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Polyhydroxylated pyrrolidines, III. Synthesis of new protected 2,5-dideoxy-2,5-iminohexitols from D-fructose☆

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Abstract—The readily available 3-*O*-benzoyl-4-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose (**6**) was straightforwardly transformed into 5-azido-3-*O*-benzoyl-4-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose (**8**), after treatment under modified Garegg's conditions followed by reaction of the resulting 3-*O*-benzoyl-4-*O*-benzyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-L-sorbopyranose (**7**) with lithium azide in DMF. *O*-debenzoylation at C(3) in **8**, followed by oxidation and reduction caused the inversion of the configuration to afford the corresponding β-D-psicopyranose derivative **11** that was transformed into the related 3,4-di-*O*-benzyl derivative **12**. Cleavage of the acetonide of **12** to give **13** followed by *O*-*tert*-butyldiphenylsilylation afforded a resolvable mixture of **14** and **15**. Compound **14** was transformed into (2*R*,3*R*,4*S*,5*R*)- (**17**) and (2*R*,3*R*,4*S*,5*S*)-3,4-dibenzyloxy-2′,5′-di-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (**18**) either by a tandem Staudinger/intramolecular aza-Wittig process and reduction of the resulting intermediate Δ^2-pyrroline (**16**), or only into **18** by a high stereoselective catalytic hydrogenation. When **15** was subjected to the same protocol, (2*S*,3*S*,4*R*,5*R*)- (**21**) and (2*R*,3*S*,4*R*,5*R*)-3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (**22**) were obtained, respectively.

1. Introduction

In previous papers, we have reported on the highly stereoselective synthesis of orthogonally protected derivatives of 2,5-dideoxy-2,5-imino-D-glucitol (DGDP)[1] and 2,5-dideoxy-2,5-imino-D-mannitol (DMDP),[2] from the cheap and commercially available D-fructose. Both compounds were shown to be excellent chiral key intermediates for the preparation of natural[3] and unnatural hyacinthacines,[4] potent glycosidase inhibitors.[5]

Figure 1 shows the synthetic potentiality of (2*R*,3*S*,4*R*,5*R*)-3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine [**22**, 2,5-dideoxy-2,5-imino-D-altritol (DALDP) displaying the retrosynthesis of a great variety of hyacinthacines, recently isolated from different natural sources,[6] where clearly is shown that **22** must be considered an appropriate chiral starting material for the synthesis of such target molecules. Thus, protection interchange between the hydroxyl groups at C(2′)–C(5′), carbon-chain lengthening at C(2′) (the original C(1) of D-fructose) in a two more carbon atoms fragment suitably functionalised, followed by a further cyclization, could lead to pyrrolizidines, which stereochemistry at C(1,2,3,7a) belonging to that of the natural hyacinthacines.

Continuing with our efforts on the title topic, we describe herein, the highly stereoselective synthesis of **22** together with that of its C(2)-epimer (**21**) using a D-psicose derivative (**12**) as key intermediate, which is available from D-fructose as source of chirality and functionalization.

2. Results and discussion

In order to obtain the above mentioned intermediate **12**, it was necessary to prepare 3,4-di-*O*-benzyl-1,2-*O*-ispropylidene-β-D-psicopyranose (**4**). This was initially attempted by a well established protocol consisting in: partial deacetonation of the already known 3-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranose (**1**)[7] to the corresponding 1,2-*O*-isopropylidene derivative (**2**), subsequent 4,5-*O*-di-*n*-butylstannylation to the not characterized **3**, and finally regioselective ring opening by benzyl bromide (see Scheme 1), but conversely to many other cases,[1,8] where the main product comes from the electrophilic attack of the reagent at the oxygen with the equatorial disposition [O(4)], no regioselectivity was observed and an unresolvable mixture of the corresponding 3,4- (**4**) and 3,5-di-*O*-benzyl (**5**) derivatives was produced in low yield. The use of any

☆ For Part II, see Ref. 2.

Keywords: D-fructose; Stereoselective síntesis; Polyhydroxylated pyrrolidines; 2,5-Dideoxy-2,5-iminohexitols; DADP; DALDP.
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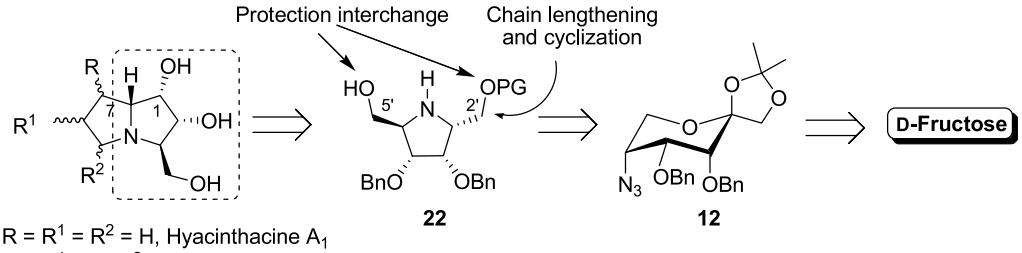
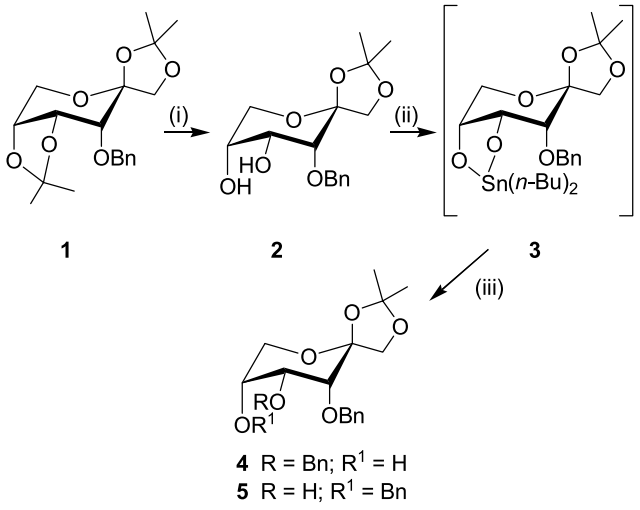


R = R^1 = R^2 = H, Hyacinthacine A$_1$
R = R^1 = H; R^2 = Me, (5*R*)-Hyacinthacine A$_6$
(5*S*)-Hyacinthacine A$_7$
R = R^1 = H, R^2 = CH$_2$OH, (5*R*)-Hyacinthacine B$_1$
(5*S*)-Hyacinthacine B$_2$
R = OH; R^1 = H; R^2 = Me, (5*R*,7*R*)-Hyacinthacine B$_3$
(5*R*,7*S*)-Hyacinthacine B$_5$
R = R^1 = OH; R^2 = Me, (5*R*,6*R*,7*R*)-Hyacinthacine C$_1$

Figure 1. Retrosynthesis of natural hyacinthacines.



