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Polyhydroxylated pyrrolidines. Part 4: Synthesis from D-fructose of protected 2,5-dideoxy-2,5-imino-D-galactitol derivatives☆

Isidoro Izquierdo,* María T. Plaza, Miguel Rodríguez, Juan A. Tamayo and Alicia Martos

Department of Medicinal and Organic Chemistry, Faculty of Pharmacy, University of Granada, 18071 Granada, Spain

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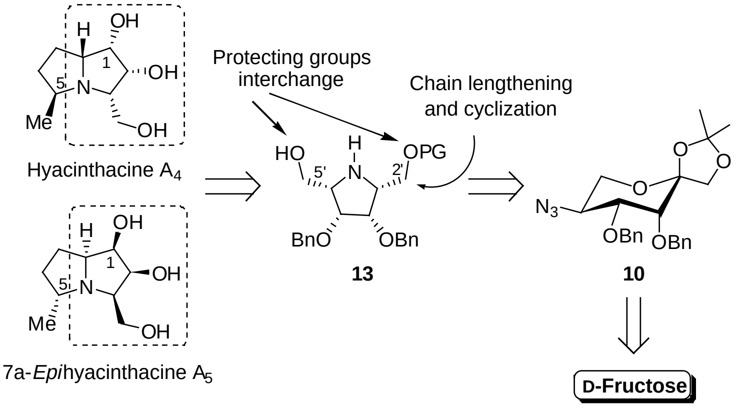
Abstract—The readily available 3-*O*-benzoyl-4-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-β-D-fructopyranose (**5**) was straightforwardly transformed into its D-*psico* epimer (**8**), after *O*-debenzoylation followed by oxidation and reduction, which caused the inversion of the configuration at C(3). Compound **8** was treated with lithium azide yielding 5-azido-4-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-L-tagatopyranose (**9**) that was transformed into the related 3,4-di-*O*-benzyl derivative **10**. Cleavage of the acetonide in **10** to give **11**, followed by regioselective 1-*O*-pivaloylation to **12** and subsequent catalytic hydrogenation gave (2*R*,3*S*,4*R*,5*S*)-3,4-dibenzyloxy-2,5-bis(hydroxymethyl)-2′-*O*-pivaloylpyrrolidine (**13**). Stereochemistry of **13** could be determined after *O*-deacylation to the symmetric pyrrolidine **14**. Total deprotection of **14** gave 2,5-imino-2,5-dideoxy-D-galactitol (**15**, DGADP).

1. Introduction

In a very recent paper, our group reported on preparation of orthogonally protected derivatives of 2,5-dideoxy-2,5-imino-D-*allo*- (DADP) and -D-*altro*-hexitol (DALDP),[1] in a stereoselective manner, using commercially available D-fructose as the chiral starting material. Continuing with our efforts on this topic, we reported herein on the highly stereoselective synthesis of the D-galacto isomer (**13**) of the above mentioned 2,5-iminohexitols.

Scheme 1 shows the synthetic potentiality of (2*R*,3*S*,4*R*,5*S*)-3,4-dibenzyloxy-2,5-bis(hydroxymethyl)-2′-*O*-pivaloylpyrrolidine (**13**) displaying the retrosynthesis of hyacinthacines A_4 and 7a-*epi*-A_5, the former recently isolated from *Scilla sibirica*,[2] where clearly is shown that **13** must be considered an appropriate chiral starting material for the synthesis of such target molecules. Thus, *O*-protecting groups interchange between the hydroxyl groups at C(2′)–C(5′), carbon-chain lengthening at either C(2′) (the original C(1) of D-fructose) or C(5′) in a two more carbon atoms fragment



Scheme 1. Retrosynthesis of natural hyacinthacine A_4 and 7a-*epi*-A_5.

☆ For Part III, see Ref. 1.

Keywords: D-Fructose; Stereoselective synthesis; Polyhydroxylated pyrrolidines; 2,5-Dideoxy-2,5-iminohexitols; DGADP.

