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A facile synthesis of 1,4-dideoxy-1,4-imino-L-ribitol (LRB) and (−)-8a-*epi*-swainsonine from D-glutamic acid

Xiao-Ling Wang [a], Wen-Feng Huang [a], Xin-Sheng Lei [b,*], Bang-Guo Wei [a,*], Guo-Qiang Lin [a,b]

[a] Department of Chemistry and Institutes of Biomedical Sciences, Fudan University, 220 Handan Road, Shanghai 200433, China
[b] School of Pharmacy, Fudan University, 826 Zhangheng Road, Shanghai 201203, China

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ABSTRACT

A facile synthesis of (−)-8a-*epi*-swainsonine **2** and 1,4-dideoxy-1,4-imino-L-ribitol (LRB) **4** has been achieved by using the versatile building block **3**, which was available from cheap D-glutamic acid. The new forming stereogenic center in synthesis of **2** was constructed by highly selective reduction of the ketone **13** with Li(*t*-BuO)$_3$AlH in THF (dr=95:5).

1. Introduction

(−)-Swainsonine **1** (see Fig. 1) was firstly isolated from the fungus *Rhizoctonia leguminicola*[1] and subsequently found in the Australian plant *Swainsona canescens*[2] and also other plant[3] and fungi.[4] (−)-Swainsonine **1** exhibits lysosomal *R*-mannosidase and mannosidase II inhibitory properties[5] and shows to be a potent inhibitor of cancer, HIV, and immunological disorders.[6] Currently, (−)-swainsonine **1** is under phase II clinical trials as an anticancer drug.[7] Due to its promising biological activities and intriguing structure, the study for (−)-swainsonine **1** has attracted considerable attention, and a number of synthetic approaches have been reported.[8] Additionally, the relative analogues have been confirmed to exhibit different activities compared with swainsonine **1**.[9] For example, (−)-8a-*epi*-swainsonine has also been demonstrated to be an effective inhibitor of lysosomal *R*-D-mannosidase, with 93% potency of swainsonine **1**.[9b] Thus, unnatural diastereomers of swainsonine have become attractive synthetic targets and several synthetic routes for preparation of 8a-*epi*-swainsonine have been published.[10]

Among these synthetic approaches for swainsonine and its analogues, the most challenging part is the asymmetric construction of indolizidine unit bearing four chiral centers. Recently, we have been devoted to exploring some multifunctional building blocks and utilizing them in the asymmetric synthesis of some natural products, including bioactive piperidine alkaloids and depsipeptides.[11] In 2010, an efficient method for preparation of (2*S*,3*S*,4*S*)-3,4-dihydroxy-5-(hydroxymethyl)pyrrolidine lactam **3** and its application for synthesis of ceramide sphingolipid have been reported by our group.[12] As part of this program aiming at the synthesis of polyhydroxylated indolizidine alkaloids, azasugars and their analogues, we have developed a concise approach for stereoselective synthesis of (−)-8a-*epi*-swainsonine **2** and 1,4-dideoxy-1,4-imino-L-ribitol **4**.[13,14] Herein we describe this convenient method for synthesis of these two compounds using lactam **3** as a chiral building block (Scheme 1).

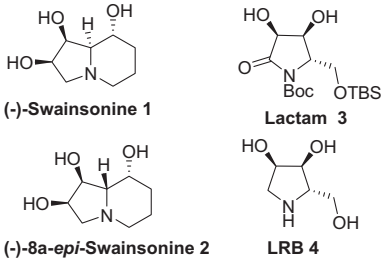

Fig. 1. The structures of (−)-swainsonine and (−)-8a-*epi*-swainsonine.

2. Results and discussion

As shown in Scheme 2, the lactam **3** would be a desirable building block for the synthesis of (−)-8a-*epi*-swainsonine **2** and LRB **4**. Protection of the two hydroxyl groups of lactam **3** with 2,2-dimethoxypropane (DMP) afforded the compound **7** in 96% yield. Then, the

* Corresponding authors. E-mail address: bgwei1974@fudan.edu.cn (B.-G. Wei).

