A new synthetic access to bicyclic polyhydroxylated alkaloid analogues from pyranosides†

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A facile, versatile and stereoselective synthesis of bicyclic polyhydroxylated alkaloids as castanospermine analogues is described. The synthetic route started from methyl pyranosides. The key steps involved a high-yielding expeditious one-pot tandem reaction from alkenes to *N*-substituted δ-lactams. The δ-lactams were stereoselectively vinylated to give the dienes, which were followed by the ring-closing metathesis to produce the cyclized products. The functional group transformations of the resulting bicyclic compounds furnished diverse polyhydroxylated alkaloids in good yields.

Introduction

Naturally occurring polyhydroxylated alkaloids, also known as iminosugars, have increasingly attracted great interest from synthetic chemists because they are frequently found to be potent inhibitors of many carbohydrate-processing enzymes involved in important biological systems.[1] These unique molecules have tremendous potential as therapeutic agents in a wide range of diseases such as diabetes,[2] viral infections,[3] tumor metastasis,[4] and lysosomal storage disorders.[5] Bicyclic polyhydroxylated alkaloids, for example, (+)-castanospermine (**1**) and (−)-swainsonine (**2**) (Fig. 1), and their chemically modified derivatives are also effective antiviral, antitumor, and immunomodulating agents.[6] However, less than 10 naturally occurring bicyclic polyhydroxylated iminosugars have been isolated so far, covering only a small fraction of the possible iminosugars that could hold therapeutic potential.[7] Therefore, to test the entire chemical space occupied by these iminosugars, diversity-oriented synthesis of these compounds is in great demand.

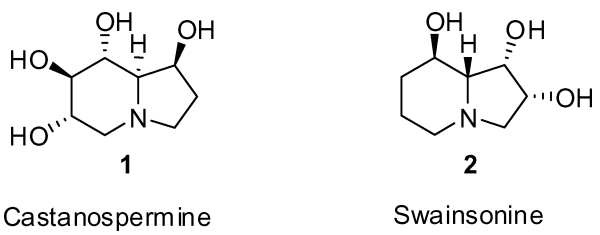

Fig. 1 Structures of castanospermine and swainsonine.

In the past decades, a number of different hydroxyl substituted and ring-expanded analogues of these iminosugars were synthesized by many research groups.[8–12] The majority of the published synthetic pathways to these bicyclic polyhydroxylated iminosugars used carbohydrates as the starting materials, taking advantage of the carbohydrates' stereocenters.[13] In recent years, asymmetric synthesis from non-carbohydrate substrates has also become popular.[14] However, most methods mentioned above only provided one type of target with a certain ring size. To meet the ever-growing needs for diverse bicyclic polyhydroxylated iminosugars for drug discovery and structure–activity relationship studies, more flexible, universal, and efficient methods that could lead to more targets with shorter synthetic routes are desired.

In this article, we describe a new access to bicyclic polyhydroxylated iminosugars that involves only 7–8 synthetic steps from commercially available methyl D-pyranosides and the diverse target iminosugars that are obtained by using this synthetic access (Scheme 1). As shown in Scheme 1, starting from different pyranosides, the different final polyhydroxylated alkaloids will be constructed. The amine moiety will be introduced *via* a reductive amination process. The use of alkenylamines with different side chain lengths will allow the achievement of different ring sizes for the final bicyclic frameworks. A ring-closing metathesis will be applied to form a double bond in the bicyclic framework, which will be subjected to hydroxylation and/or deprotection to result in the polyhydroxylated alkaloids.

Results and discussion

The starting material glucosyl alkene **3** was easily obtained from methyl α-D-glucopyranoside *via* three steps[15] or five steps in high overall yield (77%).[16] As shown in Scheme 2, the δ-lactams were hinged on various side chains on nitrogen, allowing the introduction of the alkenyl chains. The *N*-substituted δ-lactams **4a–c** were produced from **3** in high yields through a one-pot tandem procedure with lactone as intermediate following the recent procedure reported by us.[17] The δ-lactams **4a–c** were then treated with vinylmagnesium bromide followed by hydride reduction to yield the expected diene products **5a–c**. It is noteworthy that only one isomer of the two possible stereo-isomers was obtained in acceptable yields (60–70%). It is assumed that the reduction process involves the iminium ion (Scheme 3).[18] If reaction pathways are restricted in chair-like transition states, an analysis of the relative energy of two transition states, namely **8** and **9** can be made. Quantum chemistry studies in conformational analysis

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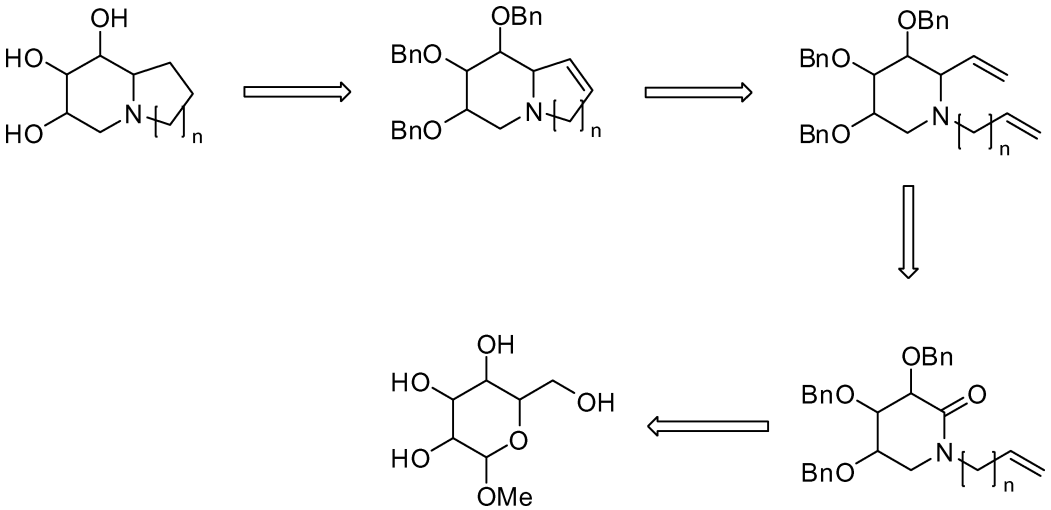
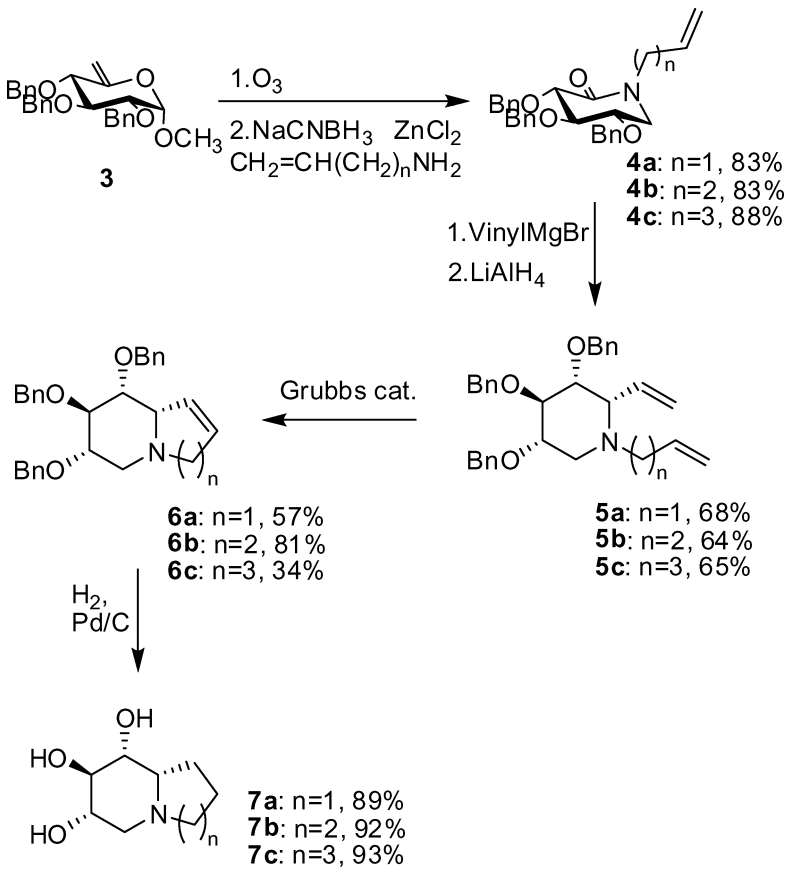
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for compounds. See DOI: 10.1039/b923180c



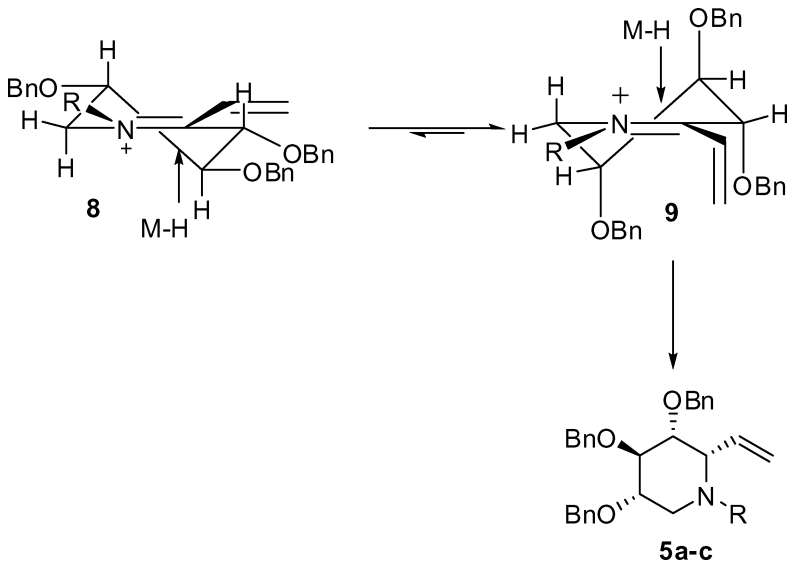
Scheme 1 Design of the synthetic route.



