A Facile and Rapid Route to a New Series of Pyrrolizidines Structurally Related to (+)-Alexine and (+)-Australine

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Addition of allylmagnesium chloride to protected L-xylofuranosylamine gave, after intramolecular cyclization, the corresponding polyhydroxylated 2-allylpyrrolidines. New series of analogues of (+)-alexine and (+)-australine were readily obtained from these intermediates by dihydroxylation, intramolecular nucleophilic displacement and subsequent deprotection. The determination of the configuration at the newly formed stereocentres was based on NMR experiments.

Introduction

Australine (**1**, from *Castanospermum australe*)[1] and alexine (**2**, from *Alexa leiopetala*)[2] were the first naturally occurring 3-(hydroxymethyl)pyrrolizidines to be isolated, in 1988. Additional isomers and structural analogues of these polyhydroxylated pyrrolizidines have since been isolated from other sources.[3] The potential of this class of compounds as selective glycosidase inhibitors,[1−3,4] as well as their antiviral and retroviral activities,[5] have attracted a good deal of synthetic interest.

A variety of approaches for the synthesis of 3-(hydroxymethyl)pyrrolizidines have been described; most commonly, sugars[6] or amino acids[7] were used as chiral building blocks. More recently, other efficient and stereoselective methods have been reported,[8] utilizing metathesis,[9] cycloadditions[10] and enzymatic[11] processes as key steps.

It is now well established that the biological activity exhibited by these polyhydroxylated alkaloids varies with the position and stereochemistry of the hydroxy groups on the pyrrolizidine skeletons.[12] For biological evaluation of other members of this class of compounds, we found it interesting to explore a flexible and rapid route to a new series of tetrahydroxylated pyrrolizidines structurally related to australine (compounds **3** and **4**, Figure 1) or alexine (compounds **5** and **6**).

In this report we describe such a strategy for the synthesis of all four diastereomeric pyrrolizidines **3**−**6**, starting from L-xylose.

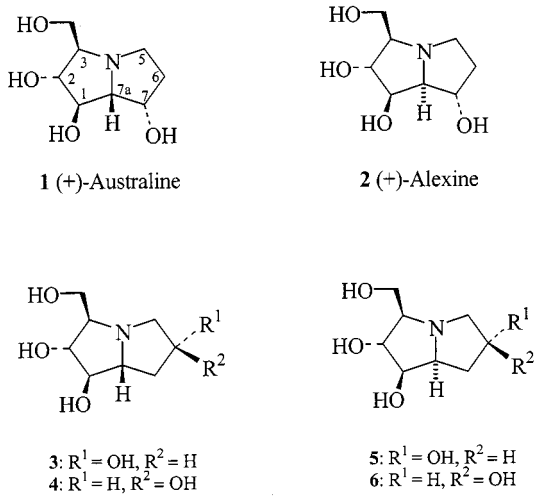

Figure 1. Structure of compounds **1**−**6**

Results and Discussion

The addition of organometallic compounds to glycosylamines is an efficient and versatile method to obtain functionalised pyrrolidines, introduced by Nicotra.[13] The synthetic applications of this reaction have been demonstrated both by our group[14] and by others[15] for the synthesis of glycosidase or glycosyltransferase inhibitors, and recently for total syntheses of alexine and 7-deoxyalexine.[16] By this procedure, the new diastereoisomeric pyrrolizidine targets **3**−**6** could also readily be obtained from a common carbohydrate precursor by simple functional group manipulation, owing to the fact that stereoselective diversity could be achieved in each key step (Scheme 1).

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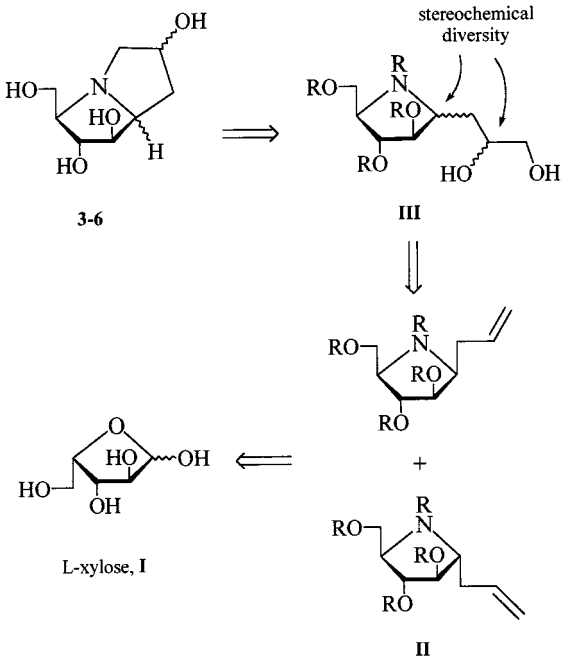


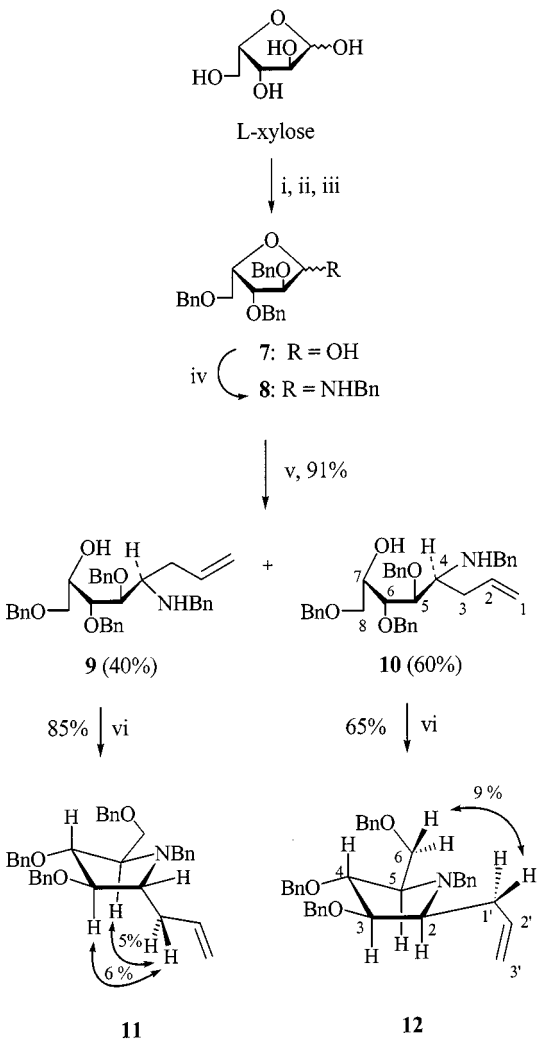
Scheme 1. Retrosynthetic route to pyrrolizidines **3**−**6** from L-xylose