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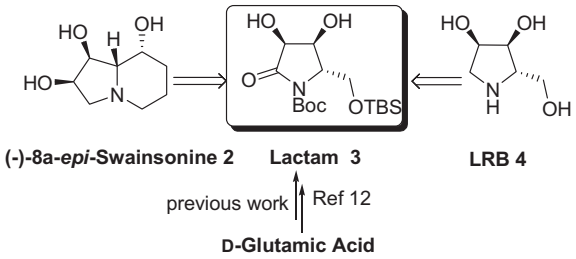
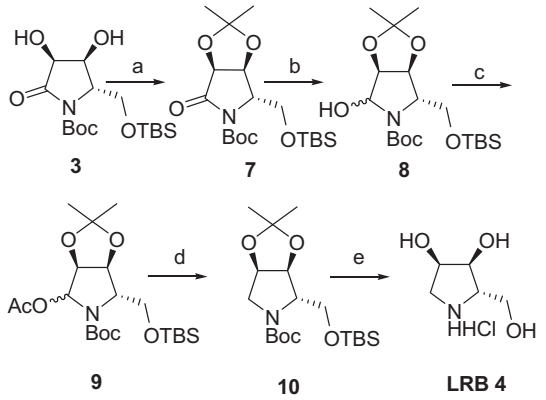


Scheme 1. Synthetic strategy of (−)-8a-*epi*-swainsonine **2** and LRB **4**.

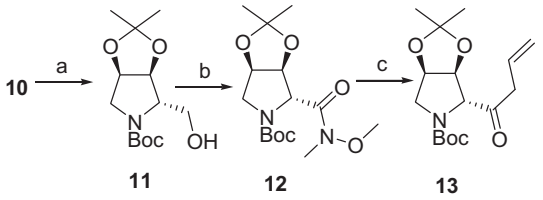


Scheme 2. Asymmetric synthesis of LRB **4**. Reagents and conditions: a. *p*-TsOH, DMP, acetone, 0 °C to rt, 3 h, 96%; b. $LiEt_3BH$, THF, −78 °C, 30 min; c. DMAP, Et_3N, acetic anhydride, DCM, 0 °C to rt, 10 h, 94% two steps; d. Triethylsilane, $BF_3{\cdot}Et_2O$, DCM, −78 °C, 5 h, 85%; e. $(COCl)_2$, MeOH, rt, 2 days, 59%.

regioselective reduction of carbonyl was examined. While $BH_3{\cdot}SMe_2$ was used as reducing agent, the reduction of compound **7** only gave a small quantity of corresponding amide **10** in 23% yield. Therefore, an indirect approach for selective reduction of carbonyl was examined. Although the imide of piperidine was easily converted to the corresponding alcohol in $NaBH_4$/MeOH system,[11b] this reductive condition was not effective for the reduction of the imide **7**. Gratefully, when $LiBEt_3H$ was used, the imide **7** was easily converted to alcohol **8** at −78 °C in quantitative yield as diastereomers. The following reduction of alcohol **8** with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ gave compound **10** in a low yield (41%). However, acetylation (Ac_2O, TEA, DMAP) of compound **8** and subsequent reduction ($BF_3{\cdot}Et_2O$, Et_3SiH) could give the corresponding protective LRB **10** {$[\alpha]_D^{25}$ +66.2 (*c* 1.0, $CHCl_3$); lit.[15] $[\alpha]_D^{25}$ +60.2 (*c* 0.3, $CHCl_3$)} in 81% overall yield. Finally, removal of protective group by $(COCl)_2$/MeOH system gave 1,4-dideoxy-1,4-imino-L-ribitol **4**·HCl {$[\alpha]_D^{25}$ −50.9 (*c* 0.52, H_2O); lit.[14l] $[\alpha]_D^{25}$ −52 (*c* 0.41, H_2O) } in 59% yield. The spectroscopic and physical data of the synthetic LRB **4** were identical with the reported data.[14l] Thus, a very concise method for the asymmetric synthesis of LRB **4** was established based on the lactam **3**.

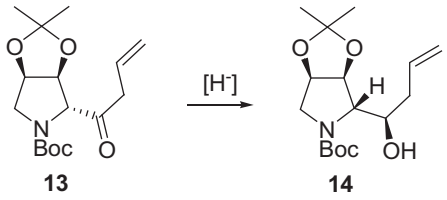
To synthesize (−)-8a-*epi*-swainsonine **2** in an asymmetric way, the following synthetic route was explored. Removal (TBAF, THF) of the protective group of amide **10** gave primary alcohol **11** in 90% yield. Then, the oxidation of compound **11** with $NaIO_4$ and $RuCl_3{\cdot}xH_2O$,[16] followed by subsequent treatment of the resulting compound with *N*-methoxymethanamine hydrochloride in the presence of HOBt and EDCI gave Weinreb amide[17] **12** as a colorless oil in 74% overall yield. Treatment of compound **12** with allylmagnesium chloride at −78 °C generated the corresponding ketone **13** in 76% yield[18] (Scheme 3).