Scheme 2 Synthesis of polyhydroxylated alkaloids **7a–c** from glucosyl alkene **3**.

using Gaussian 03 software (semi-empirical AM1 method) suggest that the energy transition state **9** holds, and will be favored over that of **8**. The higher energy of **8** might be attributed to the stronger intramolecular van der Waals repulsive force because of the approach of 1,3-diaxial protons on both faces. Thus, the conformational analysis would predict **9** to be more stable because of its lower energy (around 10 kcal mol^{-1} lower than **8**), leading to the formation of products **5a–c** in a stereoselective manner, that is, the reductant attacks on the less hindered face opposite to the 1,3-diaxial benzyloxy substituents to yield products.

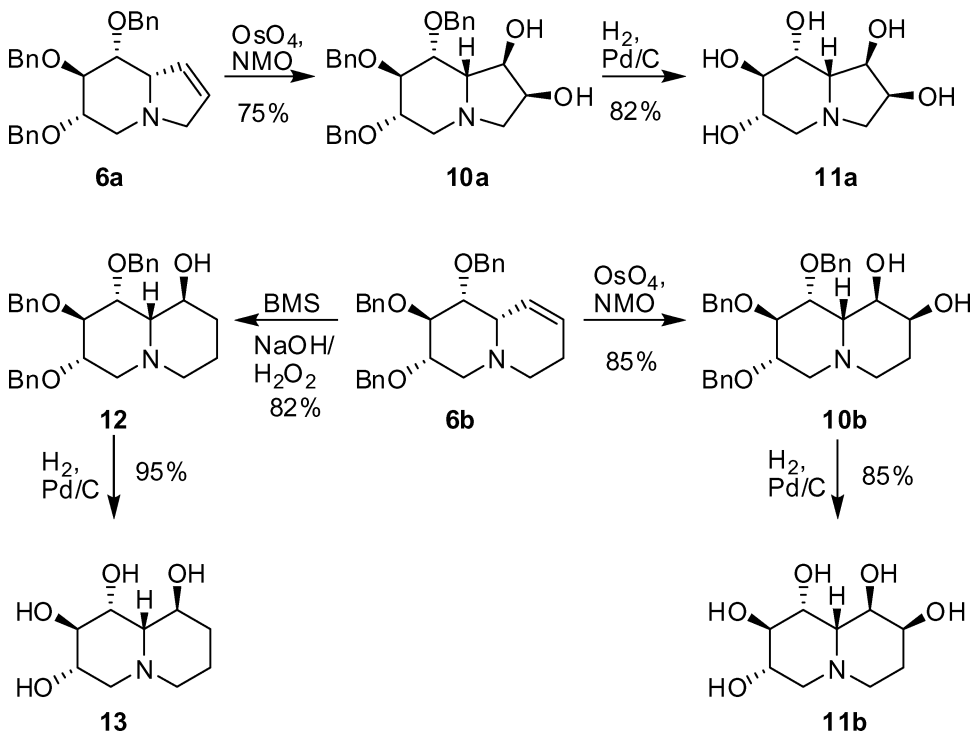
With the dialkenylamines **5a–c** in hand, the next key step is the construction of the desired bicyclic framework by way of a ring-closing metathesis (RCM). However, in most cases, an acyl or a benzyl protected amine is necessary when applying RCM reaction to construct the *N*-heterocycles.[19a–c] It was once



Scheme 3 Conformational analyses of **8** and **9**.

reported that RCM by using Grubbs catalyst could be performed with no decrease in yield when an amine protected by an alkyl group was converted to its hydrochloride salt form.[19d] Inspired by these results, dialkenylamines **5a–c** were also converted to the hydrochloride salts. Different metathesis catalysts (Grubbs 1st generation and Grubbs 2nd generation) were tried in both toluene and CH_2Cl_2 at various temperatures, and the best results were finally obtained by using Grubbs 1st generation catalyst (25% mol) in CH_2Cl_2 at 45 °C. Though some aromatic products were detected, the desired cyclized products **6a–c** were produced in 34–81% isolated yields. Catalytic hydrogenolysis of compounds **6a–c** afforded the corresponding bicyclic trihydroxylated alkaloids **7a–c** in nearly quantitative yield (Scheme 2).

To increase structural diversity, more alkaloid analogues were prepared from precursors **6a–b** (Scheme 4). The alkene **6a** was oxidized by *N*-methylmorpholine *N*-oxide in the presence of catalytic amount of OsO_4[20–22] resulting in the desired dihydroxylated product **10a**, which was subjected to catalytic hydrogenolysis over Pd/C to provide the pentahydroxylated alkaloid **11a**. In the same way, alkaloid **11b** was also obtained smoothly from alkene **6b**. In addition, to further test the flexible functional group transformations of the double bond, the monohydroxylated

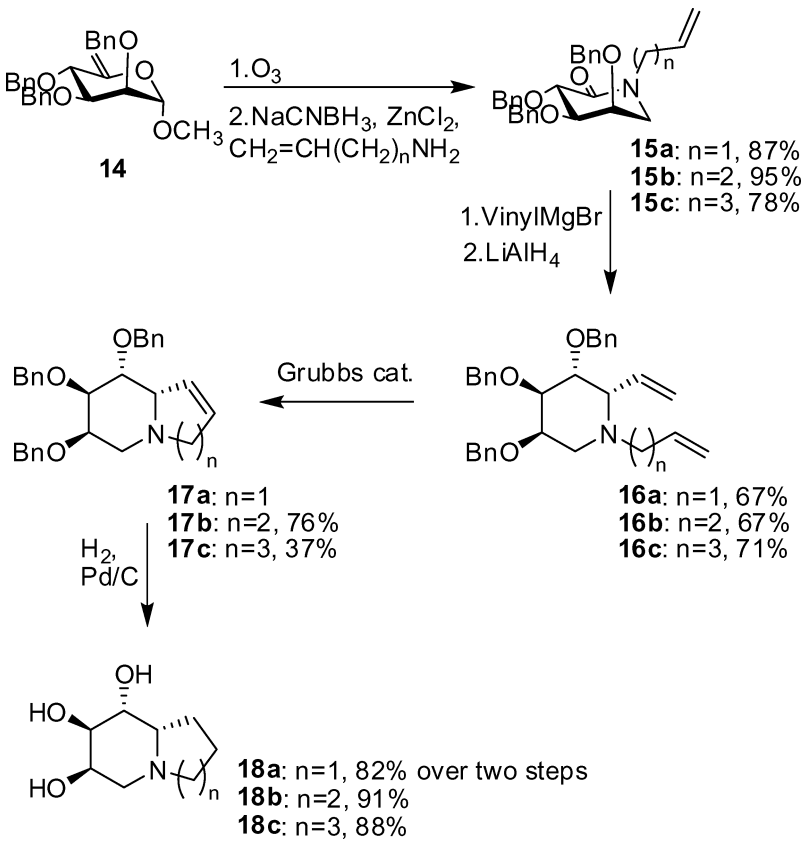


Scheme 4 Synthesis of polyhydroxylated alkaloids **11a**, **11b**, and **13**.

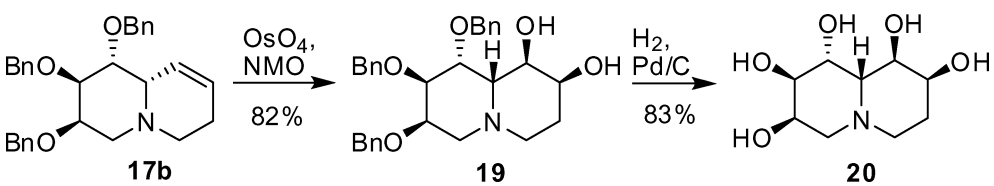
compound **12** was prepared from alkene **6b** by hydroboration with borane–methyl sulfide followed by oxidation with H_2O_2.[23] Full deprotection of **12** led to the tetrahydroxylated alkaloid **13** in almost quantitative yield. Theoretically, the modification of the double bond could possibly produce other stereo-isomers. However, the reaction took place highly stereoselectively and only a single isomer was isolated. This could be explained by the fact that the oxidation occurred antiperiplanarly to the β-benzyloxy groups of the alkenes in the ring systems due to steric hindrance. In such systems, the antiperiplanar attacks were much more favored, affording compounds **10a**, **10b**, and **12** as pure stereo-isomers.

