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Polyhydroxylated pyrrolidines: synthesis from D-fructose of new tri-orthogonally protected 2,5-dideoxy-2,5-iminohexitols☆

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Abstract—The readily available 3-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose (**2**) was transformed into its 5-*O*- (**3**) and 4-*O*-benzoyl (**4**) derivative. Compound **4** was straightforwardly transformed into 5-azido-4-*O*-benzoyl-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose (**7**) via the corresponding 5-deoxy-5-iodo-α-L-sorbopyranose derivative **6**. Cleavage of the acetonide in **7** to give **8**, followed by regioselective 1-O-silylation to **9** and subsequent catalytic hydrogenation gave a mixture of (2*S*,3*R*,4*R*,5*R*)- (**10**) and (2*R*,3*R*,4*R*,5*R*)-4-benzoyloxy-3-benzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (**12**) that was resolved after chemoselective N-protection as their Cbz derivatives **11** and **1a**, respectively. Stereochemistry of **11** and **1a** could be determined after total deprotection of **11** to the well known DGDP (**13**). Compound **2** was similarly transformed into the tri-orthogonally protected DGDP derivative **18**.

1. Introduction

Figure 1 shows the retrosynthesis of different naturally occurring hyacinthacines[2] from tri-orthogonally protected derivatives (**1a** and **1b**) of 2,5-dideoxy-2,5-imino-D-mannitol (DMDP), a polyhydroxylated pyrrolidinic alkaloid also present in different natural sources.[3] On the other hand, our group has reported on a highly stereocontrolled synthesis of **1b**[4] from the common sugar D-fructose and its use, as source of chirality and functionalization, in the preparation of protected derivatives of hyacinthacines A_2[2g] and A_3[2i] as well. These pyrrolizidines could also be excellent intermediates for the preparation of the recently discovered hyacinthacines A_1[2b,5] and A_6,[2c] the latter not described so far, being only necessary an inversion of the configuration at C(1)[6] in the former target molecules. For this purpose, it is necessary the presence in such position of a functional group that could be manipulated without affecting the other ones, in our case the benzoyloxy was the group of choice.

Extension of the above methodology would allow the synthesis of many other hyacinthacines such as those displayed in Figure 1.

According to Figure 2, compound **1a** could be synthesized through the intermediate 5-azido-4-*O*-benzoyl-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose (**7**), starting from the readily available D-fructose after appropriated protection and functional groups interchange.

Thus, continuing with our efforts on this topic, we reported herein a synthetic route for the requisite **1a** and that of its C(5) epimer (**18**) as well.

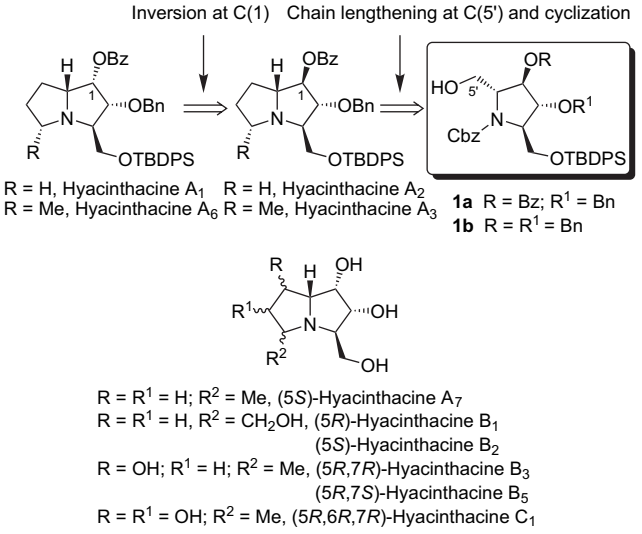

Figure 1. Retrosynthetic analysis and structures of several naturally occurring hyacinthacines from tri-orthogonally protected derivatives of DMDP (**1a** and **1b**).

☆ Part V of the series. For Part IV, see Ref. 1.

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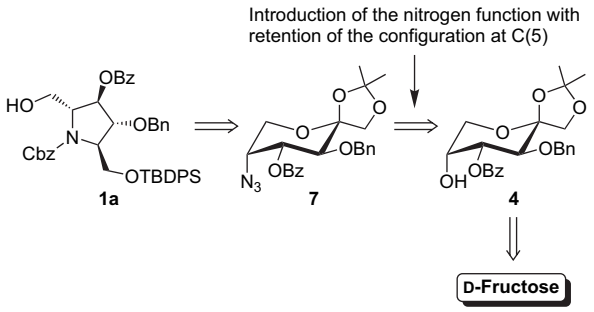
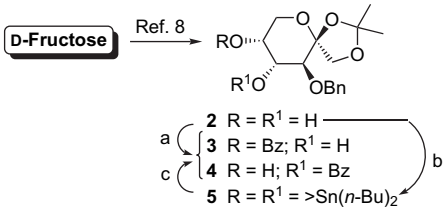


Figure 2. Retrosynthesis of partially protected pyrrolidine **1a** from D-fructose.

2. Results and discussion

2.1. Synthesis of tri-orthogonally protected DMDP derivatives from D-fructose

In order to synthesize the key intermediate **7**, the protected derivative of D-fructose, 4-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose (**4**) was required, according to the synthetic route outlined in Scheme 1. Thus, the well known 3-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose (**2**)[7] was chosen as the starting material. In a first attempt, we tried the low temperature regioselective benzoylation of compound **2** but on the contrary to previous results,[8] the corresponding 5-*O*-benzoylated derivative (**3**) was the main isolated (88% yield) product, whereas the requisite 4-*O*-regioisomer (**4**) was produced in a 12% yield.

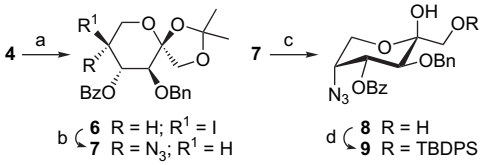


Scheme 1. Synthesis of **3** and **4**. Reagents and conditions: (a) BzCl/Py/DCM/−65 °C; (b) *n*-Bu_2SnO/MeOH/Δ; (c) BzCl/TEA/dioxane, 0 °C.

This result could be attributed to the change of the O(3) protecting group, benzyl instead of benzoyl,[8] and not to the change of the reaction conditions, since benzoylation of the 3-*O*-benzoyl derivative under condition a of Scheme 1, gave results similar to those previously reported.[8c]

On the basis of the above results, an alternative approach was essayed, consisting in the formation of the 4,5-*O*-stannylene derivative (**5**) followed by its regioselective ring opening at the equatorial position [O(4)] with benzoyl chloride in dioxane at 0 °C, resulting in the formation of the required 4-*O*-benzoyl derivative **4** (57% yield). Change of the ring opening reaction conditions (DMF at −60 °C) slightly lowered the yield of **4**.

