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Contribution to the synthesis of polyhydroxylated indolizidines starting from sugar isothiocyanates

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ABSTRACT

A straightforward stereoselective route towards castanospermine analogues starting from the corresponding D-*gluco*- and L-*ido*-hexofuranose isothiocyanates (5*S*)-**2** and (5*R*)-**2** is described. The key transformations of this approach rely on ring-closing metathesis and reductive amination to form the final polyhydroxylated indolizidines **10**–**13** in good overall yields.

1. Introduction

Polyhydroxylated indolizidine alkaloids have attracted considerable attention from synthetic chemists due to their unique structures and remarkable biological properties, such as anticancer, antiviral, and antidiabetic activities as well as their impressive glycosidase inhibitory profile.[1] The latter activity is due to their ability to mimic the transition state included in the substrate hydrolysis.[2] Members of the aforementioned class of alkaloids have been found in various plant and fungi sources, and castanospermine **1** (Fig. 1) is one of the most representative examples. Recent investigations revealed that **1** has potential use as a therapeutic agent against viral infections,[3] various cancer types,[4] and diabetes.[5] Moreover, castanospermine has displayed antiinflammatory[6] and immunosuppressant potency.[7] The source of this significant plethora of the biological activity has been ascribed to its selective glycosidase inhibitory properties, which are important in the carbohydrate-mediated cell adhesion and signalling.[8] For these promising reasons, a number of synthetic methodologies towards polyhydroxyindolizidines have been developed.[9,10] In particular, the construction of the unnatural epimeric congeners and the other related structural analogues has stimulated extensive synthetic efforts because structural modifications in iminosugars based on the number, position and stereochemistry of the hydroxyl functionalities in the parent skeletons can induce significant changes in their activities.[11]

Our previous success with the total synthesis of biologically active α-substituted α-amino acid scaffolds[12] from sugar templates suggested that the [3,3]-sigmatropic rearrangements on structurally appropriate allylic substrates effectively installed the C—N bond. In continuation of our studies, we were interested in investigating the use of the rearranged products (5*R*)-**2** and (5*S*)-**2**, which were effectively prepared on a multigram scale, for the general preparation of tri- and pentahydroxylated indolizidine alkaloids. In keeping with our earlier work,[13] we herein report modifications into 1-deoxycastanospermine **11** and its congeners via ring-closing metathesis and reductive amination to create the required bicyclic unit.

2. Results and discussion

The key aspect of our strategy is the use of the isothiocyanate scaffolds (5*S*)-**2** and (5*R*)-**2** to accomplish the construction of target compounds **10**, **11**, **12** and **13** based on the retrosynthetic analysis outlined in Figure 1. The starting diastereoisomers (5*S*)-**2** and (5*R*)-**2** were built up according to our previous work via the thermal aza-Claisen rearrangement of the corresponding thiocyanate[13] derived from D-glucose. At first, we pursued the conversion of both derivatives (5*S*)-**2** and (5*R*)-**2** into amines (5*S*)-**4** and (5*R*)-**4**. This was achieved by the following sequence. Compound (5*S*)-**2** to sodium methoxide in MeOH and subsequent replacement of the sulfur atom to oxygen with mesitylnitrile oxide in the generated thiourethane resulted in the formation of carbamate (5*S*)-**3** in 88% yield over two steps (Scheme 1). In a parallel fashion, isothiocyanate (5*S*)-**2** was converted into the corresponding derivative (5*R*)-**3** (86%). The desired amines (5*S*)-**4** and (5*R*)-**4** were then obtained by treatment of both (5*S*)-**3** and (5*R*)-**3** with 6 M NaOH in EtOH in 85% and 84% yields, respectively. With the allylic amines (5*S*)-**4** and (5*R*)-**4** in hand, we were now in a position to explore the ring-closing metathesis (RCM) conditions required for the formation of a new dihydropyrrole core. However, in most cases it was found necessary to have the amino function protected with the acyl or benzyl moieties during the RCM reaction leading

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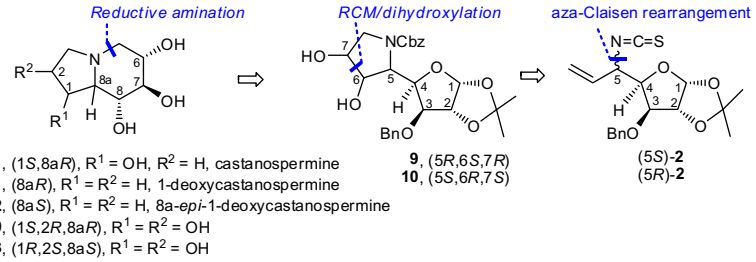
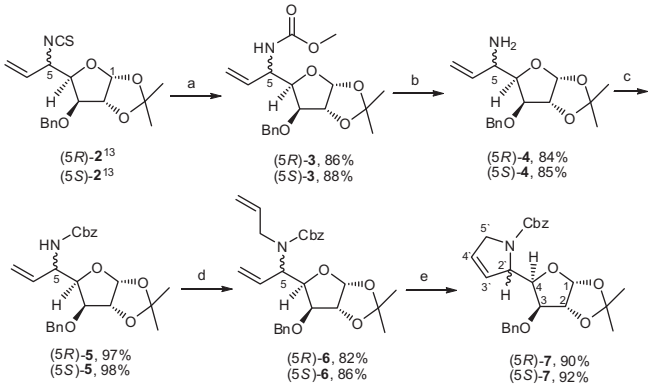


Figure 1. Structures of several indolizidines and applied retrosynthesis.

to *N*-heterocycles.[14–16] Thus, the liberated amines (5*S*)-**4** and (5*R*)-**4** were immediately treated with benzyloxycarbonyl chloride to furnish *N*-benzyloxy carbamates (5*S*)-**5** and (5*R*)-**5** in 98% and 97% yields, respectively. Their subsequent allylation step realized under standard conditions (allyl bromide, NaH, DMF) afforded alkenes (5*S*)-**6** (86%) and (5*R*)-**6** (82%).

The key metathesis of (5*S*)-**6** and (5*R*)-**6** was conducted in CH_2Cl_2 in the presence of Grubbs' first-generation catalyst and led to the production of the corresponding heterocyclic ring[17] on the sugar moiety to afford (5*S*)-**7** and (5*R*)-**7** in 92% and 90% yields. We tested different conditions to enhance the efficiency in RCM reaction; both Grubbs I and II catalysts were tested, and the reactions were carried out in toluene and CH_2Cl_2 at various temperatures. Ultimately, the use of Grubbs I catalyst (10% mol) in dry CH_2Cl_2 was found to be the most optimal (Scheme 1).



Scheme 1. Reagents and conditions: (a) (i) NaH, MeOH, 0 °C→rt, 4 h; (ii) mesitylnitrile oxide, MeCN, rt; (b) 6 M NaOH, EtOH, reflux; (c) CbzCl, $NaHCO_3$, EtOH/H_2O (1:1), 0 °C→rt; (d) allyl bromide, NaH, DMF, 0 °C→rt; (e) Grubbs I, DCM, 0 °C→rt.