In seeking a method for the diastereoselective reduction of carbonyl for compound **13**, various conditions were tested, and the results were summarized in Table 1. The table showed that when $NaBH_4$ was used, the reaction smoothly occurred and produced secondary alcohol **14** in 82% yield with low diastereoselectivity



Scheme 3. Asymmetric synthesis of **13**. Reagents and conditions: a. TBAF, THF, 0 °C to rt, 2 h, 90%; b. (i) $NaIO_4$, $RuCl_3{\cdot}xH_2O$, CH_3CN, H_2O, rt, 5 h; (ii) MeO(Me)NH·HCl, EDCI, HOBt, *i*-Pr_2NEt, DCM, rt, 16 h, 74% two steps; c. Allylmagnesium chloride, THF, −78 °C to rt, 5 h, 76%.

Table 1
The *anti* diastereoselective reduction of **13**



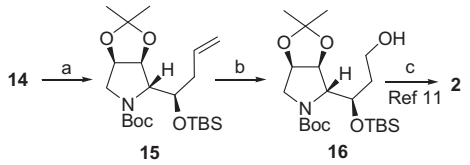
Entry[a]	Solvent	*T* °C	[H⁻]	Y[b] %	*anti*/*cis*[c]
1	EtOH	20	$NaBH_4$	82	53:47
2	EtOH	−78	$NaBH_4$	71	64:36
3[d]	THF	−78	$LiEt_3BH$	73	71:29
4	PhMe	−78	DIBAL-H	84	67:33
5[e]	EtOH	−78	Li(*t*-BuO)$_3$AlH	76	78:22
6[f]	THF	−78	Li(*t*-BuO)$_3$AlH	81	95:5

[a] The reaction was performed with 2.0 mmol reductive reagents and 1 mmol ketone **13**.
[b] Combined yield of *cis*/*trans* products.
[c] All the diastereoselectivity was examined by HPLC.
[d] THF, −78 °C, 0.5 h.
[e] EtOH, −78 °C, 4 h.
[f] THF, −78 °C, 4 h.

(entry 1), even at low temperature (entry 2). $LiEt_3BH$ and DIBAL-H were also screened and the results showed that the reaction occurred smoothly under all these conditions, while the diastereoselectivity of product **14** were not significantly increased (entries 3 and 4). Although the diastereoselective chelation-controlled reduction of the ketone by using Li(*t*-OBu)$_3$AlH[19] could produce high diastereoselectivity, the result **14** was dissatisfying (entry 5) when the reaction took place in EtOH. Interestingly, when THF was used under the same condition, the reaction gave an encouraging result with high diastereoselectivity (*anti*/*cis*=95:5, entry 6).

Finally, we turned our attention to explore the asymmetric synthesis of (−)-8a-*epi*-swainsonine **2**. Protection of secondary alcohol **14** as its TBS ether (TBSOTf, 2,6-lutidine) gave compound **15** in 75% yield. Next, hydroboration of compound **15** with $BH_3{\cdot}SMe_2$ in tetrahydrofuran at room temperature followed by oxidation of resulting intermediate with H_2O_2 smoothly gave primary alcohol **16** in 64% overall yield. Then treatment of compound **16** with methanesulfonyl chloride in the presence of pyridine gave crude product without further purification. Removal of protective group with TMSOTf/2,6-lutidine and subsequent cyclization of the resulting crude product gave the protective (−)-8a-*epi*-swainsonine in one-pot manner, which was not easily purified due to the minor 2,6-lutidine. In the end, the removal of protective (−)-8a-*epi*-swainsonine with MeOH/$(COCl)_2$ gave **2** {$[\alpha]_D^{25}$ −63.4 (*c* 1.02, MeOH); lit.[10f] $[\alpha]_D^{25}$ −64 (*c* 1, MeOH); lit.[10g] $[\alpha]_D^{25}$ −63 (*c* 0.95, MeOH)} in 76% overall yield according to the references.[10] The spectroscopic and physical data of the synthetic (−)-8a-*epi*-swainsonine **2** were identical with the reported data.[10f,g] Thus, a novel convenient method for the asymmetric synthesis of (−)-8a-

epi-swainsonine **2** was also established based on the versatile building block **3** (Scheme 4).



