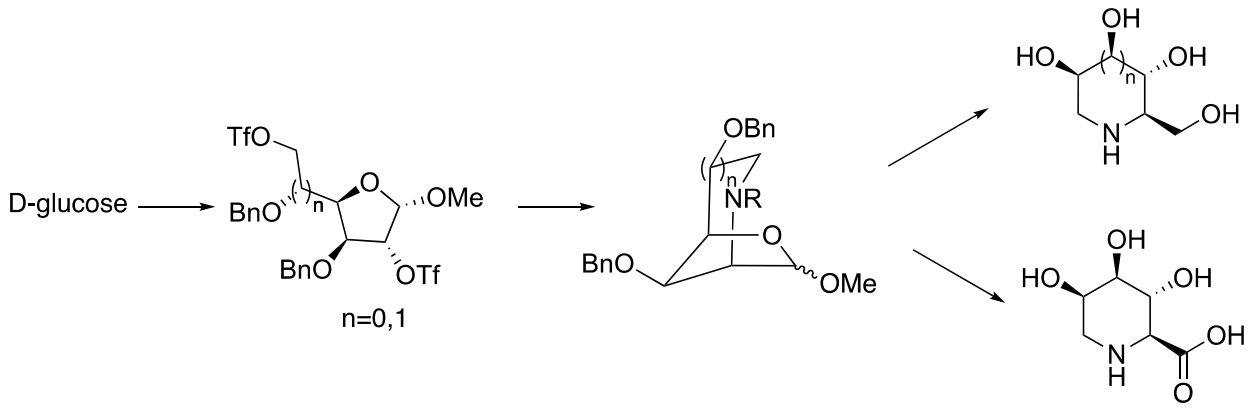
[1]Stable ditriflates of D-glucose in the synthesis of iminosugars and polyhydroxyolated pipecolic acids

Rosalino Balo,[a] Andrés Fernández,[a] David Reza,[a] Pablo López,[a]
George W. J. Fleet[b], Ramón J. Estévez[a, b] and Juan C. Estévez [a,*]

a) Departamento de Química Orgánica and Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares, Campus Vida, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, SPAIN.

b) Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Oxford, OX1 3TA, United Kingdom.

juancarlos.estevez@usc.es



A synthesis of the five membered iminosugar DAB and a divergent synthesis of the six membered iminosugar 1-dehydromannojirimycin (DMJ) and the corresponding sugar iminoacid are reported. They involve double nucleophilic displacements of a D-xylose ditriflate by benzyl carbazate and a D-glucose ditriflate by allyl amine, respectively. They are followed by a similar protocol consisting of hydrolysis and oxidation or reduction of the resulting bicyclic glycosides. This allowed DMJ to be obtained from the cheap sugar D-glucose.

Introduction

Iminosugars are natural and synthetic polyhydroxylated monocyclic (pyrrolidine, piperidine, azepane) and bicyclic (pyrrolizidine, indolizidine, nortropane) nitrogenated compounds that can be considered as sugar mimetics resulting from the replacement of the oxygen ring by nitrogen.[1,2] Past and current interest on these compounds lie on their capacity to act as strong inhibitors of both glycosidases and glycoxyltransferases,[3] and the consequent potential for the treatment of diverse diseases,[4-6] including diabetes, viral infections, tumor metastasis and lysosomal storage disorders.[7] This is the reason why from the isolation of D-nojirimicin (**1**) in 1996, iminosugars have received considerable attention, both from the chemical and biological point of view. In fact, its *N*-alkylated derivatives Miglustat[8] (**2**) and Miglitol[9] (**3**), are clinically approved drugs used for the treatment of Gaucher's disease and of type II

diabetes, respectively. D-deoxymannojirimycin (DMJ, **4**, Figure 1) exhibits promising mammalian α-fucosidase activity.[10] And a representative polyhydroxylated pyrrolidine is iminocyclopentitol l,4-dideoxy-l,4-imino-D-arabinitol (DAB, **5**, Figure 1), a natural product that has shown to be an efficient inhibitor of α-glucosidases.[11]

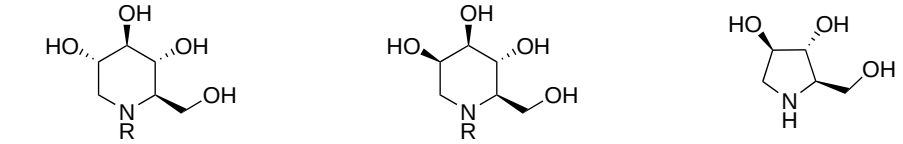
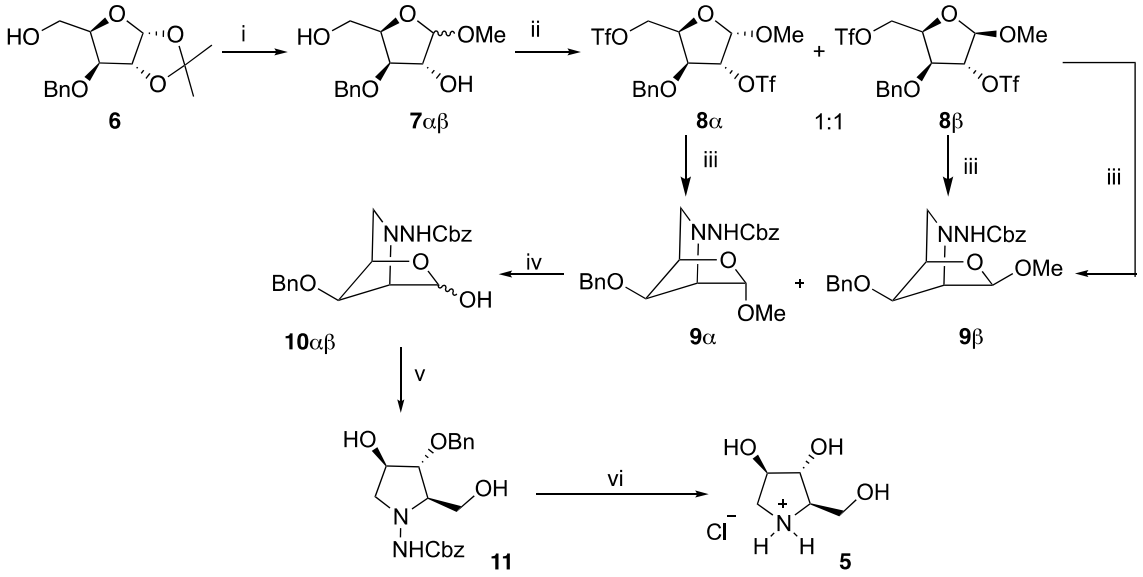


Figure 1. *Structures of a selection of iminosugars*

Carbohydrates diols are a suitable source for the synthesis of iminosugars. Sequential approaches require multistep procedures, involving the reduction of nitro or azido sugars to amino sugars, from which the second C-N bond if generated by intramolecular displacement of a OMs, OTs or OTf leaving group.[12] An alternative to this approach to this targets involved the simultaneous generation of the two C-N bonds by a double displacement of open chain sugar dimesylates, ditosylates or dihalides by amines.[13,14] Recently it was described the more attractive preparation of iminosugars from stable sugar ditrifates, a variant that takes advantage of allowing to use weak nitrogen nucleophiles. The first reported example consisted of an efficient synthesis of azetidines.[15-20] More recently this approach has been applied to a divergent the synthesis of iminocyclopentitols and 3,4-dihydroxyprolines.[21] This paper reports the application of this methodology to a new synthesis of DAB (**5**) from a D-xylose ditriflates **8α** and **8β** (Scheme 1), together a divergent synthesis of 1-deoxymannojirimycin (DMJ, **4**) and the corresponding polyhydroxylated pipecolic acid **26** from D-glucose ditriflates **18αβ** (Scheme 2 and Scheme 3).