With the synthesis of (5*S*)-**7** and (5*R*)-**7** established, our next task was to accomplish the modification of each olefin into the final indolizidines **10**–**13**. For this purpose, alkene (5*R*)-**7** was converted via an Upjohn dihydroxylation (K_2OsO_4,[18–20] NMO) into diol **8** (76%), which after treatment with 60% TFA was submitted to subsequent catalytic hydrogenation (10% Pd/C) to provide the pentahydroxylated indolizidine **10** in 78% yield over two steps. The spectroscopic data, melting point and specific rotation of **10** matched the values published in the literature for the same product mp 170–173 °C, Ref. 27 mp 171–173 °C, Ref. 28 170–172 °C, Ref. 29 174–178 °C, {$[\alpha]_D^{25} = -4.0$ (*c* 0.15, MeOH, Ref. 27 $[\alpha]_D^{25} = -5.2$ (*c* 0.40, H_2O), Ref. 28 $[\alpha]_D^{25} = -10.0$ (*c* 0.67, MeOH), Ref. 29 $[\alpha]_D = -4.4$ (*c* 1.2, H_2O), temperature not reported}. In the same way, diastereoisomer (5*S*)-**7** was then elaborated into indolizidine **13** in 75% overall yield (Scheme 2). The $[\alpha]_D$ value for **13** {$[\alpha]_D^{25} = +20.1$ (*c* 0.17, MeOH), Ref. 26 $[\alpha]_D^{25} = +19.4$ (*c* 0.0026, MeOH), Ref. 27 $[\alpha]_D^{25} = +21.7$ (*c* 0.35, H_2O)} and spectroscopic data were in agreement with those previously reported.

In order to further verify the configuration of the prepared structures, we collected complete data sets (^1H, ^{13}C, COSY, HSQC) including 1D-NOESY spectra for both molecules **10** and **13** in D_2O. In some cases spectral overlap hinders the detailed analysis of the specific NMR resonances. This situation was especially noticeable in compounds **10** and **13**, where the signals of the protons H-5a and H-8a in **10** and the signals of H-7 and H-8 in **13** overlapped (Supplementary data).

To enhance the structural diversity, two further analogues of castanospermine **1** were derived from the common precursor molecules (5*S*)-**7** and (5*R*)-**7** as well. Their exposure to the acid hydrolysis (TFA) followed by hydrogenolysis resulted in the formation of 1-deoxycastanospermine **11** and 8a-*epi*-1-deoxycastanospermine **12** in 65% and 62% yields over two steps, respectively (Scheme 2). It should be noted that indolizidines **10**–**13** are known compounds and their structures were further assigned by comparison of our data with those reported in the literature.[24–28]

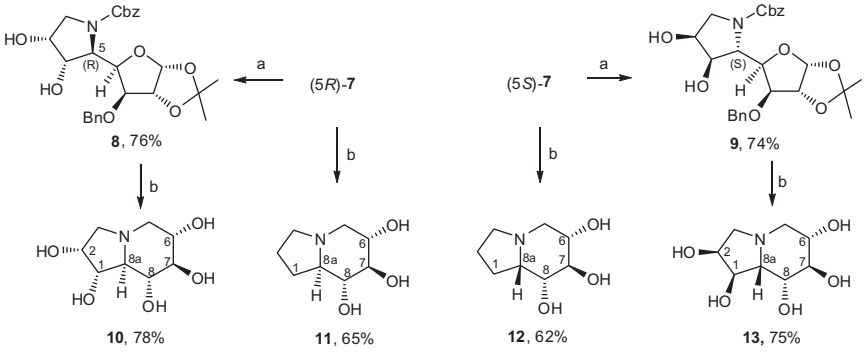
3. Conclusions

In conclusion, we have developed an efficient route towards 1-deoxycastanospemine **11** and its analogues (compounds **10**, **12** and **13**) from the appropriate sugar isothiocyanates (5*S*)-**2** and (5*R*)-**2**. The key transformations are the ring-closing metathesis to create the new dihydropyrrole skeleton and reductive amination to establish the required indolizidine backbone. The final products **10**–**13** were constructed via six- or seven-step sequences in good overall yields (30–36%).

4. Experimental

4.1. General

All commercial reagents were used in the highest available purity from Aldrich, Merck and Acros Organics without further purification. Solvents were dried and purified before use according to standard procedures. For flash column chromatography on silica gel, Kieselgel 60 (0.040–0.063 mm, 230–400 mesh, Merck) was used. Solvents for chromatography (*n*-hexane, ethyl acetate, methanol, dichloromethane) were distilled before use. Thin layer chromatography was run on Merck silica gel 60 F_{254} analytical plates; detection was carried out with either ultraviolet light (254 nm), or spraying with a solution of phosphomolybdic acid, a basic potassium permanganate solution, or a solution of concentrated H_2SO_4, with subsequent heating. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD and C_6D_6 on a Varian Mercury Plus 400 FT NMR (400.13 MHz for ^1H and 100.6 MHz for ^{13}C) or on a Varian Premium COMPACT 600 (599.87 MHz for ^1H and 150.84 MHz for ^{13}C) spectrometer using TMS as internal reference. For ^1H, δ are given in parts per million (ppm) relative to TMS ($\delta = 0.0$), CD_3OD ($\delta = 4.84$) and C_6D_6 ($\delta = 7.15$) and for ^{13}C relative



Scheme 2. Reagents and conditions: (a) K_2OsO_4, NMO, *t*-BuOH/H_2O (1:1), 40 °C; (b) (i) 60% TFA, rt (ii) H_2, 10% Pd/C, MeOH, rt.

to $CDCl_3$ (δ = 77.0), CD_3OD (δ = 49.05) and C_6D_6 (δ = 128.02). The multiplicity of the ^{13}C NMR signals concerning the ^{13}C–^1H coupling was determined by the DEPT method. Chemical shifts (in ppm) and coupling constants (in Hz) were obtained by first-order analysis; assignments were derived from COSY and H/C correlation spectra. Infrared (IR) spectra were measured with a Nicolet 6700 FT-IR spectrometer and expressed in ν values (cm^{-1}). Optical rotations were measured on a P-2000 Jasco polarimeter and reported as follows: $[\alpha]_D$ (*c* in grams per 100 mL, solvent). Melting points were recorded on a Kofler hot block and are uncorrected. Microwave reactions were carried out on the focused microwave system (CEM Discover). The temperature content of the vessel was monitored using a calibrated infrared sensor mounted under the vessel. At the end of all reactions, the contents of vessel were cooled rapidly using a stream of compressed air. Small quantities of reagents (μL) were measured with appropriate syringes (Hamilton). All reactions were performed under an atmosphere of nitrogen, unless otherwise noted.

