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Polyhydroxylated pyrrolidines. Part 2: Highly stereoselective synthesis of partially protected DMDP derivatives from D-fructose

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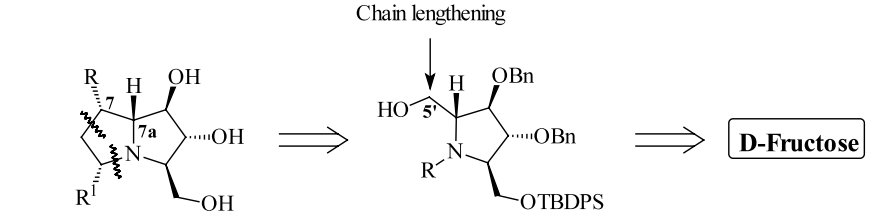
Abstract—The readily available 3,4-di-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose **2** was straightforwardly transformed into 5-azido-3,4-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose **4**, after treatment under modified Garegg's conditions followed by reaction of the resulting 3,4-di-*O*-benzyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-L-sorbopyranose **3** with sodium azide in DMF. Cleavage of the acetonide of **4** to afford **6** followed by regioselective *O*-*tert*-butyldiphenylsilylation at C(1)OH afforded **7**. Hydrogenation of **7** proceeded with high stereoselectivity yielding 3,4-di-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-2,5-dideoxy-2,5-imino-D-mannitol **1**, confirmed by its *O*-desilylation to **8**. Compound **1** was subjected to different *N*-protection reactions to afford the corresponding *N*-allyl (**1a**), *N*-benzyl (**1b**), and *N*-*tert*-butyloxycarbonyl (**1c**) derivatives.

1. Introduction

In two previous papers, we reported on the highly stereoselective synthesis, starting from the cheap and commercially available D-fructose, of appropriately protected polyhydroxypyrrolidines, such as those derived from 2,5-dideoxy-2,5-imino-D-glucitol (DGDP),[1] and later on the use of DGDP as an excellent chiral key intermediate for the synthesis[2] of two isomeric analogues [7a-*epi*-hyacinthacine A_2 (7-deoxyalexine) and 5,7a-di*epi*-hyacinthacine A_3] of the recently isolated[3] hyacinthacines, which are potent glycosidase inhibitors.

Continuing with these efforts, we describe herein the highly stereoselective synthesis, starting from the same hexulose, of those isomeric and partially protected polyhydroxypyrrolidines derived from the natural glycosidase inhibitor, 2,5-dideoxy-2,5-imino-D-mannitol (DMDP).[4]

Retrosynthetic analysis (Fig. 1) shows the potential of **1** in the preparation of polyhydroxylated pyrrolizidines (australine and hyacinthacines A_2 and A_3), where it can be clearly seen that an adequately protected DMDP **1** is an excellent chiral starting material for the synthesis of such target molecules. Thus, chain extension at C(5′)



R = OH; R^1 = H, Australina
R = R^1 = H, Hyacinthacine A_2
R = H; R^1 = CH_3, Hyacinthacine A_3

1 (*N*-Protected DMDP)

Figure 1. Retrosynthesis of polyhydroxylated pyrrolizidines.

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(originally C(6) of D-fructose) by a suitably functionalized two carbon fragment, followed by further cyclization, could lead to pyrrolizidines which stereochemistry at C(7a) belonging to that of the australine series.

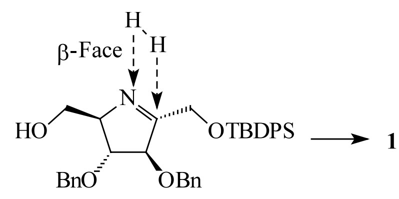
2. Results and discussion

According to Scheme 1, the reaction of 3,4-di-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose[1] **2** under modified Garreg's conditions,[5] caused the slow substitution of the C(5) hydroxyl group, with concomitant inversion of configuration, to afford the corresponding 5-deoxy-5-iodo-α-L-*sorbo* derivative **3**, which had the same analytical and spectroscopic data to those previously reported.[6] Treatment of **3** with sodium azide in *N*,*N*-DMF effected S_N2 substitution to yield 5-azido-2,3-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose **4**.[6]

In order to shorten the synthesis, an attempt to transform **2**→**4** in a one-pot reaction, by treatment of the former with $CBr_4/Ph_3P/NaN_3$/DMF/110°C,[7] resulted in the isolation of **5**, the 5-bromo-5-deoxy analogue of **3** and **4**, both in low yield.