Scheme 4. Asymmetric synthesis of (−)-8a-*epi*-swainsonine **2**. Reagents and conditions: a. 2,6-lutidine, TBSOTf, DCM, 0 °C to rt, 4 h, 75%; b. $BH_3{\cdot}SMe_2$, THF, 0 °C to rt, 8 h, then NaOH (3 M), H_2O_2 (30%), 0 °C, 1 h, 64%. c. (i) MsCl, Py, rt, 1 h (ii) 2,6-lutidine, TMSOTf, DCM, 24 h (iii) $(COCl)_2$, MeOH, 0 °C to rt, 12 h, 76% three steps.

3. Conclusions

In summary, an efficient approach for synthesis of (−)-8a-*epi*-swainsonine **2** has been developed based on the versatile building block **3**. In addition, a convenient method for synthesis of 1,4-dideoxy-1,4-imino-L-ribitol **4** has also been described. All these results display again promising synthetic application of glutamic acid (Scheme 1). Continuation of the exploration and application of building block **3** in total synthesis of other active natural products are now in progress in our laboratory.

4. Experimental section

4.1. General

THF was distilled from sodium/benzophenone. All reactions were monitored by thin layer chromatography (TLC) on glass plates coated with silica gel with fluorescent indicator (Huanghai HSGF254). Flash chromatography was performed on silica gel (Huanghai 300–400) with petroleum/EtOAc as eluent. Melting points were recorded on a Mel-Temp apparatus and uncorrected. Optical rotations were measured on a JASCO P-1030 polarimeter with a sodium lamp. Mass spectra were recorded on an HP-5989 instrument and HRMS (MALDI/DHB) were measured on an LCMS-IT-TOF (Shimazu Corporation) apparatus. IR spectra were recorded using KBr disks or film, on a Fourier Transform Infrared Spectrometer, Type: Avatar 360 E.S.P, manufactured by Thermo Nicolet Corporation, USA. NMR spectra were recorded on a Varian or a Bruker spectrometer (300 or 400 MHz), and chemical shifts are reported in d (ppm) referenced to an internal TMS standard for ^{1}H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR.

4.1.1. (3aS,4S,6aS)-tert-Butyl 4-((tert-butyldimethylsilyloxy)methyl)-2,2-dimethyl-6-oxo-tetrahydro-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate ***7***. To a solution of compound **3** (359 mg, 0.99 mmol) and *p*-TsOH (30 mg, 0.17 mmol) were stirred in dry acetone (14 mL), then DMP (1.2 mL) was dropped under argon atmosphere. After stirring for 3 h at room temperature, the mixture was quenched with saturated $NaHCO_3$ aqueous solution and extracted with EtOAc for three times. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Filtered and concentrated, the residue was purified by chromatography on silica gel to give **7** (382 mg, yield 96%) as a colorless oil. $[\alpha]_D^{20}$ +92.6 (*c* 1.0, $CHCl_3$); IR (film): ν_{max} 2988, 2938, 1783, 1373, 1298, 1258, 1158, 1116 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.65 (d, *J*=5.7 Hz, 1H), 4.52 (d, *J*=5.4 Hz, 1H), 4.23 (br s, 1H), 3.99 (dd, *J*=2.1, 10.5 Hz, 1H), 3.77 (dd, *J*=1.2, 10.5 Hz, 1H), 1.54 (s, 9H), 1.46 (s,3H), 1.38 (s,3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.9, 149.9, 111.8, 83.5, 78.2, 75.7, 61.9, 61.8, 27.9, 27.1, 25.8, 25.6, 18.1, −5.7, −5.6 ppm; MS (ESI): 424 (M+Na$^+$); HRMS (MALDI/DHB) calcd for [$C_{19}H_{35}NO_6Si$+Na$^+$]: 424.2131, found: 424.2141.