Moreover, to widen the substrate scope of this synthetic strategy, some polyhydroxylated alkaloid analogues **18a–c** were also prepared in high yields from mannose-type alkene **14** in the same way mentioned above (Scheme 5). Similarly, the polyhydroxylated alkaloid **20** was successfully derived from the alkene intermediate **17b** (Scheme 6).

All structures of target polyhydroxylated alkaloids **7a–c**, **11a–b**, **13**, **18a–c**, and **20** were identified by careful analyses of the 1D- (^{1}H, ^{13}C) and 2D-NMR spectra (COSY, HSQC, gHMBC, NOESY) of either themselves or their precursors. The configuration determination of **10b** (the precursor of **11b**) and **20** is exemplified in Fig. 2 and Table 1. Firstly we identified most of the proton signals such as H-1, H-2, and H-9a signals through their COSY spectra (Fig. 2) since they are not superimposed in their ^{1}H NMR spectra. The stereochemistry of three *O*-benzyl groups in the starting materials **3** and **14** ensures the configuration of the substituents at C-7, C-8, C-9 positions in compound **10b** (H_7–H_8 *trans*, H_8–H_9 *trans*) and the substituents at C-1, C-2, C-3 positions in **20** (H_1–H_2 *trans*, H_2–H_3 *syn*). Based on the coupling constants (the coupling constants for axial–axial coupling are in the range of 9.5–12.0 Hz, whereas the coupling constants for axial–equatorial or equatorial–equatorial couplings are in the range of 1.0–5.0 Hz), the coupling constants of **10b** ($J_{1,9a} = 9.5$ Hz, $J_{9,9a} = 2.5$ Hz, $J_{1,2} = 3.5$ Hz) indicated the *trans*-diaxial relationship between H-1 and H-9a, the *syn*-relationship between H-9 and H-9a, and further concluded the *syn*-relationship between H-1 and H-2; the key coupling constants of **20** ($J_{1,9a} = 1.0$ Hz, $J_{9,9a} = 10.5$ Hz, $J_{8,9} = 3.0$ Hz) indicated the *syn*-relationship between H-1 and H-9a, the *trans*-diaxial relationship between H-9 and H-9a, and further



Scheme 5 Synthesis of polyhydroxylated alkaloids **18a–c** from mannosyl alkene **14**.



Scheme 6 Synthesis of polyhydroxylated alkaloid **20**.

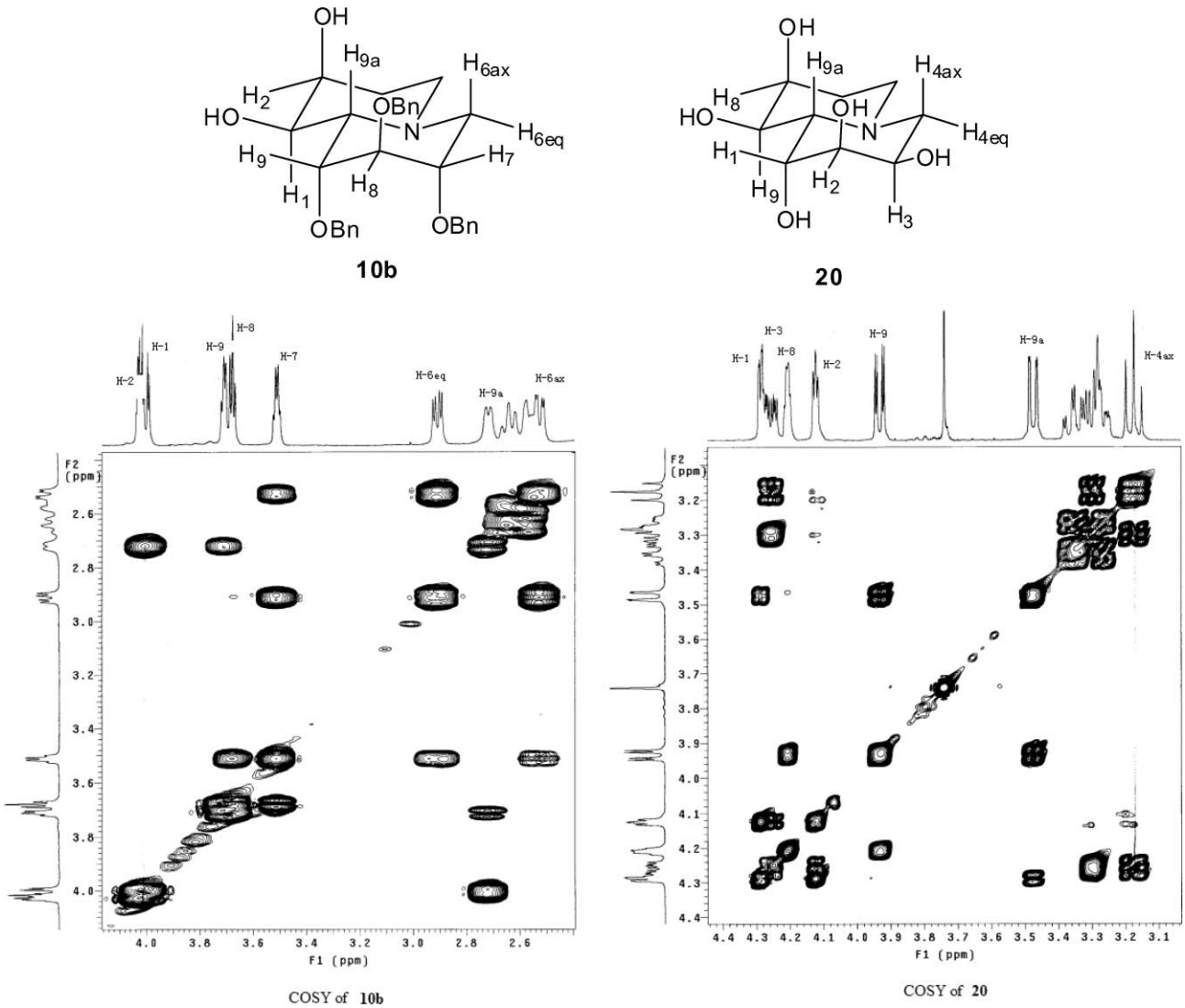


Fig. 2 2D-NMR spectra of **10b** and **20**.

Table 1 Selective coupling constants J [Hz] for **10b** and **20**

compound	$J_{1,2}$	$J_{9,9a}$	$J_{1,9a}$	$J_{8,9}$	$J_{6ax,7}$	$J_{6eq,7}$	$J_{7,8}$
10b	3.5	2.5	9.5		3.5	5.0	
	$J_{8,9}$	$J_{1,9a}$	$J_{9,9a}$	$J_{1,2}$	$J_{3,4ax}$	$J_{3,4eq}$	$J_{2,3}$
20	3.0	1.0	10.5	4.0	12.0		3.5

concluded the *syn*-relationship between H-8 and H-9. So the structures of **10b** and **20** were unambiguously determined. With the structures of compounds **10b** and **20** determined, the steric structures of their related compounds **11b**, **7b**, **5b**, and **18b** were easily determined. Furthermore, in order to confirm the structure determination of the target compounds, the NMR spectra of some important intermediates such as **16a** were also carefully analyzed, proving the coincident configuration with **18a** (see supplementary information). In a similar way, the stereochemistry of other target compounds was assigned. In addition, compounds **7a**, **7b**, **11a**, **13**, and **18a** are known compounds and their structures were further confirmed by comparison with the published data.[22,24–26]

Conclusion

A new efficient route to bicyclic polyhydroxylated alkaloid analogues from pyranosides was developed. Through this access, 10 polyhydroxylated alkaloids were smoothly prepared by a seven- or eight-step sequence in good overall yields (around 20%). The synthetic pathway is rapid, flexible, and highly stereoselective. The synthesis can be easily altered by changing either the starting pyranosides or the amines used in the reductive amination to produce various bicyclic iminosugar structures. Owing to the less synthetic steps involved and the versatility of synthetic targets, the disclosed strategy may find wide applications in the synthesis of polyhydroxylated alkaloids.