* Corresponding author. Tel.: +34 958 249583; fax: +34 958 243845; e-mail: isidoro@ugr.es

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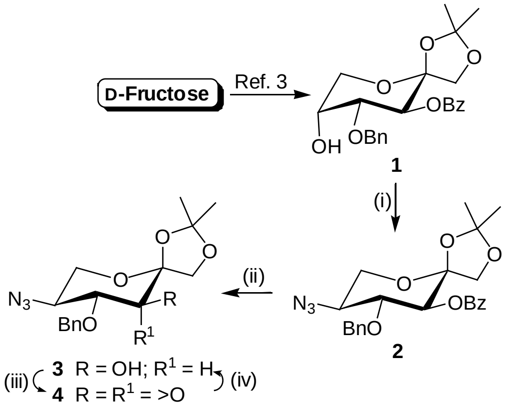
suitably functionalized, followed by a further cyclization, could lead to pyrrolizidines, which stereochemistry at C(1,2,3,7a) belonging either to that of the natural hyacinthacine A_4 or the 7a-*epi*-A_5.

2. Results and discussion

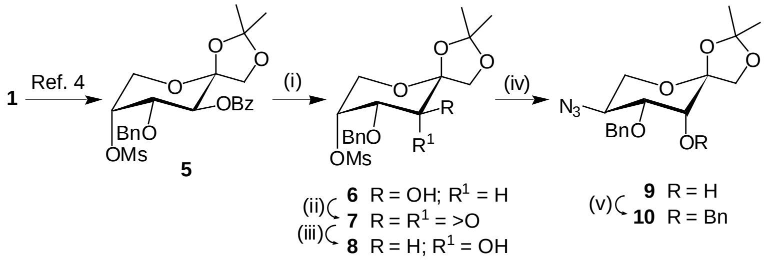
A first attempt of synthesizing the required key intermediate 3,4-di-*O*-benzy1-1,2-*O*-isopropylidene-α-L-tagatopyranose (**10**) according to the synthetic route outlined in Scheme 2, where the well known 3-*O*-benzoyl-4-*O*-benzy1-1,2-*O*-isopropylidene-β-D-fructopyranose (**1**)[3] was chosen as the chiral starting material was unsuccessful. Even though the transformation of **1** into the already reported 5-azido-5-deoxy-α-L-sorbopyranose derivative **2**,[4] after its treatment with diphenylphorphoryl azide (DPPA)/Ph_3P/DEAD,[5] occurred with total stereocontrol and high yield, as well as its 3-*O*-debenzoylation to **3**, and subsequent oxidation to the corresponding 2,3-diulose **4**, the sodium borohydride reduction of the latter took place with high stereoselectivity but by the α-face regenerating **3**.[6]



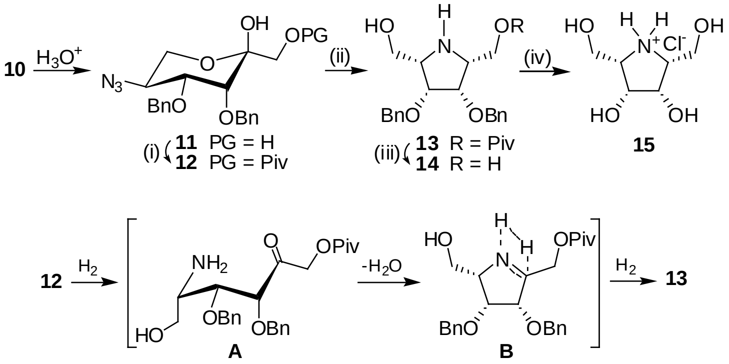
Scheme 2. Synthesis of **3** from **1**. Reagents and conditions: (i) Ph_3P/DEAD/$(PhO)_2PON_3$/THF; (ii) NaMeO/MeOH; (iii) Dess–Martin periodinane/Cl_2CH_2; (iv) $NaBH_4$/MeOH.

On the basis of the above results, an alternative synthetic route was explored (see Scheme 3). Thus, **1** was straightforwardly transformed into the corresponding 5-*O*-methanesulfonyl derivative **5**,[4] which was de-*O*-benzoylated to **6** by standard Zemplen conditions without observing any substitution or elimination of the mesyloxy group at C(5). Oxidation of **6** with the Dess–Martin reagent gave the not fully characterized 2,3-diulose **7**, which was exclusively reduced to 4-*O*-benzy1-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-β-D-psicopyranose (**8**). Reaction of **8** with lithium azide in DMF gave 5-azido-4-*O*-benzy1-5-deoxy-1,2-*O*-isopropylidene-α-L-tagatopyranose (**9**), which was finally benzylated to the required **10**.