4.1.2. (3aS,6S,6aS)-tert-Butyl 4-acetoxy-6-((tert-butyldimethylsilyloxy)methyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate ***9***. To a solution of **7** (220 mg, 0.55 mmol) in THF (15 mL) was stirred at −78 °C, then a solution of $LiEt_3BH$ (1.65 mL, 1 M in THF) was slowly dropped and the reaction was stirred for 30 min. Absolute MeOH (4 mL) was carefully dropped and stirred for 5 min. The mixture was treated with saturated $NaHCO_3$ aqueous solution and warmed to room temperature. Then the solvent was removed in vacuo and the residue was diluted with EtOAc and separated. The aqueous layer was extracted with EtOAc for three times and the combined organic layers were washed with brine. Dried and concentrated gave crude compound **8** as a mixture of diastereomers without further purification. The crude **8** and DMAP (37 mg, 0.30 mmol) were dissolved in dry DCM (15 mL) and stirred at 0 °C. Then a solution of TEA (0.23 mL, 1.64 mmol) and acetic anhydride (0.15 mL, 1.65 mmol) was dropped. After being stirred for 10 h, the reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution and extracted with DCM for three times. The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by chromatography on silica gel to give **9** (232 mg, 94%), the major **9** as a white foam. $[\alpha]_D^{20}$ +89.5 (*c* 1.0, $CHCl_3$); IR (film): ν_{max} 2986, 2933, 1747, 1712, 1379, 1257, 1207, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.18 (d, *J*=6.0 Hz, 1H), 4.72 (dd, *J*=5.0, 5.8 Hz, 1H), 4.55 (d, *J*=5.4 Hz, 1H), 4.17–4.11 (m, 2H), 3.61–3.58 (m, 1H), 2.10 (br s, 3H), 1.52–1.36 (m, 15H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.3, 153.0, 112.2, 81.6, 81.2, 80.7, 77.9, 61.9, 61.3, 28.2, 25.8, 25.5, 25.4, 20.9, 18.1, −5.5, −5.6 ppm; MS (ESI): 468 (M+Na$^+$); HRMS (MALDI/DHB) calcd for [$C_{21}H_{39}NO_7Si$+Na$^+$]: 468.2394, found:468.2386.

4.1.3. (3aS,4S,6aR)-tert-Butyl 4-((tert-butyldimethylsilyloxy)methyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate ***10***. To a solution of **9** (100 mg, 0.22 mmol) and Et_3SiH (0.35 mL) in DCM (15 mL) were stirred at −78 °C under argon atmosphere, then a solution of $BF_3{\cdot}Et_2O$ (0.08 mL, 0.66 mmol) in dry DCM (2 mL) was slowly dropped. After stirring for 5 h at −78 °C, the mixture was quenched with saturated $NaHCO_3$ aqueous solution and diluted with DCM. The organic layer was separated and the aqueous layer was extracted with DCM for three times. The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by chromatography on silica gel to give **10** (74 mg, 85%) as a colorless oil. $[\alpha]_D^{20}$ +66.2 (*c* 1.0, $CHCl_3$); IR (film): ν_{max} 2957, 2933, 1701, 1405, 1382, 1376, 1255, 1176, 1123 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.71–4.67 (m, 2H), 4.01 (br s, 1/2H), 3.95–3.92 (m, 1H), 3.74–3.48 (m, 7/2H), 1.44 (br s, 12H), 1.23 (br s, 3H), 0.92 (br s, 9H), 0.02 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.1, 111.2, 83.2, 82.6, 79.6, 64.7, 63.5, 53.8, 28.4, 27.0, 25.8, 25.0, 18.0, −5.7 ppm; MS (ESI): 410 (M+Na$^+$); HRMS (MALDI/DHB) calcd for [$C_{19}H_{37}NO_5Si$+H$^+$]: 388.2519, found: 388.2541.

4.1.4. (2S,3S,4R)-2-(Hydroxymethyl)pyrrolidine-3,4-diol hydrochloride (LRB) ***4***. To a solution of **10** (74 mg, 0.19 mmol) in absolute MeOH (10 mL) were stirred at −10 °C under argon atmosphere, then a solution of $(COCl)_2$ (1.3 mL, 18 mmol) was slowly dropped. After stirring for 2 days at room temperature, the mixture was concentrated and the residue was triturated with absolute Et_2O at −78 °C to rt for three times to give LRB **4** (19 mg, 59%) as a white solid. Mp 125–127 °C [lit.[14m] 128–130 °C]; $[\alpha]_D^{25}$ −50.9 °C (*c* 0.52, H_2O) [lit.[14m] $[\alpha]_D^{25}$ −52 °C (*c* 0.41, H_2O)]; IR (film): ν_{max} 3407, 1619, 1407, 1142, 1065 cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 4.40–4.34 (m, 1H); 4.21 (dd, *J*=4.1, 8.2 Hz, 1H), 3.95 (dd, *J*=3.4, 12.3 Hz, 1H), 3.83 (dd, *J*=5.7, 12.3 Hz, 1H), 3.65–3.61 (m, 1H), 3.47 (dd, *J*=4.0, 12.5 Hz, 1H), 3.39–3.35 (m, 1H) ppm; ^{13}C NMR (D_2O, 100 Hz): δ 71.6, 69.7,

62.1, 58.8, 49.6 ppm; HRMS (MALDI/DHB) calcd for [$C_5H_{11}NO_3$+H^+]: 134.0817, found: 134.0831.

