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Note

A practical route to partially protected pyrrolidines as precursors for the stereoselective synthesis of alexines

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Abstract

Either 3-*O*-benzoyl- (**2a**) or 3-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose (**2b**) were regioselectively *O*-benzylated at C-4 to give **4a** and **4b**, respectively, which were transformed into 5-azido-3-*O*-benzoyl-4-*O*-benzyl- (**6a**) and 5-azido-3,4-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-L-sorbopyranose (**6b**) by nucleophilic displacement of the corresponding 5-*O*-mesyl derivatives **5a** and **5b** by sodium azide in DMF, respectively. Compound **6b** was also prepared from **4b** in one step by the Mitsunobu methodology. Deacetonation of **6a** and **6b** gave the partially protected free azidouloses **8a** and **8b**, respectively, that were protected as their 1-*O*-TBDPS derivatives **9a** and **9b**. Hydrogenation of **9b** over Raney nickel gave stereoselectively (2*R*,3*R*,4*R*,5*S*)-3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (**12**) which was identified by transformation into the well known (2*R*,3*R*,4*R*,5*S*)-3,4-dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine (**1**, DGDP).

Keywords: D-Fructose; Stereoselective synthesis; Polyhydroxypyrrolidines

The pyrrolizidine skeleton 1-aza-bicyclo-[3.3.0]octane is the basic framework of a group of alkaloids isolated from both plant and animal sources such as alexine, australine and casuarine. Alexine, a tetrahydroxy-pyrrolizidine isolated from *Alexa leiopetala* by Nash et al.[1] in 1988 shows inhibitory activity against glycosidase and could then be of use as chemotherapeutic agents.[2] According to the retrosynthetic scheme (Scheme 1), D-fructose could be considered a suitable chiral starting material for the synthesis of compounds of alexine type, since it contains the appropriate chiral information and can be easily transformed into the adequately protected (2*R*,3*R*,4*R*,5*S*)-3,4-dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine (2,5-dideoxy-2,5-imino-D-glucitol, DGDP, **1**), a versatile key intermediate, which after two carbon-chain lengthening at C-6 (C-5′ when the heterocyclic nomenclature is used) and subsequent cyclization would provide the required polyhydroxypyrrolizidine bicyclic system.

Compound **1** has been previously prepared from 5-azido-5-deoxy-L-sorbose and 5-keto-D-fructose, respectively, by chemoenzymatic approaches.[3,4] However, this does not allow the suitable protection for the synthesis of alexine compounds. With this objective in mind, a

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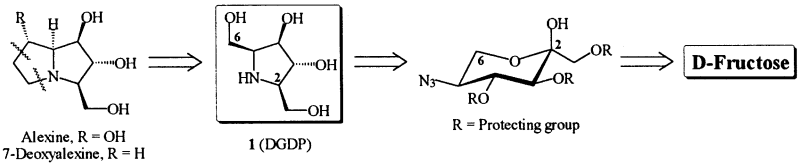
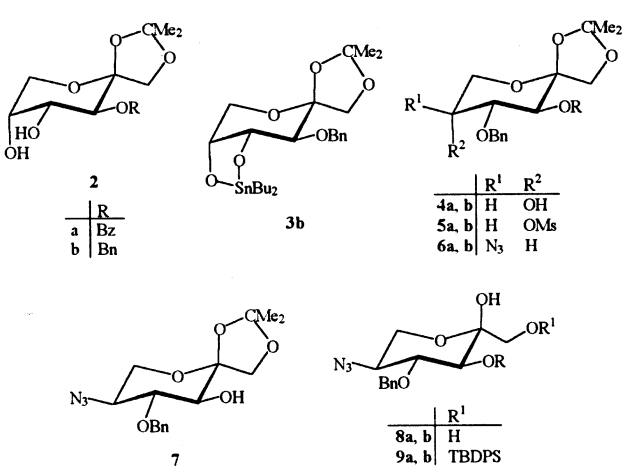


Scheme 1. Retrosynthetic scheme for the preparation of alexine and 7-deoxyalexine from D-fructose.

synthesis of adequately protected **1**, starting from a readily available 3-*O*-substituted derivative of 1,2-*O*-isopropylidene-β-D-fructopyranose is now reported.

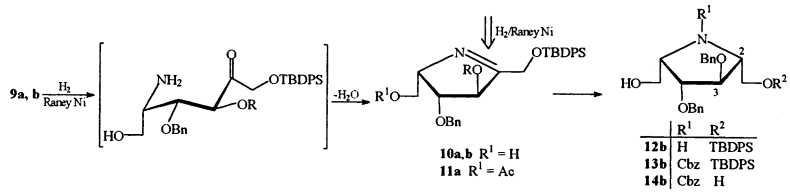
Reaction of 3-*O*-benzoyl-4-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose[5] (**4a**) with methanesulfonyl chloride gave the corresponding 5-*O*-methanesulfonyl derivative **5a** that was subsequently transformed into the related 5-azido-3-*O*-benzoyl-4-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-L-sorbopyranose (**6a**) by treatment with sodium azide in DMF. The acidic removal of the 1,2-*O*-isopropylidene group afforded crystalline 5-azido-3-*O*-benzoyl-4-*O*-benzyl-5-deoxy-α-L-sorbopyranos e (**8a**). The $^{2}C_{5}$ conformation and α configuration of **8a** were reasonably assigned on the basis of its ^{13}C NMR spectrum which showed a single signal for C-2 at δ 97.13. The HO-1 in **8a** was protected as its *O*-*tert*-butyldiphenylsilyl ether **9a** before hydrogenation to the intermediate pyrrolidine, since it has been reported[6] that decomposition takes place in an analogous compound when a free hydroxyl group was present at the same position (Scheme 2).