Scheme 1. Synthesis of **4** and **5** from **1**. Reagents and conditions: (i) 75% aq AcOH/45 °C, 2 h; (ii) *n*-Bu$_2$SnO/MeOH/reflux; (iii) BnBr/DMF/110 °C.

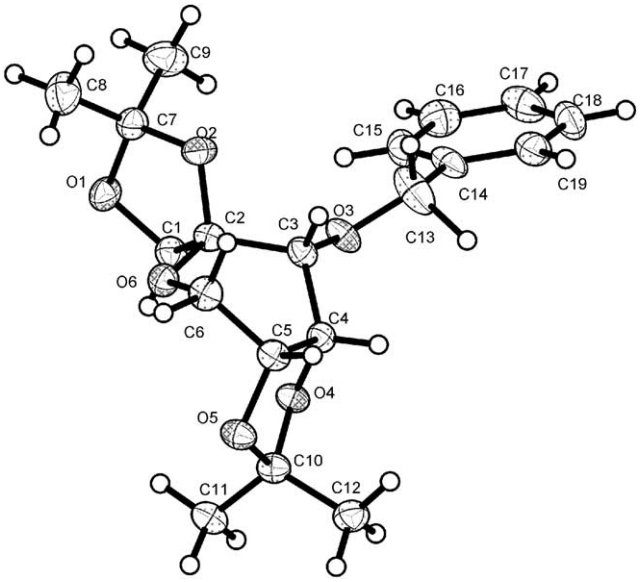
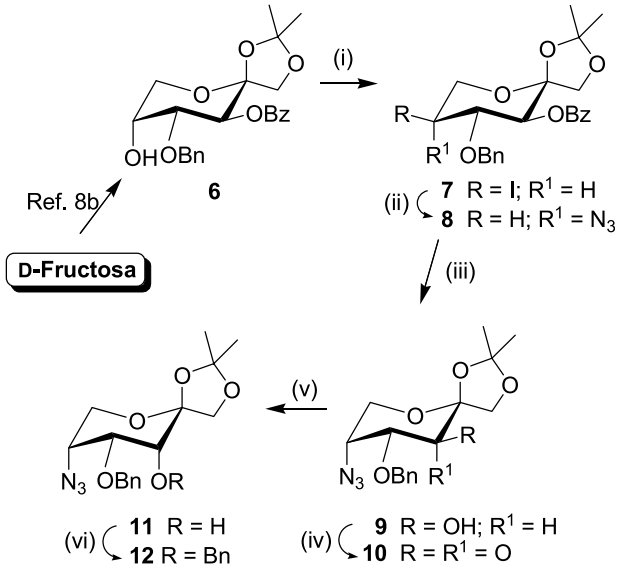


Figure 2. ORTEP view of compound **1**. Thermal ellipsoid enclosed 50% of electron density.

other electrophilic reagent (BzCl, TBDMSCl, MEMCl, etc.) also gave the same result.

These unexpected results could be explained if intermediate **3** would adopt a ^{3,6}B conformation similar to that found in **1** (see Fig. 2), and presuming that a $Me_2C<\rightarrow n$-$Bu_2Sn<$ change must not be of great stereochemical significance. It can be observed the oxygen atoms at C(4,5) adopt a parallel disposition, in such a way that both can be attacked by the electrophilic reagent giving **4** and **5**, without regioselectivity.

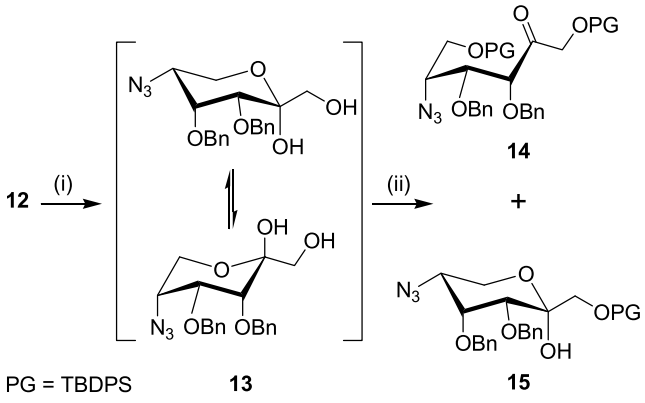
On the basis of the above results a new synthetic route was designed (see Scheme 2), consisting in the introduction of the appropriate funtionalization and stereochemistry at C(5) in 3-*O*-benzoyl-4-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose (**6**)[8b] prior to the inversion of the configuration at C(3). Thus, reaction of **6** under the Garegg's conditions[9] afforded the corresponding 5-deoxy-5-iodo-α-L-*sorbo* derivative (**7**), which treatment with LiN_3 in DMF effected S_N2 substitution to yield 5-azido-3-*O*-benzoyl-4-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose (**8**).



Scheme 2. Synthesis of **12** from D-fructose. Reagents and conditions: (i) I_2/Ph_3P/imidazole/MePh, reflux; (ii) LiN_3/DMF/100 °C; (iii) MeOH/MeONa (cat), rt; (iv) Dess–Martin/Cl_2CH_2, rt; (v) $NaBH_4$/MeOH, 0 °C; (vi) NaH/DMF/BnBr, rt.

Zemplen debenzoylation of **8** gave the 3-*O*-deprotected **9**, that was subsequently oxidized to 2,3-diulose **10**, not totally characterized but reduced to 5-azido-4-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-psicopyranose (**11**). The high stereoselectivity found was in accordance with that observed by Tipson et al. in the reduction of 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulo-2,6-pyranose.[10] Compound **11** was straightforwardly transformed into the totally protected derivative **12**.

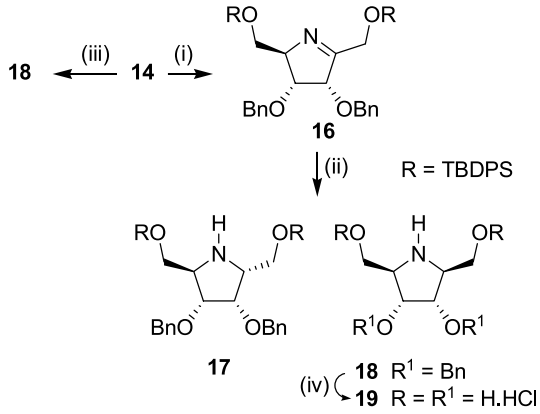
According to Scheme 3, deacetonation of **12** in acid medium gave **13**, existing as a ≈2:1 mixture of α- and β-pyranoses in $^5C_2$ and $^2C_5$ conformations, respectively, according to their ^1H and ^{13}C NMR data (see Tables 1 and 2).



Scheme 3. Synthesis of protected uloses **14** and **15**. Reagents and conditions: (i) aq 60% TFA, rt; (ii) TBDPSCl/imidazole//DMF, rt.