4.1.5. (3aS,4S,6aR)-tert-Butyl 4-(hydroxymethyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate ***11***. To a solution of **10** (507 mg, 1.31 mmol) in dry THF (10 mL) was stirred at 0 °C under argon atmosphere, then a solution of TBAF (2.6 mL, 1 M) in THF was slowly dropped. After stirring for 2 h at room temperature, the mixture was quenched with saturated $NaHCO_3$ aqueous solution and the resulting mixture was extracted with EtOAc for three times. The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by chromatography on silica gel to give **11** (321 mg, 90%) as a colorless oil. $[\alpha]_D^{24}$ +29.4 (*c* 1.04, $CHCl_3$); IR (film): ν_{max} 3440, 2979, 1674, 1479, 1417, 1162, 1056, 858 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.74–4.50 (m, 2H), 4.13–4.01 (m, 1H), 3.83–3.66 (m, 3H), 3.51–3.48 (m, 2H) 1.46 (br s, 9H), 1.32 (br s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.5, 111.8, 82.9, 82.1, 80.3, 65.2, 63.3, 63.0, 52.7, 28.4, 27.1, 25.1, 14.4 ppm; MS (ESI): 296 (M+Na^+); HRMS (MALDI/DHB) calcd for [$C_{13}H_{23}NO_5$+Na^+]: 296.1474, found: 296.1477.

4.1.6. (3aS,4R,6aR)-tert-Butyl 4-(methoxy(methyl)carbamoyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate ***12***. To a solution of **11** (130 mg, 0.476 mmol) in CCl_4 (3 mL) and CH_3CN (3 mL) was stirred at 0 °C, and then water (6 mL) was dropped. $NaIO_4$ (405 mg, 1.90 mmol) was added in one portion and stirred for 15 min. The mixture was treated with a catalytic amount of $RuCl_3 \cdot xH_2O$ and stirred for 5 h at room temperature. Et_2O (5 mL) was poured and stirred for 2 h until the color of the mixture turn to white. The mixture was diluted with water and extracted with EtOAc for three times. The combined organic layers were washed with brine for one time, dried, and concentrated to give the crude acid without further purification. To a mixture of above crude acid and HOBt (109 mg, 0.809 mmol) in dry DMF (6 mL) were stirred at 0 °C, then EDC (100 mg, 0.524 mmol) was added in one portion. After stirring for 30 min, the resulting mixture was treated with MeO(Me)NH·HCl (56 mg, 0.571 mmol) and *i*-Pi_2NEt (0.33 mL, 1.90 mmol) and stirred for 16 h. The reaction mixture was diluted with water and extracted with EtOAc for three times. The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by chromatography on silica gel to give **12** (111 mg, 74%) as a yellow foam. $[\alpha]_{D25}$ +20.27 (*c* 1.04, $CHCl_3$); IR (film): ν_{max} 2987, 1797, 1697, 1663, 1396, 1371, 1295, 1152, 1001 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.78–4.69 (m, 2H), 4.67–4.46 (m, 1H), 3.89 (br s, 3H), 3.74 (br s, 3H), 3.28–3.21 (m, 2H), 1.46 (br s, 9H), 1.42 (br s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.9, 112.2, 83.4, 82.6, 80.1, 64.4, 61.5, 53.3, 32.3, 28.4, 27.0, 26.9, 25.8 ppm; MS (ESI): 331 (M+H^+); HRMS (MALDI/DHB) calcd for [$C_{15}H_{26}N_2O_6$+H^+]: 331.1869, found: 331.1872.

