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Concise and divergent total synthesis of swainsonine, 7-alkyl swainsonines, and 2,8a-diepilentiginosine via a chiral heterocyclic enaminoester intermediate

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ABSTRACT

The concise and divergent total syntheses of (−)-swainsonine, (−)-7-alkyl swainsonines, and (−)-2,8a-diepilentiginosine from a common chiral heterocyclic enaminoester intermediate in five-step sequences are presented. The highly efficient annulation reaction of the chiral heterocyclic enaminoester with various α,β-unsaturated carboxylates, and a straightforward carboxy inversion constituted the key features of the synthetic pathway. This work provides an example for divergent synthesis of different natural and unnatural polyhydroxylated indolizidines from a readily available platform.

1. Introduction

Polyhydroxylated indolizidine alkaloids[1] such as (+)-lentiginosine **1**,[2] (−)-2-*epi*-lentiginosine **2**,[3] (−)-swainsonine **3**,[4] and (+)-castanospermine **4**[5] (Fig. 1) have been attracting enormous attention since their isolation owing to their biological activities. Lentiginosine, swainsonine, and castanospermine, for instance, have been shown to inhibit various glycosidases.[6] They show significant anti-HIV,[7] antimetastatic,[8] immunoregulating,[9] antitumor-proliferative,[10] and anticancer activities.[11] Because of their interesting and stereochemically rich structures, and also due to the need of their analogues in the study of structure–activity relationships, the interest in the synthesis of lentiginosine and swainsonine remains undiminished. Numerous syntheses documented to date are based on carbohydrate starting materials or asymmetric reactions using non-carbohydrate substrates.[12] Although some syntheses are efficient and useful, further development of general and practical methods for the preparation of natural and unnatural polyhydroxylated indolizidine products is of great importance.

Heterocyclic secondary enamines are versatile building blocks in organic synthesis.[13] As the bis-nucleophilic species, their annulation reaction with bis-electrophiles have generated a variety of *N*-fused heterocycles. Applications of heterocyclic secondary enamines in natural product synthesis have been reported.[13] Surprisingly, however, utilization of heterocyclic secondary enamines in the synthesis of polyhydroxylated indolizidine alkaloids has remained largely unexplored. Very recently, we showed the first example of the synthesis of polyhydroxylated indolizidine derivatives from post-transformations of the fused *N*-heterocycles derived from the annulation reaction of a dihydroxylated heterocyclic secondary enamine.[14] We envisioned that the fused *N*-heterocyclic intermediate would serve as the key platform for the synthesis of naturally occurring indolizidines. Herein, we report the concise and divergent synthesis of (−)-2,8a-diepilentiginosine, (−)-swainsonine, and its 7-alkylated analogues starting from a dihydroxylated chiral heterocyclic enaminoester.

2. Results and discussion

We started our study with the total synthesis of (−)-swainsonine. Retrosynthetically, the *N*-fused ring system of (−)-swainsonine might be constructed by the annulation of either a five-membered heterocyclic enaminoester **5** with an α,β-unsaturated component or a six-membered heterocyclic enaminoester **6** with a two-carbon

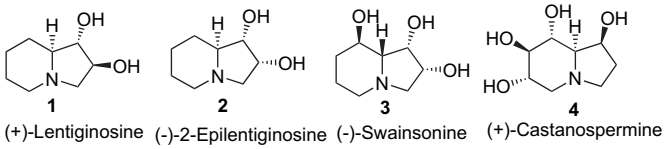

Figure 1. Some polyhydroxylated indolizidine alkaloids.

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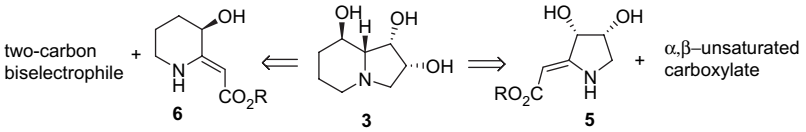


Figure 2. Retrosynthetical pathways using chiral heterocyclic enamine as the key intermediate.

bis-electrophilic reagent (Fig. 2). Having considered the stereochemistry of (−)-swainsonine **3**, and the availability of D-erythronic acid γ-lactone, in which the diol has the same absolute configurations as that in (−)-swainsonine, we decided to choose the annulation strategy using a five-membered heterocyclic enamine with a α,β-unsaturated carboxylate. Another advantage of the choice is that the enamine intermediate **5** might also act as the precursor for 2-epilentiginosine, as they have the identically configured vicinal diol structure.

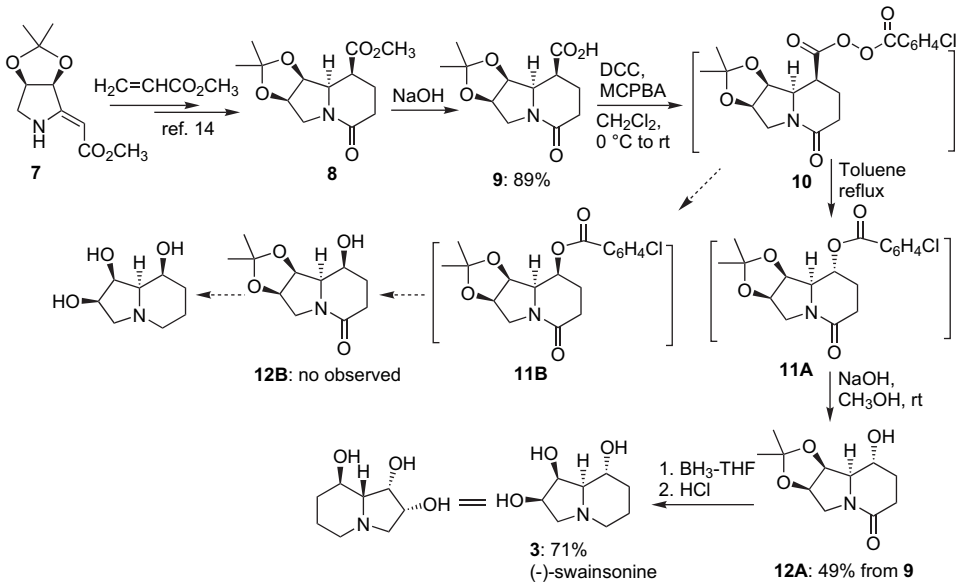
The isopropylidene-protected chiral heterocyclic enaminoester **7**, namely (3*S*,4*R*)-3,4-isopropylidenedioxypyrrolidin-2-ylidene acetate, was prepared in six steps from commercially available D-erythronic acid γ-lactone based on the literature method.[15] D-Erythronic acid γ-lactone can also be prepared in a large scale by oxidation of the very cheap D-(−)-isoascorbic acid.[16]

In our previous work,[14] we have shown the efficient synthesis of octahydroindolizinone-8-carboxylate **8** from the annulation reaction of **7** with methyl acrylate followed by highly diastereoselective hydrogenation (Scheme 1). The stereochemistry of C-1, C-2, and C-8a of octahydroindolizinone **8** resembled that of the natural (−)-swainsonine. The challenge now is to convert the 8-methoxycarbonyl group into the 8-hydroxyl group stereospecifically. The 'conventional' transformation of an ester into a hydroxyl group involves lengthy and tedious multistep reactions, which give low overall yield. Apparently, a successful synthesis of (−)-swainsonine requires an efficient and short functional group transformation.

