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Article

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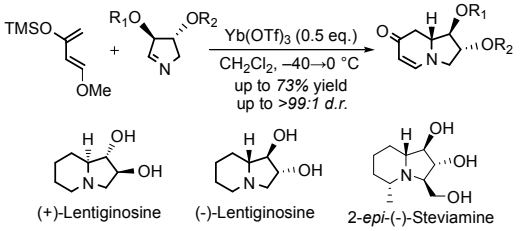
A Diastereoselective Cyclic Imine Cycloaddition Strategy to Access Polyhydroxylated Indolizidine Skeleton: Concise Syntheses of (+)-/(–)-Lentiginosines and (–)-2-*epi*-Steviamine

Jia Shao and Jinsong Yang*

Key Laboratory of Drug Targeting, Ministry of Education, and Department of Chemistry of Medicinal Natural Products, West China School of Pharmacy, Sichuan University, Chengdu 610041, P. R. China

Corresponding author. *E-mail address*: yjs@scu.edu.cn, yjscd@163.com (J.-S. Yang).

Graphic Abstract

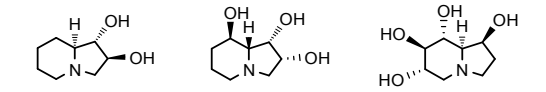


ABSTRACT: We describe in this paper the development of a novel diastereoselective cyclic imine cycloaddition strategy to access polyhydroxylated indolizidine skeleton, and its application in the concise syntheses of (+)-/(–)-lentiginosines and (–)-2-*epi*-steviamine.

INTRODUCTION

Polyhydroxylated indolizidine alkaloids (iminosugars or azasugars), a series of sugar mimics such as lentiginosine (**1**), swainsonine (**2**), and castanospermine (**3**) (Figure 1), and their stereoisomers are widespread in plants and microorganisms.[1] Their intriguing structure combined with their potent ability to inhibit glycosidases as well as for the anticancer, anti-HIV, and immunoregulatory activities[2] have inspired considerable synthetic efforts directed both at the naturally-occurring compounds such as **1**–**3**,[3] and at the structurally related analogues for pharmacological evaluation.[4]

Figure 1. Natural Polyhydroxylated Indolizidines



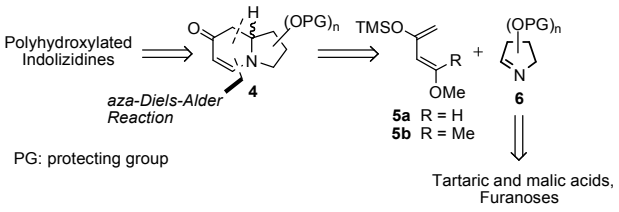
(+)-Lentiginosine (**1**) (-)-Swainsonine (**2**) (+)-Castanospermine (**3**)

So far, several conceptual synthetic approaches have been adopted in this field, namely a chiral pool, an enantio-, and a diastereoselective approaches.[5–7] The first method typically employs natural carbohydrates as starting material and introduces the ring nitrogen through their manipulation, thereby often leading to lengthy synthetic sequences and lacking enough flexibility for the preparation of a wide range of derivatives. On the other hand, up to date, a variety of the latter two strategies have been devised and applied successfully in the synthesis of polyhydroxyindolizidine-based compounds. However, most of the published methods rely on a linear and multi-step procedure consisting of forming either the five- or six-membered pyrrolidine or piperidine unit and followed later by installing the second ring through intramolecular cyclization to construct the indolizidine bicyclic core. Although a convergent strategy depending on the 1,3-dipolar cycloaddition of chiral nitrones with

olefins was utilized by both Brandi[6,8] and Tamayo[4o] groups to synthesize **1** and other indolizidine iminosugars, the formation of the indolizidine skeleton still requires further elaboration of the primary cycloadducts. Moreover, despite the fact that the intramolecular thermal imino Diels–Alder[9] and double ring closure reactions[3p,10] were developed to provide a direct entry into the indolizidine bicycle, the former suffers from the poor cycloaddition stereoselectivity and the harsh high-temperature activation conditions while the latter is confined to parallel syntheses of the target molecules. Therefore, the development of a more reliable and facile synthetic methodology, especially a useful solution to address the problem associated with indolizidine ring construction is still desirable for the synthesis of this biologically important class of natural products.

The retrosynthetic plan we intended to use for this goal is illustrated in Scheme 1. We envisioned that the target indolizidine could be gained from hydroxyindolizidine enaminone **4** via a sequence of functional group transformations.[11] In turn, the crucial indolizidine scaffold would be generated in a convergent fashion from an intermolecular [4+2] aza-Diels–Alder reaction of electron-rich Danishefsky-type silyloxydienes **5** and oxygenated five-membered aldimine ring **6**. The latter was proposed to originate from cheap and commercially available chiral compounds. If this cycloaddition process worked well, in particular if the stereochemistry of the bridgehead C8a position could be rigorously controlled, the method would serve as a straightforward and general route to the polyhydroxylated indolizidine as it not only builds up the technically challenging indolizidine 5,6-fused ring system in a single operation, but also allows various indolizidine iminosugars and analogues to be produced from a common pathway.

Scheme 1. Retrosynthetic Strategy

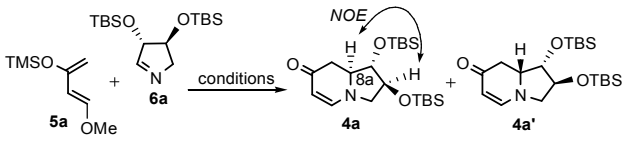


The asymmetric aza-Diels–Alder reaction has long proven an invaluable aid in giving access to the highly functionalized six-membered nitrogen-containing heterocycles.[12] In contrast to the intensive study on the acyclic imine-participated aza-Diels–Alder reactions, very few examples were devoted so far to the above-mentioned cycloaddition version employing unactivated cyclic imine as dienophile.[13] The synthetic value held by such type of cyclocondensation reaction has been outlined by the pioneering works of Vacca, Danishefsky, and Weinreb in the rapid synthesis of yohimbine derivatives[14] and racemic indolizidine alkaloid ipalbidine,[15] and in the assembly of the A ring portion of tetracyclic alkaloid phyllanthine,[16] respectively. More recently, the power of the cyclic imine [4+2] annulation strategy was also exemplified by Gin et al. in their elegant creation of the complex tricyclic core structure of the batzelladine alkaloids.[17] Here, we wish to present the use of flexible, unactivated, and optically active Δ^1-pyrroline species as coupling partners to achieve a highly diastereoselective aza-Diels–Alder cycloaddition en route to a range of bicyclic hydroxyindolizidinones, in which the C8a stereogenic center is efficiently established in a substrate-stereocontrolled manner. Furthermore, the synthetic potential of this new method is demonstrated with the short total synthesis of three natural and non-natural polyhydroxylated indolizidines (+)-/(–)-lentiginosines and (–)-2-*epi*-steviamine.

RESULTS AND DISCUSSION

We began our studies by investigating the model cycloaddition reaction of the known *trans*-(3*S*,4*S*)-di-*O*-TBS protected pyrrolidine imine **6a**[18] with an excess of diene **5a** under a range of conditions, which mainly focused on varying the nature of the catalyst and solvent (Table 1). Eventually, use of a stoichiometric amount of zinc chloride as catalyst in THF afforded indolizidinone cycloadducts **4a** and **4a′** as a 1.9:1 mixture of separable diastereomers at C8a in favour of **4a** (36% yield) with a *trans* arrangement for H1 and H8a (Table 1, entry 1). A similar trend was observed in toluene (Table 1, entry 2). The isolated yield (65%) of **4a** was improved in CH_2Cl_2 but the d.r. value was still unsatisfactory (Table 1, entry 3; d.r. 4/1). The stereochemical assignment at the ring junction (C8a) in each of the adducts was firmly established by NOE experiment. In the case of **4a**, the NOE spectrum showed a correlation between protons H2 and H8a, which was evidently absent in the spectrum of isomeric *cis*-H1/H8a adduct **4a′**.