Deacetonation of **10** in acid medium (see Scheme 4) yielded the corresponding free hexulose **11** that was shown as the crystalline α-epimer in a $^2C_5$ conformation with H(4,5,6ax) in trans-diaxial disposition in accordance with the $J_{4,5}$ and $J_{5,6ax}$ values of 10.0 and 11.2 Hz, respectively. Reaction of **11** with pivaloyl chloride gave in a highly regioselective manner 5-azido-3,4-di-*O*-benzyl-5-deoxy-1-*O*-pivaloyl-α-L-tagatopyranose (**12**). Hydrogenation of **12** under the presence of Raney nickel catalyst occurred in moderate yield but with high stereoseletivity affording (2*R*,3*S*,4*R*,5*S*)-3,4-dibenzyloxy-2,5-bis(hydroxylmethyl)-2′-*O*-pivaloyl-pyrrolidine (**13**). Formation of **13** must occur through the intermediate aminocarbonyl sugar **A** that reacted in a fast



Scheme 3. Synthesis of **10** from **1**. Reagents and conditions: (i) MeOH/MeONa (cat.), rt; (ii) Dess–Martin/Cl_2CH_2, rt; (iii) $NaBH_4$/MeOH, 0 °C; (iv) LiN_3/DMF, 100 °C; (v) NaH/DMF/BnBr, rt.



Scheme 4. Synthesis of polyhydroxylated pyrrolidines **13–15**. Reagents and conditions: (i) PivCl/TEA/Cl_2CH_2, rt; (ii) Raney Ni/H_2/MeOH; (iii) NaMeO/MeOH; (iv) 10% Pd–C/H_2/MeOH/HCl.

intramolecular process to its cyclic imine intermediate **B**, which was finally hydrogenated to **13**. The stereochemistry of **13** could be easily established after its 2′-de-*O*-acylation to **14**, which ^{1}H- and ^{13}C NMR spectra contained signals only consistent with the presence of a symmetry plane in the molecule and hence with a D-*galacto* configuration in **13**. The total removal of the protection group in **14** yielded (2*R*,3*S*,4*R*,5*S*)-3,4-dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine hydrochloride [2,5-dideoxy-2,5-imino-D-galactitol (DGADP)] (**15**), which analytical and spectroscopic data were in agreement with those previously reported.[7] Compound **15** has been also described as the free base.[8]

Comments merit the high stereoselectivity found in the catalytic hydrogenation of intermediate Δ^1-pyrroline **B** (see Scheme 4), where the entry of the hydrogen molecule took place by the β-face resulting in a cis-disposition for all substituents. These results are in accordance with those previously reported, where the authors[9] stated that in five-membered ring systems the stereochemistry at the new stereogenic centre [C(2)] is controlled by that existing at C(4), in such a way that the substituents at both carbon atoms resulted cis-positioned.

Compound **15** was reported[8a] as a potent inhibitor of α-galactosidase from coffee bean with K_i 5×10^{-8} M.

3. Conclusions

D-Fructose is an appropriate chiral starting material for the stereoselective synthesis of orthogonally protected polyhydroxylated pyrrolidines alkaloids. Highly diastereoselective hydrogenation of a 5-azido-5-deoxy-α-L-tagatose derivative is an excellent synthetic route to the partially protected target molecule DGADP.

4. Experimental

4.1. General procedures

Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The ^{1}H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300, and ARX-400 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin-Elmer 782 instrument and mass spectra with a Micromass Mod. Platform II and Autospec-Q mass spectrometers. Optical rotations were measured for solutions in $CHCl_3$ (1-dm tube) with a Jasco DIP-370 polarimeter. TLC was performed on precoated E. Merck silica gel 60 F_{254} aluminium sheets with detection by charring with H_2SO_4 or employing a mixture of 10% ammonium molybdate (w/v) in 10% aqueous sulphuric acid containing 0.8% cerium sulphate (w/v) and heating. Column chromatography was performed on silica gel (E. Merck, 7734). The no crystalline compounds, for which elemental analyses were not obtained, were shown to be homogeneous by chromatography and characterized by NMR spectroscopy and FAB-HRMS with thioglycerol matrix.