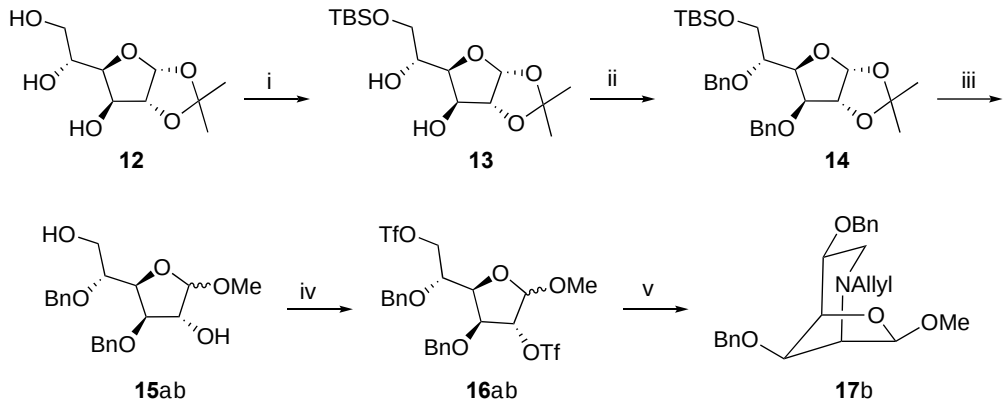
Scheme 1. Synthesis of the iminosugar DAB (**5**). *Conditions*: i) AcCl, MeOH/H_2O, rt, 2 h. ii) Tf_2O, DIEA, CH_2Cl_2, -30 .C, 2 h (85%). iii) $CbzNHNH_2$, DIEA, MeCN, 50 ºC, 19 h (83% for **9α**, 32% for

9β). iv) TFA/H_2O (1:1), rt, 2 h. v) $NaBH_4$, EtOH/H_2O (3:1), rt, 2 h (41%, two steps). vi) a. H_2, 10% Pd/C, MeOH, rt, 4 h. b. 1 M HCl, Et_2O (99%, 2 steps)

Ditriflates **8α** and **8β** were obtained as previously,[21] as a 1:1 anomeric separable mixture, by treatment of D-xylose derivative mixture **7αβ** with Tf_2O and DIEA, and this mixture and its components were separately transformed into DAB (**5**), as shown in Scheme 1. Thus, reaction of ditriflate **8α** with benzyl carbazate provided the azabicycle glycoside **9α** in 83% yield, as established from the presence in its ^{1}H NMR of a broad singlet at 6.84 ppm and a singlet at 5.11 ppm, dues to the NH and the CH_2 groups of the carbazate substituent. In addition, the α configuration of its anomeric center was deduced from a singlet at 4.79 ppm, corresponding to its anomeric proton. When the reaction was carried out with the anomer **8β**, the bicyclic compound **9β** was obtained in 32% yield. The configuration of its anomeric center was established from the presence in its ^{1}H NMR of a doublet at 5.01 ppm (J=1.9 Hz), due to the anomeric proton. The low yield achieved for anomer **8β** was attributed to steric reasons. The orientation of its methoxy substituent could interfere with the approaching of the carbazate nucleophile to the carbon at C-2, bearing the OTf leaving group. On the other hand, when the anomeric mixture **8αβ** was subjected to the conditions for the transformation of **8α** into **9α**, a mixture of **9αβ** resulted.

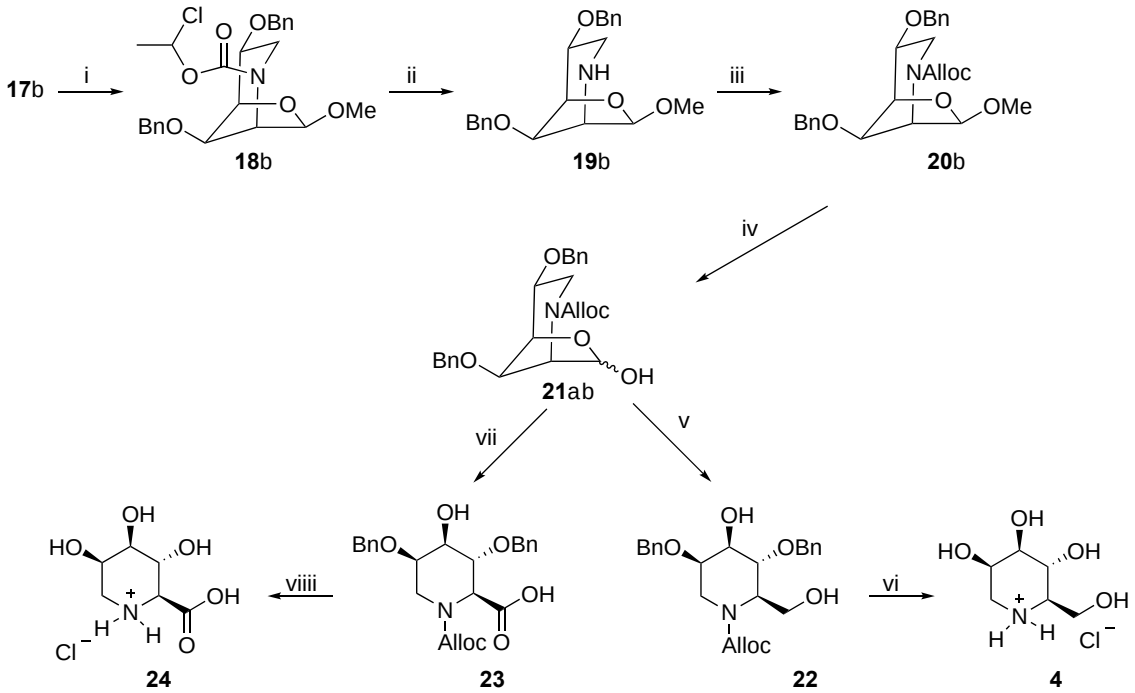
According to our plan, the acidic hydrolysis of the glycoside subunit of the mixture **9αβ** with TFA provided the anomeric mixture **10αβ**, which was directly reacted with $NaBH_4$, to provide prolinol **11** in 41% yield, as established from its spectroscopic and analytical data, mainly from the presence in its ^{1}H NMR of a doublet at 3.58 ppm (J=12.4 Hz) and a doublet of doublets at 3.72 ppm (J=12.4 Hz and J'=2.7 Hz), both corresponding to the CH_2 groups. Finally, catalytic hydrogenation of this 1-aminoprolinol **11** provided the expected iminosugar DAB (**5**) quantitatively, as a result of the hydrogenolysis of the N-N bond and the removal of the Bn groups. This compound was identical to a sample of this compound, previously obtained.[21]

On the other hand, this strategy for the synthesis of iminocyclitols from sugar ditriflates was next extended to the hexose D-glucose. This required the preparation of sugar 2,6-ditriflates **16αβ**. They were obtained as an inseparable mixture from of the known trihydroxy D-glucose derivative **14** (Scheme 2),[22] which was prepared by the new approach stated in Scheme 2. It involved treatment of **12** with TBSCl, for selective protection of the OH group at its C-6 position. This was followed by reaction of the resulting compound **13** with BnBr for protection of the remaining OH groups, and finally treatment of compound **14** with H_2SO_4 provided a 1:1.5 anomeric mixture **15a,β.** Then, proceeding as for **8α,β**, treatment of **15αβ**[23] with Tf_2O and pyridine provided the expected ditriflate mixture **16αβ**, which was directly reacted with allyl amine and DIEA, the result being the formation of the bicyclic furanoside **17β** only. The 55% yield achieved led us to assume that it arises from the major anomer **15β** via ditriflate **16β** and thence to assign the configuration of its anomeric position. It is in accordance with its ^{1}H NMR spectrum, which shows a doublet at 5.00 ppm (J=2.0 Hz), due to its *endo* anomeric proton (coupled with the H-4 proton).