For our strategy we envisaged the formation of the two diastereoisomeric allylpyrrolidines **II** from L-xylose (**I**). This sugar possesses the required functionalities necessary to obtain both pyrrolidines **II** in only a few steps, including amination of the anomeric carbon atom and allylation with an organometallic reagent. Cyclization to azasugars **II** by intramolecular nucleophilic displacement could then be employed to induce a configurational switch from the L-*xylo* to the required D-*arabino* series.

The stereogenic centres at C-6 in **3**−**6** could be established from each of the four possible stereoisomers **III** obtained by Sharpless asymmetric dihydroxylation (AD reaction) at the terminal olefin in **II**. Finally, construction of the bicyclic pyrrolizidine rings in **3**−**6** could be achieved by a classical S_N2 displacement at an activated primary carbinol centre in **III**.

Synthesis

Anomerization of L-xylose with methanol/HCl gave a mixture of both methyl furanosides,[17a] which were benzylated by classical procedures. After deprotection of the acetal (1 M HCl in dioxane), the resulting 2,3,5-tri-*O*-benzyl-L-xylofuranose (**7**)[17b] was treated with an excess of benzylamine to give the corresponding glycosylamine **8** in quantitative yield (Scheme 2). Since glycosylamines are easily hydrolysed back to the parent sugar,[18] **8** was used without prior purification as the crude material in the next step. Addition of allylmagnesium chloride to **8** (Scheme 2) was conducted at 0 °C, and afforded a mixture of the two possible diastereoisomers **9** and **10** in good yield (91%). The reaction favoured the formation of the *anti* adduct, as previously observed,[13] in moderate excess (20% *de*). At this stage, the two isomers **9** and **10** were easily separable by



Scheme 2. Reagents and conditions: (i) MeOH/HCl, 100%; (ii) BnBr, $Ba(OH)_2$, DMF, 40%; (iii) aq. HCl, refluxing dioxane, 50%; (iv) $BnNH_2$, CH_2Cl_2, mol. sieves (4 Å), 98%; (v) allylMgCl, THF, 0 °C; (vi) MsCl, Py

chromatography on silica gel, with elution with diethyl ether/petroleum ether (1:1, v/v).

The configuration at the newly created asymmetric carbon atom C-4 in **9** and **10** was firmly assigned after their conversion into the respective pyrrolidines **11** and **12**. This was easily achieved in one step by treatment of these amino alcohols with methanesulfonyl chloride. The corresponding mesylates were formed, but were not isolated, and underwent intramolecular cyclization with the secondary amine with concomitant inversion at C-7 (in **9** and **10**) to give **11** (85% yield) and **12** (65% yield), respectively.

Examination of nuclear Overhauser effects carried out on pyrrolidines **11** and **12** allowed determination of the configuration at C-2 (designated as C-4 in compounds **9** and **10**). Thus, for **11** the enhancement observed on the 3-H and 5-H signals after irradiation of the allylic 1′-H protons proved that the orientations of all these atoms were directed to the same side of the pyrrolidine ring plane. Irradiation of the allylic protons in epimer **12** resulted in a substantial NOE

on the 6-H protons, showing the *cis* relationship between the two substituents (Scheme 2).

Having obtained and characterized these two allylpyrrolidines **11** and **12**, we attempted Sharpless asymmetric dihydroxylation to prepare all four stereoisomeric 2-(2,3-dihydroxypropyl)pyrrolidines **13**−**16**. We anticipated that this process, which had been used successfully by Takahata et al. for the enantioselective synthesis of 2-(2-hydroxypropyl)-pyrrolidine,[19] would occur in a highly selective manner, thus allowing the stereoselective introduction of the stereogenic centre at C-6 in **3**−**6**. However, as shown in Table 1, AD reactions carried out on **11** and **12** with AD-mixture α and AD-mixture β were poorly selective. Moreover, the process was slow (several days) and a large excess of the AD-mixtures was needed to complete the reaction. This puzzling result, in view of the reactivity of 2-allyl-*N*-(benzyloxycarbonyl)pyrrolidine,[19] can be explained by the presence of the basic nitrogen atom in the substrates used in this study.[20]

Table 1. Stereoselection of the dihydroxylation of **13** and **14** using OsO_4 or AD mixtures