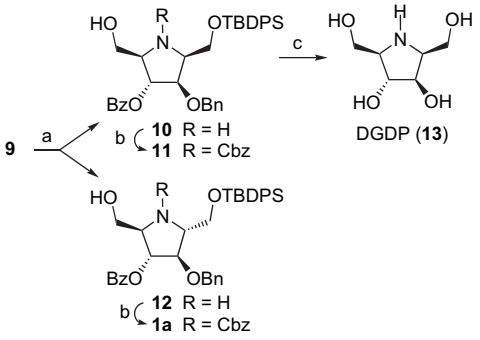
According to Scheme 2, the reaction of **4** under modified Garegg's conditions,[9] caused the substitution of the hydroxyl group at C(5), with concomitant inversion in configuration, to afford the corresponding 5-deoxy-5-iodo-α-L-*sorbo* derivative **6**, which had analytical and spectroscopic data according to the expected structure. Treatment of **6** with lithium azide in DMF effected S_N2 substitution to yield 5-azido-4-*O*-benzoyl-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose (**7**). Cleavage of 1,2-*O*-isopropylidene group in **7** by treatment with 60% aq TFA afforded 5-azido-4-*O*-benzoyl-3-*O*-benzyl-5-deoxy-β-D-fructopyranose **8**. Reaction of **8** with *tert*-butyldiphenylchlorosilane catalyzed by imidazole (Im) took place mainly at the primary hydroxyl group affording the corresponding 1-*O*-silylated derivative **9**. Compound **8** exists in a β-D-pyranose form, according to the δ value (98.41 ppm) for the C(2) resonance signal,[10] in a $^2C_5$ conformation, with all bulkiest groups occupying equatorial positions, with H(3,4) and H(4,5) in *trans*-diaxial and *cis*-axial–equatorial dispositions in accordance with the $J_{3,4}$ and $J_{4,5}$ values of 9.8 and 3.5 Hz, respectively, with the anomeric effect operating at the same time.



Scheme 2. Synthesis of partially protected 5-azido-5-deoxy-D-fructose derivatives. Reagents and conditions: (a) I_2/Ph_3P/Im/PhMe, 110 °C; (b) LiN_3/DMF, 100 °C; (c) 60% TFA/H_2O, rt; (d) TBDPSCl/DMF/Im, rt.

Catalytic (Raney nickel) hydrogenation of **9** caused the reduction of 5-azido group to the corresponding 5-amino function, which internally condensed with the carbonyl group at C(2) to produce a Δ^1-pyrroline (**A**, not isolated but detected by TLC), which is finally hydrogenated to the expected partially *O*-protected pyrrolidines **10** (minor) and **12** (major). Resolution of **10** and **12** could be achieved, after chemoselective N-protection as the Cbz derivatives **11** and **1a** (in an ~1:2.2 ratio), respectively.

The (*S*)-configuration of the new C(2) stereogenic centre in **11**, and hence (*R*)-configuration in **12**, could be easily determined through its total deprotection to the well known 2,5-imino-2,5-dideoxy-D-glucitol (DGDP, **13**)[3a,11] (Scheme 3).



Scheme 3. Synthesis and configurational assignment of pyrrolidines **10** and **12**. Reagents and conditions: (a) H_2/Raney Ni/MeOH, 70 psi, rt; (b) CbzCl/K_2CO_3/Me_2CO, rt; (c) (i) *n*-$Bu_4N^+F^-\cdot 3H_2O$/THF, rt; (ii) MeONa (cat.)/MeOH, rt; (iii) HCl/H_2/10% Pd/C, rt; (iv) Amberlite IR-400 (OH^-).

The stereoselectivity resulted in the hydrogenation of **A**, where **12** was the main isolated pyrrolidine, merits comment (see Fig. 3). Thus, the formation of **12** would be in accordance with our results[4] and those of other authors,[12] where

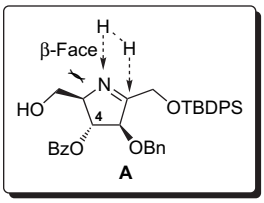


Figure 3.

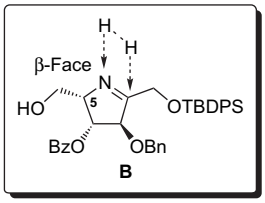


Figure 5.

the preferential addition of hydrogen occurs at the β-face giving a product with the C(2)–C(3)- and C(2)–C(4)-substituent in a *trans*- and *cis*-disposition, respectively, whereas the slight steric hindrance of the hydroxymethyl group at C(5) and the incoming hydrogen molecule would account for the formation of the minor compound **10**, which is a result of an α-addition.

2.2. Synthesis of tri-orthogonally protected DGDP derivatives from D-fructose

In accordance with the retrosynthesis displayed in Figure 4, protected 2,5-imino-2,5-dideoxy-D-glucitol (DGDP) derivative (**18**) could be readily prepared from the intermediate 5-azido-4-*O*-benzoyl-3-*O*-benzyl-5-deoxy-α-L-sorbopyranose (**14**), which could be synthesized from **4** by introducing the azido function at C(5) with a concomitant inversion in the configuration.

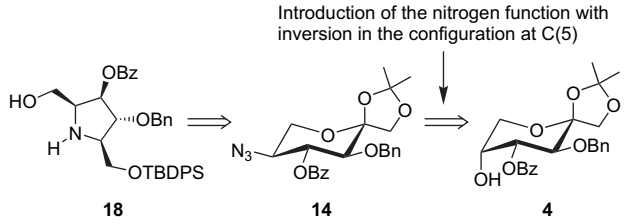
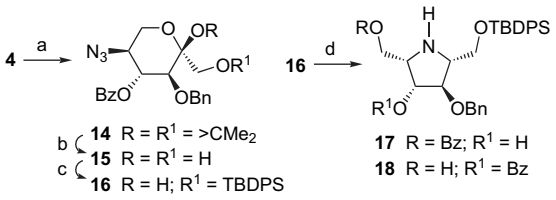


Figure 4. Retrosynthesis of pyrrolidine **18** from **4**.

Reaction of **4** with diphenylphosphorylazide (DPPA) under Mitsunobu's conditions (see Scheme 4) gave **14**. The structure of **14** was established on the basis of its analytical and spectroscopic data. Thus, the IR spectrum contained an absorption band (2105 cm^{-1}) for the azido function at C(5), whereas the $J_{3,4}=J_{4,5}$ value (9.6 Hz) clearly indicated a *trans*-diaxial disposition for H(3,4,5) and, hence, that an inversion in the configuration at that position had took place.



Scheme 4. Synthesis of **17** and **18** from **4**. Reagents and conditions: (a) Ph_3P/DIAD/DPPA/THF, 0 °C→rt; (b) 70% TFA/H_2O, rt; (c) TBDPSCl/Im/DMF, rt; (d) Raney Ni/H_2/MeOH, 60 psi.

Reaction of **14** with aq TFA caused the removal of 1,2-*O*-isopropylidene group affording the free hexulose **15**, presumably as the pyranosic α-anomer in the most stable $^2C_5$ conformation, with all bulky groups in equatorial disposition, according to its ^1H and ^{13}C NMR spectra. Regioselective silylation at O(1) in **15** occurred after conventional treatment with TBDPSCl giving **16** that was finally hydrogenated (Raney nickel) to afford in a highly stereoselective manner a mixture of the expected tri-orthogonally protected 2,5-dideoxy-2,5-imino-D-glucitol (**18**) and its O(4)→O(5′) benzoyl group migration product **17** (see Scheme 4). The chemical shift of H(4) in **18** [H(3) in **17**], was crucial in order to establish the position of the benzoyl group, thus whereas the resonance signal for H(4) in **18** appeared as expected at 5.54 ppm, consequence of the deshielding effect of the geminal benzoyloxy group, such resonance signal appeared at 4.13 ppm in **17** (not deshielding effect).

The stereoselectivity found in the catalytic hydrogenation of intermediate Δ^1-pyrroline **B** was surprisingly high, with the exclusive entry, in this case, of the hydrogen molecule through the β-face (see Fig. 5), which is now favoured by the α-disposition of the hydroxymethyl group at C(5). This result was in agreement with other previously reported results by our group.[11] On the other hand according to Figure 6, the above benzoyl group migration would be due to the own basic character of **18**, that could act as the required **B** promoter, and due to the *cis* disposition of the benzoyloxy and hydroxymethyl groups, this is supported by the fact that such benzoyl group migration was not observed in **1a**, where involved functional groups were in a *trans* disposition.