In 1965, Denney and Sherman[17a] reported a straightforward transformation from a carboxyl group to a hydroxyl group, so-called carboxy-inversion reaction.[17] The reaction was proposed to proceed via a diacyl peroxide intermediate, which afforded alcohol product through thermolytic rearrangement followed by basic hydrolysis. Despite its simplicity in operation, surprisingly, the straightforward carboxy inversion has been overlooked. Its application has only been scatteringly found in literature.[17b,c,18] We applied the carboxy-inversion reaction as the shortest route to introduce the 8-hydroxyl group of swainsonine. Thus, acid **9**, which was derived from the hydrolysis of ester **8**, was treated with *m*-chloroperbenzoic acid (MCPBA) and dicyclohexylcarbodiimide (DCC) in dichloromethane at 0 °C. The resulting diacyl peroxide intermediate **10**, without isolation, was converted into **11A** through the thermolytic rearrangement in toluene. Subsequent hydrolysis in the presence of NaOH in methanol afforded 8-hydroxylated indolizinone **12A** in 49% yield from acid **9**. We accomplished the total synthesis of (−)-swainsonine **3** after the reduction of 8-hydroxylindolizinone **12A** with borane followed by hydrolysis under acidic conditions (Scheme 1). The physical and spectral data of the synthetic compound is in agreement with those reported for (−)-swainsonine.[19]

The stereochemistry of the carboxy-inversion merits comments. The carboxy-inversion reaction has been proposed to proceed via a caged radical or an ion-pair mechanism in the rearrangement of diacyl peroxide to ester (see the conversion of **10** to **11A** in Scheme 1).[20] In many examples,[17b,c,21] the carboxy-inversion reactions have been shown to occur predominantly with retention of configuration of the migrated group. That feature has been successfully applied in the total synthesis of some natural products such as prostaglandins[17b] and widdrol.[17c] In sharp contrast to that documented in the literature, however, we found that the carboxy inversion of acid **9** produced an alcohol **12A** with the *inversion* of configuration, since none of the epimer **12B** was observed. Although the detailed mechanism awaits further study, we proposed that the rearrangement of diacyl peroxide **10** to ester **11** took place from the less sterically hindered face of the fused heterocycle, yielding **11A** in a highly stereoselective manner.

To further demonstrate the synthetic potential of heterocyclic secondary enamine chiral building block **7**, we then attempted the synthesis of (−)-swainsonine analogues, which have an alkyl group at 7-position. We have known that the annulation reaction of **7**



Scheme 1. Synthesis of (−)-swainsonine from enaminoester **7** and methyl acrylate.

with methyl crotonate and the subsequent hydrogenation gave rise to the two diastereoisomeric (7*S*)- and (7*R*)-methylindolizinones **13A** and **13B** (**13A**:**13B**~3:2), and the major product **13A** has a cis relationship between the methyl and dioxy substituents.[14] Thus, indolizinones **13A** and **13B** were prepared from **7** and methyl crotonate, and were converted, respectively, into acids **14A** and **14B** by basic hydrolysis. Carboxy-inversion reaction of **14A** or **14B** under identical conditions as that for acid **9** produced alcohols **15A** or **15B** in 54% or 56% yield, respectively. The configuration of **15B** was determined by X-ray diffraction analysis (Fig. 3),[22] which demonstrated unambiguously that the conversion of the carboxy to the hydroxyl group has once again been accompanied with the inversion of the configuration. The stereochemistry of **15B** further supported our assumption that, to avoid steric hindrance, the rearrangement of diacyl peroxide to *m*-chlorobenzoate took place predominantly from the opposite face of isopropylidenedioxy substituent (convex face). Reduction of 7-methyl-8-hydroxyl-indolizinones **15A** and **15B** with borane followed by acidic hydrolysis gave two isomeric (−)-7-methyl swainsonines **16A** and **16B** in 88% and 78% yields, respectively (Scheme 2).

Since the annulation reaction of enaminoester **7** with methyl crotonate gave two isomeric hexahydroindolizinones with low diastereoselectivity, a highly selective synthesis of 7-alkyl swainsonines was then explored by taking the advantage of highly diastereoselective hydrogenation reaction. Thus, tetrahydro-5-indolizinone **17** or **18** was prepared in 88% or 85% yield from the reaction of **7** with methyl 4-ethyl or 4-isopropyl allenoate. Hydrogenation of **17** or **18** afforded the fully cis-substituted octahydroindolizinone **19** in 93% or **20** in 97% yield as a single diastereoisomer. Through a series of reactions, including hydrolysis, carboxy inversion, reduction of the amide, and deprotection, the indolizinone **19** and **20** were transformed into 7-propyl swainsonine **25** and 7-isobutyl swainsonine **26**, respectively (Scheme 3).

After the successful synthesis of swainsonine and 7-alkyl swainsonine derivatives from enaminoester **7**, we then turned our attention to the synthesis of *epi*-lentiginosine. The synthesis required the removal of the 8-carboxylate group of indolizinone **8**, however, the excision with aqueous HBr (40%) under refluxing was found inefficient. Since decarboxylation of an aromatic acid is generally more efficient than an aliphatic one. Therefore, tetrahydroindolizinone-8-carboxylate **27** was prepared in 83% yield from the reaction of enaminoester **7** with methyl propiolate catalyzed by

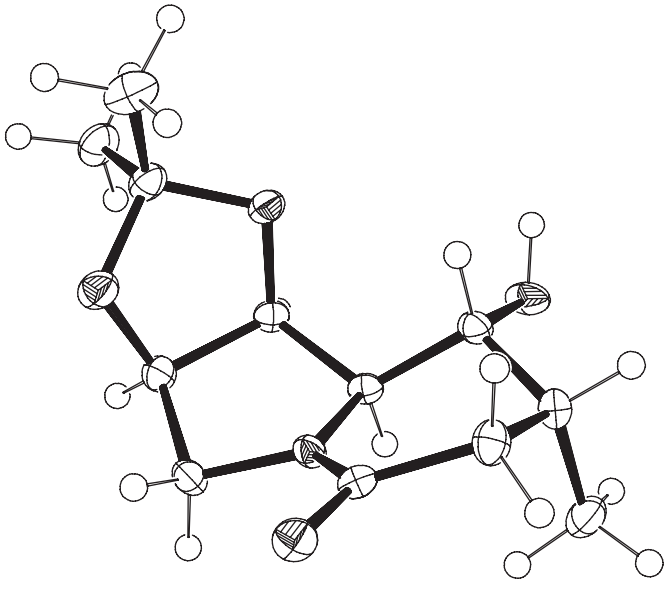
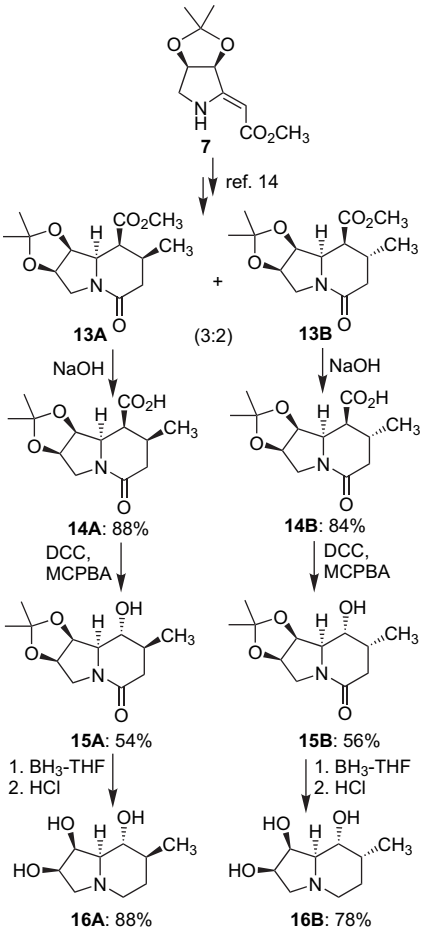


Figure 3. The ORTEP drawing of single crystal structure of **15B**.



