Carbohydrate Research 374 (2013) 14–22

Contents lists available at SciVerse ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Stereoselective synthesis of (2*S*,3*S*,4*R*,5*S*)-3,4-dihydroxy-2,5-dihydroxymethyl pyrrolidine from L-sorbose

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ARTICLE INFO

Article history:
Received 25 December 2012
Received in revised form 5 March 2013
Available online 29 March 2013

Keywords:
L-Sorbose
Selective reduction
Ketoxime
Rare sugar
Iminosugar

ABSTRACT

One of the most frequently synthesized iminosugar derivatives is DMDP. Starting from L-sorbose, a practical method for the synthesis of derivatives of this five-membered iminocyclitol has been developed, involving straightforward steps and a convenient selective reduction of a ketoxime intermediate.

1. Introduction

2,5-Dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP, **1**, Fig. 1), is a secondary metabolite first isolated from *Derris elliptica*[1] which has since then been found in diverse microorganisms and plant species, together with its unnatural analogues. These compounds have been known to show interesting biological activities (glycosidase inhibitors, antiviral and anticancer therapeutic drugs, immunomodulators).[2]

Such a scope of useful activities makes this an interesting target for synthetic chemists and many syntheses of DMDP **1** have been described, most of them starting from diverse carbohydrates,[3] such as L-sorbose,[3a] D-glucose,[3d] or D-fructose,[3j,k,l] involving hydrogenation under catalytic conditions, D-glucose with an epoxide opening as key step,[3b,c] or a S_N2-type cyclisation,[3f,q] D-arabinose through a mercury cyclisation,[3e] use of a nitrone with an hydride reduction,[3n] or a nucleophilic addition,[3o] D-mannitol with a ring contraction on a mesylate,[3g,h] or less usual derivatives like L-xylose[3i,m] and L-glucose[3p] using S_N2-type cyclisations, L-pyroglutamic acid,[4] following an enzymatic[5] or asymmetric approaches.[6]

Interestingly, the first synthetic effort towards DMDP[3a] was greatly influenced by the preliminary study of Cheng,[3o] and involved L-sorbose as the starting material. In our opinion, this compound has been highly neglected in the context of total synthesis of natural products.[7] This efficient approach was only applied to DMDP, and as a library of O-alkylated DMDP analogues might also be useful,[3m] we decided to develop a strategy starting from L-sorbose, with compound **2** as a key intermediate (Scheme 1). It should be noted, however, that if L-sorbose has been a cheap starting material because of its availability in the synthesis of vitamin C, this source is no longer easily accessible.[8] Other sources are now available such as the technology of Izumoring.[9] Our partner Soliance, a French cosmetic company produces a significant amount of L-sorbose on a multi-ton scale as a side-product during industrial dihydroxyacetone preparation by regio-controlled dehydrogenation of D-sorbitol using *Gluconobacter oxydans*.[10]

Selective hydride-type reductions of diverse nitrones have been studied (Table 1).[3n] Interestingly, Cheng and collaborators have

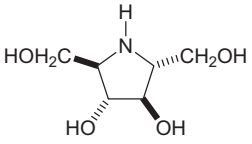
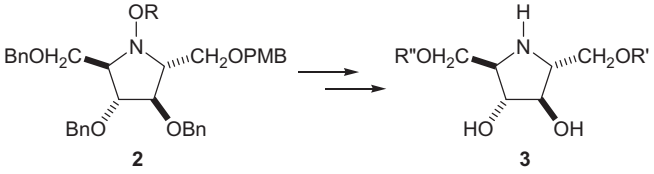


Figure 1. 2,5-Dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP **1**).



Scheme 1. Selectively protected DMDP derivative **2** and possible transformations.