The use of **18** as synthetic key intermediate for the preparation of the more complex polyhydroxylated pyrrolizidic alkaloids requires its N-protection and in this context, compound **18** was treated with CbzCl under reaction conditions (MeOH/TEA) that assure such protection, but surprisingly two products, the expected one (**20**, minor) and that from the above mentioned *O*-benzoyl migration (**19**, major) could be isolated from the reaction mixture (Scheme 5). The same results were achieved when **17** was subjected to the same procedure. Compounds **19** and **20** were convergently transformed into **21**. Any other N-protection (benzylation and

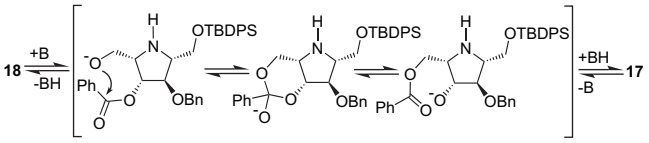
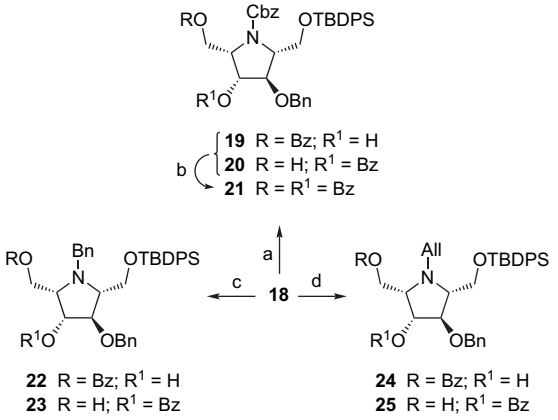


Figure 6. Formation of **17** through an O(4)→O(5′)-benzoyl group migration in **18**.

allylation) of **18**, even changing the reaction conditions, always afforded similar results (see Section 4).



Scheme 5. Orthogonal protection of polyhydroxylated pyrrolidine **18**. Reagents and conditions: (a) CbzCl/TEA/MeOH, rt; (b) BzCl/DCM/TEA, rt; (c) BnBr/DBU/acetonitrile, rt; (d) AllBr/K_2CO_3/Me_2CO, rt.

3. Conclusions

D-Fructose is an appropriate chiral starting material for the stereoselective synthesis of tri-orthogonally protected polyhydroxylated pyrrolidine alkaloids. Thus, the highly stereoselective hydrogenation of protected derivatives of 5-azido-5-deoxy-β-D-fructose and 5-azido-5-deoxy-α-L-sorbose, prepared from the above mentioned ketose, is an excellent synthetic route to the target derivatives of 2,5-dideoxy-2,5-imino-D-mannitol (DMDP, **1a**) and its C(5) epimer (DGDP, **18**).

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 ^1H 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% aq sulfuric acid containing 0.8% cerium sulfate (w/v) and heating. Column chromatography was performed on silica gel (E. Merck, 7734). The noncrystalline compounds, for which elemental analyses were not determined, were shown to be homogeneous by chromatography and characterized by NMR spectroscopy and FAB-HRMS with thioglycerol matrix.

4.1.1. 5-*O*-Benzoyl-(3) and 4-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose (4). *Method a*: to a stirred and cooled (−65 °C) solution of 3-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose[7] (**2**, 3.1 g, 10 mmol) and pyridine (2.42 mL, 30 mmol) in anhydrous dichloromethane (DCM, 20 mL) was added a solution of benzoyl chloride (1.28 mL, 11 mmol) in the same solvent (10 mL) dropwise. After 1 h, TLC (ether) showed the presence of two faster-running compounds. The excess of acylating agent was destroyed by the addition of methanol (1 mL) and the reaction mixture was washed with 10% aq hydrochloric acid, water, aq 10% sodium hydrogen carbonate, water and then concentrated. Column chromatography (1:2 ether/hexane) gave first pure **3** (3 g, 88%) as a colourless syrup; $[\alpha]_D^{24}$ −137 (*c* 1.4); *ν* (neat) 3481 (OH), 3064 and 3031 (aromatic), 1719 (CO, Bz), and 710 cm^{-1} (aromatic). ^1H NMR (300 MHz): *δ* 8.07–8.05 and 7.62–7.29 (2m, 10H, 2Ph), 5.41 (m, 1H, H-5), 4.92 and 4.76 (2d, 2H, *J* 11.4 Hz, C*H*$_2$Ph), 4.31 (ddd, 1H, $J_{3,4}$ 9.8, $J_{4,5}$ 3.7, $J_{OH,4}$ 5 Hz, H-4), 4.12 and 3.98 (2d, 2H, $J_{1,1'}$ 8.7 Hz, H-1,1′), 4.08 (dd, 1H, $J_{5,6ax}$ 1.3, $J_{6ax,6eq}$ 13.1 Hz, H-6ax), 3.87 (dd, 1H, $J_{5,6eq}$ 1.8 Hz, H-6eq), 3.78 (d, 1H, H-3), 2.31 (d, 1H, OH-4), 1.49 and 1.45 (2s, 6H, CMe_2). ^{13}C NMR: *δ* 166.52 (*C*OPh), 137.81, 133.25, 129.86, 129.78, 128.47, 128.39, 127.97 and 127.91 (Ph), 112.09 (*C*Me_2), 105.55 (C-2), 76.24, 72.78 and 70.47 (C-3,4,5), 75.14 (C-1), 71.85 (*C*H_2Ph), 62.10 (C-6), 26.80 and 26.11 (C*Me*$_2$). Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.86; H, 6.42.

Second elution gave crystalline **4** (400 mg, 12%); mp 112 °C (from ether/hexane); $[\alpha]_D^{24}$ −156 (*c* 1.4); *ν* (KBr) 3525 (OH), 3063 and 3033 (aromatic), 1723 and 1697 (CO, Bz), 1384 and 1369 (CMe_2), 711 and 696 cm^{-1} (aromatic). ^1H NMR (300 MHz): *δ* 8.07, 7.59 and 7.45 (3m, 5H, Bz), 7.23 (br s, 5H, *Ph*CH_2), 5.50 (dd, 1H, $J_{3,4}$ 10.1, $J_{4,5}$ 3.1 Hz, H-4), 4.83 and 4.62 (2d, 2H, *J* 11.4 Hz, C*H*$_2$Ph), 4.28 (m, 1H, H-5), 4.10 (dd, 1H, $J_{5,6ax}$ 0.8 Hz, H-6ax), 4.07 (d, 1H, H-3), 4.00 and 3.96 (2d, 2H, $J_{1,1'}$ 8.6 Hz, H-1,1′), 3.76 (dd, 1H, $J_{5,6eq}$ 2, $J_{6ax,6eq}$ 12.7 Hz, H-6eq), 2.28 (d, 1H, $J_{5,OH}$ 3.2 Hz, OH-5), 1.50 and 1.40 (2s, 6H, CMe_2). ^{13}C NMR: *δ* 165.53 (*C*OPh), 137.53, 133.36, 129.62, 128.53, 128.31 and 127.75 (Ph), 112.25 (*C*Me_2), 105.79 (C-2), 75.21, 73.57 and 68.30 (C-3,4,5), 71.73 (C-1, *C*H_2Ph), 63.77 (C-6), 26.89 and 26.00 (C*Me*$_2$). Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.39; H, 6.13.

Method b: to a solution of **2** (15.64 g, 50.4 mmol) in anhydrous methanol (100 mL) was added dibutyltin oxide (13.8 g, 55.4 mmol) and the suspension was heated for 7 h under reflux, then concentrated to afford the 3,4-dibutylstannylene derivative (**5**) as a solid foam that was dried under vacuum over P_2O_5 overnight.