Experimental

(3*S*,4*R*,5*S*)-1-Allyl-3,4,5-tris(benzyloxy)piperidin-2-one (4a)

A solution of **3**[27] (200 mg, 0.45 mmol) in MeOH (10 mL) at −78 °C was bubbled with O_3 until the solution became pale blue. The solution was stirred at −78 °C for 3 min and bubbled with N_2 until the solution became colorless. To the mixture, allylamine (0.07 mL, 0.9 mmol), $NaCNBH_3$ (53.7 mg, 0.9 mmol) and $ZnCl_2$ (12.0 mg, 0.09 mmol) were added, and the mixture was heated under reflux for 2 h. The reaction was quenched with saturated $NaHCO_3$. After removal of the solvent, the mixture was dissolved in ethyl acetate (80 mL) and washed with brine (2 × 20 mL). The organic phase was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (petroleum ether–ethyl acetate 6 : 1) to provide the product **4a** (168 mg, 83%) as a colorless oil. R_f 0.45 (petroleum ether–ethyl acetate, 2 : 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23-3.38 (m, 2H), 3.71-3.77 (m, 1H), 3.84 (t, J = 6.6 Hz, 1H), 3.94-4.02 (m, 3H), 4.55-4.78 (m, 5H), 5.11-5.21 (m, 3H), 5.66-5.79 (m, 1H), 7.26-7.45 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.95, 49.14, 72.13, 73.76, 74.26, 75.95, 79.28, 82.01, 118.15, 127.65, 127.70, 127.85, 127.93, 128.30, 128.35, 128.44, 132.36, 137.68, 137.93, 137.98, 168.61. Anal. Calcd for $C_{29}H_{31}NO_4$: C, 76.12; H, 6.83; N, 3.06; Found: C, 75.87; H, 6.61; N, 3.03; ESI-MS: 458 [M + H$^+$].

(3*S*,4*R*,5*S*)-3,4,5-Tris(benzyloxy)-1-(but-3-enyl)piperidin-2-one (4b)

Compound **4b** was prepared from **3** as described in the preparation of **4a** with 1-buteneamine, yielding **4b** (83% yield) as a colorless oil. R_f 0.50 (petroleum ether–ethyl acetate, 2 : 1). $[\alpha]_D^{26} = -13.9$ (c = 0.0063, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (dd, J = 6.6 Hz, J = 13.2 Hz, 2H, -CH_2–C=), 3.27-3.45 (m, 4H, NCH_2, H-6), 3.73 (dt, J = 5.1 Hz, J = 7.2 Hz, 1H, H-5), 3.82 (t, J = 6.3 Hz, 1H, H-4), 3.97 (d, J = 6.9 Hz, 1H, H-3), 4.55-4.79 (m, 5H, $PhCH_2$), 4.99-5.13 (m, 3H, $PhCH_2$, =CH_2), 5.71-5.80 (m, 1H, -CH=), 7.25-7.44 (m, 15H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.89, 46.51, 48.19, 72.15, 73.69, 74.11, 76.12, 79.38, 82.06, 116.99, 127.68, 127.72, 127.88, 127.92, 128.29, 128.35, 128.45, 135.00, 137.72, 137.97, 138.03,168.56; HRMS (ESI) Anal. Calcd for $C_{30}H_{34}NO_4$ [M + H]$^+$: 472.2482, found: 472.2483.

(3*S*,4*R*,5*S*)-3,4,5-Tris(benzyloxy)-1-(pent-4-enyl)piperidin-2-one (4c)

Compound **4c** was prepared from **3** as described in the preparation of **4a** with 1-penteneamine, yielding **4c** (88% yield) as a colorless oil. R_f 0.45 (petroleum ether–ethyl acetate, 3 : 1). $[\alpha]_D^{26} = -13.0$ (c = 0.0196, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57-1.66 (m, 2H, C-CH_2–C), 2.02-2.06 (dd, J = 6.6 Hz, J = 14.1 Hz, 2H, -CH_2–C=), 3.26-3.46 (m, 4H, NCH_2, H-6), 3.71-3.76 (m, 1H, H-5), 3.83 (t, J = 6.0 Hz, 1H, H-4), 3.98 (d, J = 7.2 Hz, 1H, H-3), 4.56 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.64-4.79 (m, 4H, $PhCH_2$), 4.95-5.03 (m, 2H, $PhCH_2$, =CH_2), 5.12 (d, J = 11.7 Hz, 1H, =CH_2), 5.73-5.79 (m, 1H, -CH=C), 7.25-7.45 (m, 15H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.42, 30.90, 46.62, 47.93, 72.06, 73.69, 74.16, 76.18, 79.36, 82.02, 115.07, 127.67, 127.74, 127.87, 127.94, 128.30, 128.35, 128.45, 137.68, 137.95, 137.99, 168.55; HRMS (ESI) Anal. Calcd for $C_{31}H_{35}NO_4Na$ [M + Na]$^+$: 508.2458, found: 508.2470.

(2*S*,3*R*,4*R*,5*S*)-1-Allyl-3,4,5-tris(benzyloxy)-2-vinylpiperidine (5a)

Vinylmagnesium bromide (1.0 M solution in THF, 2.63 mL, 2.63 mmol) was added dropwise to a solution of **4a** (300 mg, 0.66 mmol) in dry ether at 0 °C under nitrogen. The ice bath was removed and the mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C again. $LiAlH_4$ (236 mg, 6.6 mmol) was added and the mixture was stirred for 2 h. The reaction was quenched at 0 °C by the careful addition of a 10% NaOH aqueous solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 80 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether–ethyl acetate 20 : 1→15:1→12:1) to provide **5a** (205 mg, 68%) as a syrup. R_f 0.60 (petroleum ether–ethyl acetate, 3 : 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (t, J = 10.2 Hz, 1H, H-6ax), 2.85 (dd, J = 4.8 Hz, J = 11.4 Hz, 1H, H-6eq), 2.98 (dd, J = 6.3 Hz, J = 13.8 Hz, 1H, NCH_2), 3.13 (dd, J = 6.6 Hz, J = 13.8 Hz, 1H, NCH_2), 3.54-3.70 (m, 4H, H-2, H-3, H-4, H-5), 4.57-4.90 (m, 6H, $PhCH_2$), 5.09-5.15 (m, 2H, =CH_2), 5.25 (d, J = 17.1 Hz, 1H, =CH_2), 5.42 (d, J = 10.2 Hz, 1H, =CH_2), 5.67-5.80 (m, 1H, -CH=), 5.96-6.08 (m, 1H, -CH=), 7.28-7.33 (m, 15H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.64, 57.37, 63.40, 72.20, 73.06, 75.48, 78.94, 80.72, 82.58, 117.56, 121.53, 127.41, 127.56, 127.60, 127.78, 127.98, 128.26, 128.36, 130.12, 135.53, 138.42, 138.56, 139.09; HRMS (ESI) Anal. Calcd for $C_{31}H_{36}NO_3$ [M + H]$^+$: 470.2690, found: 470.2694.

(2*S*,3*R*,4*R*,5*S*)-3,4,5-Tris(benzyloxy)-1-(but-3-enyl)-2-vinylpiperidine (5b)

Compound **5b** was prepared from **4b** as described in the preparation of **5a**, yielding **5b** (64% yield) as a colorless oil. R_f 0.62 (petroleum ether–ethyl acetate, 3 : 1). $[\alpha]_D^{26} = -31.8$ (c = 0.0426, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12-2.15 (m, 2H, CH_2–C=), 2.37-2.57 (m, 3H, NCH_2, H-6ax), 2.83 (dd, J = 5.1 Hz, J = 12.0 Hz, 1H, H-6eq), 3.50 (dd, J = 3.9 Hz, J = 10.5 Hz, 1H, H-2), 3.57-3.71 (m, 3H, H-3, H-4, H-5), 4.59-4.91 (m, 6H, $PhCH_2$), 4.95-5.03 (m, 2H, =CH_2), 5.26 (dd, J = 1.8 Hz, J = 16.8 Hz, 1H, =CH_2), 5.41 (dd, J = 1.8 Hz, J = 10.2 Hz, 1H, =CH_2), 5.67-5.81 (m, 1H, -CH=), 5.96-6.09 (m,1H, -CH=), 7.26-7.37 (m, 15H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.06, 49.97, 53.54, 63.41, 72.30, 73.09, 75.42, 78.94, 80.74, 82.65, 115.52, 121.11, 127.37, 127.55, 127.77, 127.94, 128.22, 128.34, 130.31, 136.42, 138.42, 138.56, 139.09; HRMS (ESI) Anal. Calcd for $C_{32}H_{38}NO_3$ [M + H]$^+$: 484.2846, found: 484.2852.

(2*S*,3*R*,4*R*,5*S*)-3,4,5-Tris(benzyloxy)-1-(pent-4-enyl)-2-vinylpiperidine (5c)

Compound **5c** was prepared from **4c** as described in the preparation of **5a**, yielding **5c** (65% yield) as a colorless oil. R_f 0.60 (petroleum ether–ethyl acetate, 4 : 1). $[\alpha]_D^{26} = -2.56$ (c = 0.0156, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41-1.55 (m, 2H, -CH_2-), 1.97-2.04 (m, 2H, -CH_2–C=), 2.29-2.51 (m, 3H, NCH_2, H-6ax), 2.81 (dd, J = 5.4 Hz, J = 12.0 Hz, 1H, H-6eq), 3.45-3.57 (dd, J = 3.9 Hz, J = 9.6 Hz, 1H, H-2), 3.59-3.71 (m, 3H, H-3,

H-4, H-5), 4.59-4.69 (m, 3H, $PhCH_2$), 4.74 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.82 (d, J = 10.8 Hz, 1H, $PhCH_2$), 4.87-5.01 (m, 3H, $PhCH_2$, $=CH_2$), 5.24 (dd, J = 1.8 Hz, J = 16.8 Hz, 1H, $=CH_2$), 5.40 (dd, J = 1.8 Hz, J = 10.2 Hz, 1H, $=CH_2$), 5.71-5.85 (m, 1H, -CH=), 5.96-6.08 (m, 1H, -CH=), 7.25-7.37 (m, 15H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.66, 31.32, 50.02, 53.42, 63.44, 72.35, 73.13, 75.47, 79.10, 80.86, 82.78, 114.59, 121.04, 127.39, 127.57, 127.61, 127.80, 127.97, 127.99, 128.24, 128.28, 128.37, 130.41, 138.52, 138.63, 139.16; HRMS (ESI) Anal. Calcd for $C_{33}H_{40}NO_3$ $[M + H]^+$: 498.3003, found: 498.3014.

