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De novo asymmetric syntheses of D-, L- and 8-*epi*-D-swainsonine

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Abstract

A highly enantioselective and stereocontrolled approach to D-, L- and 8-*epi*-D-swainsonine has been developed from achiral furan and γ-butyrolactone. A one-pot hydrogenolysis of both azide and benzyl ether followed by an intramolecular reductive amination has been employed as key step to establish the indolizidine ring system. The absolute stereochemistry was installed by the Noyori reduction and the relative stereochemistry by the use of several highly diastereoselective palladium-catalyzed glycosylation, Luche reduction, dihydroxylation, and palladium-catalyzed azide allylation reactions. This practical approach provide multigram quantities of indolizidine natural product D-swainsonine in 13 steps and 25% overall yield.
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1. Introduction

Over the past decade, polyhydroxylated indolizidine alkaloids have received considerable attention because of their interesting structures and their diverse biological activities (e.g., antiviral, antitumor, and immunomodulating activities).[1] The most well-known member D-swainsonine (**1**) (Fig. 1), a trihydroxyindolizidine alkaloid, was isolated from the fungus *Rhizoctonia leguminicola*[2] and *Metarhizium anisopliae*,[3] as well as found in the legume *Swainsona canescens*[4] and the spotted locoweed *Astragalus lentiginosus*.[5] This natural product has shown to be a potent inhibitor of both lysosomal α-mannosidase[6] and mannosidase II[7] and has been applied to clinical testing as anticancer drug[8] to inhibit tumor growth and metastasis.

Fleet has shown that the enantiomer of D-swainsonine (**1**), L-swainsonine (**2**) selectively inhibited narginase (L-rhamnosidase, K_i=0.45 μM), whereas the D-swainsonine showed no inhibitory activity toward this enzyme.[9] Due to the biological importance, of both D- and L-swainsonine, as well as several epimers and analogues have become attractive targets for syntheses. Thus, over 35 syntheses of both D- and L-swainsonine have been reported since the first syntheses by Richardson and Fleet.[10] Most of these syntheses reported to date utilize carbohydrate starting materials to introduce asymmetry; whereas, only eight syntheses used achiral starting materials.[10a–d,h] Herein we report the full account of a short and efficient de novo syntheses of D- and L-swainsonine (**1** and **2**) from achiral commercially available starting material.[11] In addition to describing our optimized route (multigram scale) to D- and L-swainsonine we disclose for first time the use of this approach for the syntheses of 8-*epi*-D-swainsonine (**3**) and 8-hydroxyindolizidine (**4**).

Our strategy for the synthesis of D-swainsonine is outlined in Scheme 1, which involves a key one-pot reductive

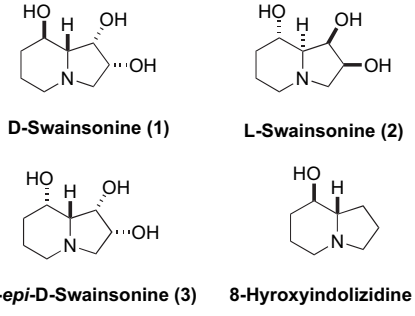

Figure 1. Swainsonine and analogues.

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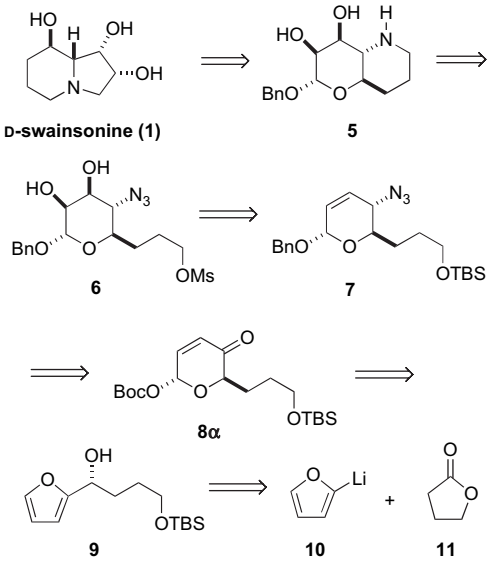
cyclization of azidosugar **6** into **1**. Thus, we envisioned that D-swainsonine could be obtained by hydrogenolytic deprotection and reductive amination of bicyclic amine intermediate **5**, which can be derived from azide-sugar **6** by reductive N-alkylation. The *manno*-stereochemistry of azide **6** could be readily installed by diastereoselective dihydroxylation of **7**. The allylic azide **7** in turn could be prepared from palladium-catalyzed azide allylation, Luche reduction, and stereoselective palladium-catalyzed protection of pyranone **8α**. A Noyori reduction and Achmatowicz oxidation should convert the furfuryl alcohol **9** into pyranone **8α**. Eventually, the furfuryl alcohol could be derived from commercially available furan and γ-butyrolactone **11**. In addition to providing either swainsonine enantiomer (**1** and **2**), we envisioned with route being able to provide the diastereomeric and deoxy-analogues **3** and **4**.

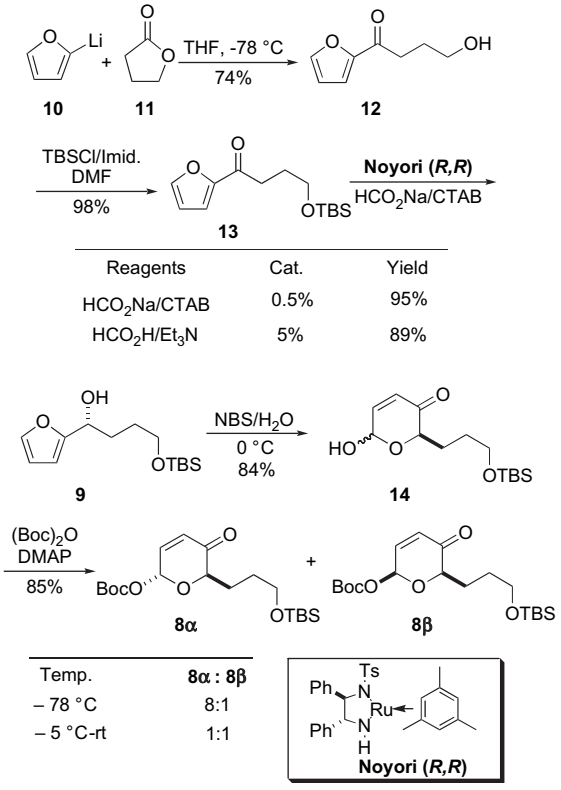


Scheme 1. Retrosynthetic analysis of (−)-D-swainsonine (**1**).

2. Results and discussion

2.1. Approach to pyranones

The syntheses of D- and L-swainsonine as well as 8-*epi*-D-swainsonine began with commercially available achiral γ-butyrolactone **11** and furan (Scheme 2).[12] Treatment of γ-butyrolactone **11** with 2-lithiofuran **10** in THF solution afforded furfuryl ketone **12** in 74% yield. Protection of primary alcohol **12** gave TBS-ether **13** (TBSCl/imid. in DMF) in excellent yield (98%). The furfuryl alcohol **9** was obtained from furfuryl ketone **12** by employing a phase transfer variant of the asymmetric Noyori reduction in high enantiomeric excess (>96% ee) and excellent yield (95%) using an aqueous solution of HCOONa/cetyltrimethylammonium bromide (CTAB).[13] Alternatively, the Noyori reduction could be accomplished using a THF solution of $HCOOH/Et_3N$ (1:1) in 89% yield, however, this required a 10-fold amount of Noyori catalyst and afforded a slightly lower yield of product. Exposure of furfuryl alcohol **9** to the Achmatowicz conditions[14] (NBS in THF/H_2O) provided the oxidative rearrangement product hemiacetal **14** (84%), which was converted ($(Boc)_2O$ at −78 °C) to a mixture of Boc-protected pyranones **8α** and **8β** in a good yield (85%) and diastereoselectivity (8:1; α/β).[15] The diastereoselectivity of the Boc-acylation to form pyranones **8α** and **8β** was decreased (**8α/8β** in 1:1 ratio) when the reaction was performed at elevated temperature (0 °C to rt).