Attempt to protect **13** as its 1-*O*-*tert*-butyldiphenylsilyl derivative under the conventional conditions (silylating reagent/imidazole/DMF) resulted in the formation of 5-azido-3,4-di-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-5-deoxy-α-D-psicopyranose (**15**, 70%) together with an appreciable amount of the unexpected 5-azido-3,4-di-*O*-benzyl-1,6-di-*O*-*tert*-butyldiphenylsilyl-5-deoxy-D-psicose (**14**, 26%), that were separated by chromatographic means.

Compounds **14** and **15** were the key intermediates for the synthesis of the target 2,5-dideoxy-2,5-iminohexitols (see Scheme 4). In a first approach, submission of **14** to an intramolecular tandem Staudinger/aza-Wittig reaction[11] afforded the expected (3*S*,4*R*,5*R*)-3,4-dibenzyloxy-2′,5′-di-



Scheme 4. Synthesis of total and partially protected polyhydroxylated pyrrolidines **17** and **18**. Reagents and conditions: (i) Ph_3P/THF, reflux; (ii) $NaCNBH_3$/THF/AcOH, 0 °C; (iii) Raney-Ni/H_2/MeOH–THF; (iv) *n*-$Bu_4N^+F^-$ 3 H_2O/THF, then 10% Pd–C/H_2/MeOH/HCl.

O-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)-Δ^1-pyrroline (**16**) in almost quantitative yield that could be characterized, but decomposed on standing. Conventional reduction of **16** with sodium cianoborohydride gave a 2:1 mixture of (2*R*,3*R*,4*S*,5*R*)- (**17**) and (2*R*,3*R*,4*S*,5*S*)-3,4-dibenzyloxy-2′,5′-di-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (**18**). The absolute configuration at the new generated stereogenic centre [C(5)] in **17**, and hence that of **18**, was easily determined after recording their optical, ^1H and ^{13}C NMR data. Thus, **18** was optically inactive indicating the presence of a symmetry plane, confirmed by the presence of half of the resonance signals in its NMR spectra. On the other hand, hydrogenation of **14** under the presence of Raney-Ni occurred with high stereoselectivity to afford only **18**. Compound **18** was totally *O*-deprotected to the already known[12] 2,5-dideoxy-2,5-imino-D-allitol (**19** DADP) as its hydrochloride salt.

Following the above protocol but in **15** (see Scheme 5), the intramolecular Staudinger/aza-Wittig reaction afforded the expected Δ^1-pyrroline **20** (TLC evidence) that could not be characterized due to its instability, but reduced to give only one compound identified as (2*S*,3*S*,4*R*,5*R*)-3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)-pyrrolidine (**21**), whereas the catalytic hydrogenation of **15** gave the (2*R*,3*S*,4*R*,5*R*)-isomer (**22**). De-*O*-silylation of **22** gave the corresponding **23**, which analytical and

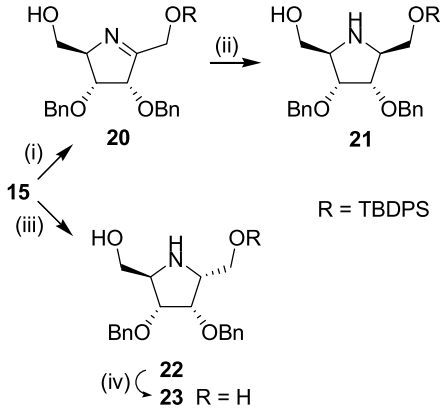
Table 1. ^1H RMN chemical shifts (δ) and *J* (Hz) values for compound **13α** and **13β**

Compound	H-1	H-1′	H-3	H-4	H-5	H-6ax	H-6eq	C*H*$_2$Ph	C*H*$_2$Ph	OH
13α	3.69d, $J_{1,1'}$ = 11.6 Hz	3.46d	3.58d, $J_{3,4}$ = 2.5 Hz	4.22br s	3.31ddd, $J_{4,5}$ = 2.5 Hz, $J_{5,6eq}$ = 5.3 Hz	4.07t, $J_{5,6ax}$ = 11.4 Hz, $J_{6,ax,6eq}$ = 11.4 Hz	3.74dd	4.85d, 4.78d, J = 10.6 Hz	4.63s	
13β	3.93d, $J_{1,1'}$ = 11.8 Hz	3.26d	3.74m	4.10br s	3.86m	3.92dd, $J_{5,6ax}$ = 2.4 Hz, $J_{6,ax,6eq}$ = 12.4 Hz	3.74m	5.00d, 4.69d, J = 11.6 Hz	4.76d, 4.68d, J = 11.9 Hz	5.57br s, 2.11br s

Table 2. ^{13}C RMN chemical shifts (δ) values for compound **13α** and **13β**

Compound	C-1	C-2	C-3	C-4	C-5	C-6	*C*H$_2$Ph
13α	64.46	97.86	76.86[a]	73.12[a]	57.09	56.77	75.98, 72.27
13β	65.91	97.67	76.46[a]	75.26[a]	56.28	62.15	74.89, 71.42

[a] Assignments may be interchanged.



Scheme 5. Synthesis of partially protected polyhydroxylated pyrrolidines **21** and **22**. Reagents and conditions: (i) Ph_3P/THF, reflux; (ii) $NaCNBH_3$/THF/AcOH, 0 °C; (iii) Raney-Ni/H_2/MeOH; (iv) n-$Bu_4N^+F^-$ 3 H_2O/THF.

spectroscopic data were consistent with the assigned stereochemistry.

Comments merit the high stereoselectivity found in the catalytic hydrogenation of **14** and **15** (see Fig. 3). Contrary to that previously reported,[13] where the authors stated that the stereochemistry of five-membered ring system is controlled by that at C(4), our results seemed to indicate that the size of the substituent at C(5′) must play an important roll in the steric course of the reaction, since either the presence, in **14**, or absence, in **15**, of bulky TBDPS protecting group at C(5′) makes either the bottom or top face the preferable for the hydrogen attack, respectively.

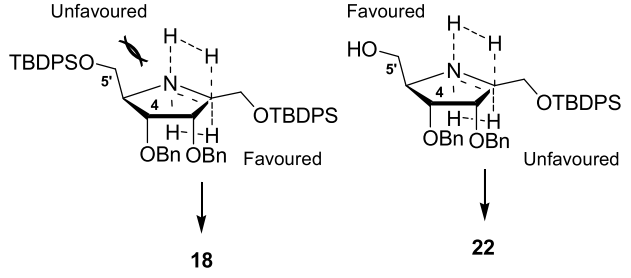


Figure 3. Transition states for catalytic hydrogenation of **14** and **15**.

3. Conclusions

D-fructose was an excellent chiral starting material for the stereoselective synthesis of polyhydroxylated pyrrolidines alkaloids. Highly diastereoselective hydrogenation of protected 5-azido-5-deoxy-D-psicose derivatives was the best synthetic route to the target molecules.