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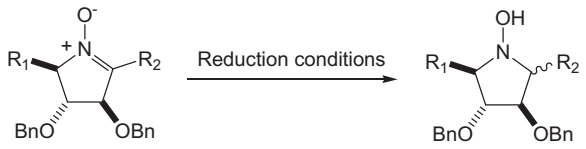
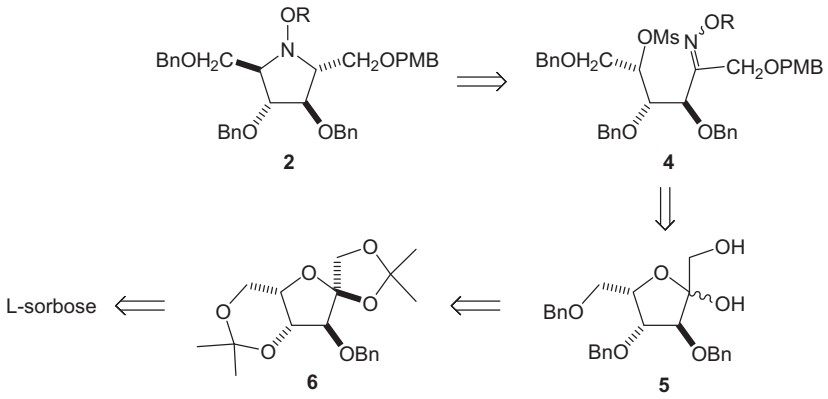
http://dx.doi.org/10.1016/j.carres.2013.03.017

Table 1
Selective hydride-type reductions of nitrones



Entry	R_1	R_2	Reduction conditions	Yield (%)	α:β
1	$BnOCH_2$	CH_2OBn	$NaBH_4$	100	43:57
2	$BnOCH_2$	CH_2OBn	L-Selectride	100	5:95
3	$BnOCH_2$	CN	$NaBH_4$	100	>3:97
4	$BnOCH_2$	Ph	DIBAH—80 °C	100	>4:96
5	Ph	CH_2OBn	L-Selectride	96	>3:97



Scheme 2. Retrosynthetic approach to DMDP derivatives **2**.

also studied the reduction of related imines under hydride conditions.[3o]

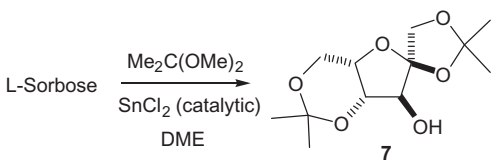
Starting from the observation that these hydride-reductions gave DMDP derivatives only as very minor diastereoisomers, we decided to study conveniently functionalised open chain derivatives of L-sorbose, following the retrosynthetic Scheme 2, expecting that the diastereoselective reductions of ketoximes **4** would be easier, compared to benzylimines, because of their higher stability and easy purification.

Interestingly, oxime cyclisations with a leaving group to obtain nitrone derivatives related to our target[11] have only been described with aldehyde derived oximes. Several interesting silyloximes proved to be efficient, with a TBDMS[12] or a TBDPS[13] protecting group, and we wondered if we could apply this concept to bulkier ketone-derived oximes.

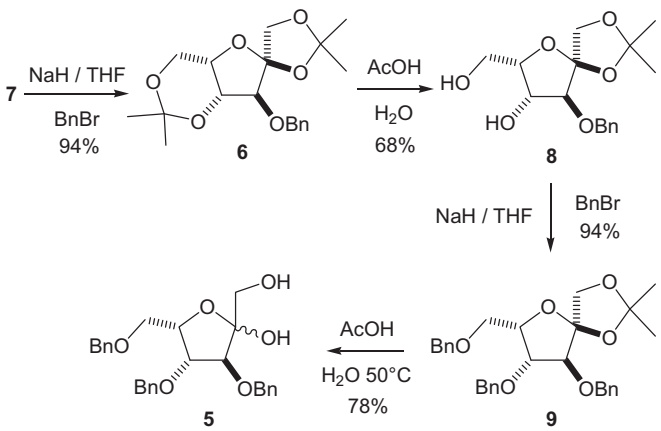
2. Results and discussion

Our synthesis started with the kinetic diprotection in the 1,2 and 4,6 positions of L-sorbose with acetonide moieties using a previously described procedure[14] to give the compound **7** with a 61% yield (Scheme 3). It is important to note that no silica gel chromatography was necessary at this point and a simple filtration allow to eliminate the remaining starting material and tin salts.