Scheme 2.

Treatment of **8a** with *tert*-butylchlorodiphenylsilane–imidazole in DMF afforded 5-azido-3-*O*-benzoyl-4-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-5-deoxy-α-L-sorbopyranose (**9a**) in quantitative yield. Hydrogenation of **9a** over 10% Pd–C gave the corresponding pyrroline **10a**, characterized through its 5′-*O*-acetyl derivative **11a**. An attempt to continue the hydrogenation of **10a** to the pyrrolidine stage was unsuccessful and only an extensive decomposition was observed. On the basis of this results, a change of protective group at C-3 was considered and 3-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose (**2b**)[7] was used as chiral starting material. O-Benzylation at C-4 of **2b** was carried out via its 4,5-*O*-stannylene derivative **3** by regioselective ring opening with benzyl bromide at the oxygen in equatorial position to give the corresponding 3,4-di-*O*-benzyl derivative **4b**, straightforwardly transformed into 5-azido-3,4-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-L-sorbo pyranose (**6b**) through the 5-*O*-mesyl derivative **5b** as above. Compound **6b** was also synthesized from **6a** by Zemplén debenzoylation to **7** followed by 3-O-benzylation and finally, in order to shorten the synthesis, by a Mitsunobu reaction on **4b** with hydrogen azide.[8] Deacetonation of **6b** in acidic medium gave 5-azido-3,4-di-*O*-benzyl-5-deoxy-α-L-sorbopyranose (**8b**), which enantiomer has been reported.[9] As in the case of **8a**, compound **8b** existed as only one anomer (^{13}C NMR) (Scheme 3).

Chemoselective protection at C-1 of **8b** to give the azidohexulose **9b**, as above, followed by catalytic hydrogenation over Raney nickel allowed the formation of the corresponding aminocarbonyl sugar that rearranged in a fast process to its cyclic imine intermediate **10b** which was finally hydrogenated in a highly stereocontrolled manner to afford (2*R*,3*R*,4*R*,5*S*) -3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine



Scheme 3.

(**12**) in accordance with results previously reported.[3a,c,10] The configuration of **12**, as well as that of its easier to handle *N*-Cbz derivative **13**, were established on the basis of its analytical and spectroscopic data and by total deprotection to the known DGDP **1**.[3,4,11,12]

Compound **13** is an interesting molecule, since depending on whether the chain lengthening occurred, either at C-1 or C-6, the target compounds would belong either to the alexine or australine series.

1. Experimental

General methods.—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 Hewlett–Packard HP-5988-A and Fisons mod. Platform II and VG 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} aluminum sheets with detection by charring with H_2SO_4. Column chromatography was performed on Silica Gel (E. Merck, 7734). The noncrystalline 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.

3-O-Benzoyl-4-O-benzyl-1,2-O-isopropylidene-5-O-methanesulfonyl-β-D-fructopyranose (**5a**).—To an ice-water cooled and stirred solution of 3-*O*-benzoyl-4-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose[5] (**4a**, 5.1 g, 12.3 mmol) and triethylamine (2 mL, 14.4 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise methanesulfonyl chloride (1 mL, 13 mmol), and the mixture was maintained at rt overnight. TLC (2:1 ether–hexane) then revealed a faster-running compound. Methanol (1 mL) was added, and after 1 h the mixture was concentrated and the residue dissolved in CH_2Cl_2 (30 mL), washed with water, then concentrated. Column chromatography (1:1 CH_2Cl_2–ether) afforded crystalline **5a** (4.2 g, 70%), mp 156–158 °C (from ether); $[\alpha]_D^{25}$ −143° (*c* 1.7); IR (KBr): *v* 1723 (C=O, benzoate) and 1378 cm^{-1} (CMe_2); ^1H NMR: δ 8.07–8.05, 7.65–7.59, 7.50–7.45, and 7.23–7.09 (4 m, 10 H, aromatic), 5.60 (d, 1 H, $J_{3,4}$ 10.2 Hz, H-3), 5.22 (m, 1 H, H-5), 4.71 and 4.51 (2 d, 2 H, *J* 11.5, PhCH_2), 4.10 (dd, 1 H, $J_{5,6a}$ 1.1, $J_{6a,6e}$ 13.3 Hz, H-6a), 4.07 (dd, 1 H, $J_{4,5}$ 3.2 Hz, H-4), 4.05 and 3.96 (2 d, 2 H, $J_{1,1'}$ 9.3 Hz, H-1,1′), 4.02 (dd, 1 H, $J_{5,6e}$ 1.9 Hz, H-6e), 3.08 (s, 3 H, Ms), 1.49, and 1.40 (2 s, 6 H, CMe_2); ^{13}C NMR: δ 165.85 (CO), 136.84, 133.59, 129.92, 129.44, 128.64, 128.45, 128.05, and 127.98 (aromatic), 112.38 (*C*Me_2), 104.77 (C-2), 76.85 and 75.16 (C-3,5), 72.70 and 71.89 (Ph*C*H_2, C-1), 68.43 (C-4), 63.30 (C-6), 39.23 (Ms), 26.55 and 26.29 (C*Me*$_2$). Anal. Calcd for $C_{24}H_{28}O_9S$: C, 58.52; H, 5.73; S, 6.51. Found: C, 58.54; H, 5.87; S, 6.43.