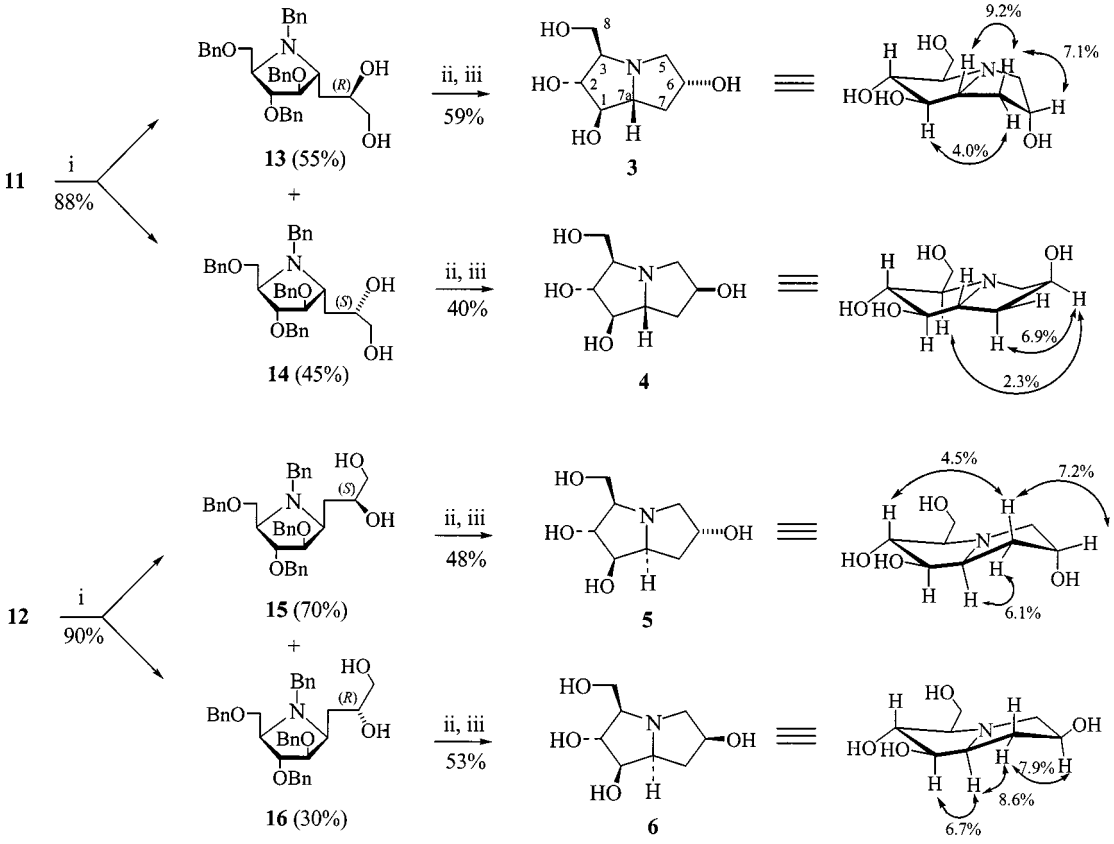
Substrate	OsO_4/NMO product ratio:[a] (2′*R*)/(2′*S*)	AD-mixture α product ratio:[a] (2′*R*)/(2′*S*)	AD-mixture β product ratio:[a] (2′*R*)/(2′*S*)
11	55:45	55:45	55:45
12	30:70	50:50	55:45

[a] As determined by ^{1}H NMR spectroscopy.

As an alternative strategy, we therefore adopted the use of osmium tetroxide/NMO as an oxidant (Scheme 3). This bis(hydroxylation) procedure, when conducted on **11** and **12**, in each case provided − in high yield (90%) − a mixture of the corresponding diols **13/14** and **15/16**, which could be separated by HPLC, in 55:45 and 30:70 ratios, respectively.

The configurations of the newly formed asymmetric carbon centres in diols **13**−**16** were more efficiently determined after annulation, on the final pyrrolizidines **3**−**6**. This annulation could be achieved in one step, as reported previously, by selective activation of the primary alcohol function with toluenesulfonyl chloride and spontaneous cyclization.[6b,7] The crystallised quaternary salts thus obtained were washed with ether before debenzylation. This deprotecting step was fairly difficult, and was best achieved by Pd^0-catalysed transfer hydrogenation, which afforded pyrrolizidines **3**−**6** after purification by ion exchange chromatography (Dowex 50 W-X8, H^+ form). The compounds thus obtained were analytically pure, as verified by LCMS analysis (electrospray detection).

The proton assignment in **3**−**6** was performed by successive proton decoupling, starting from the easily distinguishable signals of 7-H. Starting from the configurations of pyrrolidines **13**−**16**, firmly established previously (Scheme 2), the absolute configuration of the asymmetric centre formed



Scheme 3. Reagents and conditions: (i) cat. OsO_4, NMO, acetone/water; (ii) TsCl, Py; (iii) 10% Pd/C, HCO_2NH_4, MeOH, 60 °C

during the osmylation process, which is designated as C-6 in pyrrolizidines **3**−**6**, was deduced from NOE experiments on the fused five-membered ring systems, as depicted in Scheme 3.

In addition, analysis of the coupling constants for pyrrolizidines **3**−**6** also provided information about the favoured conformations of these molecules in solution. For instance, the observation of coupling constants of above 7.5 Hz between 7a-H/1-H, 1-H/2-H and 2-H/3-H in pyrrolizidines **3** and **4** indicated that all these protons were in a *trans*-diaxial arrangement.[21] Furthermore, the $^3J_{H,H}$ coupling constants between 1-H, 2-H and 3-H (above 7.5 Hz) in pyrrolidines **5** and **6** also indicated a *trans*-diaxial relationship between these atoms, and consequently determined the *cis*-diaxial proton arrangement between 7a-H and 1-H (7.2 Hz).

The pseudoaxial or pseudoequatorial orientation of 6-H can also be deduced from the $^3J_{H,H}$ coupling constants with its neighbouring atoms; all of them are below 7.5 Hz in **3**−**5**, indicating that 6-H is pseudoequatorial. A specific *trans*-diaxial coupling constant (7.8 Hz) appears only for compound **6**, revealing the pseudoaxial orientation of 6-H in this case. The different ring conformations deduced from these results are illustrated in Scheme 3.

Conclusion

In summary, we describe a straightforward method for the synthesis of a new series of polyhydroxylated pyrrolizidines, starting from L-xylose. The inhibition potency of these and other related structures against a variety of glycosidases, including amyloglucosidase, glycosidase I and II, β-glucosidase and α-mannosidase, will be reported in due course.

Experimental Section

General Remarks: All reactions were performed under a constant flow of dry argon. Merck F254 silica gel (0.2 mm) was used for TLC plates, with detection being carried out by spraying with an alcoholic solution of phosphomolybdic acid, followed by heating. Flash column chromatography (FC) was performed on Merck 9385 (40−63 μm) Kieselgel 60 silica gel. IR spectra were recorded with an IR plus MIDAC spectrophotometer and are expressed in cm^{-1}. NMR spectra were recorded with a Bruker AC 250 spectrometer (250 MHz for ^{1}H, 62.5 MHz for ^{13}C) or a Bruker AC 500 when indicated. Chemical shifts are expressed in ppm from TMS (^{1}H and ^{13}C) as internal standard. Coupling constants are in Hz and splitting pattern abbreviations are: b, broad; s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet. Optical rotations were determined with a Perkin−Elmer Model 241 polarimeter. Elemental analyses were performed with a Perkin−Elmer CHN 2400 apparatus. Mass spectra were recorded with a Jeol D 30 spectrometer, at 70 eV.