(6*S*,7*R*,8*R*,8a*S*)-6,7,8-Tris(benzyloxy)-3,5,6,7,8,8a-hexahydroindolizine (6a)

To a solution of **5a** (21.0 mg, 0.045 mmol) in dichloromethane (4 mL), hydrogen chloride (1.25 M in methanol, 0.1 mL) was added. The solvent was then removed. The residue was redissolved in dry dichloromethane (3 mL) and Grubbs 1st generation catalyst (10.0 mg, 0.011 mmol) was added. The reaction mixture was stirred at 45 °C for 24 h under argon atmosphere. The flask was opened to the air for 24 h before the addition of 0.1 N NaOH. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The organic layers were combined and dried over Na_2SO_4. After removal of the volatiles, the residue was purified by column chromatography on silica gel (chloroform) to yield **6a** (11.0 mg, 57%) as a yellow syrup. R_f 0.60 (chloroform–methanol 30 : 1). $[\alpha]_D^{26}$ = −21.2 (c = 0.00042, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.79 (t, J = 9.9 Hz, 1H), 3.20 (dd, J = 3.3 Hz, J = 9.9 Hz, 1H), 3.50-3.54 (m, 1H), 3.62 (br.s, 1H), 3.69-3.80 (m, 3H), 3.97 (br.s, 1H), 4.44-4.70 (m, 6H), 5.70-5.72 (m, 1H), 5.94-5.96 (m, 1H), 7.26-7.34 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.89, 61.56, 65.26, 71.73, 71.89, 78.59, 79.23, 80.50, 127.49, 127.57, 127.66, 127.75, 128.24, 128.37, 129.30, 138.22, 138.45. HRMS (ESI) Anal. Calcd for $C_{29}H_{32}NO_3$ $[M + H]^+$: 442.2377, found: 442.2386.

(1*R*,2*R*,3*S*,9a*S*)-1,2,3-Tris(benzyloxy)-2,3,4,6,7,9a-hexahydro-1*H*-quinolizine (6b)

Compound **6b** was prepared from **5b** as described in the preparation of **6a**, yielding **6b** (81% yield) as a yellow syrup. R_f 0.65 (chloroform–methanol 30 : 1). $[\alpha]_D^{26}$ = −8.73 (c = 0.00875, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83-1.90 (m, 1H), 2.42 (br.s, 1H), 2.64-2.67 (m, 1H), 2.83-2.96 (m, 3H), 3.50-3.57 (m, 4H), 4.56-4.70 (m, 6H), 5.69 (d, J = 10.5 Hz, 1H), 5.81-5.85 (m, 1H), 7.26-7.32 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.03, 50.82, 51.12, 57.88, 72.31, 72.59, 74.04, 78.67, 124.86, 126.39, 127.55, 127.82, 127.90, 127.98, 128.25, 128.33, 138.60, 138.65, 138.73; HRMS (ESI) Anal. Calcd for $C_{30}H_{34}NO_3$ $[M + H]^+$: 456.2533, found: 456.2533.

(1*R*,2*R*,3*S*,10a*S*,*Z*)-1,2,3-Tris(benzyloxy)-1,2,3,4,6,7,8,10a-octahydropyrido[1,2-*a*]azepine (6c)

Compound **6c** was prepared from **5c** as described in the preparation of **6a**, yielding **6c** (34% yield) as a yellow syrup. R_f 0.75 (chloroform–methanol 30 : 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33-1.38 (m, 1H, H-7), 1.67-1.80 (m, 1H, H-7), 2.13-2.22 (m, 1H, H-8), 2.29-2.34 (m, 1H, H-8), 2.62 (dd, J = 3.9 Hz, J = 11.1 Hz, 1H, H-4), 2.82-2.89 (m, 1H, H-4), 3.01-3.09 (m, 1H, H-6), 3.17-3.22 (m, 1H, H-6), 3.57-3.69 (m, 3H, H-1, H-2, H-3), 3.94 (br.s, 1H, H-10a), 4.63-4.92 (m, 6H, $PhCH_2$), 5.86-5.90 (m, 1H, H-10), 6.03-6.04 (m, 1H, H-9), 7.27-7.36 (m, 15H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.15, 29.20, 48.95, 58.55, 59.36, 71.82, 72.88, 75.50, 79.86, 80.97, 82.79, 127.36, 127.42, 127.51, 127.60, 127.72, 128.02, 128.21, 128.25, 128.33, 129.63, 133.90, 138.70, 139.20; HRMS (ESI) Anal. Calcd for $C_{31}H_{36}NO_3$ $[M + H]^+$: 470.2690, found: 470.2690.

(6*S*,7*R*,8*R*,8a*S*)-Octahydroindolizine-6,7,8-triol (7a)

To the solution of **6a** (20.1 mg, 0.046 mmol) in MeOH (4 mL) were added hydrogen chloride (1.25 M in methanol, 0.2 mL) and Pd/C (10% wt, 8.0 mg). The reaction mixture was stirred under the atmosphere of hydrogen gas for 2 days. The mixture was filtered through Celite pad and the filtrate was concentrated. The residue was subjected to a C-18 reversed-phase column chromatography (H_2O as eluent) to give **7a** (7.1 mg, 89%) as a foam after lyophilization. $[\alpha]_D^{26}$ = +40.9 (c = 0.00042, MeOH). ^{1}H NMR (500 MHz, CD_3OD) δ 1.70-1.86 (m, 3H), 1.88-1.94 (m, 1H), 2.33 (q, J = 9.0 Hz, J = 18.0 Hz, 1H), 2.60-2.63 (m, 2H), 3.01 (dd, J = 3.0 Hz, J = 12.0 Hz, 1H), 3.04-3.08 (m, 1H), 3.71-3.73 (m, 2H), 3.84 (t, J = 3.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 21.34, 24.74, 55.16, 55.32, 63.72, 70.98, 71.18, 71.29; HRMS (ESI) Anal. Calcd for $C_8H_{16}NO_3$ $[M + H]^+$: 174.1125, found: 174.1129. The spectroscopic data coincide with those reported previously.[24]

(1*R*,2*R*,3*S*,9a*S*)-Octahydro-1*H*-quinolizine-1,2,3-triol (7b)

Compound **7b** was prepared from **6b** as described in the preparation of **7a**, yielding **7b** (92% yield) as a foam. $[\alpha]_D^{26}$ = +14.9 (c = 0.0154, MeOH). ^{1}H NMR (500 MHz, D_2O) δ 1.52-1.54 (m, 1H), 1.66-1.71 (m, 2H), 1.81-1.87 (m, 3H), 2.99 (dt, J = 3.0 Hz, J = 13.0 Hz, 1H), 3.24 (td, J = 1.5 Hz, J = 13.0 Hz, 1H), 3.32-3.37 (m, 3H), 3.74-3.75 (m, 1H), 3.95-3.97 (m, 2H); ^{13}C NMR (125 MHz, D_2O) δ 22.16, 23.40, 26.21, 56.26 (2C), 62.22, 66.98, 67.73, 70.74; HRMS (ESI) Anal. Calcd for $C_9H_{18}NO_3$ $[M + H]^+$: 188.1281, found: 188.1287. The spectroscopic data coincide with those reported previously.[25]

(1*R*,2*R*,3*S*,10a*S*)-Decahydropyrido[1,2-a]azepine-1,2,3-triol (7c)

Compound **7c** was prepared from **6c** as described in the preparation of **7a**, yielding **7c** (93% yield) as a colorless oil. $[\alpha]_D^{26}$ = +33.6 (c = 0.00235, MeOH). ^{1}H NMR (500 MHz, D_2O) δ 1.43-1.52 (m, 2H), 1.66 (br.s, 2H), 1.80-1.91 (m, 4H), 2.84-2.93 (m, 3H), 3.06-3.11 (m, 1H), 3.19 (d, J = 6.0 Hz, 1H), 3.53 (br.s, 1H), 3.67 (br.s, 2H); ^{13}C NMR (100 MHz, D_2O) δ 22.84, 25.61 (2C), 26.96, 55.50, 63.23 (2C), 69.89, 72.23 (2C); HRMS (ESI) Anal. Calcd for $C_{10}H_{20}NO_3$ $[M + H]^+$: 202.1438, found: 202.1437.