To a cooled (0 °C) and stirred solution of **5** and TEA (7.7 mL, 55.4 mmol) in anhydrous dioxane (150 mL) was added a solution of benzoyl chloride (6.4 mL, 55.4 mmol) in the same solvent (30 mL) dropwise. The reaction mixture was left to reach room temperature and stirred for additional 4 h. TLC (ether) then revealed the presence of two new compounds of higher mobility. Methanol (4 mL) was added and after 30 min the mixture was concentrated to a residue that was dissolved in DCM (100 mL) and washed with brine. The organic phase was concentrated and the residue was subjected to flash chromatography (1:1 → 2:1, ether/hexane) to afford first pure **3** (8.71 g, 38%). Second elution gave **4** (13.1 g, 57%).

4.1.2. 4-*O*-Benzoyl-3-*O*-benzyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-L-sorbopyranose (6). To a solution of triphenylphosphine (3.2 g, 12.4 mmol), Im (1.8 g, 24.8 mmol) and iodine (3.1 g, 12.4 mmol) in dry toluene (60 mL) was added **4** (2.54 g, 6.2 mmol) and the mixture was heated at 110 °C for 2 h. TLC (3:2, ether/hexane) then revealed a faster-running compound. The reaction mixture was cooled, washed with 10% aq sodium thiosulfate, brine and then concentrated. Column chromatography (1:1, DCM/hexane) afforded crystalline **6** (2.66 g, 82%); mp 171–173 °C (from ether); $[\alpha]_D^{26}$ −18.3, $[\alpha]_{405}^{26}$ −25.5 (*c* 1); *ν* (KBr) 3089, 3064 and 3032 (aromatic), 1729 (CO, Bz), 1386 and 1373 (CMe_2), 752 and 706 cm^{-1} (aromatic). ^1H NMR (400 MHz): *δ* 8.09, 7.60 and 7.48 (3m, 5H, Bz), 7.21–7.13 (m, 5H, CH_2Ph), 5.83 (t, 1H, $J_{3,4}=J_{4,5}=10.0$ Hz, H-4), 4.63 and 4.47 (2d, 2H, *J* 11.6 Hz, CH_2Ph), 4.22–4.13 (m, 2H, H-6ax,6eq), 3.93 and 3.86 (2d, 2H, $J_{1,1'}$ 8.4 Hz, H-1,1′), 3.93–3.90 (m, 1H, H-5), 3.61 (d, 1H, H-3), 1.52 and 1.41 (2s, 6H, CMe_2). ^{13}C NMR (inter alia): *δ* 165.26 (COPh), 113.05 (CMe_2), 105.78 (C-2), 78.78 (C-3,4), 75.35 and 71.78 (C-1 and CH_2Ph), 65.80 (C-6), 27.31 and 26.16 (CMe_2), and 23.53 (C-5). Anal. Calcd for $C_{23}H_{25}IO_6$: C, 52.68; H, 4.81. Found: C, 52.81; H, 4.98.

4.1.3. 5-Azido-4-*O*-benzoyl-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose (7). A stirred solution of **6** (2.33 g, 4.4 mmol) and lithium azide (640 mg, 13.2 mmol) in dry DMF (50 mL) was heated at 100 °C for 24 h. TLC (4:1, DCM/hexane) then revealed a slightly slower-running compound. The mixture was concentrated to a residue that was dissolved in ether (40 mL), washed with brine and concentrated. Column chromatography (2:1→3:1, DCM/hexane) of the residue afforded crystalline **7** (1.1 g, 56%); mp 64–66 °C (from DCM/ether); $[\alpha]_D^{27}$ −57 (*c* 1.1); *ν* (neat) 3090, 3064 and 3033 (aromatic), 2108 (N_3), 1721 (CO, Bz), 1386 and 1373 (CMe_2), 752 and 707 cm^{-1} (aromatic). ^1H NMR (300 MHz): *δ* 8.09 (br d, 2H, H*ortho*), 7.60 (t, 1H, H*para*), 7.47 (t, 2H, H*meta*), 7.34 (br s, 5H, CH_2Ph), 5.63 (dd, 1H, $J_{3,4}$ 10, $J_{4,5}$ 3.8 Hz, H-4), 4.84 and 4.64 (2d, 2H, *J* 12.1 Hz, CH_2Ph), 4.24 (m, 1H, H-5), 4.14 (dd, 1H, $J_{5,6ax}$ 1.5, $J_{6ax,6eq}$ 12.7 Hz, H-6ax), 4.02 (d, 1H, H-3), 3.98 and 3.94 (2d, 2H, $J_{1,1'}$ 8.7 Hz, H-1,1′), 3.75 (dd, 1H, $J_{5,6eq}$ 1.7 Hz, H-6eq), 1.49 and 1.40 (2s, 6H, CMe_2). ^{13}C NMR (inter alia): *δ* 165.75 (COPh), 112.61 (CMe_2), 105.83 (C-2), 75.55 (CH_2Ph), 74.36 (C-4), 73.93 (C-3), 71.84 (C-1), 61.80 (C-6), 60.76 (C-5), 27.00 and 26.07 (CMe_2). Anal. Calcd for $C_{23}H_{25}N_3O_6$: C, 62.86; H, 5.73; N, 9.56. Found: C, 62.61; H, 5.96; N, 9.41.

4.1.4. 5-Azido-4-*O*-benzoyl-3-*O*-benzyl-5-deoxy-β-D-fructopyranose (8). A solution of **7** (4.13 g, 9.4 mmol) in 60% aq TFA (10 mL) was kept at room temperature for 2 h. TLC (3:1, ether/hexane) then revealed a slower-running compound. The mixture was concentrated and the residue was dissolved in DCM and washed with 10% aq sodium hydrogen carbonate and water. Removal of the solvent gave crystalline **8** that was recrystallized from ether/hexane to yield pure **8** (3 g, 80%); mp 54–56 °C; $[\alpha]_D^{29}$ −22 (*c* 1); *ν* (KBr): 3456 (OH), 3064 and 3033 (aromatic), 2106 (N_3), 1723 (CO, Bz), 739 and 712 cm^{-1} (aromatic). ^1H NMR (400 MHz): *δ* 8.09, 7.63 and 7.48 (3m, 5H, Bz), 7.25–7.22 (m, 5H, CH_2Ph), 5.70 (dd, 1H, $J_{3,4}$ 9.8, $J_{4,5}$ 3.5 Hz, H-4), 4.79 and 4.67 (2d, 2H, *J* 11.0 Hz, CH_2Ph), 4.24–4.16 (m, 3H, H-5,6ax,6eq), 3.78 (d, 1H, H-3), 3.60 and 3.56 (2d, 2H, $J_{1,1'}$ 11.4 Hz, H-1,1′) and 2.08 (br s, 2H, 2OH). ^{13}C NMR (inter alia): *δ* 165.95 (COPh), 98.41 (C-2), 75.88 (CH_2Ph), 74.12 (C-4), 73.55 (C-3), 65.84 (C-1), 61.58 (C-6) and 60.74 (C-5). Anal. Calcd for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52. Found: C, 59.75; H, 5.41; N, 10.24.