2,3,5-Tri-*O*-benzyl-L-xylose (7): L-Xylose (10.0 g, 0.067 mol) was stirred in 628 mL of a refluxing MeOH/HCl solution (3.29 mmol/L) for 4 h as described,[17a] to yield 10.9 g (0.067 mol, 100%) of the corresponding methylfuranosides as a colourless oil. Benzylation of the crude material with BnBr (72 mL, 0.61 mol) and $Ba(OH)_2$ (40.9 g, 0.24 mol) in DMF (140 mL) for 28 h at room temp. yielded the protected sugar (11.54 g, 40%) as a yellow oil after FC purification (eluent: EtOAc/petroleum ether, 2:8, v/v). Hydrolysis of this mixture of anomers with 0.5% HCl (18 mL) in refluxing dioxane (60 mL) for 24 h gave **7**[17b] (5.58 g, 50%; β/α, 60:40) as a colourless oil after FC purification (eluent: EtOAc/petroleum ether, 25:75, v/v). ^{1}H NMR (C_6D_6, 500 MHz): δ = 7.35−7.20 (m, 15 H, Ar-H), 5.48 (d, 0.4 H, *J* = 4.0 Hz, 1α-H), 5.25 (s, 0.6 H, 1β-H), 4.62−4.45 (6 H, C*H*$_2$Ph), 4.39 (m, 1 H, 4α,β-H), 4.10 (dd, 0.6 H, *J* = 3.1, 5.3 Hz, 3β-H), 4.05 (dd, 0.4 H, *J* = 2.1, 4.2 Hz, 3α-H), 4.00 (d, 0.6 H, *J* = 3.1 Hz, 2β-H), 3.93 (dd, 0.4 H, *J* = 2.1, 4.0 Hz, 2α-H), 3.75 (dd, 0.6 H, *J* = 5.0, 9.9 Hz, 5aβ-H), 3.71 (dd, 0.6 H, *J* = 4.3, 9.9 Hz, 5bβ-H), 3.69 (m, 0.8 H, 5α-H). These ^{1}H NMR spectroscopic data were identical to those reported for the enantiomer of **7**. ^{13}C NMR (C_6D_6, 125 MHz): δ = 138.6−138.2 (Ar-C), 128.2−127.4 (Ar-C), 101.7 (C-1β), 96.2 (C-1α), 86.5 (C-2β), 81.2 (C-3β), 81.1 (C-2α), 81.0 (C-3α), 79.8 (C-4β), 77.4 (C-4α), 73.7, 73.4, 73.0, 72.6, 72.3, 71.8 (6 × *C*H$_2$Ph), 68.6 (C-5β), 68.2 (C-5α). IR (film): $\tilde{\nu}$ = 3431, 3067, 3030, 2916, 2854, 1498, 1446, 1059. MS (EI): *m*/*z* (%) = 420 (100) [M$^+$]. $C_{26}H_{28}O_5$ (420.51): calcd. C 74.26, H 6.71; found C 74.15, H 6.47.

***N*-Benzyl-2,3,5-tri-*O*-benzyl-L-xylofuranosylamine (8):** A solution of **7** (7.53 g, 17.9 mmol) and benzylamine (8.00 mL, 73.0 mmol) in CH_2Cl_2 (20.0 mL) was stirred for 48 h at room temperature in the presence of molecular sieves (4 Å; 7.0 g). Filtration and evaporation of the volatiles gave an anomeric mixture (β/α, 60:40) of **8** as a yellow oil (9.00 g, 98%), which was not purified further. ^{1}H NMR (C_6D_6, 250 MHz): δ = 7.40−7.07 (m, 20 H, Ar-H), 5.12 (d, 0.4 H, *J* = 3.8 Hz, 1α-H), 4.90 (d, 0.6 H, *J* = 2.5 Hz, 1β-H), 4.63 (m, 0.4 H, 4-Hα), 4.40 (m, 0.6 H, 4β-H), 4.45−4.20 (m, 6 H, OC*H*$_2$Ph), 4.12 (d, 0.4 H, J_{AB} = 13.0 Hz, NC*H*$_2$Ph), 4.09 (d, 0.6 H, J_{AB} = 13.0, NC*H*$_2$Ph), 4.02−3.92 (m, 1.6 H, 3α-H, 3β-H, 2β-H), 3.90 (d, 0.6 H, J_{AB} = 13.0, NC*H*$_2$Ph), 3.87−3.70 (m, 2.8 H, NC*H*$_2$Ph, 2α-H, 5α-H, 5β-H). ^{13}C NMR (C_6D_6, 62.5 MHz): δ = 141.2−138.6 (Ar-C), 128.6−126.9 (Ar-C), 94.7 (C-1β), 90.4 (C-1α), 86.8 (C-2β), 82.3 (C-3β), 82.1 (C-3α), 81.9 (C-2α), 79.0 (C-4β), 77.7 (C-4α), 73.6, 73.6, 72.9, 72.3, 72.3, 71.7 (6 × OC*H*$_2$Ph), 69.5 (C-5β), 69.4 (C-5α), 50.4 (α-NC*H*$_2$Ph), 50.2 (β-NC*H*$_2$Ph). MS (EI): *m*/*z* (%) = 509 (100) [M$^+$]. IR (film): $\tilde{\nu}$ = 3090, 3030, 2924, 2864, 1500, 1358.

(4*R*,5*R*,6*S*,7*S*)-4-Benzylamino-5,6,8-tris(benzyloxy)-7-hydroxyoct-1-ene (**9**) and (4*S*,5*R*,6*S*,7*S*)-4-Benzylamino-5,6,8-tris(benzyloxy)-7-hydroxyoct-1-ene (**10**): Allylmagnesium chloride (7.3 mL of a 2 M solution in THF, 14.6 mmol) was added dropwise at 0 °C to a solution of **8** (1.492 g, 2.93 mmol) in THF (9 mL). After 4 h at 0 °C, the reaction was quenched with saturated NH_4Cl (10 mL), and Et_2O (30 mL) was added. After extraction, the organic layer was dried ($MgSO_4$) and the solvents were evaporated to give the crude mixture of diastereomers, which were separated and purified by careful FC (eluent: Et_2O/petroleum ether, 7:3, v/v). Compounds **9** (0.59 g, 36%) and **10** (0.88 g, 55%) were isolated as colourless oils.

