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PAPER

Asymmetric total synthesis of (+)-swainsonine†

Soontorn Chooprayoon, Chutima Kuhakarn, Patoomratana Tuchinda, Vichai Reutrakul and Manat Pohmakotr*

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A concise asymmetric synthesis of (+)-swainsonine (*ent*-**1**) is described starting from **2**, which was readily prepared from commercially available L-glutamic acid. The method features installation of the indolizidine ring *via* an intramolecular cyclisation of α-sulfinyl carbanion as a key step. (+)-Swainsonine was obtained in 11.8% overall yield in 10 steps.

Introduction

Polyhydroxylated indolizidine alkaloids have attracted significant attention from the synthetic community due to their interesting structures and potent biological activities.[1,2] Among those, (−)-swainsonine (**1**) (Fig. 1), which was first isolated from the fungus *Rhizoctonia leguminicola*[3] and later found in several plants and fungi,[4] exhibits potent and selective glycosidase inhibitory properties.[5] It has also been tested as a treatment for cancer, HIV and immunological disorders.[6] Its biological importance and interesting structure has triggered a number of synthetic approaches toward the total syntheses of natural occurring (−)-swainsonine (**1**) and its analogues[7,8] as well as (+)-swainsonine (*ent*-**1**) (Fig. 1).[9] These classes of molecule are still attractive targets for organic chemists to develop new synthetic strategies and methodologies.

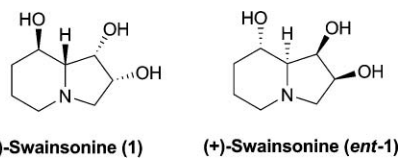

Fig. 1 Structures of (−)-swainsonine (**1**) and (+)-swainsonine (*ent*-**1**).

Our analysis of an efficient route to (+)-swainsonine (*ent*-**1**) evolved from our previously reported work on intramolecular cyclisation of an α-sulfinyl carbanion as a convenient strategy for the preparation of 1-azabicyclic compounds.[10] In the early studies, we demonstrated the synthetic utility of this strategy for syntheses of (±)-tashiromine, (±)-lupinine, (±)-epilupinine, and (±)-indolizidines 167B and 209D.[11,12] To further advance our synthetic methodology, we describe herein a concise asymmetric synthesis of (+)-swainsonine (*ent*-**1**) *via* an intramolecular cyclisation of an α-sulfinyl carbanion.

Department of Chemistry and Center for Innovation in Chemistry, Faculty of Science, Mahidol University, Rama VI Road, Bangkok, 10400, Thailand. E-mail: scmpk@mahidol.ac.th; Fax: +66 2 354 7151; Tel: +66 2 201 5158

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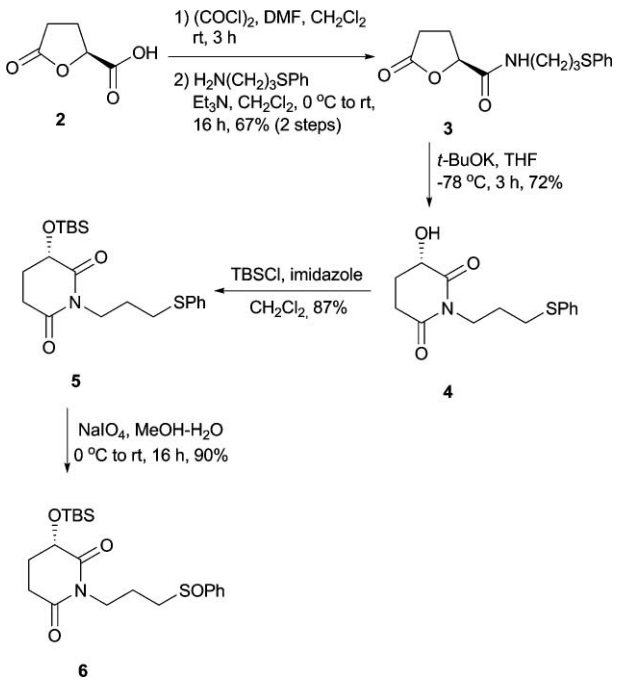
Results and discussion

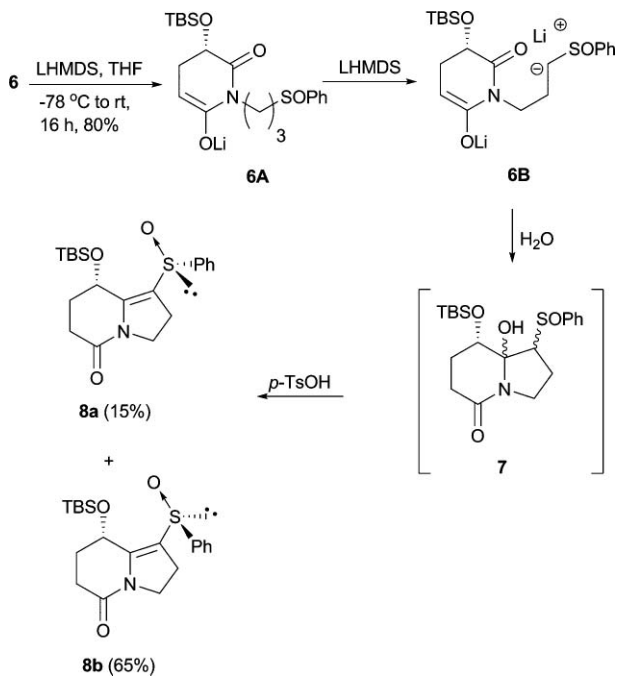
As shown in Scheme 1, the synthesis of (+)-swainsonine (*ent*-**1**) commenced with chiral carboxylic acid **2**, which was readily prepared from L-glutamic acid by following the previously reported procedure.[13] The reaction of the carboxylic acid **2** with oxalyl chloride in the presence of a catalytic amount of DMF followed by treatment with 3-phenylsulfanyl-1-aminopropane afforded amide **3** in 67% yield. The requisite chiral hydroxyimide **4** was obtained in 72% yield by treatment of the amide **3** with *t*-BuOK in THF at −78 °C. The hydroxyl group of **4** was protected with a TBS group under standard conditions which afforded **5** in 87% yield. Subsequent sulfide oxidation with sodium metaperiodate ($NaIO_4$) in aqueous methanol furnished the prerequisite chiral



Scheme 1 Preparation of the starting chiral sulfinylimide **6** from L-glutamic acid.

sulfinylimide **6** in 90% yield as an inseparable mixture of two diastereomers (Scheme 1).