Table 1. Optimization of Aza-Diels–Alder Reaction of Diene 5a and Cyclic Imine 6a[a]



Entry	Catalyst (equiv)	*T* (°C)/Solvent	Yield (%)[b]	dr[c]
1	$ZnCl_2$ (1.0)	–40 → rt/THF	36	1.9/1
2	$ZnCl_2$ (1.0)	–40 → rt/toluene	43	1.2/1
3	$ZnCl_2$ (1.0)	–40 → rt/CH_2Cl_2	65	4/1
4	$AlCl_3$ (1.0)	–40/CH_2Cl_2	70	4.9/1
5	$BF_3{\cdot}Et_2O$ (1.0)	–40/CH_2Cl_2	<15	n.d.[d]

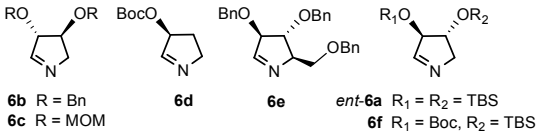
6	AgOTf (1.0)	–40 → rt/CH_2Cl_2	<15	n.d.[d]
7	$Yb(OTf)_3$ (1.0)	–40/CH_2Cl_2	73	11/1
8	$Yb(OTf)_3$ (0.5)	–40 → 0/CH_2Cl_2	73	11/1

[a]Reactions were performed with **5a** (3.0 equiv), **6a** (1.0 equiv), and catalyst in anhydrous organic solvent for 3 h. [b]Isolated yield of the pure diastereomer **4a**. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Not determined.

Using CH_2Cl_2 as reaction medium, we next turned to probe the effect of catalyst on the reaction. Changing the catalyst to $AlCl_3$ brought about an improved yield and stereoselectivity (Table 1, entries 4 vs 3). Both $BF_3{\cdot}Et_2O$ and AgOTf displayed rather low catalytic activity, affording less than 15% yield of the expected products (Table 1, entries 5 and 6). Gratifyingly, when one equiv of $Yb(OTf)_3$ was used as catalyst, the reaction gave the highest efficiency in excellent yield and diastereoselectivity (Table 1, entry 7; 73% yield, d.r. 11/1). In addition, the catalyst loading could be decreased to 0.5 equiv without a loss of reactivity or selectivity (Table 1, entry 8).

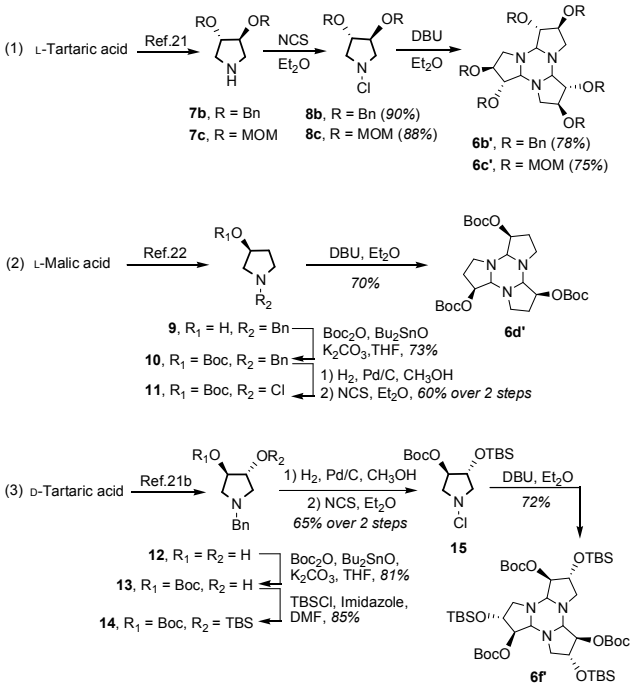
With the optimal reaction conditions (0.5 equiv of $Yb(OTf)_3$ in CH_2Cl_2 at –40 → 0 °C), we set out to examine a panel of enantiopure hydroxylated cyclic imines *ent*-**6a** and **6b**–**f** (*cf.* Figure 2) to establish the reaction generality.

Figure 2. Optically Active Five-Membered Cyclic Imines



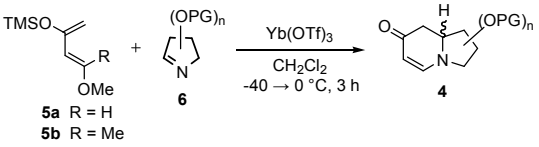
The known cyclic imines *ent*-**6a**[18,19] and **6e**[20] were prepared according to the literature procedures. As depicted in Scheme 2, starting from optically active tartaric and malic acids, the other imine substrates **6b–d** and **6f** were conveniently prepared and characterized as their homochiral trimers **6b′–d′** and **6f′**,[23] respectively, by the use of the published approach involving *N*-chlorination of the corresponding substituted pyrrolidine with *N*-chlorosuccinimide (NCS)[24] and then dehydrochlorination of the resulting pyrrolidine *N*-chlorides with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[18,25,26] The DBU dehydroalogenations of pyrrolidine *N*-chlorides **11** and **15** displayed a complete regioselectivity. In both cases (Scheme 2, eqs 2 and 3), the eliminations occurred exclusively on the side of the BocO group since the electron-withdrawing property of Boc functionality increases the acidity of H2,[27] thus giving rise to triazines **6d′** and **6f′** in 70% and 72% yield, respectively. The structures of these obtained triazine derivatives were confirmed by 1D (^{1}H, ^{13}C, 400 MHz) NMR spectroscopy and ESI MS. Take compound **6c′** for example. In its ^{1}H NMR spectrum, the H2 protons appear as a doublet at δ_H 3.03 ppm ($J_{2,3}$ = 5.2 Hz), while the ^{13}C NMR spectrum shows a peak at δ_C 83.0 ppm for C2. Further support for its structure comes from high-resolution ESI-TOF MS data, which gives an $(M+Na)^+$ signal at *m/z* 590.2905 (calcd 590.2901).

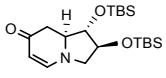
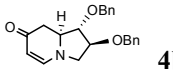
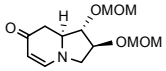
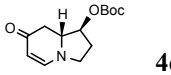
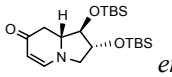
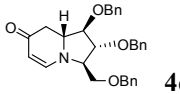
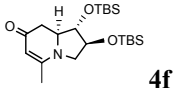
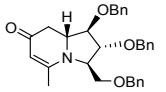
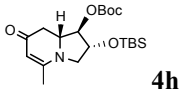
Scheme 2. Synthesis of Optically Active Five-Membered Cyclic Imines



As shown in Table 2, cyclic imines **6a**–**c** bearing various protecting groups including silyl (TBS) ether, benzyl (Bn) ether, and methoxymethyl (MOM) acetal all reacted smoothly with diene **5a**,**b**, affording predominantly the bicyclic *trans*-H1/H8a adducts **4a**–**c** and **4f** with reasonable yields and high level of diastereomeric ratios (Table 2, entries 1–3 and 7). The bulkiness of the oxygen-containing substitution close to the imine carbon–nitrogen double bond had a significant effect on the stereochemical outcome. For example, cycloadditions of the TBS- and Bn-protected **6a** and **6b** gave greater diastereoselectivity ratios of 11:1, 10:1, and 11:1, respectively, instead of the 5:1 ratio obtained by using the MOM-protected **6c** (Table 2, entries 1, 2, and 7 vs entry 3).

Table 2. Substrate Profile[a]

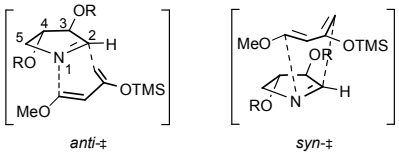


Entry	Diene	Imine	Major Product	Yield (%)[b]	dr[c]
1	**5a**	**6a**	 **4a**	73	11:1
2		**6b**[d]	 **4b**	65	10:1
3		**6c**[d]	 **4c**	62	5:1
4		**6d**[d]	 **4d**	73	>99:1
5		*ent*-**6a**	 *ent*-**4a**	71	10:1
6		**6e**	 **4e**	63	>99:1
7	**5b**	**6a**	 **4f**	70	11:1
8		**6e**	 **4g**	65	>99:1
9		**6f**[d]	 **4h**	62	10:1

[a]Reactions were performed with diene (9.0 equiv), imine trimer (1.0 equiv), and $Yb(OTf)_3$ (1.5 equiv) for entries 2–4, and 9 or with diene (3.0 equiv), imine monomer (1.0 equiv), and $Yb(OTf)_3$ (0.5 equiv) for entries 1, and 5–8 in anhydrous CH_2Cl_2 at –40 → 0 °C for 3 h. [b]Isolated yield of the pure major product. [c]Determined by ^1H NMR analysis of the crude reaction mixture. [d]The trimeric imines could be converted *in situ* into the corresponding monomeric form under the cycloaddition conditions.

Thus, the C3 stereocenter of the five-membered cyclic imine as a key factor in determining the stereoselectivity was demonstrated. The extent of diastereoselectivity was accordingly influenced by the size of the C3 hydroxy protecting group. We reasoned that, due to the steric requirement, the attack of the diene *anti* to the OR function at C3 position of the imine ring should be preferable over the possible *syn* attack (Figure 3). As a result, the larger OH protecting groups will give the better *anti* facial preferences.