Compound 9: $[\alpha]_D^{20}$ = 9.9 (*c* = 1.56, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.30−7.10 (m, 20 H, Ar-H), 5.68 (ddd, 1 H, *J* = 10.0, 17.0 Hz, 6.3 Hz, 2-H), 5.04−4.90 (m, 2 H, 1a,b-H), 4.60−4.32 (m, 6 H, OC*H*$_2$Ph), 4.10 (dd, *J* = 8.0, 6.0 Hz, 1 H, 7-H), 3.88−3.60 (m, 6 H, NC*H*$_2$Ph, 6-H, 5-H, 8a,b-H), 3.12 (dd, *J* = 9.0, 3.5 Hz, 1 H, 4-H), 2.56 (m, 1 H, 3a-H), 2.19 (m, 1 H, 3b-H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 139.0−138.0 (Ar-C), 135.4 (C-2), 128.6−127.3 (Ar-C), 117.6 (C-1), 77.3 (C-5), 74.6 (C-6), 75.5, 73.0, 72.6 (3 × OC*H*$_2$Ph), 70.3 (C-8), 66.2 (C-7), 53.9 (C-4), 50.3 (NC*H*$_2$Ph), 34.6 (C-3). IR (film): $\tilde{\nu}$ = 2921, 2863, 1496, 1454, 1070, 1028. MS (CI/NH_3): *m*/*z* (%) = 552 (100) [MH$^+$]. HRMS (CI/NH_3): calcd. for $C_{36}H_{42}NO_4$ [MH$^+$] 552.3114, found 552.3148.

Compound 10: $[\alpha]_D^{20} = -3.7$ ($c = 0.86$, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.37−7.17 (m, 20 H, Ar-H), 5.68 (m, 1 H, 2-H), 5.11−5.06 (m, 2 H, 1a,b-H), 4.63−4.39 (m, 6 H, OCH_2Ph), 4.05 (d, J = 13.0 Hz, 1 H, 7-H), 3.85 (d, 1 H, J_{AB} = 12.5, NCH_2Ph), 3.81 (d, J = 5.0 Hz, 1 H, 6-H), 3.73 (d, 1 H, NCH_2Ph), 3.70 (dd, J = 5.0, 5.0 Hz, 1 H, 5-H), 3.58 (dd, J = 9.0, 5.5 Hz, 1 H, 8a-H), 3.51 (m, 1 H, 8b-H), 3.00 (dd, J = 11.0, 5.5 Hz, 1 H, 4-H), 2.53 (m, 1 H, 3a-H), 2.44 (m, 1 H, 3b-H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 139.2−138.6 (Ar-C), 135.3 (C-2), 128.5−127.2 (Ar-C), 118.0 (C-1), 79.1 (C-5), 78.5 (C-6), 73.9, 73.1, 72.9 (3 × OCH_2Ph), 70.9 (C-8), 67.5 (C-7), 57.7 (C-4), 50.9 (NCH_2Ph), 33.7 (C-3). IR (film): ṽ = 2863, 1496, 1454, 1071. MS (CI/NH_3): m/z (%) = 552 (100) [MH^+]. HRMS (CI/NH_3): calcd. for $C_{36}H_{42}NO_4$ [MH^+] 552.3114, found 552.3102.

(2*R*,3*R*,4*R*,5*R*)-2-Allyl-*N*-benzyl-3,4-bis(benzyloxy)-5-[(benzyloxy)methyl]pyrrolidine (11): Cyclisation of **9** (0.251 g, 0.456 mmol) was performed in pyridine (0.5 mL) by stirring overnight in the presence of methanesulfonyl chloride (0.066 mL, 0.91 mmol). Pyridine was evaporated under reduced pressure, and the residue was diluted in Et_2O, washed with water and dried ($MgSO_4$). Evaporation of the solvent and purification of the crude material by FC (Et_2O/petroleum ether, 7:3, v/v) gave **11** (207 mg, 85%) as a yellow oil. $[\alpha]_D^{20} = -198.8$ ($c = 0.86$, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.30−7.10 (m, 20 H, Ar-H), 5.78 (m, 1 H, $CH_2-CH=CH_2$), 5.01−4.96 (m, 2 H, $CH_2-CH=CH_2$), 4.53 (d, 1 H, J_{AB} = 12.0, OCH_2Ph), 4.49 (d, 1 H, J_{AB} = 12.0, OCH_2Ph), 4.47 (d, 1 H, J_{AB} = 12.0, OCH_2Ph), 4.45 (d, 1 H, J_{AB} = 12.0, OCH_2Ph), 4.48 (s, 2 H, OCH_2Ph), 4.04 (d, 1 H, J_{AB} = 13.8, NCH_2Ph), 3.95 (dd, J = 2.1, 3.1 Hz, 1 H, 4-H), 3.85 (dd, J = 2.1, 3.9 Hz, 1 H, 3-H), 3.69 (d, 1 H, J_{AB} = 13.8, NCH_2Ph), 3.60 (dd, J = 5.0, 9.2 Hz, 1 H, 6a-H), 3.55 (dd, J = 6.1 9.2 Hz, 1 H, 6b-H), 3.23 (ddd, 1 H, J = 3.1, 5.0 Hz, 6.1 Hz, 5-H), 3.14 (dt, 1 H, J = 2 × 3.9, 8.2 Hz, 2-H), 2.46 (m, 1 H, $CH_2-CH=CH_2$), 2.30 (m, 1 H, $CH_2-CH=CH_2$). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 139.3−138.2 (Ar-C), 135.2 ($CH_2-CH=CH_2$), 128.2−126.6 (Ar-C), 116.9 ($CH_2-CH=CH_2$), 85.8 (C-3), 85.7 (C-4), 73.1, 71.3 and 71.2 (3 × OCH_2Ph), 69.4 (C-6), 64.4 (C-5), 64.2 (C-2), 50.9 (NCH_2Ph), 32.4 ($CH_2-CH=CH_2$). IR (film): ṽ = 2860, 1495, 1454, 1098. MS (CI/NH_3): m/z (%) = 534 (55) [MH^+], 492 (68). HRMS (CI/NH_3): calcd. for $C_{36}H_{40}NO_3$ [MH^+] 534.3008, found 534.2987.