4.1.1. 3-*O*-Benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-(methoxycarbonylamino)-α-D-*gluco*-hept-6-enfuranose (5*R*)-3 and 3-*O*-benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-(methoxycarbonylamino)-β-L-*ido*-hept-6-enfuranose (5*S*)-3

To a solution of isothiocyanate (5*R*)-**2** (0.2 g, 0.484 mmol) in dry MeOH (4.9 mL) was added sodium methoxide (28.6 mg, 0.53 mmol) at room temperature. After 6.5 h, no starting material was detected (judged by TLC) in the reaction mixture. The solvent was evaporated in vacuo, and the residue was partitioned between CH_2Cl_2 (10 mL) and water (2 mL). The aqueous layer was extracted with further portions of CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was evaporated, and the residue was purified through a short column of silica gel (*n*-hexane/ethyl acetate, 11:1) to give 0.174 g (81%) of thiocarbamate as a colourless oil, which was used immediately in the subsequent reaction without spectral characterization.

To a solution of the obtained thiocarbamate (0.17 g, 0.381 mmol) in dry MeCN (3.4 mL) was added mesitylnitrile oxide (68 mg, 0.42 mmol), and the resulting mixture was stirred for 3 h at room temperature. Evaporation of solvent and chromatography of the residue on silica gel (*n*-hexane/ethyl acetate, 9:1) afforded 0.147 g (86%) of carbamate (5*R*)-**3** as a colourless oil.

The reaction of (5*S*)-**2** (0.5 g, 1.44 mmol) with sodium methoxide (86 mg, 1.59 mmol) in dry MeOH (10 mL) and subsequent reaction of the crude thiocarbamate with mesitylnitrile oxide (0.255 g, 1.58 mmol) using the same procedure as described for the preparation of (5*R*)-**3** provided carbamate (5*S*)-**3** (0.523 g, 88%, colourless oil).

Diastereoisomer (5*R*)-**3**: $[\alpha]_D^{25}$ = +44.2 (*c* 0.33, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 3.99 (d, 1H, $J_{3,4}$ = 3.3 Hz, H_3), 4.19 (m, 1H, H_4), 4.47 (d, 1H, $J_{H,H}$ = 11.5 Hz, CH_2Ph), 4.57 (d, 1H, $J_{1,2}$ = 3.9 Hz, H_2), 4.65 (d, 1H, $J_{H,H}$ = 11.5 Hz, CH_2Ph), 4.75 (m, 1H, H_5), 5.16 (ddd, 1H, $J_{6,7cis}$ = 10.4 Hz, $J_{5,7cis}$ = 1.2 Hz, $J_{7cis,7trans}$ = 1.2 Hz, H_{7cis}), 5.29 (ddd, 1H, $J_{6,7trans}$ = 17.1 Hz, $J_{5,7trans}$ = 1.2 Hz, $J_{7cis,7trans}$ = 1.2 Hz, H_{7trans}), 5.71 (m, 1H, NH), 5.77 (ddd, 1H, $J_{6,7trans}$ = 17.1 Hz, $J_{6,7cis}$ = 10.4 Hz, $J_{5,6}$ = 5.5 Hz, H_6), 5.96 (d, 1H, $J_{1,2}$ = 3.9 Hz, H_1), 7.40–7.31 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2 (CH_3), 26.7 (CH_3), 52.0 (OCH_3), 52.8 (C_5), 72.2 (CH_2Ph), 79.8 (C_4), 81.5 (C_2), 82.8 (C_3), 104.9 (C_1), 111.6 (C_q), 116.5 (C_7), 128.1 (2 × CH_{Ph}), 128.3 (CH_{Ph}), 128.6 (2 × CH_{Ph}), 134.9 (C_6), 136.6 (C_i), 156.7 (C=O). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.68; H, 6.81; N, 3.70.

Diastereoisomer (5*S*)-**3**: $[\alpha]_D^{25}$ = +19.3 (*c* 0.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 3.90 (d, 1H, $J_{3,4}$ = 3.2 Hz, H_3), 4.06 (dd, 1H, $J_{3,4}$ = 3.2 Hz, $J_{4,5}$ = 7.6 Hz, H_4), 4.47 (d, 1H, $J_{H,H}$ = 11.6 Hz, CH_2Ph), 4.54–4.61 (m, 1H, H_5), 4.62 (d, 1H, $J_{1,2}$ = 3.8 Hz, H_2), 4.66 (d, 1H, $J_{H,H}$ = 11.6 Hz, CH_2Ph), 5.00–5.05 (m, 1H, NH), 5.16 (ddd, 1H, $J_{5,7cis}$ = $J_{7cis,7trans}$ = 1.3 Hz, $J_{6,7cis}$ = 10.4 Hz, H_{7cis}), 5.29 (ddd, 1H, $J_{5,7trans}$ = $J_{7cis,7trans}$ = 1.3 Hz, $J_{6,7trans}$ = 17.0 Hz, H_{7trans}), 5.75 (ddd, 1H, $J_{5,6}$ = 5.9 Hz, $J_{6,7cis}$ = 10.4 Hz, $J_{6,7trans}$ = 17.0 Hz, H_6), 5.95 (d, 1H, $J_{1,2}$ = 3.8 Hz, H_1), 7.29–7.38 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2 (CH_3), 26.7 (CH_3), 52.0 (OCH_3), 52.6 (C_5), 71.9 (CH_2Ph), 81.1 (C_4), 81.8 (C_2), 81.9 (C_3), 104.9 (C_1), 111.6 (C_q), 116.8 (C_7), 127.8 (2 × CH_{Ph}), 128.1 (CH_{Ph}), 128.5 (2 × CH_{Ph}), 135.3 (C_6), 137.0 (C_i), 156.5 (C=O). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.65; H, 6.96; N, 3.73.

4.1.2. 3-*O*-Benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-amino-α-D-*gluco*-hept-6-enfuranose (5*R*)-4 and 3-*O*-benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-amino-β-L-*ido*-hept-6-enfuranose (5*S*)-4

A solution of carbamate (5*R*)-**3** (1.05 g, 2.89 mmol) in EtOH (20 mL) was treated with a 6 M aq NaOH solution (20 mL), and the resulting mixture was stirred and heated at reflux for 26 h. After cooling to room temperature, the mixture was then extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated, and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate/Et_3N, 1:5:0.05) to furnish 0.741 g (84%) of amine (5*R*)-**4** as a colourless oil.

The reaction of (5*S*)-**3** (0.950 g, 2.62 mmol) with 6 M aq NaOH solution (16 mL) in EtOH (16 mL) under the same reaction conditions as described for the preparation of (5*R*)-**4**, afforded amine (5*S*)-**4** (0.680 g, 85%, colourless oil).