4.1.1. 5-Azido-3-*O*-benzoyl-4-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-L-sorbopyranose (2). To an ice-water cooled and stirred solution of 3-*O*-benzoyl-4-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose[3] (**1**, 1.1 g, 3.6 mmol) in dry THF (30 mL) were consecutively added triphenylphosphine (1 g, 3.8 mmoL), a 40% solution of DEAD in toluene (1.75 mL, 3.8 mmol) and after 10 min DPPA (1 mL, 4.6 mmol). The mixture was allowed to reach room temperature and then left overnight. TLC (3:2, ether/hexane) then revealed a new faster running compound. The mixture was concentrated, supported on silica gel and then submitted to chromatography (1:3, ether/hexane) to afford pure crystalline **2** (1.23 g, 78%), which analytical and spectroscopy data were in accordance with those previously reported.[4]

4.1.2. 4-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-β-D-fructopyranose (6). To a solution of 3-*O*-benzoyl-4-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-β-D-fructopyranose[4] (**5**, 4.93 g, 10 mmol) in anhydrous methanol (20 mL) was treated with 0.1 M NaOMe in methanol (5 mL) overnight. TLC (4:1, ether/hexane) then revealed the absence of **5** and the presence of a slower-running compound. The reaction mixture was neutralized with AcOH, concentrated and the residue dissolved in Cl_2CH_2 (25 mL) washed with water and concentrated again. Flash chromatography (1:1, ether/hexane) of the residue afforded pure syrupy **6** (3.67 g, 94%); $[\alpha]_\mathrm{D}^{26}$ -150 (*c* 1.1); IR (neat): υ 3520 cm^{-1} (OH). ^{1}H NMR (300 MHz): δ 7.40–7.30 (m, 5H, Ph), 5.10 (dt, 1H, H-5), 4.82 and 4.68 (2d, 2H, $J=11.0$ Hz, CH_2Ph), 4.21 and 4.02 (2d, 2H, $J_{1,1'}=8.8$ Hz, H-1,1′), 4.00 (dd, 1H, $J_{5,6}=1.6$ Hz, $J_{6,6'}=13$ Hz, H-6), 3.94 (dd, 1H, $J_{5,6'}=1.6$ Hz, H-6′), 3.86 (d, 1H, $J_{3,4}=9.8$ Hz, H-3), 3.69 (dd, 1H, $J_{4,5}=3.2$ Hz, H-4), 3.02 (s, 3H, Ms), 1.90 (br s, 1H, OH), 1.49 and 1.44 (2s, 6H, CMe_2). ^{13}C NMR: δ 137.27, 128.68, and 128.28 (Ph), 112.37 (CMe_2), 105.71 (C-2), 77.46 (C-4), 76.79 (C-5), 72.94 (CH_2Ph), 71.99 (C-1), 63.12 (C-6), 39.11 (Ms), 26.57 and 26.31 (CMe_2). HRMS: *m/z* 411.1088 $[M^+ + Na]$. For $C_{17}H_{24}O_8NaS$ 411.1089 (deviation +0.3 ppm).

4.1.3. 4-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-β-D-psicopyranose (8). To a stirred suspension of Dess–Martin periodinane (5.93 g, 13.9 mmol) in dry CH_2Cl_2 (25 mL) was added dropwise a solution of **6** (4 g, 10.3 mmol) in the same solvent (25 mL) under Ar. The mixture was stirred at room temperature overnight. TLC (4:1, ether/hexane) then revealed the presence of a faster-running product. The reaction mixture was filtered and the filtrate washed with 10% aqueous Na_2CO_3, brine and water, then concentrated. The residue was percolated (3:2, ether/hexane) through a short column of silica gel to afford fractions containing presumably ketone **7** [3.8 mg, 96%; IR (neat): υ 1757 cm^{-1}], that was used in the next step.

To a stirred and ice-water cooled solution of **7** (3.8 g, 9.8 mmol) in dry methanol (25 mL) $NaBH_4$ (0.44 g, 11.5 mmol) was added portionwise. After 1 h, TLC (4:1, ether/hexane) showed no ketone **7** and the presence of a new product of lower mobility. The reaction mixture was neutralized with AcOH, concentrated and the residue was dissolved in Cl_2CH_2, washed with water then concentrated.