(2*S*,3*R*,4*R*,5*R*)-2-Allyl-*N*-benzyl-3,4-bis(benzyloxy)-5-[(benzyloxy)methyl]pyrrolidine (12): Cyclisation of **10** (0.578 g, 1.05 mmol) was performed in pyridine (1.0 mL), by stirring overnight with methanesulfonyl chloride (0.16 mL, 2.1 mmol). Pyridine was evaporated under reduced pressure, and the residue was diluted in Et_2O, washed with water and dried ($MgSO_4$). Evaporation of the solvent and purification of the crude material by FC (Et_2O/petroleum ether, 7:3, v/v) gave **14** (365 mg, 65%) as a yellow oil. $[\alpha]_D^{20} = 26.5$ ($c = 1.32$, $CHCl_3$). ^1H NMR (C_6D_6, 250 MHz): δ = 7.40−7.10 (m, 20 H, Ar-H), 5.80 (m, 1 H, $CH_2-CH=CH_2$), 5.11−5.00 (m, 2 H, $CH_2-CH=CH_2$), 4.58, 4.49, 4.38, 4.21, 4.18 and 4.11 (6d, 6 H, J_{AB} = 12.0, 6 × OCH_2Ph), 4.13 (t, J = 1.3 Hz, 1 H, 4-H), 3.91 (d, 1 H, J_{AB} = 13.0, NCH_2Ph), 3.89 (ddd, 1 H, J = 0.8, 1.3 Hz , 4.6 Hz, 3-H), 3.63 (d, 1 H, J_{AB} = 13.0, NCH_2Ph), 3.51 (t, J = 9.2 Hz, 1 H, 6a-H), 3.33 (dddd, 1 H, J = 0.8, 1.3, 4.7 Hz, 9.2 Hz, 5-H), 3.25 (dt, 1 H, J = 2 × 4.6, 9.2 Hz, 2-H), 3.20 (dd, J = 4.7, 9.2 Hz, 1 H , 6b-H), 2.70 (m, 1 H, $CH_2-CH=CH_2$), 2.35 (m, 1 H, $CH_2-CH=CH_2$). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 139.3−138.2 (Ar-C), 136.1 ($CH_2-CH=CH_2$), 129.3−126.9 (Ar-C), 116.3 ($CH_2-CH=CH_2$), 82.5 (C-3), 82.3 (C-4), 72.9, 72.0 and 71.7 (3 × OCH_2Ph), 70.6 (C-6), 69.1 (C-5), 66.6 (C-2), 58.4 (NCH_2Ph), 33.0 ($CH_2-CH=CH_2$). IR (film): ṽ = 2861, 1496, 1454, 1101. MS (CI/NH_3): m/z (%) = 534 (100) [MH^+]. HRMS (CI/NH_3): calcd. for $C_{36}H_{40}NO_3$ [MH^+] 534.3008, found 534.2925.

Synthesis of Diols 13−16

General Procedure: A solution of OsO_4 (250 mg OsO_4 in 50 mL of *t*BuOH and 0.25 mL of *t*BuOOH, 2.0 mL) was added drop by drop to a solution of alkene **11** (1.151 g, 2.16 mmol) and NMO (0.581 g, 4.30 mmol) in acetone/water (3.5 mL/1.0 mL), and the mixture was stirred for 24 h at room temp. Saturated Na_2SO_3 (20 mL) was then added, and the solution was extracted twice with EtOAc (2 × 30 mL). The organic layer was washed with water and brine and dried ($MgSO_4$). Evaporation of the volatiles gave a crude mixture of the diols, which were separated by FC ($CHCl_3/Et_2O$, 5:2, v/v) to yield 0.584 g (48%) of **13** and 0.487 g (40%) of **14** as yellow oils. The same procedure was applied to **12** and yielded, after purification by FC (Et_2O), 0.376 g (25%) of **15** and 0.979 g (65%) of **16** as yellow oils. Compounds **13−16** were also obtained by the described procedure,[19] using the AD-mixtures.

Compound 13: $[\alpha]_D^{20} = -17.7$ ($c = 2.06$, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.40−7.20 (m, 20 H, Ar-H), 4.58 (d, 1 H, J_{AB} = 12.0, OCH_2Ph), 4.57 (d, 1 H, J_{AB} = 12.0, OCH_2Ph), 4.45−4.38 (m, 4 H, OCH_2Ph), 4.10 (m, 3 H, 4-H, 3-H, NCH_2Ph), 3.80 (m, 1 H, 2′-H), 3.60−3.50 (m, 4 H, 6a-H, 2-H, 3′a-H, NCH_2Ph), 3.35−3.25 (m, 3 H, 3′b-H, 6b-H, 5-H), 1.92 (ddd, 1 H, J = 4.9, 10.3 Hz, 14.3 Hz, 1′a-H), 1.68 (d, J = 14.3 Hz, 1 H, 1′b-H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.0−137.7 (Ar-C), 128.5−127.1 (Ar-C), 86.4 (C-3), 83.3 (C-4), 73.2, 71.7 and 71.3 (3 × OCH_2Ph), 69.9 (C-5), 66.7 (C-6), 66.2 (C-3′), 66.1 (C-2), 62.8 (C-2′), 51.5 (NCH_2Ph), 30.2 (C-1′). IR (film): ṽ = 3405, 3029, 2863, 1496, 1454, 1097, 1028. MS (CI/NH_3): m/z (%) = 568 (100) [MH^+]. HRMS (CI/NH_3): calcd. for $C_{36}H_{42}NO_5$ [MH^+] 568.3063, found 568.3045.