(1*R*,2*S*,6*S*,7*R*,8*R*,8a*S*)-6,7,8-Tris(benzyloxy)octahydroindolizine-1,2-diol (10a)

To the solution of **6a** (12.1 mg, 0.027 mmol) in acetone (0.8 mL) and H_2O (0.2 mL), were added 4-methylmorpholine-*N*-oxide (50% w/w aqueous solution, 12 µL, 0.054 mmol) and OsO_4 (1 M solution in *t*-butanol, 18 µL, 0.018 mmol). After stirring at 0 °C for 1 h, $NaHSO_3$ (excess) was added, and the mixture was stirred for another 30 min. The reaction mixture was then filtered through a

short column ($NaHSO_3$) and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (chloroform–methanol 50 : 1) to yield **10a** (9.0 mg, 75%) as a yellowish syrup. R_f 0.35 (chloroform–methanol 30 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.27 (dd, J = 4.0 Hz, J = 10.0 Hz, 1H, H-3), 2.46-2.52 (m, 2H, H-5, H-8a), 2.99 (dd, J = 3.5 Hz, J = 12.0 Hz, 1H, H-5), 3.47-3.50 (m, 2H, H-3, H-6), 3.65 (t, J = 2.5 Hz, 1H, H-7), 3.72 (br.s, 1H, H-8), 4.22-4.28 (m, 2H, H-1, H-2), 4.38-4.68 (m, 6H, $PhCH_2$), 7.18-7.35 (m, 15H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.58, 61.98, 65.31, 67.71, 69.86, 71.44, 71.85, 72.32, 72.56, 73.19, 73.89, 126.05, 127.62, 127.71, 127.83, 127.95, 128.32, 128.40, 128.49, 137.92, 138.32, 138.54; HRMS (ESI) Anal. Calcd for $C_{29}H_{34}NO_5$ [M + H]$^+$: 476.2431, found: 476.2438.

(1*R*,2*S*,7*S*,8*R*,9*R*,9a*S*)-7,8,9-Tris(benzyloxy)octahydro-1*H*-quinolizine-1,2-diol (10b)

Compound **10b** was prepared from **6b** as described in the preparation of **10a**, yielding **10b** (85% yield) as a yellowish syrup. R_f 0.38 (chloroform–methanol 30 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71-1.74 (m, 1H, H-3), 1.93-2.00 (m, 1H, H-3), 2.51 (dd, J = 3.5 Hz, J = 12.0 Hz, 1H, H-6ax), 2.53-2.56 (m, 1H, H-4eq), 2.61-2.65 (m, 1H, H-4ax), 2.70 (dd, J = 2.5 Hz, J = 9.5 Hz, 1H, H-9a), 2.90 (dd, J = 5.0 Hz, J = 12.5 Hz, 1H, H-6eq), 3.51 (dd, J = 4.0 Hz, J = 8.0 Hz, 1H, H-7), 3.67-3.71 (m, 2H, H-8, H-9), 4.00 (dd, J = 3.5 Hz, J = 10.0 Hz, 1H, H-1), 4.01-4.03 (m, 1H, H-2), 4.46-4.62 (m, 5H, $PhCH_2$), 4.71 (d, J = 12.0 Hz, 1H, $PhCH_2$), 7.25-7.35 (m, 15H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.61, 48.60, 53.23, 57.97, 66.86, 67.95, 71.74, 72.90, 73.13, 74.03, 74.60, 74.83, 127.63, 127.77, 127.81, 127.89, 128.10, 128.35, 128.41, 128.55, 128.62, 137.97, 138.17, 138.54; HRMS (ESI) Anal. Calcd for $C_{30}H_{36}NO_5$ [M + H]$^+$: 490.2588, found: 490.2592.

(1*R*,2*S*,6*S*,7*R*,8*R*,8aS)-Octahydroindolizine-1,2,6,7,8-pentaol (11a)

Compound **11a** was prepared from **10a** as described in the preparation of **7a**, yielding **11a** (82% yield) as a solid after lyophilization. $[\alpha]_D^{26}$ = +19.4 (c = 0.0026, MeOH). ^{1}H NMR (300 MHz, D_2O) δ 2.11 (dd, J = 5.4 Hz, J = 10.5 Hz, 1H), 2.33-2.45 (m, 2H), 2.77 (dd, J = 3.0 Hz, J = 12.6 Hz, 1H), 3.25 (dd, J = 6.6 Hz, J = 10.8 Hz, 1H), 3.66 (br.s, 1H), 3.77-3.78 (m, 2H), 3.89 (t, J = 7.8 Hz, 1H), 4.03 (dd, J = 6.9 Hz, J = 12.3 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 53.98, 60.75, 65.12, 67.28, 68.54, 69.19, 69.65 (2C). The spectroscopic data coincide with those reported previously.[26]

(1*R*,2*R*,3*S*,8*S*,9*R*,9a*S*)-Octahydro-1*H*-quinolizine-1,2,3,8,9-pentaol (11b)

Compound **11b** was prepared from **10b** as described in the preparation of **7a**, yielding **11b** (85% yield) as a solid after lyophilization. $[\alpha]_D^{26}$ = +35.0 (c = 0.0099, MeOH). ^{1}H NMR (300 MHz, D_2O) δ 1.87-1.90 (m, 2H, H-7), 3.12-3.28 (m, 3H, H-4, H-6), 3.32-3.39 (m, 2H, H-4, H-9a), 3.85 (dd, J = 2.7 Hz, J = 10.8 Hz, 1H, H-9), 3.91-3.94 (m, 1H, H-3), 3.95-3.96 (m, 1H, H-2), 4.05-4.06 (m, 2H, H-1, H-8); ^{13}C NMR (125 MHz, D_2O) δ 27.62, 49.54, 56.49, 59.37, 66.00, 66.14, 66.36, 66.77, 67.56; HRMS (ESI) Anal. Calcd for $C_9H_{18}NO_5$ [M + H]$^+$: 220.1180, found: 220.1179.

(1*S*,7*S*,8*R*,9*R*,9a*S*)-7,8,9-Tris(benzyloxy)octahydro-1*H*-quinolizin-1-ol (12)

To a solution of **6b** (20.0 mg, 0.044 mmol) in dry THF (4 mL), borane–methyl sulfide (1.0 M solution in THF, 88 µL, 0.09 mmol) was added at 0 °C under nitrogen atmosphere. The ice bath was removed and the mixture was stirred at room temperature for 2 h. The reaction was followed by hydrolyzing with a solution of THF–glycerol–3 N HCl (1 : 1 : 1, 3 mL). After the completion of the reaction, the reaction mixture was oxidized by using 6 N NaOH (1 mL) and 30% hydrogen peroxide (1 mL). After 5 h, the aqueous phase was saturated with anhydrous K_2CO_3 and was extracted with ethyl acetate (3 × 20 mL). The crude reaction mixture was dried over Na_2SO_4. After removal of the volatiles, the residue was purified by column chromatography on silica gel (chloroform–methanol 50 : 1) to yield **12** (17.0 mg, 82%) as a syrup. R_f 0.40 (chloroform–methanol 30 : 1). $[\alpha]_D^{26}$ = +13.8 (c = 0.00315, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$–D_2O) δ 1.25-1.31 (m, 1H), 1.50-1.55 (m, 1H), 1.75-1.84 (m, 1H), 2.01-2.18 (m, 3H), 2.44 (dd, J = 3.0 Hz, J = 12.0 Hz, 1H), 2.80 (d, J = 11.7 Hz, 1H), 2.89 (dd, J = 3.9 Hz, J = 12.0 Hz, 1H), 3.49-3.50 (m, 1H), 3.67-3.76 (m, 2H), 3.95 (dt, J = 4.2 Hz, J = 10.2 Hz, 1H), 4.43-4.64 (m, 5H), 4.70 (d, J = 11.7 Hz, 1H), 7.26-7.33 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.63, 33.67, 53.97, 55.55, 65.34, 65.50, 71.55, 72.67, 73.31, 73.98, 74.27, 77.20, 127.57, 127.75, 127.82, 127.88, 128.07, 128.33, 128.40, 128.55, 128.66, 138.11, 138.21, 138.71; HRMS (ESI) Anal. Calcd for $C_{30}H_{36}NO_4$ [M + H]$^+$: 474.2639, found: 474.2655.