Flash chromatography (1:1, ether/hexane) afforded crystalline **8** (2.9 g, 76%); mp 93–94 °C (from ether/hexane); $[\alpha]_D^{28}$ −97 (*c* 1.2); ν (KBr) 3549 (OH), 3089, 726 and 696 cm^{-1} (aromatic). ^{1}H NMR (300 MHz): δ 7.40–7.30 (m, 5H, Ph), 4.97 (dt, 1H, H-5), 4.73 and 4.66 (2d, 2H, J=11.3 Hz, CH$_2$Ph), 4.20 and 4.14 (2d, 2H, $J_{1,1'}$=9.6 Hz, H-1,1′), 4.04 (d, 2H, $J_{5,6}$=1.7 Hz, H-6,6), 3.88–3.83 (m, 2H, H-3,4), 3.04 (s, 3H, Ms), 1.46 and 1.37 (2s, 6H, CMe$_2$). ^{13}C NMR: δ 136.98, 128.69, 128.32, and 128.12 (Ph), 112.68 (*C*Me$_2$), 105.47 (C-2), 77.06 (C-5), 73.62 (C-1), 71.90 (C-4), 70.66 (*C*H$_2$Ph), 70.40 (C-3), 63.33 (C-6), 39.03 (Ms), 26.61 and 26.42 (C*Me*$_2$). Anal. Calcd for $C_{17}H_{24}O_8S$: C, 52.57; H, 6.23; S, 8.25. Found: C, 52.86; H, 6.53; S, 8.07.

4.1.4. 5-Azido-4-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-L-tagatopyranose (9). A stirred solution of **8** (3.8 g, 9.7 mmol) and lithium azide (1.43 g, 29.2 mmol) in dry DMF (20 mL) was heated at 100 °C for 2 h. TLC (4:1, ether/hexane) then revealed a faster-running compound. The mixture was concentrated to a residue that was dissolved in ether (40 mL), washed with brine and concentrated. Flash chromatography (2:1, ether/hexane) of the residue afforded crystalline **9** (2.7 g, 82%); mp 74–76 °C (from ether–hexane); $[\alpha]_D^{26}$ −112.5 (*c* 0.9); IR (neat): ν 3492 (OH), 3064 (aromatic), 2105 (N$_3$), 1384 and 1372 (CMe$_2$), 752 and 699 cm^{-1} (aromatic). ^{1}H NMR (400 MHz): δ 7.45–7.30 (m, 5H, Ph), 4.73 and 4.67 (2d, 2H, J=11.2 Hz, CH$_2$Ph), 4.11 and 4.02 (2d, 2H, $J_{1,1'}$=9.4 Hz, H-1,1′), 3.87–3.73 (m, 4H, H-3,4,5,6eq), 3.51 (t, 1H, $J_{5,6ax}$=$J_{6ax,6eq}$=11.1 Hz, H-6ax), 1.46 and 1.37 (2s, 6H, CMe$_2$). ^{13}C NMR: δ 137.15, 128.75, 128.40, and 128.22 (Ph), 112.29 (*C*Me$_2$), 104.54 (C-2), 78.96 (C-3), 73.26 (*C*H$_2$Ph), 72.31 (C-1), 69.98 (C-4), 61.60 (C-6), 57.10 (C-5), 26.60 and 26.44 (C*Me*$_2$). HRMS: *m/z* 358.1377 [M$^+$+Na]. For $C_{16}H_{21}N_3O_5Na$ 358.1379 (deviation +0.4 ppm).