Compound 14: $[\alpha]_D^{20} = -21.5$ ($c = 3.12$, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.40−7.15 (m, 20 H, Ar-H), 4.70−4.40 (m, 6 H, OCH_2Ph), 4.12 (t, J = 2.2 Hz, 1 H, 3-H), 4.01 (dd, J = 2.2, 5.0 Hz, 1 H, 4-H), 3.85 (m, 2 H, 2′-H, NCH_2Ph), 3.70 (m, 3 H, 6a-H, 2-H, 3′a-H), 3.55 (m, 2 H, NCH_2Ph, 3′b-H), 3.40 (m, 2 H, 6b-H, 5-H), 1.92 (m, 1 H, 1′a-H), 1.53 (m, 1 H, 1′b-H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.6−137.6 (Ar-C), 128.5−127.0 (Ar-C), 88.8 (C-3), 84.6 (C-4), 73.0, 71.5 and 71.4 (3 × OCH_2Ph), 69.6 (C-5), 66.9 (C-6), 66.6 (C-3′), 63.4 (C-2), 63.3 (C-2′), 51.7 (NCH_2Ph), 33.1 (C-1′). IR (film): ṽ = 3384, 3030, 2926, 1496, 1454, 1098, 1028. MS (CI/NH_3): m/z (%) = 568 (100) [MH^+]. HRMS (CI/NH_3): calcd. for $C_{36}H_{42}NO_5$ [MH^+] 568.3063, found 568.2988.

Compound 15: $[\alpha]_D^{20} = 11.7$ ($c = 0.36$, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.40−7.15 (m, 20 H, Ar-H), 4.65, 4.62, 4.51, 4.40, 4.32 and 4.28 (6d, 6 H, J_{AB} = 12.0, OCH_2Ph), 4.11 (dd, 1 H, J = 2 × 4.7, 4-H), 4.02 (dd, J = 4.7, 5.0 Hz, 1 H, 3-H), 4.00 (d, 1 H, J_{AB} = 13.0, NCH_2Ph), 3.70 (d, 1 H, J_{AB} = 13.0, NCH_2Ph), 3.63 (m, 1 H, 2′-H), 3.50 (dd, J = 3.7, 10.1 Hz, 1 H, 3′a-H), 3.40 (m, 1 H, 2-H), 3.35 (dd, J = 6.0, 10.1 Hz, 1 H, 3′b-H), 3.18 (m, 2 H, 6a,b-H), 3.07 (m, 1 H, 5-H), 1.70 (t, J = 6.8 Hz, 2 H, 1′a,b-H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.1−137.5 (Ar-C), 128.5−127.5 (Ar-C), 82.8 (C-3), 82.7 (C-4), 73.0, 72.0 and 71.9 (3 × OCH_2Ph), 70.4 (C-5), 67.2 (C-6), 66.7 (C-2), 65.8 (C-3′), 63.5 (C-2′), 61.1 (NCH_2Ph), 31.2 (C-1′). IR (film): ṽ = 3045, 3029, 2863, 1454, 1072, 1028. MS (CI/NH_3): m/z (%) = 568 (100) [MH^+]. HRMS (CI/NH_3): calcd. for $C_{36}H_{42}NO_5$ [MH^+] 568.3063, found 568.3045.

Compound 16: $[\alpha]_D^{20} = 11.6$ ($c = 0.50$, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.38−7.20 (m, 20 H, Ar-H), 4.60, 4.58, 4.50, 4.41,

4.38 and 4.31 (6 d, 6 H, J_{AB} =12.0, OCH_2Ph), 4.20 (m, 1 H, 2′-H), 4.05 (m, 3 H, 3-H, 4-H, NCH_2Ph), 3.70 (d, 1 H, J_{AB} =13.0, NCH_2Ph), 3.56 (dd, J = 3.7, 10.1 Hz, 1 H, 3′a-H), 3.32 (m, 3 H, 3′b-H, 2-H, 6a-H), 3.15 (m, 1 H, 6b-H), 3.08 (m, 1 H, 5-H), 1.85 (m, 1 H, 1′a-H), 1.60 (m, 1 H, 1′b-H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.1−137.5 (Ar-C), 128.5−127.5 (Ar-C), 84.8 (C-3), 82.7 (C-4), 73.0, 72.9 and 72.6 (3 × OCH_2Ph), 71.8 (C-5), 67.9 (C-6), 67.3 (C-2), 66.7 (C-3′), 63.5 (C-2′), 59.8 (NCH_2Ph), 30.7 (C-1′). IR (film): $\tilde{\nu}$ = 3405, 3029, 2921, 2863, 1496, 1454, 1072, 1028. MS (CI/NH_3): *m*/*z* (%) = 568 (100) [MH^+]. HRMS (CI/NH_3): calcd. for $C_{36}H_{42}NO_5$ [MH^+] 568.3063, found 568.3053.

Synthesis of Pyrrolizidines 3−6

General Procedure: TsCl (107 mg, 0.56 mmol) was added to a solution of diol **16** (288 mg, 0.51 mmol) in pyridine (0.8 mL) and CH_2Cl_2 (2 mL) which was stirred at room temperature for 16 h. Evaporation of the solvent gave a yellow oil, which crystallised in ether. The protected pyrrolizidinesulfonate salt thus obtained after filtration (230 mg) was directly debenzylated in refluxing MeOH (4.5 mL) over 2 h in the presence of 10% Pd/C (438 mg) and ammonium formate (0.421 g). After evaporation of the volatiles, water (2 mL) was added to the resulting oil and the solution was lyophilised. This procedure was repeated twice to eliminate the excess of ammonium formate. Finally, the water solution was passed through Dowex 50WX-8 (H^+ form), which was first eluted with water (to eliminate TsOH), and then with 0.6 M NH_4OH. Fractions containing **6** were lyophilised to give 46 mg (53% from **16**) of **6** as a yellow oil. The same procedure gave pyrrolizidines **3**, **4** and **5** from the corresponding diols (yields are given in Scheme 3).

Compound 3: $[\alpha]_D^{20}$ = 10.9 (*c* = 0.11, H_2O). ^{1}H NMR (D_2O, 250 MHz): δ = 4.40 (ddd, *J* = 3.0, 4.0, 4.7 Hz, 1 H, 6-H), 4.05 (t, 1 H, *J* = 8.0, 1-H), 3.72 (dd, *J* = 3.7, 11.7 Hz, 1 H, 8-H), 3.70 (t, 1 H, *J* = 8.0, 2-H), 3.53 (dd, *J* = 6.7, 11.7 Hz, 1 H, 8′-H), 3.18 (ddd, *J* = 4.2, 8.0, 8.0 Hz, 1 H, 7a-H), 3.03 (ddd, *J* = 3.7, 6.7, 8.0 Hz, 1 H, 3-H), 3.00 (dd, *J* = 4.0, 11.7 Hz, 1 H, 5-H), 2.80 (dd, *J* = 3.0, 11.7 Hz, 1 H, 5′-H), 2.10 (ddd, 1 H, *J* = 4.7, 8.0, 13.2 Hz, 7β-H), 1.85 (ddd, 1 H, *J* = 4.0, 8.0, 13.2 Hz, 7α-H). ^{13}C NMR (D_2O, 62.5 MHz): δ = 82.6 (C-1), 78.6 (C-2), 75.3 (C-6), 72.9 (C-7a), 68.7 (C-3), 63.8 (C-8), 63.5 (C-5), 39.4 (C-7). MS (CI/NH_3): *m*/*z* (%) = 190 (65) [MH^+], 158 (100) [M − CH_2OH]. HRMS (CI/NH_3): calcd. for $C_8H_{16}NO_4$ [MH^+] 190.1079, found 190.1039. LCMS (ES^+): only one peak (retention time: 0.39 min). MS: *m*/*z* = 190.46.