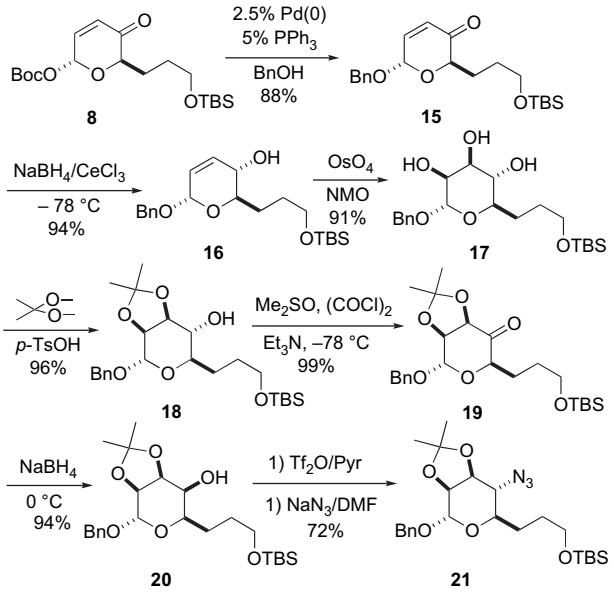


Scheme 2. Enantioselective synthesis of pyranones.

2.2. Synthesis of D-swainsonine *1* via protected swainsonine

With the successful synthesis of pyranone **8α**, we next installed *manno*-stereochemistry and C-1 benzyl ether (Scheme 3). Exposure of the pyranone **8α** and benzyl alcohol to our palladium glycosylation conditions[16] (2.5% Pd(0)/5% PPh_3) afforded OBn-protected pyranone **15** as a single diastereomer and in an excellent yield (88%). Diastereoselective reduction of the C-4 ketone in **15** under the Luche condition[17] ($NaBH_4/CeCl_3$, −78 °C) gave an equatorial allylic alcohol **16** in excellent yield (94%). Dihydroxylation of allylic alcohol **16** using the Upjohn conditions[18] (OsO_4/NMO) afforded triol **17** by in excellent yield (91%). The C-2/C-3 *cis*-diol **25** was selectively protected as acetonide **18** by treatment with 2,2-dimethoxypropane and catalytic amount of *p*-TsOH (96%).

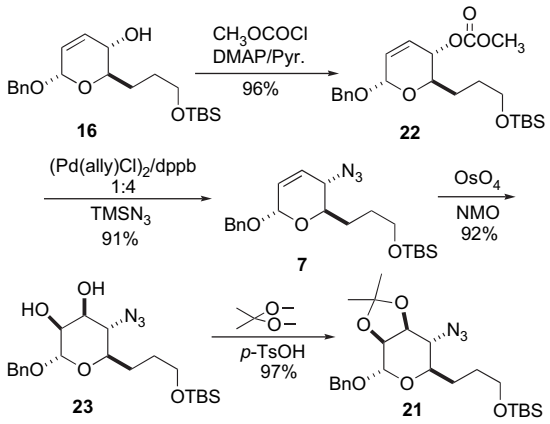
In order to convert the C-4 equatorial hydroxyl group into an equatorial azide, an oxidation/reduction/inversion sequence was employed. Swern oxidation of alcohol **18**, provided the C-4 ketone **19**, which was reduced with $NaBH_4$ to provide



Scheme 3. Diastereoselective synthesis of azide **21**.

the C-4 axial alcohol **20** in excellent yield for the two steps (93%). Finally, treatment of alcohol **20** with triflic anhydride gave a triflate, which without further purification underwent an S_N2 azide displacement (NaN_3/DMF) to provide azide **21** in 72% yield from **20**.

Alternatively, the acetonide **21** could also be prepared by a short and efficient route that involved a palladium-catalyzed azide installation (Scheme 4),[19] this would eliminate the need for the double inversion at C-4 (**18** to **20** to **21**). To perform the palladium coupling reaction, a C-4 carbonate leaving group was required. Thus, allylic alcohol **16** was treated with methyl chloroformate and catalytic amount of DMAP to produce allylic carbonate **22** in excellent yield (96%). The allylic azide **7** was formed by a regio- and stereoselective Pd-catalyzed allylation of methyl carbonate **22** with $TMSN_3$ in the presence of $(allylPdCl)_2$ and bis(diphenylphosphino)butane in excellent yield (91%). Once again diastereoselective dihydroxylation of allylic azide **7** generated diol **23** (92%), which was protected



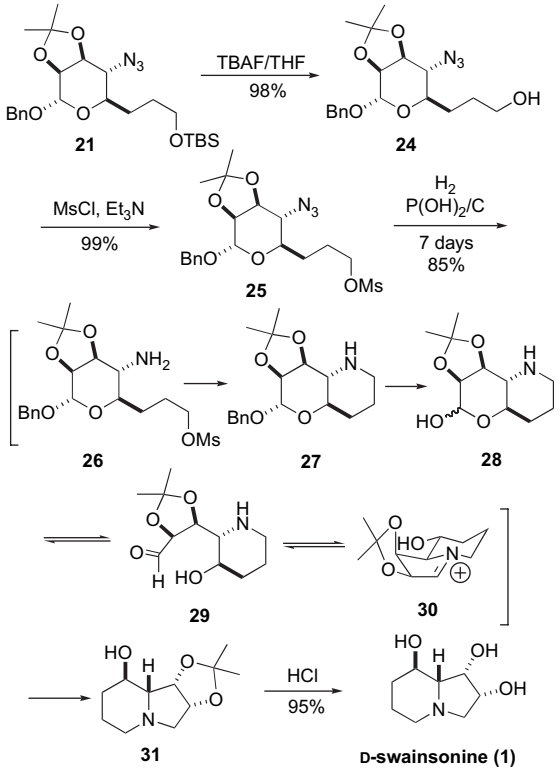
Scheme 4. Synthesis of azide **21** via palladium-catalyzed azide allylation and dihydroxylation.

(2,2-dimethoxypropane/p-$TsOH_{(cat)}$) to give acetonide **21** in good yield (97%) and two fewer steps.

To complete the synthesis of D-swainsonine, a one-pot reductive cyclization was employed to furnish indolizidine ring (Scheme 5). TBS-ether **21** was deprotected to yield primary alcohol **24** by treatment with TBAF. Once again mesylation of **24** ($MsCl/Et_3N$) produced mesylate **25** in excellent yield (97%, two steps). The azidosugar **25** was converted into a protected swainsonine **31** via a cascade of transformations (global hydrogenolysis, N-alkylation, and reductive amination). Mechanistically, this is believed to begin with an azide reduction to produce aminosugar **26**, which undergoes an intramolecular N-alkylation to generate amine **27**. Hydrogenolytic removal of Bn-protecting group at the anomeric position should result in hemiacetal **28**, which exist in equilibrium with hydroxy aldehyde **29**. A reductive amination of **29**, via bicyclic iminium ion intermediate **30**, provided the protected swainsonine **31**. This one-pot reaction was performed with hydrogen (1 atm) in a THF/ethanol solution and required 7 days for complete conversion (85%). Finally, acidic hydrolysis of the acetonide **31** followed by ion-exchange chromatography (basic OH^- form) gave D-swainsonine (**1**) in excellent yield (95%).

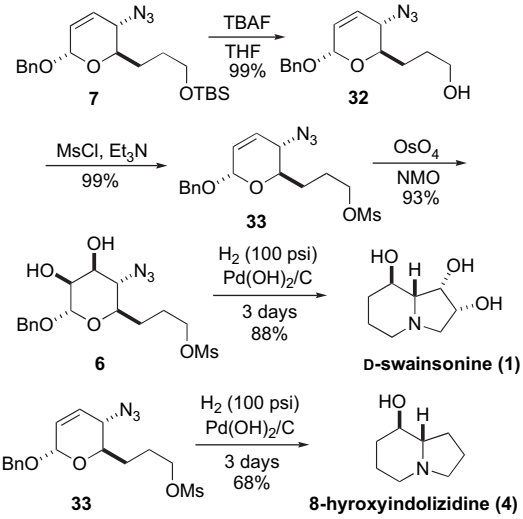
2.3. Alternative synthesis of swainsonine

Using the same strategy, we found D-swainsonine (**1**) could also be efficiently synthesized without acetonide protection in four steps from allylic azide **7** (Scheme 6). Deprotection of TBS-ether **7** with a TBAF solution (99%) afforded the primary alcohol **32**, which after mesylation ($MsCl/Et_3N$) gave mesylate



Scheme 5. Synthesis of D-swainsonine (**1**) via a one-pot reductive cyclization.