5-Azido-3-O-benzoyl-4-O-benzyl-5-deoxy-1,2-O-isopropylidene-α-L-sorbopyranose (**6a**).—A stirred solution of **5a** (4 g, 8.13 mmol) and NaN_3 (1.05 g, 16.2 mmol) in dry DMF (30 mL) was heated at 80 °C for 15 h. TLC (2:1 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. Column chromatography (1:1 ether–hexane) of the residue afforded crystalline **6a** (3 g, 84%), mp 97–98 °C (from ether–hexane); $[\alpha]_D^{26}$ −222° (*c* 1.4); IR (KBr): *v* 2109

(N_3), 1724 (C=O, benzoate), 1383 and 1374 cm^{-1} (CMe_2); ^1H NMR: δ 8.10–8.02, 7.63–7.58, 7.50–7.45, and 7.19–7.08 (4 m, 10 H, aromatic), 5.31 (d, 1 H, $J_{3,4}$ 9.7 Hz, H-3), 4.76 and 4.62 (2 d, 2 H, J 10.5, PhCH_2), 3.97 and 3.91 (2 d, 2 H, $J_{1,1'}$ 9.3 Hz, H-1,1′), 3.84–3.64 (m, 4 H, H-4,5,6a,6e), 1.50 and 1.42 (2 s, 6 H, CMe_2); ^{13}C NMR: δ 165.74 (CO), 137.29, 133.63, 129.93, 129.40, 128.69, 128.35, 128.20, and 127.90 (aromatic), 112.48 (CMe_2), 104.44 (C-2), 80.12 (C-3), 75.47 (PhCH_2), 71.69 (C-1), 71.39 (C-4,5), 61.52 (C-6), 26.73 and 26.25 (CMe_2). Anal. Calcd for $C_{23}H_{25}N_3O_6$: C, 62.86; H, 5.73; N, 9.56. Found: C, 63.10; H, 6.09; N, 9.58.

5-Azido-4-O-*benzyl-5-deoxy-1,2*-O-*isopropylidene-α*-L-*sorbopyranose* (**7**).—Compound **6a** (2 g, 4.5 mmol) in anhyd MeOH (15 mL) was treated with 0.1 M NaOMe in MeOH (5 mL) overnight. TLC (2:1 ether–hexane) then showed the absence of **6a** and the presence of a slower-running compound. The mixture was neutralized with AcOH, and after the usual work-up the resulting residue was chromatographed (1:5 → 1:1 ether–hexane) to afford syrupy **7** (1.4 g, 92%); $[\alpha]_D^{27}$ −145° (*c* 1); IR (film): *v* 3483 (OH), 3068 and 3036 (aromatic), 2110 (N_3), 1385 and 1373 (CMe_2), 733 and 698 cm^{-1} (aromatic); ^1H NMR: δ 7.45–7.28 (m, 5 H, *Ph*CH_2), 4.94 and 4.68 (2 d, 2 H, J 10.8, PhCH_2), 4.15 and 3.94 (2 d, 2 H, $J_{1,1'}$ 8.8 Hz, H-1,1′), 3.73–3.51 (2 m, 5 H, H-3,4,5,6a,6e), 1.49 and 1.45 (2 s, 6 H, CMe_2); ^{13}C NMR: δ 137.91, 128.58, 128.26, and 128.06 (*Ph*CH_2), 112.49 (CMe_2), 105.41 (C-2), 82.76 (C-3), 75.36 (C-1), 72.04 (C-4), 71.95 (PhCH_2), 61.47 (C-6), 60.93 (C-5), 26.68 and 26.35 (CMe_2). HRMS: *m/z* 358.13777 $[M + Na]^+$. For $C_{16}H_{21}N_3NaO_5$ 358.13789 (deviation 0.3 ppm).

5-Azido-3-O-*benzoyl-4*-O-*benzyl-5-deoxy-α*-L-*sorbopyranose* (**8a**).—A solution of **6a** (2.75 g, 6.3 mmol) in 70% aq TFA (10 mL) was kept at rt 5 h. TLC (2:1 ether–hexane) then revealed a slower-running compound. The mixture was diluted with water and the precipitated **8a** was collected by filtration, washed with water and finally air-dried (2.43 g, quantitative). An aliquot was chromatographed (1:1 → 2:1 ether–hexane) to afford pure **8a** (100 mg), mp 97–98 °C (from ether–hexane); $[\alpha]_D^{23}$ −197° (*c* 1); IR (KBr): *v* 3528 and 3259 (OH), 2107 (N_3), and 1717 cm^{-1} (C=O, benzoate); ^{13}C NMR: δ 166.17 (CO), 137.22, 133.77, 130.03, 129.11, 128.69, 128.37, 128.23, and 127.94 (aromatic), 97.13 (C-2), 79.11 (C-3), 75.58 (PhCH_2), 72.54 (C-4), 65.33 (C-1), 61.70 (C-5), and 60.80 (C-6). Anal. Calcd for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52. Found: C, 59.98; H, 5.73; N, 10.47.