Compound 4: $[\alpha]_D^{20}$ = 16.0 (*c* = 0.21, H_2O). ^{1}H NMR (D_2O, 250 MHz): δ = 4.52 (ddd, *J* = 4.1, 4.6, 5.0 Hz, 1 H, 6-H), 3.80 (m, 2 H, 1-H, 2-H), 3.78 (dd, *J* = 3.4, 12.0 Hz, 1 H, 8-H), 3.60 (dd, *J* = 6.8, 12.0 Hz, 1 H, 8′-H), 3.48 (ddd, *J* = 7.5, 7.5, 8.4 Hz, 1 H, 7a-H), 3.07 (dd, *J* = 2.7, 12.0 Hz, 1 H, 5-H), 2.95 (dd, *J* = 4.6, 12.0 Hz, 1 H, 5′-H), 2.82 (ddd, *J* = 3.4, 6.8, 9.5 Hz, 1 H, 3-H), 2.10 (ddd, 1 H, *J* = 4.1, 7.5, 13.4 Hz, 7β-H), 1.95 (ddd, 1 H, *J* = 5.0, 8.4, 13.4 Hz, 7α-H). ^{13}C NMR (D_2O, 62.5 MHz): δ = 82.6 (C-1), 80.0 (C-2), 74.7 (C-6), 72.9 (C-7a), 68.5 (C-3), 64.3 (C-5), 63.4 (C-8), 40.2 (C-7). MS (CI/NH_3): *m*/*z* (%) = 190 (35) [MH^+], 158 (100) [M − CH_2OH]. HRMS (CI/NH_3): calcd. for $C_8H_{16}NO_4$ [MH^+] 190.1079, found 190.1089. LCMS (ES^+): only one peak (retention time: 0.39 min). MS: *m*/*z* = 190.44.

Compound 5: $[\alpha]_D^{20}$ = 15.8 (*c* = 0.92, H_2O). ^{1}H NMR (D_2O, 250 MHz): δ = 4.63 (bd, 1 H, *J* = 3.8, 6-H), 4.23 (ddd, *J* = 7.2, 8.1, 9.0 Hz, 1 H, 7a-H), 4.20 (dd, *J* = 7.2, 7.7 Hz, 1 H, 1-H), 3.98 (dd, *J* = 7.7, 8.6 Hz, 1 H, 2-H), 3.90 (dd, *J* = 4.1, 12.7 Hz, 1 H, 8-H), 3.80 (dd, *J* = 8.6, 12.7 Hz, 1 H, 8′-H), 3.45 (ddd, *J* = 4.1, 8.6, 8.6 Hz, 1 H, 3-H), 3.26 (d, 1 H, J_{AB} = 12.0, 5-H), 3.24 (d, 1 H, J_{AB} == 12.0, 5′-H), 2.22 (ddd, 1 H, *J* = 3.8, 9.0, 13.8 Hz, 7β-H), 1.95 (ddd, 1 H, *J* = 1.0, 8.1, 13.8 Hz, 7α-H). ^{13}C NMR (D_2O, 62.5 MHz): δ = 76.3 (C-1), 75.5 (C-2), 73.1 (C-6), 68.2 (C-7a), 67.5 (C-3), 59.5 (C-8), 58.5 (C-5), 34.5 (C-7). MS (CI/NH_3): *m*/*z* (%) = 190 (35) [MH^+], 158 (100) [M − CH_2OH]. HRMS (CI/NH_3): calcd. for $C_8H_{16}NO_4$ [MH^+] 190.1079, found 190.1065. LCMS (ES^+): only one peak (retention time: 0.39 min). MS: *m*/*z* = 190.47.

Compound 6: $[\alpha]_D^{20}$ = 6.2 (*c* = 0.58, H_2O). ^{1}H NMR (D_2O, 250 MHz): δ = 4.29 (dq, 1 H, *J* = 3 × 7.8, 5.7 Hz, 6-H), 4.01 (dd, *J* = 6.0, 7.2 Hz, 1 H, 1-H), 3.90 (dd, *J* = 6.0, 8.3 Hz, 1 H, 2-H), 3.78 (d, 2 H, *J* = 6.1, 8-H), 3.53 (td, 1 H, *J* = 7.2, 2 × 7.8, 7a-H), 3.02 (dd, *J* = 9.2, 7.8 Hz, 1 H, 5-H), 2.90 (td, 1 H, *J* = 2 × 6.1, 8.3 Hz, 3-H), 2.65 (dd, *J* = 5.7, 9.2 Hz, 1 H, 5′-H), 2.05 (ddd, 1 H, *J* = 7.8, 7.8, 13.3 Hz, 7α-H), 1.75 (ddd, 1 H, *J* = 7.8, 7.8, 13.3 Hz, 7β-H). ^{13}C NMR (D_2O, 62.5 MHz): δ = 79.5 (C-1), 79.1 (C-2), 73.5 (C-6), 67.2 (C-7a), 65.3 (C-3), 62.0 (C-8), 55.9 (C-5), 34.6 (C-7). MS (CI/NH_3): *m*/*z* (%) = 190 (60) [MH^+], 158 (100) [M − CH_2OH]. HRMS (CI/NH_3): calcd. for $C_8H_{16}NO_4$ [MH^+] 190.1079, found 190.1055. LCMS (ES^+): only one peak (retention time: 0.39 min). MS: *m*/*z* = 190.44.

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