Scheme 2. Synthesis of (7*S*) and (7*R*)-7-methyl swainsonines **16A** and **16B** from enaminoester **7** and methyl crotonate.

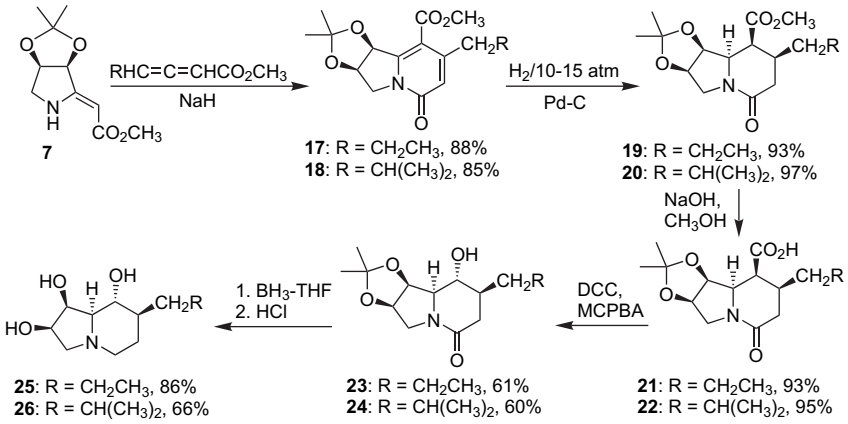
NaOMe, and then was decarboxylated in refluxing aqueous HBr (40%) to form 1,2-dihydroxyl-1,2,3,5-tetrahydro-5-indolizinone **28** in 79% yield (Scheme 4). Protection of 1,2-dihydroxyl-5-indolizinone **28** followed by PtO_2-catalyzed hydrogenation of 1,2-isopropylidenedioxy-5-indolizinone **29** under 10–15 atm of H_2 afforded 90% yield of octahydroindolizinone **30**. Reduction of **30** using fresh prepared borane and deprotection with acidic hydrolysis gave 2,8a-diepilentiginosine **31** in 74% yield (Scheme 4).

In conclusion, on the basis of our previous work,[14] we have provided the concise and stereoselective synthesis of (−)-swainsonine, (−)-7-alkyl swainsonines, and (−)-2,8a-diepilentiginosine from a chiral heterocyclic enaminoester intermediate in five steps, which was readily prepared from commercially available D-erythronic acid γ-lactone in six steps. The highly efficient annulation reaction of heterocyclic enaminoester with various α,β-unsaturated carboxylates and a straightforward carboxy-inversion reaction constituted the key features of the synthetic pathway for (−)-swainsonine and its 7-alkylated analogues. The easy availability of chiral heterocyclic enaminoester, very cheap reagents and reactants, and simple chemical manipulations render our approach powerful and practical in the synthesis of diverse natural and unnatural polyhydroxylated indolizidines.

3. Experimental section

3.1. General

Melting points are uncorrected. ^{1}H NMR (500, 400 or 300 MHz) and ^{13}C NMR (125 or 100 MHz) spectra were recorded in the



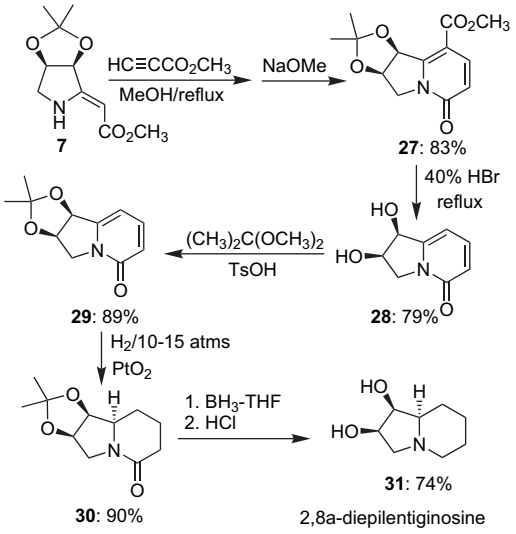
Scheme 3. Synthesis of (7*S*)-7-propyl or 7-*iso*-butyl substituted swainsonine **25** or **26** from enaminoester **7** and methyl 4-ethyl or 4-*iso*-propylallenoate.

solvent as indicated. THF was distilled from sodium benzophenone ketyl. Petroleum ether refers to that of bp 60–90 °C. The key intermediate, *cis*-(3*S*,4*R*)-3,4-isopropylidenedioxypyrrolidin-2-ylidene acetate **7**, was synthesized following the Buchanan's method[15] from 2,3-*O*-isopropylidene-D-erythrose that was prepared from D-erythronic acid γ-lactone.[16]

3.2. Total synthesis of swainsonine 3, 7-alkyl swainsonines 16A, 16B, 25, and 26

*3.2.1. General procedure for the reaction of heterocyclic enamine **7** with methyl 4-alkylallenic carboxylates*

Under nitrogen atmosphere and at 0 °C, a solution of heterocyclic enamine **7**[15a] (1 mmol) in dry THF (10 mL) was added dropwise to the suspension of NaH (0.5 mmol, 50% in mineral oil) in THF (10 mL), and the resulting mixture was stirred until no evolution of hydrogen gas. To this mixture, the solution of allenic carboxylate (methyl 4-ethyl or 4-isopropylallenic carboxylate) (1.5 mmol) in THF (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and for another 4 h at ambient temperature. After removal of the solvent, the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether and ethyl acetate (4:1 to 1:1) to give tetrahydro-5-indolizinones **17** and **18**, respectively.



Scheme 4. Synthesis of (−)-2,8a-diepilentiginosine from enaminoester **7** and methyl propiolate.

*3.2.1.1. Methyl (1S,2R)-1,2-O-isopropylidenedioxy-7-propyl-1,2,3,5-tetrahydro-5-indolizinone-8-carboxylate **17**.* Yield 88%, mp 66–67 °C, $[\alpha]_D^{20}$ −191.9 (*c* 0.59, $CHCl_3$). IR *ν* (cm^{-1}) 1714, 1668; ^1H NMR (500 MHz, $CDCl_3$): 6.40 (s, 1H), 5.90 (d, *J*=5.3 Hz, 1H), 4.94 (br s, 1H), 4.46 (d, *J*=14.0 Hz, 1H), 4.09 (br d, *J*=10.6 Hz, 1H), 3.90 (s, 3H), 2.84–2.90 (m, 1H), 2.56–2.62 (m, 1H), 1.55–1.59 (m, 2H), 1.42 (s, 3H), 1.24 (s, 3H), 0.97 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 165.8, 161.0, 155.7, 151.7, 118.9, 112.6, 109.6, 82.6, 74.7, 52.8, 52.1, 35.5, 27.2, 26.0, 23.0, 13.8. MS (EI): 43 (100), 202 (62), 218 (50), 250 (55), 275 (47), 307 (M^+, 33%). Anal. Calcd for $C_{16}H_{21}NO_5$: C 62.53, H 6.89, N 4.56; Found: C 62.14, H 7.29, N 4.40.