5-Azido-3-O-*benzoyl-4*-O-*benzyl-1*-O-*tert-butyldiphenylsilyl-5-deoxy-α*-L-*sorbopyranose* (**9a**).—To a stirred solution of **8a** (1.82 g, 4.6 mmol) in dry DMF (7 mL) were added imidazole (340 mg, 5 mmol) and *tert*-butylchlorodiphenylsilane (1.3 mL, 5 mmol) and the mixture was left at rt 5 h. TLC (2:1 ether–hexane) then revealed a faster-running compound. The mixture was concentrated and the residue dissolved in ether (30 mL) and the resulting solution was washed with brine and concentrated. Column chromatography (1:4 ether–hexane) of the residue afforded pure **9a** (2.24 g, 96%) as a syrup; $[\alpha]_D^{22}$ −85.5° (*c* 1.2); IR (film): *v* 3511 (OH), 3074 (aromatic), 2110 (N_3), 1733 (C=O, benzoate), and 709 cm^{-1} (aromatic); ^1H NMR: δ 8.09–8.02 and 7.70–7.15 (2 m, 20 H, aromatic), 5.16 (dd, 1 H, $J_{3,4}$ 9.5, $J_{3,OH}$ 1 Hz, H-3), 4.82 and 4.69 (2 d, 2 H, J 10.6 Hz, PhCH_2), 4.12 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 4.04 (d, 1 H, HO-2), 3.86 (d, 2 H, $J_{5,6}$ 8.6 Hz, H-6,6), 3.77 (q, 1 H, H-5), 3.73 and 3.61 (2 d, 2 H, $J_{1,1'}$ 10.5 Hz, H-1,1′), and 1.09 (s, 9 H, CMe_3); ^{13}C NMR (inter alia): δ 165.60 (*C*OPh), 96.90 (C-2), 79.44 (C-3), 75.50 (PhCH_2), 72.34 (C-4), 65.90 (C-1), 61.77 (C-5), 60.70 (C-6), 26.82 (CMe_3), and 19.30 (CMe_3). HRMS: *m/z* 660.25067 $[M + Na]^+$. For $C_{36}H_{39}N_3NaO_6Si$ 660.25058 (deviation −0.1 ppm).

Hydrogenation of **9a**.—Compound **9a** (1.89 g, 3 mmol) in MeOH–ether (50 mL) was hydrogenated at 69 KPa over 10% Pd–C (0.3 g) overnight. TLC (1:0.1 ether–triethylamine) then revealed the presence of only a slower-running compound. The catalyst was filtered off, washed with MeOH–ether, and the combined filtrate and washings were concentrated to give (3*R*,4*R*,5*S*)-3-benzoyloxy-4-benzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)-1-pyrroline (**10a**, 1.64 g, 94%) as a clear syrup, that was characterized through its 5′-*O*-acetate (**11a**). Thus, conventional acetyl

ation of **10a** (100 mg, 0.17 mmol) in dry CH_2Cl_2 (6 mL) with Ac_2O (0.5 mL) and triethylamine (0.6 mL) gave, after usual work-up and column chromatography (1:1 ether–hexane), pure **11a** (65 mg, 60%) as a colorless syrup; $[\alpha]_D^{22}$ −47° (*c* 1.8); IR (film): *v* 1744 (C=O, acetate), 1728 (C=O, benzoate), and 1659 cm^{-1} (C=N); ^1H NMR (inter alia): δ 6.26 (s, 1 H, H-3), 4.88 and 4.67 (2 d, 2 H, *J* 12 Hz, PhCH_2), 2.00 (s, 3 H, Ac), and 1.00 (s, 9 H, CMe_3); ^{13}C NMR: δ 174.92 (C-2), 171.00 (*C*OMe), 165.64 (*C*OPh), 80.86 and 80.34 (C-3,4), 72.07 (Ph*C*H_2), 71.88 (C-5), 62.95 and 62.59 (C-2′,5′), 26.73 (C*Me*$_3$), 21.09 (CO*Me*), and 19.16 (*C*Me_3). HRMS: *m*/*z* 658.26005 $[M+Na]^+$. For $C_{38}H_{41}NNaO_6Si$ 658.26009 (deviation 0.1 ppm).