(1*R*,2*R*,3*S*,9*S*,9a*S*)-Octahydro-1*H*-quinolizine-1,2,3,9-tetraol (13)

Compound **13** was prepared from **12** as described in the preparation of **7a**, yielding **13** (95% yield) as a solid after lyophilization. $[\alpha]_D^{26}$ = +34.3 (c = 0.0106, MeOH). ^{1}H NMR (400 MHz, D_2O) δ 1.52 (dt, J = 4.0 Hz, J = 12.4 Hz, 1H, H-7), 1.69-1.74 (m, 1H, H-7), 1.86-1.90 (m, 1H, H-8), 2.08-2.12 (m, 1H, H-8), 2.97 (dt, J = 3.2 Hz, J = 12.8 Hz, 1H, H-6), 3.07 (dd, J = 1.6 Hz, J = 10.4 Hz, 1H, H-4), 3.29-3.39 (m, 3H, H-4, H-6, H-9a), 3.83-3.89 (m, 1H, H-9), 3.95-3.96 (m, 1H, H-3), 4.00 (t, J = 2.8 Hz, 1H, H-2), 4.17-4.18 (m, 1H, H-1). The spectroscopic data coincide with those reported previously.[25]

(3*S*,4*R*,5*R*)-1-Allyl-3,4,5-tris(benzyloxy)piperidin-2-one (15a)

Compound **15a** was prepared from **14**[28] as described in the preparation of **4a**, yielding **15a** (87% yield) as a solid. R_f 0.46 (petroleum ether–ethyl acetate, 2 : 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.22 (dd, J = 4.5 Hz, J = 12.3 Hz, 1H, H-6), 3.43 (dd, J = 6.3 Hz, J = 12.3 Hz, 1H, H-6), 3.85 (dd, J = 2.1 Hz, J = 6.3 Hz, 1H, H-4), 3.92-3.97 (m, 2H, NCH_2), 4.03-4.08 (m, 1H, H-5), 4.19 (d, J = 6.6 Hz, 1H, H-3), 4.55-4.71 (m, 4H, $PhCH_2$), 4.75 (d, J = 11.4 Hz, 1H, $PhCH_2$), 5.06-5.21 (m, 3H, $PhCH_2$, $=CH_2$), 5.66-5.79 (m, 1H, -CH=), 7.27-7.40 (m, 15H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.06, 48.96, 71.67, 72.41, 74.54, 117.55, 127.62, 127.79, 128.16, 128.32, 128.42, 131.96, 137.82, 138.07, 167.86; HRMS (ESI) Anal. Calcd for $C_{29}H_{32}NO_4$ [M + H]$^+$: 458.2326, found: 458.2322.

(3*S*,4*R*,5*R*)-3,4,5-Tris(benzyloxy)-1-(but-3-enyl)piperidin-2-one (15b)

Compound **15b** was prepared from **14** as described in the preparation of **4a** with 1-buteneamine, yielding **15b** (95% yield) as a colorless oil. R_f 0.50 (petroleum ether–ethyl acetate, 2 : 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26-2.33 (m, 2H, CH_2–C=), 3.27 (dd, J = 4.5 Hz, J = 12.0 Hz, 1H, H-6), 3.35-3.40 (m, 2H, NCH_2), 3.47 (dd, J = 6.6 Hz, J = 12.0 Hz, 1H, H-6), 3.83 (dd, J = 2.0 Hz, J = 6.1 Hz, 1H, H-4), 4.05 (br.s, 1H, H-5), 4.14 (d, J = 6.3 Hz, 1H, H-3), 4.54-4.76 (m, 5H, $PhCH_2$), 4.99-5.08 (m, 3H, $PhCH_2$, =CH_2), 5.72-5.81 (m, 1H, -CH=), 7.21-7.36 (m, 15H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.18, 46.34, 47.82, 71.55, 72.22, 74.26, 76.64, 76.73, 116.79, 127.47, 127.49, 127.52, 127.68, 128.02, 128.16, 128.19, 128.30, 134.85, 137.74, 137.95, 138.00, 167.70; HRMS (ESI) Anal. Calcd for $C_{30}H_{33}NO_4Na$ $[M + Na]^+$: 494.2302, found: 494.2308.

(3*S*,4*R*,5*R*)-3,4,5-Tris(benzyloxy)-1-(pent-4-enyl)piperidin-2-one (15c)

Compound **15c** was prepared from **14** as described in the preparation of **4a** with 1-penteneamine, yielding **15c** (78% yield) as a colorless oil. R_f 0.45 (petroleum ether–ethyl acetate, 3 : 1). $[\alpha]_D^{26}$ = −66.2 (c = 0.019, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56-1.68 (m, 2H), 2.05 (dd, J = 6.9 Hz, J = 14.1 Hz, 2H), 3.22-3.30 (m, 2H), 3.34-3.48 (m, 2H), 3.84 (dd, J = 1.5 Hz, J = 5.7 Hz, 1H), 4.05 (br.s, 1H), 4.14 (d, J = 6.0 Hz, 1H), 4.54-4.76 (m, 5H), 4.94-5.08 (m, 3H), 5.75-5.84 (m, 1H), 7.29-7.36 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.77, 30.76, 46.42, 47.58, 71.64, 72.28, 74.40, 76.69, 76.83, 114.94, 127.53, 127.74, 128.08, 128.23, 128.36, 137.67, 137.78, 137.99, 138.02, 167.75; HRMS (ESI) Anal. Calcd for $C_{31}H_{35}NO_4Na$ $[M + Na]^+$: 508.2458, found: 508.2470.

(2*S*,3*R*,4*R*,5*R*)-1-Allyl-3,4,5-tris(benzyloxy)-2-vinylpiperidine (16a)

Compound **16a** was prepared from **15a** as described in the preparation of **5a**, yielding **16a** (67% yield) as a colorless oil. R_f 0.60 (petroleum ether–ethyl acetate, 3 : 1). $[\alpha]_D^{26}$ = +11.0 (c = 0.0138, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (t, J = 10.5 Hz, 1H, H-6ax), 2.84-2.91 (m, 2H, H-6eq, NCH_2), 3.09 (d, J = 8.7 Hz, 1H, H-2), 3.32 (dd, J = 5.7 Hz, J = 13.8 Hz, 1H, NCH_2), 3.47 (br.s, 1H, H-3), 3.61 (t, J = 3.3 Hz, 1H, H-4), 3.86-3.90 (m, 1H, H-5), 4.34-4.67 (m, 6H, $PhCH_2$), 5.12-5.21 (m, 4H, =CH_2), 5.83-6.00 (m, 2H, -CH=), 7.17-7.32 (m, 15H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.56, 58.26, 64.04, 71.05, 72.62, 73.54, 74.27, 79.83, 117.92, 118.25, 127.49, 127.62, 127.69, 128.26, 128.44, 134.32, 138.11, 138.65, 138.86; HRMS (ESI) Anal. Calcd for $C_{31}H_{36}NO_3$ $[M + H]^+$: 470.2690, found: 470.2691.

(2*S*,3*R*,4*R*,5*R*)-3,4,5-Tris(benzyloxy)-1-(but-3-enyl)-2-vinylpiperidine (16b)

Compound **16b** was prepared from **15b** as described in the preparation of **5a**, yielding **16b** (67% yield) as a colorless oil. R_f 0.62 (petroleum ether–ethyl acetate, 3 : 1). $[\alpha]_D^{26}$ = +1.88 (c = 0.0016, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16-2.24 (dd, J = 7.5 Hz, J = 15.3 Hz, 2H), 2.43-2.52 (m, 1H), 2.63-2.72 (m, 2H), 2.86 (dd, J = 3.9 Hz, J = 10.5 Hz, 1H), 3.15 (d, J = 9.0 Hz, 1H), 3.45 (br.s, 1H), 3.60 (br.s, 1H), 3.87-3.90 (m, 1H), 4.34-4.67 (m, 6H), 4.93-5.22 (m, 4H), 5.67-5.76 (m, 1H), 5.88-5.96 (m, 1H), 7.17-7.32 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.68, 49.56, 54.29, 63.49, 71.11, 72.64, 73.58, 73.99, 74.38, 79.90, 115.46, 117.49, 127.48, 127.52, 127.62, 127.68, 127.79, 128.24, 128.33, 128.42, 136.75, 137.89, 138.16, 138.67, 138.88; HRMS (ESI) Anal. Calcd for $C_{32}H_{38}NO_3$ $[M + H]^+$: 484.2846, found: 484.2851.

(2*S*,3*R*,4*R*,5*R*)-3,4,5-Tris(benzyloxy)-1-(pent-4-enyl)-2-vinylpiperidine (16c)

Compound **16c** was prepared from **15c** as described in the preparation of **5a**, yielding **16c** (71% yield) as a colorless oil. R_f 0.60 (petroleum ether–ethyl acetate, 4 : 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51-1.56 (m, 2H), 1.94-1.97 (m, 2H), 2.29-2.39 (m, 1H), 2.56-2.63 (m, 2H), 2.86 (dd, J = 4.5 Hz, J = 10.5 Hz, 1H), 3.10-3.13 (m, 1H), 3.46 (br.s, 1H), 3.60-3.62 (m, 1H), 3.84-3.91 (m, 1H), 4.34-4.67 (m, 6H), 4.90-5.23 (m, 4H), 5.73-5.99 (m, 2H), 7.17-7.39 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.58, 31.70, 49.59, 54.46, 63.83, 71.10, 72.62, 73.51, 74.40, 77.18, 79.91, 114.40, 127.50, 127.62, 127.69, 127.74, 127.92, 127.99, 128.24, 128.39, 128.53, 138.57, 138.70, 138.89; HRMS (ESI) Anal. Calcd for $C_{33}H_{40}NO_3$ $[M + H]^+$: 498.3003, found: 498.3015.