Scheme 2. i) TBSCl, imidazole, DMF, -20 ºC, 4 h (89%). ii) a. NaH, nBu_4NI, THF, 0 ºC, 10 min; b. BnBr, 50 ºC, 40 h (79%). iii) H_2SO_4, MeOH, 0 ºC->rt, 26 h (90%). iv) Tf_2O, pyr, CH_2Cl_2, - 30 ºC, 3 h. v) allylamine, DEA, CH_3CN, 50 ºC, 23 h (55%, two steps).

Then, an attempt to hydrolize the glycosidic moiety of bicyclic glycoside **17β** failed. It was attributed to the basic character of the nitrogen atom, because when the allyl group was replaced by an alloc group, satisfactory results were achieved. Thus, as shown in Scheme 3, reaction of **17β** with $ClCO_2CHClCH_3$ provided the carbamate **18β** and methanolysis of this compound allowed the nitrogen protecting group to be removed, to give bicycle **19β**, which was finally reacted with alloc chloride and K_2CO_3 to furnish the desired *N*-alloc protected bicycle **20β** in 81% yield (3 steps), as a rotamer mixture, as deduced from its ^1H NMR and ^{13}C NMR spectra, the later showing at 155.*7* and 156.3 ppm signals of carbonyl groups.



Scheme 3. Divergent synthesis of iminosugar **4** and polyhydroxylated pipecolic acid **24**. *Conditions:* i) a. $ClCO_2CHClCH_3$, $ClCH_2CH_2Cl_2$, reflux, 48 h. ii) MeOH, reflux, 24 h. iii) AllocCl, K_2CO_3, 18-crown-6, THF, 0 ºC to rt, 15 h (81%, 3 steps). iv) THF/H_2O (3:1), rt, 4 h. v) $NaBH_4$, EtOH/H_2O (2:1), rt, 1 h (73·%). vi) a. $Pd(Ph_3)_4$, Ph_3SiH, THF, rt, 90 min; b. a. H_2, 20% $Pd(OH)_2$/C, HCl, MeOH, rt, 14 h (79%, 2 steps). vii) $NaClO_2$, $NaH_2PO_4.H_2O$, 2-methyl-2-butene, *t*BuOH/H_2O 1:1 (8.8 mL). viii) a. $Pd(Ph_3)_4$, Ph_3SiH, THF, rt, 23 h; b. H_2, 20% $Pd(OH)_2$/C, HCl, MeOH, rt, 14 h (77%, 2 steps).

According to our plan, reaction of the *N*-alloc bicycle **20β** with aqueous TFA led to the expected anomeric mixture **21αβ**, which upon direct oxidation with $NaClO_2$ gave the polysubstitutted pipecolic acid **23**. This compound was finally converted into the trihydroxylated pipecolic acid **24**,[24,25] by removing the alloc group by reaction with PhSH and $Pd(Ph)_3$ and by ulterior catalytic hydrogenation of the resulting debenzylated pipecolic acid, for removal of the Bn groups.

Moreover, treatment of the mixture **23αβ** with $NaBH_4$ provided the poysubstituted imnosugar **22** and removal of the alloc and Bn groups of this compound, under the protocol for the transformation of **23** into **24**, gave the iminohexitol 1-dehydromannojirimycin (**4**),[26-29] a well known inhibitor of a bovine α-L-fucosidase and of mannosidase I of glycoprotein processing.[30,31]

Conclusions.

To sum up, we have developed a second synthesis of the iminosugar DAB is shorter than our previous synthesis of this target, both starting from the same stable sugar ditriflates **8α** and **8β**.

As an additional example of the synthetical potential of sugar ditriflates, we have developed a new divergent synthesis of 1-deoxymannojirimycin (**4)** and the corresponding polyhydroxylated pipecolic acid **24**, The key step for the route leading to these targets involved a double displacement of sugar ditriflates **16α,β** by a primary amine, a process that was accompanied by the inversion of the configuration at C-2. This allowed to start from the cheap sugar D-glucose. An additional advantage is that this approach to **4** is shorter than a previous synthesis of this target, which involved a sequential formation of the endocyclic C-N bonds.

Work is now in progress in order to extend this methodology to the preparation of other iminocyclopentitols and iminocyclohexitols, in order to establish the scope and limitation of this suitable methodology for the access to iminosugars.

Experimental

All non-aqueous reactions were carried out under an atmosphere of argon in flame-dried glassware unless otherwise stated. Air- and moisture-sensitive liquid reagents were added by dry syringe or cannula. Anhydrous tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under

argon and all other solvents and reagents were used as obtained from commercial sources without further purification unless stated. Flash chromatography was performed using 60 Merck 230–400 mesh (flash, 0.04–0.063) silica. Thin layer chromatography (t.l.c.) was carried out on aluminum backed sheets coated with 60 GF254 silica. Plates were developed using a spray of 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid, or in 5% w/v ninhydrin in methanol. Melting points were recorded on a Köfler hot block and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 250 MHz for ^{1}H and 62.5 MHz for ^{13}C, or at 300 MHz for ^{1}H and 75 MHz for ^{13}C, or at 400 MHz for ^{1}H and 100 MHz for ^{13}C or at 500 MHz for ^{1}H and 125 MHz for ^{13}C, at room temperature, unless otherwise stated. All chemical shifts are quoted on the δ scale using residual solvent as internal standard; s, d, t, q, m, and br designate singlet, doublet, triplet, quadruplet, multiplet, and broad, respectively. Coupling constants (*J*) are measured in Hz. Low resolution mass spectra were recorded by chemical ionisation (NH_3, Cl), as stated. Infrared spectra were measured in KBr and only the characteristic peaks are quoted (in units of cm^{-1}); st, m, and br designate strong, medium, and broad, respectively. Optical rotations were measured with a path length of 0.5 dm and Na (589 nm) lamp. Concentrations are given in g/100 mL. Compounds **5**, **6**, **7αβ** and **8αβ** were prepared according to previously reported procedures.

Benzyl ((1*R*,3*S*,4*S*,7*R*)-7-(benzyloxy)-3-methoxy-2-oxa-5-azabicycle[2.2.1]heptan-5-yl)carbamate (9α)

0.37 mL (2.12 mmol, 2.5 eq) of DIEA and 0.120 g (0.72 mmol, 1.1 eq) of $CbzNHNH_2$ were added to a solution of 0.340 g (0.66 mmol) of compound **8α** in MeCN (13 mL) and the resulting solution was stirred at 50 ºC overnight and then it was concentrated to dryness in a rotary evaporator. The resulting crude residue was subjected to column chromatography (AcOEt/Hex 1:1) and compound **9α** (0.208 g, 83%) was isolated as a colorless oil. Rf 0.4 (AcOEt/Hex 1:6). $[\alpha]_D^{22}$: +59.3 (*c* 3.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): 2.88 (d, *J*=11.3 Hz, 1H, H-6), 3.31 (s, 4H, CH3+ H- 4), 3.50 (d, *J*=11.3 Hz, 1H, H-6'), 4.21 (s, 1H, H-7), 4.27 (d, *J*=1.3 Hz, 1 H, H-1), 4.56 (ABq, *J*=11.6 Hz, 2 H, CH_2-OBn), 4.79 (s, 1 H, H-3), 5.11 (s, 2 H, CH_2-OBn), 6.84 (bs, 1 H, NH), 7.23-7.40 (m, 10 H, 10xAr-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 55.2 (CH_3), 62.1 (CH_2), 66.6 (CH_2), 68.4 (CH), 72.7 (CH_2), 75.2 (CH), 80.7 (CH), 104.9 (CH), 127.9, 128.0, 128.2, 128.4, 128.4, 128.6 (8xCH), 136.2 (C), 136.8 (C), 155.6 (CO). HRMS (ESI^+): calculated for $C_{21}H_{25}N_2O_5$, 385.1758; found, 385.1759. IR (ν, cm^{-1}): 3335 (NH), 1728 (CO).