3,4-di-O-*benzyl-1,2*-O-*isopropylidene-β*-D-*fructopyranose* (**4b**).—To a solution of 3-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose[7] (**2b**, 8 g, 25 mmol) in anhyd MeOH (70 mL) was added dibutyltin oxide (6.6 g, 26.5 mmol) and the suspension was heated for 2 h under reflux, then concentrated to afford the 3,4-dibutylstannylene derivative **3** as a solid foam that was dried under vacuum over P_2O_5 overnight. A solution of **3** in dry DMF (60 mL) was treated with BnBr (6 mL, 51 mmol) and heated at 110 °C for 4 h. TLC (ether) then revealed a main faster-running product. Evaporation of the solvent gave a residue, a solution of which in ether was washed with brine and water, then concentrated. Column chromatography (1:3 ether–hexane) of the residue afforded **4b** (5.7 g, 55%) as syrup; $[\alpha]_D^{26}$ −82° (*c* 1); IR (film): *v* 3500 (OH), 3030 and 3020 (aromatic), 1385 and 1375 (CMe_2), 710 and 680 cm^{-1} (aromatic); ^1H NMR: δ 7.37 (m, 10 H, 2 CH_2*Ph*), 4.99 and 4.67 (2 d, 2 H, *J* 11.5 Hz, PhCH_2), 4.77 and 4.55 (2 d, 2 H, *J* 11.8 Hz, PhCH_2), 4.06 (dd, 1 H, H-4), 4.05 and 3.95 (2 d, 2 H, $J_{1,1'}$ 8.6 Hz, H-1,1′), 3.91–3.80 (m, 2 H, H-6a,6e), 3.66 (d, 1 H, $J_{3,4}$ 9.6 Hz, H-3), 1.49 and 1.42 (2 s, 6 H, CMe_2); ^{13}C NMR: δ 138.38, 137.73, 128.64, 128.42, 128.07, 127.98, 127.83, and 127.71 (CH_2*Ph*), 111.96 (*C*Me_2), 105.64 (C-2), 76.93 and 71.68 (C-3,4,5), 75.13 (C-1), 71.88 and 71.59 (2 Ph*C*H_2), 60.35 (C-6), 27.06 and 26.15 (C*Me*$_2$). HRMS: *m*/*z* 423.17835 $[M+Na]^+$. For $C_{23}H_{28}NaO_6$ 423.17836 (deviation 0.0 ppm).

3,4-di-O-*Benzyl-1,2*-O-*isopropylidene-5-O-methanesulfonyl-β*-D-*fructopyranose* (**5b**).—To an ice-water cooled and stirred solution of **4b** (5.26 g, 13 mmol) and triethylamine (5.2 mL, 37.6 mmol) in dry CH_2Cl_2 (25 mL) was added dropwise methanesulfonyl chloride (1.67 mL, 17.2 mmol), and the mixture was maintained at rt overnight. TLC (3:1 ether–hexane) then revealed a faster-running compound. MeOH (1 mL) was added and after 1 h the mixture was concentrated and the residue dissolved in CH_2Cl_2 (30 mL) washed with water and concentrated. Column chromatography (1:3 → 1:2 ether–hexane) afforded crystalline **5b** slightly impurified that was recrystallized (1:9 ether–hexane) giving pure compound (4.6 g, 74%), mp 78–80 °C; $[\alpha]_D^{27}$ −109° (*c* 1.1); IR (KBr): *v* 3064 and 3032 (aromatic), 1385 and 1375 (CMe_2), 738 and 697 cm^{-1} (aromatic); ^1H NMR: δ 7.34 (m, 10 H, 2 *Ph*CH_2), 5.14 (m, 1 H, H-5), 4.98 and 4.66 (2 d, 2 H, *J* 11.4 Hz, PhCH_2), 4.80 and 4.67 (2 d, 2 H, *J* 10.7 Hz, PhCH_2), 4.01 (dd, 1 H, $J_{4,5}$ 3.2 Hz, H-4), 4.00 (bd, 1 H, H-6a), 3.99 and 3.94 (2 d, 2 H, $J_{1,1'}$ 8.6 Hz, H-1,1′), 3.93 (dd, 1 H, $J_{5,6e}$ 1.9, $J_{6a,6e}$ 13.4 Hz, H-6e), 3.74 (d, 1 H, $J_{3,4}$ 9.8 Hz, H-3), 3.04 (s, 3 H, Ms), 1.48 and 1.44 (2 s, 6 H, CMe_2); ^{13}C NMR: δ 137.97, 137.34, 128.61, 128.56, 128.50, 128.45, 128.40, 128.31, 128.27, 128.10, 127.83, 127.79, and 127.75 (aromatic), 112.32 (*C*Me_2), 105.64 (C-2), 77.95, 77.52, and 74.66 (C-3,4,5), 75.45 (C-1), 72.93 and 71.73 (2 Ph*C*H_2), 62.74 (C-6), 39.03 (Ms), 26.99 and 26.14 (C*Me*$_2$). Anal. Calcd for $C_{24}H_{30}O_8S$: C, 60.23; H, 6.31. Found: C, 59.87; H, 6.60.