33 in near quantitative yield (99%). Upjohn dihydroxylation of allylic azide **33** exclusively gave diol **6** (OsO_4/NMO, 93%). Finally, the natural product D-swainsonine **1** was obtained by an analogous azide reduction/N-alkylation/reductive amination sequence under hydrogenation condition (100 psi H_2, $Pd(OH)_2$/C).



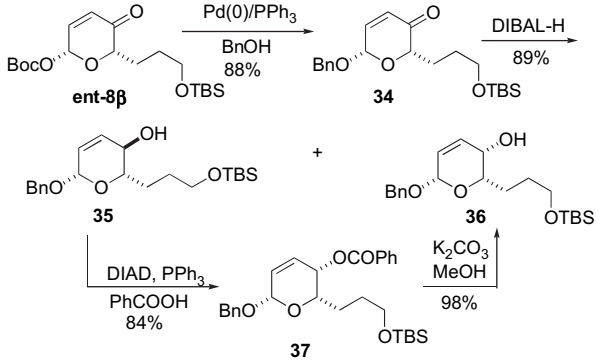
Scheme 6. Synthesis of D-swainsonine (**1**) and 8-hydroxyindolizidine (**4**).

In addition, the known indolizidine analogue 8-hydroxyindolizidine (**4**)[20] was also prepared by the same one-pot hydrogenation of allylic azide **33** (68%). It is worth noting this sans-acetonide approach provided 8-hydroxyindolizidine (**4**) as well as either enantiomer of swainsonine (**1** and **2**) while using only two protecting groups (Bn and TBS). The route to swainsonine can provide multigram quantities of both enantiomers (3 g of the D-isomer was prepared). The physical and spectral data of our synthetic both D- and L-swainsonine by either way is completely identical to those of the natural materials (^{1}H NMR, ^{13}C NMR, optical rotation, and melting point).[21]

2.4. Synthesis of 8-epi-D-swainsonine

Encouraged by these results, we next investigated the use of this approach for the synthesis of 8-*epi*-D-swainsonine (Scheme 7). We envisioned this approach starting with the L-pyranone *ent*-**8β**. This enantiomeric β-anomer of **8α** was readily prepared in three steps from furfuryl ketone **13** by switching to the use of the (*S*,*S*)-Noyori catalyst and performing the Boc-acylation at higher temperature (0 °C to rt) to ensure more β-pyranone *ent*-**8β** was produced (cf., Scheme 2).

Palladium-catalyzed glycosylation of pyranone *ent*-**8β** with benzyl alcohol diastereoselectively afforded the C-1 BnO-pyranone **34** in 88% yield (Scheme 7). Unfortunately, the Luche reduction ($NaBH_4/CeCl_3$) of pyranone **34** provided a 1:1.3 mixture of allylic alcohols **35** and **36** in 86% yield. Improved diastereoselectivity was obtained (**35**/**36** in a 1:2.5 ratio) when DIBAL-H was used as the reducing agent (89%). The easily separated minor diastereomer, equatorial allylic alcohol **35**, could be easily converted into axial allylic alcohol **36** via

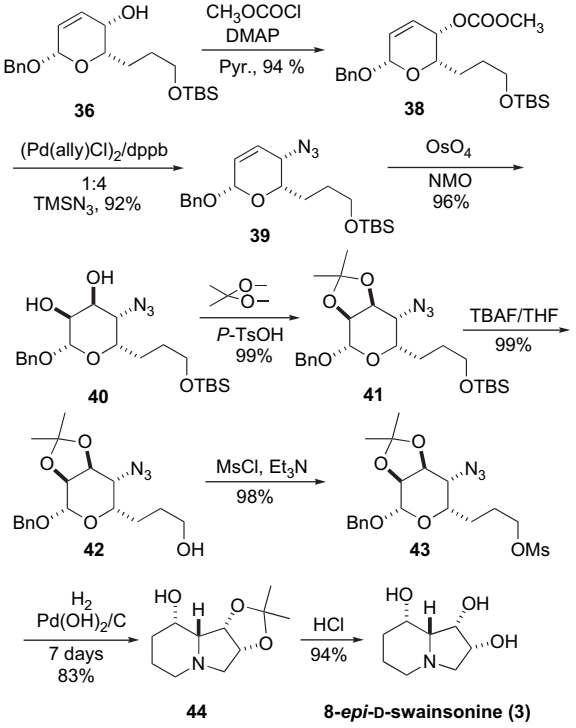


Reagents	Ratio (35 : 36)	yields
DIBAL-H	1 : 2.5	89%
$NaBH_4$	1 : 1.3	86%

Scheme 7. Synthesis of allylic alcohol **36**.

a two-step Mitsunobu/ester hydrolysis sequence. Thus, exposure of allylic alcohol **35** to typical Mitsunobu reaction conditions (BzOH, DIAD and PPh_3) yielded benzoate ester **37** with inverted stereochemistry at C-4. Methanolysis of ester **37** (K_2CO_3/MeOH) provided allylic alcohol **35** in good yield (82%, two steps).

With a practical route to allylic alcohol **36** (the C-5 diastereomer of **16**) in hand, we explored the analogous application of this approach for the synthesis of 8-*epi*-D-swainsonine (**3**) (Scheme 8). Treatment of allylic alcohol **36** with methyl chloroformate formed carbonate **38** (Pyr/DMAP) in 94% yield. The carbonate **38** was coupled with $TMSN_3$ to give allylic azide ($(allylPdCl)_2$/dppb) in excellent yield (92%). Stereoselective dihydroxylation of allylic azide **38** under Upjohn conditions



Scheme 8. Synthesis of 8-*epi*-D-swainsonine (**3**).

(OsO_4/NMO) afforded diol **40** as a single *talo*-diastereomer. Diol **40** was protected as acetonide **41** in excellent yield (95% two steps). Deprotection of TBS-ether **41** provided primary alcohol **42** (TBAF, 99% yield), which was followed by mesylation to afford mesylate **43** in 98% yield. A one-pot global hydrogenation/hydrogenolysis of azide **43** produced protected 8-*epi*-D-swainsonine (**3**) in excellent yield (83%). Eventually, 8-*epi*-D-swainsonine (**3**) was obtained by treatment with HCl in 94% yield. The spectral and physical data of 8-*epi*-D-swainsonine (**3**) by our approach match those of references reported (^{1}H NMR, ^{13}C NMR, optical rotation, and melting point).[22]

3. Conclusions

In conclusion, a de novo asymmetric approach to D-swainsonine (**1**), L-swainsonine (**2**), 8-*epi*-D-swainsonine (**3**) as well as 8-hydroxylindolizidine (**4**) has been developed. Both D- and L-swainsonine were achieved in 13 steps and 25% overall yield from achiral furan **10**. These practical syntheses are comparable to the previous carbohydrate-based routes.[10] Key to the successful approach is the use of the Noyori reduction, palladium-catalyzed glycosylation, diastereoselective dihydroxylation, palladium-catalyzed azide allylation, and one-pot reductive cyclization. The 8-*epi*-D-swainsonine (**3**) was also synthesized in 10 steps in 34% overall yield from Boc-pyranone *ent*-**8β** (15 steps from furan **10** in 8% overall yield). Further application of this approach to the synthesis of various analogues is ongoing.

4. Experimental section[23]

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on either a Jeol 270 MHz or a Varian 600 MHz spectrometer. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) or $CDCl_3$ (δ 7.26 ppm) or CD_3OD (δ 4.89 ppm) for ^{1}H and $CDCl_3$ (δ 77.1 ppm) or CD_3OD (δ 49.15 ppm) for ^{13}C. Optical rotations were measured with a digital polarimeter in the solvent specified. Infrared (IR) spectra were obtained on a FT-IR spectrometer. Flash column chromatography was performed on ICN reagent 60 (60–200 mesh) silica gel. Analytical thin-layer chromatography was performed with precoated glass-backed plates (K6F 60 Å, F254) and visualized by quenching of fluorescence and by charring after treatment with *p*-anisaldehyde or phosphomolybdic acid or potassium permanganate stain. R_f values were obtained by elution in the stated solvent ratios (v/v). Ether, THF, methylene chloride, and triethylamine were dried by passing through activated alumina (8×14 mesh) column with nitrogen gas pressure. Commercial reagents were used without purification unless otherwise noted. Air and/or moisture-sensitive reactions were carried out under an atmosphere of argon/nitrogen using oven/flame-dried glassware and standard syringe/septa techniques.