Diastereoisomer (5*R*)-**4**: $[\alpha]_D^{25}$ = −53.2 (*c* 0.13, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (s, 2H, NH_2), 1.32 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.69–3.74 (m, 1H, H_5), 3.92 (dd, 1H, $J_{3,4}$ = 3.3 Hz,

$J_{4,5}$ = 8.6 Hz, H_4), 4.02 (d, 1H, $J_{3,4}$ = 3.3 Hz, H_3), 4.49 (d, 1H, $J_{H,H}$ = 11.6 Hz, CH_2Ph), 4.63 (d, 1H, $J_{1,2}$ = 3.9 Hz, H_2), 4.73 (d, 1H, $J_{H,H}$ = 11.6 Hz, CH_2Ph), 5.14 (ddd, 1H, $J_{7cis,7trans}$ = 1.4 Hz, $J_{5,7cis}$ = 1.4 Hz, $J_{6,7cis}$ = 10.5 Hz, H_{7cis}), 5.27 (ddd, 1H, $J_{7cis,7trans}$ = 1.5 Hz, $J_{5,7trans}$ = 1.5 Hz, $J_{6,7trans}$ = 17.3 Hz, H_{7trans}), 5.95 (d, 1H, $J_{1,2}$ = 3.8 Hz, H_1), 5.99 (ddd, 1H, $J_{5,6}$ = 6.1 Hz, $J_{6,7cis}$ = 10.5 Hz, $J_{6,7trans}$ = 17.2 Hz, H_6), 7.28–7.40 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2 (CH_3), 26.7 (CH_3), 52.2 (C_5), 71.7 (CH_2Ph), 81.6 (C_3), 81.7 (C_2), 83.7 (C_4), 105.1 (C_1), 111.5 (C_q), 115.0 (C_7), 128.0 (2 × CH_{Ph}), 128.1 (CH_{Ph}), 128.6 (2 × CH_{Ph}), 137.1 (C_i), 137.5 (C_6). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.84; H, 7.61; N, 4.55.

Diastereoisomer (5*S*)-**4**: $[\alpha]_D^{25}$ = −44.4 (*c* 0.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.63 (s, 2H, NH_2), 3.81–3.86 (m, 1H, H_5), 3.87 (d, 1H, $J_{3,4}$ = 3.1 Hz, H_3), 3.91 (dd, 1H, $J_{3,4}$ = 3.1 Hz, $J_{4,5}$ = 8.6 Hz, H_4), 4.46 (d, 1H, $J_{H,H}$ = 11.6 Hz, CH_2Ph), 4.63 (d, 1H, $J_{1,2}$ = 3.8 Hz, H_2), 4.66 (d, 1H, $J_{H,H}$ = 11.6 Hz, CH_2Ph), 5.12 (ddd, 1H, $J_{7cis,7trans}$ = 1.4 Hz, $J_{5,7cis}$ = 1.4 Hz, $J_{6,7cis}$ = 10.5 Hz, H_{7cis}), 5.30 (ddd, 1H, $J_{7cis,7trans}$ = 1.5 Hz, $J_{5,7trans}$ = 1.5 Hz, $J_{6,7trans}$ = 17.2 Hz, H_{7trans}), 5.76 (ddd, 1H, $J_{5,6}$ = 6.1 Hz, $J_{6,7cis}$ = 10.5 Hz, $J_{6,7trans}$ = 17.3 Hz, H_6), 5.95 (d, 1H, $J_{1,2}$ = 3.8 Hz, H_1), 7.27–7.39 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3 (CH_3), 26.7 (CH_3), 52.3 (C_5), 72.0 (CH_2Ph), 82.0 (C_3), 82.1 (C_2), 84.4 (C_4), 104.9 (C_1), 111.7 (C_q), 116.3 (C_7), 127.7 (2 × CH_{Ph}), 128.0 (CH_{Ph}), 128.5 (2 × CH_{Ph}), 137.2 (C_i), 137.6 (C_6). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.81; H, 7.65; N, 4.62.

4.1.3. 3-*O*-Benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-(benzyloxycarbonylamino)-α-D-*gluco*-hept-6-enfuranose (5*R*)-5 and 3-*O*-benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-(benzyloxycarbonylamino)-β-L-*ido*-hept-6-enfuranose (5*S*)-5

To a solution of amine (5*R*)-**4** (0.741 g, 2.43 mmol) in a mixture of 1:1 EtOH/H_2O (25 mL) that had been pre-cooled to 0 °C were successively added $NaHCO_3$ (0.551 g, 6.56 mmol) and CbzCl (0.52 mL, 3.64 mmol). The resulting mixture was stirred at 0 °C for 10 min and then for 1.5 h at room temperature before the addition of H_2O (10 mL). After extraction with CH_2Cl_2 (3 × 70 mL), the combined organic layers were dried over Na_2SO_4, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate, 3:1) to afford 1.0 g (97%) of compound (5*R*)-**5** as a colourless oil.

The reaction of (5*S*)-**4** (0.680 g, 2.23 mmol) with $NaHCO_3$ (0.506 g, 6.02 mmol) and CbzCl (0.48 mL, 3.35 mmol) in a mixture of 1:1 EtOH/H_2O (25 mL) according to the same procedure described for the preparation of (5*R*)-**5** gave carbamate (5*S*)-**5** (0.960 g, 98%, colourless oil).

Diastereoisomer (5*R*)-**5**: $[\alpha]_D^{25}$ = −10.9 (*c* 0.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 4.01 (d, 1H, $J_{3,4}$ = 3.4 Hz, H_3), 4.21 (dd, 1H, $J_{3,4}$ = 3.4 Hz, $J_{4,5}$ = 6.0 Hz, H_4), 4.48 (d, 1H, $J_{H,H}$ = 11.5 Hz, CH_2Ph), 4.55 (d, 1H, $J_{1,2}$ = 3.9 Hz, H_2), 4.62 (d, 1H, $J_{H,H}$ = 11.5 Hz, CH_2Ph), 4.71–4.81 (m, 1H, H_5), 5.08–5.12 (m, 2H, $COOCH_2Ph$), 5.17 (dd, 1H, $J_{7cis,7trans}$ = 1.5 Hz, $J_{6,7cis}$ = 10.4 Hz, H_{7cis}), 5.28 (dd, 1H, $J_{7cis,7trans}$ = 1.5 Hz, $J_{6,7trans}$ = 17.2 Hz, H_{7trans}), 5.66 (s, 1H, NH), 5.83 (ddd, 1H, $J_{5,6}$ = 5.5 Hz, $J_{6,7cis}$ = 10.4 Hz, $J_{6,7trans}$ = 17.2 Hz, H_6), 5.94 (d, 1H, $J_{1,2}$ = 3.8 Hz, H_1), 7.27–7.39 (m, 10H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3 (CH_3), 26.8 (CH_3), 53.0 (C_5), 66.5 (C_{Cbz}) 72.4 (CH_2Ph), 80.2 (C_4), 81.9 (C_2), 83.1 (C_3), 105.1 (C_1), 111.7 (C_q), 116.3 (C_7), 128.0 (2 × CH_{Ph}), 128.2 (CH_{Ph}), 128.2 (2 × CH_{Ph}), 128.3 (CH_{Ph}), 128.5 (2 × CH_{Ph}), 128.8 (2 × CH_{Ph}), 135.3 (C_6), 136.9 (C_i), 137.0 (C_i), 156.0 (C=O). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.40; H, 6.63; N, 3.25.