5-Azido-3,4-di-O-*benzyl-5-deoxy-1,2*-O-*isopropylidene-α*-L-*sorbopyranose* (**6b**).—(a) A stirred solution of **5b** (4 g, 8 mmol) and NaN_3 (690 mg, 10.6 mmol) in dry DMF (30 mL) was heated at 100 °C for 2 days. TLC (3:1 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. Column chromatography (1:4 ether–hexane) of the residue afforded syrupy **6b** (3.36 g, 98%); $[\alpha]_D^{25}$ −107° (*c* 1.2); IR (film): *v* 3067 and 3035 (aromatic), 2109 (N_3), 1384 and 1373 (CMe_2), 736 and 696 cm^{-1} (aromatic); ^1H NMR: δ 7.41–7.31 (m, 10 H, 2 *Ph*CH_2), 4.98 and 4.67 (2 d, 2 H, *J* 11.5 Hz, PhCH_2), 4.90 (s, 2 H,

PhCH_2), 3.93 and 3.85 (2 d, 2 H, $J_{1,1'}$ 8.6 Hz, H-1,1′), 3.86 (dt, 1 H, $J_{5,6e}$ 1.6, $J_{4,5} = J_{5,6a} = 9.3$ Hz, H-5), 3.79–3.58 (m, 3 H, H-4,6a,6e), 3.44 (d, 1 H, $J_{3,4}$ 9.3 Hz, H-3), 1.51 and 1.47 (2 s, 6 H, CMe_2); ^{13}C NMR: δ 137.90, 137.87, 128.56, 128.29, 128.01, 127.94, and 127.90 (aromatic), 112.47 (CMe_2), 105.30 (C-2), 82.56 (C-3), 78.64 (C-4), 75.75 and 75.47 (2 PhCH_2), 71.57 (C-1), 61.94 (C-5), 61.28 (C-6), 27.16 and 26.19 (CMe_2). HRMS: m/z 448.18493 $[M + Na]^+$. For $C_{23}H_{27}N_3NaO_5$ 448.18484 (deviation −0.2 ppm).

(b) Compound **6b** was also obtained in quantitative yield from **7** (1.31 g, 3.9 mmol) by treatment with NaH (187 mg, 7.8 mmol) and BnBr (0.7 mL, 5.8 mmol) in dry THF (15 mL), after usual work-up.

(c) To a stirred solution of **4b** (400 mg, 1 mmol) in dried $CHCl_3$ (6 mL), triphenylphosphine (390 mg, 1.5 mmol) and a 1 M solution of hydrogen azide (2 mL) in the same solvent were added. The resulting mixture was cooled (ice-water) and diethyl azodicarboxylate (DEAD) (0.24 mL, 1.5 mmol) was added dropwise. The solution was allowed to warm slowly to rt. After 2 h, more HN_3 solution (2 mL, 2 mmol), PPh_3 (390 mg, 1.5 mmol) and DEAD (0.24 mL, 1.5 mmol) were added and the mixture left at rt overnight. TLC (3:1 ether–hexane) then showed the absence of **4b** and the presence of **6b**. The reaction mixture was supported on silica gel and chromatographed as above to afford pure **6b** (340 mg, 80%) according to its analytical and spectroscopic data.

5-Azido-3,4-di-O-*benzyl-5-deoxy*-α-L-*sorbopyranose* (**8b**).—A solution of **6b** (3.36 g, 7.9 mmol) in 70% aq trifluoroacetic acid (10 mL) was kept at rt for 24 h. TLC (3:1 ether–hexane) then revealed a slower-running compound. The mixture was concentrated and repeatedly co-distilled with water and then dissolved in CH_2Cl_2 and concentrated. Column chromatography (1:1 ether–hexane) gave crystalline **8b** (2.41 g, 78.4%), mp 76–78 °C, $[\alpha]_D^{28}$ −49° (*c* 1), lit. for the D enantiomer 72–75 °C;[9] $[\alpha]_D^{22}$ +46° (*c* 0.5);[9] IR (KBr): *v* 3500 and 3280 (OH), 3070 and 3030 (aromatic), 2130 (N_3), 750 and 700 cm^{-1} (aromatic); ^{1}H NMR: δ 7.41–7.28 (m, 10 H, 2 *Ph*CH_2), 4.94 and 4.90 (2 d, 2 H, *J* 10.7 Hz, PhCH_2), 4.93 and 4.67 (2 d, 2 H, *J* 11.3 Hz, PhCH_2), 3.91 (t, 1 H, $J_{3,4} = J_{4,5} = 9.2$ Hz, H-4), 3.76–3.37 (m, 7 H, H-1,1′,3,5, 6,6′, OH-2), and 2.15 (t, 1 H, $J_{1,OH}$ 6.5 Hz, OH-1); ^{13}C NMR: δ 137.78, 137.41, 128.76, 128.74, 128.72, 128.65, 128.58, 128.53, 128.49, 128.39, 128.27, and 128.04 (aromatic), 97.72 (C-2), 81.63 (C-3), 78.93 (C-4), 75.78 and 75.54 (2 PhCH_2), 65.53 (C-1), 61.91 (C-5), and 60.95 (C-6). Anal. Calcd for $C_{20}H_{23}N_3O_5$: C, 62.32; H, 6.01; N, 10.90. Found: C, 62.60; H, 6.19; N, 11.12.