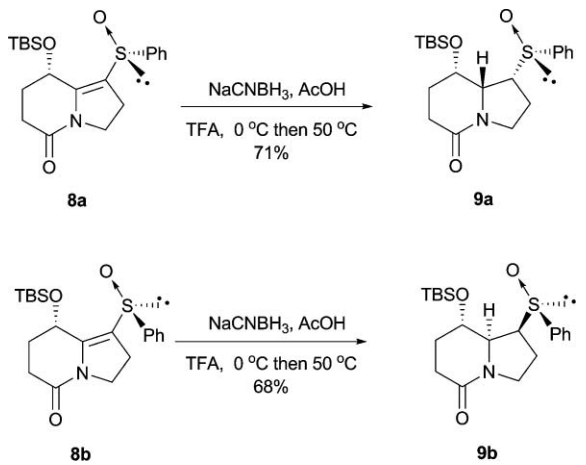
Through extensive investigation of various experimental parameters, particularly the mole equivalents of lithium hexamethyldisilazide (LHMDS) employed, we established that cyclisation of **6** to give **7** required treatment of **6** with 2.2 equiv of LHMDS in THF at −78 C followed by slowly warming up to room temperature for 16 h. Recovery of **6** was observed when LHMDS was utilised in lesser amount. These results implied competitive proton abstraction that occurred preferentially at the α-imide proton rather than the α-proton adjacent to the phenylsulfinyl moiety of sulfinylimide **6**. Therefore, proton abstraction of the initially formed enolate **6A** by a second equivalent of LHMDS gave α-sulfinyl carbanion **6B** which readily underwent cyclisation to yield hydroxyindolizidine amide **7**. Formation of the enolate **6A** was found crucial to protection of the carbonyl group at the 6-position from intramolecular nucleophilic attack by the α-sulfinyl carbanion. On this basis, cyclisation took place chemoselectively at the carbonyl carbon at the 2-position. Without prior purification, the crude residue of hydroxyindolizidine amide **7** was exposed to *p*-TsOH in refluxing CH_2Cl_2 to afford, after column chromatography, **8a** and **8b** in 15% and 65% yields, respectively. Poorer yields were obtained if the reactions were carried out at room temperature even at longer reaction time, leading to **8** in 25–30% yield. The structures of compounds **8a** and **8b** were established by ^{1}H NMR (500 MHz), COSY-45 and HMQC spectra (see ESI†). Since the absolute configurations at the sulfinyl groups of **8a** and **8b** could not be determined, it was tentatively assumed that **8a** and **8b** possessed *R*- and *S*-configurations, respectively, as shown in Scheme 2.



Scheme 2 Intramolecular cyclisation of the α-sulfinyl carbanion derived from **6** to **8a** and **8b**.

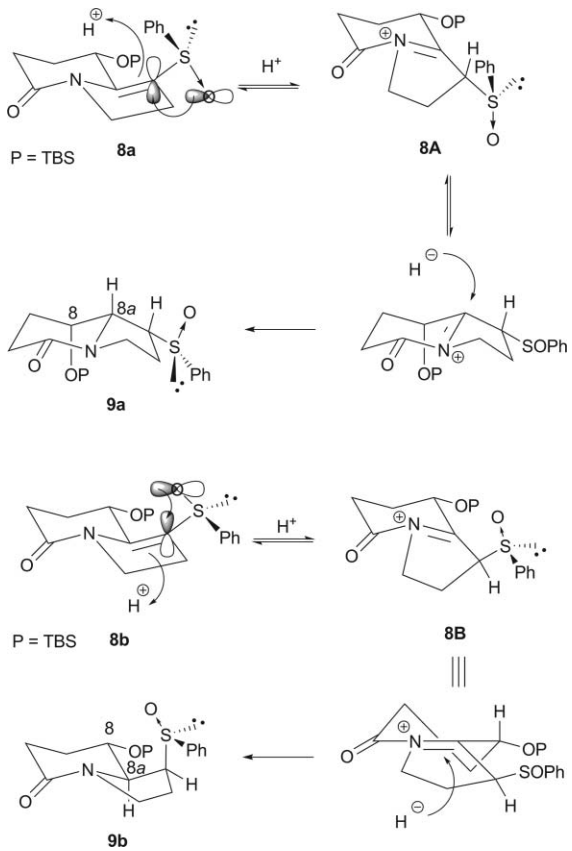
With success at the construction of the core indolizidine structure, conversion of the unsaturated phenylsulfinyl derivatives **8** into the corresponding saturated phenylsulfoxide **9** was attempted. Initially, catalytic hydrogenation of a diastereomeric mixture of **8a** and **8b** [H_2 (1 atm), PtO_2 (cat.), EtOAc, 16 h] gave complete recovery of the starting material. By performing the reaction under 4 atm of H_2, both **8a** and **8b** underwent reductive deoxygenation of the sulfoxide moiety to furnish the corresponding phenylsulfanyl derivative in 58% yield. Similar results were observed when the reaction was performed under 1 atm of H_2 in the presence of 10 mol% of trifluoroacetic acid, affording the phenylsulfanyl derivative in 50% yield.