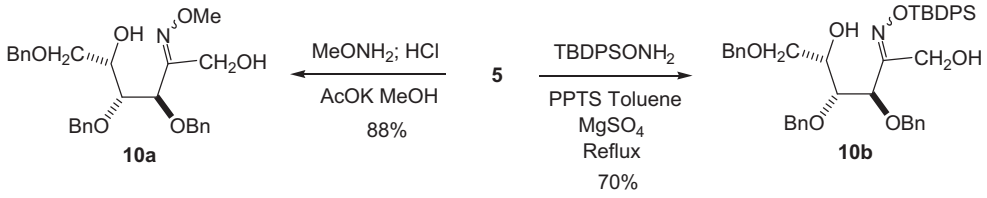
Initially, we had planned to selectively deprotect the 4,6 position, in order to benzylate the three free hydroxyl functions, but the overall yield of this approach was very low, probably due to solubility problems of intermediates. An additional step was added to the synthesis and this decision proved to be very efficient. Monobenzylation in position 3, giving **6** followed by a clean isopropylidene deprotection gave **8** in 68% yield (interestingly, in this step, it is easy to incorporate another benzyl-type substituent to individualise this position).[15] Then, a clean dibenzylation of the



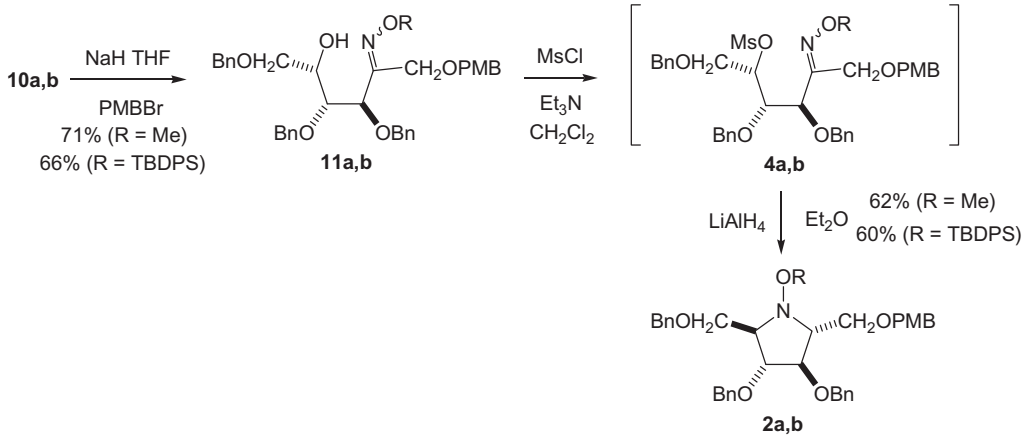
Scheme 3. Kinetic diprotection of L-sorbose.



Scheme 4. Formation of the hemiketal **5** in the L-sorbose series.



Scheme 5. Formation of ketoximes **10a** and **10b**.

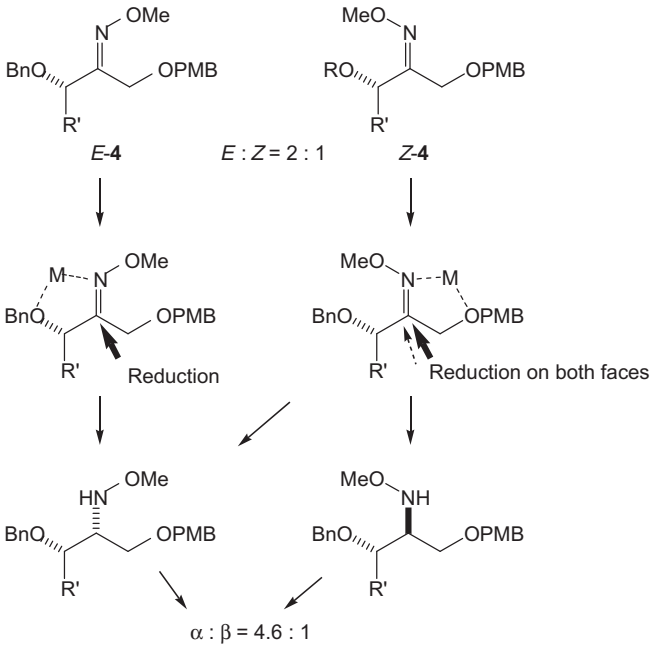


Scheme 6. Formation of cyclised structures **2a** and **2b**.

free hydroxyl functions, followed by acid treatment gave the key hemiketal **5** (Scheme 4).

