiral acylnitroso compound.

As outlined in Scheme 1, our approach to the synthesis of **1** began with (2*R*,4*R*)-4-formyl-2-phenyl-1,3-dioxane (**2**), available in three steps from D-malic acid.[12] Wittig reaction of **2** with allyltriphenylphosphonium bromide and *t*-BuOK gave a mixture of (*Z*)- and (*E*)-dienes **3** in 60% combined yield. One of the serious problems encountered with the Wittig reaction is epimerization of the enolizable

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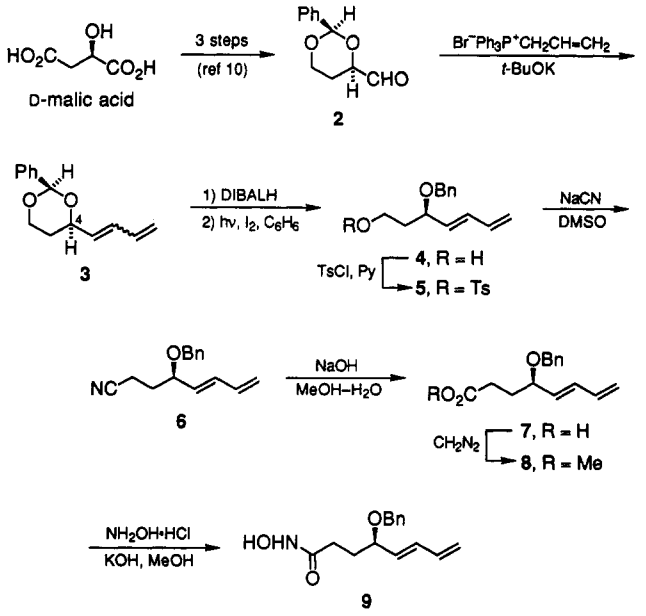
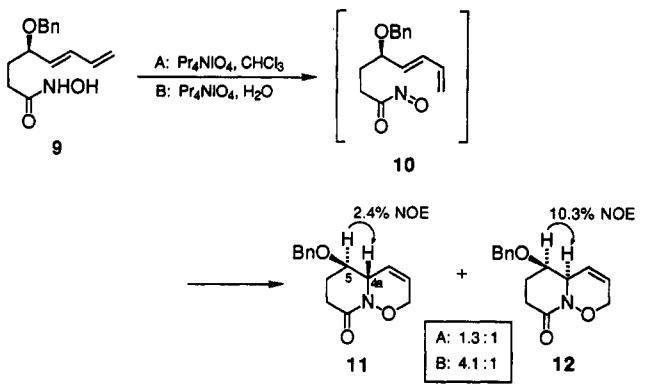
Scheme 1



stereogenic center adjacent to the carbonyl function.[13] In the present case of the Wittig reaction, however, no epimerization at the C-4 chiral center was observed presumably due to an unfavorable equilibrium.[14] In an attempt to photoisomerize the major (*Z*)-isomer to the desired (*E*)-diene, this *Z*/*E* mixture **3** was irradiated in benzene in the presence of iodine. This, however, resulted in the formation of a complex mixture. After ring-opening of the benzylidene acetal with DIBALH, photoisomerization (I_2, benzene) of the resulting *Z*/*E* mixture of **4** could be achieved to generate the (5*E*)-diene **4** in 68% overall yield from **3**. The geometrically pure enol **4** obtained was sequentially subjected to tosylation, displacement by cyanide, alkaline hydrolysis, and then diazomethane esterification to afford the ester **8** (79% overall yield), which was then treated with hydroxylamine under the alkaline conditions (KOH/MeOH, 0 °C) to produce the hydroxamic acid **9** in 96% yield.

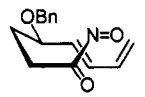
The pivotal step in our synthesis of swainsonine was intramolecular hetero Diels–Alder reaction of the chiral acylnitroso diene. Thus, first we conducted oxidation of the chiral hydroxamic acid **9** with Pr_4NIO_4 under the conventional nonaqueous conditions[15] using $CHCl_3$ as a solvent to generate the intermediacy acylnitroso compound **10**, which underwent [4 + 2] cycloaddition to give a chromatographically separable mixture of the *trans*- and *cis*-1,2-oxazinolactams **11** and **12** with a low diastereoselection of 1.3:1 in 76% combined yield (Scheme 2). The

Scheme 2



relative configurations of the cycloadducts **11** and **12** were deduced from the results of difference NOE experiments: on irradiation of 5-H a large NOE enhancement (10.3%) of 4a-H occurred, indicating the cis relation between these protons for **12**, whereas a small NOE (2.4%) between the corresponding protons was observed for **11** possessing trans relationship. In contrast to the cycloaddition in the $CHCl_3$ solution, pronounced enhancements in the trans selectivity (4.1:1) as well as yield (89%) were observed when the corresponding reaction of **9** was performed in the water solvent.[16]

The formation of the trans adduct **11** can be rationalized by the boatlike endo transition state **13** with the oxygen functional group in the connecting chain adopting a quasiequatorial position, which is considered to be the most favorable conformer among the four possible transition states including two chairlike and two boatlike conformers wherein the *s-cis-N*-acylnitroso group is endo to the diene.[18] The increased preference for the endo transition states in water solvent would be attributed to producing some extra charge separation resulting from both secondary orbital interaction and "hydrophobic packing effect"[19] of the substrate. The latter effect would be particularly important and may serve for stabilizing the most compact transition state conformer **13**, leading to the trans selectivity, in the aqueous medium.



13

The described significant trans selectivity led us to utilize the oxazinolactam **11** for the enantioselective entry to (-)-swainsonine (**1**). To this end, we initially attempted to introduce the vicinal hydroxy groups, which correspond to the hydroxy groups at C-1 and C-2 in swainsonine, to the olefin function of **11**. Upon treatment of **11** with a catalytic amount of OsO_4 and *N*-methylmorpholine oxide,

(13) Epimerization in Wittig reaction: Soffer, M. D. *Tetrahedron Lett.* **1970**, 211. Sowerby, R. L.; Coates, R. M.; Burk, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 4758, and references cited therein.

(14) Compound **2** with the 2-phenyl and 4-formyl groups both adopting an equatorial orientation would be favored over the corresponding 4-epimeric form **2'** with axially oriented 4-formyl group.

2 2'

(15) The intermediate RCO–N=O is a short-lived, extremely reactive species (Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1), which has not been detected so far, and has been shown to undergo rapid solvolysis (Corrie, J. E. T.; Kirby, G. W.; Mackinnon, J. W. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 883). Accordingly, acylnitroso Diels–Alder reactions have conventionally been employed under nonaqueous conditions using organic solvents such as $CHCl_3$ and CH_2Cl_2.

(16) Subsequent to the submission of this paper for publication, a description of the synthesis of a stereoisomer of swainsonine was published by Keck and co-worker,[17] in which a very similar acylnitroso cycloaddition using a hydroxamic acid with the 4-hydroxy group protected by the *tert*-butyldiphenylsilyl group instead of the benzyl group as in **9** was employed. In the present work, we have performed the acylnitroso cycloaddition by using the same hydroxamic acid bearing the *tert*-butyldiphenylsilyl protecting group under both nonaqueous and aqueous conditions. In this case, however, only modest enhancement of the trans selectivity from 1.6:1 to 2.5:1 (both at 0 °C) was observed by changing the solvent from $CHCl_3$ to water–DMF (1:1).

(17) Keck, G. E.; Romer D. R. *J. Org. Chem.* **1993**, *58*, 6083.

(18) (a) Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16. (b) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187.

(19) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159.