Figure 3. Diastereoselectivity of the Cycloaddition



Moreover, the cycloadditions of imino-dienophiles *ent*-**6a** and **6d**–**f** each having a β-substituent at C3 position to dienes **5a**,**b** also followed the less sterically hindered *anti* stereocontrol mode and furnished indolizidinones *ent*-**4a**, **4d**,**e**, and **4g**,**h** with identical H1–H8a *trans* relative configurations as major Diels–Alder cycloadducts in high chemical yields and good to excellent diastereoselectivities (Table 2, entries 4–6, 8, and 9). In fact, the bulky 3-*O*-*tert*-butyloxycarbonyl (Boc)-protected **6d** and the highly congested **6e** derived from D-arabinose are the best cycloaddition building blocks and the corresponding bicyclic adducts **4d**,**e**, and **4g** could be obtained in high yields as single products (Table 2, entries 4, 6, and 8, d.r. >99:1).

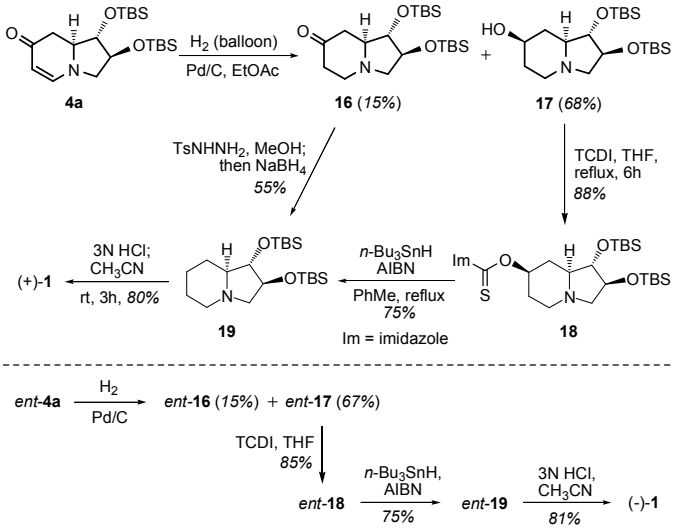
Having realized a practical method to the bicyclic indolizidine enaminones, we then planned to explore their usefulness as key advanced intermediates for making polyhydroxyindolizidine iminosugars.

trans-1,2-Dihydroxyindolizidine (+)-lentiginosine ((+)-**1**), originally extracted by Elbein and co-workers in 1990 from the leaves of *Astragalus lentiginosus*, is a potent and selective indolizidine inhibitor of the fungal α-glucosidase and amyloglucosidase.[6,28] Interestingly, in recent work by Macchi and Brandi et al., the non-natural laevorotatory enantiomer (–)-lentiginosine ((–)-**1**) is found to be able to induce remarkable levels of apoptosis in some tumor cell lines whereas the natural (+)-**1** can not.[29] Over the years, being interested in the two enantiomers, the synthetic community made out of their way to prepare them in greater quantities and to use them as a tool to validate new methodologies.[5,6] We chose lentiginosine as our initial synthetic target since its relatively structural simplicity would enable us to easily check the basic principles of the developed method. Here, we describe an alternative synthetic approach to (+)- and (–)-**1** based on the use of cycloadducts **4a** and *ent*-**4a**.

The synthesis of (+)-lentiginosine is summarized in Scheme 3. The vinylogous amide moiety of **4a** was hydrogenated over palladium-on-carbon (10%) to a 1:4.5 mixture of **16** and **17**, which could be easily separated by silica gel chromatography (15% and 68% yields from **4a**, respectively). Then, the secondary C7 hydroxy group of alcohol **17** was eliminated to generate the TBS-protected lentiginosine **19** through the Barton–McCombie radical deoxygenation method[30] involving esterification of **17** with thionocarbonyl-1,1′-diimidazole (TCDI, 2.0 equiv) in refluxing THF,

followed by radical reduction of the resulting thiocarbonylimidazolide intermediate **18** with tributyltinhydride (4.0 equiv) in the presence of 2,2′-azobisisobutyronitrile (AIBN). Alternatively, **19** could be easily acquired in 55% yield from 7-indolizidinone **16** upon reduction with $NaBH_4$ via its tosylhydrazone ($TsNHNH_2$, MeOH, reflux, 3 h, then $NaBH_4$).[31] Final hydrolysis of **19** with 3 N hydrochloric acid (HCl) in aqueous acetonitrile at room temperature, followed by neutralization of the resulting hydrochloride salt with ion-exchange resin (Dowex OH^- form), furnished an 80% yield of free base (+)-**1** as a white solid. The ^1H and ^{13}C NMR spectral data obtained from this material agreed with those described for the natural substance (see the Supporting Information).[28a] In addition, the optical rotation of the synthetic (+)-**1** {$[\alpha]_D^{20}$ = +3.1 (*c* 0.3, MeOH)} closely matched the value previously reported {lit.[28b] $[\alpha]_D^{25}$ = +3.2 (*c* 0.27, MeOH); lit.[32] $[\alpha]_D$ = +1.7 (*c* 0.6, MeOH)}.

Scheme 3. Synthesis of (+)-/(–)-Lentiginosines ((+)/(–)-1)



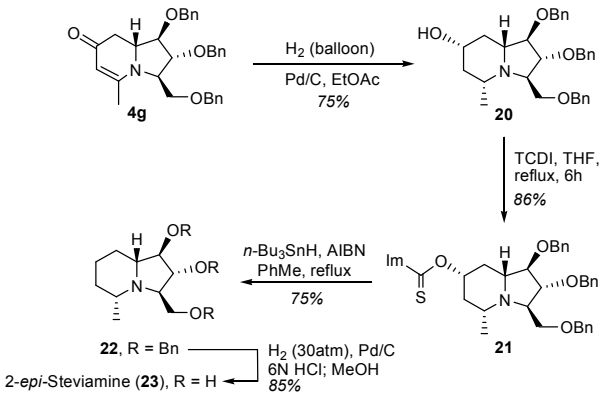
Next, the same synthetic sequence was successfully applied to *ent*-**4a** to prepare (–)-**1** with comparable overall yield (*cf.* Scheme 3). The product obtained was spectroscopically identical to the

literature data reported for (–)-lentiginosine. The optical rotation of (–)-**1** {$[\alpha]_D^{20}$ = –1.8 (*c* 0.32, MeOH); lit.[28b] $[\alpha]_D^{23}$ = –1.6 (*c* 0.24, MeOH)} was opposite to that of the (+)-lentiginosine.

This promising aza-Diels–Alder reaction strategy could also be effectively expanded to the preparation of structural analogue of relevant indolizidine iminosugars. (–)-Steviamine was recently isolated from *Stevia rebaudiana* (Asteraceae) leaves and represents a new type of polyhydroxyindolizidines with a methyl group at C5 position.[33a] Yu's group first synthesized the enantiomer and its C5 epimer of this iminosugar employing nucleophilic addition of organometallic reagents to a D-ribose-derived cyclic nitrone followed by intramolecular reductive amination or S_N2 displacement as key steps to form the indolizidine framework.[33b] Furthermore, (–)-steviamine was disclosed by them as the first natural molecule that possesses a weak inhibitory activity against α-galactosaminidase (GalNAcase).[33b] With the aim of studying the structure-activity relationship and searching for possible anti-GalNAcase candidate with improved bioactivity, we now report on the synthesis of (–)-2-*epi*-steviamine (**23**), a C2 epimer of (–)-steviamine, by exploiting 5-methyl indolizidinone **4g** as key precursor (Scheme 4). The synthesis began with a fully diastereoselective hydrogenolysis of **4g**, which cleanly delivered saturated **20** as a sole isomer in 75% yield. The absolute stereochemistries of the newly formed asymmetric C5 and C7 of **20** were determined to be *R* and *S*, respectively (characteristic NOE correlations: H7–H8a, H5–H9, and H5–H7). Product **20** derives from the preferred equatorial attack of the hydrogen on **4g**.[34] Again, by means of the same two-step deoxygenation protocol, **20** was transformed via **21** into the corresponding deoxygenated **22**, which was catalytically hydrogenated in acidic medium (H_2, 10% Pd/C, 6 N HCl, MeOH, 50 °C, 20 h) to yield triol **23** as a white solid in a good 85% yield from **22** after ion-exchange chromatography

(OH$^-$ form). The structure of the final product was unambiguously confirmed on the basis of 1D and 2D NMR, as well as high-resolution ESI-TOF MS spectral analysis.