Efforts to carry out the reduction using Et_3SiH as a hydride source under acidic conditions were briefly investigated. Under the reaction conditions [Et_3SiH (3 equiv), trifluoroacetic acid (2 equiv), 0 C to rt, 16 h], the reaction of **8** as a diastereomeric mixture yielded the required reduction product **9** in only 20% yield along with a complex mixture of unidentified products. The reactions employing $NaBH_4$/MeOH, $NaCNBH_3$/MeOH, $NaCNBH_3$/AcOH or $NaCNBH_3$/AcOH/TFA (10 mol%) at 0 C to room temperature for 16 h did not give the reduction product **9** but led to recovery of the starting material. Thankfully, treatment of **8a** or **8b** using $NaCNBH_3$/AcOH/TFA (10 mol%) at 0 C followed by heating at 50 C for 5 h furnished the respective product **9a** or **9b** in good yields, each as a single isomer (Scheme 3).



Scheme 3 Reduction of **8a** and **8b** to the corresponding sulfoxides **9a** and **9b**.

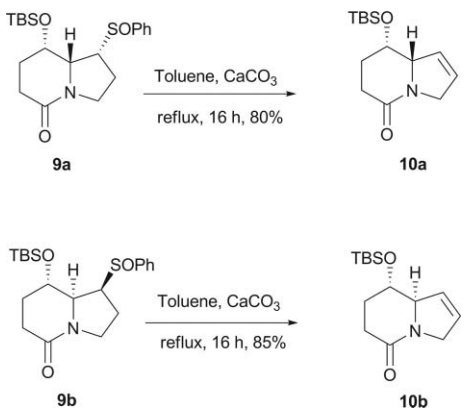
The stereoselectivity of the reduction was realised and the stereochemical outcomes can be rationalized by Cieplak effect as shown in Scheme 4.[14] Facial selection of protonation was governed by homoconjugative assistance of the lone-pair electrons of the oxygen atom of the sulfinyl group (Cieplak effect) and minimized steric interaction between the phenyl group and the silyloxy group. As a result, **8a** underwent protonation leading to an iminium intermediate **8A**. Subsequent trapping by a hydride from the less sterically hindered face furnished the reduction product **9a** whose bridgehead hydrogen is *trans* relative to the silyloxy group. According to the same reasons, protonation of **8b** occurred from the opposite face to that of **8a** leading to an iminium intermediate **8B**. A hydride approaches from the bottom face leading to the reduction product **9b** whose bridgehead hydrogen is *cis* relative to the silyloxy group. The relative stereochemistries at the 8- and 8*a*-position of **9a** and **9b** were assigned by means of NOE experiments (See ESI†). It is worth mentioning that the relative stereochemistries obtained in **9a** and **9b** also supported and were



Scheme 4 Proposed transition states for the reduction of **8a** and **8b** to the corresponding **9a** and **9b**.

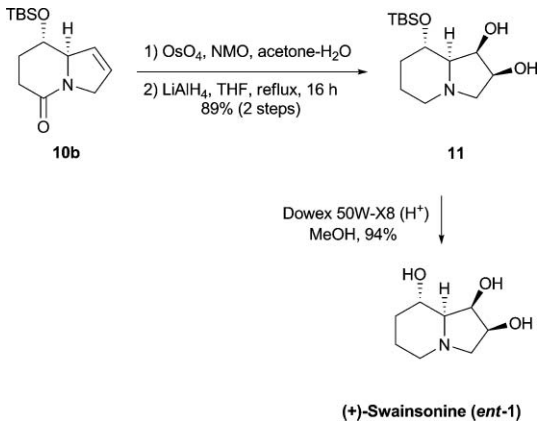
in good agreement with the assumed absolute stereochemistries assigned for the sulfinyl groups of **8a** and **8b**.

Removal of the phenylsulfinyl group in compounds **9a** and **9b** was achieved by pyrolysis under refluxing toluene in the presence of anhydrous $CaCO_3$ to afford the corresponding compounds **10a** and **10b** in 80% and 85% yields, respectively, as shown in Scheme 5. The relative stereochemistries assigned to the 8- and 8*a*-positions of **10a** and **10b** are based upon the NOE experiments (See ESI†).



Scheme 5 Sulfoxide elimination of **9a** and **9b** to **10a** and **10b**.

To complete the synthesis of (+)-swainsonine (*ent*-**1**), *cis*-dihydroxylation of **10b** with NMO and a catalytic amount of OsO_4 in aqueous acetone provided the crude dihydroxylated product. Without chromatographic purification, the crude mixture was subjected to reduction using LAH in refluxing THF to give **11** in 89% yield as a single isomer without contamination of the isomer (Scheme 6). The facial selectivity in the osmylation of **10b** can be rationalised according to Hirama's explanation.[9] It is worth mentioning that facial selection was governed by both 1,3-steric interaction and 1,2-torsional strain. In this case, the oxidizing agent approaches the double bond of **10b** from the face opposite to the two axially oriented allylic hydrogens (H_3 and H_{8a}) to avoid the two 1,2-torsional strain since the 1,3-steric interaction is less important when the reagent is small.



Scheme 6 Conversion of **10b** to (+)-swainsonine (*ent*-**1**).

Finally, removal of the silyl group from protected swainsonine **11** was firstly carried out under standard conditions (TBAF, THF, rt, 16 h). The ^{1}H-NMR spectrum of crude product indicated the characteristic signals of the expected (+)-swainsonine (*ent*-**1**) but it was not possible to isolate it in pure form by using conventional chromatography. Attempted deprotection using KF in aqueous methanol at room temperature for 16 h led to recovery of the starting compound **11**. Fortunately, treatment of **11** with Dowex 50W-X8 (H^+ form) in methanol at room temperature for 24 h afforded 94% yield of (+)-swainsonine (*ent*-**1**). The ^{1}H-NMR data (see ESI†) as well as the optical rotation ($[\alpha]_D^{25}$ +78.97 (*c* 0.63, MeOH)) of our synthesized product were consistent with the values reported in the literature.[9,15] The relative stereochemistries at the 1-, 2-, 8- and 8*a*-positions of (+)-swainsonine (*ent*-**1**) were assigned by the NOE experiments.