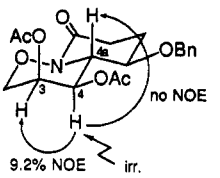
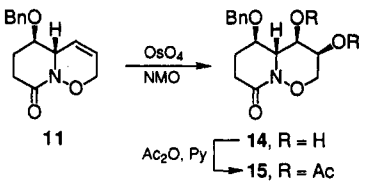


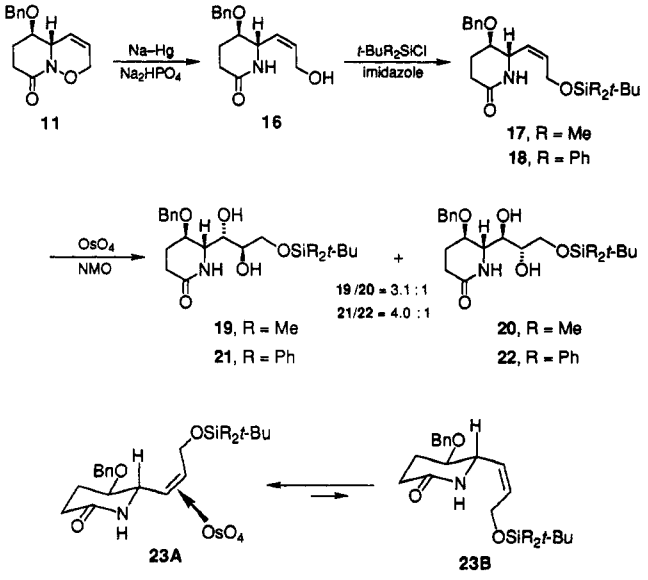
Figure 1. NOE enhancement of **15**.

the diol **14** was generated as a single diastereomer with, however, undesired 3*S*,4*R* configurations,[20] which were assigned based on NOE studies of the diacetyl derivative **15** (Figure 1): irradiation at the H-4 frequency caused enhancement of the H-3 absorption but not H-4a.



Compound **11** was then subjected to reductive cleavage of the N–O bond with sodium amalgam to afford the alcohol **16** (85% yield), which was protected with *tert*-butyldimethylsilyl chloride to give **17** in 88% yield (Scheme 3). Catalytic osmylation of **17** gave a separable mixture

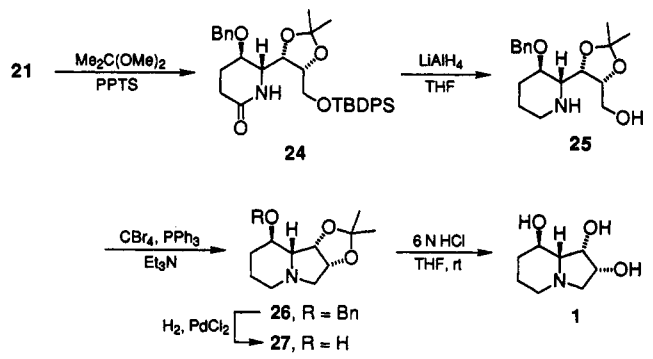
Scheme 3



of the diols **19** and **20** in 3.1:1 diastereoselectivity in favor of **19** (combined yield of **19** and **20**: 88%). When this osmylation was performed using **18** with the primary alcohol protected with the *tert*-butyldiphenylsilyl group, improved diastereoselectivity (product ratio **21**/**22**, 4.0:1) was obtained. Although the stereochemical assignments for these products based on spectral analysis were difficult to ascertain at this stage, we judged the major isomers **19** and **21** to have the desired 7*S*,8*R* configurations from the following mechanistic point of view. For the lactams **17** and **18** having a *Z* olefinic system in an equatorial orientation, the conformation **23A** is strongly favored, because the alternative conformation **23B** is severely

(20) Subsequent to the submission of this paper for publication, very similar results were represented by Keck and co-worker[17] on the hydroxylation of the bicyclic 1,2-oxazine with OsO_4.

Scheme 4



destabilized by allylic 1,3-strain.[21] The diastereofacial outcome of the osmylation process in this case may be formulated as arising from preferential approach of OsO_4 from the direction anti with respect to the C-3 bearing the bulky benzyloxy group in the conformation **23A**.

The diol **21** was protected as the acetonide **24** by treatment with 2,2-dimethoxypropane and pyridinium *p*-toluenesulfonate in 74% yield. Reduction of **24** with $LiAlH_4$ proceeded concomitantly by desilylation to give the amino alcohol **25** in 59% yield. Exposure of **25** at room temperature to CBr_4 and PPh_3 and then to Et_3N led to intramolecular cyclodehydration,[22] providing the indolizidine **26** in 85% yield. Hydrogenolytic removal of the benzyl group by using $PdCl_2$ as a catalyst afforded **27** in 86% yield. Finally, acidic hydrolysis of the acetonide converted **27** to (−)-swainsonine (**1**) in 66% yield after Dowex 1-X8 ion-exchange chromatography. The ^1H NMR spectrum of synthetic **1** was identical with that of natural material,[1b] and its observed optical rotation and melting point also were found to be in accord with the literature values.[1b,2]

In conclusion, a new chiral route to (−)-swainsonine based on a noncarbohydrate approach has been developed. The key feature in the synthesis is an intramolecular asymmetric hetero Diels–Alder reaction of an acylnitroso diene which under aqueous conditions show significant enhancement of the trans stereoselectivity compared with the reaction under conventional nonaqueous conditions.

Experimental Section

General Procedures. Melting points are uncorrected. Optical rotations were measured on a digital polarimeter in a 1-dm cell. IR spectra were recorded on an FTIR instrument. ^1H NMR spectra were run at 300, 400, or 500 MHz. ^{13}C NMR spectra were determined at 75, 100, or 125 MHz. Chemical shifts were reported in δ relative to $CHCl_3$ as an internal reference (7.26 ppm for ^1H and 77.05 ppm for ^{13}C), unless otherwise indicated. DMSO (2.50 ppm for ^1H and 39.5 ppm for ^{13}C), DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate, 0.015 ppm for ^1H), and acetonitrile (1.6 ppm for ^{13}C) were occasionally used as internal references. Mass spectra were measured at 70 eV. TLC was performed on precoated silica gel 60 F 254 plates (Merck), and silica gel 60 (230–400 mesh) (Merck) was used for column chromatography. Microanalyses were carried out by the Microanalytical Laboratory at Tokyo College of Pharmacy.

(21) (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (b) Hoffmann, R. W. *Ibid.* **1989**, *89*, 1841.

(22) For methodology for the construction of the indolizidine ring by the intramolecular cyclodehydration utilizing carbon tetrahalide and PPh_3, see ref 11a. See also: (a) Gallagher, T.; Giles, M.; Subramanian, R. S.; Hardley, M. S. *J. Chem. Soc., Chem. Commun.* **1992**, 166. (b) Chen, Y.; Vogel, P. *Tetrahedron Lett.* **1992**, *33*, 4917. (c) Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L.; Ulgheri, F. *J. Org. Chem.* **1993**, *58*, 3397.

(2*R*,4*R*)-4-(1,3-Butadienyl)-2-phenyl-1,3-dioxane (3). To a stirred suspension of allyltriphenylphosphonium bromide (50.3 g, 131 mmol) in THF (150 mL) was added a solution of *t*-BuOK (13.7 g, 122 mmol) in THF (240 mL) under Ar at rt, and stirring was continued for 20 min. To the resulting deep red solution was added dropwise a solution of **2** (11.8 g, 61.4 mmol) in THF (170 mL) over a period of 5 min. After being stirred for 5 min at rt, the mixture was cooled in an ice bath and quenched by addition of water (50 mL). The resulting mixture was diluted with Et_2O (600 mL), washed with saturated brine (2 × 50 mL), and dried ($MgSO_4$). Removal of the solvent and purification by chromatography on silica gel (hexane–EtOAc (20:1)) gave **3** (6.49 g, 49%) as a *Z*/*E* mixture (4.3:1, in favor of the *Z* isomer, by ^1H NMR) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.51–1.65 (1 H, m), 1.90–2.07 (1 H, m), 3.96–4.08 (1 H, m), 4.27–4.33 (1 H, m), 4.40–4.47 and 4.80–4.88 (total 1 H in 1:4.3 ratio, m each), 5.10–5.32 (2 H, m), 5.52–5.83 (1 H, m, including 1 H, s at δ 5.60), 6.10, 6.27–6.41, and 6.63–6.76 (total 2 H in 4.3:2:4.3 ratio, t (*J* = 11.1 Hz), m, and m, respectively), 7.30–7.62 (5 H, m). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.44; H, 7.56.