Diastereoisomer (5*S*)-**5**: $[\alpha]_D^{25}$ = −52.1 (*c* 0.13, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.92 (d, 1H, $J_{3,4}$ = 3.3 Hz, H_3), 4.08–4.13 (m, 1H, H_4), 4.48 (d, 1H, $J_{H,H}$ = 11.7 Hz, CH_2Ph), 4.56–4.61 (m, 1H, H_5), 4.64 (d, 1H, $J_{H,H}$ = 11.8 Hz, CH_2Ph), 4.70 (d, 1H, $J_{1,2}$ = 3.9 Hz, H_2), 5.01–5.13 (m, 3H, $COOCH_2Ph$, NH), 5.15 (dd, 1H, $J_{7cis,7trans}$ = 1.3 Hz, $J_{6,7cis}$ = 10.4 Hz, H_{7cis}), 5.28 (dd, 1H, $J_{7cis,7trans}$ = 1.4 Hz, $J_{6,7trans}$ = 17.2 Hz, H_{7trans}), 5.79 (ddd, 1H, $J_{5,6}$ = 6.0 Hz, $J_{6,7cis}$ = 10.5 Hz, $J_{6,7trans}$ = 17.2 Hz, H_6), 5.94 (d, 1H, $J_{1,2}$ = 3.9 Hz, H_1), 7.27–7.40 (m, 10H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3 (CH_3), 26.9 (CH_3), 52.8 (C_5), 66.7 (C_{Cbz}) 72.1 (CH_2Ph), 81.2 (C_4), 82.2 (C_2), 82.3 (C_3), 105.1 (C_1), 111.8 (C_q), 116.7 (C_7), 128.0 (2 × CH_{Ph}), 128.1 (CH_{Ph}), 128.2 (2 × CH_{Ph}), 128.2 (CH_{Ph}), 128.6 (2 × CH_{Ph}), 128.7 (2 × CH_{Ph}), 135.7 (C_6), 137.0 (C_i), 137.0 (C_i), 156.0 (C=O). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.43; H, 6.59; N, 3.22.

4.1.4. 3-*O*-Benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-[allyl-(benzyloxycarbonyl)amino]-α-D-*gluco*-hept-6-enfuranose (5*R*)-6 and 3-*O*-benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-[allyl-(benzyloxycarbonyl)amino]-β-L-*ido*-hept-6-enfuranose (5*S*)-6

To a solution of (5*R*)-**5** (1.0 g, 2.28 mmol) in dry DMF (25 mL) that had been pre-cooled to 0 °C was added NaH (0.109 g, 4.54 mmol, 60% dispersion in mineral oil), and the resulting suspension was stirred for 30 min at 0 °C before the addition of allyl bromide (0.50 mL, 5.78 mmol). The mixture was allowed to warm to room temperature and then it was continued for another 1.5 h. After cautious addition of NH_4Cl (5 mL), the reaction mixture was extracted with Et_2O (3 × 70 mL), and the combined organic layers were dried over Na_2SO_4. Evaporation of solvent and chromatography of the residue on silica gel (*n*-hexane/ethyl acetate, 5:1) afforded 0.895 g (82%) of derivative (5*R*)-**6** as a colourless oil.

The reaction of (5*S*)-**5** (0.960 g, 2.18 mmol) with NaH (0.105 g, 4.36 mmol) and allyl bromide (0.47 mL, 5.45 mmol) using the same procedure as described for the preparation of (5*R*)-**6** gave product (5*S*)-**6** (0.899 g, 86%, colourless oil).

Diastereoisomer (5*R*)-**6**: $[\alpha]_D^{25}$ = −44.2 (*c* 0.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 3H, CH_3), 1.42 (s, 1H, CH_3), 3.61 (dd, 1H, $J_{8,9}$ = 7.4 Hz, $J_{8,8}$ = 15.6 Hz, H_8), 3.93 (d, 1H, $J_{3,4}$ = 3.3 Hz, H_3), 4.07–4.21 (m, 1H, H_8), 4.47 (d, 1H, $J_{H,H}$ = 11.7 Hz, CH_2Ph), 4.53 (d, 1H, $J_{1,2}$ = 3.9 Hz, H_2), 4.55–4.65 (m, 3H, H_4, H_5, CH_2Ph), 5.00–5.10 (m, 3H, $COOCH_2Ph$, 2 × H_{10}), 5.12–5.23 (m, 3H, $COOCH_2Ph$, 2 × H_7), 5.74 (m, 1H, H_9), 5.91 (d, 1H, $J_{1,2}$ = 3.8 Hz, H_1), 6.03–6.17 (m, 1H, H_6), 7.27–7.36 (m, 10H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.6 (CH_3), 27.0 (CH_3), 50.4 (C_8), 58.5 (C_5), 67.5 (C_{Cbz}), 72.2 (CH_2Ph), 80.4 (C_4), 82.1 (C_2), 82.5 (C_3), 105.3 (C_1), 111.9 (C_q), 2 × 117.2 (C_7, C_{10}), 128.0 (2 × CH_{Ph}), 128.1 (CH_{Ph}), 128.2 (2 × CH_{Ph}), 128.3 (2 × CH_{Ph}), 128.6 (3 × CH_{Ph}), 2 × 135.1 (C_6, C_9), 136.9 (C_i), 137.7 (C_i), 156.2 (C=O). Anal. Calcd for $C_{28}H_{33}NO_6$: C, 70.13; H, 6.94; N, 2.92. Found: C, 70.14; H, 6.97; N, 2.96.

Diastereoisomer (5*S*)-**6**: $[\alpha]_D^{25}$ = −4.07 (*c* 0.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 3H, CH_3), 1.44 (s, 1H, CH_3), 3.79–3.95 (m, 2H, H_8, H_3), 4.08 (dd, 1H, $J_{8,9}$ = 5.6 Hz, $J_{8,8}$ = 16.1 Hz, H_8), 4.45 (d, 1H, $J_{H,H}$ = 11.6 Hz, CH_2Ph), 4.58 (d, 1H, $J_{1,2}$ = 3.8 Hz, H_2), 4.62 (d, 1H, $J_{H,H}$ = 11.6 Hz, CH_2Ph), 4.66–4.80 (m, 1H, H_5), 5.02–5.27 (m, 6H, 2 × H_7, 2 × H_{10}, $COOCH_2Ph$), 5.80–6.01 (m, 3H, H_1, H_6, H_9), 7.27–7.38 (m, 10H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.6 (CH_3), 27.0 (CH_3), 49.6 (C_8), 59.3 (C_5), 67.1 (C_{Cbz}), 72.1 (CH_2Ph), 78.6 (C_4), 81.9 (C_2), 82.1 (C_3), 105.1 (C_1), 111.8 (C_q), 116.3 (C_7), 118.9 (C_{10}), 127.8 (2 × CH_{Ph}), 127.9 (3 × CH_{Ph}), 128.0 (1 × CH_{Ph}), 128.5 (2 × CH_{Ph}), 128.6 (2 × CH_{Ph}), 133.3 (C_6), 135.6 (C_9), 137.0 (C_i), 137.4 (C_i), 156.2 (C=O). Anal. Calcd for $C_{28}H_{33}NO_6$: C, 70.13; H, 6.94; N, 2.92. Found: C, 70.10; H, 6.86; N, 2.93.