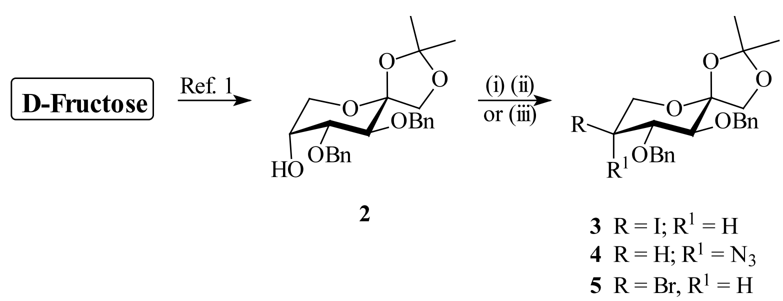
Cleavage of the acetonide group of **4** by treatment with 70% aqueous trifluoroacetic acid afforded 5-azido-2,3-di-*O*-benzyl-5-deoxy-β-D-fructopyranose **6**. Reaction of **6** with *tert*-butyldiphenylchlorosilane took place selectively at the primary hydroxyl group affording the corresponding 1-*O*-silylated derivative **7**. Compounds **6** and **7** existed as only one anomer (^{13}C NMR data). Catalytic (Raney nickel) hydrogenation of **7** caused reduction of the 5-azido group to the corresponding 5-amino function which internally condensed with the carbonyl group at C(2) to produce a Δ^2-pyrroline (**A**, not isolated but detected by TLC) which is finally hydrogenated to the expected partially *O*-protected pyrrolidine **1**. The (*R*)-configuration of the new C(2) stereogenic center in **1**, could be easily determined through its *O*-desilylation to **8**, whose ^{1}H and ^{13}C NMR spectra were consistent with its C_2-symmetry (Scheme 2).

The high stereoselectivity found in the hydrogenation of **7**, where **1** was the only pyrrolidine detected and isolated, merits comment. The formation of **1** could be explained, according to our results[1] and those of other authors,[8] by the addition of hydrogen to the same β-face occupied by the substituent next to the N=C bond, giving a product with the C(2)- and C(3)-substituents in a *trans*-disposition (see Fig. 2).

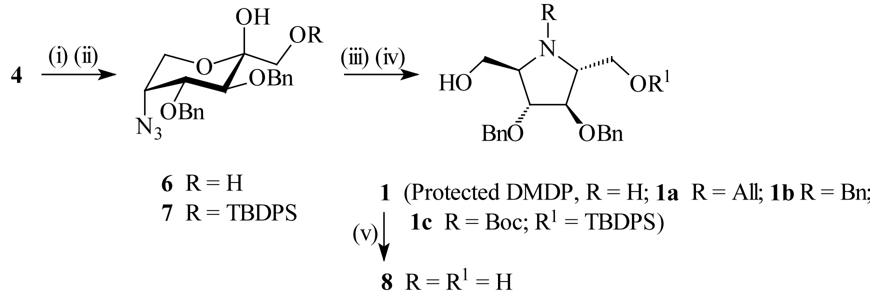


A

Figure 2. Proposed stereochemistry for the hydrogenation pathway of intermediate Δ^2-pyrroline (**A**).



Scheme 1. Synthesis of protected 5-azido-5-deoxy-D-fructose derivative **4**. *Reagents and conditions*: (i) Ph_3P/I_2/imidazole/DMF/Δ; (ii) NaN_3/DMF/Δ; (iii) $CBr_4/Ph_3P/NaN_3$/DMF/Δ.