(*E*)-(3*R*)-3-(Benzyloxy)-4,6-heptadienol (4). To a cold (0 °C) and stirred solution of the above *Z*/*E* mixture of **3** (2.08 g, 9.62 mmol) in CH_2Cl_2 (20 mL) was added dropwise DIBALH (51.7 mL of a 0.93 M solution in hexane, 48.1 mmol), and the mixture was stirred at rt for 1.5 h. The reaction was quenched with water (1 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (hexane–EtOAc (9:1)) to give a *Z*/*E* mixture of **4** (1.95 g, 96%) as a colorless oil, which was dissolved in benzene (500 mL), and I_2 (10 mg) was added. After the solution was irradiated through Pyrex with a 100-W high-pressure Hg lamp for 30 min, it was washed with 5% aqueous $Na_2S_2O_3$ (20 mL) and water, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (hexane–EtOAc (9:1)) to give isomerically pure **4** (1.34 g, 69%) as a colorless oil: $[\alpha]^{26}_D$ +60.7° (*c* 1.09, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.77–1.94 (2 H, m), 2.35 (1 H, br s), 3.71–3.82 (2 H, m), 4.07 (1 H, td, *J* = 8.0, 4.5 Hz), 4.36 and 4.62 (2 H, AB q, *J* = 11.8 Hz), 5.15 (1 H, dd, *J* = 10.3, 1.0 Hz), 5.26 (1 H, dd, *J* = 16.7, 1.0 Hz), 5.67 (1 H, dd, *J* = 15.2, 8.0 Hz), 6.25 (1 H, dd, *J* = 15.2, 10.3 Hz), 6.38 (1 H, dt, *J* = 16.7, 10.3 Hz), 7.27–7.37 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 38.1, 60.6, 70.4, 79.0, 118.1, 127.7, 127.8 (2 carbons), 128.5 (2 carbons), 133.4, 133.5, 136.1, 138.3; EIMS *m*/*z* (rel intensity) 218 (M^+, 0.1), 200 (0.2), 173 (4), 130 (27), 114 (6), 91 (100). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.88; H, 8.31.

(*E*)-(*R*)-3-(Benzyloxy)-1-[(*p*-tolylsulfonyl)oxy]-4,6-heptadiene (5). To a cold (0 °C), stirred solution of **4** (4.31 g, 19.7 mmol) in pyridine (20 mL) was added dropwise a solution of *p*-toluenesulfonyl chloride (11.3 g, 59.1 mmol) in pyridine (22 mL), and the mixture was stirred at 0 °C for 2 h and then at rt for 2 h. The mixture was poured into 10% aqueous HCl (200 mL) and extracted with CH_2Cl_2 (2 × 250 mL). The combined organic phases were washed with water (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane–EtOAc (9:1)) to give **5** (7.01 g, 95%) as a colorless oil: $[\alpha]^{26}_D$ +0.92° (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.82–2.00 (2 H, m), 2.42 (3 H, s), 3.92 (1 H, td, *J* = 8.0, 5.0 Hz), 4.10 (1 H, dt, *J* = 9.8, 5.6 Hz), 4.20–4.25 (2 H, m, with 1/2 AB q, *J* = 11.4 Hz at δ 4.23), 4.51 (1 H, 1/2 AB q, *J* = 11.4 Hz), 5.14 (1 H, dd, *J* = 10.3, 1.3 Hz), 5.23 (1 H, dd, *J* = 16.9, 1.3 Hz), 5.53 (1 H, dd, *J* = 15.2, 8.0 Hz), 6.18 (1 H, dd, *J* = 15.2, 10.3 Hz), 6.38 (1 H, dt, *J* = 16.9, 10.3 Hz), 7.22–7.52 (7 H, m), 7.77 (2 H, d, *J* = 8.3 Hz); EIMS *m*/*z* (rel intensity) 281 (M^+ − $PhCH_2$, 7), 155 (30), 130 (39), 91 (100). Anal. Calcd for $C_{21}H_{24}O_4S$: C, 67.72; H, 6.49. Found: C, 67.71; H, 6.51.

(*E*)-(*R*)-4-(Benzyloxy)-5,7-octadienonitrile (6). To a solution of **5** (2.85 g, 7.65 mmol) in DMSO (30 mL) was added NaCN (487 mg, 9.94 mmol), and the mixture was stirred at 60 °C for 1 h. The mixture was poured into ice–water (30 mL) and extracted with Et_2O (3 × 50 mL). The combined ethereal solutions were washed with water (2 × 20 mL), dried ($MgSO_4$), and concentrated. Subsequent chromatography on silica gel (hexane–EtOAc (10:1)) gave **6** (1.73 g, 99%) as a colorless oil: $[\alpha]^{26}_D$+36.6° (*c* 2.57, $CHCl_3$); IR (neat) 3032, 2933, 2863, 2246, 1604, 1454, 1094, 1061, 1028, 1008, 740, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83–1.99 (2 H, m), 2.38–2.52 (1 H, m), 3.95 (1 H, td, *J* = 7.9, 4.9 Hz), 4.35 and 4.60 (2 H, AB q, *J* = 11.6 Hz), 5.19 (1 H, dd, *J* = 10.5, 1.9 Hz), 5.29 (1 H, dd, *J* = 16.8, 1.9 Hz), 5.59 (1 H, dd, *J* = 14.9, 7.9 Hz), 6.29 (1 H, dd, *J* = 14.9, 10.5 Hz), 6.38 (1 H, dt, *J* = 16.8, 10.5 Hz), 7.30–7.38 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 13.5, 31.4, 70.6, 77.4, 118.8, 119.5, 127.8, 127.9 (2 carbons), 128.5 (2 carbons), 132.3, 134.5, 135.8, 138.1; CIMS (isobutane) *m*/*z* 228 (MH^+). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.53; N, 6.16. Found: C, 79.26; H, 7.59; N, 6.17.

(*E*)-(*R*)-4-(Benzyloxy)-5,7-octadienoic Acid (7). To a solution of **6** (1.73 g, 7.61 mmol) in MeOH (35 mL) was added 25% aqueous NaOH (17 mL), and the mixture was heated at reflux for 9 h. After being cooled to rt, the mixture was acidified with 5% aqueous HCl (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with saturated brine (2 × 20 mL), dried ($MgSO_4$), and concentrated. The product was purified by chromatography on silica gel (hexane–EtOAc (19:1)) to give **7** (1.44 g, 77%) as a colorless oil: $[\alpha]^{26}_D$ +36.8° (*c* 1.43, $CHCl_3$); IR (neat) 2925, 1709, 1601, 1454, 1414, 1263, 1207, 1176, 1097, 1027, 977, 740, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85–2.00 (2 H, m), 2.47 (2 H, t, *J* = 7.5 Hz), 3.87 (1 H, dt, *J* = 7.5, 5.7 Hz), 4.35 and 4.59 (2 H, AB q, *J* = 11.8 Hz), 5.14 (1 H, dd, *J* = 10.1, 1.3 Hz), 5.25 (1 H, dd, *J* = 16.9, 1.3 Hz), 5.61 (1 H, dd, *J* = 15.3, 7.8 Hz), 6.23 (1 H, dd, *J* = 15.1, 10.6 Hz), 6.37 (1 H, dt, *J* = 16.9, 10.3 Hz), 7.25–7.36 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 30.0, 30.5, 70.4, 78.4, 118.0, 127.6, 127.8 (2 carbons), 128.4 (2 carbons), 133.5, 133.7, 136.1, 138.4, 178.2; CIMS (isobutane) *m*/*z* 247 (MH^+); EIMS *m*/*z* (rel intensity) 229 (M^+ − OH, 0.3), 181 (0.3), 155 (22), 130 (19), 91 (100). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.04; H, 7.39.