4.2. (2S,3S,4S,5S,6R)-2-(Benzyloxy)-tetrahydro-6-(3-tert-butyldimethylsilyloxypropyl)-2H-pyran-3,4,5-triol (17)

To a *tert*-butanol/acetone (0.53 mL, 1:1, 1 M) solution of allylic alcohol **16** (200 mg, 0.53 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide/water (0.25 mL). Crystalline OsO_4 (1.4 mg, 1 mol %) was added and the reaction was stirred for 24 h. The reaction mixture was concentrated with a small silica gel under reduced pressure, purified using silica gel flash chromatography eluting with 100% EtOAc to give triol **17** (199 mg, 0.48 mmol, 91%). R_f=0.29 (70% EtOAc/hexane); $[\alpha]_D^{25}$ +48 (*c* 3.11, MeOH); IR (thin film, cm^{-1}) 3397, 2928, 2857, 1455, 1389, 1253, 1061, 833; ^{1}H NMR (600 MHz, CD_3OD) δ 7.36–7.43 (m, 5H), 4.91 (s, 1H), 4.78 (d, *J*=11.4 Hz, 1H), 4.57 (d, *J*=11.4 Hz, 1H), 3.97 (m, 1H), 3.83 (dd, *J*=9.0, 3.0 Hz, 1H), 3.77 (m, 2H), 3.64 (dd, *J*=9.0, 9.0 Hz, 1H), 3.59 (m, 1H), 2.00–2.11 (m, 1H), 1.90–1.97 (m, 1H), 1.66–1.73 (m, 1H), 1.58–1.64 (m, 1H), 1.01 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (150 MHz, CD_3OD) δ 138.9, 129.5, 129.0, 128.8, 100.5, 73.6, 72.7, 72.4, 72.1, 64.5, 30.3, 29.0, 26.6, 19.2, −4.9; CIHRMS: [$C_{21}H_{36}O_6SiNa^+$]: calculated for 435.2176, found: 435.2179.

4.3. (3aS,4S,6R,7R,7aS)-4-(Benzyloxy)-tetrahydro-6-(3-tert-butyldimethylsilyloxypropyl)-2,2-dimethyl-3aH-[1,3]dioxolo[4,5-c]pyran-7-ol (18)

para-Toluenesulfonic acid monohydrate (19.4 mg, 5 mol %) was added to a stirred solution of diol **17** (840 mg, 2.08 mmol) and 2,2-dimethoxypropane (5.87 mL) in acetone (31.2 mL) for 0.5 h at 0 °C. The reaction mixture was quenched with sodium bicarbonate solution (5 mL), removed acetone in vacuo, extracted with Et_2O (3×25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 15% EtOAc/hexane to give 904 mg (2.0 mmol, 96%) of colorless oil, acetonide **18**. R_f (20% EtOAc/hexane)=0.40; $[\alpha]_D^{25}$ +36 (*c* 1.52, CH_2Cl_2); IR (thin film, cm^{-1}) 3467, 2930, 2857, 1382, 1248, 1087, 835; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.06 (s, 1H), 4.74 (d, *J*=11.4 Hz, 1H), 4.51 (d, *J*=11.4 Hz, 1H), 4.18 (d, *J*=6.0 Hz, 1H), 4.11 (dd, *J*=6.0, 7.2 Hz, 1H), 3.67 (m, 2H), 3.56 (ddd, *J*=9.0, 9.0, 3.0 Hz, 1H), 3.48 (m, 1H), 2.15 (d, *J*=3.0 Hz, 1H), 1.83–1.95 (m, 2H), 1.52–1.65 (m, 2H), 1.51 (s, 3H), 1.31 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.0, 128.6, 128.3, 128.1, 109.5, 96.2, 78.6, 75.9, 73.2, 69.8, 69.1, 63.3, 28.8, 28.1, 27.9, 26.3, 26.1, 18.5, −5.2; CIHRMS: calculated for [$C_{24}H_{40}O_6SiNa^+$]: 475.2491, found: 475.2492.

4.4. (3aS,4S,6R,7aR)-4-(Benzyloxy)-dihydro-6-(3-tert-butyldimethylsilyloxypropyl)-2,2-dimethyl-6H-[1,3]dioxolo[4,5-c]pyran-7(7aH)-one (19)

To a solution of $(COCl)_2$ (0.15 mL, 1.76 mmol) in CH_2Cl_2 (3.5 mL) was added DMSO (0.51 mL, 3.52 mmol) at −78 °C,

and the mixture was stirred for 10 min. A solution of alcohol **18** (400 mg, 0.88 mmol) in 1.76 mL CH_2Cl_2 was added to the resulting mixture, stirred for 0.5 h at −78 °C. Then triethylamine (0.50 mL, 3.52 mmol) was added at −78 °C and the reaction mixture was warmed to 0 °C for 1 h. Water (50 mL) was added to quench the mixture, and the aqueous mixture was extracted (3×80 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 15% EtOAc/hexane to give ketone **19** (392 mg, 0.87 mmol, 99%) as a colorless oil. R_f (20% EtOAc/hexane)=0.61; $[\alpha]_D^{25}$ +74 (*c* 2.0, CH_2Cl_2); IR (thin film, cm^{-1}) 2954, 2929, 2857, 1741, 1472, 1253, 1077, 1023, 834; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.03 (d, *J*=1.2 Hz, 1H), 4.76 (d, *J*=11.4 Hz, 1H), 4.57 (d, *J*=11.4 Hz, 1H), 4.47 (dd, *J*=6.6, 1.2 Hz, 1H), 4.46 (d, *J*=6.6, 1H), 4.18 (dd, *J*=4.8, 8.4 Hz, 1H), 3.65 (m, 2H), 1.90−1.96 (m, 1H), 1.72−1.84 (m, 2H), 1.58−1.65 (m, 1H), 1.48 (s, 3H), 1.35 (s, 3H) 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 196.5, 143.3, 137.1, 128.6, 128.2 (two carbon), 127.9, 92.1, 74.0, 70.6, 62.9, 28.5, 26.0, 18.4, −5.2; CIHRMS: calculated for $[C_{24}H_{38}O_6Si+H^+]$: 451.2514, found: 451.2516.

*4.5. (3aS,4S,6R,7S,7aS)-4-(Benzyloxy)-tetrahydro-6-(3-tert-butyldimethylsilyloxypropyl)-2,2-dimethyl-3aH-[1,3]dioxolo[4,5-c]pyran-7-ol (**20**)*

A CH_2Cl_2 (1 mL) solution of ketone **19** (370 mg, 0.82 mmol) and MeOH (1 mL, 1 M) was cooled to 0 °C. $NaBH_4$ (37 mg, 0.98 mmol) was added and the reaction mixture was stirred at 0 °C for 20 min. The reaction mixture was diluted with ether (20 mL) and quenched with 15 mL of saturated $NaHCO_3$, extracted (3×30 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 15% EtOAc/hexane to give colorless oil, 323 mg (0.71 mmol, 87%) of alcohol **20**. R_f (20% EtOAc/hexane)=0.41; $[\alpha]_D^{25}$ +16 (*c* 1.6, CH_2Cl_2); IR (thin film, cm^{-1}) 3568, 2928, 2857, 1381, 1251, 1070, 833; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.15 (s, 1H), 4.76 (d, *J*=11.4 Hz, 1H), 4.55 (d, *J*=11.4 Hz, 1H), 4.22 (dd, *J*=4.8, 6.0 Hz, 1H), 4.11 (d, *J*=6.0 Hz, 1H), 3.76 (dd, *J*=4.8, 9.0 Hz, 1H), 3.63−3.70 (m, 2H), 3.61 (d, *J*=6.0, 6.0 Hz, 1H), 3.48 (m, 1H), 2.21 (d, *J*=6.0 Hz, 1H), 1.84−1.90 (m, 1H), 1.73−1.80 (m, 1H), 1.65−1.71 (m, 1H), 1.59−1.64 (m, 1H), 1.58 (s, 3H), 1.38 (s, 3H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.1, 128.6, 128.3, 128.1, 109.3, 96.7, 73.6, 72.9, 69.4, 68.5, 66.1, 63.1, 29.4, 27.6, 26.1, 25.9, 25.4, 18.4, −5.2; CIHRMS: calculated for $[C_{24}H_{40}O_6SiNa^+]$: 475.2491, found: 475.2490.