4.1.5. 5-Azido-3,4-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-L-tagatopyranose (10). To a stirred suspension of NaH (60% oil dispersion, 387 mg, 16.1 mmol) in dry DMF (5 mL), compound **9** (2.7 g, 8.0 mmol) in the same solvent (10 mL) was added at room temperature. After 15 min, the mixture was cooled (ice-water), benzyl bromide (1.2 mL, 10.4 mmol) was added and the mixture was allowed to reach room temperature, then left for 4 h. TLC (1:2, ether/hexane) then showed the presence of a faster-running compound. The mixture was cautiously poured into ice-water, and extracted with ether (4×30 mL). The combined extracts were washed with brine, water, and concentrated. Flash chromatography (1:5, ether/hexane) of the residue gave **10** (2.9 g, 85%) as a colourless syrup; $[\alpha]_D^{26}$ −65 (*c* 1); ν (neat) 3031 (aromatic), 2110 (N$_3$), 1382 and 1372 (CMe$_2$), 736 and 697 cm^{-1} (aromatic). ^{1}H NMR (300 MHz): δ 7.46–7.26 (m, 10H, 2 Ph), 4.93 and 4.57 (2d, 2H, J=11.5 Hz, CH$_2$Ph), 4.80 and 4.75 (2d, 2H, J=11.4 Hz, CH$_2$Ph), 4.01 (dt, 1H, H-5), 3.96 and 3.73 (2d, 2H, $J_{1,1'}$=9.3 Hz, H-1,1′), 3.83 (dd, 1H, $J_{4,5}$=9.7 Hz, H-4), 3.79 (dd, 1H, $J_{5,6eq}$=5.5 Hz, $J_{6ax,6eq}$=11.1 Hz, H-6eq), 3.66 (d, 1H, $J_{3,4}$=2.6 Hz, H-3), 3.49 (t, 1H, $J_{5,6ax}$=11.1 Hz, H-6ax), 1.43 and 1.31 (2s, 6H, CMe$_2$). ^{13}C NMR: δ 137.95, 137.73, 128.65, 128.53, 128.25, 128.12, and 128.06 (Ph), 112.21 (*C*Me$_2$), 105.21 (C-2), 80.28 (C-3), 76.92 (C-4), 74.70 and 72.96 (*C*H$_2$Ph), 73.42 (C-1), 62.30 (C-6), 57.98 (C-5), 26.70 and 26.44 (C*Me*$_2$). HRMS: *m/z* 448.1842 [M$^+$+Na]. For $C_{23}H_{27}N_3O_5Na$ 448.1848 (deviation +1.5 ppm).

4.1.6. 5-Azido-3,4-di-*O*-benzyl-5-deoxy-α-L-tagatopyranose (11). A solution of **10** (3.74 g, 8.8 mmol) in 70% aqueous TFA (10 mL) was kept at room temperature for 24 h. TLC (2:1, ether/hexane) then revealed a slower running compound. The mixture was concentrated and repeatedly codistilled with water and then dissolved in dichloromethane, washed with 10% aqueous sodium carbonate and water, then concentrated. Column chromatography (1:5→1:1, ether/hexane) gave pure crystalline **11** (2.62 g, 78%) as α-anomer; mp 83–85 °C; $[\alpha]_D^{25}$ −36 (*c* 0.9); ν (KBr) 3386 (OH), 3088 (aromatic), 2106 (N$_3$), 749 and 699 cm^{-1} (aromatic). ^{1}H NMR (300 MHz): δ 7.45–7.28 (m, 10H, 2 Ph), 4.90 and 4.54 (2d, 2H, J=11.5 Hz, CH$_2$Ph), 4.78 and 4.74 (2d, 2H, J=11.9 Hz, CH$_2$Ph), 4.03 (br dt, 1H, H-5), 3.93 (dd, 1H, $J_{3,4}$=2.5 Hz, $J_{4,5}$=10.0 Hz, H-4), 3.78 (d, 1H, H-3), 3.78 and 3.21 (2d, 2H, $J_{1,1'}$=11.6 Hz, H-1,1′), 3.76 (dd, 1H, $J_{5,6eq}$=5.6 Hz, $J_{6ax,6eq}$=11.2 Hz, H-6eq), 3.55 (t, 1H, $J_{5,6ax}$=11.2 Hz, H-6ax), 3.42 (br s, 1H, OH). ^{13}C NMR (inter alia): δ 97.54 (C-2), 79.87 (C-3), 75.17 (C-4), 74.78 and 72.76 (*C*H$_2$Ph), 66.39 (C-1), 61.91 (C-6), 58.25 (C-5). HRMS: *m/z* 408.1540 [M$^+$+Na]. For $C_{20}H_{23}N_3O_5Na$ 408.1535 (deviation −1.0 ppm).