Methyl (*E*)-(*R*)-4-(Benzyloxy)-5,7-octadienoate (8). To an ice-cold and stirred solution of **7** (1.14 g, 4.63 mmol) in Et_2O (15 mL) was added a solution of diazomethane in Et_2O to sustain yellowish color. After 15 min at 0 °C, AcOH was added at 0 °C until the yellowish color disappeared, and the mixture was washed with saturated aqueous $NaHCO_3$ and water. Drying over $MgSO_4$ followed by concentration left an oil, which was purified by chromatography on silica gel (hexane–EtOAc (19:1)) to give **8** (1.19 g, 99%) as a colorless oil: $[\alpha]^{26}_D$ +38.7° (*c* 2.07, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.79–2.02 (2 H, m), 2.39–2.44 (2 H, m), 3.63 (3 H, s), 3.85 (1 H, dt, *J* = 7.6, 5.6 Hz), 4.34 (1 H, 1/2 AB q, *J* = 11.9 Hz), 4.58 (1 H, 1/2 AB q, *J* = 11.9 Hz), 5.13 (1 H, dd, *J* = 10.3, 1.3 Hz), 5.24 (1 H, dd, *J* = 17.0, 1.3 Hz), 5.61 (1 H, dd, *J* = 15.1, 7.2 Hz), 6.23 (1 H, dd, *J* = 15.1, 10.3 Hz), 6.37 (1 H, dt, *J* = 17.0, 10.3 Hz), 7.27–7.36 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 30.1, 30.8, 51.5, 70.3, 78.5, 117.9, 127.5, 127.8 (2 carbons), 128.4 (2 carbons), 133.5, 133.8, 136.2, 138.6, 173.9; CIMS (isobutane) *m*/*z* 261 (MH^+). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.63; H, 7.77.

(*E*)-(*R*)-4-(Benzyloxy)-*N*-hydroxy-5,7-octadienamide (9). To a cold (0 °C), stirred solution of hydroxylamine hydrochloride (107 mg, 1.54 mmol) in MeOH (1 mL) was added a solution of KOH (202 mg, 3.08 mmol) in MeOH (1 mL), and the mixture was stirred for 5 min. To this mixture was added a solution of **8** (100 mg, 0.384 mmol) in MeOH (1 mL) at 0 °C, and the mixture was stirred at the same temperature for 30 min. The mixture was diluted with CH_2Cl_2 (15 mL) and neutralized with 5% aqueous HCl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, washed with water (5 mL), and dried ($MgSO_4$). The solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (hexane–EtOAc (1:1)) to give **9** (96 mg, 96%) as a colorless oil: $[\alpha]^{27}_D$ +43.4° (*c* 0.57, $CHCl_3$); IR (neat) 3225, 3032, 2923, 2853, 1654, 1455, 1093, 1069, 1028, 1007, 738, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84–1.98 (2 H, m), 2.25 (2 H, m), 3.82 (1 H, br dt, *J* = 7.1, 5.9 Hz), 4.33 and 4.60 (2 H, AB q, *J* = 11.7 Hz), 5.15 (1 H, dd, *J* = 10.3, 1.3 Hz), 5.26 (1 H, dd, *J* = 16.8, 1.3 Hz), 5.60 (1 H, dd, *J* = 15.2, 7.7 Hz), 6.24 (1 H, dd, *J* = 15.2, 10.3 Hz), 6.36 (1 H, dt, *J* = 16.8, 10.3 Hz), 7.29–7.38 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 29.1, 31.0, 70.4, 78.4, 118.2, 127.8, 128.0 (2 carbons), 128.5 (2 carbons), 133.2, 133.7, 136.0, 138.2, 171.2; CIMS (isobutane) *m*/*z* 262 (MH^+), 260; EIMS *m*/*z* (rel intensity) 224 (M^+ − OH, 0.1), 185 (0.2), 170 (3), 137 (15), 91 (100). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.17; H, 7.37; N, 5.33.

Intramolecular Acylnitroso Diels–Alder Reaction of 9. A. In Chloroform. To a stirred, cold (0 °C) suspension of Pr_4NIO_4 (moistured with 10% water, 275 mg, 0.730 mmol) in $CHCl_3$

(5 mL) was added in one portion a solution of **9** (159 mg, 0.608 mmol) in $CHCl_3$ (55 mL), and the mixture was stirred at 0 °C for 10 min. To this mixture was added 10% aqueous $Na_2S_2O_3$ (6 mL), and the mixture was briefly stirred to quench the periodate. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (5 mL) and then water (5 mL). The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated to give a crude oil, which was purified by chromatography on silica gel (hexane–EtOAc (1:1)) to afford a 1.3:1 mixture (based on ^1H NMR) of the cycloadducts **11** and **12** in favor of **11** as a colorless oil (combined yield 120 mg, 76%). This mixture was separated by further chromatography on silica gel (CH_2Cl_2–acetone (19:1)), and the first elutions afforded (4a*S*,5*R*)-5-(benzyloxy)-2,-4a,5,6,7,8-hexahydropyrido[1,2-*b*][1,2]oxazin-8-one (**11**) (65 mg, 41%) as a colorless oil, which was solidified during storage in a refrigerator. Recrystallization from $CHCl_3$–acetone resulted in colorless needles: mp 28–30 °C; $[\alpha]^{26}_D$ +102.8° (*c* 1.01, $CHCl_3$); IR (neat) 3033, 2873, 1674, 1455, 1397, 1371, 1103, 1068, 1028, 836, 738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78–1.88 (1 H, m), 2.03–2.10 (1 H, m), 2.35 (1 H, ddd, *J* = 17.3, 10.3, 5.6 Hz), 2.67 (1 H, dt, *J* = 17.3, 5.4 Hz), 3.50 (1 H, ddd, *J* = 9.4, 7.2, 3.2 Hz), 4.27–4.35 (1 H, m), 4.39–4.42 (1 H, m), 4.55 (1 H, 1/2 AB q, *J* = 11.7 Hz), 4.63–4.68 (1 H, m), 4.69 (1 H, 1/2 AB q, *J* = 11.7 Hz), 5.94 (2 H, br s), 7.29–7.39 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 24.3, 29.0, 60.7, 69.0, 71.4, 76.4, 124.5, 125.4, 127.8 (2 carbons), 128.1, 128.6 (2 carbons), 137.5, 165.3.

The second elutions afforded (4a*R*,5*R*)-5-(benzyloxy)-2,-4a,5,6,7,8-hexahydropyrido[1,2-*b*][1,2]oxazin-8-one (**12**) (47 mg, 30%) as a colorless oil: IR (neat) 2927, 1652, 1455, 1404, 1305, 1204, 1072, 1025, 849, 813, 742, 701 cm^{-1}; $[\alpha]^{26}_D$ +99.8° (*c* 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.77–1.86 (1 H, m), 2.02–2.09 (1 H, m), 2.43 (1 H, dt, *J* = 17.1, 4.9 Hz), 2.66 (1 H, ddd, *J* = 17.1, 11.1, 5.8 Hz), 3.93 (1 H, m), 4.31 (1 H, dddd, *J* = 15.7, 4.2, 2.4, 1.8 Hz), 4.50 (1 H, 1/2 AB q, *J* = 12.1 Hz), 4.56 (1 H, m), 4.66 (1 H, 1/2 AB q, *J* = 12.1 Hz), 4.73 (1 H, dddd, *J* = 15.7, 3.5, 2.3, 1.5 Hz), 5.81 (1 H, ddt, *J* = 5.81, 2.1, 1.8 Hz), 5.99 (1 H, dddd, *J* = 10.3, 4.0, 2.2, 1.7 Hz), 7.29–7.39 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 23.2, 28.5, 60.5, 69.1, 71.1, 73.0, 123.7, 125.6, 127.7 (2 carbons), 128.0, 128.6 (2 carbons), 137.6, 165.7; CIMS (isobutane) *m/z* 260 (MH^+); EIMS *m/z* (rel intensity) 260 (M^+ + 1, 4), 173 (5), 151 (2), 138 (1), 125 (3), 91 (100).