Benzyl ((1*R*,3*R*,4*S*,7*R*)-7-(benzyloxy)-3-methoxy-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)carbamate (9β)

When compound **8β** (0.150 g, 0.29 mmol) was subject to the procedure for the transformation of its anomer **8α** into **9α**, bicyclic compound **9β** (0.035 g, 32%) was isolated as a colorless oil. Rf= 0.1 (AcOEt/Hex 1:6). $[\alpha]_D^{22}$: —15.9 (*c* 3.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): 3.23-3.41 (m, 2 H, H-6, H-6'), 3.43 (s, 3 H, CH_3), 3.53 (s, 1 H, H-4), 4.02 (dd, *J*=2.5, 1.1 Hz, 1 H, H-7), 4.18-4.27 (s, 1 H, H-1), 4.60 (ABq, *J*=11.7 Hz, 2 H, CH_2Bn), 5.01 (d, *J*=1.9 Hz, 1 H, H-3), 5.14 (s, 2 H, CH_2Bn), 6.20 (bs, 1H, NH), 7.18-7.44 (m, 10 H, 10xAr-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 56.3 (CH_3), 60.9 (CH_2), 65.4 (CH_2), 66.7 y 67.3 (CH), 72.1 (CH_2), 78.5 (CH), 80.5 (CH), 106.1 (CH), 128.0, 128.1,

128.2, 128.3, 128.4, 128.6, 128.6 (8xCH), 136.0 y 136.5 (C), 137.0 (C), 156.1 (CO). HRMS (ESI^+): calculated for $C_{21}H_{25}N_2O_5$, 385.1758; found, 385.1758. IR (ν, cm^{-1}): 3355 (NH), 1725 (CO).

Benzyl ((2*R*,3*R*,4*R*)-3-(benzyloxy)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)carbamate (11)

A solution of compound **9α** (100 mg, 0.26 mmol) in 1:1 TFAA/H_2O (6 mL) was stirred at rt for 2 hours and then concentrated to dryness in a rotary evaporator. The crude residue was solved in 3:1 EtOH/H_2O (4 mL), $NaBH_4$ (20 mg, 0.52 mmol) was added and the stirring was continued at rt for 2 hours. This reaction mixture was then concentrated to dryness and the residue was subjected to column chromatography (AcOEt/Hex 3:1), and compound **11** (40 mg, 41%) was isolated as a yellow oil. Rf 0.3 (AcOEt/Hex 2:1). $[\alpha]_D^{22}$: +27.2 (*c* 3.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz, ppm): 2.82 (dd, *J*=4.3, 2.3 Hz, 1 H, H-2), 3.10-3.30 (m, 2 H, H-5,H-5'), 3.58 (d, *J*=12.4 Hz, 1 H, CH_2-OH), 3.72 (dd, *J*=12.4, 2.7 Hz, 1H, CH_2- OH), 3.91 (d, *J*=4.5 Hz, 1 H, H-4), 3.99-4.24 (m, 3 H, 2xOH+H-3), 4.59 (d, *J*=11.7 Hz, 2 H, CH_2OBn), 5.11 (s, 2H, CH_2OBn), 6.14 (bs, 1 H, NH), 7.15-7.51 (m, 10 H, 10xAr-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 59.1 (CH_2), 61.7 (CH_2), 67.5 (CH_2), 72.3 (CH_2), 72.4 (CH), 85.7 (2xCH), 127.7, 127.9, 128.2, 128.4, 128.4, 128.5, 128.6 (8xCH), 135.7, 137.8 (2xC), 156.9 (CO). HRMS (ESI^+): calculated for C20H25N2O5, 373.1767; found, 373.1758**.** IR (ν, cm^{-1}): 3340 (NH), 1710 (CO).

(2*R*,3*R*,4*R*)-2-(Hydroxymethyl)pyrrolidine-3,4-diol (5)

10% Pd/C (89 mg) were added to a deoxygenated solution of compound **11** (0.089 g, 0.239 mmol) in MeOH (6 mL) and the mixture was stirred under a hydrogen atmosphere (1 atm) at rt for 4 hours. The suspension was then filtered through a celite pad and the filtrate was concentrated to dryness. The residue was solved in 1 M HCl (1 mL), Et_2O was added, and the precipitate was filtered off. This provided the hydrochloride of compound **5** (36 mg, 99%), as a hygroscopic white solid, identical to a sample previously obtained.

6-*O*-*tert*-Butyildimethylsilyl-1,2-*O*-isopropilene-α-D-glucofuranose (13)

Imidazole (2.55 g, 37.46 mmol) and TBSCl (4.141 g, 27.47 mmol) were successively added to a solution of **12** (5.50 g, 24.98 mmol) in DMF (50 mL) keeped at -20 °C. After stirring then at this temperature for 4 hours, the reaction mixture was diluted with AcOEt (250 mL) and washed with NaCl (3x100 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered and concentrated to dryness in a rotary evaporator. Column chromatography of the crude residue (AcOEt/Hex 1:2) provided compound **13** (7.43 g, 89%) as an amorphous white solid. Rf=0.9 /AcOEt). $[\alpha]_D^{22}$: -14.0 (c 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz, ppm): 0.07 (s, 6 H, 2x CH_3), 0.88 (s, 9 H, 2x CH_3), 1.28 (s, 3 H, CH3), 1.44 (s, 3 H, CH_3), 3.12 (s, 1 H, -OH), 3.60 (s, 1 H, -OH), 3.67-3.91 (m, 2 H, H- 6, H-6'), 3.93-4.08 (m, 2 H), 4.31 (d, *J*=2.5 Hz, 1 H), 4.50 (d, *J*=3.7 Hz, 1 H, H-2), 5.91 (d, *J*=3.7 Hz, 1 H, H-1). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): -5.3 (2xCH_3), 18.4 (C), 25.9 (3x CH_3), 26.3 (CH_3), 26.9 (CH_3), 64.3 (CH_2), 70.3 (CH), 75.7 (CH), 79.7 (CH), 85.2 (CH), 105.1 (CH), 111.7 (C). HRMS (ESI^+): calculated for $C_{15}H3_0NaO_6Si$, 357.1704; found, 357.1704. IR (ν, cm-^{1}): 3434, 3327 (OH).