Scheme 2. Synthesis of protected pyrrolidine **1**. *Reagents and conditions*: (i) 70% aq. TFAA; (ii) TBDPSCl/DMF/imidazole; (iii) Raney-Ni/H_2; (iv) AllBr/K_2CO_3/Me_2CO/rt; (iv) BnBr/K_2CO_3/Me_2CO/rt; (iv) (t-BuOCO)$_2$O/TEA/Cl_2CH_2; (v) t-$Bu_4N^+F^-\cdot 3H_2O$/THF.

Table 1. ^{1}H NMR chemical shifts (δ) with multiplicities and J (Hz) values for compounds **1**, **1a–c**, and **5–8**

Compd	H-1	H-1′	H-2	H-2′a	H-2′b	H-3	H-4	H-5	H-5′a	H-5′b	H-6	H-6′	PhCH_2[a]	Me_3C
1[b]	–	–	3.28q, $J_{2,3}=4.9$	3.80dd, $J_{2'a,2'b}=10.7$, $J_{2,2'a}=4.7$	3.76dd, $J_{2,2'b}=4.9$	4.00bt	3.88t, $J_{3,4}=3.9$, $J_{4,5}=3.9$	3.35bq	3.59dd, $J_{5,5'a}=5.0$, $J_{5'a,5'b}=11.2$	3.56dd, $J_{5,5'b}=6.7$	–	–	3.54s, 4.46s	1.07
1a[c]	–	–	3.47dd, $J_{2,2'b}=8.5$	3.85dd, $J_{2,2'a}=4.5$, $J_{2'a,2'b}=10.1$	3.75t	4.18s	4.07d, $J_{4,5}=3.8$	3.12bt, $J_{5,5'a}=3.3$	3.74dd	3.60bd, $J_{5'a,5'b}=11.3$	–	–	4.59d and 4.53d, $J=12.1$, 4.58d and 4.51d, $J=11.8$	1.05
1b[d]	–	–	3.39bt	3.75m	3.63dd, $J_{2,2'b}=6.5$, $J_{2'a,2'b}=11.0$	4.24s	4.14bd, $J_{4,5}=4.8$	3.24bt	3.85–3.77m		–	–	4.61d and 4.48d, $J=11.8$, 4.58d and 4.52d, $J=13.5$, 3.86d and 3.73d, $J=14.2$	1.03
1c	–	–	4.15–4.06m, 3.98dt, 3.92–3.80m, and 3.72t			4.40s	4.15–4.06m, 3.98dt, 3.92–3.80m, and 3.72t				–	–	4.66d and 4.59d, $J=12.2$, 4.51s	1.30, 1.06
5[e]	3.90d, $J=8.6$	3.82d	–	–	–	4.00–3.84m		3.39m	–	–	4.00–3.84m		4.98d and 4.83d, $J=10.2$, 4.95d and 4.64d, $J=11.4$	–
6	3.56d, $J=11.53$	3.46d	–	–	–	3.85d, $J_{3,4}=9.5$	4.10dd, $J_{4,5}=3.7$	3.90m	–	–	3.97dd, $J_{5,6}=1.4$, $J_{6,6'}=13.5$	3.66dd, $J_{5,6'}=1.8$	4.94d and 4.67d, $J=11.1$, 4.77d and 4.73d, $J=11.6$	–
7	3.69d, $J=10.1$	3.56d	–	–	–	3.79d, $J_{3,4}=9.5$	4.17dd, $J_{4,5}=3.6$	3.94m	–	–	4.93bd, $J_{6,6'}=12.4$	3.71bd	4.90d and 4.56d, $J=11.1$, 4.79d and 4.76d, $J=12.0$	1.07
8[f]	–	–	3.32m	3.64dd, $J_{2,2'a}=4.3$, $J_{2'a,2'b}=11.3$	3.59dd, $J_{2,2'b}=6.7$	3.81bd, $J_{2,3}=3.8$	3.81bd, $J_{4,5}=3.8$	3.32m	3.64dd, $J_{5,5'a}=4.3$, $J_{5'a,5'b}=11.3$	3.59dd, $J_{5,5'b}=6.7$	–	–	4.54s	

[a] Signals for phenyl groups are not included.
[b] Signal for OH at 2.82 ppm.
[c] Signals for allyl group at 5.78dddd, 5.02dd, 5.00bd, 3.29dd and 3.20dd; signal for OH at 2.82 ppm.
[d] Signal for OH at 2.86 ppm.
[e] Signals for Me_2C at 1.51 and 1.45 ppm.
[f] Signal for OH and NH at 3.21 ppm.