Conclusions

The synthesis of (+)-swainsonine (*ent*-**1**) reported here is concise and highly efficient. The synthetic strategy illustrates the utility of α-sulfinyl carbanion cyclisation. We believe that this strategy can be tailored to the preparation of a range of biologically active polyhydroxylated indolizidine and quinolizidine alkaloids by starting from appropriate chiral imides or lactams.

Experimental

General

The ^{1}H NMR spectra were recorded on a Bruker Avance-500 (500 MHz) spectrometer using tetramethylsilane as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker

Avance-500 (125 MHz) using residual non-deuterated solvent peak as an internal standard. Assignments of individual signals were carried out using COSY, HMQC, HMBC, DEPT experiments. The IR spectra were recorded on either a Jasco A-302 or a Perkin Elmer 683 infrared spectrometer. The mass spectra were recorded by using Thermo Finnigan Polaris Q mass spectrometer. The high resolution mass spectra were recorded on an MS Micromass model VQ-TOF2. Melting points were recorded on a Buchi 501 Melting Point Apparatus and were uncorrected. The optical rotations were recorded on a Jasco DIP-370 Digital Polarimeter.

(*S*)-5-Oxotetrahydrofuran-2-carboxylic acid (2)

To a solution of L-glutamic acid (18.0 g, 122.4 mmol) and $NaNO_2$ (9.29 g, 134.6 mmol) in H_2O (120 mL), was slowly added 2 N H_2SO_4 (60 mL) at 0 C. After the mixture was allowed to stir at 0 C for 3 h, it was slowly warmed up to room temperature and stirring was continued for an additional 16 h. The resulting colorless solution was concentrated until a white and sticky mixture was obtained. The mixture was diluted using hot acetone followed by filtration. The filtrate was concentrated to give a colorless viscous liquid which was diluted with EtOAc. The EtOAc solution was stirred in anhydrous Na_2SO_4 at room temperature for 16 h. Filtration and removal of solvent furnished a white solid of compound **2** [7.8 g, 49% yield, m.p. 71.2–72.4 C, $[\alpha]_D^{25}$ +9.17 (*c* 1.1, MeOH)] [Lit.[13b] $[\alpha]_D^{20}$ +10.6 (*c* 5.0, MeOH)]. The spectroscopic data are consistent with the literature.[13b] ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.84 (br s, 1H), 5.04–5.00 (m, 1H), 2.56–2.17 (m, 3H), 2.47–2.39 (m, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 175.9, 173.5, 75.1, 26.6, 25.8. IR (neat): ν 3451 (O–H), 1760 (C═O) cm^{-1}. MS (EI) [*m*/*z* (% relative intensity)]: 131 (M^+ + H, 13), 86 (5), 85 (100), 59 (4), 58 (54), 55 (4).

(*S*)-5-Oxo-*N*-(3-(phenylsulfanyl)propyl)tetrahydrofuran-2-carboxamide (3)

A solution of carboxylic acid **2** (5.7 g, 44.0 mmol) and oxalyl chloride (4.5 mL, 52.8 mmol) in CH_2Cl_2 (100 mL) in the presence of a catalytic amount of *N*,*N*-dimethylformamide (DMF) was stirred at room temperature for 3 h. An excess of oxalyl chloride was removed *in vacuo*. The residue was dissolved in dry CH_2Cl_2 (90 mL). The resulting solution was brought to 0 C followed by addition of triethylamine (7.3 mL, 52.8 mmol) and a solution of 3-(phenylsulfanyl)propan-1-amine (8.8 mL, 52.8 mmol) in CH_2Cl_2 (30 mL) under an argon atmosphere. After being stirred at room temperature overnight (16 h), water (20 mL) was added. Layers were separated and the aqueous phase was extracted with CH_2Cl_2 (4 × 60 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give a white solid of **3** [8.2 g, 67% yield, m.p. 77.3–77.9 C, $[\alpha]_D^{24}$ –7.68 (*c* 0.86, $CHCl_3$)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.35–7.28 (m, 4H), 7.22–7.18 (m, 1H), 6.59 (br s, 1H), 4.83 (t, *J* = 7.1 Hz, 1H), 3.49–3.37 (m, 2H), 2.94 (t, *J* = 7.1 Hz, 2H), 2.67–2.61 (m, 1H), 2.58–2.52 (m, 2H), 2.36–2.26 (m, 1H), 1.90–1.84 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 175.6, 169.3, 135.7, 129.6, 129.0, 126.3, 77.4, 38.3, 31.3, 28.7, 27.5, 25.8. IR (neat): ν 3367 (N–H), 1780 (C═O, lactone), 1652 (C═O, amide) cm^{-1}. MS (EI) [*m*/*z* (% relative intensity)]: 280 (M^+ + H, 46), 279 (M^+, 25), 171 (10), 170 (100), 142 (7), 109 (5). HRMS (ESI-TOF) Calc. for $C_{14}H_{18}NO_3S$ $(M + H)^+$, 280.1007; found, 280.1016.