*3.2.1.2. Methyl (1S,2R)-1,2-O-isopropylidenedioxy-7-isobutyl-1,2,3,5-tetrahydro-5-indolizinone-8-carboxylate **18**.* Yield 85%, mp 128–129 °C, $[\alpha]_D^{20}$ −232 (*c* 0.4, $CHCl_3$). IR *ν* (cm^{-1}) 1731, 1661; ^1H NMR (500 MHz, $CDCl_3$): 6.35 (s, 1H), 5.90 (d, *J*=5.5 Hz, 1H), 4.94 (t, *J*=4.9 Hz, 1H), 4.46 (d, *J*=14.3 Hz, 1H), 4.09 (dd, *J*=14.3, 4.5 Hz, 1H), 3.89 (s, 3H), 2.95 (dd, *J*=13.1, 6.0 Hz, 1H), 2.33 (dd, *J*=13.0, 8.1 Hz, 1H), 1.73–1.78 (m, 1H), 1.41 (s, 3H), 1.24 (s, 3H), 0.95 (d, *J*=6.6 Hz, 3H), 0.88 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 165.9, 160.8, 154.7, 151.7, 119.9, 112.6, 109.8, 82.6, 74.7, 52.8, 52.1, 42.6, 29.0, 27.2, 26.0, 22.7, 22.0. MS (TOF-EI): 232 (80), 264 (95), 274 (90), 289 (100), 321 (M^+, 85%). Anal. Calcd for $C_{17}H_{23}NO_5$: C 63.54, H 7.21, N 4.36; Found: C 63.43, H 7.51, N 4.64.

*3.2.2. General procedure for hydrogenation of the tetrahydro-5-indolizinones **17** and **18***

The tetrahydro-5-indolizinone **17** or **18** (1 mmol) was mixed with palladium on activated carbon (10%, 0.5 g) in methanol (20 mL). The reaction mixture was stirred under hydrogen atmosphere (10–15 atm) for 30–72 h at 40–50 °C. After removal of the catalyst and solvent, the octahydro-5-indolizinone **19** or **20** was isolated by chromatography on a silica gel column eluting with ethyl acetate and acetone (9:1).

*3.2.2.1. Methyl (1S,2R,7S,8S,8aR)-1,2-O-isopropylidenedioxy-7-propyl-octahydro-5-indolizinone-8-carboxylate **19**.* Yield 93%, mp 200–202 °C, $[\alpha]_D^{20}$ −67.4 (*c* 0.38, $CHCl_3$) [lit.[14] mp 204–205 °C, $[\alpha]_D^{20}$ −68.2 (*c* 0.245, $CHCl_3$)].

*3.2.2.2. Methyl (1S,2R,7S,8S,8aR)-1,2-O-isopropylidenedioxy-7-isobutyl-octahydro-5-indolizinone-8-carboxylate **20**.* Yield 97%, mp 180–182 °C, $[\alpha]_D^{20}$ −61.7 (*c* 0.235, $CHCl_3$). IR *ν* (cm^{-1}) 1731, 1638, 1629; ^1H NMR (500 MHz, $CDCl_3$): 4.76–4.80 (m, 2H), 4.14 (d, *J*=13.6 Hz, 1H), 3.68–3.70 (m, 1H), 3.67 (s, 3H), 3.28 (dd, *J*=13.6, 4.7 Hz, 1H), 3.00 (t, *J*=3.8 Hz, 1H), 2.56 (dd, *J*=17.5, 12.2 Hz, 1H), 2.40 (dd, *J*=17.7, 6.2 Hz, 1H), 2.18–2.23 (m, 1H), 1.69–1.74 (m, 1H), 1.40 (s,

3H), 1.30 (s, 3H), 1.13–1.22 (m, 2H), 0.90 (d, J=6.4 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 170.9, 169.5, 112.7, 80.8, 77.3, 62.9, 51.2, 50.3, 42.3, 34.7, 34.4, 25.4, 24.6, 24.4, 22.7, 22.3. MS (EI): 250 (61), 326 (M+1, 100%). Anal. Calcd for $C_{17}H_{27}NO_5$: C 62.75, H 8.36, N 4.30; Found: C 63.27, H 8.32, N 4.29.

3.2.3. Hydrolysis of methyl octahydro-5-indolizinone-8-carboxylates **8**, **13A**, **13B**, **19**, and **20**.

The octahydro-5-indolizinone-8-carboxylate **8**,[14] **13A**,[14] **13B**,[14] **19** or **20** (1 mmol) was mixed with aqueous sodium hydroxide (20%, 2 mL) in ethanol (95%, 15 mL). The mixture was stirred for 6 h at room temperature and then was acidified with HCl (6 M) to pH ~3–4. After evaporating the solvents under vacuum, the residue was chromatographed on a silica gel column to give acid **9**, **14A**, **14B**, **21** or **22** (eluting solvents: from pure ethyl acetate to ethyl acetate/methanol=9:1).

3.2.3.1. (1S,2R,8S,8aR)-1,2-O-Isopropylidenedioxy-octahydro-5-indolizinone-8-carboxylic acid **9**.

Yield 89%, mp >250 °C, $[\alpha]_D^{20}$ −21.4 (c 0.21, DMSO). IR ν (cm^{-1}) 2730–3250 (br), 1724, 1619; ^{1}H NMR (500 MHz, DMSO-d_6): 4.70 (t, J=1.9 Hz, 2H), 3.92 (d, J=13.3 Hz, 1H), 3.65 (dd, J=10.4, 2.8 Hz, 1H), 3.02 (dd, J=13.0, 2.4 Hz, 1H), 2.70 (dt, J=10.2, 3.2 Hz, 1H), 2.24–2.29 (m, 2H), 2.09–2.13 (m, 1H), 1.80–1.85 (m, 1H), 1.30 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6+CD_3OD): 173.8, 169.0, 111.2, 80.3, 77.5, 61.6, 49.7, 39.1, 30.4, 25.6, 24.6, 23.7; MS (EI): 45 (100), 55 (83), 256 (M+1, 20%). Anal. Calcd for $C_{12}H_{17}NO_5$: C 56.46, H 6.71, N 5.49; Found: C 56.52, H 7.15, N 5.55.

3.2.3.2. (1S,2R,7S,8S,8aR)-1,2-O-Isopropylidenedioxy-7-methyl-octahydro-5-indolizinone-8-carboxylic acid **14A**.

Yield 88%, mp 216–218 °C, $[\alpha]_D^{20}$ −18.1 (c 0.215, $CHCl_3$). IR ν (cm^{-1}) 2730–3250 (br), 1720, 1614; ^{1}H NMR (500 MHz, $CDCl_3$): 4.77 (s, 1H), 4.70 (t, J=4.6 Hz, 1H), 4.26 (d, J=13.5 Hz, 1H), 3.77 (dd, J=10.4, 3.9 Hz, 1H), 3.16 (dd, J=13.6, 4.8 Hz, 1H), 2.68 (dt, J=10.9, 3.3 Hz, 1H), 2.61 (dd, J=17.4, 4.5 Hz, 1H), 2.25 (br, 1H), 2.14 (dd, J=17.3, 12.2 Hz, 1H), 1.44 (s, 3H), 1.33 (s, 3H), 1.15 (d, J=4.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 175.4, 168.7, 112.3, 79.7, 77.5, 62.7, 50.3, 46.6, 39.0, 31.4, 26.4, 24.7, 19.1. MS (EI): 166 (47), 270 (M+1, 100%). Anal. Calcd for $C_{13}H_{19}NO_5$: C 57.98, H 7.11, N 5.20; Found: C 57.64, H 7.07, N 5.01.