B. In Water. To a stirred, cold (0 °C) mixture of **9** (228 mg, 0.872 mmol) and water (82 mL) (a part of **9** was suspended in the water solution) was added in one portion a solution of $NaIO_4$ (280 mg, 1.31 mmol) in water (5 mL), and the mixture was stirred at 0 °C for 10 min. To this mixture was added 10% aqueous $Na_2S_2O_3$ (10 mL), and the mixture was briefly stirred and extracted with $CHCl_3$ (2 × 100 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (30 mL) and water (50 mL) and then dried ($MgSO_4$). Evaporation of the solvent followed by purification by chromatography on silica gel (hexane–EtOAc (1:1)) provided a 4.0:1 mixture (based on ^1H NMR) of the cycloadducts **11** and **12** in favor of **11** as a colorless oil (combined yield 202 mg, 89%), which were separated in a manner similar to that described above in A, yielding **11** (157 mg, 69%) and **12** (36 mg, 16%).

(3*S*,4*R*,4a*R*,5*R*)-5-(Benzyloxy)-3,4-dihydroxy-2,3,4,4a,5,6,7,8-octahydropyrido[1,2-*b*][1,2]oxazin-9-one (14). To a stirred solution of **11** (20 mg, 0.077 mmol) in acetonitrile–H_2O (2:1, 0.7 mL) were added *N*-methylmorpholine *N*-oxide hydrate (21 mg, 0.154 mmol) and 4% aqueous OsO_4 (0.05 mL, 0.008 mmol) at rt. After the mixture was stirred at rt for 12 h, 2% aqueous $NaHSO_3$ (2 mL) was added, and the stirring was continued at rt for an another 1 h. The dark gray solid that precipitated was collected by filtration and washed with water to give **14** (13 mg, 58%) as gray crystals: mp 234–238 °C; ^1H NMR (DMSO-d_6, ref DMSO) δ 1.88–1.95 (2 H, m), 2.07–2.16 (1 H, m), 2.38–2.47 (1 H, m), 3.50 (1 H, m), 3.75 (1 H, br s), 3.85 (1 H, A part of ABX, *J* = 12.1, 1.2 Hz), 3.87 (1 H, B part of ABX, *J* = 12.1, 1.7 Hz), 4.01 (1 H, br d, *J* = 10.5 Hz), 4.08 (1 H, br s), 4.56 and 4.57 (2 H, AB q, *J* = 13.4 Hz), 7.28–7.35 (5 H, m).

Compound **14** was found to be very sparingly soluble in usual organic solvents other than organic polar solvents such as DMF and DMSO and, therefore, used without further purification for the following reaction.

(3*S*,4*R*,4a*R*,5*R*)-5-(Benzyloxy)-3,4-diacetoxy-2,3,4,4a,5,6,7,8-octahydropyrido[1,2-*b*][1,2]oxazin-8-one (15). To a suspension of **14** (19 mg, 0.0648 mmol) in Ac_2O (0.4 mL) was added pyridine (0.1 mL), and the mixture was stirred at rt. After 3.5 h at rt, the mixture was ice-cooled, and saturated aqueous $NaHCO_3$ (5 mL) was added with stirring. After 5 min, the mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined extracts were washed with water (2 × 2 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel ($CHCl_3$–MeOH (19:1)) to give **15** (23 mg, 94%) as a colorless oil: $[\alpha]^{26}_D$ +66.3° (*c* 0.32, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.83–1.93 (1 H, s), 1.96 (3 H, s), 2.00–2.07 (1 H, m), 2.18 (3 H, s), 2.38 (1 H, dddd, *J* = 17.0, 4.1, 2.7, 1.0 Hz), 2.77 (1 H, ddd, *J* = 17.0, 13.2, 5.5 Hz), 3.73 (1 H, br s), 4.10–4.18 (2 H, m), 4.33 (1 H, dt, *J* = 3.5, 1.5 Hz), 7.29–7.39 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 20.5, 20.9, 21.9, 27.6, 61.5, 66.8, 67.6, 70.5, 70.6, 73.1, 127.7 (2 carbons), 128.1, 128.6 (2 carbons), 137.4, 165.5, 169.7, 170.2; EIMS *m/z* (rel intensity) 378 (M^+ + 1, 0.3), 292 (11), 244 (8), 151 (4), 91 (100); HRMS calcd for $C_{19}H_{24}NO_7$ (M^+ + 1) 378.1553, found 378.1582.

(2*S*,3*R*)-3-(Benzyloxy)-2-[(*Z*)-3-hydroxy-1-propenyl]piperidin-6-one (16). To an ice-cooled stirred solution of **11** (560 mg, 2.16 mmol) in EtOH (22 mL) was added Na_2HPO_4 (1.45 g, 1.02 mmol). To this stirred mixture was added 5% sodium amalgam (10.0 g) in small portions, and the stirring was continued for 1 h under ice cooling. After additions of ice–water (50 mL) and $CHCl_3$ (100 mL), the mixture was stirred at rt for another 15 min and filtered through a Celite pad. The organic phase was separated, and the aqueous phase was extracted with $CHCl_3$ (2 × 50 mL). The combined organic phases were washed with water and dried ($MgSO_4$). Evaporation of the solvent followed by purification by column chromatography on silica gel ($CHCl_3$–MeOH (20:1)) gave colorless crystals, which was recrystallized from benzene–hexane to give **16** (475 mg, 85%) as colorless needles: mp 100–101 °C; $[\alpha]^{26}_D$ −70.6° (*c* 0.51, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.90 (1 H, ddt, *J* = 13.5, 8.6, 6.1 Hz), 2.09 (1 H, ddt, *J* = 13.5, 6.1, 3.0 Hz), 2.29 (1 H, ddd, *J* = 17.9, 8.6, 6.1 Hz), 2.43 (1 H, dt, *J* = 17.9, 6.1 Hz), 3.47 (1 H, ddd, *J* = 8.6, 6.2, 3.0 Hz), 4.01 (1 H, dt, *J* = 13.1, 5.5 Hz), 4.24 (1 H, ddd, *J* = 13.1, 8.5, 4.3 Hz), 4.37 (1 H, m), 4.52 and 4.63 (2 H, AB q, *J* = 11.7 Hz), 5.39 (1 H, dd, *J* = 10.7, 9.4 Hz), 5.87 (1 H, dddd, *J* = 10.7, 8.5, 5.5, 1.1 Hz), 7.28–7.37 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 24.0, 28.1, 53.7, 58.1, 71.2, 75.0, 127.8 (2 carbons), 128.1, 128.6 (2 carbons), 130.0, 133.8, 137.6, 172.1; EIMS *m/z* (rel intensity) 262 (M^+ + 1, 0.9), 243 (0.6), 170 (8), 91 (100). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.84; H, 7.32; N, 5.41.