Table 2. ^{13}C NMR chemical shifts (δ) for compounds **1**, **1a–c**, and **5–8**

Compd	C-1	C-2	C-2′	C-3	C-4	C-5	C-5′	C-6	Ph*C*H$_2$[a]	*Me*$_3$C	Me$_3$*C*	Me$_2$*C*	*Me*$_2$C
1	–	63.31[b]	62.96[c]	85.77[d]	85.10[d]	63.23[b]	62.10[c]	–	72.10, 72.01	27.00	19.38	–	–
1a	–	67.21	60.97	83.36	86.11	67.95	59.96	–	71.89, 71.35	26.92	19.26	–	–
1b	–	66.35	61.31	83.45	86.07	68.01	60.04	–	71.91, 71.36, 51.01	26.90	19.21	–	–
1c[e]	–	65.47	64.78	81.66	84.21	66.69	62.01	–	71.53, 71.43	28.31, 26.92	19.31	–	–
5	71.55	105.48	–	83.84[b]	79.73[b]	48.16	–	64.00	76.17, 75.52	–	–	112.56	26.19, 26.16
6	65.68	97.96	–	78.93[b]	75.38[b]	59.92	–	61.51	75.74, 72.68	–	–	–	–
7	65.89	98.21	–	79.07[b]	75.24[b]	60.22	–	61.17	75.66, 72.72	26.86	19.34	–	–
8	–	63.51	62.30	85.48	85.48	63.51	62.30	–	72.07	–	–	–	–

[a] Signals for the phenyl groups are not included.
[b] Interchangeable assignments.
[c] Interchangeable assignments.
[d] Interchangeable assignments.
[e] Signal for CO at 155.67 ppm.

3. Experimental

3.1. General

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} aluminum sheets with detection by 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.

3.2. 3,4-Di-*O*-benzyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-L-sorbopyranose 3

To a solution of triphenylphosphine (6.43 g, 24.55 mmol), imidazole (3.24 g, 49.08 mmol) and iodine (6.22 g, 24.55 mmol) in dry DMF (50 mL) was added 3,4-di-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose[1] **2** (4.91 g, 12.27 mmol) and the mixture heated at 110°C for 2 days. TLC (2:1 ether–hexane) then revealed a less polar product. The solvent was evaporated under vacuum and the residue dissolved in ether (50 mL) and washed with 10% aqueous sodium thiosulphate and water, then concentrated. Column chromatography (2:3 ether–hexane) afforded crystalline **3** (3 g, 48%); mp 93–94°C (lit.[6] mp 85–87°C). Compound **3** had the same optical and spectroscopy data to those previously reported.[6]

3.3. 5-Azido-3,4-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose 4

A stirred solution of **3** (2.93 g, 5.7 mmol) and sodium azide (1.52 g, 23.4 mmol) in dry DMF (50 mL) was heated at 100°C for 5 days. TLC (1:1 ether–hexane) then revealed a slightly more polar 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 **4** (2.05 g, 85%), which had the same optical and spectroscopy data to those previously reported.[6]

3.4. 3,4-Di-*O*-benzyl-5-bromo-5-deoxy-1,2-*O*-isopropylidene-α-L-sorbopyranose 5 and 4

To a stirred solution of **2** (1.7 g, 4.25 mmol) in dry DMF (30 mL) were added triphenylphosphine (1.67 g, 6.38 mmol), carbon tetrabromide (2.12 g, 6.38 mmol), and sodium azide (0.83 g, 12.8 mmol). The mixture was heated at 110°C overnight. TLC (2:1 ether–hexane) then revealed a complex mixture. The solvent was eliminated and the residue dissolved in dichloromethane (30 mL) and washed with water, then concentrated. Column chromatography (1:4 ether–hexane→ether) afforded first crystalline **5** (150 mg); mp 77–80°C; $[\alpha]_D^{24}$ −16° (*c* 1.1). For NMR data, see Tables 1 and 2. Anal. calcd for $C_{23}H_{27}BrO_5$: C, 59.61; H, 5.87. Found: C, 60.11; H, 5.99%. Eluted second was **4** (150 mg).