4.1.5. 5-Azido-4-*O*-benzoyl-3-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-5-deoxy-β-D-fructopyranose (9). To a stirred solution of **8** (3.4 g, 8.5 mmol) in dry DMF (40 mL) were added Im (630 mg, 9.3 mmol) and *tert*-butylchlorodiphenylsilane (2.2 mL, 8.5 mmol) and the mixture was left at room temperature for 72 h. TLC (1:1 ether/hexane) then showed a faster-running compound. The reaction mixture was diluted with ether (150 mL) and washed with brine, water and then concentrated to a residue that was subjected to chromatography (1:2, ether/hexane→ether) to afford **9** (3.6 g, 78%) as a colourless syrup; $[\alpha]_D^{25}$ −23 (*c* 1); *ν* (neat) 3476 (OH), 3070 and 3032 (aromatic), 2102 (N_3), 1725 (CO, Bz) and 709 cm^{-1} (aromatic). ^1H NMR (400 MHz, inter alia): *δ* 5.73 (dd, 1H, $J_{3,4}$ 10.0, $J_{4,5}$ 3.6 Hz, H-4), 4.72 and 4.53 (2d, 2H, *J* 11.2 Hz, CH_2Ph), 4.27–4.24 (m, 2H, H-5,6ax), 4.08 (d, 1H, $J_{6ax,6eq}$ 10.4 Hz, H-6eq), 3.81 (d, 1H, H-3), 3.71 and 3.63 (2d, 2H, $J_{1,1'}$ 10.0 Hz, H-1,1′), 3.57 (br s, 1H, OH) and 1.01 (s, 9H, CMe_3). HRMS (LSIMS): *m/z* 660.2507 [M$^+$+Na]; calcd for $C_{36}H_{39}N_3O_6NaSi$: 660.2506 (deviation −0.2 ppm). Starting material (0.5 g) was also recovered.

4.1.6. Catalytic hydrogenation of 9. Compound **9** (3.6 g, 5.6 mmol) in MeOH (30 mL) was hydrogenated at 70 psi over wet Raney nickel (3 g, Fluka) for 24 h. TLC (ether) then revealed the presence of two slower-running compounds. The catalyst was filtered off, washed with MeOH and the combined filtrate and washings were concentrated to a residue that was subjected to column chromatography (1:1, ether/hexane) to afford an unresolvable mixture (2.64 g, 86%) of (2*S*,3*R*,4*R*,5*R*)- (**10**) and (2*R*,3*R*,4*R*,5*R*)-4-benzoyloxy-3-benzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (**12**) as a syrup that was chemoselectively *N*-protected as follows.

4.1.7. (2*S*,3*R*,4*R*,5*R*)- (11) and (2*R*,3*R*,4*R*,5*R*)-4-benzoyloxy-3-benzyloxy-*N*-benzyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (1a). To a well stirred solution of **10** and **12** (2.64 g, 4.44 mmol) in dry acetone (40 mL), anhydrous potassium carbonate (1.8 g) and a solution of benzyl chloroformate (0.9 mL, 6.3 mmol) in the same solvent (10 mL) were added and the mixture was kept at room temperature overnight. TLC (3:1 ether/hexane) then revealed the presence of two faster-running compounds. The mixture was filtered and the solid was thoroughly washed with acetone and the filtrate and washings were concentrated to a residue that was subjected to chromatography (1:2 ether/hexane) to give first **11** as colourless syrup (714 mg, 22%); $[\alpha]_D^{29}$ −27 (*c* 1); *ν* (neat) 3442 (OH), 3069 and 3032 (aromatic), 1706 (C=O, Bz and Cbz), 709 and 701 cm^{-1} (aromatic). ^1H NMR (300 MHz, inter alia): *δ* 8.10–7.20 (m, 25H, 5Ph), 5.78 (br t, 1H, $J_{3,4}=J_{4,5}=4.9$ Hz, H-4), 5.13 and 5.08–4.98 (d and br d, 2H, *J* 12.2 Hz, CH_2Ph), 4.66 (s, 2H, Cbz), 4.35 (t, 1H, *J* 7.0 Hz, H-3), 4.19–3.85 (m, 6H, H-2,2′a,2′b,5,5′a,5′b) and 1.08 (s, 9H, CMe_3). ^{13}C NMR (inter alia): *δ* 166.04

(*C*OPh), 80.13 and 77.31 (C-3,4), 73.03 (*C*H_2Ph), 67.72 (*C*H_2Ph, Cbz), 64.90 and 60.47 (C-2,5), 64.75 and 61.35 (C-2′,5′), 26.99 (C*Me*$_3$) and 19.21 (*C*Me$_3$). HRMS (LSIMS): *m/z* 752.3016 [M$^+$+Na]; calcd for $C_{44}H_{47}NO_7NaSi$: 752.3020 (deviation +0.5 ppm).

Second elution gave syrupy **1a** (1.51 g, 47%); $[\alpha]_D^{29}$ −21 (*c* 1); *ν* (neat) 3453 (OH), 3069 and 3033 (aromatic), 1722 (CO, Bz), 1706 (CO, Cbz), 709 and 700 cm^{-1} (aromatic). ^{1}H NMR (300 MHz): *δ* 7.95–7.12 (m, 25H, 5Ph), 5.53–4.72 (3m, 5H, two rotamers), 4.49–3.58 (4m, 7H, two rotamers), 1.05 and 0.95 (2s, 9H, CMe$_3$ for two rotamers). ^{13}C NMR (inter alia): *δ* 165.49 (*C*OPh), 155.52 (Cbz), 82.01 and 78.86 (C-3,4), 71.94 (*C*H_2Ph), 67.49 (Cbz), 66.96 and 65.75 (C-2,5), 63.33 and 62.14 (C-2′,5′), 26.78 (C*Me*$_3$) and 19.18 (*C*Me$_3$). HRMS (LSIMS): *m/z* 752.3014 [M$^+$+Na]; calcd for $C_{44}H_{47}NO_7NaSi$: 752.3020 (deviation +0.8 ppm).

A mixture of **11** and **1a** (738 mg) was also obtained.

4.1.8. (2*R*,3*R*,4*R*,5*S*)-3,4-Dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine (DGDP, 13). To a stirred solution of **11** (330 mg, 0.45 mmol) in THF (10 mL) was added TBAF·3H$_2$O (200 mg, 0.63 mmol) and the mixture was left at room temperature for 4 h. TLC (ether) then revealed a new compound of lower mobility. The mixture was concentrated and the residue was dissolved in ether and washed with brine, water and then concentrated. Column chromatography of the residue (1:1 ether/hexane → ether) afforded the corresponding desilylated compound (200 mg, 90%) that was not investigated but used in the next step.

Conventional Zemplen debenzoylation of the above compound in anhydrous methanol (10 mL) with 0.4 M MeONa in methanol (0.7 mL) gave the related trihydroxypyrrolidine (TLC evidence) that was fully deprotected by hydrogenation (balloon) over 10% Pd/C (100 mg) in acid medium (HCl) for 2 days at room temperature. Neutralization (Amberlite IRA-400, OH$^-$ form) of the hydrogenated mixture and column chromatography afforded the title compound **13** (60 mg, 89%), which had optical and spectroscopic data identical to those previously reported.[11]