4.1.5. (2′*R*,4*R*)-4-*C*-[1′-(Benzyloxycarbonyl)-2′,5′-dihydro-1′*H*-pyrrol-2′-yl]-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*gluco*-furanose (5*R*)-7 and (2′*S*,4*R*)-4-*C*-[1′-(benzyloxycarbonyl)-2′,5′-dihydro-1′*H*-pyrrol-2′-yl]-3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-*threo*-furanose (5*S*)-7

To a solution of (5*R*)-**6** (0.895 g, 1.87 mmol) in dry CH_2Cl_2 (55 mL) that had been pre-cooled to 0 °C was added Grubb's

first-generation catalyst (0.154 g, 0.187 mmol). After stirring at room temperature for 30 min, the solvent was evaporated, and the residue was subjected to flash chromatography on Al_2O_3 (*n*-hexane/ethyl acetate, 6:1) to afford 0.758 g (90%) of (5*R*)-**7** as a colourless oil.

The reaction of (5*S*)-**6** (0.898 g, 1.87 mmol) with Grubbs I (0.154 g, 0.187 mmol) in dry CH_2Cl_2 (55 mL) using the same reaction conditions as described for the preparation of (5*R*)-**7** gave derivative (5*S*)-**7** (0.777 mg, 92%, colourless oil).

Diastereoisomer (5*R*)-**7**: $[\alpha]_D^{25}$ = +68.7 (*c* 0.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 4.06–4.34 (m, 3H, 2 × H_8, H_3), 4.56 (d, 1H, $J_{1,2}$ = 3.8 Hz, H_2), 4.58–4.71 (m, 3H, CH_2Ph, H_4), 4.80–4.96 (m, 1H, H_5), 5.11 (d, 1H, $J_{H,H}$ = 12.4 Hz, $COOCH_2Ph$), 5.21 (d, 1H, $J_{H,H}$ = 12.4 Hz, $COOCH_2Ph$), 5.77–5.84 (m, 1H, H_7), 5.86 (d, 1H, $J_{1,2}$ = 3.9 Hz, H_1), 5.86–5.94 (m, 1H, H_6), 7.27–7.39 (m, 10H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.5 (CH_3), 26.9 (CH_3), 53.5 (C_8), 63.9 (C_5), 66.9 (C_{Cbz}), 72.3 (CH_2Ph), 81.2 (C_4), 82.6 (C_2), 83.6 (C_3), 105.0 (C_1), 111.8 (C_q), 125.8 (C_7), 127.7 (CH_{Ph}), 127.9 (2 × CH_{Ph}), 128.0 (2 × CH_{Ph}), 128.3 (CH_{Ph}), 128.5 (2 × CH_{Ph}), 128.6 (2 × CH_{Ph}), 128.8 (C_6), 137.0 (C_i), 137.7 (C_i), 155.0 (C=O). Anal. Calcd for $C_{26}H_{29}NO_6$: C, 69.16; H, 6.47; N, 3.10. Found: C, 69.30; H, 6.43; N, 3.15.

Diastereoisomer (5*S*)-**7**: $[\alpha]_D^{25}$ = −0.9 (*c* 0.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.88 (d, 1H, $J_{3,4}$ = 3.3 Hz, H_3), 3.97–4.07 (m, 1H, H_8), 4.18–4.28 (m, 1H, H_4), 4.29–4.38 (m, 1H, H_8), 4.42 (d, 1H, $J_{H,H}$ = 11.8 Hz, CH_2Ph), 4.52 (d, 1H, $J_{1,2}$ = 3.8 Hz, H_2), 4.64 (d, 1H, $J_{H,H}$ = 11.8 Hz, CH_2Ph), 5.02–5.16 (m, 2H, $COOCH_2Ph$, H_5), 5.23 (d, 1H, $J_{H,H}$ = 12.5 Hz, $COOCH_2Ph$), 5.63–5.70 (m, 1H, H_7), 5.71–5.78 (m, 1H, H_6), 5.92–6.02 (m, 1H, H_1), 7.27–7.43 (m, 10H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.5 (CH_3), 27.0 (CH_3), 54.3 (C_8), 63.8 (C_5), 67.2 (C_{Cbz}), 72.0 (CH_2Ph), 81.8 (C_4), 82.2 (C_2), 83.0 (C_3), 105.4 (C_1), 111.7 (C_q), 126.9 (C_7), 127.9 (CH_{Ph}), 127.9 (2 × CH_{Ph}), 128.1 (CH_{Ph}), 128.3 (2 × CH_{Ph}), 128.5 (2 × CH_{Ph}), 128.6 (2 × CH_{Ph}), 128.8 (C_6), 137.3 (C_i), 137.6 (C_i), 155.5 (C=O). Anal. Calcd for $C_{26}H_{29}NO_6$: C, 69.16; H, 6.47; N, 3.10. Found: C, 69.23; H, 6.53; N, 3.05.

4.1.6. (6*S*,7*R*,8*R*,8a*R*)-6,7,8-Trihydroxyindolizidine (1-deoxycastanospermine) 11

To a solution of (5*R*)-**7** (0.20 g, 0.44 mmol) in CH_2Cl_2 (2 mL) that had been pre-cooled to 0 °C was added 60% TFA (5 mL). After stirring at room temperature for 5 h, the solvent was co-evaporated three times with toluene. The obtained crude product was dissolved in dry MeOH (5 mL), 10% Pd/C/20% $Pd(OH)_2$/C (120 mg/10 mg) mixture was added, and the resulting suspension was stirred at room temperature for 20 h under an atmosphere of hydrogen. The catalyst was filtered through a small pad of Celite and washed with MeOH. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel (chloroform/methanol, 3:2) to furnish 50 mg (65%) of product **11** as white crystals; mp 177–179 °C (Ref. 21 mp 178–181 °C, Ref. 22 mp 177–179.5 °C, Ref. 23 mp 179–180 °C, Ref. 24 mp 176–178 °C); $[\alpha]_D^{25}$ = +50.2 (*c* 0.1, MeOH), {(Ref. 1 $[\alpha]_D$ = +50.6 (*c* 0.2, MeOH), Ref. 22 $[\alpha]_D^{22}$ = +47.8 (*c* 0.006, MeOH), Ref. 23 $[\alpha]_D^{29}$ = +50 (*c* 1.2, MeOH), Ref. 24 $[\alpha]_D$ = +50.1 (*c* 0.7, MeOH)}. ^{1}H NMR (400 MHz, D_2O): δ 1.43–1.56 (m, 1H, H_1), 1.72–1.87 (m, 2H, 2 × H_2), 1.98–2.08 (m, 1H, H_1), 2.09–2.22 (m, 2H, H_{8a}, H_5), 2.34 (1H, dt, $J_{3,3}$ = 9.1 Hz, $J_{2,3}$ = 9.2 Hz, H_3), 2.95–3.05 (m, 1H, H_3), 3.17 (dd, 1H, $J_{5,6}$ = 5.3 Hz, $J_{5,5}$ = 11.1 Hz, H_5), 3.19–3.28 (m, 2H, H_7, H_8), 3.6 (ddd, 1H, $J_{5,6}$ = 5.3 Hz, $J_{6,7}$ = 8.8 Hz, $J_{5,6}$ = 10.9 Hz, H_6); ^{13}C NMR (100 MHz, CD_3OD): δ 22.7 (C_2), 29.2 (C_1), 54.6 (C_3), 57.4 (C_5), 69.3 (C_{8a}), 72.1 (C_6), 76.4 (C_8), 80.8 (C_7). Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.53; H, 8.75; N, 8.01.