3.5. 5-Azido-3,4-di-*O*-benzyl-5-deoxy-β-D-fructopyranose 6

A solution of **4** (570 mg, 1.34 mmol) in 70% aqueous trifluoroacetic acid (2 mL) was kept at room temperature for 5 h. TLC (2.1 ether–hexane) then revealed a more polar product. The mixture was concentrated and repeatedly co-distilled with water and then dissolved in CH_2Cl_2 and concentrated. The residue was purified by chromatography on silica gel and (2:1 ether–hexane) to yield syrupy **6** (450 mg, 87%), $[\alpha]_D^{27}$ −47 (*c* 1.4); ν_{max}^{film} 3484 and 3446 (OH), 3082 and 3030 (aromatic), 2102 (N_3), 740 and 697 cm^{-1} (aromatic). For NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): *m*/*z* 408.1536 [M^++Na] for $C_{20}H_{23}N_3NaO_5$ 408.1535 (deviation –0.2 ppm).

3.6. 5-Azido-3,4-di-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-5-deoxy-β-D-fructopyranose 7

To a stirred, ice-water cooled solution of **6** (4.49 g, 11.6 mmol) in dry DMF (30 mL) were added imidazole (840 mg, 12.3 mmol) and *tert*-butylchlorodiphenylsilane (3.2 mL, 12.3 mmol) and the mixture was left at room temperature 12 h. TLC (2:1 ether–hexane) then revealed a less polar product. The mixture was concentrated and the residue dissolved in ether (15 mL) and the resulting solution was washed with brine and concentrated. Column chromatography purification (1:2 ether–hexane) of the residue afforded pure **7** (5.2 g, 72%) as a viscous syrup; $[\alpha]_D^{27}$ −27 (*c* 1); ν_{max}^{film} 3469 (OH), 3068 and 3030 (aromatic), 2102 (N_3), 738 and 700 cm^{-1} (aromatic). For NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): *m*/*z* 646.2716 [M^++Na] for $C_{36}H_{41}N_3NaO_5Si$ 646.2713 (deviation –0.4 ppm).

3.7. Hydrogenation of 7

Compound **7** (5.18 g, 8.3 mmol) in MeOH (50 mL) was hydrogenated at 50 psi over wet Raney nickel (2.5 g) for 4 h. TLC (ether) then revealed the presence of a slower-running compound (presumably the Δ^2-pyrroline) together with a non-mobile compound. The hydrogenation was continued for additional 20 h, when TLC (ether) indicated the presence of only the above-mentioned non-mobile compound. The catalyst was removed by filtration and washed with MeOH. The combined filtrate and washings were concentrated to a residue that was submitted to column chromatography (ether with 0.1% Et_3N) to afford (2*R*,3*R*,4*R*,5*R*)-3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (**1**, 4.6 g, 97%) as a colorless syrup; $[\alpha]_D^{25}$ +11 (*c* 1). For NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): *m*/*z* 604.2854 [M^++Na] for $C_{36}H_{43}NNaO_4Si$ 604.2859 (deviation +0.8 ppm).