In order to introduce the nitrogen on the future skeleton of the pyrrolidine, we decided to study the selective reduction of ketoximes. Protected hydroxylamines were synthesized in high yield, giving the expected ketoximes **10a** and **10b** in a ratio 2/1 in favor of the *E*-isomers (Scheme 5).

After a selective protection with a PMB group in position 1, giving **11a** and **11b** in correct yield and mesylation in position 5, the resulting ketoxime mixture **4a** (R = Me) or **4b** (R = TBDPS) was reduced with lithium aluminum hydride, nicely giving the targeted pyrrolidine **2a** (R = Me), with an α:β ratio of 4.6:1 and **2b** (R = TBDPS), with a complete diastereoselectivity for the α configuration (Scheme 6). After several attempts to improve the reduction selectivity of **2a**, we were unable to find a better result ($NaBH_4$ in MeOH; $Zn(BH_4)_2$ in Et_2O; R-CBS/BH_3·THF in THF). Noteworthy, the NMR data observed for **2b**, even after NOE experiments and high field NMR experiments, were not sufficiently convincing and the configuration was established after the final step by comparison of the DMDP with data described in the literature.



Scheme 7. Reduction of diastereoisomeric ketoxime mixtures **4a** and **4b**.

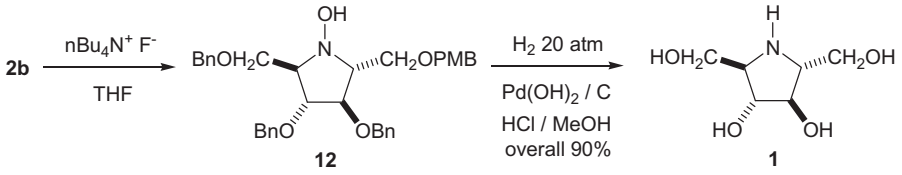
This final ratio can be explained by considering the different chelation of the diastereoisomeric ketoximes, the *E*-ketoxime giving predominantly a reduction resulting in α-pyrrolidine **2**, the *Z*-ketoxime being presumably unselective (Scheme 7). We think that in the case of **4b**, because of the steric hindrance, the chelated *Z* isomer is largely unfavored.

It would have been very interesting to individually reduce pure *E*- and *Z*-oximes, however even if their separation was possible by HPLC on a small scale, we were surprised to observe their rapid interconversion when dissolved in a usual organic solvent. This point was checked by NMR measurements.

In the **a** series, despite the fact that several methods have been described in the literature for such a clivage,[12b,13a,d,f,16] all attempts were unsuccessful to deprotect the OMe part (H_2/Pd on C in AcOH or in AcOH with 1.2 M HCl; H_2, Raney Nickel in MeOH; Zn in wet AcOH). Compound **2b** however could be deprotected in two successive steps, with tetra-*n*-butylammonium fluoride[17] and direct catalytic hydrogenation process,[16c,18] using Pearlman's reagent, giving **1** in overall 90% yield, this compound having properties identical to the one described in the literature (Scheme 8).

3. Conclusion

We have developed a short and efficient procedure to synthesise 2,5-dihydroxymethyl-3,4-di-hydroxypyrrolidine (DMDP) in



Scheme 8. Final deprotection to give DMDP **1**.