4. Experimental

4.1. Crystal structure determination

Single crystal of **1** was mounted on a Bruker-Smart Apex area detector diffractometer (Mo Kα $\lambda=0.71073$ Å). The cell parameters were determined from reflections taken from one steps in phi angle) each at 20 s exposure. The structures were solved using direct methods (SHELXS[14]) and refined against F^2 using the SHELXS12 software.[14] The absorption was non-corrected. All non-hydrogen atoms were generated according to stereochemistry and refined using a riding model in SHELXS97.

$C_{19}H_{26}O_6$: $M=350.40$ g mol^{-1}; triclinic; space group P-1; $a=5.881(10)$ Å, $b=8.052(14)$ Å, $c=10.490(18)$ Å, $\alpha=67.714(2)°$, $\beta=84.247(3)°$, $\gamma=78.551(3)°$, $V=450.39(13)$ Å^3, $Z=1$, $\rho_{calcd}=1.292$ g cm^{-3}, $\mu=0.095$ mm^{-1}, $F(000)=180$. Colourless crystal, dimensions $0.27\times0.13\times0.07$ mm^3. A total of 5288 reflections were collected with $2.10°<\theta<28.36°$; 3885 independent reflections with 3644 having $I<2\sigma<(I)$; 233 parameters; $R_1=0.0412$; $wR_2=0.1018$; Goof$=1.081$; maximum residual electronic density$=0.481$ e^{-1} Å^3.

Full data collection parameters and structural data are available as supporting information. Crystallographic data for the crystal structure have been deposited with the Cambridge Crystallographic Data Centre, CCDC 269114. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail, deposit@ccdc.cam.ac.uk; web, http://www.ccdc.cam.ac.uk).

4.2. 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.

4.2.1. 3-*O*-benzyl-1,2-*O*-isopropylidene-β-D-psicopyranose (2). A solution of 3-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranose[7] (**1**, 3.50 g, 10 mmol) in 75% aqueous acetic acid (50 mL) was heated at 45 °C for 2 h. TLC (ether) then revealed a new slower running compound. The mixture was concentrated and repeatedly codistilled with water and then dissolved in ethanol (60 mL), neutralized with solid K_2CO_3 and concentrated. Column chromatography (1:1 ether/hexane) gave pure syrupy **2** (2.50 g, 79%); $[\alpha]_D^{27}-90$ (c 1); IR (neat): υ 3484 and 3451 (OH), 3031 (aromatic), 1373 and 1245 (CMe_2), 745 and 700 cm^{-1} (aromatic). ^{1}H NMR (400 MHz): δ 7.33 (m, 5H, Ph), 4.86 and 4.69 (2d, 2H, $J=11.3$ Hz, CH_2Ph), 4.06 and 3.80 (2d, 2H, $J_{1,1'}=9.3$ Hz, H-1,1′), 3.96 (t, 1H, $J_{3,4}$, $J_{4,5}=3.5$ Hz, H-4), 3.96 (dd, 1H, $J_{5,6}=2$ Hz, $J_{6,6'}=12.3$ Hz, H-6), 3.86 (dd, 1H, $J_{5,6'}=2.3$ Hz, H-6′), 3.74 (m, 1H, H-5), 3.66

(br d, 1H, H-3), 2.60 (br s, 2H, HO-4,5), 1.47 and 1.35 (2s, 6H, CMe_2). ^{13}C NMR: δ 137.15, 128.69, 128.38, and 128.16 ($PhCH_2$), 112.06 (CMe_2), 104.88 (C-2), 80.99 (C-3), 76.02 (C-1), 73.27 (CH_2Ph), 69.28 and 67.43 (C-4,5), 65.33 (C-6), 26.78 and 26.29 (CMe_2). HRMS: *m/z* 333.1319 [M^++Na]. For $C_{16}H_{22}O_6Na$ 333.1314 (deviation −1.5 ppm).

4.2.2. 3-*O*-benzoyl-4-*O*-benzyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-L-sorbopyranose (7). To a solution of triphenylphosphine (8.82 g, 33.62 mmol), imidazole (4.57 g, 67.20 mmol), and iodine (8.52 g, 23.57 mmol) in dry toluene (120 mL) was added 3-*O*-benzoyl-4-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose[8b] (**6**, 6.95 g, 17.79 mmol) in the same solvent (50 mL) and the mixture 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% aqueous sodium thiosulphate and brine, then concentrated. Column chromatography (1:3 ether/hexane) afforded crystalline **7** (6.7 g, 76%); mp 166–168 °C (from ether); $[\alpha]_D^{26}$ −64.5 (*c* 1.1); IR (KBr): υ 3033 (aromatic), 1727 (ester), 1382 and 1274 (CMe_2), 713 and 693 cm^{-1} (aromatic). ^1H NMR (300 MHz): δ 8.10–8.07, 7.63–7.58, 7.49–7.44, and 7.17–7.10 (4m, 10H, 2 Ph), 5.30 (d 1H, $J_{3,4}$=8.8 Hz, H-3), 4.84 and 4.59 (2d, 2H, J=10.1 Hz, CH_2Ph), 4.22–3.92 (m, 4H, H-4,5,6_{ax},6_{eq}), 3.97 and 3.92 (2d, 2H, $J_{1,1'}$=9.3 Hz, H-1,1′), 1.52 and 1.43 (2s, 6H, CMe_2). ^{13}C NMR (inter alia): δ 165.56 (COPh), 112.52 (CMe_2), 104.93 (C-2), 81.88 (C-3), 75.57 (C-1), 72.67 (C-4), 71.88 (CH_2Ph), 66.20 (C-6), 26.77 and 26.30 (CMe_2), and 25.57 (C-5). Anal. Calcd for $C_{23}H_{25}IO_6$: C, 52.68; H, 4.81. Found: C, 53.21; H, 5.04.

4.2.3. 5-Azido-3-*O*-benzoyl-4-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose (8). A stirred solution of **7** (3 g, 5.72 mmol) and lithium azide (0.84 g, 17.1 mmol) in dry DMF (25 mL) was heated at 100 °C for 6 h. TLC (3:2 ether/hexane) then revealed a lower-running compound. The mixture was concentrated to a residue that was dissolved in ether (40 mL), washed with brine and concentrated. Flash column chromatography (1:1 ether/hexane) of the residue afforded **8** (2.5 g, 99%) as a colourless syrup; $[\alpha]_D^{26}$ −127 (*c* 0.7); IR (neat): υ 3033 (aromatic), 2105 (N_3), 1724 (ester), 1372 (CMe_2), 710 cm^{-1} (aromatic). ^1H NMR (300 MHz): δ 8.08–8.06, 7.63–7.57, 7.49–7.44, and 7.22–7.17 (4m, 10H, 2 Ph), 5.64 (d 1H, $J_{3,4}$=9.9 Hz, H-3), 4.65 and 4.58 (2d, 2H, J=12.1 Hz, CH_2Ph), 4.12 (dd, 1H, $J_{4,5}$=3.8 Hz, H-4), 4.02 and 3.94 (2d, 2H, $J_{1,1'}$=9.3 Hz, H-1,1′), 4.00–3.94 (m, 2H, H-5,6), 3.76 (dd, 1H, $J_{5,6'}$=2 Hz, $J_{6,6'}$=13 Hz, H-6′), 1.47 and 1.37 (2s, 6H, CMe_2). ^{13}C NMR (inter alia): δ 165.80 (COPh), 112.22 (CMe_2), 104.87 (C-2), 76.83 (C-3), 72.49 and 71.97 (C-1 and CH_2Ph), 68.93 (C-4), 62.26 (C-6), 59.86 (C-5), 26.66 and 26.27 (CMe_2). HRMS: *m/z* 462.1640 [M^++Na]. For $C_{23}H_{25}N_3O_6Na$ 462.1641 (deviation +0.3 ppm).