3.2.3.3. (1S,2R,7R,8S,8aR)-1,2-O-Isopropylidenedioxy-7-methyl-octahydro-5-indolizinone-8-carboxylic acid **14B**.

Yield 84%, mp 283–284 °C, $[\alpha]_D^{20}$ −17.6 (c 0.295, CH_3OH). IR ν (cm^{-1}) 2750–3250 (br), 1724, 1625; ^{1}H NMR (500 MHz, $CDCl_3$): 4.87 (t, J=5.8 Hz, 1H), 4.77 (t, J=5.2 Hz, 1H), 4.34 (d, J=13.5 Hz, 1H), 3.75 (dd, J=11.3, 4.1 Hz, 1H), 3.18 (dd, J=10.8, 3.6 Hz, 1H), 3.12 (dd, J=13.6, 4.6 Hz, 1H), 2.75 (br, 1H), 2.64 (dd, J=17.4, 5.5 Hz, 1H), 2.36 (d, J=17.4 Hz, 1H), 1.42 (s, 3H), 1.34 (s, 3H), 1.07 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 175.2, 167.9, 111.9, 80.5, 77.7, 57.5, 50.2, 42.5, 38.3, 29.3, 26.4, 24.7, 15.6. MS (EI): 69 (100), 108 (82), 142 (69), 166 (94), 194 (95), 211 (70), 254 (65), 269 (M^+, 44%). Anal. Calcd for $C_{13}H_{19}NO_5$: C 57.98, H 7.11, N 5.20; Found: C 57.99, H 7.50, N 5.17.

3.2.3.4. (1S,2R,7S,8S,8aR)-1,2-O-Isopropylidenedioxy-7-propyl-octahydro-5-indolizinone-8-carboxylic acid **21**.

Yield 93%, mp 189–191 °C, $[\alpha]_D^{20}$ −15.6 (c 0.32, $CHCl_3$). IR ν (cm^{-1}) 2877–3250 (br), 1720, 1608; ^{1}H NMR (500 MHz, $CDCl_3$): 4.76 (t, J=5.2 Hz, 1H), 4.68 (t, J=5.2 Hz, 1H), 4.25 (d, J=13.6 Hz, 1H), 3.75 (dd, J=10.3, 3.9 Hz, 1H), 3.16 (dd, J=13.6, 5.0 Hz, 1H), 2.78 (t, J=10.7 Hz, 1H), 2.65 (dd, J=17.2, 4.5 Hz, 1H), 2.18–2.22 (m, 1H), 2.09 (dd, J=17.1, 11.8 Hz, 1H), 1.55–1.58 (m, 1H), 1.48–1.52 (m, 1H), 1.45 (s, 3H), 1.34 (s, 3H), 1.28–1.36 (m, 2H), 0.94 (t, J=7.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 175.7, 168.8, 112.3, 79.8, 77.5, 62.7, 50.3, 45.7, 36.2, 35.8, 35.5, 26.4, 24.7, 19.2, 14.0. MS (EI): 84 (100), 96 (70), 141 (55), 195 (55), 221 (55), 297 (M^+, 20%). Anal. Calcd for $C_{15}H_{23}NO_5$: C 60.59, H 7.80, N 4.71; Found: C 60.39, H 7.81, N 4.69.

3.2.3.5. (1S,2R,7S,8S,8aR)-1,2-O-Isopropylidenedioxy-7-isobutyl-octahydro-5-indolizinone-8-carboxylic acid **22**.

Yield 95%, mp 202–204 °C, $[\alpha]_D^{20}$ −17.8 (c 0.325, $CHCl_3$). IR ν (cm^{-1}) 2543–2750 (br), 1719, 1605; ^{1}H NMR (500 MHz, $CDCl_3$): 4.76 (t, J=5.4 Hz, 1H), 4.69 (t, J=4.4 Hz, 1H), 4.25 (d, J=13.6 Hz, 1H), 3.77 (dd, J=10.3, 4.0 Hz, 1H), 3.17 (dd, J=13.6, 4.9 Hz, 1H), 2.67–2.75 (m, 2H), 2.21–2.23 (m, 1H), 2.04 (dd, J=17.5, 12.0 Hz, 1H), 1.64–1.69 (m, 1H), 1.44 (s, 3H), 1.33 (s, 3H), 1.31–1.34 (m, 2H), 0.93 (d, J=6.5 Hz, 3H), 0.86 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 175.5, 169.0, 112.3, 79.7, 77.4, 62.7, 50.3, 46.2, 42.8, 36.3, 33.8, 26.4, 24.69, 24.68, 24.0, 21.0. HRMS (TOF-ESI): 312.1805, $C_{16}H_{26}NO_5$ required 312.1811 (M+1).

3.2.4. Conversion of acids **9**, **14A**, **14B**, **21**, and **22** to alcohols **12A**, **15A**, **15B**, **23**, and **24** via carboxy-inversion reaction

At 0 °C and under nitrogen atmosphere, the acid **9**, **14A**, **14B**, **21** or **22** (1 mmol) was mixed with m-chloroperbenzoic acid (1.8 mmol) in CH_2Cl_2 (15 mL) (note: 2 mL of DMF was used as co-solvent for acid **9**), and then the solution of dicyclohexylcarbodiimide (1.8 mmol) in CH_2Cl_2 (15 mL) was added dropwise to the reaction mixture. The mixture was stirred at 0 °C for 2 h and then at room temperature for 4 h. After removal of the insoluble by-product dicyclohexyl urea (DCU) and the solvent dichloromethane, the residue was added toluene (20 mL) and was heated in refluxing toluene for 12 h. The toluene was evaporated under vacuum and the residue was dissolved in ethanol (20 mL) and was treated with aqueous NaOH (20%, 2 mL) for 4 h. After removal of the solvents, the product **12A**, **15A**, **15B**, **23** or **24** was isolated by chromatography on a silica gel column eluting with ethyl acetate.

3.2.4.1. (1S,2R,8R,8aR)-1,2-O-Isopropylidenedioxy-8-hydroxyl-octahydro-5-indolizinone **12A**.

Yield 49%, mp 123–125 °C, $[\alpha]_D^{20}$ +12.8 (c 0.305, $CHCl_3$). IR ν (cm^{-1}) 3373 (br), 1606; ^{1}H NMR (500 MHz, $CDCl_3$): 4.84 (t, J=5.5 Hz, 1H), 4.77 (t, J=5.3 Hz, 1H), 4.22 (d, J=13.9 Hz, 1H), 4.16–4.18 (m, 1H), 3.36 (dd, J=8.0, 4.5 Hz, 1H), 3.16 (dd, J=13.5, 4.6 Hz, 1H), 2.54 (dd, J=17.2, 5.0 Hz, 1H), 2.42–2.49 (m, 1H), 2.14–2.17 (m, 1H), 2.04 (br, 1H), 1.87–1.93 (m, 1H), 1.45 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 168.3, 112.2, 79.8, 77.6, 66.1, 65.6, 50.6, 29.74, 29.69, 26.3, 24.6. HRMS (FT-ICR): 228.1226, $C_{11}H_{18}NO_4$ required 228.1230 (M+1).

3.2.4.2. (1S,2R,7S,8R,8aR)-1,2-O-Isopropylidenedioxy-8-hydroxyl-7-methyl-octahydro-5-indolizinone **15A**.