(2*S*,3*R*)-3-(Benzyloxy)-2-[(*Z*)-3-(*tert*-butyldimethylsiloxy)-1-propenyl]piperidin-6-one (17). To a solution of **16** (479 mg, 1.83 mmol) in DMF (2.5 mL) were added imidazole (390 mg, 5.73 mmol) and *tert*-butyldimethylsilyl chloride (415 mg, 2.75 mmol), and the mixture was stirred at rt for 1 h. The mixture was diluted with Et_2O (30 mL), washed with saturated brine (2 × 10 mL), and dried ($MgSO_4$). Concentration followed by purification by chromatography on silica gel (hexane–EtOAc (4:1)) gave **17** (667 mg, 97%) as a colorless oil: $[\alpha]^{26}_D$ −44.0° (*c* 1.24, $CHCl_3$); IR (neat) 3204, 2928, 2856, 1659, 1462, 1403, 1256, 1076, 838, 778, 734, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (6 H, s), 0.89 (9 H, s), 1.87–2.10 (2 H, m), 2.32 (1 H, dt, *J* = 17.9, 6.8 Hz), 2.54 (1 H, dt, *J* = 17.9, 6.6 Hz), 3.47 (1 H, ddd, *J* = 7.5, 5.5, 2.7 Hz), 4.11 (1 H, ddd, *J* = 13.8, 4.9, 1.5 Hz), 4.25–4.33 (2 H, m), 4.52 and 4.62 (2 H, AB q, *J* = 11.8 Hz), 5.31–5.38 (1 H, m), 5.67–5.75 (2 H, m), 7.29–7.37 (5 H, m); ^{13}C NMR ($CDCl_3$) δ −5.2 (2 carbons), 18.3, 23.7, 25.9 (3 carbons), 27.9, 54.5, 59.4, 71.0, 75.1, 127.5 (2 carbons), 127.8, 128.4 (2 carbons), 129.1, 133.9, 137.8, 170.9; CIMS (isobutane) *m/z* 376 (MH^+), 318. Anal. Calcd for $C_{21}H_{33}NO_3Si$: C, 67.16; H, 8.86; N, 3.73. Found: C, 66.96; H, 8.81; N, 3.72.

Hydroxylation of 17 with OsO_4. To a solution of **17** (383 mg, 1.02 mmol) in acetonitrile–water (2:1, 12 mL) were added *N*-methylmorpholine *N*-oxide monohydrate (354 mg, 2.62 mmol) and 4% aqueous OsO_4 (0.83 mL, 0.13 mmol), and the mixture was stirred at rt for 6 h. After addition of 2% aqueous $NaHSO_3$ (15 mL), the mixture was stirred for an another 1 h at rt and extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were dried ($MgSO_4$), concentrated, and purified by chromatography on silica gel (hexane–EtOAc (1:1)) to give a 3.1:1 mixture (based on ^1H NMR) of the glycols (**19** and **20** in favor of **19**) as a colorless oil (combined yield 369 mg, 88%). This mixture was separated by further chromatography on silica gel ($CHCl_3$–acetone (4:1)).

The first fractions afforded (2*R*,3*R*)-3-(benzyloxy)-2-[(1*R*,2*S*)-3-(*tert*-butyldimethylsiloxy)-1,2-dihydroxypropyl]piperidin-6-one (**20**) (76 mg, 18%) as a colorless oil: $[\alpha]^{26}_D$ -32.0° (*c* 0.30, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.092 (3 H, s), 0.093 (3 H, s), 0.91 (9 H, s), 1.91 (1 H, m), 2.10–2.17 (1 H, m), 2.27 (1 H, dt, *J* = 17.6, 6.4 Hz), 2.52 (1 H, ddd, *J* = 17.6, 7.7, 6.0 Hz), 3.20 (1 H, br s), 3.62 (1 H, m), 3.66–3.74 (3 H, m), 3.81 (1 H, m), 3.90 (1 H, br s), 4.04 (1 H, m), 4.56 and 4.64 (2 H, AB q, *J* = 11.5 Hz), 6.62 (1 H, br s), 7.27–7.37 (5 H, m); ^{13}C NMR ($CDCl_3$) δ -5.4 (2 carbons), 18.3, 23.7, 25.9 (3 carbons), 27.6, 59.0, 64.9, 70.7, 72.0, 72.3, 73.9, 127.8 (2 carbons), 128.0, 128.6 (2 carbons), 137.7, 172.3; EIMS *m/z* (rel intensity) 410 (M^+ + 1, 17), 352 (100), 244 (15), 204 (86), 175 (6), 144 (20), 117 (89).

The second fractions afforded (2*R*,3*R*)-3-(benzyloxy)-2-[(1*S*,2*R*)-3-(*tert*-butyldimethylsiloxy)-1,2-dihydroxypropyl]piperidin-6-one (**19**) (270 mg, 65%) as a colorless oil, which was solidified by cooling: mp 93–96 °C; $[\alpha]^{26}_D$ -29.5° (*c* 1.28, $CHCl_3$); IR (Nujol) 3379, 3202, 1620, 1255, 1115, 1053, 838, 786, 697, 672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (3 H, s), 0.07 (3 H, s), 0.88 (9 H, s), 1.80–1.89 (1 H, m), 2.17–2.33 (2 H, m), 2.43–2.50 (1 H, m), 2.17–2.33 (2 H, m), 2.43–2.50 (1 H, m), 3.66–3.88 (6 H, m), 4.10 (1 H, br s), 4.54 and 4.63 (2 H, AB q, *J* = 11.7 Hz), 6.97 (1 H, br s), 7.27–7.36 (5 H, m); ^{13}C NMR ($CDCl_3$) δ -5.4 (2 carbons), 18.2, 24.4, 25.9 (3 carbons), 28.1, 58.1, 64.7, 70.8, 71.2, 73.0, 73.3, 127.7 (2 carbons), 127.8, 128.5 (2 carbons), 138.1, 173.3; EIMS *m/z* (rel intensity) 410 (M^+ + 1, 5), 352 (64), 244 (11), 204 (70), 175 (6), 144 (23), 117 (100). Anal. Calcd for $C_{21}H_{35}NO_5Si$: C, 61.58; H, 8.61; N, 3.42. Found: C, 61.20; H, 8.59; N, 3.39.

(2*R*,3*R*)-3-(Benzyloxy)-2-[(*Z*)-3-(*tert*-butyldiphenylsiloxy)-1-propenyl]piperidin-6-one (18). To a stirred solution containing **16** (102 mg, 0.390 mmol) and imidazole (77 mg, 1.13 mmol) in DMF (0.5 mL) was added *tert*-butyldiphenylsilyl chloride (148 mg, 0.538 mmol), and the mixture was stirred at rt. After 1 h, water (5 mL) was added, and the mixture was extracted with $CHCl_3$ (2 × 10 mL). The combined extracts were washed with water (5 mL) and dried ($MgSO_4$). Evaporation of the solvent in vacuo and purification by chromatography on silica gel (hexane–EtOAc (2:1)) gave **18** (176 mg, 90%) as a colorless oil: $[\alpha]^{24}_D$ -32.0° (*c* 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.04 (9 H, s), 1.77–2.00 (2 H, m), 2.27 (1 H, ddd, *J* = 17.8, 7.1, 6.2 Hz), 2.50 (1 H, ddd, *J* = 17.8, 7.7, 6.3 Hz), 3.32 (1 H, ddd, *J* = 7.3, 5.3, 2.7 Hz), 4.15 (1 H, ddd, *J* = 13.7, 4.9, 1.7 Hz), 4.28 (1 H, ddd, *J* = 13.7, 7.5, 1.5 Hz), 4.39 and 4.47 (2 H, AB q, *J* = 11.9 Hz), 5.26 (1 H, ddt, *J* = 11.0, 9.2, 1.7 Hz), 5.34 (1 H, br s), 5.76 (1 H, dddd, *J* = 11.0, 7.5, 4.9, 1.1 Hz), 7.17–7.26 (5 H, m), 7.36–7.49 (6 H, m), 7.65–7.68 (4 H, m); ^{13}C NMR ($CDCl_3$) δ 19.1, 23.7, 26.8 (3 carbons), 27.8, 54.3, 60.1, 70.9, 74.9, 127.46 (2 carbons), 127.51, 127.76 (4 carbons), 127.80 (2 carbons), 128.4, 129.2, 129.8, 129.9, 133.3 (2 carbons), 134.8, 135.6 (2 carbons), 135.7 (2 carbons), 181.8; CIMS (isobutane) *m/z* 500 (MH^+); EIMS *m/z* (rel intensity) 442 (M^+ - *t*-Bu, 89), 362 (50), 334 (5), 274 (41), 243 (12), 199 (100), 159 (9), 135 (44); HRMS calcd for $C_{27}H_{28}NO_3Si$ (M^+ - *t*-Bu) 442.1838, found 442.1838. Anal. Calcd for $C_{31}H_{37}NO_3Si$: C, 74.51; H, 7.46; N, 2.80. Found: C, 74.10; H, 7.65; N, 2.68.