Scheme 4. Synthesis of (–)-2-*epi*-Steviamine (23)



CONCLUSION

In conclusion, we have developed an Yb (III)-mediated [4+2] cycloaddition reaction between Danishefsky-type dienes and a broad spectrum of chiral, unactivated, five-membered cyclic aldimines with complete regioselectivity and high degree of diastereoselectivity. The stereoselectivity of the cycloaddition is generally controlled by the C3 stereocenter of the imine heterodienophile. This methodology opens a convergent and ready access to stereochemically rich indolizidine enaminones that are extremely useful synthons for transformation into diverse arrays of polyhydroxyindolizidine iminosugars. Starting from the obtained indolizidinones **4a**/*ent*-**4a**, and **4g**, concise syntheses of (+)-/(–)-lentiginosines (**1**) and non-natural (–)-2-*epi*-steviamine (**23**) have been accomplished in four steps with overall yields of 36%, 35%, and 41%, respectively. Research is now underway to prepare more complex indolizidine glycosidase inhibitors.

EXPERIMENTAL SECTION

(3*S*,4*S*)-*N*-Chloro-3,4-bis(benzyloxy)pyrrolidine (8b). To a solution of **7b** (285 mg, 1.01 mmol) in dry Et_2O (10 mL) was added NCS (135 mg, 1.01 mmol), the mixture was stirred under N_2 at room temperature for 30 min. The reaction mixture was diluted with Et_2O (10 mL) and washed with water (20 mL). The aqueous layer was extracted with Et_2O (20 mL × 2) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (30:1, petroleum ether–EtOAc) to afford compound **8b** as a colorless oil (289 mg, 90%). R_f 0.50 (20:1, petroleum ether–EtOAc). $[\alpha]_D^{20}$ +30.5 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.31 (m, 10H), 4.52 (d, 2H, *J* = 12.4 Hz), 4.48 (d, 2H, *J* = 12.4 Hz), 4.09 (t, 2H, 4.8 Hz), 3.52 (dd, 2H, *J* = 6.4, 10 Hz), 3.23 (dd, 2H, *J* = 3.6, 10 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 66.2, 71.6, 82.4, 127.7, 127.8, 128.4, 137.4; IR (KBr) 3064, 3029, 2969, 2889, 1455 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{20}ClNO_2$ $[M+H]^+$ 318.1261, found 318.1258.

(3*S*,4*S*)-3,4-Bis(benzoyloxy)pyrroline trimer (6b′). To a solution of **8b** (280 mg, 0.88 mmol) in dry Et_2O (18 mL) was added DBU (0.53 mL, 3.52 mmol). The reaction mixture was stirred under N_2 at room temperature for 4 h. The reaction was diluted with Et_2O, and the mixture was washed with water and brine. The organic layer was separated, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (7:1, petroleum ether–EtOAc) to afford compound **6b′** as a colorless oil (193 mg, 78%). R_f 0.45 (4:1, petroleum ether–EtOAc). $[\alpha]_D^{20}$ +16.7 (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.27 (m, 30H), 4.56 (s, 6H), 4.51 (d, 3H, *J* = 12.0 Hz), 4.42 (d, 3H, *J* = 12.0 Hz), 4.01–3.98 (m, 3H), 3.90 (dd, 3H, *J* = 3.2, 4.8 Hz), 3.09–3.05 (m, 6H), 2.64 (dd, 3H, *J* = 6.8, 9.6 Hz);

^{13}C NMR (100 MHz, $CDCl_3$): δ 50.4, 71.2, 71.6, 82.1, 84.2, 85.3, 127.6, 127.7, 127.9, 128.28, 128.3, 137.9, 138.0; IR (KBr) 3062, 3030, 2921, 2860, 1454 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{54}H_{57}N_3O_6$ $[M+Na]^+$ 866.4145, found 866.4138.

(3*S*,4*S*)-*N*-Chloro-3,4-bis(methoxymethoxy)pyrrolidine (8c). Prepared from **7c** (300 mg, 1.57 mmol) and NCS (210 mg, 1.57 mmol) in dry Et_2O (15 mL) following the procedure similar to that for **7b** → **8b**. The residue was purified by silica gel column chromatography (6:1, petroleum ether–EtOAc) to afford compound **8c** as a colorless oil (311 mg, 88%). R_f 0.30 (5:1, petroleum ether–EtOAc). $[\alpha]_D^{20}$ –1.3 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.71 (d, 2H, *J* = 7.2 Hz), 4.65 (d, 2H, *J* = 6.8 Hz), 4.20–4.17 (m, 2H), 3.55 (dd, 2H, *J* = 6, 10.4 Hz), 3.38 (s, 6H), 3.19 (dd, 2H, *J* = 4.4, 10.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5, 66.5, 80.7, 95.8; IR (KBr) 2944, 2893, 1470, 1152, 1111, 1039 cm^{-1}; HRMS (ESI-TOF) calcd for $C_8H_{16}ClNO_4$ $[M+H]^+$ 226.0846, found 226.0845.

(3*S*,4*S*)-3,4-Bis(methoxymethoxy)pyrroline trimer (6c′). Prepared from **8c** (300 mg, 1.33 mmol) and DBU (0.80 mL, 5.32 mmol) in dry Et_2O (26 mL) following the procedure similar to that for **8b** → **6b′**. The residue was purified by silica gel column chromatography (3:1, petroleum ether–EtOAc) to afford compound **6c′** as a colorless oil (188 mg, 75%). R_f 0.40 (1:1, petroleum ether–EtOAc). $[\alpha]_D^{20}$ +35.3 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 (d, 3H, *J* = 7.2 Hz), 4.71 (d, 6H, *J* = 6.8 Hz), 4.65 (d, 3H, *J* = 6.8 Hz), 4.10–4.05 (m, 6H), 3.40 (s, 9H), 3.38 (s, 9H), 3.15 (dd, 3H, *J* = 3.2, 10.0 Hz), 3.03 (d, 3H, *J* = 5.2 Hz), 2.81 (dd, 3H, *J* = 6.4, 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.2, 55.4, 55.5, 79.9, 83.0, 84.5, 95.5, 95.6; IR (KBr) 2942, 2893, 1466, 1152, 1039 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{45}N_3O_{12}$ $[M+Na]^+$ 590.2901, found 590.2905.

(*S*)-*N*-Benzyl-3-*tert*-butoxycarbonyloxypyrrolidine (10). To a solution of **9** (1.00 g, 5.65 mmol) in dry THF (20 mL) were added a catalytic amount of Bu_2SnO (141 mg, 0.56 mmol), K_2CO_3 (1.46 g,

11.3 mmol), and Boc_2O (2.46 g, 11.3 mmol) at room temperature. The mixture was stirred at 30 °C for 24 h. Then the mixture was poured into water and extracted with ethyl acetate (30 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (3:1, petroleum ether–EtOAc) to afford compound **10** as a colorless oil (1.14 g, 73%). R_f 0.50 (2:1, petroleum ether–EtOAc). $[\alpha]_D^{20}$ –5.1 (*c* 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.28 (m, 4H), 7.25–7.23 (m, 1H), 5.06–5.02 (m, 1H), 3.65 (d, 1H, *J* = 12.8 Hz), 3.59 (d, 1H, *J* = 12.8 Hz), 2.88 (dd, 1H, *J* = 4.8, 10.8 Hz), 2.71 (dd, 1H, *J* = 7.2, 16.0 Hz), 2.64 (dd, 1H, *J* = 4.2, 10.8 Hz), 2.49 (dd, 1H, *J* = 8.0, 14.4 Hz), 2.29–2.20 (m, 1H), 1.93–1.86 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 31.8, 52.4, 59.6, 60.0, 76.5, 81.9, 126.9, 128.2, 128.7, 138.5, 153.2; IR (KBr) 3062, 3028, 2978, 2793, 1737, 1454 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{23}NO_3$ $[M+H]^+$ 278.1756, found 278.1759.