3.8. *O*-Desilylation of 1

Compound **1** (86 mg, 0.14 mmol) in THF (3 mL), was treated with a solution of tetra-*n*-butylammonium fluoride trihydrate (70 mg, 0.22 mmol) for 2 h at room temperature. TLC (ether/methanol, 20:1) then showed the presence of a more polar product. The reaction mixture was concentrated and the residue dissolved in dichloromethane (10 mL) and washed with water. The organic phase was separated and concentrated. Column chromatography [7:1 ether–methanol, 0.1% Et_3N] of the residue yielded crystalline (2*R*,3*R*,4*R*,5*R*)-3,4-dibenzyloxy-2,5-bis(hydroxymethyl)pyrrolidine **8** (30 mg, 56%); mp 80–81°C; $[\alpha]_D^{27}$ +25 (*c* 1). For NMR data, see Tables 1 and 2. Anal. calcd for $C_{20}H_{25}NO_4$: C, 69.94; H, 7.34; N, 4.08. Found: C, 69.70; H, 6.97; N, 4.21%.

3.9. (2*R*,3*R*,4*R*,5*R*)-*N*-Allyl-3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine 1a

To a solution of **1** (460 mg, 0.8 mmol) in dry acetone (10 mL) was added anhydrous potassium carbonate (540 mg) and the mixture sonicated for 15 min, then allyl bromide (250 μL, 3 mmol) was added and the mixture was stirring at room temperature. After 12 h TLC (ether) revealed the presence of a less polar compound. The mixture was filtered and the solid thoroughly washed with acetone and the filtrate and washings concentrated to a residue that was partitioned in dichloromethane/water. The organic phase was separated and concentrated to a residue that was submitted to chromatography (1:1 ether–hexane) to give **1a** as a colorless syrup (425 mg, 86%); $[\alpha]_D^{22}$ +22 (*c* 1); ν_{max}^{film} 3458 (OH), 3031 and 3020, 736 and 700 cm^{-1} (aromatic). For NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): *m*/*z* 644.3170 [M^++Na] for $C_{39}H_{47}NNaO_4Si$ 644.3172 (deviation +0.3 ppm).

3.10. (2*R*,3*R*,4*R*,5*R*)-*N*-Benzyl-3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine 1b

To a solution of **1** (211 mg, 0.36 mmol) in dry acetone (4 mL) was added anhydrous potassium carbonate (250 mg) and the mixture sonicated for 15 min, then benzyl bromide (160 μL, 1.4 mmol) was added and the mixture was left at room temperature with stirring. After 5 h TLC (2:1 ether–hexane) revealed the presence of a less polar product. The mixture was filtered and the solid thoroughly washed with acetone and the filtrate and washings concentrated to a residue that was submitted to chromatography (1:1 ether–hexane) to give **1b** as a colorless syrup (240 mg, quantitative); $[\alpha]_D^{27}$ −12 (*c* 1). For NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): *m*/*z* HRMS 694.3328 [M^++Na] for $C_{43}H_{49}NNaO_4Si$ 694.3329 (deviation +0.1 ppm).

3.11. (2*R*,3*R*,4*R*,5*R*)-3,4-Dibenzyloxy-*N*-*tert*-butyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine 1c

To an ice-water cooled, stirred solution of **1** (224 mg, 0.39 mmol) in dry dichloromethane (3 mL), TEA (62 μL, 0.46 mmol) and di-*tert*-butyl dicarbonate (92 mg, 0.42 mmol) were added and the mixture was left at room temperature. After 5 h TLC (ether) revealed the presence of a faster-running compound. The reaction mixture was quenched with dry methanol (0.3 mL),

then supported on silica gel and chromatographed (1:1 ether–hexane) to afford **1c** (250 mg, quantitative) as a colorless syrup; $[\alpha]_D^{27}$ −5 (*c* 1); ν_{max}^{film} 3441 (OH), 3065 and 3031 (aromatic) 1693 (CO), 737 and 699 cm^{-1} (aromatic). For NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): *m*/*z* HRMS 704.3384 [M^++Na] for $C_{41}H_{51}NNaO_6Si$ 704.3383 (deviation −0.2 ppm).