(*S*)-3-Hydroxy-1-(3-(phenylsulfanyl)propyl)piperidine-2,6-dione (4)

To a suspension of potassium *tert*-butoxide (1.86 g, 16.6 mmol) in THF (10 mL), was added a solution of **3** (8.0 g, 28.7 mmol) in THF (80 mL) at –78 C under an argon atmosphere. After being stirred for 3 h at –78 C, the reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with H_2O (3 × 20 mL), brine (20 mL), dried over anhydrous Na_2SO_4. Filtration followed by removal of solvent gave a crude product, which was purified by column chromatography (SiO_2, 40% EtOAc in hexanes) to give a white solid of **4** [5.8 g, 72% yield, m.p. 76.7–78.3 C, $[\alpha]_D^{24}$ –26.75 (*c* 0.88, $CHCl_3$)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.35–7.26 (m, 4H, Ar*H*), 7.21–7.17 (m, 1H, Ar*H*), 4.21 (ddd, *J* = 12.5, 5.5, 1.3 Hz, 1H, CH_2CHOH), 3.95 (dt, *J* = 13.3, 6.8 Hz, 1H, $NCHHCH_2$), 3.86 (dt, *J* = 13.3, 6.8 Hz, 1H, $NCHHCH_2$), 3.53 (d, *J* = 1.3 Hz, 1H, O*H*), 2.90 (t, *J* = 7.3 Hz, 2H, CH_2SPh), 2.89 (ddd, *J* = 18.0, 4.7, 2.6 Hz, 1H, $COCHHCH_2$) 2.63 (ddd, *J* = 18.0, 13.8, 5.4 Hz, 1H, $COCHHCH_2$), 2.36–2.31 (m, 1H, $CH_2CHHCHOH$), 1.94–1.84 (m, 3H, $CH_2CHHCHOH$ and $NCH_2CH_2CH_2$). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 175.2 (C═O), 171.1 (C═O), 136.0 (C), 129.8 (2 × CH), 128.9 (2 × CH), 126.3 (CH), 68.3 (CH), 39.6 (CH_2), 31.6 (CH_2), 30.8 (CH_2), 27.4 (CH_2), 25.3 (CH_2). IR (film): ν 3460 (O–H), 1731, 1674 cm^{-1}. MS (EI) [*m*/*z* (% relative intensity)]: 280 (M^+ + H, 35), 279 (M^+, 42), 170 (100), 151 (10), 142 (28), 58 (7). HRMS (ESI-TOF) Calc. for $C_{14}H_{18}NO_3S$ $[M + H]^+$, 280.1007; found, 280.0997.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-(3-(phenylsulfanyl)propyl)-piperidine-2,6-dione (5)

To a mixture of **4** (5.5 g, 19.7 mmol), imidazole (2.7 g, 39.0 mmol) and a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP) in CH_2Cl_2 (40 mL) at 0 C under an argon atmosphere, was slowly added a solution of *tert*-butyldimethylchlorosilane (3.54 g, 23.6 mmol) in CH_2Cl_2 (20 mL). After being stirred at room temperature overnight, water (10 mL) was added. The aqueous phase was separated and the organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration followed by removal of solvent gave a crude product, which was purified by column chromatography (SiO_2, 20% EtOAc in hexanes) to give a colourless viscous liquid of **5** [6.74 g, 87% yield, $[\alpha]_D^{24}$ –10.83 (*c* 0.75, $CHCl_3$)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.35–7.33 (m, 2H, Ar*H*), 7.29–7.26 (m, 2H, Ar*H*), 7.19–7.16 (m, 1H, Ar*H*), 4.29 (dd, *J* = 8.0, 4.1 Hz, 1H, CH_2CHOSi), 3.86 (t, *J* = 7.2 Hz, 2H, NCH_2CH_2), 2.93–2.87 (m, 1H, $COCHHCH_2$), 2.88 (t, *J* = 7.5 Hz, 2H, CH_2SPh), 2.59 (ddd, *J* = 17.8, 8.1, 5.3 Hz, 1H, $COCHHCH_2$), 2.06–1.97 (m, 2H, CH_2CH_2CHOSi), 1.85 (quint, *J* = 7.3 Hz, 2H, $NCH_2CH_2CH_2$), 0.96 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H).^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.3 (C═O), 171.8 (C═O), 135.2 (C), 129.7 (2 × CH), 128.9 (2 × CH), 126.1 (CH), 69.3 (CH), 39.0 (CH_2), 31.5 (CH_2), 29.1 (CH_2), 27.5 (CH_2), 26.5 (CH_2), 25.6 (3 × CH_3), 18.2 (C), –4.7(CH_3), –5.4(CH_3). IR (neat): ν 1735, 1685 cm^{-1}; MS (EI) [*m*/*z* (% relative intensity)]: 394 (M^+ + H, 5), 336 (47), 151 (100),

123 (20), 75 (4). HRMS (ESI-TOF) Calc. for $C_{20}H_{32}NO_3SSi$ [M + H]$^+$, 394.1872; found, 394.1795.

(3*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-(3-(phenylsulfinyl)propyl)-piperidine-2,6-dione (6)

A solution of **5** (6.7 g, 17.0 mmol) in MeOH (10 mL) was slowly added to a suspension of $NaIO_4$ (4.0 g, 18.7 mmol) in MeOH (48 mL) and H_2O (12 mL) at 0 C. The mixture was vigorously stirred and slowly warmed up to room temperature overnight (12 h). The precipitates of $NaIO_3$ were filtered and washed with EtOAc (3 × 60 mL). The combined extracts were washed with H_2O (3 × 20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration followed by removal of solvent gave a crude product, which was purified by column chromatography (SiO_2, 70% EtOAc in hexanes) to afford a colourless viscous liquid of **6** as a mixture of two diastereomers (6.3 g, 90% yield). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.63–7.61 (m, 4H), 7.53–7.49 (m, 6H), 4.31–4.29 (m, 2H), 3.92–3.82 (m, 4H), 2.9–2.74 (m, 6H), 2.63–2.60 (m, 2H), 2.09–1.94 (m, 6H), 1.88–1.79 (m, 2H), 0.90 and 0.86 (s each, 18H), 0.14 and 0.13 (s each, 12H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.46, 172.44, 171.85, 171.77, 143.6, 130.95, 130.93, 129.2, 124.02, 124.01, 69.22, 69.20, 54.74, 54.67, 38.58, 38.52, 29.14, 29.08, 26.4, 25.6, 21.1, 18.2, –4.7, –5.4. IR (neat): ν 1732, 1682 cm^{-1}. MS (EI) [*m*/*z* (% relative intensity)]: 410 (M$^+$ + H, 6), 352 (42), 284 (21), 226 (53), 167 (100), 143 (11), 109 (9). HRMS (ESI-TOF) Calc. for $C_{20}H_{32}NO_4SSi$ [M + H]$^+$, 410.1821; found, 410.1833.