(*S*)-*N*-Chloro-3-*tert*-butoxycarbonyloxypyrrolidine (11). To a solution of **10** (1.00 g, 3.61 mmol) in CH_3OH (15 mL) was added 10% Pd/C (200 mg). The suspension was stirred under a hydrogen atmosphere at room temperature for 4 h, then the insoluble material was filtered off, the filtrate was concentrated under reduced pressure to give a residue which was extracted with Et_2O. The organic extract was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to dryness. The residue was directly used for the next step without further purification. NCS (482 mg, 3.61 mmol) was added to a solution of obtained residue in dry Et_2O (30 mL). The mixture was stirred under N_2 at room temperature for 30 min, then was diluted with Et_2O (30 mL). The resulting mixture was washed with water and brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by

silica gel column chromatography (20:1, petroleum ether–EtOAc) to afford compound **11** as a colorless oil (479 mg, 60% over two steps). R_f 0.50 (10:1, petroleum ether–EtOAc). $[\alpha]_D^{20}$ –2.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.16–5.11 (m, 1H), 3.53 (dd, 1H, *J* = 6.4, 12.4 Hz), 3.40–3.34 (m, 1H), 3.30 (dd, 1H, *J* = 3.2, 12.4 Hz), 3.18–3.12 (m, 1H), 2.47–2.37 (m, 1H), 2.06–1.98 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.6, 30.9, 60.9, 67.7, 75.1, 82.3, 152.8; IR (KBr) 2981, 2852, 1740, 1457 cm^{-1}; HRMS (ESI-TOF) calcd for $C_9H_{16}ClNO_3$ $[M+H]^+$ 222.0897, found 222.0900.

(*S*)-3-*tert*-Butoxycarbonyloxypyrroline trimer (6d′). Prepared from **11** (400 mg, 1.80 mmol) and DBU (1.08 mL, 7.20 mmol) in dry Et_2O (36 mL) following the procedure similar to that for **8b** → **6b′**. The residue was purified by silica gel column chromatography (10:1, petroleum ether–EtOAc) to afford compound **6d′** as a colorless oil (233 mg, 70%). R_f 0.50 (4:1, petroleum ether–EtOAc). $[\alpha]_D^{20}$ –3.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.93–4.90 (m, 3H), 3.21(d, 3H, *J* = 4.8 Hz), 3.05 (dt, 3H, *J* = 3.6, 8.4 Hz), 2.65 (dd, 3H, *J* = 8.4, 16.0 Hz), 2.44–2.34 (m, 3H), 1.79–1.71 (m, 3H), 1.48 (s, 27H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 28.9, 44.5, 76.8, 82.3, 84.8, 153.0; IR (KBr) 2978, 2928, 2853, 1739, 1457 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{27}H_{45}N_3O_9$ $[M+Na]^+$ 578.3053, found 578.3048.

(3*R*,4*R*)-*N*-Benzyl-3-*tert*-butoxycarbonyloxy-4-hydroxypyrrolidine (13). Prepared from **12** (1.00 g, 5.21 mmol), Bu_2SnO (130 mg, 0.52 mmol), K_2CO_3 (1.44 g, 10.4 mmol), and Boc_2O (1.36 g, 6.25 mmol) in dry THF (20 mL) following the procedure similar to that for **9** → **10**. The residue was purified by silica gel column chromatography (40:1, CH_2Cl_2–MeOH) to afford compound **13** as a colorless oil (1.24 g, 81%). R_f 0.50 (12:1, CH_2Cl_2–MeOH). $[\alpha]_D^{20}$ +18.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.25 (m, 5H), 4.68–4.71 (m, 1H), 4.25–4.22 (m, 1H), 3.67 (d, 1H, *J* = 12.8 Hz), 3.55 (d, 1H, *J* = 12.8 Hz), 3.00–2.94 (m, 2H), 2.65 (dd, 1H, *J* = 4.0, 10.8 Hz), 2.52 (dd, 1H, *J* =

5.6, 9.6 Hz), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 57.5, 59.66, 59.7, 76.8, 82.8, 84.0, 127.1, 128.2, 128.8, 137.8, 153.9; IR (KBr) 3414, 3063, 3029, 2978, 2933, 2800, 1739, 1454 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{23}NO_4$ $[M+Na]^+$ 316.1525, found 316.1532.

(3*R*,4*R*)-*N*-Benzyl-3-*tert*-butyldimethylsilyloxy-4-*tert*-butoxycarbonyloxypyrrolidine (14). To a solution of **13** (1.00 g, 3.41 mmol) in dry DMF (10 mL) were added imidazole (469 mg, 6.82 mmol) and TBDMSCl (614 mg, 4.09 mmol) at 0 °C. The reaction mixture was warmed gradually to room temperature and stirred for 3 h at the same temperature. The resulting mixture was added to water (20 mL), extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (40:1, petroleum ether–EtOAc) to afford compound **14** as a colorless oil (1.18 g, 85%). R_f 0.50 (20:1, petroleum ether–EtOAc). $[\alpha]_D^{20}$ –30.5 (*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.28 (m, 4H), 7.26–7.23 (m, 1H), 4.85–4.83 (m, 1H), 4.31 (dt, 1H, *J* = 2.4, 6.0 Hz), 3.66 (d, 1H, *J* = 13.2 Hz), 3.55 (d, 1H, *J* = 13.2 Hz), 3.06 (dd, 1H, *J* = 6.4, 9.6 Hz), 2.86 (dd, 1H, *J* = 6.4, 10.8 Hz), 2.74 (dd, 1H, *J* = 2.4, 10.8 Hz), 2.30 (dd, 1H, *J* = 5.6, 9.6 Hz), 1.47 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ –5.0, –4.9, 18.0, 25.7, 27.7, 58.1, 60.1, 60.9, 76.7, 82.0, 83.5, 127.0, 128.2, 128.7, 138.3, 153.1; IR (KBr) 3063, 3029, 2955, 2931, 2857, 1741, 1469 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{37}NO_4Si$ $[M+H]^+$ 408.2570, found 408.2567.

(3*R*,4*R*)-*N*-Chloro-3-*tert*-butyldimethylsilyloxy-4-*tert*-butoxycarbonyloxypyrrolidine (15). Prepared from **14** (1.16 g, 2.85 mmol) following the procedure similar to that for **10** → **11**. The residue was purified by silica gel column chromatography (60:1, petroleum ether–EtOAc) to afford compound **15** as a colorless oil (652 mg, 65% over two steps). R_f 0.50 (40:1, petroleum ether–EtOAc).

$[\alpha]_D^{20}$ –34.9 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.86–4.83 (m, 1H), 4.36–4.32 (m, 1H), 3.60 (dd, 1H, *J* = 6.4, 10.4 Hz), 3.56 (dd, 1H, *J* = 6.0, 12.0 Hz), 3.30 (dd, 1H, *J* = 2.4, 12.0 Hz), 2.99 (dd, 1H, *J* = 5.2, 10.4 Hz), 1.48 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ –5.1, –5.0, 17.9, 25.6, 27.7, 66.3, 68.7, 75.7, 82.4, 82.7, 152.7; IR (KBr) 2956, 2932, 2857, 1744, 1470 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{30}ClNO_4Si$ $[M+Na]^+$ 374.1530, found 374.1559.

(3*R*,4*R*)-3-*tert*-Butoxycarbonyloxy-4-(*tert*-butyldimethylsilyloxy)pyrroline trimer (6f′). Prepared from **15** (400 mg, 1.14 mmol) and DBU (0.68 mL, 4.56 mmol) in dry Et_2O (23 mL) following the procedure similar to that for **8b → 6b′**. The residue was purified by silica gel column chromatography (20:1, petroleum ether–EtOAc) to afford compound **6f′** as a colorless oil (258 mg, 72%). R_f 0.50 (15:1, petroleum ether–EtOAc). $[\alpha]_D^{20}$ –31.3 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.91–4.89 (m, 3H), 4.23–4.21 (m, 3H), 3.11–3.05 (m, 6H), 2.89–2.85 (m, 3H), 1.48 (s, 27H), 0.88 (s, 27H), 0.09–0.03 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ –5.0, 18.0, 25.7, 27.7, 53.7, 75.1, 82.3, 83.0, 84.2, 152.6; IR (KBr) 2956, 2890, 2857, 1745, 1467 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{45}H_{87}N_3O_{12}Si_3$ $[M+Na]^+$ 968.5495, found 968.5487.

General Procedure for Aza-Diels-Alder Reaction of Cyclic Imines with Danishefsky-Type Dienes. To a suspension of $Yb(OTf)_3$ (0.075 mmol) in dry CH_2Cl_2 (1 mL) was added a solution of imine monomer (0.15 mmol) or imine trimer (0.05 mmol) in dry CH_2Cl_2 (1 mL) at –40 °C under N_2. The mixture was stirred for 10 min at the same temperature, then a solution of Danishefsky-type diene (0.45 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise. After being stirred for 2.5 h at the same temperature, the mixture was warmed gradually to 0 °C within 30 min. The solution was quenched with saturated $NaHCO_3$, diluted with CH_2Cl_2, and then the resulting mixture was washed with water and brine. The organic layer was separated, dried over anhydrous Na_2SO_4, and filtered. The filtrate

was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography to give the corresponding cycloadducts.