4.1.7. 5-Azido-3,4-di-*O*-benzyl-5-deoxy-1-*O*-pivaloyl-α-L-tagatopyranose (12). To an ice-water cooled and stirred solution of **11** (0.5 g, 1.3 mmol) in dry Cl$_2$CH$_2$ (15 mL) were added TEA (200 μL, 1.5 mmol) and pivaloyl chloride (175 μL, 1.5 mmol) and the mixture was left at room temperature for 5 h. TLC (2:1, ether/hexane) then showed a faster-running compound. MeOH (0.5 mL) was added and after 15 min the reaction mixture was washed with water, then concentrated to a residue that was submitted to flash-chromatography (1:2, ether/hexane) to afford syrupy **12** (535 mg, 88%) as a colourless syrup; $[\alpha]_D^{24}$ −30 (*c* 1); ν (neat) 3440 (OH), 3065 (aromatic), 2110 (N$_3$), 1734 (ester C=O), 734 and 698 cm^{-1} (aromatic). ^{1}H NMR (300 MHz): δ 7.45–7.25 (m, 10H, 2 Ph), 4.92 and 4.56 (2d, 2H, J=11.0 Hz, CH$_2$Ph), 4.79 and 4.72 (2d, 2H, J=11.5 Hz, CH$_2$Ph), 4.39 and 4.02 (2d, 2H, $J_{1,1'}$=11.7 Hz, H-1.1′), 4.01 (dt, 1H, H-5), 3.91 (dd, 1H, $J_{3,4}$=2.6 Hz, $J_{4,5}$=9.9 Hz, H-4), 3.76 (dd, 1H, $J_{5,6eq}$=5.5 Hz, $J_{6ax,6eq}$=11.1 Hz, H-6eq), 3.75 (d, 1H, H-3), 3.58 (t, 1H, $J_{5,6ax}$=11.1 Hz, H-6ax), 3.18 (br s, 1H, HO), and 1.20 (s, 9H, CMe$_3$). ^{13}C NMR (inter alia): δ 179.49 (ester C=O), 97.97 (C-2), 79.52 (C-4), 75.13 and 72.83 (2 *C*H$_2$Ph), 74.93 (C-3), 65.78 (C-6), 61.81 (C-6), 58.00 (C-5), 39.02 (C*Me*$_3$) and 27.24 (*C*Me$_3$). HRMS: *m/z* 492.2112 [M$^+$+Na]. For $C_{25}H_{31}N_3O_6Na$ 492.2111 (deviation −0.3 ppm).

4.1.8. Hydrogenation of 12. Compound **12** (1.4 g, 3 mmol) in MeOH (40 mL) was hydrogenated at 60 psi over wet Raney nickel (500 mg, Fluka) for 5 h. TLC (5:1, ether/methanol) then revealed the presence of a slower-running compound. The catalyst was filtered off, washed with MeOH, and the combined filtrate and washings were concentrated to a residue that was submitted to column chromatography (ether→10:1, ether/methanol) to afford syrupy (2*R*,3*S*,4*R*,5*S*)-3,4-dibenzyloxy-2,5-bis(hydroxymethyl)-2′-*O*-pivaloylpyrrolidine (**13**, 680 mg, 53%); $[\alpha]_D^{26}$ −11 (*c* 0.5); ν (neat) 3268 (OH, NH), 3064, (aromatic), 1726 (ester C=O), 736 and 698 cm^{-1} (aromatic). ^{1}H NMR (300 MHz): δ 7.40–7.24 (m, 10H, 2 Ph), 4.76 and 4.63 (2d, 2H, $J=11.2$ Hz, CH_2Ph), 4.69 and 4.56 (2d, 2H, $J=11.8$ Hz, CH_2Ph), 4.31 (dd, 1H, $J_{2,2'a}=6.4$ Hz, $J_{2'a,2'b}=11.1$ Hz, H-2′a), 4.22 (dd, 1H, $J_{2,2'b}=7.0$ Hz, H-2′b), 4.14 (dd, 1H, $J_{3,4}=4.0$ Hz, $J_{4,5}=7.6$ Hz, H-4), 4.01 (t, 1H, $J_{2,3}=4.2$ Hz, H-3), 3.82 (dd, 1H, $J_{5,5'a}=4.5$ Hz, $J_{5'a,5'b}=11.5$ Hz, H-5′a), 3.65 (dd, 1H, $J_{5,5'b}=4.8$ Hz, H-5′b), 3.47 (dt, 1H, H-5), 3.41 (dt, 1H, H-2), 2.35 (br s, 1H, OH), and 1.18 (s, 9H, CMe_3). ^{13}C NMR (inter alia): δ 178.44 ($\mathit{C}OCMe_3$), 81.46 (C-4), 78.36 (C-3), 74.05 and 73.24 (2 $\mathit{C}H_2Ph$), 64.29 (C-2′), 61.64 (C-5′), 58.82 (C-5), 57.69 (C-2), 38.85 ($CO\mathit{C}Me_3$), and 27.30 ($COC\mathit{Me}_3$). HRMS: *m*/*z* 450.2250 [M^++Na] for $C_{25}H_{33}NO_5Na$ 450.2256 (deviation +1.4 ppm).