4.1.9. 5-Azido-4-*O*-benzoyl-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-L-sorbopyranose (14). To a cooled (0 °C) and stirred solution of **4** (3.75 g, 9 mmol) in dry THF (50 mL) were consecutively added triphenylphosphine (2.63 g, 10.1 mmol), a solution of DIAD (2 mL, 9.9 mmol) in the same solvent (10 mL) dropwise and after 10 min DPPA (2.6 mL, 12 mmol). The mixture was allowed to reach room temperature and then left overnight. TLC (2:1 ether/hexane) then revealed a new faster-running compound. The mixture was concentrated, supported on silica gel and then subjected to chromatography (4:1 DCM/hexane) to afford pure crystalline **14** (3.53 g, 89%); mp 114–115 °C (from ether/hexane); $[\alpha]_D^{23}$ −69 (*c* 1); *ν* (KBr) 3065 and 3033 (aromatic), 2105 (N$_3$), 1729 (CO, Bz), 1385 and 1373 (CMe$_2$), 710 and 701 cm^{-1} (aromatic). ^{1}H NMR (300 MHz): *δ* 8.08, 7.54 and 7.47 (3m, 5H, Bz), 7.21–7.13 (m, 5H, CH$_2$*Ph*), 5.70 (t, 1H, $J_{3,4}$=$J_{4,5}$=9.6 Hz, H-4), 4.68 and 4.52 (2d, 2H, *J* 11.3 Hz, C*H*$_2$Ph), 3.96 and 3.88 (2d, 2H, $J_{1,1'}$ 8.7 Hz, H-1,1′), 3.86–3.65 (m, 3H, H-5,6ax,6eq), 3.62 (d, 1H, H-3), 1.50 and 1.40 (2s, 6H, CMe$_2$). ^{13}C NMR: 165.35 (*C*OPh), 137.09, 133.34, 129.73, 129.45, 128.49, 128.30, 127.84 and 127.79 (Ph), 112.77 (*C*Me$_2$), 104.98 (C-2), 76.76 and 74.61 (C-3,4), 75.01 (C-1), 71.43 (*C*H_2Ph), 60.84 (C-6), 60.12 (C-5), 26.99 and 25.87 (C*Me*$_2$). Anal. Calcd for $C_{23}H_{25}N_3O_6$: C, 62.86; H, 5.73; N, 9.56. Found: C, 63.18; H, 5.40; N, 9.57.

4.1.10. 5-Azido-4-*O*-benzoyl-3-*O*-benzyl-5-deoxy-α-L-sorbopyranose (15). A solution of **14** (9.1 g, 20.7 mmol) in 70% aq TFA (50 mL) was kept at room temperature for 2.5 h. TLC (ether) then revealed a slower-running compound. The mixture was diluted with water and the white precipitate was filtered, washed with water and air dried to give pure crystalline **15** (8.11 g, 98%); mp 150–151 °C; $[\alpha]_D^{26}$ −30 (*c* 1.1); *ν* (KBr) 3505 and 3488 (OH), 3088 (aromatic), 2109 (N$_3$), 1716 (CO, Bz), 707 and 698 cm^{-1} (aromatic). ^{1}H NMR (300 MHz): *δ* 8.07, 7.61 and 7.48 (3m, 5H, Bz), 7.18 (m, 5H, CH$_2$*Ph*), 5.72 (t, 1H, $J_{3,4}$=$J_{4,5}$=9.7 Hz, H-4), 4.64 and 4.58 (2d, 2H, *J* 11.0 Hz, C*H*$_2$Ph), 3.90 (t, 1H, $J_{5,6ax}$=$J_{6ax,6eq}$=11.2 Hz, H-6ax), 3.84 (dd, 1H, $J_{5,6eq}$ 5.8 Hz, H-6eq), 3.81 (d, 1H, H-3), 3.71 (dt, 1H, H-5), 3.59 and 3.53 (2d, 2H, $J_{1,1'}$ 11.6 Hz, H-1,1′), 3.47 (br s, OH). ^{13}C NMR: 165.65 (*C*OPh), 136.79, 133.53, 129.89, 129.47, 128.63, 128.53, 128.45 and 128.27 (Ph), 97.83 (C-2), 76.78 and 74.05 (C-3,4), 75.31 and 65.53 (C-1, *C*H_2Ph), 60.66 (C-6) and 60.07 (C-5). Anal. Calcd for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52. Found: C, 60.05; H, 5.68; N, 10.29.

4.1.11. 5-Azido-4-*O*-benzoyl-3-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-5-deoxy-α-L-sorbopyranose (16). To a stirred solution of **15** (8.35 g, 20.9 mmol) in dry DMF (30 mL) were added Im (1.50 g, 22 mmol) and *tert*-butylchlorodiphenylsilane (5.63 mL, 22 mmol) and the mixture was left at room temperature overnight. TLC (ether) then showed a faster-running compound. The reaction mixture was diluted with ether (150 mL) and washed with brine, water and then concentrated to a residue that was subjected to chromatography (2:5 ether/hexane) to afford **16** (10.3 g, 77%) as a colourless syrup; $[\alpha]_D^{22}$ −15.5 (*c* 1); *ν* (neat) 3522 (OH), 3051 (aromatic), 2108 (N$_3$), 1730 (CO, Bz) and 709 cm^{-1} (aromatic). ^{1}H NMR (300 MHz, inter alia): *δ* 5.76 (t, 1H, $J_{3,4}$=$J_{4,5}$=9.7 Hz, H-4), 4.59 and 4.47 (2d, 2H, *J* 11.0 Hz, C*H*$_2$Ph), 3.92 (t, 1H, $J_{5,6ax}$=$J_{6ax,6eq}$=11.2 Hz, H-6ax), 3.85 (dd, 1H, $J_{5,6eq}$ 5.8 Hz, H-6eq), 3.76 and 3.60 (2d, 2H, $J_{1,1'}$ 10.3 Hz, H-1,1′), 3.72 (d, 1H, H-3), 3.68 (dt, 1H, H-5), and 1.10 (s, 9H, CMe$_3$). ^{13}C NMR (inter alia): *δ* 98.08 (C-2), 77.21 and 74.18 (C-3,4), 75.25 (*C*H_2Ph), 66.00 (C-6), 60.58 (C-1), 60.29 (C-5), 26.95 (C*Me*$_3$) and 19.39 (*C*Me$_3$). HRMS (LSIMS): *m/z* 660.2509 [M$^+$+Na]; calcd for $C_{36}H_{39}N_3O_6NaSi$: 660.2506 (deviation −0.5 ppm).

4.1.12. Catalytic hydrogenation of 16. Compound **16** (6.4 g, 10 mmol) in MeOH (50 mL) was hydrogenated at 60 psi over wet Raney nickel (7.8 g, Fluka) for 24 h. TLC (20:1 ether/methanol) then revealed the presence of two slower-running compounds. The catalyst was filtered off, washed with MeOH, and the combined filtrate and washings were concentrated to a residue that was subjected to column chromatography (ether → 20:1 ether/methanol) to afford first syrupy (2*S*,3*R*,4*R*,5*R*)-2′-*O*-benzoyl-4-benzyloxy-5′-*O*-*tert*-butyldiphenylsilyl-3-hydroxy-2,5-bis(hydroxymethyl)pyrrolidine (**17**, 500 mg, 8.4%); $[\alpha]_D^{26}$ +19 (*c* 1.5); *ν* (neat) 3379

and 3273 (OH, NH), 3064 (aromatic), 1724 (CO, Bz), 739 and 704 cm^{-1} (aromatic). ^1H NMR (300 MHz): δ 8.10–7.23 (3m, 20H, 4Ph), 4.65 (dd, 1H, $J_{2,2'a}$ 6.6, $J_{2'a,2'b}$ 11.1 Hz, H-2′a), 4.59 and 4.52 (2d, 2H, J 11.9 Hz, CH_2Ph), 4.46 (dd, 1H, $J_{2,2'b}$ 6.5 Hz, H-2′b), 4.13 (d, 1H, $J_{2,3}$ 3.3 Hz, H-3), 3.88 (d, 1H, $J_{4,5}$ 2.3 Hz, H-4), 3.73 (dd, 1H, $J_{5,5'a}$ 3.9, $J_{5'a,5'b}$ 10.5 Hz, H-5′a), 3.68 (dd, 1H, $J_{5,5'b}$ 3.6 Hz, H-5′b), 3.62 (dt, 1H, H-2), 3.34 (q, 1H, H-5), and 1.05 (s, 9H, CMe$_3$). ^{13}C NMR (inter alia): δ 166.80 (*C*OPh), 87.36 and 74.81 (C-3,4), 71.82 (*C*H$_2$Ph), 65.56 and 64.09 (C-2′,5′), 65.01 and 60.69 (C-2,5), 26.92 (C*Me*$_3$) and 19.24 (*C*Me$_3$). HRMS (LSIMS): *m/z* 618.2653 [M$^+$+Na]; calcd for $C_{36}H_{41}NO_5NaSi$: 618.2652 (deviation −0.1 ppm).