*4.6. (3aR,9R,9aR,9bS)-Octahydro-2,2-dimethyl-[1,3]dioxolo[4,5-a]indolizin-9-ol (**31**)*

To a solution of acetonide **25** (7.79 g, 17.6 mmol) in dry EtOH/THF (76 mL, v/v=1:1) was added $Pd(OH)_2/C$ (1.9 g) and the mixture was stirred under H_2 at an 100 psi pressure for 3 days at room temperature. The catalyst was filtered off through a short pad of Celite, concentrated under reduced pressure. The resulting crude was purified using silica gel flash chromatography eluting with 30% MeOH/EtOAc to give protected swainsonine **31** (3.2 g, 15.0 mmol, 85%) as colorless needles. R_f=0.44 (10% MeOH/EtOAc); $[\alpha]_D^{25}$ −72 (*c* 1.0, CH_2Cl_2); mp 102−104; IR (neat, cm^{-1}) 3194, 2942, 2793, 1466, 1371, 1260, 1209, 1113, 1068; ^1H NMR (600 MHz, $CDCl_3$) δ 4.67 (dd, *J*=6.2, 4.8 Hz, 1H), δ 4.24 (dd, *J*=6.0, 4.2 Hz, 1H), 3.79 (ddd, *J*=10.9, 8.9, 4.4 Hz, 1H), 3.11 (d, *J*=10.8 Hz, 1H), 2.96 (dt, *J*=10.8, 3.0 Hz, 1H), 2.52 (br s, 1H), 2.09 (dd, *J*=10.8, 4.8 Hz, 1H), 2.00−2.03 (m, 1H), 1.82 (ddd, *J*=10.8, 10.8, 3.6 Hz, 1H), 1.61−1.65 (m, 1H), 1.59 (dd, *J*=9.0, 4.8 Hz, 1H), 1.48 (s, 3H), 1.31 (s, 3H), 1.25 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 111.3, 79.2, 78.2, 73.8, 67.3, 60.0, 51.6, 33.0, 26.0, 24.9, 24.1.

*4.7. (2S,6S)-6-(Benzyloxy)-2-(3-tert-butyldimethylsilyloxypropyl)-2H-pyran-3(6H)-one (**34**)*

To a solution of Boc-protected pyranone **8b** (5.86 g, 15.8 mmol) and benzyl alcohol (3.28 g, 30.4 mmol) in dry CH_2Cl_2 (8 mL), were added $Pd_2(DBA)_3\cdot CHCl_3$ (97.7 mg, 0.9 mol % Pd) and PPh_3 (101.5 mg, 3.6 mol %) at 0 °C under argon atmosphere. After stirring for 2 h at 0 °C to room temperature, the reaction mixture was quenched with 200 mL of saturated $NaHCO_3$, extracted (3×200 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 6% EtOAc/hexane to give benzyl ether **34** (5.02 g, 13.30 mmol, 88%) as a colorless oil. R_f (10% EtOAc/hexane)=0.75; $[\alpha]_D^{25}$ +10 (*c* 1.4, CH_2Cl_2); IR (thin film, cm^{-1}) 2954, 2929, 2856, 1695, 1471, 1254, 1092, 1024, 832; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36 (m, 5H), 6.89 (dd, *J*=10.2, 1.8 Hz, 1H), 6.10 (dd, *J*=10.2, 1.2 Hz, 1H), 5.37 (d, *J*=1.2 Hz, 1H), 4.95 (d, *J*=11.4 Hz, 1H), 4.71 (d, *J*=11.4 Hz, 1H), 4.09 (dd, *J*=7.8, 3.6 Hz, 1H), 3.66 (m, 2H), 2.03−2.09 (m, 1H), 1.85−1.91 (m, 1H), 1.75−1.82 (m, 1H), 1.67−1.74 (m, 1H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.0, 146.5, 137.0, 128.6, 128.15 (two carbon), 128.1, 94.6, 78.9, 70.3, 62.9, 28.5, 28.0, 26.0, 18.4, −5.2; CIHRMS: calculated for $[C_{21}H_{32}O_4SiNa^+]$: 399.1962, found: 399.1970.

*4.8. (2S,3S,6S)-6-(Benzyloxy)-3,6-dihydro-2-(3-tert-butyldimethylsilyloxypropyl)-2H-pyran-3-ol (**36**)*

To a solution of pyranone **34** (6.7 g, 17.7 mmol) in 130 mL THF was added dropwise 1.0 M DIBAL-H in hexane (17.8 mL, 17.8 mmol) at −78 °C under nitrogen atmosphere. The reaction mixture was kept stirring for 3 h at −78 °C, then treated with 1.0 M Na/K tartaric solution (50 mL) and allowed to warm to room temperature. The resulting mixture was extracted with diethyl ether (3×200 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/

hexane to afford colorless oil, 6.0 g (15.8 mmol, 89%) of allylic alcohol **35** and **36** in 1:2.5. Compound **36**: R_f (20% EtOAc/hexane)=0.61; $[\alpha]_D^{25}$ +52 (*c* 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 3417, 2952, 2928, 2856, 1471, 1254, 1094, 1056, 834; ^1H NMR (600 MHz, $CDCl_3$) δ 7.27–7.38 (m, 5H), 6.10 (dd, *J*=9.6, 4.8 Hz, 1H), 5.86 (d, *J*=9.6 Hz, 1H), 5.09 (d, *J*=1.2 Hz, 1H), 4.92 (d, *J*=11.4 Hz, 1H), 4.67 (d, *J*=11.4 Hz, 1H), 3.70 (m, 1H), 3.69 (m, 2H), 3.54 (ddd, *J*=7.2, 4.8, 2.4 Hz, 1H), 1.97 (d, *J*=2.4 Hz, 1H), 1.78–1.84 (m, 1H), 1.69–1.77 (m, 2H), 1.62–1.67 (m, 1H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.6, 131.4, 130.9, 128.4, 128.1, 127.8, 97.2, 75.6, 70.0, 63.9, 63.2, 28.7, 27.3, 26.0, 18.4, −5.2; CIHRMS: calculated for $[C_{21}H_{34}O_4SiNa^+]$: 401.2118, found: 401.2132. Compound **35**: R_f (20% EtOAc/hexane)=0.58; $[\alpha]_D^{25}$ +53 (*c* 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 3426, 2932, 2928, 2856, 1471, 1254, 1093, 1056, 834; ^1H NMR (600 MHz, $CDCl_3$) δ 7.26–7.37 (m, 5H), 5.95 (ddd, *J*=9.6, 3.0, 1.8 Hz, 1H), 5.81 (ddd, *J*=9.6, 3.6, 1.2 Hz, 1H), 5.16 (dd, *J*=3.6 1.8 Hz, 1H), 4.87 (d, *J*=11.4 Hz, 1H), 4.64 (d, *J*=11.4 Hz, 1H), 3.99 (ddd, *J*=7.8, 7.2, 2.4 Hz, 1H), 3.68 (m, 2H), 3.47 (ddd, *J*=7.8, 7.2, 3.6 Hz, 1H), 2.29 (d, *J*=7.2 Hz, 1H), 1.77–1.92 (m, 2H), 1.61–1.71 (m, 2H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.7, 132.8, 128.8, 128.4, 128.0, 127.7, 96.0, 78.2, 69.5, 67.2, 63.2, 28.9, 28.8, 26.0, 18.4, −5.2; CIHRMS: calculated for $[C_{21}H_{34}O_4SiNa^+]$: 401.2118, found: 401.2132.