Yield 54%, mp 189–190 °C, $[\alpha]_D^{20}$ −7.2 (c 0.195, $CHCl_3$). IR ν (cm^{-1}) 3360, 1624; ^{1}H NMR (500 MHz, $CDCl_3$): 4.83 (t, J=4.7 Hz, 1H), 4.78 (t, J=5.6 Hz, 1H), 4.20 (d, J=13.6 Hz, 1H), 3.74 (t, J=9.2 Hz, 1H), 3.37 (dd, J=8.7, 4.5 Hz, 1H), 3.17 (dd, J=13.5, 4.9 Hz, 1H), 2.58 (dd, J=17.0, 4.8 Hz, 1H), 2.12 (dd, J=16.9, 12.1 Hz, 1H), 1.92 (br, 1H), 1.46 (s, 3H), 1.36 (s, 3H), 1.13 (d, J=6.1 Hz, 3H); ^{13}C NMR (125 MHz, D_2O): 171.5, 112.2, 79.2, 77.6, 69.2, 65.2, 50.2, 37.3, 33.9, 25.4, 23.7, 15.9. HRMS (FT-ICR): 242.1388, $C_{12}H_{20}NO_4$ required 242.1387 (M+1).

3.2.4.3. (1S,2R,7R,8R,8aR)-1,2-O-Isopropylidenedioxy-8-hydroxyl-7-methyl-octahydro-5-indolizinone **15B**.

Yield 54%, mp 167–168 °C, $[\alpha]_D^{20}$ −24 (c 0.225, $CHCl_3$). IR ν (cm^{-1}) 3440, 1626; ^{1}H NMR (300 MHz, DMSO-d_6): 4.65–4.71 (m, 2H), 3.94 (dd, J=7.2, 3.6 Hz, 1H), 3.86 (d, J=13.1 Hz, 1H), 3.27 (dd, J=6.9, 4.6 Hz, 1H), 2.96 (dd, J=12.6, 2.2 Hz, 1H), 2.25 (dd, J=18.2, 6.1 Hz, 1H), 2.03–2.10 (m, 2H), 1.27 (s, 3H), 1.25 (s, 3H), 0.92 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 168.2, 112.1, 80.0, 77.7, 67.1, 62.3, 50.4, 36.9, 32.6, 26.4, 24.7, 13.5. HRMS (TOF-EI): 241.1317, $C_{12}H_{19}NO_4$ required 241.1314.

3.2.4.4. (1S,2R,7S,8R,8aR)-1,2-O-Isopropylidenedioxy-8-hydroxyl-7-propyl-octahydro-5-indolizinone **23**.

Yield 61%, mp 141–143 °C, $[\alpha]^{20}$ +21.8 (c 0.165, $CHCl_3$). IR ν (cm^{-1}) 3338, 1606; ^{1}H NMR

(500 MHz, $CDCl_3$): 4.83 (t, J=5.8 Hz, 1H), 4.77 (t, J=5.2 Hz, 1H), 4.20 (d, J=13.5 Hz, 1H), 3.80 (t, J=9.5 Hz, 1H), 3.36 (dd, J=8.6, 4.4 Hz, 1H), 3.17 (dd, J=13.5, 4.8 Hz, 1H), 2.64 (dd, J=17.5, 5.1 Hz, 1H), 2.06 (dd, J=17.3, 11.8 Hz, 1H), 1.94–1.96 (m, 1H), 1.81–1.88 (m, 1H), 1.81 (br, 1H), 1.48–1.51 (m, 1H), 1.45 (s, 3H), 1.36 (s, 3H), 1.28–1.32 (m, 1H), 1.16–1.22 (m, 1H), 0.96 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 168.4, 112.2, 79.8, 77.7, 69.5, 65.8, 50.5, 39.1, 36.0, 33.5, 26.4, 24.7, 19.3, 14.2. MS (EI) 68 (100), 84 (72), 269 (M^+, 22%). Anal. Calcd for $C_{14}H_{23}NO_4$: C 62.43, H 8.61, N 5.20; Found: C 61.98, H 8.85, N 4.95.

3.2.4.5. (1S,2R,7S,8R,8aR)-1,2-O-Isopropylidenedioxy-8-hydroxyl-7-isobutyl-octahydro-5-indolizinone ***24***. Yield 60%, mp 170–173 °C, $[\alpha]^{20}$ +12.9 (*c* 0.34, $CHCl_3$). IR *v* (cm^{-1}) 3322, 1606; ^{1}H NMR (500 MHz, $CDCl_3$): 4.83 (t, J=5.4 Hz, 1H), 4.78 (t, J=5.4 Hz, 1H), 4.20 (d, J=13.5 Hz, 1H), 3.76 (t, J=9.0 Hz, 1H), 3.38 (dd, J=8.4, 4.3 Hz, 1H), 3.18 (dd, J=13.5, 4.6 Hz, 1H), 2.63–2.67 (m, 1H), 2.16 (br, 1H), 2.01–2.06 (m, 2H), 1.66–1.70 (m, 2H), 1.45 (s, 3H), 1.36 (s, 3H), 1.11 (t, J=9.3 Hz, 1H), 0.97 (d, J=5.8 Hz, 3H), 0.89 (d, J=5.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 168.3, 112.2, 79.8, 77.7, 69.7, 65.8, 50.5, 40.9, 37.1, 36.1, 26.4, 24.7, 24.1, 21.1. MS (EI): 168 (90), 208 (94), 284 (M^+, 100%). Anal. Calcd for $C_{15}H_{25}NO_4$: C 63.58, H 8.89, N 4.94; Found: C 63.29, H 9.06, N 4.98.

3.2.5. Preparation of swainsonine and 7-alkyl swainsonines from reduction of 8-hydroxyl-octahydro-5-indolizinone

At 0 °C and under nitrogen atmosphere, the solution of borane THF complex (3 mmol, 1 M in THF) was added dropwise to the 8-hydroxyl-octahydro-5-indolizinone **12A**, **15A**, **15B**, **23** or **24** (0.5 mmol) in THF (20 mL). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 2–5 h. The reaction was quenched by adding methanol (5 mL) until no hydrogen evolution. After removal of the solvent, the residue was dissolved in methanol (20 mL) and refluxed for 6 h to decompose the boron complex of product. The volatiles were removed again under vacuum, and the pure 1,2-*O*-isopropylidenedioxy-8-hydroxyoctahydroindolizine (isopropylidene-protected swainsonine or 7-alkyl swainsonine) was isolated by chromatography on a neutral aluminum oxide column eluting with ethyl acetate. Deprotection procedure was furnished with 6 N HCl (1 mL) in THF (2 mL) within 10 h at room temperature. The acidic reaction mixture was basified using Na_2CO_3 powder to pH ~8–9, and then concentrated under vacuum to dryness. The (−)-swainsonine or (−)-7-alkyl swainsonine was isolated from repeating extraction of inorganic salts with dichloromethane (10×5 mL) and acetone (10×5 mL) and purified by recrystallization.

3.2.5.1. (−)-Swainsonine ***3***. Yield 71%, mp 133–134 °C, $[\alpha]_D^{20}$ −71.7 (*c* 0.12, CH_3OH) [lit.[4] mp 136–139 °C, $[\alpha]_D^{20}$ −74.9 (*c* 1.15, CH_3OH)]. IR *v* (cm^{-1}) 3407 (br); ^{1}H NMR (500 MHz, D_2O): 4.23–4.25 (m, 1H), 4.14 (dd, J=5.6, 3.7 Hz, 1H), 3.69 (td, J=10.2, 4.2 Hz, 1H), 2.78–2.83 (m, 2H), 2.50 (t, J=9.4 Hz, 1H), 1.88–1.95 (m, 3H), 1.61(br d, J=13.8 Hz, 1H), 1.40 (qt, J=13.3, 4.3 Hz, 1H), 1.13 (qd, J=12.4, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, D_2O): 72.5, 69.3, 68.7, 66.0, 60.3, 51.3, 32.1, 22.8. HRMS (TOF-EI): 173.1053, $C_8H_{15}NO_3$ required 173.1052.