4.1.7. (6*S*,7*R*,8*R*,8a*S*)-6,7,8-Trihydroxyindolizidine (8a-*epi*-1-deoxycastanospermine) 12

The reaction of (5*S*)-**7** (0.160 g, 0.35 mmol) with 60% TFA (2 mL) and subsequent hydrogenation in dry MeOH (5 mL) using 10% Pd/C/20% $Pd(OH)_2$/C (110 mg/10 mg) mixture following the same procedure as described for the preparation of compound **11** gave 8a-*epi*-1-deoxycastanospermine **12** (colourless foam, 38 mg, 62%); mp 147–149 °C, (Ref. 22 149–150 °C, Ref. 25 190–192 °C); $[\alpha]_D^{25}$ = +42.2 (*c* 0.15, MeOH), {(Ref. 25 $[\alpha]_D^{20}$ = +44.4 (*c* 1.3, H_2O), Ref. 22 $[\alpha]_D^{22}$ = +41.8 (*c* 0.0057, MeOH), Ref. 24 $[\alpha]_D^{20}$ = +23.0 (*c* 0.72, MeOH), Ref. 6 $[\alpha]_D^{26}$ = +40.9 (*c* 0.00042, MeOH)}. ^{1}H NMR (400 MHz, CD_3OD): δ 1.70–1.87 (m, 3H, H_1, 2 × H_2), 1.90–1.98 (m, 1H, H_1), 2.36 (m, 1H, H_5), 2.60–2.70 (m, 2H, H_{8a}, H_3), 3.02–3.14 (m, 2H, H_3, H_5), 3.72–3.78 (m, 2H, H_6, H_8), 3.85 (t, 1H, $J_{6,7}$ = $J_{7,8}$ = 3.2 Hz, H_7); ^{13}C NMR (100 MHz, CD_3OD): δ 21.3 (C_2), 24.7 (C_1), 55.1 (C_3), 55.4 (C_5), 53.9 (C_{8a}), 70.9 (C_6), 70.9 (C_8), 71.0 (C_7). Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.38; H, 8.84; N, 8.08.

4.1.8. (4*R*)-4-*C*-[(2′*R*,3′*S*,4′*R*)-1′-(Benzyloxycarbonyl)-3′,4′-dihydroxypyrrolidin-2′-yl]-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*gluco*-furanose 8 and (4*R*)-4-*C*-[(2′*S*,3′*R*,4′*S*)-1′-(benzyloxycarbonyl)-3′,4′-dihydroxypyrrolidin-2′-yl]-3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-threofuranose 9

To a solution of (5*R*)-**7** (0.20 g, 0.44 mmol) in a mixture of 1:1 *t*-BuOH/H_2O (4 mL) were added NMO (77 mg, 0.57 mmol) and $K_2OsO_4{\cdot}2H_2O$ (8 mg, 0.02 mmol), and the resulting mixture was stirred at 40 °C for 4 h. After the cautious addition of H_2O (3 mL), the mixture was extracted with ethyl acetate (3 × 15 mL), and the combined organic layers were successively washed with a saturated $Na_2S_2O_3$ solution (15 mL), then with brine (5 ml) and finally dried. The solvent was subsequently evaporated and the residue was subjected to flash chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1) to give 0.158 g (76%) of diol **8** as a colourless oil.

The reaction of (5*S*)-**7** (0.230 g, 0.51 mmol) with $K_2OsO_4{\cdot}2H_2O$ (8 mg, 0.02 mmol) in the presence of NMO (89 mg, 0.66 mmol) in a mixture of 1:1 *t*-BuOH/H_2O (5 mL) using the same procedure as described for the preparation of **8** gave compound **9** (0.184 g, 74%, colourless oil).

Diastereoisomer **8**: $[\alpha]_D^{25}$ = +23.8 (*c* 0.16, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.55 (s, 1H, OH), 3.06 (s, 1H, OH), 3.50 (dd, 1H, $J_{7,8}$ = 4.6 Hz, $J_{8,8}$ = 11.8 Hz, H_8), 3.61–3.71 (m, 1H, H_8), 3.99–4.05 (m, 1H, H_5), 4.23–4.29 (m, 1H, H_7), 4.45–4.50 (m, 1H, H_6), 4.50–4.58 (m, 1H, CH_2Ph), 4.63 (d, 1H, $J_{1,2}$ = 3.9 Hz, H_2), 4.72 (d, 1H, $J_{H,H}$ = 11.2 Hz, CH_2Ph), 4.75–4.88 (m, 1H, H_4), 5.08 (d, 1H, $J_{H,H}$ = 12.0 Hz, $COOCH_2Ph$), 5.15 (d, 1H, $J_{H,H}$ = 12.0 Hz, $COOCH_2Ph$), 5.92 (d, 1H, $J_{1,2}$ = 3.9 Hz, H_1), 7.26–7.43 (m, 10H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3 (CH_3), 26.8 (CH_3), 51.3 (C_8), 62.3 (C_5), 66.9 (C_{Cbz}), 70.4 (C_7), 71.2 (C_6), 72.5 (CH_2Ph), 79.4 (C_4), 81.9 (C_2), 83.9 (C_3), 104.8 (C_1), 112.0 (C_q), 127.8 (CH_{Ph}), 127.9 (CH_{Ph}), 128.2 (2 × CH_{Ph}), 128.4 (2 × CH_{Ph}), 128.6 (2 × CH_{Ph}), 128.8 (2 × CH_{Ph}), 136.1 (C_i), 136.5 (C_i), 155.4 (C=O). Anal. Calcd for $C_{26}H_{31}NO_8$: C, 64.32; H, 6.44; N, 2.88. Found: C, 64.40; H, 6.44; N, 2.83.