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References

1. Izquierdo, I.; Plaza, M.-T.; Robles, R.; Franco, F. *Carbohydr. Res.* **2001**, *330*, 401–408.
2. Izquierdo, I.; Plaza, M.-T.; Robles, R.; Franco, F. *Tetrahedron: Asymmetry* **2001**, *12*, 2481–2487.
3. (a) Kato, A.; Adachi, I.; Miyauchi, M.; Ikeda, K.; Komae, T.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Wormald, M. R.; Fleet, G. W. J.; Asano, N. *Carbohydr. Res.* **1999**, *316*, 95–103; (b) Asano, N.; Kuroi, H.; Ikeda, K.; Kizu, H.; Kameda, Y.; Kato, A.; Adachi, I.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1–8.
4. Isolation from natural sources: (a) Evans, S. V.; Fellows, L. E.; Shing, T. K. M.; Fleet, G. W. J. *Phytochemistry* **1985**, *24*, 1953–1956; (b) Asano, N.; Oseki, K.; Kizu, H.; Matsui, K. *J. Med. Chem.* **1994**, *37*, 3701–3706; (c) Watson, A. A.; Nash, R. J.; Wormald, M. R.; Harvey, D. J.; Dealler, S.; et al. *Phytochemistry* **1997**, *46*, 255–260; (d) Asano, N.; Nishida, M.; Kizu, H.; Matsui, K. *J. Nat. Prod.* **1997**, *60*, 98–101; (e) Asano, N.; Kato, A.; Miyauchi, M.; Kizu, H.; Kameda, Y.; et al. *J. Nat. Prod.* **1998**, *61*, 625–628; (f) Kato, A.; Adachi, I.; Miyauchi, M.; Ikeda, K.; Komae, T.; et al. *Carbohydr. Res.* **1999**, *316*, 95–103; (g) Kim, H. S.; Kim, Y. H.; Hong, Y. S.; Paek, M. S.; Lee, H. S.; Kim, T. H.; Kim, K. W.; Lee, J. J. *Planta Med.* **1999**, *65*; 437–439; (h) Ikeda, K.; Takahashi, M.; Nishida, M.; Miyauchi, M.; Kizu, H.; Kameda, Y.; Arisawa, M.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Asano, N. *Carbohydr. Res.* **2000**, *323*, 73–80. For previous syntheses, see: (a) Card, P. J.; Hitz, W. D. *J. Org. Chem.* **1985**, *50*, 891–893; (b) Fleet, G. W. J.; Smith, P. W. *Tetrahedron* **1987**, *43*, 971–978; (c) Hung, R. R.; Straub, J. A.; Whitesides, G. M. *J. Org. Chem.* **1991**, *56*, 3849–3855; (d) Legler, G.; Korth, A.; Berger, A.; Ekhart, C.; Gradnig, G.; Stütz, A. E. *Carbohydr. Res.* **1993**, *250*, 67–78; (e) Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175–3185; (f) Park, K. H.; Yoon, Y. J.; Lee, S. G. *Tetrahedron Lett.* **1994**, *35*, 9737–9740; (g) Chorghade, M. S.; Cseke, C. T.; Liu, P. S. *Tetrahedron: Asymmetry* **1994**, *5*, 2251–2254; (h) Ikota, N. *Heterocycles* **1995**, *41*, 983–994; (i) Asano, N.; Kizu, H.; Oseki, K.; Tomioka, E.; Matsui, K.; et al. *J. Med. Chem.* **1995**, *38*, 2349–2356; (j) Le Merrer, Y.; Poitout, L.; Depazay, J.-C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M.-J. *Biorg. Med. Chem.* **1997**, *5*, 519–533.
5. Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin 1* **1980**, 2866–2868.
6. Tatibouët, A.; Lefoix, M.; Nadolny, J.; Martin, O. R.; Rollin, P.; Yang, J.; Holman, G. D. *Carbohydr. Res.* **2001**, *333*, 327–334. In this paper, compound **3** was mistakenly named with the β-L-*sorbo* configuration.
7. Beaupere, D.; Stasik, B.; Uzan, R.; Demailly, G. *Carbohydr. Res.* **1989**, *191*, 163–166.
8. (a) Liu, K. K.-C.; Kajimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6280–6289; (b) Kajimoto, T.; Chen, L.; Liu, K. K.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6678–6680; (c) Takayama, S.; Martin, R.; Wu, J.; Laslo, K.; Siuzdak, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 8146–8151.