*4.9. (2S,3S,6S)-6-(Benzyloxy)-3,6-dihydro-2-(3-tert-butyldimethylsilyloxypropyl)-2H-pyran-3-yl benzoate (**37**)*

Allylic alcohol **35** (1.1 g, 3.38 mmol) was dissolved in THF (5 mL). The solution was cooled to 0 °C and triphenylphosphine (1.77 g, 6.75 mmol), benzoic acid (0.82 g, 6.75 mmol), and diisopropyl azodicarboxylate (1.33 mL, 6.75 mmol) were added to the solution. The solution was stirred overnight, quenched with saturated aqueous sodium bicarbonate (50 mL), and extracted with ether (3×50 mL). The organic fractions were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 5% EtOAc/hexane to afford colorless oil, 1.38 g (2.85 mmol, 84%) of allylic ester **37**. R_f (20% EtOAc/hexane)=0.64; $[\alpha]_D^{25}$ +122 (*c* 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 2953, 2927, 2857, 1790, 1717, 1452, 1268, 1108, 1061, 835; ^1H NMR (600 MHz, $CDCl_3$) δ 8.09–8.10 (m, 2H), 7.52–7.57 (m, 2H), 7.28–7.45 (m, 6H), 6.19 (ddd, *J*=10.2, 4.8, 1.8 Hz, 1H), 6.05 (d, *J*=10.2 Hz, 1H), 5.28 (ddd, *J*=7.2, 4.8, 2.4 Hz, 1H), 5.20 (d, *J*=1.2 Hz, 1H), 4.94 (d, *J*=11.4 Hz, 1H), 4.74 (d, *J*=11.6 Hz, 1H), 3.78 (ddd, *J*=7.8, 4.8, 3.0 Hz, 1H), 3.60–3.68 (m, 2H), 1.84–1.90 (m, 1H), 1.75–1.82 (m, 1H), 1.67–1.73 (m, 1H), 1.58–1.65 (m, 1H), 0.08 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 137.8, 134.6, 130.6, 129.9, 128.9, 128.5, 128.4, 128.1, 127.8, 127.1, 96.7, 74.0, 69.6, 66.0, 63.1, 28.9, 27.5, 26.0, 18.4, −5.3; CIHRMS: calculated for $[C_{28}H_{38}O_5SiNa^+]$: 505.2381, found: 505.2386.

*4.10. (2S,3S,6S)-6-(Benzyloxy)-3,6-dihydro-2-(3-tert-butyldimethylsilyloxypropyl)-2H-pyran-3-yl-methyl carbonate (**38**)*

To a solution of allylic alcohol **36** (4.0 g, 10.6 mmol) and pyridine (2.62 g, 31.6 mmol) in dry CH_2Cl_2 (53 mL) at 0 °C, was added DMAP (260 mg), and added dropwise methyl chloroformate (6.24 g, 63.6 mmol). After stirring 1 h at 0 °C, a saturated Cu_2SO_4 solution (500 mL) was added and then the mixture was extracted with CH_2Cl_2 (3×300 mL), dried (Na_2SO_4), concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 5% EtOAc/hexane to give 4.34 g (9.96 mmol, 94%) of colorless oil, carbonate **38**. R_f (20% EtOAc/hexane)=0.62; $[\alpha]_D^{25}$ +110 (*c* 1.4, CH_2Cl_2); IR (thin film, cm^{-1}) 2955, 2929, 2886, 2857, 1745, 1442, 1264, 1098, 1059, 833; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.12 (ddd, *J*=10.2, 4.8, 1.2 Hz, 1H), 6.03 (d, *J*=10.2 Hz, 1H), 5.13 (d, *J*=1.2 Hz, 1H), 4.88 (d, *J*=11.4 Hz, 1H), 4.87 (dd, *J*=4.8, 1.8 Hz, 1H), 4.68 (d, *J*=11.4 Hz, 1H), 3.78 (s, 3H), 3.62–3.73 (m, 3H), 1.73–1.84 (m, 2H), 1.64–1.70 (m, 1H), 1.57–1.63 (m, 1H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.8, 137.7, 133.7, 128.4, 128.1, 127.8, 126.5, 96.5, 73.6, 69.4, 69.2, 63.1, 55.0, 28.9, 27.1, 26.0, 18.4, −5.2; CIHRMS: calculated for $[C_{23}H_{36}O_6SiNa^+]$: 459.2173, found: 459.2179.

*4.11. (2S,3S,6S)-3-Azido-6-(benzyloxy)-3,6-dihydro-2-(3-tert-butyldimethylsilyloxyprop-yl)-2H-pyran (**39**)*

To a mixture of carbonate **38** (2.2 g, 5.45 mmol), allylpalladium chloride dimer (43.5 mg, 0.11 mmol) and 1,4-bis(diphenylphosphino)butane (189 mg, 0.44 mmol) in dry THF (1.2 mL) was added $TMSN_3$ (684 mg, 5.95 mmol) under argon atmosphere. The solution was stirred at room temperature for 0.5 h. Then the reaction mixture was passed through Celite pad, concentrated under reduced pressure, and then purified using silica gel flash chromatography eluting with 4% EtOAc/hexane to give 2.0 g (4.96 mmol, 91%) allylic azide **39** as colorless oil. R_f (20% EtOAc/hexane)=0.64; $[\alpha]_D^{25}$ +197 (*c* 1.9, CH_2Cl_2); IR (thin film, cm^{-1}) 2953, 2929, 2857, 2099, 1472, 1253, 1098, 835; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36 (m, 5H), 6.10 (d, *J*=10.2 Hz, 1H), 5.92 (ddd, *J*=10.2, 4.8, 1.2 Hz, 1H), 5.17 (d, *J*=1.2 Hz, 1H), 4.90 (d, *J*=11.4 Hz, 1H), 4.68 (d, *J*=11.4 Hz, 1H), 3.72 (ddd, *J*=7.2, 4.8, 1.8 Hz, 1H), 3.68 (m, 2H), 3.63 (dd, *J*=4.8, 3.0, 1.8 Hz, 1H), 1.81–1.89 (m, 1H), 1.69–1.75 (m, 2H), 1.59–1.64 (m, 1H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.8, 133.3, 128.4, 128.1, 127.8, 126.1, 96.8, 75.5, 69.3, 63.1, 55.3, 28.7, 28.6, 26.0, 18.4, −5.2; CIHRMS: calculated for $[C_{21}H_{33}N_3O_6SiNa^+]$: 426.2183, found: 426.2189.

*4.12. (2S,3S,4S,5S,6S)-5-Azido-2-(benzyloxy)-tetrahydro-6-(3-tert-butyldimethylsilyloxypropyl)-2H-pyran-3, 4-diol (**40**)*

To a *tert*-butanol/acetone (13.4 mL, 1:1, 1 M) solution of allylic azide **39** (2.7 g, 6.7 mmol) at 0 °C was added a solution

of (50% w/v) of *N*-methyl morpholine *N*-oxide/water (4 mL). Crystalline OsO_4 (17 mg, 1 mol %) was added and the reaction mixture was stirred for 24 h. The reaction mixture was quenched with 20 mL saturated $Na_2S_2O_3$ solution, extracted with ether (3×200), dried (Na_2SO_4), concentrated under reduced pressure, and then purified using silica gel flash chromatography eluting with 30% EtOAc/hexane to give diol **40** (2.81 g, 6.43 mmol, 96%) as colorless oil. R_f=0.47 (40% EtOAc/hexane); $[\alpha]_D^{25}$ +41 (*c* 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 3426, 2953, 2929, 2858, 2102, 1471, 1077, 835; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.93 (d, *J*= 11.4 Hz, 1H), 4.63 (d, *J*=7.8 Hz, 1H), 4.56 (d, *J*=11.4 Hz, 1H), 4.23 (dd, *J*=4.2, 2.4, 1.2 Hz, 1H), 3.95 (ddd, *J*=7.8, 4.2, 1.2 Hz, 1H), 3.62–3.72 (m, 3H), 3.56 (dd, *J*=3.0, 1.2 Hz, 1H), 2.73 (d, *J*=1.2, 1H), 2.53 (d, *J*=2.4 Hz, 1H), 1.80–1.87 (m, 1H), 1.71–1.77 (m, 1H), 1.57–1.68 (m, 2H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.1, 128.6, 128.3, 128.2, 99.6, 72.5, 70.8, 70.1, 68.9, 63.6, 62.9, 29.3, 27.7, 26.1, 18.4, −5.2; CIHRMS: calculated for $[C_{21}H_{35}N_3O_5SiNa^+]$: 460.2238, found: 460.2243.