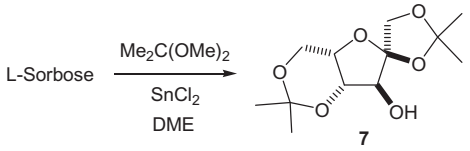
an approach which will be easy to generalise to O-alkylated analogues. We hope this methodology will help chemists interested in these kinds of compounds and, more generally will lead to a wider use of L-sorbose as a starting material in the total synthesis of natural products.

4. Experimental

4.1. General methods

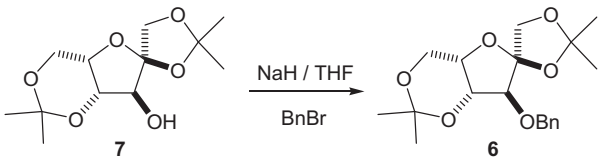
All reactions were carried out under argon. Dry solvents were used in all experiments. Thin layer chromatography was performed on E. Merck pre-coated 60 F_{254} plates and compounds were observed by UV or by charring the plates with an acidic anisaldehyde system. Flash column chromatography separations (silica gel, 15–40 μm or 40–63 μm) were carried out with light petroleum ether–ethyl acetate mixtures as eluent. NMR spectra were recorded on DRX 500 Bruker spectrometer (250 MHz for ^{1}H and 63 MHz for ^{13}C), using standard pulse programs. Chemical shifts (δ) reported are referred to internal tetramethylsilane. FT IR spectra were recorded on Nicolet Avatar 320 FT-IR as films. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Elemental analyses were performed with a Thermo Flash EA 1112 Series. Electrospray ionization mass spectrometry experiments (MS and HRMS) were obtained on a hybrid tandem quadrupole/time-of-flight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Micromass, Manchester, UK) operated in positive mode (EV = 30 V, 80 °C, injection flow 5 μL/min).

4.2. 1,2-4,6-Di-*O*-isopropylidene L-sorbose (7)



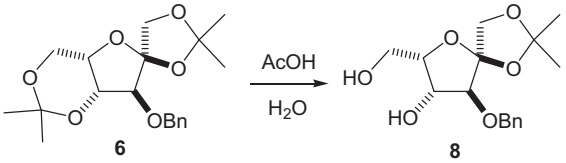
L-Sorbose (50 g, 277 mmol) was suspended in 1,2-dimethoxyethane (10 mL) containing $SnCl_2$ (250 mg, 1.3 mmol), and then 2,2-dimethoxypropane (150 mL) was added. The reaction mixture was heated to 70 °C for 2 h. After quench with Et_3N (1.25 mL), a simple filtration on wool and sand gave after evaporation, **7** as a crude syrup which could be used for the next step without any further purification (43.9 g, 169 mmol, 61%) having the same physical characteristics as described in the literature.[8] ^{1}H NMR ($CDCl_3$): δ 4.16 (m, 1H, CH), 4.07 (m, 3H, 1 CH + CH_2), 3.88 (m, 3H, CH + CH_2), 2.89 (large s, 1H, OH), 1.45 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.26 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 111.2 (C-2), 110.5 (C-8), 97.4 (C-7), 79.3 (C-6), 74.3 (C-4), 72.9, 72.4 (C-1, C-5), 60.3 (C-3), 28.2 (CH_3 isopropylidene), 26.4 (CH_3 isopropylidene), 25.4 (CH_3 isopropylidene), 19.2 (CH_3 isopropylidene).

4.3. 3-*O*-Benzyl-1,2-4,6-di-*O*-isopropylidene L-sorbose (6)