Second elution gave syrupy (2*R*,3*R*,4*R*,5*S*)-4-benzoyloxy-3-benzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (**18**, 2.57 g, 43%); $[\alpha]_D^{25}$ −9; $[\alpha]_{405}^{26}$ −35 (*c* 1.6); ν (neat) 3593 and 3500 (OH, NH), 3063 (aromatic), 1721 (CO, Bz), 709 and 700 cm^{-1} (aromatic). ^1H NMR (300 MHz): δ 8.10–7.25 (3m, 20H, 4Ph), 5.54 (dd, 1H, $J_{3,4}$ 1.8, $J_{4,5}$ 4.2 Hz, H-4), 4.78 and 4.60 (2d, 2H, J 11.8 Hz, CH_2Ph), 4.12 (dd, 1H, $J_{2,3}$ 4.8 Hz, H-3), 3.88 (dd, 1H, $J_{2,2'a}$ 5.2, $J_{2'a,2'b}$ 10.4 Hz, H-2′a), 3.80 (dd, 1H, $J_{2,2'b}$ 4.8 Hz, H-2′b), 3.77–3.67 (m, 3H, H-5,5′a,5′b), 3.37 (q, 1H, H-2), 2.90 (br s, 2H, NH, OH) and 1.05 (s, 9H, CMe$_3$). ^{13}C NMR (inter alia): δ 166.0 (*C*OPh), 85.07 and 79.27 (C-3,4), 72.22 (*C*H$_2$Ph), 64.82 and 61.61 (C-2,5), 64.22 and 60.82 (C-2′,5′), 26.82 (C*Me*$_3$) and 19.21 (*C*Me$_3$). HRMS (LSIMS): *m/z* 618.2652 [M$^+$+Na]; calcd for $C_{36}H_{41}NO_5NaSi$: 618.2652 (deviation 0.0 ppm).

4.1.13. N-Benzyloxycarbonylation of 18. To a cooled (0 °C) and stirred solution of **18** (1.87 g, 3.1 mmol) in anhydrous MeOH (20 mL) and TEA (1.4 mL, 10.8 mmol) was added benzyl chloroformate (560 μL, 3.9 mmol) and the mixture was allowed to reach room temperature. TLC (3:1 ether/hexane) then showed the presence of a faster-running compound. The solvent was eliminated and the residue was partitioned in DCM/water, the organic phase was concentrated to yield an unresolvable mixture of **19** and **20** (1.9 g, 84%) (^1H NMR evidence) that was used in the next step.

When compound **17** was treated as above the same mixture was obtained.

To a stirred solution of the above mixture (**19** and **20**, 3.31 g, 4.5 mmol) and TEA (2.5 mL, 18 mmol) in anhydrous DCM (30 mL) was added dropwise benzoyl chloride (1.6 mL, 13.6 mmol) and the mixture was left at room temperature for 12 h. TLC (2:1 ether/hexane) then showed a faster-running compound. Conventional work-up and column chromatography afforded (2*S*,3*R*,4*R*,5*R*)-2′-*O*-benzoyl-3-benzoyloxy-4-benzyloxy-*N*-benzyloxycarbonyl-5′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (**21**, 3.5 g, 93%) as a colourless syrup; $[\alpha]_D^{24}$ +11 (*c* 1); ν (neat) 3065 and 3028 (aromatic), 1731 (CO, Bz), 1704 (CO, Cbz), 745 and 711 cm^{-1} (aromatic). ^1H NMR (300 MHz): δ 7.86–7.12 (3m, 30H, 6Ph), 5.78 (br s, 1H, H-3), 5.08 (br s, 2H, H-2′a,2′b), 4.80–3.72 (4m, 9H, 2CH_2Ph, H-2,4,5,5′a,5′b) and 1.05 (s, 9H, CMe$_3$). ^{13}C NMR (inter alia): δ 165.85 and 165.42 (2*C*OPh), 155.53 (CO, Cbz), 72.08 (2*C*H$_2$Ph), 67.47 (C-2′,5′), 64.63, 64.57, 62.40 and 62.17 (C-2,3,4,5), 26.89 (C*Me*$_3$) and 19.25 (*C*Me$_3$). HRMS (LSIMS): *m/z* 856.2918 [M$^+$+Na]; calcd for $C_{51}H_{51}NO_8NaSi$: 856.2917 (deviation −0.1 ppm).

4.1.14. N-Benzylation of 18. To a stirred solution of **18** (780 mg, 1.3 mmol) in dry acetonitrile (10 mL), DBU (0.8 mL, 5.2 mmol) and benzyl bromide (0.5 mL, 3.9 mmol) were added and the mixture was left at room temperature for 4 days. TLC (2:1, ether/hexane) then showed the presence of two less polar compounds. The reaction mixture was concentrated and the residue was subjected to column chromatography (1:2 → 1:1 ether/hexane) to yield first (2*S*,3*R*,4*R*,5*R*)-2′-*O*-benzoyl-*N*-benzyl-4-benzyloxy-5′-*O*-*tert*-butyldiphenylsilyl-3-hydroxy-2,5-bis(hydroxymethyl)-pyrrolidine (**22**, 460 mg, 52%) as a colourless syrup; $[\alpha]_D^{23}$ +27 (*c* 1); ν (neat) 3444 (OH), 3068 and 3025 (aromatic), 1719 (CO, Bz) and 704 cm^{-1} (aromatic). ^1H NMR (400 MHz): δ 8.06–8.03, 7.66–7.55 and 7.46–7.20 (3m, 25H, 5Ph), 4.65 (dd, 1H, $J_{2,2'a}$ 8.0, $J_{2'a,2'b}$ 11.0 Hz, H-2′a), 4.57 (dd, 1H, $J_{2,2'b}$ 6.0 Hz, H-2′b), 4.60 and 4.54 (2d, 2H, J 12.0 Hz, OCH_2Ph), 4.21 (dd, 1H, $J_{3,4}$ 10.3, $J_{2,3}$ 3.6 Hz, H-3), 4.08 and 3.80 (2d, 2H, J 14.1 Hz, NCH_2Ph), 3.98 (br s, 1H, OH), 3.96 (d, 1H, H-4), 3.62 (m, 1H, H-2), 3.43 (dd, 1H, $J_{5,5'a}$ 2.7, $J_{5'a,5'b}$ 10.5 Hz, H-5′a), 3.36 (dd, 1H, $J_{5,5'b}$ 3.8 Hz, H-5′b), 3.09 (br t, 1H, H-5) and 1.06 (s, 9H, CMe$_3$). ^{13}C NMR (inter alia): δ 166.68 (*C*OPh), 85.69 (C-4), 74.10 (C-3), 71.69 (C-5), 71.25 (OCH_2Ph), 66.10 (C-2), 65.03 (C-5′), 63.30 (C-2′), 58.26 (NCH_2Ph), 26.88 (C*Me*$_3$) and 19.16 (*C*Me$_3$). HRMS (LSIMS): *m/z* 708.3122 [M$^+$+Na]; calcd for $C_{43}H_{47}NO_5NaSi$: 708.3121 (deviation −0.2 ppm).