4.2.4. 5-Azido-4-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose (9). Compound **8** (2.47 g, 5.62 mmol) in anhyd. MeOH (50 mL) was treated with 0.5 M NaMeO in MeOH (10 mL) for 24 h. TLC (3:2 ether/hexane) then revealed a slower-running compound. The mixture was neutralized with AcOH, concentrated and the residue was partitioned in Cl_2CH_2-water. The organic phase was separated, concentrated and the residue submitted to flash chromatography (hexane → 1:1 ether/hexane) to afford crystalline **9** (1.83 g, 97%); mp 76–78 °C (from ether/hexane); $[\alpha]_D^{27}$ −132 (*c* 0.9); ν (KBr) 3521 (OH), 3039 (aromatic), 2099 (N_3), 1373 (CMe_2), 741 and 697 cm^{-1} (aromatic). ^1H NMR (300 MHz): δ 7.45–7.25 (m, 5H, Ph), 4.77 and 4.72 (2d, 2H, J=11.6 Hz, CH_2Ph), 4.19 and 3.99 (2d, 2H, $J_{1,1'}$=8.8 Hz, H-1,1′), 3.93–3.86 (m, 3H, H-3,5,6), 3.76 (dd, 1H, $J_{4,5}$=3.5 Hz, $J_{3,4}$=9.5 Hz, H-4), 3.70 (dd, 1H, $J_{5,6'}$=2.2 Hz, $J_{6,6'}$=12.8 Hz, H-6′), 1.48 and 1.43 (2s, 6H, CMe_2). ^{13}C NMR: δ 137.62, 128.67, 128.16, and 127.98 (CH_2Ph), 112.27 (CMe_2), 105.76 (C-2), 79.59 (C-3), 72.73 and 72.01 (C-1 and CH_2Ph), 68.23 (C-4), 62.17 (C-6), 59.41 (C-5), 26.72 and 26.27 (CMe_2). Anal. Calcd for $C_{16}H_{21}N_3O_5$: C, 57.30; H, 6.31; N, 12.53. Found: C, 57.15; H, 6.77; N, 12.05.

4.2.5. 5-Azido-4-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-psicopyranose (11). To a stirred suspension of Dess–Martin periodinane (3.48 g, 8.18 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise a solution of **9** (1.83 g, 5.46 mmol) in the same solvent (15 mL) under Ar. The mixture was stirred at room temperature for 1 h. TLC (3:2, 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 **10** [1.7 g, 93.4%; IR: υ (neat) 1753 cm^{-1}], that was used in the next step.

To a stirred and ice-water cooled solution of **10** (1.7 g, 5.1 mmol) in dry methanol (20 mL) $NaBH_4$ (0.29 g, 7.5 mmol) was added portionwise. After 1 h, TLC (3:2 ether/hexane) showed no ketone **10** and the presence of a new product of higher mobility. The reaction mixture was neutralized with AcOH, concentrated and the residue was dissolved in Cl_2CH_2, washed with water then concentrated. Flash column chromatography (1:1 ether/hexane) afforded crystalline **11** (1.51 g, 88%); mp 60–61 °C (from ether/hexane); $[\alpha]_D^{24}$ −117 (*c* 1); ν (KBr) 3509 (OH), 3033 (aromatic), 2124 (N_3), 1368 (CMe_2), 744 and 693 cm^{-1} (aromatic). ^1H NMR (300 MHz): δ 7.42–7.26 (m, 5H, Ph), 4.80 and 4.63 (2d, 2H, J=11.8 Hz, CH_2Ph), 4.17 and 4.08 (2d, 2H, $J_{1,1'}$=9.5 Hz, H-1,1′), 3.96 (dd, 1H, $J_{5,6ax}$=2.2 Hz, $J_{6ax,6eq}$=12.8 Hz, H-6ax), 3.89 (t, 1H, $J_{3,4}$, $J_{4,5}$=3.5 Hz, H-4), 3.85–3.80 (m, 3H, H-3,5,6eq), 3.17 (br d, 1H, $J_{OH,3}$=8.8 Hz, OH), 1.45 and 1.36 (2s, 6H, CMe_2). ^{13}C NMR: δ 137.48, 128.63, 128.08, and 127.77 (CH_2Ph), 112.48 (CMe_2), 105.70 (C-2), 73.72 (C-1), 73.26 (C-4), 70.83 (C-3), 70.43 (CH_2Ph), 62.34 (C-6), 58.86 (C-5), 26.74 and 26.42 (CMe_2). Anal. Calcd for $C_{16}H_{21}N_3O_5$: C, 57.30; H, 6.31; N, 12.53. Found: C, 57.50; H, 6.29; N, 12.63. HRMS: *m/z* 358.1380 [M^++Na]. For $C_{16}H_{21}N_3O_5Na$ 358.1379 (deviation −0.2 ppm).

4.2.6. 5-Azido-3,4-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-psicopyranose (12). To a stirred suspension of NaH (60% oil dispersion, 0.27 g, 6.76 mmol) in dry DMF (10 mL), compound **11** (1.51 g, 4.51 mmol) in the same solvent (10 mL) was added at room temperature. After 15 min, the mixture was cooled (ice-water) benzyl bromide (580 μL, 4.96 mmol) was added and the mixture was allowed to reach room temperature, then left for 2 h. TLC