To a suspension of sodium hydride 60% in mineral oil (10 g, 250 mmol) in THF (300 mL) at 0 °C was added dropwise a solution of **7** (52.3 g, 200 mmol) in THF (300 mL). After addition of tetra-*n*-butylammonium iodide (2.5 g, 6.8 mmol), benzyl bromide (27.3 mL, 230 mmol) was added dropwise and then the yellow suspension was stirred at room temperature for 3 h. The reaction was quenched by the addition of methanol (10 mL) at 0 °C and after addition of water (50 mL), reaction mixture has been extracted with CH_2Cl_2 (3 × 500 mL). Combined organic phases have been dried with $MgSO_4$, and after filtration and evaporation to dryness, the residue was purified by column chromatography to give **6** (70 g, 200 mmol, quantitative) as a colourless oil. $[\alpha]_D^{20}$ −17.5° (*c* 1.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.37–7.26 (m, 5H, H_{Ar}), 4.78 (d, 1H, J_{gem} 12.5 Hz, CH_2Ph), 4.69 (d, 1H, CH_2Ph), 4.29 (m, 1H, H-4), 4.20 (m, 1H, $J_{5,6b}$ 3.1 Hz, H-5), 4.17 (d, 1H, J_{gem} 9.3 Hz, H-1a), 4.03 (d, 1H, H-1b), 3.97 (dd, 1H, J_{gem} 12.5 Hz, $J_{6a,5}$ 3.2 Hz, H-6a), 3.86 (dd, 1H, H-6b), 3.81 (m, 1H, H-3), 1.55 (s, 3H, 1 CH_3), 1.49 (s, 3H, 1 CH_3), 1.39 (s, 3H, 1 CH_3), 1.34 (s, 3H, 1 CH_3); ^{13}C NMR ($CDCl_3$): δ 138.2 (Cq_{Ar}), 128.8 (C_{Ar}), 128.3 (C_{Ar}), 111.3 (Cq isopropylidene), 111.2 (C-2), 98.3 (Cq isopropylidene), 85.3 (C-3), 74.3 (C-4), 73.7 (C-1), 73.4 (CH_2Ph), 72.5 (C-5), 61.0 (C-6), 28.4 (CH_3 isopropylidene), 26.6 (CH_3 isopropylidene), 26.4 (CH_3 isopropylidene), 20.6 (CH_3 isopropylidene); IR (neat) ν_{max}: 2990, 2936, 2876, 1497, 1455, 1377, 1265, 1196, 1116, 1069, 1009, 856, 741, 700 cm^{-1}; HRMS (*m/z*, ESI) calculated for $C_{19}H_{26}O_6Na$: (M+Na) = 373.1627 (calculated), 373.1632 (found).

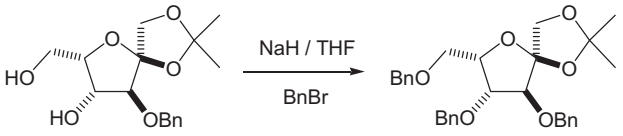
4.4. 3-*O*-Benzyl-1,2-*O*-isopropylidene L-sorbose (8)



A solution of **6** (70 g, 200 mmol) in a mixture AcOH/water (360 mL/40 mL) was stirred overnight at room temperature. The reaction mixture was then diluted with ethyl acetate (1 L) and slowly washed with a saturated sodium bicarbonate solution until acid was quenched. After extraction with ethyl acetate (3 × 100 mL), organic phases were combined, dried with $MgSO_4$, and after filtration and evaporation to dryness, the residue was

purified by column chromatography to give **8** (42.2 g, 136 mmol, 68%) as a white solid. mp = 102 °C; $[\alpha]_D^{20}$ −48.3° (*c* 0.92, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.43–7.25 (m, 5H, H_{Ar}), 4.76 (m, 2H, CH_2Ph), 4.55 (t, 1H, $J_{4,3}$ 6.5 Hz, $J_{4,5}$ 6.5 Hz, H-4), 4.24 (m, 1H, $J_{5,6}$ 2.7 Hz, H-5), 4.06 (d, 1H, J_{gem} 9.2 Hz, H-1a), 3.98 (d, 1H, H-1b), 3.85 (d, 2H, H-6), 3.79 (d, 1H, H-3), 2.74 (large s, 2H, 2 OH), 1.51 (s, 3H, 1 CH_3), 1.46 (s, 3H, 1 CH_3); ^{13}C NMR ($CDCl_3$): δ 137.9 (Cq_{Ar}), 128.6 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 111.7 (Cq isopropylidene), 108.3 (C-2), 84.7 (C-3), 76.9 (C-4, C-5), 72.4 (*C*H_2Ph), 71.3 (C-1), 61.6 (C-6), 26.7 (CH_3 isopropylidene), 26.3 (CH_3 isopropylidene); IR (neat) ν_{max}: 3357, 3033, 2996, 2928, 1455, 1370, 1246, 1210, 1124, 1107, 1065, 1033, 900, 885, 757, 740, 700 cm^{-1}; HRMS (*m/z*, ESI) calculated for $C_{16}H_{22}O_6Na$: (M+Na) = 333.1314 (calculated), 333.1298 (found).