*4.13. (3-((3aS,4S,6S,7R,7aS)-7-Azido-4-(benzyloxy)-tetrahydro-2,2-dimethyl-3aH-[1,3]dioxolo[4,5-c]-pyran-6-yl)propoxy)(tert-butyl)dimethylsilane (**41**)*

para-Toluenesulfonic acid monohydrate (61.5 mg, 5 mol %) was added to a stirred solution of diol **40** (2.9 g, 6.6 mmol) and 2,2-dimethoxypropane (18.6 mL) in acetone (99 mL) for 0.5 h at 0 °C. The reaction mixture was quenched with sodium bicarbonate solution (100 mL), removed acetone in vacuo, extracted with Et_2O (3×200 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 5% EtOAc/hexane to give 3.12 g (6.53 mmol, 99%) of colorless oil, acetonide **41**. R_f (20% EtOAc/hexane)=0.67; $[\alpha]_D^{25}$ +96 (*c* 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 2952, 2930, 2857, 2102, 1249, 1049, 835; ^1H NMR (600 MHz, $CDCl_3$) δ 7.27–7.37 (m, 5H), 4.91 (d, *J*=11.4 Hz, 1H), 4.66 (d, *J*= 11.4 Hz, 1H), 4.42 (dd, *J*=5.4, 1.8 Hz, 1H), 4.41 (d, *J*=7.8 Hz, 1H), 4.05 (dd, *J*=7.2, 5.4 Hz, 1H), 3.72 (ddd, *J*=8.4, 4.8, 1.8 Hz, 1H), 3.67 (m, 2H), 3.55 (dd, *J*=1.8, 1.8 Hz, 1H), 1.84–1.90 (m, 1H), 1.65–1.78 (m, 2H), 1.57–1.64 (m, 1H), 1.37 (s, 3H), 1.31 (s, 3H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.2, 128.4, 128.0, 127.8, 109.6, 101.0, 75.8, 74.4, 73.0, 70.1, 62.9, 60.2, 28.7, 29.1, 27.8, 26.3, 26.0, 18.3, −5.2; CIHRMS: calculated for $[C_{24}H_{39}N_3O_5SiNa^+]$: 500.2551, found: 500.2556.

*4.14. 3-((3aS,4S,6S,7R,7aS)-7-Azido-4-(benzyloxy)-tetrahydro-2,2-dimethyl-3aH-[1,3]dioxolo[4,5-c]-pyran-6-yl)propan-1-ol (**42**)*

To a solution of TBS-ether **41** (540 mg, 1.13 mmol) in dry THF (1.1 mL), TBAF (1.3 mL, 1.3 mmol) was added at room temperature under argon atmosphere. After 12 h, the reaction mixture was quenched with sodium bicarbonate solution (500 mL), extracted with Et_2O (3×100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 40% EtOAc/hexane to give alcohol **42** (401 mg, 1.11 mmol, 98%) as colorless oil. R_f=0.45 (40% EtOAc/hexane); $[\alpha]_D^{25}$ +127 (*c* 0.8, CH_2Cl_2); IR (thin film, cm^{-1}) 3434, 2988, 2941, 2875, 2102, 1383, 1221, 1046, 854; ^1H NMR (600 MHz, $CDCl_3$) δ 7.26–7.38 (m, 5H), 4.90 (d, *J*= 11.4 Hz, 1H), 4.66 (d, *J*=11.4 Hz, 1H), 4.42 (dd, *J*=5.4, 1.8 Hz, 1H), 4.41 (d, *J*=7.8 Hz, 1H), 4.06 (dd, *J*=7.8, 5.4 Hz, 1H), 3.73 (ddd, *J*=8.4, 4.8, 1.8 Hz, 1H), 3.67 (m, 2H), 3.55 (dd, *J*=1.8, 1.8 Hz, 1H), 1.88–1.95 (m, 1H), 1.73–1.81 (m, 1H), 1.65–1.71 (m, 2H), 1.37 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.2, 128.4, 128.2, 127.8, 109.7, 101.1, 75.7, 74.3, 73.1, 70.2, 62.5, 60.3, 29.1, 27.8, 26.3; CIHRMS: calculated for $[C_{18}H_{25}N_3O_5Na^+]$: 386.1686, found: 386.1680.

*4.15. 3-((3aS,4S,6S,7R,7aS)-7-Azido-4-(benzyloxy)-tetrahydro-2,2-dimethyl-3aH-[1,3]dioxolo[4,5-c]-pyran-6-yl)propyl methanesulfonate (**43**)*

To a stirred solution of alcohol **42** (1.8 g, 4.95 mmol) and Et_3N (1.5 g, 14.9 mmol) in dry CH_2Cl_2 (4.95 mL) was added dropwise CH_3SO_2Cl (1.7 g, 1.49 mmol) at 0 °C. The reaction mixture was allowed to keep stirring for 0.5 h, and then water 30 mL was added, extracted with Et_2O (3×200 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting crude product was purified using silica gel flash chromatography eluting with 45% EtOAc/hexane to give mesylate **43** (2.14 g, 4.85 mmol, 98%) as a colorless solid. R_f=0.61 (50% EtOAc/hexane); mp: 85–87 °C; $[\alpha]_D^{25}$ +110 (*c* 1.2, CH_2Cl_2); IR (thin film, cm^{-1}) 2988, 2940, 2870, 2104, 1354, 1173, 1051, 832; ^1H NMR (600 MHz, $CDCl_3$) δ 7.26–7.37 (m, 5H), 4.90 (d, *J*=11.4 Hz, 1H), 4.67 (d, *J*=11.4 Hz, 1H), 4.43 (d, *J*=7.8 Hz, 1H), 4.42 (dd, *J*=5.4, 1.8 Hz, 1H), 4.30 (m, 1H), 4.25 (m, 1H), 4.06 (dd, *J*=7.8, 5.4 Hz, 1H), 3.73 (ddd, *J*=8.4, 4.8, 1.8 Hz, 1H), 3.53 (dd, *J*=1.8, 1.8 Hz, 1H), 3.01 (s, 3H), 1.92–2.01 (m, 2H), 1.81–1.89 (m, 1H), 1.67–1.72 (m, 1H), 1.37 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.1, 128.4, 128.0, 127.8, 109.8, 101.2, 75.6, 74.3, 72.5, 70.4, 69.5, 60.1, 37.5, 27.7, 27.4, 26.3, 26.0; CIHRMS: calculated for $[C_{19}H_{27}N_3O_7SNa^+]$: 464.1462, found: 464.1467.

*4.16. (3aR,9S,9aR,9bS)-Octahydro-2,2-dimethyl-[1,3]dioxolo[4,5-a]indolizin-9-ol (**44**)*

To a solution of acetonide **43** (410 mg, 0.928 mmol) in dry EtOH/THF (4 mL, v/v=1:1) was added $Pd(OH)_2/C$ (100 mg) and the mixture was stirred under an atmosphere of H_2 at room temperature. After reacting for 1 day, the mixture was concentrated, simply passed through a short pad of silica gel to remove palladium toxicity byproduct and concentrated again. The resulting residue was dissolved in EtOH/THF (4 mL, v/v=1:1) and $Pd(OH)_2/C$ (200 mg) was added. The suspended mixture was stirred for another 6 days under an atmosphere of H_2 at room temperature. Then the catalyst was filtered off through a short pad of Celite, concentrated under

reduced pressure. The resulting crude product was purified using silica gel flash chromatography eluting with 30% MeOH/EtOAc to give protected (−)-8-*epi*-D-swainsonine **44** (164 mg, 0.769 mmol, 83%) as colorless needles. R_f=0.77 (50% MeOH/EtOAc); $[\alpha]_D^{25}$ −33 (*c* 1.08, CH_2Cl_2); mp: 57.4–59.3 °C; IR (neat, cm^{-1}) 3513, 2982, 2937, 2786, 1464, 1373, 1262, 1209, 1135, 1018; ^1H NMR (600 MHz, $CDCl_3$) δ 4.67 (dd, *J*=6.0, 4.2 Hz, 1H), 4.56 (dd, *J*=6.0, 4.2 Hz, 1H), 3.79 (ddd, *J*=10.9, 8.9, 4.4 Hz, 1H), 3.11 (d, *J*=10.8 Hz, 1H), 2.96 (dt, *J*=10.8, 3.0 Hz, 1H), 2.52 (br s, 1H), 2.09 (dd, *J*=10.8, 4.8 Hz, 1H), 2.00–2.03 (m, 1H), 1.82 (ddd, *J*=10.8, 10.8, 3.6 Hz, 1H), 1.61–1.65 (m, 1H), 1.59 (dd, *J*=9.0, 4.8 Hz, 1H), 1.51 (s, 3H), 1.36–1.40 (m, 1H), 1.28 (s, 3H), 1.21–1.32 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 111.5, 82.0, 78.1, 68.7, 65.8, 60.1, 53.3, 31.4, 25.8, 24.2, 19.7; CIHRMS: calculated for $[C_{11}H_{19}NO_3H^+]$: 214.1443, found: 214.1438.