Compounds 4a and 4a′. 4a: colorless oil (73% yield, 11:1 dr); R_f 0.53 (1:1, petroleum ether–EtOAc). $[\alpha]_D^{20}$ +300.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, 1H, *J* = 7.2 Hz), 4.93 (d, 1H, *J* = 7.2 Hz), 4.11 (dd, 1H, *J* = 4.8, 13.6 Hz), 3.91 (t, 1H, *J* = 4.8 Hz), 3.73 (dd, 1H, *J* = 5.6, 10.4 Hz), 3.64 (dt, 1H, *J* = 5.6, 16.4 Hz), 3.26 (dd, 1H, *J* = 4.4, 10.4 Hz), 2.54 (t, 1H, *J* = 16.0 Hz), 2.43 (dd, 1H, *J* = 5.6, 16.0 Hz), 0.89 (s, 9H), 0.88 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.8, –4.7, –4.6, –4.3, 17.8, 17.81, 25.6, 25.7, 39.1, 55.5, 63.1, 77.2, 82.3, 97.5, 150.3, 191.7; IR (KBr) 2955, 2931, 2889, 2857, 1640, 1588, 1465 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{39}NO_3Si_2$ $[M+H]^+$ 398.2547, found 398.2539. **4a′**: colorless oil (6% yield); R_f 0.55 (1:1, petroleum ether–EtOAc). $[\alpha]_D^{20}$ –215.3 (*c* 0.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, 1H, *J* = 7.2 Hz), 4.94 (d, 1H, *J* = 7.2 Hz), 4.11–4.09 (m, 1H), 4.04 (d, 1H, *J* = 16.4 Hz), 3.96–3.94 (m, 1H), 3.73 (dd, 1H, *J* = 4.8, 10.8 Hz), 3.25 (d, 1H, *J* = 10.8 Hz), 2.72 (t, 1H, *J* = 16.4 Hz), 2.13 (dd, 1H, *J* = 5.2, 16.0 Hz), 0.89 (s, 9H), 0.88 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.9, –4.8, –4.6, –4.7, 17.8, 17.9, 25.6, 25.7, 35.2, 56.0, 59.5, 75.8, 77.6, 96.3, 150.2, 192.6; IR (KBr) 2954, 2927, 1642, 1586, 1461 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{39}NO_3Si_2$ $[M+H]^+$ 398.2547, found 398.2546.

Compound 4b. Colorless oil (65% yield, 10:1 dr); R_f 0.40 (85:1, CH_2Cl_2–CH_3OH); $[\alpha]_D^{20}$ +136.4 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.30 (m, 10H), 7.04 (d, 1H, *J* = 7.2 Hz), 4.96 (d, 1H, *J* = 7.2 Hz), 4.63 (s, 2H), 4.60 (d, 1H, *J* = 11.6 Hz), 4.55 (d, 1H, *J* = 12.0 Hz), 4.17–4.13 (m, 1H), 3.97–3.95 (m, 1H), 3.82–3.75 (m, 1H), 3.69 (dd, 1H, *J* = 2.0, 11.2 Hz), 3.46 (dd, 1H, *J* =3.6, 11.2 Hz), 2.53 (d, 1H, *J* = 1.2 Hz), 2.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.9, 53.4, 61.7, 72.1, 72.4,

82.0, 87.0, 98.3, 127.7, 128.1, 128.6, 137.2, 150.1, 191.5; IR (KBr) 3057, 3032, 2966, 2922, 2851, 1638, 1576, 1467 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{23}NO_3$ $[M+H]^+$ 350.1756, found 350.1759.

Compound 4c. Colorless oil (62% yield, 5:1 dr); R_f 0.45 (1:1, acetone–cyclohexane); $[\alpha]_D^{20}$ +291.2 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, 1H, J = 7.2 Hz), 4.98 (d, 1H, J = 7.2 Hz), 4.79 (d, 1H, J = 7.2 Hz), 4.74 (d, 1H, J = 6.8 Hz), 4.67 (dd, 2H, J = 2.8, 6.8 Hz), 4.20 (dd, 1H, J = 4.8, 11.2 Hz), 4.06–4.03 (m, 1H), 3.80 (dd, 1H, J = 6.8, 11.2 Hz), 3.74–3.70 (m, 1H), 3.46 (dd, 1H, J = 5.2, 11.2 Hz), 3.39 (s, 3H), 3.38 (s, 3H), 2.62–2.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.5, 53.4, 55.7, 55.8, 60.9, 80.4, 85.1, 96.3, 96.5, 98.3, 150.0, 191.7; IR (KBr) 2946, 2894, 2826, 1636, 1581, 1460, 1152, 1106, 1039 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{19}NO_5$ $[M+Na]^+$ 280.1161, found 280.1201.

Compound 4d. Pale yellow oil (73% yield, >99:1 dr); R_f 0.35 (1:3, petroleum ether–EtOAc); $[\alpha]_D^{20}$ –263.7 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, 1H, J = 6.8 Hz), 4.94–4.87 (m, 2H), 3.75 (dt, 1H, J = 5.2, 16.4 Hz), 3.64–3.58 (m, 1H), 3.53–3.48 (m, 1H), 2.59 (dd, 1H, J = 5.2, 16.0 Hz), 2.49–2.42 (m, 1H), 2.41 (t, 1H, J = 16.4 Hz), 2.09–2.00 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.6, 30.8, 39.3, 47.6, 62.3, 79.5, 83.1, 98.2, 149.8, 152.6, 191.2; IR (KBr) 2959, 2927, 2855, 1740, 1630, 1577, 1459 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{19}NO_4$ $[M+Na]^+$ 276.1212, found 276.1207.

Compound *ent*-4a. Colorless oil (71% yield, 10:1 dr); $[\alpha]_D^{20}$ –295.3 (*c* 1.0, $CHCl_3$); its spectroscopic data were identical with those of **4a**.

Compound 4e. Yellow oil (63% yield, >99:1 dr); R_f 0.45 (2:3, petroleum ether–EtOAc); $[\alpha]_D^{20}$ –139.6 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.19 (m, 15H), 7.20 (d, 1H, J = 7.2 Hz), 4.95 (d, 1H, J = 7.6 Hz), 4.61 (d, 4H, J = 3.2 Hz), 4.49 (s, 2H), 3.96 (d, 2H, J = 5.2 Hz), 3.90 (dd, 1H,

J = 7.2, 14,4 Hz), 3.80 (d, 1H, J = 3.2 Hz), 3.56–3.46 (m, 2H), 2.55 (s, 1H), 2.52 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.5, 61.3, 64.5, 69.2, 72.3, 72.5, 73.4, 84.2, 87.9, 98.1, 127.7, 127.71, 127.8, 128.0, 128.07, 128.1, 128.5, 128.52, 128.53, 128.56, 137.1, 137.3, 149.9, 191.3; IR (KBr) 3061, 3031, 2923, 2861, 1638, 1576, 1455 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{30}H_{31}NO_4$ $[M+H]^+$ 470.2331, found 470.2334.

Compound 4f. Yellow oil (70% yield, 11:1 dr); R_f 0.50 (1:3, acetone–cyclohexane). $[\alpha]_D^{20}$ +261.1 (c 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.91 (s, 1H), 4.13–4.10 (m, 1H), 3.92 (t, 1H, J = 5.2 Hz), 3.71 (dd, 1H, J = 6.4, 10.8 Hz), 3.62 (dt, 1H, J = 14.4, 6.0 Hz), 3.28 (dd, 1H, J = 5.2, 10.8 Hz), 2.50–2.40 (m, 2H), 1.98 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.7, –4.66, –4.5, –4.3, 17.8, 19.9, 25.66 , 25.7, 39.1, 52.5, 63.8, 76.4, 81.8, 98.5, 160.5, 191.0; IR (KBr) 2957, 2930, 2892, 2858, 1619, 1543, 1471 cm^{-1}; HRMS: calcd for $C_{21}H_{41}NO_3Si_2$ $[M+H]^+$, 412.2703, found 412.2699.

Compound 4g. Yellow oil (65% yield, >99:1 dr); R_f 0.40 (2:3, petroleum ether–EtOAc); $[\alpha]_D^{20}$ +138.8 (c 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.28 (m, 10H), 7.24–7.21 (m, 5H), 4.90 (s, 1H), 4.56 (d, 2H, J = 12.0 Hz), 4.49 (s, 2H), 4.45 (s, 2H), 4.08–4.05 (m, 2H), 3.95 (dt, 1H, J = 4.0, 16.0 Hz), 3.84 (d, 1H, J = 3.2 Hz), 3.55 (d, 2H, J = 7.2 Hz), 2.53 (t, 1H, J = 16.0 Hz), 2.40 (dd, 1H, J = 5.2, 16.0 Hz), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 39.8, 63.8 (2C), 68.2, 71.4, 71.6, 73.3, 84.2, 86.9, 99.4, 127.5, 127.6, 127.7, 127.9, 128.0, 128.4, 128.5, 137.0, 137.3, 137.4, 160.6, 190.7; IR (KBr) 3061, 3030, 2920, 2864, 1627, 1548, 1453 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{31}H_{33}NO_4$ $[M+H]^+$ 484.2488, found 484.2494.