Hydroxylation of 18 with OsO_4. To a stirred solution of **18** (88 mg, 0.176 mmol) in acetonitrile–water (2:1, 3 mL) was added *N*-methylmorpholine *N*-oxide monohydrate (48 mg, 0.355 mmol) and 4% aqueous OsO_4 (0.17 mL, 0.027 mmol). The mixture was stirred at rt for 14 h. After addition of 2% aqueous $NaHSO_3$ (5 mL), the mixture was stirred an another 1 h at rt and extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were washed with saturated brine (5 mL) and dried ($MgSO_4$). Removal of the solvent and purification by chromatography on silica gel ($CHCl_3$–MeOH (100:1)) gave a 4.0:1 mixture (based on ^1H NMR) of the glycols (**21** and **22**, in favor of **21**) as a colorless oil (combined yield 89 mg, 95%), which was further subjected to chromatography on silica gel ($CHCl_3$–acetone (9:1)). The first elutions gave (2*R*,3*R*)-3-(benzyloxy)-2-[(1*R*,2*S*)-3-(*tert*-butyldiphenylsiloxy)-1,2-dihydroxypropyl]piperidin-6-one (**22**) (14 mg, 15%) as a colorless oil: $[\alpha]^{24}_D$ -14.7° (*c* 0.72, $CHCl_3$); IR (neat) 3359, 2931, 2858, 1651, 1645, 1634, 1471, 1455, 1428, 1113, 1044, 739, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (9 H, s), 1.81–1.93 (1 H, m), 2.09–2.28 (2 H, m), 2.44–2.54 (1 H, m), 2.99 (1 H, br s), 3.59 (1 H, br s), 3.63–3.88 (5 H, m), 3.98 (1 H, ddd, *J* = 11.1, 5.0, 3.2 Hz), 4.52 and 4.64 (2 H, AB q, *J* = 11.4 Hz), 6.46 (1 H, br s), 7.29–7.47 (11 H, m), 7.64–7.68 (4 H, m); ^{13}C NMR ($CDCl_3$) δ 19.3, 24.1, 27.0 (3 carbons), 27.8, 59.1, 65.6, 70.8, 72.4, 72.7, 73.7, 127.8 (2 carbons), 128.0 (4 carbons), 128.1, 128.6 (2 carbons), 130.1 (2 carbons), 132.8, 135.6 (4 carbons), 137.6, 172.0; CIMS (isobutane) *m/z* 534 (MH^+); EIMS *m/z* (rel intensity) 476 (M^+ - *t*-Bu, 100), 398 (15), 366 (3), 290 (5), 241 (29), 199 (78), 163 (86), 135 (47), 105 (22); HRMS calcd for $C_{27}H_{30}NO_5Si$ (M^+ - *t*-Bu) 476.1893, found 476.1902.

The second elutions gave (2*R*,3*R*)-3-(benzyloxy)-2-[(1*S*,2*R*)-3-(*tert*-butyldiphenylsiloxy)-1,2-dihydroxypropyl]piperidin-6-one (**21**) (71 mg, 76%) as a colorless oil: $[\alpha]^{21}_D$ -17.1° (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.03 (9 H, s), 1.77–1.86 (1 H, m), 2.15–2.32 (2 H, m), 2.39–2.49 (1 H, m), 3.48 (1 H, br s), 3.64–3.86 (5 H, m), 3.93–4.00 (1 H, m), 4.03 (1 H, br s), 4.51 and 4.61 (2 H, AB q, *J* = 5.6 Hz), 6.90 (1 H, br s), 7.26–7.42 (11 H, m), 7.62–7.65 (4 H, m); ^{13}C NMR ($CDCl_3$) δ 19.1, 24.3, 26.8 (3 carbons), 28.1, 58.0, 65.2, 69.7, 71.1, 72.8, 73.8, 127.65 (2 carbons), 127.72, 127.8 (4 carbons), 128.4 (2 carbons), 129.9 (2 carbons), 132.8 (2 carbons), 135.54 (2 carbons), 135.58 (2 carbons), 138.0, 173.4; CIMS (isobutane) *m/z* 534 (MH^+); EIMS *m/z* (rel intensity) 476 (M^+ - *t*-Bu, 100), 398 (11), 366 (5), 290 (3), 241 (26), 199 (68), 163 (86), 135 (49), 105 (22); HRMS calcd for $C_{27}H_{30}NO_5Si$ (M^+ - *t*-Bu) 476.1893, found 476.1895.

(2*R*,3*R*)-3-(Benzyloxy)-2-[(1*S*,2*R*)-3-(*tert*-butyldiphenylsiloxy)-1,2-(isopropylidenedioxy)propyl]piperidin-6-one (24). To a solution of **21** (48.2 mg, 0.0904 mmol) in benzene (0.5 mL) were added pyridinium *p*-toluenesulfonate (1.1 mg, 0.0045 mmol) and 2,2-dimethoxypropane (94 mg, 0.903 mmol), and the mixture was stirred at 55 °C for 13 h. After addition of saturated aqueous $NaHCO_3$ (3 mL), the mixture was extracted with $CHCl_3$ (2 × 5 mL), and the combined extracts were washed with water and dried ($MgSO_4$). Concentration followed by chromatography on silica gel (hexane–EtOAc (4:1)) gave **24** (51.4 mg, 99%) as a colorless oil: $[\alpha]^{26}_D$ -32.6° (*c* 0.59, $CHCl_3$); IR (neat) 3387, 2928, 2856, 1671, 1654, 1459, 1372, 1255, 1215, 1153, 1073, 838, 791, 736, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06, (9 H, s), 1.33 (3 H, s), 1.45 (3 H, s), 1.65–1.83 (1 H, m), 2.13–2.20 (1 H, m), 2.29 (1 H, ddd, *J* = 17.6, 9.6, 6.1 Hz), 2.49 (1 H, dt, *J* = 17.6, 5.7 Hz), 3.61 (1 H, br d, *J* = 6.8 Hz), 3.64–3.69 (1 H, m), 3.87 (2 H, d, *J* = 5.1 Hz), 4.22–4.27 (1 H, m), 4.48 and 4.62 (2 H, AB q, *J* = 11.5 Hz), 6.01 (1 H, br s), 7.28–7.43 (11 H, m), 7.65–7.69 (4 H, m); ^{13}C NMR ($CDCl_3$) δ 19.2, 24.4, 25.5, 26.9 (4 carbons), 28.4, 56.6, 62.0, 71.1, 74.1, 75.9, 77.2, 109.1, 127.6 (2 carbons), 127.8, 127.9 (4 carbons), 128.5 (2 carbons), 130.0 (4 carbons), 135.7 (4 carbons), 138.2, 171.2; CIMS (isobutane) *m/z* 574 (MH^+); EIMS *m/z* (rel intensity) 558 (M^+ - Me, 2.3), 516 (M^+ - *t*-Bu, 62), 458 (23), 350 (18), 311 (17), 241 (60), 199 (75), 163 (64), 135 (100), 105 (35). Anal. Calcd for $C_{34}H_{43}NO_5Si$: C, 71.17; H, 7.55; N, 2.44. Found: C, 71.33; H, 7.34; N, 2.43.