Diastereoisomer **9**: $[\alpha]_D^{25}$ = −52.9 (*c* 0.18, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.62 (s, 1H, OH), 2.69 (s, 1H, OH), 3.22 (dd, 1H, $J_{7,8}$ = 3.8 Hz, $J_{8,8}$ = 12.1 Hz, H_8), 3.65–3.76 (m, 1H, H_8), 3.90–4.01 (m, 1H, H_5), 4.02–4.07 (m, 1H, H_3), 4.17–4.23 (m, 1H, H_7), 4.35 (d, 1H, $J_{H,H}$ = 11.5 Hz, CH_2Ph), 4.54–4.51 (m, 2H, H_2, CH_2Ph), 4.63–4.71 (m, 1H, H_6), 4.81–4.97 (m, 1H, H_4), 5.10 (d, 1H, $J_{H,H}$ = 12.3 Hz, $COOCH_2Ph$), 5.17 (d, 1H, $J_{H,H}$ = 12.2 Hz, $COOCH_2Ph$), 6.00 (d, 1H, $J_{1,2}$ = 3.7 Hz, H_1), 7.20–7.42 (10H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3 (CH_3), 26.8 (CH_3), 52.9 (C_8), 60.7 (C_5), 67.2 (C_{Cbz}), 69.9 (C_7), 72.2 (C_6), 74.1 (CH_2Ph), 78.9 (C_4), 82.1 (C_2), 83.6 (C_3), 105.2 (C_1), 112.1 (C_q),

127.6 (3 × CH_{Ph}), 128.0 (CH_{Ph}), 128.1 (2 × CH_{Ph}), 128.5 (2 × CH_{Ph}), 128.6 (2 × CH_{Ph}), 136.7 (C_i), 137.1 (C_i), 155.3 (C=O). Anal. Calcd for $C_{26}H_{31}NO_8$: C, 64.32; H, 6.44; N, 2.88. Found: C, 64.40; H, 6.44; N, 2.83.

4.1.9. (1*R*,2*S*,6*S*,7*R*,8*R*,8a*R*)-1,2,6,7,8-Pentahydroxyindolizidine 10

To a solution of **8** (0.158 g, 0.33 mmol) in CH_2Cl_2 (5 mL) that had been pre-cooled to 0 °C was added 60% TFA (5 mL), and the resulting mixture was stirred at room temperature for 4 h. After co-evaporation of the solvent three times with toluene, the obtained crude product was dissolved in MeOH (5 mL) and 10% Pd/C/20% $Pd(OH)_2$/C (90 mg/10 mg) mixture was added. The suspension was stirred at room temperature for 20 h under an atmosphere of hydrogen. The catalyst was then filtered through a small pad of Celite, the solvent was removed in vacuo, and the residue was chromatographed on silica gel (chloroform/methanol, 2:1) to afford 51 mg (78%) of **10** as white solids; mp 170–173 °C (Ref. 27 mp 171–173 °C, Ref. 28 mp 170–172 °C, Ref. 29 mp 174–178 °C); $[\alpha]_D^{25} = -4.0$ (*c* 0.15, MeOH), {(Ref. 27 $[\alpha]_D^{25} = -5.2$ (*c* 0.40, H_2O), Ref. 28 $[\alpha]_D^{25} = -10$ (*c* 0.67, MeOH), Ref. 29 $[\alpha]_D = -4.4$ (*c* 1.2, H_2O), temperature not reported}. ^1H NMR (600 MHz, CD_3OD): δ 2.04 (dd, 1H, $J_{1,8a} = 7.1$ Hz, $J_{8,8a} = 9.2$ Hz, H_{8a}), 2.08 (t, 1H, $J_{5a,5b} = J_{5a,6} = 10.5$ Hz, H_{5a}), 2.24 (dd, 1H, $J_{2,3} = 6.2$ Hz, $J_{3a,3b} = 9.5$ Hz, H_{3b}), 3.05 (dd, 1H, $J_{5b,6} = 5.3$ Hz, $J_{5a,5b} = 10.6$ Hz, H_{5b}), 3.17 (t, 1H, $J_{6,7} = J_{7,8} = 8.9$ Hz, H_7), 3.23–3.36 (m, 2H, H_{3a}, H_8), 3.50 (ddd, 1H, $J_{5b,6} = 5.3$ Hz, $J_{6,7} = 8.9$ Hz, $J_{5a,6} = 10.3$ Hz, H_6), 3.85 (t, 1H, $J_{1,2} = J_{1,8a} = 7.1$ Hz, H_1), 4.13 (q, 1H, $J_{1,2} = J_{2,3a} = J_{2,3b} = 6.9$ Hz, H_2); ^{13}C NMR (125 MHz, CD_3OD): δ 57.3 (C_5), 61.0 (C_3), 69.8 (C_2), 71.8 (C_6), 72.7 (C_{8a}), 75.1 (C_8), 75.8 (C_1), 80.9 (C_7). Anal. Calcd for $C_8H_{15}NO_5$: C, 46.82; H, 7.37; N, 6.38. Found: C, 46.77; H, 7.46; N, 6.39.

4.1.10. (1*S*,2*R*,6*S*,7*R*,8*R*,8a*S*)-1,2,6,7,8-Pentahydroxyindolizidine 13

The reaction of **9** (0.140 g, 0.29 mmol) with 60% TFA (2 mL) and subsequent hydrogenation in dry MeOH (4 mL) using 10% Pd/C/20% $Pd(OH)_2$/C (100 mg/10 mg) mixture following the same procedure as described for the preparation of compound **10** gave pentahydroxylated indolizidine derivative **13** (colourless oil, 43.8 g, 75%); $[\alpha]_D^{25} = +20.1$ (*c* 0.17, MeOH), {(Ref. 26 $[\alpha]_D^{25} = +19.4$ (*c* 0.0026, MeOH), Ref. 27 $[\alpha]_D^{25} = +217.0$ (*c* 0.35, H_2O)}. ^1H NMR (400 MHz, CD_3OD): δ 2.18 (dd, 1H, $J_{2,3a} = 5.1$ Hz, $J_{3a,3b} = 9.7$ Hz, H_{3a}), 2.44 (dd, 1H, $J_{1,8a} = 1.3$ Hz, $J_{8,8a} = 7.7$ Hz, H_{8a}), 2.56 (dd, 1H, $J_{5a,6} = 1.8$ Hz, $J_{5a,5b} = 11.6$ Hz, H_{5a}), 2.89 (dd, 1H, $J_{5b,6} = 1.8$ Hz, $J_{5a,5b} = 11.7$ Hz, H_{5b}), 3.36 (dd, 1H, $J_{2,3b} = 6.2$ Hz, $J_{3a,3b} = 9.9$ Hz, H_{3b}), 3.67–3.71 (m, 1H, H_6), 3.81–3.88 (m, 2H, H_7, H_8), 4.00–4.12 (m, 2H, H_1, H_2); ^{13}C NMR (100 MHz, CD_3OD): δ 55.5 (C_5), 62.6 (C_3), 67.1 (C_{8a}), 68.3 (C_2), 69.9 (C_7), 70.3 (C_8), 70.4 (C_1), 71.2 (C_6). Anal. Calcd for $C_8H_{15}NO_5$: C, 46.82; H, 7.37; N, 6.38. Found: C, 46.85; H, 7.39; N, 6.32.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.02.011.

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