(8*S*)-8-(*tert*-Butyldimethylsilyloxy)-1-(phenylsulfinyl)-2,3,7,8-tetrahydroindolizin-5(6*H*)-ones (8a) and (8b)

A solution of **6** (6.2 g, 15 mmol) in THF (18 mL) was added dropwise to a cooled (–78 C) THF (100 mL) solution of LiHMDS [prepared by reacting *n*-BuLi (1.35 M in hexane; 25 mL, 33.75 mmol) with a solution of hexamethyldisilazane (HMDS) (7.6 mL, 36.4 mmol) in THF (40 mL) at –78 C for 45 min] under an argon atmosphere. The resulting mixture was stirred and slowly warmed up from –78 C to room temperature overnight (15 h). The resulting yellow solution was quenched with H_2O (20 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with H_2O (3 × 20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration followed by removal of solvents furnished a crude residue of hydroxyindolizidine amide **7** (4.9 g) which was used in the next step without prior purification. A crude residue of **7** (4.9 g) was diluted with CH_2Cl_2 (50 mL). To the resulting solution was added a catalytic amount of *p*-TsOH and the mixture was brought to refluxing temperature under an argon atmosphere for 16 h. The resulting solution was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 70 mL). The combined organic extracts were washed with H_2O (3 × 20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration followed by removal of solvent gave a crude product, which was purified by column chromatography (SiO_2, 100% EtOAc) to afford colourless viscous liquid of **8a** (0.71 g, 15% yield) and **8b** (3.07 g, 65% yield).

F_1 (less polar) was obtained as a colourless viscous liquid of **8a**; $[\alpha]_D^{25}$ +40.04 (*c* 1.17, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.55–7.48 (m, 5H), 5.20 (dd, *J* = 4.0, 2.2 Hz, 1H), 3.91 (ddd, *J* = 12.0, 12.0, 5.6 Hz, 1H), 3.76 (ddd, *J* = 12.0, 12.0, 8.2 Hz, 1H), 2.94–2.85 (m, 2H), 2.47 (ddd, *J* = 17.3, 4.8, 2.8 Hz, 1H), 2.17–2.12 (m, 1H), 2.07 (ddd, *J* = 15.7, 11.5, 8.2 Hz, 1H), 1.88–1.84 (m, 1H), 0.94 (s, 9H), 0.29 (s, 3H), 0.28 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.9, 148.8, 142.2, 130.6, 129.2, 124.2, 120.8, 60.0, 44.3, 28.8, 27.1, 25.7, 22.2, 18.0, –4.4, –4.8. IR ($CHCl_3$): ν 1667, 1627 cm^{-1}. MS (EI) [*m*/*z* (% relative intensity)]: 391 (M$^+$, 0.3), 334 (100), 229 (86), 225 (88), 210 (45), 188 (43), 150 (40), 75 (34); HRMS (ESI-TOF) Calc. for $C_{20}H_{30}NO_3SSi$ [M + H]$^+$, 392.1716; found, 392.1722.

F_2 (more polar) was obtained as a colourless viscous liquid of **8b**; $[\alpha]_D^{25}$ –32.82 (*c* 1.01, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.58–7.50 (m, 2H), 7.49–7.29 (m, 3H), 5.18–5.17 (m, 1H), 3.87 (ddd, *J* = 12.0, 12.0, 6.7 Hz, 1H), 3.78 (ddd, *J* = 12.0, 12.0, 7.1 Hz, 1H), 2.83 (ddd, *J* = 16.1, 11.8, 7.1 Hz, 1H), 2.74 (ddd, *J* = 17.0, 12.5, 4.9 Hz, 1H), 2.44 (dt, *J* = 17.2, 3.8 Hz, 1H), 2.08–2.00 (m, 2H), 1.97–1.90 (m, 1H), 0.90 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.7, 149.6, 141.6, 130.2, 129.0, 124.4, 120.4, 60.7, 44.3, 28.5, 27.0, 25.6, 22.2, 17.8, –4.40, –4.36. IR ($CHCl_3$): ν 1671, 1628 cm^{-1}. MS (EI) [*m*/*z* (% relative intensity)]: 391 (M$^+$, 0.8), 334 (87), 225 (100), 170 (12), 125 (10); HRMS (ESI-TOF) Calc. for $C_{20}H_{30}NO_3SSi$ [M + H]$^+$, 392.1716; found, 392.1704.

(1*R*,8*S*,8*aR*)-8-(*tert*-Butyldimethylsilyloxy)-1-((*R*)-phenylsulfinyl)hexahydroindolizin-5(1*H*)-one (9a)