(2*R*,3*R*)-3-(Benzyloxy)-2-[(1*S*,2*R*)-3-hydroxy-1,2-(isopropylidenedioxy)propyl]piperidine (25). To an ice-cold, stirred solution of **24** (47.2 mg, 0.0819 mmol) in THF (1.5 mL) was added $LiAlH_4$ (18 mg, 0.474 mmol), and the mixture was heated at reflux for 1 h. Under ice cooling the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$. The resulting slurry was filtered through a Celite pad and washed with THF (5 mL). The combined THF solutions were dried (K_2CO_3), concentrated, and chromatographed on silica gel (hexane–EtOAc–Et_3N (100:25:1)) to provide **25** (18.7 mg, 71%) as a colorless oil: $[\alpha]^{22}_D$ -97.0° (*c* 0.69, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.34 (3 H, s), 1.36–1.42 (2 H, m), 1.50 (3 H, s), 2.32–2.39 (1 H, m), 2.49–2.59 (1 H, m), 2.64 (1 H, br d, *J* = 9.7 Hz), 2.99–3.05 (1 H, m), 3.33 (1 H, td, *J* = 10.1, 4.4 Hz), 3.65 (1 H, A part of ABX, *J* = 13.0, 1.7 Hz), 3.79 (1 H, B part of ABX, *J* = 13.0, 4.7 Hz), 4.19 (1 H, ddd, *J* = 7.6, 4.6, 1.8 Hz), 4.48 and 4.67 (2 H, AB q, *J* = 11.5 Hz), 4.68 (1 H, dd, *J* = 7.6, 1.0 Hz), 7.27–7.38 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 24.5, 26.7 (2 carbons), 30.4, 44.7, 58.8, 60.5, 71.0, 74.4, 76.4, 77.8, 107.3, 127.8, 127.9 (2 carbons), 128.5 (2 carbons), 138.4; EIMS *m/z* (rel intensity) 322 (M^+ + 1, 1.2), 306 (1.8), 228 (2.6), 190 (65), 172 (4), 142 (4), 124 (4), 91 (100), 71 (12). Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.18; H, 8.57; N, 4.36.

(1*S*,2*R*,8*R*,8a*R*)-8-(Benzyloxy)-1,2-(isopropylidenedioxy)-indolizidine (26). To a cold (0 °C), stirred solution of **25** (74 mg, 0.230 mmol) in CH_2Cl_2 (0.8 mL) were added CBr_4 (115 mg, 0.347 mmol) and PPh_3 (91 mg, 0.347 mmol), and the mixture was stirred at 0 °C. After 20 min at 0 °C with stirring, Et_3N (0.6 mL)

was added, and the mixture was stirred for another 30 min at 0 °C. The mixture was diluted with CH_2Cl_2 (10 mL), washed with water (2 × 3 mL), and dried ($MgSO_4$). Condensation of the CH_2Cl_2 solution left a semi solid, which was extracted with Et_2O (3 × 2 mL). The ethereal extracts were filtered through a pad of silica gel, and the filtrate was concentrated to give a pale yellow oil, which was purified by chromatography on silica gel (hexane–EtOAc (1:1)) to afford **26** (60 mg, 85%) as a colorless oil: $[\alpha]^{26}_D$ −58.9° (*c* 0.27, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.14–1.24 (1 H, m), 1.34 (3 H, s), 1.49 (3 H, s), 1.56 (1 H, dt, *J* = 12.0, 4.1 Hz), 1.60–1.65 (1 H, m), 1.69 (1 H, dd, *J* = 9.0, 4.3 Hz), 1.82 (1 H, td, *J* = 11.3, 2.8 Hz), 2.08 (1 H, dd, *J* = 10.6, 4.4 Hz), 2.14 (1 H, m), 2.96 (1 H, br d, *J* = 10.5 Hz), 3.12 (1 H, d, *J* = 10.6 Hz), 3.64 (1 H, ddd, *J* = 11.0, 9.0, 4.6 Hz), 4.58 (1 H, dd, *J* = 6.2, 4.4 Hz), 4.68 (2 H, s), 4.73 (1 H, dd, *J* = 6.2, 4.3 Hz), 7.24–7.41 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 24.1, 25.2, 26.2, 30.7, 51.8, 60.4, 71.5, 72.5, 74.4, 78.1, 79.6, 111.0, 127.4, 127.8 (2 carbons), 128.2 (2 carbons), 130.2; EIMS *m/z* (rel intensity) 302 (M^+ + 1, 0.6), 288 (M^+ − Me, 4.4), 260 (0.4), 228 (3), 212 (100), 197 (49), 182 (10), 156 (8), 142 (12), 120 (9), 91 (91), 71 (65). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.64. Found: C, 70.94; H, 4.51; N, 8.30.

(1*S*,2*R*,8*R*,8a*R*)-8-(Hydroxy)-1,2-(isopropylidenedioxy)indolizidine (27). To a solution of **26** (60 mg, 0.197 mmol) in MeOH (2 mL) was added $PdCl_2$ (30 mg), and the mixture was stirred under H_2 at an atmospheric pressure for 30 min. After removal of the catalyst by filtration, the methanolic solution was concentrated in vacuo and the residue was purified by chromatography on silica gel ($CHCl_3$–MeOH–30% NH_4OH (100:9:1)) to give **27** (36 mg, 86%) as colorless needles: mp 101–104 °C (lit.[1b] mp 105–107 °C; lit.[8h] mp 106–108 °C; lit.[8j] mp 100–103 °C); $[\alpha]^{26}_D$ −67.3° (*c* 0.46, MeOH) [lit.[1b] $[\alpha]^{24}_D$ −75.1° (*c* 1.54, MeOH); lit.[8h] $[\alpha]^{20}_D$ −65.8° (*c* 0.5, MeOH); lit.[8j] $[\alpha]^{25}_D$ −72.76° (*c* 0.43, MeOH)]; ^1H NMR ($CDCl_3$) δ 1.25 (1 H, m), 1.33 (3 H, s), 1.50 (3 H, s), 1.59–1.68 (3 H, m), 1.84 (1 H, m), 2.04 (1 H, m), 2.12 (1 H, dd, *J* = 10.7, 4.1 Hz), 2.21 (1 H, br s), 2.98 (1 H, m), 3.14 (1 H, d, *J* = 10.7 Hz), 3.82 (1 H, m), 4.60 (1 H, m), 4.70 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 24.2, 24.9, 26.0, 33.0, 51.6, 59.9, 67.6, 73.7, 78.3, 79.3, 111.5; EIMS *m/z* (rel intensity) 213 (M^+, 39), 198 (16), 156 (20), 138 (100), 126 (28), 113 (70), 96 (64), 81 (17), 71 (22), 61 (5); HRMS calcd for $C_{11}H_{19}NO$ (M^+) 213.1365, found 213.1367.

(1*R*,2*R*,8*R*,8a*R*)-1,2,8-Trihydroxyindolizidine [(−)-Swainsonine] [(−)-1]. To a solution of **27** (36 mg, 0.618 mmol) in THF (2 mL) was added 2 N HCl (3 mL), and the mixture was stirred at rt for 14 h. The mixture was concentrated in vacuo to dryness, and the resulting crude product was applied to ion-exchange chromatography (Dowex 1-X8, OH^- form, 100–200 mesh) eluting with water. Removal of water in vacuo provided **1** (19 mg, 66%) as colorless needles: mp 141–143 °C (lit.[1b,2] mp 144–145 °C); $[\alpha]^{26}_D$ −82.6° (*c* 1.03, MeOH) [lit.[1b] $[\alpha]^{25}_D$ −87.2° (*c* 2.1, MeOH); ^1H NMR (D_2O, ref DSS) δ 1.22 (1 H, qd, *J* = 12.3, 4.2 Hz), 1.50 (1 H, qt, *J* = 13.2, 4.0 Hz), 1.79 (1 H, br d, *J* = 13.7 Hz), 1.89 (1 H, dd, *J* = 9.7, 3.5 Hz), 1.94 (1 H, m), 2.04 (1 H, m), 2.53 (1 H, dd, *J* = 10.9, 7.9 Hz), 2.85–2.90 (2 H, m), 3.79 (1 H, app td, *J* = 10.7, 4.6 Hz), 4.24 (1 H. app t, *J* = 4.8 Hz), 4.33 (1 H, m); ^{13}C NMR (D_2O, ref MeCN) δ 23.5, 32.8, 52.0, 61.0, 66.7, 69.4, 70.0, 73.2; EIMS *m/z* (rel intensity) 173 (M^+, 14), 155 (18), 138 (9), 129 (5), 113 (100), 96 (92), 84 (22), 72 (66); HRMS calcd for $C_8H_{15}NO_3$ (M^+) 173.1052, found 173.1024.