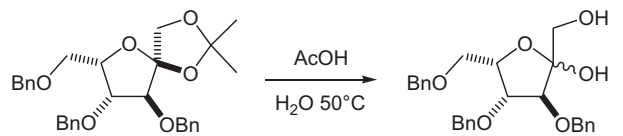
4.5. 3,4,6-Tri-*O*-benzyl-1,2-*O*-isopropylidene L-sorbose (9)



8 **9**

To a suspension of sodium hydride 60% in mineral oil (20.24 g, 506 mmol) in THF (300 mL) at 0 °C was added dropwise a solution of **8** (72 g, 232.2 mmol) in THF (500 mL). After addition of tetra-*n*-butylammonium iodide (2.88 g, 7.8 mmol), benzyl bromide (56 mL, 471 mmol) was added dropwise and then the yellow suspension was stirred overnight at room temperature. The reaction was quenched by the addition of methanol (20 mL) at 0 °C and after addition of water (50 mL), reaction mixture has been extracted with ethyl acetate (3 × 500 mL). Combined organic phases have been dried with $MgSO_4$, and after filtration and evaporation to dryness, the residue was purified by column chromatography to give **9** (93.8 g, 218.2 mmol, 94%) as a colourless oil. $[\alpha]_D^{20}$ −32.3° (*c* 1.12, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.45–7.25 (m, 15H, H_{Ar}), 4.77 (d, 1H, J_{gem} 12.0 Hz, CH_2Ph), 4.68 (d, 1H, CH_2Ph), 4.60 (m, 4H, 2 CH_2Ph), 4.48 (m, 1H, $J_{5,6a}$ 4.7 Hz, $J_{5,6b}$ 5.0 Hz, H-5), 4.34 (t, 1H, $J_{4,3}$ 5.7 Hz, $J_{4,5}$ 5.0 Hz, H-4), 4.11 (d, 1H, J_{gem} 9.2 Hz, H-1a), 4.05 (d, 1H, H-3), 3.97 (d, 1H, H-1b), 3.75 (dd, 1H, J_{gem} 10.2 Hz, H-6a), 3.64 (dd, 1H, H-6b), 1.58 (s, 3H, 1 CH_3), 1.52 (s, 3H, 1 CH_3); ^{13}C NMR ($CDCl_3$): δ 138.3 (Cq_{Ar}), 138.0 (Cq_{Ar}), 137.9 (Cq_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 111.2 (Cq isopropylidene), 108.5 (C-2), 82.8 (C-3), 82.3 (C-4), 76.6 (C-5), 73.4 (*C*H_2Ph), 72.9 (*C*H_2Ph), 72.3 (*C*H_2Ph), 72.3 (C-1), 68.9 (C-6), 26.5 (CH_3 isopropylidene), 26.3 (CH_3 isopropylidene); IR (neat) ν_{max}: 3064, 3031, 2989, 2930, 2869, 1497, 1454, 1374, 1212, 1109, 1065, 889, 738, 698 cm^{-1}; HRMS (*m/z*, ESI) calculated for $C_{30}H_{34}O_6Na$: (M + Na) = 513.2253 (calculated), 513.2249 (found).