To a solution of **8a** (0.7 g, 1.8 mmol) in AcOH (5 mL) in the presence of a catalytic amount of TFA (0.02 mL) at 0 C under an argon atmosphere, $NaCNBH_3$ (0.4 g, 5.3 mmol) was gradually added over 15 min. The mixture was stirred at 50 C for 5 h. The resulting mixture was diluted with 1 N NaOH (5 mL) and H_2O (5 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration followed by removal of solvent gave a crude product, which was purified by column chromatography (SiO_2, 100% EtOAc) to afford a colourless viscous liquid of **9a** [0.5 g, 71% yield; 76% yield calculated based on the recovered **8a**, $[\alpha]_D^{25}$ –90.07 (*c* 0.95, $CHCl_3$)] and **8a** (34 mg). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.67–7.65 (m, 2H), 7.58–7.52 (m, 3H), 4.55 (dt, *J* = 5.6, 3.0 Hz, 1H), 4.14 (ddd, *J* = 11.5, 8.6, 5.6 Hz, 1H), 3.77 (dd, *J* = 7.0, 3.1 Hz, 1H), 3.33 (app. q, *J* = 7.1 Hz, 1H), 3.26 (ddd, *J* = 11.5, 8.2, 6.7 Hz, 1H), 2.58 (dt, *J* = 17.7, 7.8 Hz, 1H), 2.43–2.33 (m, 2H), 2.22–2.15 (m, 1H), 1.95–1.87 (m, 2H), 0.99 (s, 9H), 0.27 (s, 3H), 0.22 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.6, 144.6, 131.1, 129.4, 124.5, 66.4, 66.1, 62.7, 44.9, 29.3, 27.7, 26.1, 22.2, 18.2, –3.8, –4.2. IR ($CHCl_3$): ν 1635 (C═O) cm^{-1}. MS (EI) [*m*/*z* (% relative intensity)]: 394 (M$^+$ + H, 6), 336 (68), 268 (57), 210 (50), 136 (100), 73 (43). HRMS (ESI-TOF) Calc. for $C_{20}H_{32}NO_3SSi$ [M + H]$^+$, 394.1872; found, 394.1865.

(1*S*,8*S*,8*aS*)-8-(*tert*-Butyldimethylsilyloxy)-1-((*S*)-phenylsulfinyl)-hexahydroindolizin-5(1*H*)-one (9b)

By following the procedure described for **9a**, a solution of **8b** (2.9 g, 7.4 mmol) in AcOH (20 mL) in the presence of a catalytic amount of TFA (0.01 mL) at 0 C was treated with $NaCNBH_3$ (4.9 g, 22.2 mmol) to give a crude product, which was purified by column chromatography (SiO_2, 100% EtOAc) to afford **8b** (0.2 g) and a colourless viscous liquid of **9b** [1.97 g, 68% yield; 75% yield

based on recovered **8b**, $[\alpha]_D^{25}$ +132.14 (*c* 1,05, $CHCl_3$)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.70–7.68 (m, 2H), 7.56–7.29 (m, 3H), 4.80 (ddd, *J* = 10.4, 8.1, 3.8 Hz, 1H), 3.82 (dd, *J* = 8.2, 4.1 Hz, 1H), 3.54 (dd, *J* = 6.1, 4.3 Hz, 1H), 3.29 (t, *J* = 10.6 Hz, 1H), 3.16 (dd, *J* = 18.5, 9.3 Hz, 1H), 2.55 (ddd, *J* = 17.8, 5.6, 3.4 Hz, 1H), 2.44 (ddd, *J* = 17.8, 11.9, 5.8 Hz, 1H), 2.16–2.10 (m, 1H), 1.94–1.73 (m, 3H), 0.94 (s, 9H), 0.29 (s, 3H), 0.19 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.3, 142.0, 132.1, 129.3, 125.6, 67.7, 66.6, 66.0, 43.0, 31.1, 29.6, 25.8, 23.7, 17.9, –4.4. IR ($CHCl_3$): ν 1635 (C═O) cm^{-1}. MS (EI) [*m*/*z* (% relative intensity)]: 394 (M^+ + H, 5), 336 (60), 268 (64), 210 (78), 136 (100), 108 (30), 73 (41). HRMS (ESI-TOF) Calc. for $C_{20}H_{32}NO_3SSi$ [M + H]$^+$, 394.1872; found, 394. 1909.

(8*S*,8*aS*)-8-(*tert*-Butyldimethylsilyloxy)-6,7,8,8*a*-tetrahydroindolizin-5(3*H*)-one (10a)

A toluene (5 mL) solution of **9a** (0.38 g, 0.97 mmol) in the presence of $CaCO_3$ (30 mg) was stirred at reflux under an argon atmosphere for 16 h. $CaCO_3$ was filtered off and the filtrate was evaporated to dryness to give a crude product, which was purified by preparative thin-layer chromatography (SiO_2, 100% EtOAc) to give a colourless viscous liquid of **10a** [0.21 g, 80% yield, $[\alpha]_D^{25}$ –53.73 (*c* 1.10, $CHCl_3$)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.93–5.90 (m 1H), 5.69–5.66 (m, 1H), 4.53–4.48 (m, 1H), 4.37–4.35 (m, 1H), 4.24–4.22 (m, 1H), 4.05–4.01 (m, 1H), 2.49 (dt, *J* = 17.8, 9.1 Hz, 1H), 2.40 (ddd, *J* = 17.8, 6.7, 4.3 Hz), 1.94–1.90 (m, 2H), 0.82 (s, 9H), 0.05 (s, 3H), 0.08 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.3, 127.3, 127.0, 68.9, 65.1, 53.3, 28.7, 26.7, 25.5, 17.9, –4.6, –4.9. IR ($CHCl_3$): ν 1639 (C═O) cm^{-1}. MS (EI) [*m*/*z* (% relative intensity)]: 267 (M^+, 9), 242 (46), 224 (57), 210 (92), 196 (45), 150 (81), 122 (36), 81 (39), 75 (100). HRMS (ESI-TOF) Calc. for $C_{14}H_{26}NO_2Si$ [M + H]$^+$, 268.1733; found, 268.1730.