5-Azido-3,4-di-O-*benzyl-1*-O-tert-*butyldiphenylsilyl-5-deoxy*-α-L-*sorbopyranose* (**9b**).—To a stirred solution of **8b** (5 g, 13 mmol) in dry DMF (25 mL) were added imidazole (968 mg, 14.5 mmol) and *tert*-butylchlorodiphenylsilane (3.7 mL, 14.5 mmol) and the mixture was left at rt 20 h. TLC (1:4 ether–hexane) then revealed a faster-running compound. The mixture was concentrated and the residue dissolved in ether (30 mL) and the resulting solution was washed with brine and concentrated. Column chromatography (1:6 ether–hexane) of the residue afforded pure **9b** (8.5 g, quantitative) as a syrup; $[\alpha]_D^{26}$ −33° (*c* 1.6); IR (film): *v* 3525 (OH), 3070, 3051, and 3034 (aromatic), 2114 (N_3), 741 and 699 cm^{-1} (aromatic); ^{1}H NMR: δ 7.67–7.13 (3 m, 20 H, aromatic), 4.95 and 4.91 (2 d, 2 H, *J* 10.8 Hz, PhCH_2), 4.89 and 4.57 (2 d, 2 H, *J* 11.2 Hz, PhCH_2), 3.95 (t, 1 H, $J_{3,4} = J_{4,5} = 9.3$ Hz, H-4), 3.78 (dd, 1 H, $J_{5,6e}$ 7, $J_{6a,6e}$ 10.9 Hz, H-6e), 3.73 (t, 1 H, $J_{5,6a}$ 9.7 Hz, H-6a), 3.66 and 3.48 (2 d, 2 H, $J_{1,1'}$ 10.1 Hz, H-1,1′), 3.62 (dt, 1 H, H-5), 3.54 (s, 1 H, HO-2), 3.49 (d, 1 H, H-3), and 1.07 (s, 9 H, CMe_3); ^{13}C NMR (inter alia): δ 98.00 (C-2), 81.91 (C-3), 78.94 (C-4), 75.88 and 75.51 (2 PhCH_2), 65.92 (C-1), 62.12 (C-5), 60.90 (C-6), 26.88 (CMe_3), and 19.34 (CMe_3). HRMS: m/z 646.27126 $[M + Na]^+$. For $C_{36}H_{41}N_3NaO_5Si$ 646.27132 (deviation 0.1 ppm).

Hydrogenation of **9b**.—Compound **9b** (3.21 g, 5.14 mmol) in MeOH (40 mL) was hydrogenated at 345 KPa over wet Raney nickel (Fluka, 2.6 g) for 4 h. TLC (ether) then revealed the presence of a slower-running compound. ^{13}C NMR analysis of an aliquot indicated the formation of only pyrroline **10b** (C-2 at 176.41 ppm). The hydrogenation was continued for additional 15 h, when TLC

(ether) indicated the presence of a new and slower-running compound. 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) to afford (2*R*,3*R*,4*R*,5*S*) - 3,4 - dibenzyloxy - 2′ - *O* - *tert*-butyldiphenylsilyl - 2,5 - bis(hydroxymethyl)-pyrrolidine (**12**, 2.9 g, 97%) as a colorless syrup; $[\alpha]_D^{25}$ +26° (*c* 1.3); IR (film): *v* 3374 (OH), 3088, 3070 and 3034 (aromatic), and 701 cm^{-1} (aromatic); ^1H NMR: δ 7.70–7.23 (2 m, 20 H, aromatic), 4.62 and 4.44 (2 d, 2 H, *J* 11.8 Hz, PhCH_2), 4.54 and 4.48 (2 d, 2 H, *J* 11.7 Hz, PhCH_2), 4.10 (dd, 1 H, $J_{3,4}$ 2.1, $J_{4,5}$ 5.3 Hz, H-4), 4.04 (dd, 1 H, $J_{2,3}$ 4.9 Hz, H-3), 3.94–3.79 (m, 4 H, H-2′a,2′b,5′a,5′b), 3.33 (bq, 1 H, $J_{5,5'a} = J_{5,5'b} = 4.4$ Hz, H-5), 3.22 (bq, 1 H, $J_{2,2'a} = J_{2,2'b} = 4.5$ Hz, H-2), 2.53 (bs, 2 H, NH and OH), and 1.06 (s, 9 H, CMe_3); ^{13}C NMR: δ 138.14, 137.63, 135.74, 135.72, 133.40, 133.31, 129.87, 128.71, 128.56, 128.10, 127.85, and 127.63 (aromatic), 86.94 (C-3), 84.84 (C-4), 72.10 and 71.64 (2 PhCH_2), 65.33 (C-2), 63.91 (C-2′), 61.71 (C-5′), 61.39 (C-5), 26.97 (CMe_3), and 19.41 (CMe_3). HRMS: *m*/*z* 604.28595 $[M + Na]^+$. For $C_{36}H_{43}NNaO_4Si$ 604.28591 (deviation −0.1 ppm).