(3:2 ether/hexane) then showed the presence of a faster-running compound. The mixture was poured into ice-water, and extracted with ether (4×30 mL). The combined extracts were washed with brine, water, and concentrated. Flash column chromatography (1:3 ether/hexane) of the residue gave **12** (1.37 g, 72%) as white crystals; mp 118–120° (from ether/hexane); $[\alpha]_D^{25}$ −101 (*c* 1); *ν* (KBr): 3031 (aromatic), 2103 (N_3), 1377 (CMe_2), 735 and 694 cm^{-1} (aromatic). ^1H NMR (300 MHz): *δ* 7.43–7.26 (m, 10H, 2 Ph), 4.86 and 4.76 (2d, 2H, *J*=11.7 Hz, CH_2Ph), 4.82 and 4.77 (2d, 2H, *J*=9.2 Hz, CH_2Ph), 4.14 and 3.98 (2d, 2H, $J_{1,1'}$=9.8 Hz, H-1,1′), 4.04 (t, 1H, $J_{3,4}$, $J_{4,5}$=3.0 Hz, H-4), 3.87 (dd, 1H, $J_{5,6ax}$=4.1 Hz, $J_{6ax,6eq}$=11.9 Hz, H-6ax), 3.80 (dd, 1H, $J_{5,6eq}$=6.0 Hz, H-6eq), 3.66 (d, 1H, H-3), 3.61 (m, 1H, H-5), 1.48 and 1.35 (2s, 6H, CMe_2). ^{13}C NMR: *δ* 137.99, 137.68, 128.65, 128.54, 128.50, 128.26, 127.97, and 127.85 (CH_2Ph), 111.39 (CMe_2), 105.69 (C-2), 77.22 and 77.04 (C-3,4), 74.50 (C-1), 74.49 and 73.21 (CH_2Ph), 62.01 (C-6), 56.47 (C-5), 27.20 and 26.03 (CMe_2). Anal. Calcd for $C_{23}H_{27}N_3O_5$: C, 64.93; H, 6.40; N, 9.88. Found: C, 64.49; H, 6.90; N, 10.06.

4.2.7. 5-Azido-3,4-di-*O*-benzyl-5-deoxy-D-psicopyranose (13). A solution of **12** (1.37 g, 3.22 mmol) in 60% aqueous TFA (5 mL) was kept at room temperature for 2 h. TLC (ether) then revealed two nearby and slower running compounds. The mixture was concentrated and repeatedly codistilled with water and then dissolved in dichloromethane, washed with 10% aqueous sodium carbonate and water, then concentrated. Flash column chromatography (1:1 ether/hexane) gave pure syrupy **13** (1.05 g, 85%) as ~2:1 mixture of its α and β-anomers, respectively. ^1H and ^{13}C NMR data (400 Hz), see Tables 1 and 2. HRMS: *m/z* 408.1538 [M^++Na]. For $C_{20}H_{23}N_3O_5Na$ 408.1535 (deviation −0.6 ppm).

4.2.8. Silylation of (13). To an ice-water cooled and stirred solution of **13** (4.90 g, 12.7 mmol) in dry DMF (30 mL) were added imidazole (1 g, 14.7 mmol) and *tert*-butylchlorodiphenylsilane (3.7 mL, 14.5 mmol) and the mixture was left at room temperature for 20 h. TLC (ether) then showed a complex mixture. MeOH (1 mL) was added and after 15 min the reaction mixture was diluted with water (100 mL) and extracted with ether (2×40 mL), then concentrated to a residue that was submitted to flash-chromatography (1:6, ether/hexane→ether) to afford first 5-azido-3,4-di-*O*-benzyl-1,6-di-*O*-*tert*-butyldiphenylsilyl-5-deoxy-D-psicose (**14**, 2.31 g, 26%) as a colourless syrup; $[\alpha]_D^{26}$ −1.2, $[\alpha]_{405}^{26}$ +7 (*c* 1.2); *ν* (neat) 2101 (N_3), 1735 (ketone), and 701 cm^{-1} (aromatic). ^1H NMR (300 MHz): *δ* 7.70–7.00 (4m, 30H, 6 Ph), 4.58 and 4.49 (2d, 2H, $J_{1,1'}$= 18.6 Hz, H-1,1′), 4.45 and 4.39 (2d, 2H, *J*=11.8 Hz, CH_2Ph), 4.45 and 4.33 (2d, 2H, $J_{1,1'}$=11.3 Hz, CH_2Ph), 4.20 (d, 1H, $J_{3,4}$=3 Hz, H-3), 3.92 (q, 1H, H-5), 3.82 (dd, 1H, $J_{4,5}$=7.2 Hz, H-4), 3.73 (t, 1H, $J_{5,6}$=$J_{6,6'}$=6.4 Hz, H-6), 3.71 (t, 1H, $J_{5,6'}$=6.7 Hz, H-6′), and 1.06 (s, 9H, CMe_3). ^{13}C NMR (inter alia): *δ* 206.67 (C-2), 81.77 (C-3), 79.43 (C-4), 73.27 (2 CH_2Ph), 69.11 (C-6), 64.55 (C-1), 62.94 (C-5), 26.81 (CMe_3) and 19.36 (CMe_3). HRMS: *m/z* 884.3896 [M^++Na]. For $C_{52}H_{59}N_3O_5NaSi_2$ 884.3891 (deviation −0.6 ppm).

Eluted second was 5-azido-3,4-di-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-5-deoxy-α-D-psicopyranose (**15**, 4.55 g, 70%) as a colourless syrup; $[\alpha]_D^{25}$ −37 (*c* 1.4); *ν* (neat) 3468 (OH), 2102 (N_3), and 701 cm^{-1} (aromatic). ^1H NMR (300 MHz): *δ* 7.75–7.25 (2m, 20H, 4 Ph), 5.40 (s, 1H, OH-2), 4.86 and 4.79 (2d, 2H, *J*=10.7 Hz, CH_2Ph), 4.69 (s, 2H, CH_2Ph), 4.28 (br t, 1H, H-4), 4.10 (t, 1H, $J_{5,6ax}$=$J_{6ax,6eq}$=11.3 Hz, H-6ax), 3.96 and 3.60 (2d, 2H, $J_{1,1'}$=10.5 Hz, H-1,1′), 3.90 (d, 1H, $J_{3,4}$=2.6 Hz, H-3), 3.78 (dd, 1H, $J_{5,6eq}$=5.0 Hz, H-6eq), 3.36 (ddd, 1H, $J_{4,5}$=2.5 Hz, H-5), and 1.08 (s, 9H, CMe_3). ^{13}C NMR (inter alia): *δ* 98.52 (C-2), 77.32 and 73.97 (C-3,4), 75.92 and 72.59 (2 CH_2Ph), 65.47 (C-1), 57.54 (C-5), 56.92 (C-6), 27.04 (CMe_3) and 19.43 (CMe_3). Starting material (0.87 g,) was finally recovered.