4.1.7. (3aS,4R,6aR)-tert-Butyl 4-but-3-enoyl-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate ***13***. To a cooled (−78 °C) solution of **12** (360 mg, 1.09 mmol) in dry THF (10 mL) was treated with a solution of allylmagnesium chloride (1.92 mL, 1.7 M in THF) under argon atmosphere. After stirring for 30 min at −78 °C, the mixture was warmed to room temperature and stirred for 5 h. Then the resulting mixture was quenched with saturated NH_4Cl aqueous solution and extracted with EtOAc for three times. The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by chromatography on silica gel to give **13** (258 mg, 76%) as a colorless oil. $[\alpha]_D^{24}$ +122.06 (*c* 1.05, $CHCl_3$); IR (film): ν_{max} 2980, 2937, 1701, 1456, 1395, 1212, 1168, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.94–5.88 (m, 1H), 5.23–5.14 (m, 2H), 4.65 (br s, 3H), 3.89–3.77 (m, 1H), 3.49–3.28 (m, 3H), 1.44 (br s, 9H), 1.35–1.28 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.7, 134.6, 119.0, 111.3, 83.8, 80.1, 72.4, 67.8, 60.6, 53.8, 38.6, 30.2, 28.4, 26.7, 25.0 ppm; MS (ESI): 334 (M+Na^+); HRMS (MALDI/DHB) calcd for [$C_{16}H_{25}NO_5$+Na^+]: 334.1631, found: 334.1639.

4.1.8. (3aS,4S,6aR)-tert-Butyl 4-((R)-1-hydroxybut-3-enyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate ***14***. To a solution of $(Ot\text{-}Bu)_3AlH$ (360 mg, 1.46 mmol) in dry THF (10 mL) was dropped a solution of compound **13** (226 mg, 0.72 mmol) in dry THF (4 mL) at −78 °C under argon atmosphere. After being stirred for 5 h at the same condition, the reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution and warmed to room temperature. The resulting mixture was extracted with EtOAc for three times and the combined organic layers were washed with brine, dried, and concentrated. The residue was purified by chromatography on silica gel to give **14** (182 mg, 81%) as a colorless oil. $[\alpha]_D^{24}$ +46.6 (*c* 0.675, $CHCl_3$); IR (film): ν_{max} 3445, 2979, 1697, 1673, 1415, 1367, 1163, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.89–5.82 (m, 1H), 5.24–5.18 (m, 2H), 4.73–4.64 (m, 2H), 3.96–3.82 (m, 1H), 3.54–3.48 (m, 1H), 3.42–3.34 (m, 2H), 1.46 (s, 9H), 1.50–1.41 (m, 2H), 3.34–1.26 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.9, 154.6, 129.4, 119.6, 112.5, 81.6, 80.8, 79.7, 78.8, 71.4, 70.7, 52.5, 45.4, 30.2, 28.3, 26.9 ppm; HRMS (MALDI/DHB) calcd for [$C_{16}H_{27}NO_5$+Na^+]: 336.1786, found: 336.1794.

4.1.9. (3aS,4R,6aR)-tert-Butyl 4-((R)-1-(tert-butyldimethylsilyloxy) but-3-enyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate ***15***. To a solution of compound **14** (126 mg, 0.403 mmol) and 2,6-lutidine (0.01 mL, 0.984 mmol) in dry DCM (4 mL) was stirred at 0 °C under argon atmosphere. After stirring for 15 min, the reaction mixture was slowly treated with TMSOTf (186 mg, 0.86 mmol) and stirred for 4 h at room temperature. The resulting mixture was quenched with saturated $NaHCO_3$ aqueous solution and extracted with EtOAc for three times. The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by chromatography on silica gel to give **15** (129 mg, 75%) as a colorless oil. $[\alpha]_D^{24}$ +19.83 (*c* 0.42, $CHCl_3$); IR (film): ν_{max} 2930, 1699, 1403, 1367, 1175, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.88–5.76 (m, 1H), 5.19–5.05 (m, 2H), 4.68–4.60 (m, 2H), 4.25–4.15 (m, 1H), 4.02–3.91 (m, 2H), 3.57–3.46 (m, 1H), 2.38–2.27 (m, 1H), 2.12–2.08 (m, 1H), 1.49–1.28 (m, 12H), 1.03–0.82 (m, 12H), 0.25–0.07 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.7, 134.7, 117.2, 111.2, 82.7, 79.4, 74.1, 73.0, 67.8, 54.9, 38.5, 28.5, 26.9, 25.9, 25.7, 25.3, 24.9, 17.9, −4.4, −4.6 ppm; HRMS (MALDI/DHB) calcd for [$C_{22}H_{41}NO_5Si$+Na^+]: 450.2652, found: 450.2669.