3.2.5.2. (7S)-7-Methyl swainsonine ***16A***. Yield 88%, mp 146–148 °C, $[\alpha]_D^{20}$ −60 (*c* 0.155, CH_3OH). IR *v* (cm^{-1}) 3430; ^{1}H NMR (500 Hz, D_2O): 4.23–4.26 (m, 1H), 4.13 (dd, J=5.7, 3.7 Hz, 1H), 3.25 (t, J=9.7 Hz, 1H), 2.74–2.78 (m, 2H), 2.43 (dd, J=10.8, 8.0 Hz, 1H), 1.91 (dt, J=12.6, 2.2 Hz, 1H), 1.84 (dd, J=9.4, 3.6 Hz, 1H), 1.60 (br d, J=13.3 Hz, 1H), 1.26–1.31 (m, 1H), 1.15 (qd, J=12.8, 4.1 Hz, 1H), 0.92 (d, J=6.3 Hz, 3H); ^{13}C NMR (125 MHz, D_2O): 72.0, 71.5, 69.4, 69.0, 60.2, 51.2, 37.4, 31.6, 17.0. HRMS (TOF-ESI):188.1260, $C_9H_{17}NO_3$ required 188.1287 (M+1).

3.2.5.3. (7R)-7-Methyl swainsonine ***16B***. Yield 78%, mp 180–181 °C, $[\alpha]_D^{20}$ −80 (*c* 0.145, CH_3OH). IR *v* (cm^{-1}) 3425, 3378; ^{1}H NMR (500 MHz, D_2O): 4.21–4.24 (m, 1H), 4.05 (dd, J=5.8, 3.5 Hz, 1H), 3.85 (dd, J=10.1, 5.2 Hz, 1H), 2.73 (dd, J=11.1, 2.2 Hz, 1H), 2.56 (br dd, J=11.4, 2.0 Hz, 1H), 2.48 (dd, J=10.9, 8.1 Hz, 1H), 2.14 (dd, J=10.1, 3.1 Hz, 2H), 2.09–2.11 (m, 1H), 1.64 (tt, J=13.4, 4.5 Hz, 1H), 1.45 (dd, J=14.0, 2.0 Hz, 1H), 0.82 (d, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, D_2O): 69.5, 68.7, 68.1, 64.9, 59.9, 45.7, 31.4, 29.3, 10.2. HRMS (TOF-ESI): 188.1316, $C_9H_{18}NO_3$ required 188.1287 (M+1).

3.2.5.4. (7S)-7-Propyl swainsonine ***25***. Yield 86%, mp 119–122 °C, $[\alpha]_D^{20}$ −12.1 (*c* 0.865, CH_3OH). IR *v* (cm^{-1}) 3423; ^{1}H NMR (500 MHz, D_2O): 4.22–4.25 (m, 1H), 4.12 (dd, J=5.8, 3.6 Hz, 1H), 3.33 (t, J=9.7 Hz, 1H), 2.83 (br d, J=10.5 Hz, 1H), 2.77 (d, J=11.5 Hz, 1H), 2.47 (br t, J=9.0 Hz, 1H), 1.92–1.97 (m, 2H), 1.71 (br d, J=11.0 Hz, 1H), 1.53–1.59 (m, 1H), 1.26–1.32 (m, 1H), 1.17–1.22 (m, 1H), 1.02–1.13 (m, 3H), 0.75 (t, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, D_2O): 72.3, 69.9, 69.5, 69.0, 60.2, 51.4, 41.9, 33.2, 28.4, 19.0, 13.6. HRMS (TOF-EI): 215.1523, $C_{11}H_{21}NO_3$ required 215.1521.

3.2.5.5. (7S)-7-Isobutyl swainsonine ***26***. Yield 66%, mp 114–116 °C, $[\alpha]_D^{20}$ −21.3 (*c* 0.32, CH_3OH). IR *v* (cm^{-1}) 3396; ^{1}H NMR (500 MHz, D_2O): 4.20–4.24 (m, 1H), 4.11 (dd, J=5.9, 3.6 Hz, 1H), 3.26 (t, J=9.7 Hz, 1H), 2.79 (br d, J=11.2 Hz, 1H), 2.75 (dd, J=11.1, 2.2 Hz, 1H), 2.42 (dd, J=10.9, 8.0 Hz, 1H), 1.90 (br d, J=11.5 Hz, 1H), 1.85 (dd, J=9.5, 3.3 Hz, 1H), 1.73 (br d, J=12.0 Hz, 1H), 1.52–1.57 (m, 1H), 1.38 (dt, J=13.3, 2.9 Hz, 1H), 1.20–1.26 (m, 1H), 0.93–1.01 (m, 2H), 0.76 (d, J=6.6 Hz, 3H), 0.69 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 Hz, D_2O): 72.2, 70.3, 69.4, 68.9, 60.1, 51.3, 40.8, 40.1, 28.6, 24.4, 23.6, 20.6. HRMS (TOF-EI): 229.1681, $C_{12}H_{23}NO_3$ required 229.1678.

3.3. Total synthesis of 2,8a-diepilentiginosine from heterocyclic enaminoester 7 and ethyl propiolate

3.3.1. Preparation of tetrahydro-5-indolizinone-8-carboxylate ***27*** *from the reaction of enaminoester* ***7*** *with methyl propiolate*

The solution of enaminoester **7** (1 mmol) and methyl propiolate (4 mmol) in methanol (20 mL) was heated to reflux in a sealed thick-wall tube for 16 h. To this solution, NaOMe (100 mg) was added and the mixture was then refluxed for another 1 h. After removal of methanol, the product tetrahydro-5-indolizinone-8-carboxylate **27** was isolated by chromatography on a silica gel column eluting with petroleum ether and ethyl acetate (2:1).

3.3.1.1. Methyl (1S,2R)-1,2-O-isopropylidenedioxy-1,2,3,5-tetrahydro-5-indolizinone-8-carboxylate ***27***. Yield 83%, oil, $[\alpha]_D^{20}$ −63.8 (*c* 1.2 g/100 ml, $CHCl_3$). IR *v* (cm^{-1}) 1719, 1665; ^{1}H NMR (400 MHz, $CDCl_3$): 7.94 (d, J=9.5 Hz, 1H), 6.53 (d, J=9.5 Hz, 1H), 6.07 (d, J=6.1 Hz, 1H), 5.00–5.04 (m, 1H), 4.42 (dd, J=14.4, 1.2 Hz, 1H), 4.15 (dd, J=14.4, 5.5 Hz, 1H), 3.90 (s, 3H), 1.45 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 164.1, 161.5, 153.4, 140.6, 119.2, 112.4, 107.4, 82.5, 74.1, 54.0, 52.0, 26.9, 25.4. HRMS (TOF-ESI): 266.1019, $C_{13}H_{16}NO_5$ required 266.1028 (M+1).