4.2.9. (2*R*,3*R*,4*S*,5*R*)- (17) and (2*R*,3*R*,4*S*,5*S*)-3,4-Dibenzyloxy-2′,5′-di-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (18). To a solution of **14** (418 mg, 0.48 mmol) in dry THF (10 mL) was added triphenylphosphine (250 mg, 0.95 mmol) and the mixture refluxed with stirring for 5 h. TLC (1:2 ether/hexane) then revealed a slower-running compound. The reaction mixture was supported on silica gel previously treated with ether/hexane/TEA 1:3:0.1 and chromatographed (1:3:0.1 ether/hexane/TEA) to afford (3*S*,4*R*,5*R*)-3,4-dibenzyloxy-2′,5′-di-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)-δ^2-pyrroline (**16**, 380 mg, 97%). $[\alpha]_D^{24}$ −39 (*c* 1.3); *ν* (neat) 3070, 3049, and 3031 (aromatic), 1659 (C=N), and 701 cm^{-1} (aromatic). ^1H NMR (300 MHz): *δ* 7.72–7.20 (3m, 30H, 6 Ph), 4.83 (br d, 1H, $J_{3,4}$=5.8 Hz, H-3), 4.72 and 4.63 (2d, 2H, *J*=11.2 Hz, CH_2Ph), 5.57 and 4.51 (2d, 2H, *J*=11.7 Hz, CH_2Ph), 4.61–4.54 (m, 2H, H-2′a,2′b), 4.25 (m, 1H, H-5), 4.17 (dd, 1H, $J_{4,5}$=1.9 Hz, H-4), 3.87 (dd, 1H, $J_{5,5'a}$=3.5 Hz, $J_{5'a,5'b}$=10.5 Hz, H-5′a), 3.81 (dd, 1H, $J_{5,5'b}$=4.1 Hz, H-5′b), 1.06 and 1.03 (2s, 18H, 2 CMe_3). ^{13}C NMR (inter alia): *δ* 176.40 (C-2), 82.29, 77.63 and 73.23 (C-3,4,5), 73.39 and 71.89 (2 CH_2Ph), 64.03 and 62.81 (C-2′,5′), 27.01 (2 CMe_3), 19.33 and 19.27 (2 CMe_3). Compound **16** decomposed on standing.

To a stirred and ice-water cooled solution of **16** (340 mg, 0.41 mmol) in THF (5 mL) containing acetic acid (50 μL), $NaCNBH_3$ (70 mg, 1.11 mmol) was added portionwise. After 15 min, the reaction mixture was allowed to reach room temperature. TLC (3:2 ether/hexane) then showed two slower-running compounds. The reaction mixture was slightly basified by addition of aqueous ammonia solution, then concentrated to a residue that was partitioned into ether/water, the organic phase was separated and concentrated. Column chromatography (1:3:0.1 ether/hexane/TEA) afforded first **17** (145 mg, 43%) as a colourless syrup. $[\alpha]_D^{29}$ +19 (*c* 1.5); *ν* (neat) 3070, 3049, and 701 cm^{-1} (aromatic). ^1H NMR (300 MHz): *δ* 7.70–7.20 (3m, 30H, 6 Ph), 4.69 and 4.61 (2d, 2H, *J*=11.9 Hz, CH_2Ph), 4.52 and 4.42 (2d, 2H, *J*=12.0 Hz, CH_2Ph), 4.11 (t, 1H, $J_{3,4}$=$J_{4,5}$= 4.4 Hz, H-4), 3.94 (dd, 1H, $J_{5,5'a}$=6.9 Hz, $J_{5'a,5'b}$=10.2 Hz, H-5′a), 3.93 (dd, 1H, $J_{2,3}$=6.4 Hz, H-3), 3.82 (dd, 1H, $J_{5,5'b}$=7.4 Hz, H-5′b), 3.70 (dd, 1H, $J_{2,2'a}$=4.6 Hz, $J_{2'a,2'b}$=10.7 Hz, H-2′a), 3.66 (dd, 1H, $J_{2,2'b}$=4.4 Hz, H-2′b), 3.45 (dt, 1H, H-5), 3.33 (dt, 1H, H-2), 1.90 (br s, 1H, NH), 1.09 and 1.06 (2s, 18H, 2 CMe_3). ^{13}C NMR (inter alia): *δ* 80.49 (C-3), 78.00 (C-4), 73.23 and 72.18 (2 CH_2Ph), 64.58 (C-2′), 63.72 (C-5′), 61.70 (C-2), 61.20 (C-5),

27.09 and 27.07 (2 C*Me*$_3$), and 19.39 (2 *C*Me$_3$). Anal. Calcd for $C_{52}H_{61}NO_4Si_2$: C, 76.15; H, 7.50; N, 1.71. Found: C, 75.87; H, 7.34; N, 2.05.

Eluted second was **18** (77 mg, 23%) as a colourless syrup. ν (neat) 3070, 3048, 3030 and 701 cm^{-1} (aromatic). ^{1}H NMR (300 MHz): δ 7.70–7.21 (2m, 30H, 6 Ph), 4.51 and 4.47 (2d, 4H, J=12.4 Hz, 2 CH$_2$Ph), 3.81 (br d, 2H, $J_{2,3}=J_{4,5}=$ 4.7 Hz, H-3,4), 3.76 (dd, 2H, $J_{2,2'a}=J_{5,5'a}=4.5$ Hz, $J_{2'a,2'b}=J_{5'a,5'b}=10.5$ Hz, H-2′a,5′a), 3.71 (dd, 2H, $J_{2,2'b}=J_{5,5'b}=4.4$ Hz, H-2′b,5′b), 3.41 (br q, 2H, H-2,5), 1.95 (br s, 1H, NH), and 1.03 (s, 18H, 2 CMe$_3$). ^{13}C NMR (inter alia): δ 78.43 (C-3,4), 71.87 (2 *C*H$_2$Ph), 64.47 (C-2′,5′), 63.07 (C-2,5), 27.05 (2 C*Me*$_3$), and 19.35 (2 *C*Me$_3$). Anal. Calcd for $C_{52}H_{61}NO_4Si_2$: C, 76.15; H, 7.50; N, 1.71. Found: C, 76.43; H, 7.46; N, 1.67.

4.2.10. Hydrogenation of 14. Compound **14** (1.76 g, 2.04 mmol) in MeOH/THF (2:1 v/v, 60 mL) was hydrogenated at 60 psi over wet Raney-Ni (3 g) for 5 h. TLC (3:1 ether/hexane) 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 (1:3:0.1 ether/hexane/TEA) to afford **18** (1.06 g, 73%).

4.2.11. (2*R*,3*R*,4*S*,5*S*)-3,4-dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine hydrochloride [2,5-dideoxy-2,5-imino-D-allitol (DADP, 19)]. Compound **18** (990 mg, 1.2 mmol) in THF (25 mL), was treated with a solution of tetra-*n*-butylammonium fluoride trihydrate (915 mg, 2.9 mmol) for 1 h at room temperature TLC (ether) then showed the presence of a non mobile compound. The reaction mixture was concentrated and the residue dissolved in AcOEt and washed with brine, then concentrated. Column chromatography (ether→5:1:0.1 ether/methanol/NH$_4$OH) of the residue afford fractions containing 3,4-dibenzyloxy derivative of **18** (NMR evidence), contaminated with tetra-*n*-butylammonium hydroxide, that was subsequently hydrogenated in MeOH (15 mL) and concd HCl (5 drops) over 10% Pd–C (200 mg) in an H$_2$ atmosphere for 24 h. TLC (5:1:0.1 ether/methanol/NH$_4$OH) 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$_2$CH$_2$ to yield **19** hydrochloride (90 mg, 38%) as a colourless foam. ^{1}H NMR (300 MHz, MeOH-d_4)): δ 4.10 (m, 2H, H-3,4), 3.86 (dd, 2H, $J_{2,2'a}=J_{5,5'a}=3.9$ Hz, $J_{2'a,2'b}=J_{5'a,5'b}=12.0$ Hz H-2′a,5′a), 3.77 (dd, 2H, $J_{2,2'b}=J_{5,5'b}=5.7$ Hz, H-2′b,5′b), and 3.59 (m, 2H, H-2,5). ^{13}C NMR: δ 72.44 (C-3,4), 66.21 (C-2,5), and 59.46 (C-2′,5′).