4.1.9. (*2R*,*3S*,*4R*,*5S*)-3,4-Dibenzyloxy-2,5-bis(hydroxymethyl)pyrrolidine (14). A solution of **13** (680 mg, 1.59 mmol) in anhydrous MeOH (5 mL), was treated with 0.5 M MeONa in the same solvent (0.3 mL) for 6 h at room temperature. TLC (1.5:1, ether/methanol) then showed the presence of a more polar compound. The reaction mixture was concentrated and the residue submitted to column chromatography (5:2, ether/methanol) to yield **14** (330 mg, 61%) as a colourless syrup; ν (neat) 3324 (OH, NH), 3088, 736 and 697 cm^{-1} (aromatic). ^{1}H NMR (300 MHz): δ 7.38–7.25 (m, 10H, 2 Ph), 4.70 and 4.57 (2d, 4H, $J=11.7$ Hz, 2 CH_2Ph), 4.07 (m, 2H, H-3,4), 3.92 (br s, 2H, OH,NH), 3.86 (dd, 2H, $J_{2,2'a}=J_{5,5'a}=6.0$ Hz, $J_{2'a,2'b}=J_{5'a,5'b}=11.7$ Hz, H-2′a,5′a), 3.71 (dd, 2H, $J_{2,2'b}=J_{5,5'b}=4.7$ Hz, H-2′b,5′b), and 3.38 (br q, 2H, H-2,5). ^{13}C NMR: δ 137.68, 128.64, 128.07, and 127.71 (Ph), 79.85 (C-3,4), 73.64 (2 $\mathit{C}H_2Ph$), 61.33 (C2′,5′), and 59.76 (C-2,5). HMRS: *m*/*z* 366.1687 [M^++Na] for $C_{20}H_{25}NO_4Na$ 366.1681 (deviation −1.4 ppm).

4.1.10. (*2R*,*3S*,*4R*,*5S*)-3,4-Dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine hydrochloride [2,5-dideoxy-2,5-imino-D-galactitol (DGADP, 15)]. Compound **14** (94 mg, 0.27 mmol) was hydrogenated in MeOH (5 mL) and concd HCl (5 drops) over 10% Pd–C (50 mg) in an H_2 atmosphere overnight. TLC (3:3:0.5, ether/methanol/TEA) then showed the presence of a compound of lower mobility. The catalyst was filtered off, washed with MeOH and the combined filtrate and washings concentrated to a residue that was repeatedly washed with Cl_2CH_2 to yield **15** hydrochloride (30 mg, 56%) as a colourless foam. ^{1}H NMR (400 MHz, MeOH-d_4): δ 4.37 (br d, 2H, $J=5.0$ Hz, H-3,4), 3.94 (dd, 2H, $J_{2,2'a}=J_{5,5'a}=5.0$ Hz, $J_{2'a,2'b}=J_{5'a,5'b}=11.9$ Hz H-2′a,5′a), 3.89 (dd, 2H, $J_{2,2'b}=J_{5,5'b}=8.2$ Hz, H-2′b,5′b), and 3.65 (m, 2H, H-2,5). ^{13}C NMR: δ 71.57 (C-3,4), 63.22 (C-2,5), and 59.29 (C-2′,5′). Lit.[7] ^{1}H NMR (500 MHz, D_2O): δ 3.76–3.81 (m, 2H), 3.92 (dd, 2H, $J=8.8$, 12.2 Hz), 4.01 (dd, 2H, $J=4.9$, 12.2 Hz), 4.51 (d, $J=4.9$ Hz). ^{13}C NMR: δ 60.66, 64.30, 72.86.

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