3,5-di-*O*-Benzyl-6-*O*-*tert*-butyldimetylsilyl-1,2-*O*-isopropylene-α- D-glucofuranose (14)

A solution of compound **13** (3.995 g, 11.94 mmol) in dry THF (40 mL) was added to a stirred suspension of NaH (1.195 g, 29.86 mmol, 60% in mineral oil) and NBu4I (0.221 g, 0.60 mmol, 0.05 eq) in dry THF (80 mL) keep at 0 ºC. The stirring was continued for 10 min, then BnBr (4.26 mL, 35.83 mmol, 3.0 eq) was added and the new mixture was stirred at 50 ºC for 40 h. The reaction mixture was concentrated to dryness and the residue was solved in AcOEt (150 mL), washed with water (3x100 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered and concentrated to dryness. The crude residue was purified by column chromatography (AcOEt/Hex 1:9) and compound **14** (4,83 g, 79%) was isolated as a colorless oil. Rf=0.4 (AcOEt/Hex 1:8). $[\alpha]_D^{22}$: -34.2 (*c* 2.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 0.13 (s, 6 H, 2xCH3), 0.97 (s, 9 H, 3xCH_3), 1.35 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 3.85 (dd, *J*=11.0, 5.8 Hz, 1 H, H-6), 3.99 (ddd, *J*=9.3, 5.8, 1.9 Hz, 1 H, H-5), 4.10 (dd, *J*=11.0, 1.9 Hz, 1 H, H-6), 4.16 (d, *J*=3.1 Hz, 1 H, H-3), 4.30 (dd, *J*=9.3, 3.0 Hz, 1 H, H-4), 4.54 (ABq, *J*=4.4 Hz, 2 H, -CH_2Ph), 4.63 (d, *J*=3.8 Hz, 1 H, H-2), 4.80 (ABq, *J*=11.5 Hz, 2 H, -CH_2Ph), 5.96 (d, *J*=3.8 Hz, 1 H, H-1), 7.27-7.40 (m, 10 H, 10xAr-H). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): -5.5 (CH3), -5.4 (CH_3), 18.2 (C), 26.0 (3xCH_3), 26.3 (CH_3), 26.7 (CH_3), 63.8 (CH_2), 71.7 (CH_2), 72.5 (CH_2), 76.9 (CH), 78.6 (CH), 81.7 (CH), 81.8 (CH), 105.3 (CH), 111.4(C), 127.5, 127.6, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 128.9 (10xCH), 137.6 (C), 138.9 (C). HRMS (ESI^+): calculated for $C_{29}H_{42}NaO6Si_2$, 537.4623; found, 537.4643. IR (ν, cm^{-1}): 2954, 2930, 2885, 2878 (CH).

Methyl 3,5-di-*O*-benzyl-α-D-glucofuranoside (15a,β)

H_2SO_4 (1.57 mL, 27.98 mmol) was added over a cooled (0 ºC) solution of compound **14** (4.800 g, 9.33 mL) in MeOH (150 mL) and the mixture was stirred at rt for 26 h., then neutralized with Na_2CO_3, filtered through a Celite pad and concentrated to dryness. Column chromatography (AcOEt/Hex 2:1) of the residue provided a 1:1.5 mixture of compound **15αβ** (3.16 g, 90%) as a colourless oil. Compound **15α**: $[\alpha]_D^{22}$: +13.4 (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 2.20 (s, 1 H, -OH), 2.90 (d, *J*=5.6 Hz, 1 H, -OH), 3.49 (s, 3 H, CH_3), 3.77 (dt, *J*=14.1, 6.5 Hz, 1 H, H-6), 3.85-3.96 (m, 2 H), 4.06 (dd, *J*=4.5, 2.2 Hz, 1 H, H-2), 4.27 (td, *J*=5.5, 2.2 Hz, 1 H, H-3), 4.32 (dd, *J*=7.4, 4.6 Hz, 1 H), 4.53 (s, 2H, -CH_2Ph), 4.67 (ABq, *J*=11.5 Hz, 2 H, -CH_2Ph), 5.05 (d, *J*=4.5 Hz, 1 H, H-1), 7.17- 7.48 (m, 10 H, 10xAr-H). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 56.0 (CH_3), 62.2 (CH_2), 71.7 (CH_2), 72.3 (CH_2), 76.1 (CH), 76.6 (CH), 78.5 (CH), 83.8 (CH), 102.3 (CH), 127.7 (2xC), 127.8 (4xC), 127.9 (2xC), 128.5 (2xC), 137.8 (C), 138.4 (C). HRMS (ESI^+): calculated for $C_{21}H_{26}NaO6$, 397.1622; found, 397.1607. IR (ν, cm^{-1}): 3462 (OH). Compound **15β**.- $[\alpha]_D^{22}$: -89° (*c* 1.4, $CHCl_3$). ^{1}H NMR (CDCl3, 250 MHz, ppm): 2.38 (s, 1 H, -OH), 2.63 (s, 1 H, -OH), 3.39 (s, 3 H, CH_3), 3.75-4.00 (m, 4 H), 4.18-4.24 (m, 1 H), 4.40 (dd, *J*=8.5, 4.9 Hz, 1 H), 4.47-4.68 (m, 4 H), 4.82 (d, *J*=1.0 Hz, 1 H, H-1), 7.21-7.35 (m, 10 H, 10xAr-H). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 56.2 (CH_3), 61.8 (CH_2), 72.1 (2xCH_2), 77.1 (CH), 78.2 (CH), 80.4 (CH), 82.8 (CH), 110.1 (CH), 127.8, 127.8, 127.9, 127.9, 128.5 (10xCH), 137.9 (C), 138.4(C). HRMS (ESI^+): calculated for $C_{21}H_{26}NaO_6$, 397.1622; found, 397.1626. IR (ν, cm^{-1}): 3415 (OH).

(1*S*,4*R*,5*R*,7*R*,8*R*)-2-allyl-4,8-bis(benzyloxy)-7-methoxy-6-oxa-2-azabicyclo[3.2.1]octane (17β)

Pyridine (2.59 mL, 32.05 mmol, 6.0 eq) was added to a solution of a 1:1.5 anomeric mixture **15α,β** (2.000 g, 5.34 mmol) in DCM, the new solution was cooled at -30 ºC, Tf_2O (2.70 mL, 16.03 mmol, 3.0 eq) was added drop by drop and the resulting mixture was stirred at this temperature for 2 hours, when it was established by tlc (AcOEt/Hex 1:1) the transformation of the starting material (Rf=0.3) and the formation of a main product (Rf=0.9). The reaction mixture was washed with 1 M HCl (2x50 mL) and the organic phase was dried (anhydrous Na_2SO_4) and concentrated to dryness. The crude residue was solved into CH3CN (50 mL), DIEA (2.32 mL, 13.36 mmol, 2.5 eq) and allylamine (0.44 mL, 5.88 mmol, 1.1 eq) were added, the mixture was heated at 50 ºC for 23 hours and then it was concentrated to dryness. Flash column chromatography of the residue ((AcOEt/Hex 1:6) allowed isolation of compound **17β** (1.160 g, 55% yield), as a colorless oil. Rf=0,3 (AcOEt/1:6). $[\alpha]_D^{22}$: -49.6 (c 2.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 3.05-3.19 (m, 2 H, CH_2=CH-$\underline{CH_2}$), 3.22 (dt, J=5.6, 2.6 Hz, 1 H, H-1), 3.37 (ddt, J=13.9, 5.8, 1.6 Hz, 1 H, H-3), 3.46 (s, 3 H, CH_3), 3.60 (ddt, J=13.8, 7.2, 1.3 Hz, 1 H, H-3'), 3.84 (dd, J=5.8, 4.0 Hz, 1H), 3.92 (ddd, J=9.2, 6.8, 1.2 Hz, 1 H), 4.30 (d, J=5.8 Hz, 1 H), 4.50 (d, J=12.1 Hz, 2 H, -$\underline{CH_2}$Ph), 4.54 (s, 2 H, -$\underline{CH_2}$Ph), 5.00 (d, J=2.6 Hz, 1 H, H-7), 5.08-5.15 (m, 1H, CH_2=CH-CH_2), 5.21 (dt, J=17.1, 1.7 Hz, 1 H, CH_2=CH-CH_2), 5.84 (dddd, J=17.4, 10.1, 7.2, 5.7 Hz, 1 H, CH_2=CH-CH_2), 7.23-7.44 (m, 10H, 10xAr-H). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 50.9 (CH_2), 56.7 (CH_3), 57.3 (CH), 58.4 (CH_2), 71.0 (CH_2), 71.4 (CH_2), 71.9 (CH), 75.3 (CH), 77.6 (CH), 106.8 (CH), 117.1 (CH_2), 127.5 (CH), 127.8 (CH), 127.9 (CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 136.8 (CH), 137.7 (C), 138.7 (C). HRMS (ESI^+): calculated for $C_{24}H_{30}NO_4$, 396.2169; found, 396.2167. IR (ν, cm^{-1}): 2957, 2910, 2837 (CH).