Second elution gave (2*R*,3*R*,4*R*,5*S*)-4-benzoyloxy-*N*-benzyl-3-benzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-4-hydroxy-2,5-bis(hydroxymethyl)pyrrolidine (**23**, 87 mg, 10%) as a colourless syrup; $[\alpha]_D^{24}$ −30 (*c* 1); ν (neat) 3460 (OH), 3067 and 3028 (aromatic), 1719 (CO, Bz), 736 and 708 cm^{-1} (aromatic). ^1H NMR (400 MHz): δ 8.04–8.01, 7.63–7.58 and 7.46–7.20 (3m, 25H, 5Ph), 5.57 (dd, 1H, $J_{3,4}$ 4.3, $J_{4,5}$ 6.3 Hz, H-4), 4.74 and 4.66 (2d, 2H, J 11.7 Hz, OCH_2Ph), 4.43 (t, 1H, $J_{2,3}$ 4.3 Hz, H-3), 3.92 and 3.88 (2d, 2H, J 13.6 Hz, NCH_2Ph), 3.73 (dd, 1H, $J_{2,2'a}$ 6.4, $J_{2'a,2'b}$ 10.6 Hz, H-2′a), 3.60 (dd, 1H, $J_{2,2'b}$ 4.1 Hz, H-2′b), 3.55 (dt, 1H, $J_{5,5'a}$ 2.1 Hz, H-5), 3.50 (dd, 1H, H-5′a), 3.34 (dd, 1H, $J_{5,5'b}$ 5.8, $J_{5a,5'b}$ 11.4 Hz, H-5′b), 3.21 (dt, 1H, H-2) and 1.06 (s, 9H, CMe$_3$). ^{13}C NMR (inter alia): δ 166.51 (*C*OPh), 82.05 (C-3), 78.30 (C-4), 72.12 (OCH_2Ph), 69.02 and 65.13 (C-2,5), 63.33 and 59.20 (C-2′,5′), 58.52 (NCH_2Ph), 26.89 (C*Me*$_3$) and 19.21 (*C*Me$_3$). HRMS (LSIMS): *m/z* 708.3121 [M$^+$+Na]; calcd for $C_{43}H_{47}NO_5$-NaSi: 708.3121 (deviation 0.0 ppm).

4.1.15. N-Allylation of 18. To a solution of **18** (2.53 g, 4.25 mmol) in dry acetone (30 mL), anhydrous K_2CO_3 (2.9 g) and allyl bromide (1.3 mL, 15 mmol) were added and the mixture sonicated for 30 min and then stirred at room temperature for 24 h. TLC (ether) then showed the presence of two less polar compounds. The reaction mixture was filtered and the solid was washed with acetone. Removal of the solvent gave a residue that was partitioned into DCM/water, the organic phase was separated and concentrated. Column chromatography (1:3 ether/hexane) of the residue yielded first (2*S*,3*R*,4*R*,5*R*)-*N*-allyl-2′-*O*-benzoyl-4-benzyloxy-5′-*O*-*tert*-butyldiphenylsilyl-3-hydroxy-2,5-bis(hydroxymethyl)pyrrolidine (**24**, 1.84 g, 68%) as a colourless syrup;

$[\alpha]_D^{27}$ +22 (*c* 1.1); *ν* (neat) 3460 (OH), 3068 (aromatic), 1724 (CO, Bz), 740 and 710 cm^{-1} (aromatic). ^1H NMR (300 MHz): *δ* 8.06–7.25 (m, 20H, 4 Ph), 5.84 (dddd, 1H, CH_2–C*H*=CH_2), 5.13 (br dd, 1H, J_{trans} 17.1, J_{gem} 1.6 Hz, H-trans), 5.04 (br dd, 1H, J_{cis} 10.2 Hz, H-cis), 4.65–4.55 (m, 4H, C*H*$_2$Ph, H-2′a,2′b), 4.18 (dd, 1H, $J_{3,4}$ 10.4, $J_{2,3}$ 3.6 Hz, H-3), 3.98 (br s, 1H, OH), 3.92 (d, 1H, H-4), 3.64 (dd, 1H, $J_{5,5'a}$ 3.8, $J_{5'a,5'b}$ 10.5 Hz, H-5′a), 3.57 (dd, 1H, $J_{5,5'b}$ 2.7 Hz, H-5′b), 3.46 and 3.31 (2br dd, 2H, J_{gem} 14.7 Hz, C*H*$_2$–CH=CH_2), 3.39 (ddd, 1H, $J_{2,2'a}$ 5.6, $J_{2,2'b}$ 7.1 Hz, H-2), 3.09 (br t, 1H, H-5) and 1.06 (s, 9H, CMe_3). ^{13}C NMR (inter alia): *δ* 166.70 (*C*OPh), 117.92 (CH_2–CH=*C*H$_2$), 85.77 and 74.06 (C-3,4), 71.32 (*C*H$_2$Ph), 70.29 and 64.71 (C-2,5), 64.79 and 63.20 (C-2′,5), 55.57 (*C*H$_2$–CH=CH_2), 26.76 (C*Me*$_3$) and 19.09 (*C*Me$_3$). HRMS (LSIMS): *m*/*z* 658.2963 [M^++Na]; calcd for $C_{39}H_{45}NO_5NaSi$: 658.2965 (deviation +0.2 ppm).

Second elution gave (2*R*,3*R*,4*R*,5*S*)-*N*-allyl-4-benzoyloxy-3-benzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (**25**, 350 mg, 13%) as a colourless syrup; $[\alpha]_D^{25}$ −43 (*c* 1); *ν* (neat) 3471 (OH), 3067 (aromatic), 1721 (CO, Bz), 741 and 704 cm^{-1} (aromatic). ^1H NMR (300 MHz): *δ* 8.05–7.23 (m, 20H, 4Ph), 5.84 (dddd, 1H, CH_2–C*H*=CH_2), 5.52 (dd, 1H, $J_{3,4}$ 4.2, $J_{4,5}$ 5.9 Hz, H-4), 5.18 (br dd, 1H, J_{trans} 17.1, J_{gem} 1.6 Hz, H-trans), 5.11 (br dd, 1H, J_{cis} 10.2 Hz, H-cis), 4.73 and 4.66 (2d, 2H, *J* 11.8 Hz, C*H*$_2$Ph), 4.36 (t, 1H, $J_{2,3}$ 4.3 Hz, H-3), 3.75 (dd, 1H, $J_{5,5'a}$ 4.6, $J_{5'a,5'b}$ 10.6 Hz, H-5′a), 3.71 (dd, 1H, $J_{5,5'b}$ 6.1 Hz, H-5′b), 3.58–3.44 (m, 3H, H-2′a,2′b,5), 3.40–3.25 (m, 2H, C*H*$_2$–CH=CH_2), 3.11 (br q, 1H, H-2), 3.01 (br s, 1H, OH) and 1.05 (s, 9H, CMe_3). ^{13}C NMR (inter alia): *δ* 166.50 (*C*OPh), 118.26 (CH_2–CH=*C*H$_2$), 82.27 and 78.46 (C-3,4), 72.13 (*C*H$_2$Ph), 68.28 and 64.27 (C-2,5), 63.68 and 59.23 (C-2′,5′), 56.30 (*C*H$_2$–CH=CH_2), 26.93 (C*Me*$_3$) and 19.25 (*C*Me$_3$). HRMS (LSIMS): *m*/*z* 658.2965 [M^++Na]; calcd for $C_{39}H_{45}NO_5NaSi$: 658.2965 (deviation 0.0 ppm).

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