(6*R*,7*R*,8*R*,8a*S*)-6,7,8-Tris(benzyloxy)-3,5,6,7,8,8a-hexahydroindolizine (17a)

Compound **17a** was prepared from **16a** as described in the preparation of **6a**, yielding **17a** as a yellow syrup. R_f 0.55 (chloroform–methanol 30 : 1). Compound **17a** was unstable and directly used for the next step.

(1*R*,2*R*,3*R*,9a*S*)-1,2,3-Tris(benzyloxy)-2,3,4,6,7,9a-hexahydro-1*H*-quinolizine (17b)

Compound **17b** was prepared from **16b** as described in the preparation of **6a**, yielding **17b** (76% yield) as a yellow syrup. R_f 0.60 (chloroform–methanol 30 : 1). $[\alpha]_D^{26}$ = +0.21 (c = 0.0029, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.93 (d, J = 14.0 Hz, 1H), 2.45-2.48 (m, 2H), 2.59 (t, J = 10.5 Hz, 1H), 2.83-2.88 (m, 2H), 3.02 (br.s, 1H), 3.39 (br.s, 1H), 3.77 (br.s, 1H), 3.98-4.00 (m, 1H), 4.36-4.72 (m, 6H), 5.25 (d, J = 9.5 Hz, 1H), 5.75-5.77 (m, 1H), 7.19-7.35 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.43, 52.07, 53.78, 58.95, 71.22, 72.69, 72.85, 73.44, 74.65, 77.13, 126.31, 127.07, 127.50, 127.53, 127.55, 127.75, 127.79, 127.95, 128.22, 128.29, 128.32, 128.41, 138.16, 138.71, 138.77; HRMS (ESI) Anal. Calcd for $C_{30}H_{34}NO_3$ $[M + H]^+$: 456.2533, found: 456.2540.

(1*R*,2*R*,3*R*,10a*S*,*Z*)-1,2,3-Tris(benzyloxy)-1,2,3,4,6,7,8,10a-octahydropyrido[1,2-*a*]azepine (17c)

Compound **17c** was prepared from **16c** as described in the preparation of **6a**, yielding **17c** (37% yield) as a yellow syrup. R_f 0.70 (chloroform–methanol 30 : 1). $[\alpha]_D^{26}$ = +13.4 (c = 0.0172, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (br.s, 1H), 2.12-2.32 (m, 3H), 2.52-2.63 (m, 1H), 2.78-2.82 (m, 2H), 3.24-3.34 (m, 2H), 3.68 (s, 1H), 3.90 (br.s, 1H), 4.30-4.72 (m, 6H), 5.69-5.71 (m, 2H), 7.21-7.35 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.69, 55.92, 59.35, 71.34, 72.65, 72.82, 74.59, 79.63, 126.97, 127.53, 127.65, 127.80, 128.29, 128.32, 128.49, 128.68, 130.25, 131.57, 138.06,

138.66, 138.78; HRMS (ESI) Anal. Calcd for $C_{31}H_{36}NO_3$ $[M + H]^+$: 470.2690, found: 470.2691.

(6*R*,7*R*,8*R*,8a*S*)-Octahydroindolizine-6,7,8-triol (18a)

Compound **18a** was prepared from **17a** as described in the preparation of **7a**, yielding **18a** (82% yield) as a solid after lyophilization. $[\alpha]_D^{26} = +8.97$ ($c = 0.00248$, MeOH). ^{1}H NMR (300 MHz, D_2O) δ 1.55-1.77 (m, 4H), 2.40-2.44 (m, 2H), 2.74 (br.s, 1H), 2.93-3.02 (m, 2H), 3.80 (br.s, 2H), 3.86-3.91 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 20.87, 22.89, 51.20, 53.60, 63.13, 65.28, 67.98, 70.07; HRMS (ESI) Anal. Calcd for $C_8H_{16}NO_3$ $[M + H]^+$: 174.1125, found: 174.1129. The spectroscopic data coincide with those reported previously.[22]

(1*R*,2*R*,3*R*,9a*S*)-Octahydro-1*H*-quinolizine-1,2,3-triol (18b)

Compound **18b** was prepared from **17b** as described in the preparation of **7a**, yielding **18b** (91% yield) as a colorless oil. $[\alpha]_D^{26} = -43.0$ ($c = 0.00405$, MeOH). ^{1}H NMR (500 MHz, D_2O) δ 1.57-1.82 (m, 4H, H-7, H-8, H-9), 1.91-1.94 (m, 2H, H-7, H-8), 3.06-3.13 (m, 2H, H-4, H-6), 3.21 (dd, $J = 5.0$ Hz, $J = 12.0$ Hz, 1H, H-4), 3.34 (dd, $J = 5.0$ Hz, $J = 10.0$ Hz, 1H, H-9a), 3.42-3.45 (m, 1H, H-6), 3.91 (d, $J = 4.0$ Hz, 1H, H-1), 4.08 (t, $J = 3.5$ Hz, 1H, H-2), 4.22 (ddd, $J = 3.0$ Hz, $J = 5.0$ Hz, $J = 12.0$ Hz, 1H, H-3); ^{13}C NMR (125 MHz, D_2O) δ 22.19, 23.41, 25.93, 52.64, 56.28, 61.11, 62.89, 69.11, 70.66; HRMS (ESI) Anal. Calcd for $C_9H_{18}NO_3$ $[M + H]^+$: 188.1281, found: 188.1285.

(1*R*,2*R*,3*R*,10a*S*)-Decahydropyrido[1,2-*a*]azepine-1,2,3-triol (18c)

Compound **18c** was prepared from **17c** as described in the preparation of **7a**, yielding **18c** (88% yield) as a solid after lyophilization. $[\alpha]_D^{26} = +21.0$ ($c = 0.00183$, MeOH). ^{1}H NMR (300 MHz, D_2O) δ 1.44-1.55 (m, 3H), 1.70-1.75 (m, 5H), 3.04-3.06 (m, 2H), 3.13-3.24 (m, 3H), 3.81 (s, 2H), 4.03-4.08 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.54, 26.75, 27.73, 30.27, 56.22, 60.40, 65.24, 66.16, 70.70, 75.21; HRMS (ESI) Anal. Calcd for $C_{10}H_{20}NO_3$ $[M + H]^+$: 202.1438, found: 202.1442.

(1*R*,2*S*,7*R*,8*R*,9*R*,9a*S*)-7,8,9-Tris(benzyloxy)octahydro-1*H*-quinolizine-1,2-diol (19)

Compound **19** was prepared from **17b** as described in the preparation of **10a**, yielding **19** (82% yield) as a yellowish syrup. R_f 0.40 (chloroform–methanol 30 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.78-1.85 (m, 3H), 2.49-2.61 (m, 4H), 2.85 (br.s, 1H), 3.63-3.65 (m, 1H), 3.69-3.70 (m, 1H), 3.77 (t, $J = 3.0$ Hz, 1H), 3.94-3.96 (m, 1H), 3.99 (dd, $J = 2.5$ Hz, $J = 5.5$ Hz, 1H), 4.31 (d, $J = 12.0$ Hz, 1H), 4.49-4.59 (m, 4H), 4.72 (d, $J = 12.0$ Hz, 1H), 7.19-7.36 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.90, 49.02, 53.05, 58.65, 68.01, 68.20, 71.14, 72.37, 72.70, 72.88, 73.96, 127.57, 127.91, 128.24, 128.32, 128.35, 128.57, 128.86, 138.05, 138.65, 138.81; HRMS (ESI) Anal. Calcd for $C_{30}H_{36}NO_5$ $[M + H]^+$: 490.2588, found: 490.2589.

(1*R*,2*R*,3*R*,8*S*,9*R*,9a*S*)-Octahydro-1*H*-quinolizine-1,2,3,8,9-pentaol (20)

Compound **20** was prepared from **19** as described in the preparation of **7a**, yielding **20** (83% yield) as a colorless oil. $[\alpha]_D^{26} = +28.3$ ($c = 0.0126$, MeOH). ^{1}H NMR (500 MHz, D_2O) δ 1.93-2.08 (m, 2H, H-7), 3.18 (t, $J = 12.0$ Hz, 1H, H-4ax), 3.25-3.38 (m, 3H, H-4eq, H-6), 3.47 (dd, $J = 1.5$ Hz, $J = 10.5$ Hz, 1H, H-9a), 3.93 (dd, $J = 3.0$ Hz, $J = 10.5$ Hz, 1H, H-9), 4.12 (t, $J = 3.5$ Hz, 1H, H-2), 4.21 (dd, $J = 2.5$ Hz, $J = 6.0$ Hz, 1H, H-8), 4.24-4.28 (m, 1H, H-3), 4.29 (dd, $J = 1.0$ Hz, $J = 4.0$ Hz, 1H, H-1); ^{13}C NMR (125 MHz, D_2O) δ 27.93, 49.53, 52.64, 58.41, 62.82, 66.08, 66.13, 66.31, 68.83; HRMS (ESI) Anal. Calcd for $C_9H_{18}NO_5$ $[M + H]^+$: 220.1180, found: 220.1179.

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