Allyl (1*S*,4*R*,5*R*,7*R*,8*R*)-4,8-bis(benzyloxy)-7-methoxy-6-oxa-2-azabicyclo[3.2.1]octane-2-carboxylate (18β)

1-Cloroethylchloroformate (0.36 mL, 3.34 mmol, 4.0 eq) was added to a solution of compound **17β** (0.330 g, 0.83 mmol) in dichloroethane (4.2 mL) and the resulting solution was refluxed for 48 hours. The liquids were then removed under vacuum, the residue was solved in methanol (4.2 mL) and the solution was refluxed for 24 hours and then concentrated to dryness. The residue was solved in THF (1.5 mL), the solution was cooled to 0 °C, allyl chloroformate (0.27 mL, 2.50 mmol, 3.0 eq), K_2CO_3 (0.692 g, 5.01 mmol, 6.0 eq) and 18-crown-6 ether (0.044 g, 0.17 mmol, 0.2 eq) were added, and the resulting mixture was stirred at 0 °C for 3 hours and at room temperature overnight, and then was neutralized with saturated aqueous ammonium chloride. The resulting aqueous solution was extracted with Et_2O (4x10 mL) and the pooled organic layers were washed with NaCl solution (3x25 mL), dried (anhydrous Na_2SO_4) and concentrated to dryness. The residue was subjected to flash column chromatography (eluent AcOEt/Hex 1:2) and compound **18β** (0.68 mmol, 81% yield) was isolated as a yellow oil. $[\alpha]_D^{22}$: -37.2 (*c* 2.6, $CHCl^3$). ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 3.02 (ddd, *J*=22.1, 13.2, 11.3 Hz, 1 H, H-3), 3.33- 3.44 (m, 5 H), 3.78 (dddd, *J*=13.3, 11.1, 5.2, 2.9 Hz, 1 H, H-3'), 3.94 (ddd, *J*=12.5, 3.4, 1.6 Hz, 1 H), 4.26-4.50 (m, 2 H), 4.51-4.71 (m, 5 H), 4.95 (dd, *J*=8.1, 2.1 Hz, 1 H, H-7), 5.08-5.22 (m, 1 H, CH=CH_2), 5.23-5.36 (m, 1 H,

$CH=CH_2$), 5.73-6.04 (m, 1 H, $CH=CH_2$), 7.12-7.42 (m, 10 H, Ar-H). ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): 38.1, 38.6 (CH_2), 52.0, 53.2 (CH), 53.5, 54.6 (CH_3), 55.1, 55.5 (CH), 66.2, 66.3 (CH_2), 68.2, 68.3 (CH), 71.2, 71.3, 71.4 (2xCH_2), 72.3, 72.3 (CH), 75.2, 75.3 (CH), 100.3, 101.0 (CH), 117.1, 117.3 (CH_2), 127.5, 127.7, 127.7, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.4, 128.5 (10xCH), 132.8, 133.0 (CH), 137.8, 138.0 (2xC), 155.7, 156.3 (CO). HRMS (ESI^+): calculated for $C_{25}H_{30}NO_6$, 440.2068; found, 440.2069. IR (ν, cm^{-1}): 1700 (CO).

Allyl (2*R*,3*R*,4*R*,5*R*)-3,5-bis(benzyloxy)-4-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate (22)

A solution of compound **20β** (0.148 g, 0.34 mmol) in a 3:1 TFA/H_2O mixture (2 mL) was stirred at room temperature for 4 hours and then was concentrated to dryness under vacuum. The crude residue was solved in 2:1 EtOH/H_2O (3 mL), $NaBH_4$ (0.67 mmol, 2.0 eq) was then added, and the mixture was stirred at room temperature for 1 hour and then was neutralized with 10% aqueous AcOH, and finally it was concentrated to dryness under vacuum. The crude product was purified by flash column chromatography (eluent AcOEt/Hex 2:1) and compound **22** ((0.105 g, 0.25 mmol, 73 %) was isolated as a colorless oil. $[\alpha]_D^{22}$: -22.2 (*c* 3.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz, ppm): 3.12-3.30 (m, 2 H, 2x-OH), 3.70-3.76 (m, 1 H), 3.77- 3.93 (m, 4 H), 4.06-4.11 (m, 1 H), 4.42-4.51 (m, 2 H), 4.56-4.67 (m, 6 H), 5.19 (d, *J*=10.5 Hz, 1 H, $CH=CH_2$), 5.28 (d, *J*=17.2 Hz, 1 H, $CH=CH_2$), 5.91 (m, 1 H, $CH=CH_2$), 7.23-7.43 (m, 10 H, 10xAr-H). ^{13}C NMR (CDCl3, 75 MHz, ppm): 38.0 and 39.0 (CH_2), 55.1 (CH), 61.3 (CH_2), 66.4 (CH_2), 68.1 (CH), 71.4 and 71.7 (CH_2), 72.5 (CH), 76.3 (CH), 117.6 (CH_2), 127.9 (3xCH), 128.1 (CH), 128.4 (3xCH), 128.5 (3xCH), 132.9 (CH), 137.7 (C), 137.8 (C), 156.3 (CO). HRMS (ESI^+): calculated for $C_{24}H_{29}NNaO_6$, 450.1887; found, 450.1883. IR (ν, cm^{-1}): 1694, 1649 (CO).

(2*R*,3*R*,4*R*,5*R*)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidinium chloride (4)

Ph_3SiH (0.04 mL, 0.32 mmol, 2.0 eq) and $Pd(Ph_3)_4$ (0.018 g, 0.02 mmol, 0.1 eq) were added to a solution of compound **22** (0.068 g, 0.16 mmol) in dry THF (5.6 mL), and the mixture was stirred at room temperature for 90 minutes and then it was concentrated to dryness under vacuum. The crude product was purified by column chromatography (eluent CH_2Cl_2/MeOH 15:1 to 9:1) and the main product isolated was solved in MeOH (3.6 mL), the solution was deoxygenated, $Pd(OH)_2/C$ (0.110 g) and concentrated HCl (two drops) were added and the mixture was stirred under a hydrogen atmosphere (1 atm) at room temperature overnight. Then it was filtered through a celite pad, which was washed with MeOH, and the filtrate was concentrated to dryness. This provided a white, hygroscopic solid residue of hydrochloride of compound **5** (0.13 mmol, 79%), $[\alpha]_D^{22}$: -10.1 (*c* 0.5, H2O). ^1H NMR (D_2O, 300 MHz, ppm): 3.18-3.27 (m, 1 H), 3.27-3.39 (m, 1 H), 3.42-3.54 (m, 1 H), 3.76 (dt, *J*=9.6, 2.9, Hz, 1 H), 3.83-4.18 (m, 3 H), 4.27-4.34 (m, 1 H). ^{13}C NMR (D_2O, 75 MHz, ppm): 50.4 (CH2), 60.9 (CH2), 63.2 (CH), 68.6 (CH), 68.7 (CH), 75.1 (CH). HRMS (ESI^+): calculated for $C_6H_{14}NO_4^+$, 164.0917, found, 164.0912. IR (ν, cm^{-1})**:** 3404 (OH and NH).