4.1.10. (3aS,4R,6aR)-tert-Butyl 4-((R)-1-(tert-butyldimethylsilyloxy)-4-hydroxybutyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate ***16***. To a solution of compound **15** (119 mg, 0.279 mmol) in dry THF (8 mL) was treated with a solution of $BH_3 \cdot SMe_2$ (0.1 mL) at 0 °C under argon atmosphere. After stirring for 8 h at room temperature, the reaction mixture was cooled to 0 °C again, and an aqueous solution of NaOH (1.15 mL, 3 M in water) was slowly dropped. Then, a solution of H_2O_2 (1.15 mL, 30% in water) was carefully dropped due to the formation of much bubble. The reaction mixture was stirred for 1 h and quenched with water. The resulting mixture was extracted with EtOAc for three times, and the combined organic layers were washed with brine. Dried and concentrated, the residue was purified by chromatography on silica gel to give **16** (77 mg, 64%) as a colorless oil. $[\alpha]_D^{24}$ +29.93 (*c* 0.42, $CHCl_3$); IR (film): ν_{max} 3400, 2922, 1179, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.69–4.64 (m, 2H), 4.29–4.11 (m, 1H), 3.91–3.81 (m, 2H), 3.73–3.65 (m, 2H), 3.56–3.51 (m, 2H), 1.75–1.75 (m, 2H), 1.69–1.64 (m, 2H), 1.48 (s, 9H), 1.53–1.36 (m, 3H), 1.32–1.26 (m, 3H), 0.90 (s, 9H), 0.11–0.01 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.6, 111.2, 83.3, 80.0, 77.2, 66.1, 62.2, 54.7, 30.1, 28.4, 27.0,

25.8, 24.9, 17.8, −4.3, −4.6 ppm; HRMS (MALDI/DHB) calcd for [$C_{22}H_{43}NO_6Si$+Na^+]: 468.2757, found: 468.2755.

*4.1.11. (−)-**8a**-epi-Swainsonine **2**.* To a solution of compound **16** (75 mg, 0.168 mmol) in dry pyridine (4 mL) was stirred at 0 °C, then MsCl (40 mg, 0.336 mmol) was slowly dropped. After stirring for 1 h, the resulting mixture was concentrated and the residue yellow oil was diluted with EtOAc and water. Separated, the aqueous layer was extracted with EtOAc for three times. The combined organic layers were washed with an aqueous solution of $KHSO_4$ and brine. The dried solution was concentrated to give crude compound without further purification. To a solution of above crude compound in dry DCM (10 mL) and 2,6-lutidine (0.12 mL) were cooled to −78 °C, then TMSOTf (0.20 mL) was slowly dropped. After stirring for 24 h at −78 °C to room temperature, the resulting mixture was quenched with water and extracted with DCM for three times. The combined organic layers were dried and concentrated to give crude product, which was easily separated from the minor of 2,6-lutidine by chromatography on silica gel. The above crude product was dissolved in absolute MeOH (4 mL) and stirred at −10 °C, then $(COCl)_2$ (0.25 mL) was slowly dropped. After stirring for 12 h at −10 °C to room temperature, the mixture was concentrated in vacuo to dryness. The resulting crude product was applied to ion-exchange chromatography (Dowex 50X8, H^+ form) eluting with aqueous ammonium hydroxide solution to give (−)-8a-*epi*-swainsonine **2** (22 mg, 76%) as a white powder. Mp 115–117 °C [lit.[10f] 116–118 °C; lit.[10g] 117–119 °C]; $[\alpha]_{D25}$ −63.4 °C (*c* 1.02, MeOH) [lit.[10f] $[\alpha]_D^{25}$ −64 °C (*c* 0.95, MeOH); lit.[10g] $[\alpha]_D^{25}$ −63 °C (*c* 1.0, MeOH)]; IR (film): ν_{max} 3352, 2946, 1641, 1331, 1162, 1007 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 4.26 (m, 1H); 4.08 (m, 1H), 3.88 (dd, *J*=6.64, 9.06 Hz, 1H), 3.37 (m, 1H), 2.91 (m, 1H), 2.09–2.06 (m, 3H), 1.89–1.85 (m, 1H), 1.74–1.65 (m, 1H), 1.542–1.46 (m, 2H) ppm; ^{13}C NMR (D_2O, 100 Hz): δ 71.2, 70.4, 68.3, 64.8, 62.1, 53.7, 31.4, 20.9 ppm; HRMS (MALDI/DHB) calcd for [$C_8H_{15}NO_3$+Na^+]: 196.0950, found: 196.0942.

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