4.2.12. (2*S*,3*S*,4*R*,5*R*)-3,4-Dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (21). Treatment of **15** (1.2 g, 1.93 mmol) in dry THF (30 mL) with triphenylphosphine (760 mg, 2.9 mmol) as above for 7 h, afforded after work-up and column chromatography (2:1 ether/hexane→ether) (3*S*,4*R*,5*R*)-3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)-δ^2-pyrroline (**20**, 850 mg, 77%) as an unstable pale yellow syrup, that was not characterized but used in the next step.

To a stirred and ice-water cooled solution of **20** (815 mg, 1.41 mmol) in THF (15 mL) containing acetic acid (180 μL), NaCNBH$_3$ (273 mg, 4.35 mmol) was added portionwise. After 1 h, the reaction mixture was allowed to reach room temperature. TLC (ether) then showed a non-mobile compound. The reaction mixture was concentrated and the residue dissolved in EtAcO and washed with brine, then concentrated. Column chromatography (10:1 ether/methanol) gave **21** (335 mg, 41%) as a colourless syrup. $[\alpha]_D^{27}+32$ (*c* 1.6). ν (neat) 3338 (OH), 3069, 3031, and 701 cm^{-1} (aromatic). ^{1}H NMR (300 MHz): δ 7.70–7.20 (2m, 20H, 4 Ph), 4.68 and 4.56 (2d, 2H, J=11.7 Hz, CH$_2$Ph), 4.60 and 4.48 (2d, 2H, J=11.9 Hz, CH$_2$Ph), 4.03 (t, 1H, $J_{2,3}=J_{3,4}=4.3$ Hz, H-3), 3.92 (dd, 1H, $J_{2,2'a}=$ 6.6 Hz, $J_{2'a,2'b}=10.2$ Hz, H-2′a), 3.86 (dd, 1H, $J_{2,2'b}=$ 7.3 Hz, H-2′b), 3.80 (dd, 1H, $J_{4,5}=6.1$ Hz, H-4), 3.51 (dd, 1H, $J_{5,5'a}=3.5$ Hz, $J_{5'a,5'b}=10.5$ Hz, H-5′a), 3.46 (dd, 1H, $J_{5,5'b}=3.5$ Hz, H-5′b), 3.38 (m, 1H, H-2), 3.32 (m, 1H, H-5), 2.28 (br s, 1H, NH), and 1.08 (s, 9H, CMe$_3$). ^{13}C NMR (inter alia): δ 80.89 (C-4), 78.47 (C-3), 73.23 and 72.58 (2 *C*H$_2$Ph), 62.96 (C-2′,5′), 61.46 (C-2), 61.09 (C-5), 27.05 (C*Me*$_3$), and 19.32 (*C*Me$_3$). Anal. Calcd for $C_{36}H_{43}NO_4Si$: C, 74.32; H, 7.45; N, 2.41. Found: C, 74.48; H, 7.43; N, 2.28.

4.2.13. Hydrogenation of 15. Compound **15** (3.3g, 5.3 mmol) in MeOH (40 mL) was hydrogenated at 60 psi over wet Raney-Ni (3 g) for 20 h. TLC (15:1 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→15:1 ether/methanol) to afford crystalline (2*R*,3*S*,4*R*,5*R*)-3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (**22**, 1.9 g, 62%); mp 92–94° (from ether); $[\alpha]_D^{27}+16$ (*c* 1); ν (KBr) 3270 (OH, NH), 3087, 3030, and 700 cm^{-1} (aromatic). ^{1}H NMR (400 MHz): δ 7.68–7.62 and 7.44–7.25 (2m, 20H, 4 Ph), 4.56 and 4.49 (2d, 2H, J=11.8 Hz, CH$_2$Ph), 4.52 (s, 2H, CH$_2$Ph), 3.86 (t, 1H, $J_{3,4}$, $J_{4,5}=4.5$ Hz, H-4), 3.78 (br t, 1H, $J_{2,3}=5.2$ Hz, H-3), 3.52 (br d, 2H, H-2′,2′), 3.49–3.39 (m, 4H, H-2,5,5′a,5′b), 2.05 (br s, 2H, NH,OH), and 1.05 (s, 9H, CMe$_3$). ^{13}C NMR (inter alia): δ 78.71 (C-3), 78.59 (C-4), 72.28 and 71.83 (2 *C*H$_2$Ph), 65.46 (C-2′), 62.72 and 61.50 (C-2,5), 62.05 (C-5′), 27.00 (C*Me*$_3$), and 19.34 (*C*Me$_3$). Mass spectrum (LSIMS): *m*/*z* 582.3038 [M$^+$+H] for $C_{36}H_{44}NO_4Si$ 582.3040 (deviation +0.2 ppm). Anal. Calcd for $C_{36}H_{43}NO_4Si$: C, 74.32; H, 7.45; N, 2.41. Found: C, 74.35; H, 7.29; N, 2.22.

4.2.14. (2*R*,3*R*,4*S*,5*R*)-3,4-dibenzyloxy-2,5-bis(hydroxymethyl)pyrrolidine (23). Compound **22** (110 mg, 0.2 mmol) in THF (10 mL), was treated with a solution of tetra-*n*-butylammonium fluoride trihydrate (120 mg, 0.4 mmol) for 2 h at room temperature. TLC (5:1:0.1 ether/methanol/TEA) then showed the presence of a more polar compound. The reaction mixture was concentrated and the residue submitted to column chromatography (5:1:0.1 ether/methanol/TEA) to yield **23** (50 mg, 73%) as a colourless syrup; $[\alpha]_D^{26}-3$ (*c* 1). ^{1}H NMR (400 MHz): δ 7.24–7.15 (m, 10H, 2 Ph), 4.50–4.40 (m, 4H, 2 CH$_2$Ph), 3.92 (br s, 2H, OH,NH), 3.70 (br d, 1H, $J_{2,7}=2.7$ Hz, H-3 or H-4), 3.62–3.55 and 3.43–3.30 (2m, 6H, H-4 or H-3, H-2′a,2′b,5′a,5′b, H-5 or

H-2), and 3.05 (m, 1H, H-5 or H-2). ^{13}C NMR (inter alia): δ 78.52 and 77.74 (C-3,4), 72.11 and 71.97 (2 *C*H$_2$Ph), 70.16 and 62.38 (C-2,5), 62.51 and 62.42 (C-2′,5′). Mass spectrum (LSIMS): *m/z* 366.1680 [M$^+$+Na] for $C_{20}H_{25}NO_4Na$ 366.1681 (deviation+0.2 ppm).

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