(8*S*,8*aR*)-8-(*tert*-Butyldimethylsilyloxy)-6,7,8,8*a*-tetrahydroindolizin-5(3*H*)-one (10b)[9]

According to the procedure described for **10a**, a toluene (15 mL) solution of **9b** (1.97 g, 5.0 mmol) in the presence of $CaCO_3$ (100 mg) was stirred at reflux under an argon atmosphere for 16 h. Purification by preparative thin-layer chromatography (SiO_2, 100% EtOAc) yielded a colourless viscous liquid of **10b** [1.07 g, 80% yield, $[\alpha]_D^{25}$ –53.73 (*c* 1.10, $CHCl_3$)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.96–5.90 (m, 2H), 4.50–4.46 (m, 1H), 4.17–4.14 (m, 1H), 4.06–4.03 (m, 1H), 3.57 (td, *J* = 9.5, 5.2 Hz, 1H), 2.63 (ddd, *J* = 17.8, 8.5, 3.6 Hz, 1H), 2.42 (dt, *J* = 17.9, 8.5 Hz, 1H), 2.05–1.99 (m, 1H), 1.84–1.75 (m, 1H), 0.90 (s, 9H), 0.08 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.4, 128.5, 126.7, 71.1, 69.1, 53.2, 30.2, 29.7, 25.6, 17.9, –4.3, –4.8. IR ($CHCl_3$): ν 1638 (C═O), 1613 cm^{-1}. MS (EI) [*m*/*z* (% relative intensity)]: 267 (M^+, 9), 210 (100) 196 (29), 150 (44), 122 (29), 81 (31), 75 (71). HRMS (ESI-TOF) Calc. for $C_{14}H_{26}NO_2Si$ [M + H]$^+$, 268.1733; found, 268.1741.

(1*R*,2*S*,8*S*,8*aR*)-8-(*tert*-butyldimethylsilyloxy)-octahydroindolizine-1,2-diol (11)

To a solution of **10b** (0.47 g, 1.75 mmol) in a 3 : 1 mixture of acetone–H_2O (6 mL) was added *N*-methylmorpholine *N*-oxide (0.48 g, 3.5 mmol) and 4% aqueous OsO_4, (1.0 mL). The reaction mixture was stirred at room temperature for 3 h. After addition of aqueous $NaHSO_3$ solution (3 mL), the mixture was stirred for an additional 1 h at room temperature and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. Filtration followed by removal of solvent gave the corresponding dihydroxlated product, which was used in the next step without purification.

To a suspension of $LiAlH_4$ (0.4 g, 10.5 mmol) in THF (30 mL), the crude dihydroxylated product was added. The mixture was heated at reflux for 16 h. Under ice cooling, the mixture was quenched by careful addition of water (4.0 mL) and 1 N NaOH (4.0 mL). The resulting mixture was filtered over a celite pad and the filtrate was concentrated to afford a viscous liquid of **11** [0.45 g, 89% yield, $[\alpha]_D^{25}$ +29.34 (*c* 1.06, $CHCl_3$)]. ^{1}H-NMR (500 MHz, CD_3OD): δ 4.19 (ddd, *J* = 7.9, 5.8, 2.3 Hz, 1H), 4.07 (dd, *J* = 5.9, 3.5 Hz, 1H), 3.89 (ddd, *J* = 10.3, 9.0, 4.8 Hz, 1H), 2.89 (br d, *J* = 2.3 Hz, 1H), 2.87 (br d, *J* = 2.3 Hz, 1H), 2.42 (dd, *J* = 10.5, 7.8 Hz, 1H), 1.98–194 (m, 1H), 1.85 (td, *J* = 11.4, 3.1 Hz, 1H), 1.74 (dd, *J* = 8.9, 3.5 Hz, 1H), 1.66–1.51 (m, 2H), 1.23–1.14 (m, 1H), 0.89 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H). ^{13}C-NMR (125 MHz, CD_3OD): δ 75.5, 70.9, 70.0, 68.4, 63.0, 53.2, 35.2, 26.4, 24.5, 18.8, –4.1, –4.5. IR (KBr): 3399 (O–H), 1472, 1247, 1112 cm^{-1}. MS (EI) [*m*/*z* (% relative intensity)]: 288 (M^+ + H, 3), 230 (100), 212 (32), 138 (20), 120 (52), 116 (30), 75 (16). HRMS (ESI-TOF) Calc. for $C_{14}H_{30}NO_3Si$ [M + H]$^+$, 288.1995; found, 288.1961.

(+)-Swainsonine (*ent*-1)

A mixture of **11** (90 mg, 0.31 mmol) and a cation exchange resin, Dowex 50W-X8 (H^+ form), in MeOH was stirred at room temperature for 24 h. The resin was filtered off and washed with 10% NH_4OH (30 mL). The filtrate was evaporated to dryness followed by lyophilization to give a white solid of (+)-swainsonine (*ent*-**1**) [51 mg, 94% yield, m.p. 140–143 C, $[\alpha]_D^{25}$ +78.97 (*c* 0.63, MeOH): Lit.[9] m.p. 143–145 C, $[\alpha]_D$ +83.3 (*c* 0.5, MeOH); Lit.[15b] m.p. 142–143 C, $[\alpha]_D$ +84.3 (*c* 1.02, H_2O)].

^{1}H-NMR (500 MHz, CD_3OD): δ 4.25–4.19 (m, 2H), 3.79 (ddd, *J* = 11.2, 10.1, 4.6 Hz, 1H), 2.96–2.93 (m, 2H), 2.48 (dd, *J* = 10.4, 7.5 Hz, 1H), 2.04–2.01 (m, 1H), 1.96 (td, *J* = 11.9, 2.5 Hz, 1H), 1.82 (dd, *J* = 9.1, 3.0 Hz, 1H), 1.70–1.68 (m, 1H) 1.64–1.55 (m, 1H), 1.22 (qd, *J* = 12.9, 4.6 Hz, 1H). ^{13}C-NMR (125 MHz, CD_3OD): δ 75.1, 70.6, 69.8, 66.8, 62.8, 53.0, 33.9, 24.3. IR (neat): ν 3367 (O–H), 1643, 1448, 1384, 1145, 1084 cm^{-1}. MS (EI) [*m*/*z* (% relative intensity)]: 173 (M^+, 5), 155 (36), 120 (17), 110 (27), 96 (100), 84 (26), 68 (12). HRMS (ESI-TOF): Calc. for $C_8H_{16}NO_3$ [M + H]$^+$, 174.1125; found, 174.1150.

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