Compound 4h. Pale yellow oil (62% yield, 10:1 dr); R_f 0.40 (1:3, acetone–cyclohexane); $[\alpha]_D^{20}$ –296.2 (c 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.94 (s, 1H), 4.81 (t, 1H, J = 4.0 Hz), 4.36 (d,

1H, J = 4.8 Hz), 3.81 (td, 1H, J = 4.4, 16.0 Hz), 3.72 (dd, 1H, J = 5.6, 11.2 Hz), 3.41 (dd, 1H, J = 3.2, 11.2 Hz), 2.61 (t, 1H, J = 16.0 Hz), 2.49 (dd, 1H, J = 4.8, 16.0 Hz), 1.99 (s, 3H), 1.49 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ –5.1, –4.9, 17.8, 20.1, 25.5, 27.6, 39.0, 53.0, 62.2, 73.9, 83.3, 83.7, 99.2, 152.3, 160.3, 191.0; IR (KBr) 2959, 2913, 2857, 1745, 1637, 1563, 1472 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{35}NO_5Si$ $[M+H]^+$ 398.2363, found 398.2368.

(1*S*,2*S*,8a*S*)-1,2-Bis(*tert*-butyldimethylsilyloxy)octahydroindolizin-7-one (16) and (1*S*,2*S*,7*R*,8a*S*)-l,2-Bis(*tert*-butyldimethylsilyloxy)-7-hydroxyoctahydroindolizine (17). To a solution of **4a** (300 mg, 0.75 mmol) in EtOAc (10 mL) was added 10% Pd/C (90 mg). The suspension was stirred under an atmosphere of H_2 for 3 h at 35°C. The insoluble material was filtered off. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (1:6, acetone–cyclohexane) to afford compounds **16** (45 mg, 15%) and **17** (205 mg, 68%). Products **16** and **17** are known compounds and their spectroscopic data matched the reported data.[34]

(1*S*,2*S*,7*R*,8a*S*)-7-Imidazolylthiocarbonyloxy-1,2-bis(*tert*-butyldimethylsilyloxy)octahydroindolizine (18). To a solution of alcohol **17** (100 mg, 0.25 mmol) in dry THF (3 mL) was added thionocarbonyl-1,1′-diimidazole (TCDI) (89 mg, 0.50 mmol). The mixture was heated at reflux temperature for 6 h, and then cooled to room temperature and the solvent was evaporated. The resulting residue was purified by silica gel column chromatography (1:5, acetone–cyclohexane) to afford compound **18** as a yellow oil (113 mg, 88%). R_f 0.60 (1:2, acetone–cyclohexane). $[\alpha]_D^{20}$ +25.7 (c 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.62 (s, 1H), 7.03 (s, 1H), 5.42–5.37 (m, 1H), 4.05 (s, 1H), 3.80 (dd, 1H, J = 3.2, 8.0 Hz), 3.02 (d, 1H, J = 12.0 Hz), 2.86 (d, 1H, J = 10.0 Hz), 2.59 (t, 1H, J = 8.0 Hz), 2.43 (d, 1H, J = 10.4 Hz), 2.20–2.11 (m, 2H), 2.02 (t, 1H, J = 8.8 Hz),

1.93–1.84 (m, 1H), 1.57 (dd, 1H, J = 11.2, 22.4 Hz), 0.89 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.7, –4.3, –4.2, –4.1, 17.9, 25.8, 25.9, 29.5, 33.3, 49.7, 60.9, 66.5, 78.9, 81.3, 84.9, 117.8, 130.7, 136.8, 183.2. IR (KBr) 2954, 2930, 2857, 1466, 1248 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{45}N_3O_3SSi_2$ $[M+H]^+$ 512.2798, found 512.2793.

(1*S*,2*S*,8a*S*)-1,2-Bis(*tert*-butyldimethylsilyloxy)octahydroindolizine (19). Prepared from **18**: To a refluxing solution of tri-*n*-butyltinhydride (0.21 mL, 0.76 mmol) in dry toluene (13 mL) was added a mixture of **18** (100 mg, 0.19 mmol) and AIBN (5.4 mg, 0.03 mmol) in toluene (6 mL) by syringe within 1 h. The mixture was heated under reflux for further 2 h. The solvent was evaporated and the residue was purified by silica gel column chromatography (11:1, petroleum ether–EtOAc) to give **19** (55 mg, 75%) as a colorless oil. R_f 0.55 (5:1, petroleum ether–EtOAc). $[\alpha]_D^{20}$ +17.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98 (ddd, 1H, J = 2.0, 4.0, 8.0 Hz), 3.73 (dd, 1H, J = 4.0, 8.4 Hz), 2.92 (d, 1H, J = 10.8 Hz), 2.85 (dd, 1H, J = 2.0, 10.0 Hz), 2.53 (dd, 1H, J = 8.0, 10.0 Hz), 1.94–1.74 (m, 4H), 1.58–1.54 (m, 2H), 1.18–1.22 (m, 2H), 0.89 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.7, –4.3, –4.2, –4.1, 17.8, 17.9, 23.9, 24.8, 25.8, 25.9, 28.6, 53.3, 62.1, 68.4, 78.0, 85.1; IR (KBr) 2931, 2888, 2856, 1467, 1255 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{43}NO_2Si_2$ $[M+H]^+$ 386.2911, found 386.2901.

Prepared from **16**: To a solution of **16** (40 mg, 0.10 mmol) in dry MeOH (3 mL) were added (*p*-toluenesulfonyl)hydrazine (70 mg, 0.37 mmol) and freshly activated 4 Å molecular sieves. The mixture was refluxed for 3 h (TLC monitoring). After cooling to 0 °C, a large excess of $NaBH_4$ (93 mg, 2.45 mmol) was added and the mixture was heated under reflux for 3 h. The mixture was filtered off, the filtrate was concentrated under reduced pressure to give a residue which was dissolved in water and extracted with Et_2O. The organic layer was separated, dried over anhydrous Na_2SO_4, and

filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (11:1, petroleum ether–EtOAc) to give **19** (21 mg, 55%) as a colorless oil.

(1*S*,2*S*,8a*S*)-1,2-Dihydroxyoctahydroindolizine, (+)-lentiginosine ((+)-1). To a solution of **19** (50 mg, 0.13 mmol) in CH_3CN (1 mL) was added 3 N HCl (1 mL). The mixture was stirred at 25 °C for 3 h. Then, the mixture was neutralized by addition of anhydrous Na_2CO_3 at 0 °C. The mixture was filtered and the obtained filtrate was concentrated under reduced pressure to dryness. The residue was purified by silica gel column chromatography (5:1, CH_2Cl_2–CH_3OH). The obtained compound was purified by ion-exchange chromatography (Dowex OH^- form) using distilled water to afford (+)**-1** (16 mg, 80%) as a white solid. R_f 0.30 (5:1, CH_2Cl_2–CH_3OH); mp: 106–108 °C (lit.[28b] 106–107 °C, lit.[32] 107–108 °C); $[\alpha]_D^{20}$ +3.1 (*c* 0.30, CH_3OH) {lit.[28b] $[\alpha]_D^{25}$ +3.2 (*c* 0.27, CH_3OH), lit.[32] $[\alpha]_D$ +1.7 (*c* 0.60, CH_3OH)}; ^{1}H NMR (400 MHz, D_2O): δ 4.08 (ddd, 1H, *J* = 2.0, 4.0, 7.6 Hz), 3.66 (dd, 1H, *J* = 4.0, 8.4 Hz), 2.96 (d, 1H, *J* = 11.2 Hz), 2.85 (d, 1H, *J* = 11.2 Hz), 2.66 (dd, 1H, *J* = 7.6, 11.2 Hz), 2.08 (dt, 1H, *J* = 2.8, 11.2 Hz), 1.99–1.90 (m, 2H), 1.83–1.79 (m, 1H), 1.63 (d, 1H, *J* = 13.2 Hz), 1.38–1.49 (m, 1H), 1.19–1.32 (m, 2H); ^{13}C NMR (100 MHz, D_2O): δ 25.7, 26.6, 30.2, 55.3, 62.9, 71.2, 78.2, 85.5; HRMS (ESI-TOF) calcd for $C_8H_{15}NO_2$ $[M+Na]^+$ 180.1000, found 180.0982.