(2*S*,3*R*,4*R*,5*R*)-1-((allyloxy)carbonyl)-3,5-bis(benzyloxy)-4-hydroxypiperidine-2-carboxylic acid (23)

A solution of compound **20β** (0.258 g, 0.59 mmol) in 3:1 TFA/H_2O was stirred at room temperature for 4 hour s and then was concentrated to dryness under vacuum. The residue was solved in 1:1 nBuOH/H_2O (8.8 mL), 2- methyl-2-butene (0.62 mL, 5.87 mmol, 10.0 eq), $NaH_2PO_4.2H_2O$ (0.137 g, 0.88 mmol, 1.5 eq) and $NaClO_2$ (0.080 g, 0.88 mmol, 1.5 eq) were successively added and the mixture was stirred at rt for 1 hour. The mixture was next acidified with 10% citric acid and extracted with AcOEt (3x 15 mL). The pooled organic extracts were dried (anhydrous Na_2SO_4), filtered and concentrated to dryness in a rotary evaporator. The crude residue was subjected to flash column chromatography (AcOEt/Hex 3:1)) and compound **23** (0.203 g, 0.46 mmol, 78%) was isolated as an amorphous white solid. $[\alpha]_D^{22}$: -9.0 (c 3.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): 3.21-3.45 (m, 1 H), 3.73-3.88 (m, 1 H), 3.98-4.18 (m, 2 H), 4.20-4.40 (m, 2 H), 4.39-4.75 (m, 6 H), 5.05-5.36 (m, 2 H, CH=CH_2), 5.86 (m, 1 H, CH=CH_2), 7.19-7.41 (m, 10 H, 10x Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 38.8 y 39.2 (CH_2), 53.8 y 54.4 (CH), 66.7 y 66.8 (CH_2), 67.7 and 67.7 (CH), 71.2 and 71.8 (CH_2), 71.9 (CH), 76.8 and 77.4 (CH), 117.6 and 117.8 (CH), 127.6, 127.8, 127.9, 128.0, 128.0, 128.5, 128.6 (10xCH), 132.7 (CH), 137.5, 137.6, 137.7 (C), 156.1 y 156.5 (CO), 173.9 y 173.9 (CO). HRMS (ESI^+): calculated for $C_{24}H_{28}NO_7$, 442.1860; found , 442.1866. IR (ν, cm-^{1}): 3440 (OH), 1705 (CO).

(2*S*,3*R*,4*R*,5*R*)-2-carboxy-3,4,5-trihydroxypiperidinium chloride (26)

When compound **23** (0.074 g, 0.17 mmol) was subjected to the procedure for the transformation of compound **22** into compound **4**, the hydrochloride of compound **24** (0.026 g, 73% yield) was obtained as a white solid. $[\alpha]_D^{22}$: -3.6 (*c* 0.5, H_2O). ^{1}H NMR (D_2O, 300 MHz, ppm): 3.29-3.42 (m, 1 H), 3.41-3.57 (m, 1 H), 3.82-3.97 (m, 2 H), 4.20-4.36 (m, 2 H). ^{13}C NMR (D_2O, 75 MHz, ppm): 46.6 (CH_2), 60.7 (CH), 66.0 (CH), 69.0 (CH), 72.6 (CH), 171.2 (CO). HRMS (ESI^+): calculated for $C_6H_{12}NO_5^+$, 178.0710, found, 178.0705. IR (ν, cm^{-1}): 3407 (OH y NH), 1631 (CO).

Acknowledgment. This work has received financial support from the Xunta de Galicia and the European Regional Development Fund – ERDF (ED431C 2018/30, ED431F 2020/05 and Centro singular de investigación de Galicia accreditation 2019-2022, ED431G 2019/ 03). Funding from the Agencia Estatal de Investigación (AEI) and the European Regional Development Fund - ERDF (RTI2018 098795-A-I00 and PDC2022-133402-I00) is also acknowledged. L. B. thanks Ministerio de Educación, Cultura y Deporte for a FPU fellowship (FPU13/01243).

References

(1) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. . Sugar-Mimic Glycosidase Inhibitors: Natural Occurrence, Biological Activity and Prospects for Therapeutic Application.

Tetrahedron: Asymmetry **2000**, *11* (8), 1645–1680. https://doi.org/10.1016/S0957-4166(00)00113-0.

(2) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. Polyhydroxylated Alkaloids — Natural Occurrence and Therapeutic Applications. *Phytochemistry* **2001**, *56* (3), 265–295. https://doi.org/10.1016/S0031-9422(00)00451-9.

(3) Horne, G.; Wilson, F. X.; Tinsley, J.; Williams, D. H.; Storer, R. Iminosugars Past, Present and Future: Medicines for Tomorrow. *Drug Discov. Today* **2011**, *16* (3–4), 107–118. https://doi.org/10.1016/j.drudis.2010.08.017.

(4) Compain, P.; Chagnault, V.; Martin, O. R. Tactics and Strategies for the Synthesis of Iminosugar C-Glycosides: A Review. *Tetrahedron Asymmetry* **2009**, *20* (6–8), 672–711. https://doi.org/10.1016/j.tetasy.2009.03.031.

(5) Afarinkia, K.; Bahar, A. Recent Advances in the Chemistry of Azapyranose Sugars. *Tetrahedron: Asymmetry* **2005**, *16* (7), 1239–1287. https://doi.org/10.1016/j.tetasy.2005.02.020.

(6) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. Recent Advances in the Total Synthesis of Piperidine Azasugars. *European J. Org. Chem.* **2005**, *2005* (11), 2159–2191. https://doi.org/10.1002/ejoc.200400823.

(7) Compain, P. O. M. *Iminosugars: From Synthesis to Therapeutic Applications*; 2007.

(8) Schulze, H.; Sandhoff, K. Lysosomal Lipid Storage Diseases. *Cold Spring Harb. Perspect. Biol.* **2011**, *3* (6), a004804–a004804. https://doi.org/10.1101/cshperspect.a004804.

(9) Scott, L. J.; Spencer, C. M. Miglitol: A Review of Its Therapeutic Potential in Type 2 Diabetes Mellitus. *Drugs* **2000**, *59* (3), 521–549. https://doi.org/10.2165/00003495-200059030-00012.

(10) Kato, A.; Kato, N.; Kano, E.; Adachi, I.; Ikeda, K.; Yu, L.; Okamoto, T.; Banba, Y.; Ouchi, H.; Takahata, H.; Asano, N. Biological Properties of D - and L-1-Deoxyazasugars. *J. Med. Chem.* **2005**, *48* (6), 2036–2044. https://doi.org/10.1021/jm0495881.

(11) Asano, N.; Oseki, K.; Tomioka, E.; Kizu, H.; Matsui, K. N-Containing Sugars from Morus Alba and Their Glycosidase Inhibitory Activities. *Carbohydr. Res.* **1994**, *259* (2), 243–255. https://doi.org/10.1016/0008-6215(94)84060-1.

(12) Stocker, B. L.; Dangerfield, E. M.; Win-Mason, A. L.; Haslett, G. W.; Timmer, M. S. M. Recent Developments in the Synthesis of Pyrrolidine-Containing Iminosugars. *European J. Org. Chem.* **2010**, No. 9, 1615–1637. https://doi.org/10.1002/ejoc.200901320.

(13) Taylor, C. M.; Barker, W. D.; Weir, C. A.; Park, J. H. Toward a General Strategy for the Synthesis of 3,4-Dihydroxyprolines from Pentose Sugars. *J. Org. Chem.* **2002**, *67* (13), 4466–4474. https://doi.org/10.1021/jo025538x.