4.17. (1S,2R,8R,8aR)-Octahydroindolizine-1,2,8-triol (swainsonine **1**)[24]

To a solution of diol **6** (4.0 g, 9.96 mmol) in dry EtOH (40 mL) was added $Pd(OH)_2/C$ (1.5 g) and the mixture was stirred under H_2 at 100 psi pressure for 3 days at room temperature. The catalyst was filtered off through a short pad of Celite, concentrated under reduced pressure. The resulting crude product was applied to ion-exchange chromatography (Dowex 1C 8, 200 mesh, OH^- form) eluting with water. Removal of water in vacuo gave colorless needles D-swainsonine **1** (1.48 g, 8.5 mmol, 86%). R_f=(25% MeOH/$CHCl_3$, 1% NH_4OH(aq))=0.38; mp: 143–144 °C; $[\alpha]_D^{25}$ 80 (*c* 1.1, MeOH); [lit. $[\alpha]_D^{23}$ 74.0 (*c* 0.98, MeOH);[24] $[\alpha]_D^{25}$ 82.6 (*c* 1.03, MeOH);[21b] $[\alpha]_D^{25}$ 73.8 (*c* 0.21, EtOH);[21c] $[\alpha]_D^{25}$ 75.7 (*c* 2.33, MeOH)];[21d] IR (thin film, cm^{-1}) 3287, 2953, 2722, 1639, 1405, 1338, 1141, 1076; ^1H NMR (600 MHz, CD_3OD) 4.26 (ddd, *J*=8.0, 6.0, 2.4 Hz, 1H), 4.24 (m, 1H), 3.83 (ddd, *J*=4.5, 9.3, 10.8 Hz, 1H), 2.95–2.97 (m, 2H), 2.45 (dd, *J*=7.2, 10.2 Hz, 1H), 2.08 (m, 1H), 1.92 (ddd, *J*=11.6, 11.4, 2.8 Hz, 1H), 1.75 (dd, *J*=3.6, 9.6 Hz, 1H), 1.71–1.74 (m, 1H), 1.70 (m, 1H), 1.64 (qt, *J*=13.2, 4.2 Hz, 1H), 1.25 (qd, *J*=12.6, 4.8 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 75.4, 70.9, 70.0, 67.2, 63.3, 53.3, 34.3, 24.7.

To a solution of protected swainsonine (*ent*)-**31** (100 mg, 0.47 mmol) in THF was added 6 N HCl (0.47 mL) at room temperature over night. The resulting mixture was concentrated under reduced pressure and then eluted with water through an ion exchange column (Dowex 1×8, 200 mesh, OH^-, 1 g). Removal of water in vacuo gave colorless needles swainsonine **2** (77.2 mg, 0.45 mmol, 95%). L-Swainsonine **2**: ^1H, ^{13}C NMR and IR data are same as D-swainsonine **1**, mp: 142–143 °C; $[\alpha]_D^{21}$ +75 (*c* 0.92, MeOH); [lit. $[\alpha]_D^{21}$ +84.3 (*c* 1.02, H_2O); $[\alpha]_D^{25}$ +83.3 (*c* 0.5, MeOH)].

4.18. (8R,8aS)-Octahydroindolizin-8-ol (**4**)

To a solution of mesylate **33** (42 mg, 0.1148 mmol) in dry EtOH/THF (0.5 mL, v/v=1:1) was added $Pd(OH)_2/C$ (10 mg) and the mixture was stirred under an atmosphere of H_2 at room temperature. After reacting for 1 day, the mixture was concentrated, simply passed through a short Celite pad to remove by-product and concentrated again. The resulting residue was dissolved in EtOH/THF (0.5 mL, v/v=1:1) and $Pd(OH)_2/C$ (10 mg) was added. The suspended mixture was stirred under H_2 at 100 psi pressure for another 2 days at room temperature. Then the catalyst was filtered off through a short pad of Celite, concentrated under reduced pressure. The resulting crude product was applied to ion-exchange chromatography (Dowex 1×8, 200 mesh, OH^- form) eluting with water. Removal of water in vacuo gave 8-hydroxyindolizidine **4** (11 mg, 0.078 mmol, 68%). R_f=0.25 (MeOH); $[\alpha]_D^{25}$ −7.9 (*c* 0.4, CH3OH); IR (thin film, cm^{-1}) 3365, 2936, 2805, 1639, 1328, 1069; ^1H NMR (600 MHz, CD_3OD) δ 3.32 (ddd, *J*=10.2, 9.0, 4.8 Hz, 1H), 3.06 (ddd, *J*=9.0, 9.0, 3.0 Hz, 1H), 2.99 (m, 1H), 2.21 (q, *J*=9.0 Hz, 1H), 2.11 (dddd, *J*=12.0, 10.2, 6.6, 3.6 Hz, 1H), 1.96–2.01 (m, 2H), 1.70–1.83 (m, 4H), 1.59–1.67 (m, 1H), 1.48–1.57 (m, 1H), 1.22 (dddd, *J*=15.0, 12.6, 10.2, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 73.4, 71.6, 55.1, 52.9, 34.5, 29.2, 25.1, 21.4; CIHRMS: calculated for $[C_8H_{15}NOH^+]$: 142.1232, found: 142.1228.

4.19. (1S,2R,8S,8aR)-Octahydroindolizine-1,2,8-triol ((−)-8-epi-D-swainsonine) (**3**)[22]

To a solution of protected (−)-8-*epi*-D-swainsonine **44** (120 mg, 0.56 mmol) in THF (1.2 mL) was added 6 N HCl (0.59 mL) at room temperature over night. The resulting mixture was concentrated under reduced pressure and then eluted with water through an ion exchange column (Dowex 1×8, 200 mesh, OH^-, 1 g). Removal of water in vacuo gave white powder (−)-8-*epi*-D-swainsonine **3** (92 mg, 0.53 mmol, 94%). R_f=(50% MeOH/EtOAc)=0.31; mp: 89–91 °C [lit. mp: 92–93 °C];[22a] $[\alpha]_D^{25}$ 25 (*c* 0.75, MeOH); [lit. $[\alpha]_D^{25}$ 20 (*c* 0.3, MeOH);[22b] $[\alpha]_D^{25}$ 24.8 (*c* 0.67, MeOH)];[22c] IR (thin film, cm^{-1}) 3360, 2937, 2789, 1645, 1329, 1138, 1013; ^1H NMR (600 MHz, CD_3OD) δ 4.32 (m, 2H), 4.20 (ddd, *J*=7.2, 6.6, 1.8 Hz, 1H), 3.11 (m, 1H), 2.99 (dd, *J*=10.2, 1.8 Hz, 1H), 2.34 (dd, *J*=10.2, 7.2 Hz, 1H), 1.98–2.10 (m, 3H), 1.85–1.88 (m, 1H), 1.44–1.53 (m, 2H); ^{13}C NMR (150 MHz, CD_3OD) δ 74.3, 70.0, 69.5, 67.6, 63.1, 54.4, 32.2, 20.8;[22c,d] CIHRMS: calculated for $[C_8H_{15}NO_3H^+]$: 174.1130, found: 174.1125.

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Supplementary data

Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet. Supplementary data associated with this article

can be found in the online version, at doi:10.1016/j.tet.2007.10.109.

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