(1*R*,2*R*,8a*R*)-1,2-Dihydroxyoctahydroindolizine, (–)-lentiginosine ((–)-1). Using the same four-step procedure as described for the preparation of (+)**-1**, (–)**-1** was synthesized in 35% overall yield (based on *ent*-**4a**) from *ent*-**4a** via intermediates *ent*-**17**, *ent*-**18**, and *ent*-**19**. Compound (–)**-1**: mp: 106–107 °C (lit.[28b] 106–107 °C, lit.[32] 106–107 °C); $[\alpha]_D^{20}$ –1.8 (*c* 0.32, CH_3OH) {lit.[28b] $[\alpha]_D^{23}$ –1.6 (*c* 0.24, CH_3OH), lit.[32] $[\alpha]_D$ –3.05 (*c* 1.0, CH_3OH)}; Its ^{1}H and ^{13}C NMR spectroscopic data were identical with those of (+)**-1**.

(1*R*,2*R*,3*R*,5*R*,7*S*,8a*R*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-5-methyloctahydroindolizin-7-ol (20). Prepared from **4g** (200 mg, 0.41 mmol) and 10% Pd/C (60 mg) in EtOAc (6 mL) following the procedure similar to that for **4a** → **16** and **17**. The residue was purified by silica gel column chromatography (1:6, acetone–cyclohexane) to afford compound **20** as a pale yellow oil (150 mg, 75%). R_f 0.55 (1:3, acetone–cyclohexane). $[\alpha]_D^{20}$ –20.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.21 (m, 15H), 4.65 (d, 1H, *J* = 12.0 Hz), 4.52 (d, 2H, *J* = 2.0 Hz), 4.43 (t, 3H, *J* = 12.0 Hz), 3.93 (d, 1H, *J* = 2.0 Hz), 3.70–3.64 (m, 2H), 3.57–3.51 (m, 2H), 3.43 (t, 1H, *J* = 8.4 Hz), 2.70 (t, 1H, *J* = 8.0 Hz), 2.59–2.63 (m, 1H), 2.23 (d, 1H, *J* = 10.4 Hz), 1.84 (d, 1H, *J* =11.6 Hz), 1.23–1.17 (m, 3H), 1.14 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9, 39.6, 43.2, 49.2, 62.1, 62.3, 65.4, 68.7, 71.2, 71.7, 73.4, 85.7, 89.2, 127.5, 127.56, 127.6, 127.7, 128.2, 128.3, 128.33, 138.0, 138.2; IR (KBr) 3397, 3067, 3030, 2952, 2856, 1454 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{31}H_{37}NO_4$ $[M+H]^+$ 488.2801, found 488.2798.

(1*R*,2*R*,3*R*,5*R*,7*S*,8a*R*)-7-Imidazolylthiocarbonyloxy-1,2-bis(benzyloxy)-3-(benzyloxymethyl)-5-methyloctahydroindolizine (21). Prepared from **20** (150 mg, 0.31 mmol) and thionocarbonyl-1,1′-diimidazole (TCDI) (110 mg, 0.62 mmol) in dry THF (3 mL) following the procedure similar to that for **17** → **18**. The residue was purified by silica gel column chromatography (1:6, acetone–cyclohexane) to afford compound **21** as a yellow oil (159 mg, 86%). R_f 0.51 (1:4, acetone–cyclohexane). $[\alpha]_D^{20}$ –9.2 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.59 (s, 1H), 7.59–7.21 (m, 15H), 7.02 (s, 1H), 5.38–5.40 (m, 1H), 4.66 (d, 1H, *J* = 12.6 Hz), 4.54 (dd, 2H, *J* = 12.0, 13.2 Hz), 4.74–4.40 (m, 3H), 3.73 (d, 1H, *J* = 5.2 Hz), 3.67 (dd, 1H, *J* = 3.2, 8.8 Hz), 3.55 (dd, 1H, *J* = 3.6, 7.6 Hz), 3.47 (t, 1H, *J* = 8.0 Hz), 2.85 (t, 1H, *J* = 8.0 Hz), 2.78 (s, 1H), 2.48 (d, 1H, *J* = 10.4 Hz), 2.15 (d, 1H, *J* = 11.6 Hz), 1.42–1.57 (m, 3H), 1.19 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (100

MHz, $CDCl_3$): δ 19.9, 35.1, 38.2, 49.0, 61.9, 62.2, 65.5, 71.3, 71.8, 73.5, 80.6, 85.5, 89.1, 117.8, 127.6, 127.65, 127.7, 127.8, 128.2, 128.3, 128.33, 128.4, 130.6, 136.8, 137.87, 137.9, 138.0, 183.1; IR (KBr) 3061, 3030, 2924, 2854, 1460, 1285 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{35}H_{39}N_3O_4S$ $[M+H]^+$ 598.2740, found 598.2744.

(1*R*,2*R*,3*R*,5*R*,8a*R*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-5-methyloctahydroindolizine (22). Prepared from **21** (150 mg, 0.25 mmol), AIBN (7.1 mg, 0.04 mmol) and tri-*n*-butyltinhydride (0.28 mL, 1.00 mmol) following the procedure similar to that for **18** → **19**. The residue was purified by silica gel column chromatography (6:1, petroleum ether–EtOAc) to afford compound **22** as a pale yellow oil (88 mg, 75%). R_f 0.55 (3:1, petroleum ether–EtOAc). $[\alpha]_D^{20}$ –32.9 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.22 (m, 15H), 4.67 (d, 1H, *J* = 12.4 Hz), 4.53 (dd, 2H, *J* = 12.0, 16.4 Hz), 4.45 (d, 3H, *J* =12.8 Hz), 3.90 (d, 1H, *J* = 2.0 Hz), 3.72 (dd, 1H, *J* = 3.6, 8.4 Hz), 3.67 (d, 1H, *J* = 6.4 Hz), 3.57 (dd, 1H, *J* = 3.2, 11.2 Hz), 3.45 (t, 1H, *J* = 8.8 Hz), 2.58–2.53 (m, 2H), 1.95 (d, 1H, *J* = 7.6 Hz), 1.70 (s, 1H), 1.54 (d, 1H, *J* = 7.2 Hz), 1.18 (d, 3H, *J* = 2.4 Hz), 1.12 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 24.0, 30.6, 34.1, 52.0, 62.7, 64.1, 65.1, 71.1, 71.7, 73.4, 85.2, 90.2, 127.4, 127.45, 127.5, 127.53, 127.7, 128.1, 128.2, 128.3, 138.2, 138.3, 138.4; IR (KBr) 3062, 3030, 2928, 2855, 1454 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{31}H_{37}NO_3$ $[M+H]^+$ 472.2852, found 472.2844.

(1*R*,2*R*,3*R*,5*R*,8a*R*)-3-(Hydroxymethyl)-5-methyloctahydroindolizine-1,2-diol, (–)-2-*epi*-Steviamine (23). To a solution of **22** (46 mg, 0.10 mmol) in MeOH (2 mL) were added 10% Pd/C (30 mg) and 6 N HCl (0.1 mL). The resulting suspension was stirred at 50 °C under 30 atm of H_2 for 20 h. The Pd/C was filtered off. After the solution was concentrated under reduced pressure, the residue was dissolved in MeOH and neutralized with aqueous ammonium solution, concentrated under reduced pressure. The residue was purified by ion-exchange chromatography (Dowex OH^-

form) using distilled water to afford **23** (17 mg, 85%) as a colorless oil. R_f 0.5 (3:1, CH_2Cl_2–CH_3OH). $[\alpha]_D^{20}$ –15.1 (*c* 0.80, CH_3OH); ^1H NMR (400 MHz, D_2O): δ 4.08–4.07 (m, 1H), 3.97 (dd, 1H, *J* = 4.0, 11.6 Hz), 3.77 (dd, 1H, *J* = 8.0, 11.6 Hz), 3.70 (dd, 1H, *J* = 4.4, 8.4 Hz), 3.18 (d, 1H, *J* = 4.8 Hz), 2.74–2.72 (m, 1H), 2.70–2.65 (m, 1H), 1.96 (d, 1H, *J* = 14.4 Hz), 1.81–1.71 (m, 2H), 1.35–1.08 (m, 3H), 1.14 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, D_2O): δ 21.0, 25.4, 30.8, 35.4, 54.2, 60.1, 67.4, 68.4, 81.6, 85.1; IR (KBr) 3390, 2926, 2831, 1451, 1381, 1118 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{10}H_{19}NO_3$ $[M+Na]^+$, 224.1263, found 224.1264.

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***Supporting Information**

^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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