(14) Taylor, C. M.; Jones, C. E.; Bopp, K. The Conversion of Pentoses to 3,4-Dihydroxyprolines. *Tetrahedron* **2005**, *61* (40), 9611–9617. https://doi.org/10.1016/j.tet.2005.07.072.

(15) Lenagh-Snow, G. M. J.; Araujo, N.; Jenkinson, S. F.; Rutherford, C.; Nakagawa, S.; Kato, A.; Yu, C.-Y.; Weymouth-Wilson, A. C.; Fleet, G. W. J. Inhibition of Nonmammalian Glycosidases by Azetidine Iminosugars Derived from Stable 3,5-Di- O -Triflates of Pentoses. *Org. Lett.* **2011**, *13* (21), 5834–5837. https://doi.org/10.1021/ol2024482.

(16) Lenagh-Snow, G. M. J.; Araújo, N.; Jenkinson, S. F.; Martínez, R. F.; Shimada, Y.; Yu, C.-Y.; Kato, A.; Fleet, G. W. J. Azetidine Iminosugars from the Cyclization of 3,5-Di- O -Triflates of α-Furanosides and of 2,4-Di- O -Triflates of β-Pyranosides Derived from Glucose. *Org. Lett.*

2012, *14* (8), 2142–2145. https://doi.org/10.1021/ol300669v.

(17) Araújo, N.; Jenkinson, S. F.; Martínez, R. F.; Glawar, A. F. G.; Wormald, M. R.; Butters, T. D.; Nakagawa, S.; Adachi, I.; Kato, A.; Yoshihara, A.; Akimitsu, K.; Izumori, K.; Fleet, G. W. J. Synthesis from D-Altrose of (5R,6R,7R,8S)-5,7-Dihydroxy-8-Hydroxymethylconidine and 2,4-Dideoxy-2,4-Imino-D-Glucitol, Azetidine Analogues of Swainsonine and 1,4-Dideoxy-1,4-Imino-D-Mannitol. *Org. Lett.* **2012**, *14* (16), 4174–4177. https://doi.org/10.1021/ol301844n.

(18) Glawar, A. F. G.; Jenkinson, S. F.; Thompson, A. L.; Nakagawa, S.; Kato, A.; Butters, T. D.; Fleet, G. W. J. 3-Hydroxyazetidine Carboxylic Acids: Non-Proteinogenic Amino Acids for Medicinal Chemists. *ChemMedChem* **2013**, *8* (4), 658–666. https://doi.org/10.1002/cmdc.201200541.

(19) Martínez, R. F.; Araújo, N.; Jenkinson, S. F.; Nakagawa, S.; Kato, A.; Fleet, G. W. J. (3*R*,4*S*,5*R*,6*R*,7*S*)-3,4,5,7-Tetrahydroxyconidine, an Azetidine Analogue of 6,7-Diepicastanospermine and a Conformationally Constrained d-Deoxyaltronojirimycin, from l-Arabinose. *Bioorg. Med. Chem.* **2013**, *21* (16), 4813–4819. https://doi.org/10.1016/j.bmc.2013.03.004.

(20) Martínez, R. F.; Fleet, G. W. J. Carbohydrate Derived Bicyclic Azetidin-3-Ones as Scaffolds for Highly Functionalized Azetidines. *Tetrahedron: Asymmetry* **2014**, *25* (4), 373–380. https://doi.org/10.1016/j.tetasy.2014.01.014.

(21) Balo, R.; Fernández, A. G.; Chopdat, A.; Ayadi, S. El; Kato, A.; Estévez, R. J.; Fleet, G. W. J.; Estévez, J. C. Stable D-Xylose Ditriflate in Divergent Syntheses of Dihydroxy Prolines, Pyrrolidines, Tetrahydrofuran-2-Carboxylic Acids, and Cyclic β-Amino Acids. *Org. Biomol. Chem.* **2022**, *20* (47), 9447–9459. https://doi.org/10.1039/D2OB01255C.

(22) Arévalo, J. M.; Simons, C. Convenient Synthesis of 2-Deoxy-D-Glucofuranosides. *J. Carbohydr. Chem.* **1999**, *18* (5), 535–544. https://doi.org/10.1080/07328309908544017.

(23) El Nemr, A.; Tsuchiya, T.; Kobayashi, Y. α-Hydrogen Elimination in Some Carbohydrate Triflates. *Carbohydr. Res.* **1996**, *293* (1), 31–59. https://doi.org/10.1016/0008-6215(96)00178-4.

(24) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. A Practical Synthesis of Deoxymannojirimycin and of (2s,3R,4R,5R)-3,4,5-Trihydroxypipecolic Acid from D-Glucose. *Tetrahedron* **1989**, *45* (1), 327–336. https://doi.org/10.1016/0040-4020(89)80060-2.

(25) Yoshimura, Y.; Ohara, C.; Imahori, T.; Saito, Y.; Kato, A.; Miyauchi, S.; Adachi, I.; Takahata, H. Synthesis of Both Enantiomers of Hydroxypipecolic Acid Derivatives Equivalent to 5-Azapyranuronic Acids and Evaluation of Their Inhibitory Activities against Glycosidases. *Bioorg. Med. Chem.* **2008**, *16* (17), 8273–8286. https://doi.org/10.1016/j.bmc.2008.06.016.

(26) Myeong, I.-S.; Jung, C.; Kim, J.-Y.; Park, S.-H.; Ham, W.-H. Asymmetric Total Syntheses of (+)-2,5-Dideoxy-2,5-Imino-d-Glucitol [(+)-DGDP] and (−)-1-Deoxymannojirimycin [(−)-DMJ] via an Extended Chiral 1,3-Oxazine. *Tetrahedron Lett.* **2018**, *59* (25), 2422–2425. https://doi.org/10.1016/j.tetlet.2018.05.026.

(27) Stauffert, Fabien; Lepage, Mathieu L.; Pichon, Maeva M.; Hazelard, Damien; Bodlenner, Anne; Compain, P. A Convenient, Gram-Scale Synthesis of 1-Deoxymannojirimycin. *Synthesis (Stuttg).* **2016**, *48* (8), 1177–1180.

(28) Davies, S. G.; Figuccia, A. L. A.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. Asymmetric Syntheses of (−)-1-Deoxymannojirimycin and (+)-1-Deoxyallonojirimycin via a Ring-Expansion Approach. *Org. Lett.* **2013**, *15* (8), 2042–2045. https://doi.org/10.1021/ol400735z.

(29) Malle, B. M.; Lundt, I.; Wrodnigg, T. M. Regioselective Intramolecular Ring Closure of 2-Amino-6-Bromo-2,6-Dideoxyhexono-1,4-Lactones to 5- or 6-Membered Iminuronic Acid Analogues: Synthesis of 1-Deoxymannojirimycin and 2,5-Dideoxy-2,5-Imino-D-Glucitol. *Org. Biomol. Chem.* **2008**, *6* (10), 1779–1786. https://doi.org/10.1039/b719631h.

(30) Winchester, B.; Barker, C.; Baines, S.; Jacob, G. S.; Namgoong, S. K.; Fleet, G. Inhibition of α - l -Fucosidase by Derivatives of Deoxyfuconojirimycin and Deoxymannojirimycin. *Biochem. J.* **1990**, *265* (1), 277–282. https://doi.org/10.1042/bj2650277.

(31) Lu, Y.; Xu, Y.-Y.; Fan, K.-Y.; Shen, Z.-H. 1-Deoxymannojirimycin, the A1,2-Mannosidase Inhibitor, Induced Cellular Endoplasmic Reticulum Stress in Human Hepatocarcinoma Cell 7721. *Biochem. Biophys. Res. Commun.* **2006**, *344* (1), 221–225. https://doi.org/10.1016/j.bbrc.2006.03.111.