3.3.2. Decarboxylation of 5-indolizinone-8-carboxylate ***27***

The tetrahydro-5-indolizinone-8-carboxylate **27** (1 mmol) was dissolved in hydrobromic acid (40%, 15 mL), and the solution was refluxed at 130–135 °C for 44 h. After evaporation the hydrobromic acid under vacuum, the residue was chromatographed on a silica gel column (ethyl acetate/methanol=9:1) to give (1*S*,2*R*)-1,2-dihydroxy-1,2,3,5-tetrahydro-5-indolizinone **28** in 79%.

3.3.2.1. (1S,2R)-1,2-Dihydroxy-1,2,3,5-tetrahydro-5-indolizinone ***28***. Yield 79%, mp 164–166 °C, $[\alpha]_D^{20}$ +53.3 (*c* 0.105, H_2O). IR *v* (cm^{-1}) 3237 (br), 1656, 1572; ^{1}H NMR (500 MHz, DMSO-d_6): 7.46 (t, J=7.8 Hz, 1H), 6.25 (d, J=7.9 Hz, 2H), 4.93 (d, J=3.8 Hz, 1H), 4.30 (s,

1H), 3.92 (d, *J*=13.1 Hz, 1H), 3.84 (dd, *J*=13.0, 3.3 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD+D_2O): 163.1, 151.0, 142.6, 117.1, 104.7, 73.9, 69.2, 53.7. HRMS (TOF-EI): 167.0584, $C_8H_9NO_3$ required 167.0582.

3.3.3. Protection of 1,2-dihydroxy-5-indolizinone **28**

The 1,2-dihydroxy-5-indolizinone **28** (0.5 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg) were dissolved in dimethoxypropane (4 mL) and dry dichloromethane (15 mL). The reaction mixture was stirred at room temperature for 36 h. The *p*-toluenesulfonic acid was neutralized with triethylamine (1 mL) and was filtered. After removal of solvent, 1,2-*O*-isopropylidenedioxy-5-indolizinone **29** was isolated in 89% yield by chromatography on a silica gel column eluting with ethyl acetate and petroleum ether (1:1).

*3.3.3.1. (1S,2R)-1,2-O-Isopropylidenedioxy-1,2,3,5-tetrahydro-5-indolizinone **29**.* Yield 89%, mp 128–130 °C, $[\alpha]_D^{20}$ −4.7 (*c* 0.34, CH_2Cl_2). IR *ν* (cm^{-1}) 1647, 1594, 1577; ^{1}H NMR (500 MHz, $CDCl_3$): 7.44 (dd, *J*=8.8, 7.1 Hz, 1H), 6.55 (d, *J*=9.1 Hz, 1H), 6.37 (d, *J*=6.6 Hz, 1H), 5.53 (d, *J*=5.6 Hz, 1H), 4.98 (t, *J*=5.2 Hz, 1H), 4.44 (d, *J*=14.4 Hz, 1H), 4.14 (dd, *J*=14.4, 4.9 Hz, 1H), 1.44 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 161.8, 148.6, 140.5, 119.7, 113.1, 103.0, 81.4, 75.0, 53.1, 27.3, 25.9. MS (EI): 150 (100), 192 (25), 207 (M^+, 40%). Anal. Calcd for $C_{11}H_{13}NO_3$: C 63.76, H 6.32, N 6.76; Found: C 63.53, H 6.11, N 6.68.

3.3.4. Hydrogenation of 1,2-O-isopropylidenedioxy-1,2,3,5-tetrahydro-5-indolizinone **29**

The tetrahydro-5-indolizinone **29** (0.5 mmol) was mixed with PtO_2 (100 mg) in methanol (20 mL). The reaction mixture was stirred under hydrogen atmosphere (10–15 atm) for 48 h at 40 °C. The catalyst was filtered off and washed with methanol (2×10 mL). The filtrate was concentrated under vacuum, and the residue was purified on a silica gel column eluting with ethyl acetate and acetone (1:1) to give 1,2-*O*-isopropylidenedioxy-octahydro-5-indolizinone **30** in 90% yield.

*3.3.4.1. (1S,2R,8aR)-1,2-O-Isopropylidenedioxy-octahydro-5-indolizinone **30**.* Yield 90%, mp 59–61 °C, $[\alpha]_D^{20}$ +59.5 (*c* 0.19, $CHCl_3$). IR *ν* (cm^{-1}): 1643, 1470, 1449; ^{1}H NMR (500 MHz, $CDCl_3$): 4.75 (t, *J*=5.6 Hz, 1H), 4.63 (t, *J*=5.1 Hz, 1H), 4.24 (d, *J*=13.6 Hz, 1H), 3.41–3.45 (m, 1H), 3.11 (dd, *J*=13.6, 5.1 Hz, 1H), 2.42 (br d, *J*=17.3 Hz, 1H), 2.28–2.35 (m, 1H), 1.96–2.03 (m, 2H), 1.86 (q, *J*=13.0 Hz, 1H), 1.72–1.75 (m, 1H), 1.43 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 169.3, 111.8, 81.1, 77.6, 61.2, 50.3, 31.3, 26.5, 24.8, 22.5, 21.0. HRMS (TOF-EI): 211.1206, $C_{11}H_{17}NO_3$ required 211.1208.

3.3.5. Preparation of 2,8a-diepilentiginosine **31**

At 0 °C and under nitrogen atmosphere, the solution of borane THF complex (1 M, 3 mL) was added dropwise to the solution of octahydro-5-indolizinone **30** (0.5 mmol) in THF (15 mL). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. Cooled in an ice-bath, the reaction was quenched by addition of methanol (5 mL). After removal of the solvent, the residue was dissolved in methanol (20 mL) and refluxed for 12 h. The volatiles were removed again under vacuum, and the protected diepilentiginosine was isolated by chromatography on neutral aluminum oxide eluting with ethyl acetate. Deprotection procedure was furnished using 6 N HCl (1 mL) in THF (10 mL) within 12 h at room temperature. The acidic reaction mixture was basified using Na_2CO_3 powder to pH∼8–9, and then concentrated under vacuum to dryness. The (−)-2,8a-diepilentiginosine **31** was isolated from inorganic salts by repeating extraction with dichloromethane (7×10 mL) and acetone (7×10 mL), and was further purified by chromatography on a silica gel column eluting with dichloromethane, methanol, and aqueous ammonia (10:1:0.5) (74% from **30**).

*3.3.5.1. 2,8a-Diepilentiginosine **31**.* Yield 74%, mp 104–106 °C, $[\alpha]_D^{20}$ −34.4 (*c* 0.38, CH_3OH) [lit.[23] mp 109–111 °C, $[\alpha]_D^{24}$ −37.1 (*c* 0.55, CH_3OH)]. IR *ν* (cm^{-1}) 3430 (br); ^{1}H NMR (500 MHz, D_2O): 4.21–4.24 (m, 1H), 3.94 (dd, *J*=5.9, 3.9 Hz, 1H), 2.90 (br d, *J*=10.9 Hz, 1H), 2.75 (dd, *J*=11.3, 2.0 Hz, 1H), 2.39 (dd, *J*=11.1, 7.9 Hz, 1H), 1.93–2.00 (m, 2H), 1.70 (br d, *J*=12.9, 1H), 1.59 (br d, *J*=12.7 Hz, 1H), 1.51 (br d, *J*=13.5 Hz, 1H), 1.32–1.38 (m, 2H), 1.14–1.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 72.3, 69.5, 68.1, 62.3, 53.1, 24.8, 24.7, 23.6. HRMS (TOF-EI): 157.1105, $C_8H_{15}NO_2$ required 157.1103.

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