*(2*R,*3*R,*4*R,*5*S*) - 3,4 - Dibenzyloxy* - N-*benzyloxycarbonyl-2′*-O-tert-*butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine* (**13**).—To an ice-water cooled and stirred solution of **12** (2.88 g, 4.25 mmol) in MeOH (35 mL) and triethylamine (2.3 mL, 16.6 mmol) was added dropwise benzyl chloroformiate (0.9 mL, 6.1 mmol) and the mixture was allowed to reach rt. After 2 h, TLC (ether) revealed the presence of **12** together with two new compounds of higher mobility, being the main one that with lower R_f value. Additional triethylamine (2.3 mL, 16.6 mmol) and benzyl chloroformiate (0.9 mL, 6.1 mmol) were necessary to complete the reaction. The mixture was concentrated and the residue supported on silica gel and chromatographed (1:1 ether–hexane) to give **13** (2.4 g, 68%) as a colorless syrup; $[\alpha]_D^{22}$ +10°, $[\alpha]_{405}^{22}$ +26° (*c* 0.8); IR (film): *v* 3444 (OH), 3066 and 3032 (aromatic), 1706 (CON<), 738 and 699 cm^{-1} (aromatic); ^1H NMR: δ 7.65–7.10 (m, 25 H, aromatic), 5.04 and 4.98 (2 d, 2 H, *J* 12.3 Hz, PhCH_2), 4.60 (s, 2 H, PhCH_2), 4.50 and 4.38 (2 d, 2 H, *J* 12.7 Hz, PhCH_2), 4.38–3.70 (m, 8 H), 2.63 (bs, 1 H, OH), and 1.02 (s, 9 H, CMe_3); ^{13}C NMR (inter alia): δ 156.98 (CON<), 82.60 (C-3), 80.08 (C-4), 72.29 and 71.78 (2 PhCH_2), 67.52 (>NCOOCH_2Ph), 64.59 (C-2), 63.15 (C-5), 63.03 and 62.64 (C-2′,5′), 26.95 (CMe_3), and 19.28 (CMe_3). HRMS: *m*/*z* 738.32257 $[M + Na]^+$. For $C_{44}H_{49}NNaO_6Si$ 738.32269 (deviation 0.2 ppm).

*(2*R,*3*R,*4*R,*5*S*) - 3,4 - Dibenzyloxy* - N-*benzyloxycarbonyl - 2,5 - bis(hydroxymethyl)-pyrrolidine* (**14**).—To a stirred solution of **13** (500 mg, 0.7 mmol) in THF (6 mL) was added a solution of tetrabutylammonium fluoride trihydrate (400 mg, 1.3 mmol) in the same solvent (5 mL) under Ar and the mixture was kept at rt overnight. TLC (2:1 ether–hexane) then showed the presence of a slower-running compound. The solvent was evaporated and the residue dissolved in ether (20 mL) washed with water and concentrated. Column chromatography (4:1 ether–hexane) gave pure **14** (304 mg, 92%) as a colorless syrup; $[\alpha]_D^{26}$ −4°, $[\alpha]_{405}^{22}$ −19° (*c* 0.8); IR (film): *v* 3390 (OH), 3067 and 3032 (aromatic), 1698 (CON<), 741 and 698 cm^{-1} (aromatic); ^1H NMR: δ 7.40–7.27 (m, 15 H, aromatic), 5.13 (s, 2 H, >NCOOCH_2Ph), 4.72–3.60 (3 m, 12 H), 2.85 and 2.71 (2 bs, 2 H, OH-2′,5′); ^{13}C NMR (inter alia): δ 156.36 (CON<), 82.01 (C-3,4), 72.92 and 72.41 (2 PhCH_2), 67.64 (>NCOOCH_2Ph), 63.66 (C-2,5), 62.16 and 61.51 (C-2′,5′). HRMS: *m*/*z* 500.20481 $[M + Na]^+$. For $C_{28}H_{31}NNaO_6$ 500.20491 (deviation 0.2 ppm).

*(2*R,*3*R,*4*R,*5*S*) - 3,4 - Dihydroxy - 2,5 - bis-(hydroxymethyl)pyrrolidine hydrochloride* (**15**) *and the free base* (**1**).—To a solution of **14** (300 mg, 0.2 mmol) in MeOH (25 mL) were added 10% Pd–C (150 mg) and concd HCl (three drops). The mixture was kept under H_2 (345 KPa) for 14 h. TLC (ether) then revealed the absence of **14**. The catalyst was removed by filtration and the filtrate concentrated to a residue that was dissolved in EtOH and percolated through a short column of silica gel to afford **15** (120 mg, quantitative) as a thick syrup; $[\alpha]_D^{24}$ −3.4° (*c* 1, MeOH); ^1H NMR (MeOH-d_4): δ 4.28 (bs, 1 H, H-3), 4.11 (bt, 1 H, *J* 3 Hz, H-4), 4.04–3.82 (m, 5 H, H-

2,2′a,2′b,5′a,5′b), 3.61 (bq, 1 H, J 4 Hz, H-5); ^{13}C NMR (MeOH-d_4): δ 76.26 and 74.77 (C-3,4), 67.11 and 63.42 (C-2,5), 59.54 and 57.15 (C-2′,5′).

A solution of **15** (120 mg) in MeOH (5 mL) was deionized using Amberlite IRA-400 resin (OH^- form). Evaporation of the solvent gave pure **1** (90 mg, 92%); $[\alpha]_D^{26}$ + 25° (c 1, MeOH), lit. $[\alpha]_D^{22}$ + 27.6 (c 1.3, MeOH);[4] ^{1}H and ^{13}C NMR (D_2O) data for **1** were in accordance with those previously published[3a,11,12], respectively.

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