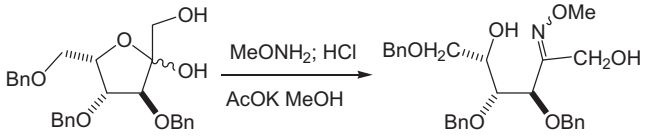
4.6. 3,4,6-Tri-*O*-benzyl-L-sorbose (5)



9 **5**

A solution of **9** (9.8 g, 20 mmol) in a mixture AcOH/water (45 mL/5 mL) was stirred overnight at 50 °C. The reaction mixture was then evaporated to dryness and the residue was purified by column chromatography to give **5** (7.0 g, 15.6 mmol, 78%) as a colourless oil. $[\alpha]_D^{20}$ +2.8° (*c* 0.97, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.36–7.12 (m, 15H, H_{Ar}), 4.55–4.39 (m, 4H, 2 CH_2Ph), 4.43 (m, 1H, H-4), 4.32 (large s, 2H, J_{gem} 12.0 Hz, CH_2Ph), 4.30 (m, 1H, H-5), 4.05 (m, 2H, H-1), 3.94 (m, 1H, H-3), 3.69–3.50 (m, 2H, H-6); ^{13}C NMR ($CDCl_3$): δ 137.9 (Cq_{Ar}), 137.0 (Cq_{Ar}), 129.1 (C_{Ar}), 129.0 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 128.1 (C_{Ar}), 106.0 (C-2), 82.3 (C-3), 81.9 (C-1), 73.9 (*C*H_2Ph), 73.8 (*C*H_2Ph), 72.5 (*C*H_2Ph), 72.5 (C-4), 72.5 (C-5), 69.0 (C-6); IR (neat) ν_{max}: 3450, 3063, 3030, 2925, 2869, 1455, 1060, 1028, 736, 698 cm^{-1}; HRMS (*m/z*, ESI) calculated for $C_{27}H_{30}O_6Na$: (M + Na) = 473.1940 (calculated), 473.1928 (found).

4.7. 3,4,6-Tri-*O*-benzyl-L-*xylo*-Hex-2-ulose methyloxime (10a)



5 **10a**

To a solution of **5** (9 g, 20 mmol) in methanol (220 mL) were successively added sodium acetate (4.41 g, 45 mmol) and methoxylammonium chloride (3.36 g, 40 mmol). After stirring for 4 days at room temperature, the reaction mixture was evaporated to dryness et directly purified by column chromatography to give **10a** (8.44 g, 88%) as a colorless oil, unseparable mixture of *E* and *Z* stereoisomers (ratio 2:1).

E stereoisomer: ^1H NMR ($CDCl_3$): δ 7.32–7.13 (m, 15H, H_{Ar}), 4.88 (d, 1H, J_{gem} 11.1 Hz, CH_2Ph), 4.65 (d, 1H, J_{gem} 11.5 Hz, CH_2Ph), 4.61 (d, 1H, CH_2Ph), 4.55 (m, 1H, H-1a), 4.52 (d, 1H, CH_2Ph), 4.52 (m, 1H, H-3), 4.51 (d, 1H, J_{gem} 11.8 Hz, CH_2Ph), 4.45 (d, 1H, CH_2Ph), 4.44 (m, 1H, H-4), 4.40 (m, 1H, H-1b), 3.86 (m, 1H, H-5), 3.93 (s, 3H, OMe), 3.52 (m, 1H, H-6a), 3.44 (m, 1H, H-6b); ^{13}C NMR ($CDCl_3$): δ 158.5 (C=N), 138.5 (Cq_{Ar}), 138.3 (Cq_{Ar}), 137.9 (Cq_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 81.7 (C-3), 79.9 (C-1), 75.6 (*C*H_2Ph), 73.8 (*C*H_2Ph), 72.7 (*C*H_2Ph), 71.4 (C-4), 70.3 (C-5), 62.8 (OMe), 57.9 (C-6).

Z stereoisomer: δ 7.32–7.13 (m, 15H, H_{Ar}), 4.77 (d, 1H, J_{gem} 11.0 Hz, CH_2Ph), 4.60 (m, 2H, CH_2Ph), 4.38 (d, 1H, CH_2Ph), 4.55 (m, 1H, H-1a), 4.52 (m, 1H, H-3), 4.44 (m, 1H, H-4), 4.40 (m, 1H, H-1b), 4.31 (d, 1H, J_{gem} 14.8 Hz, CH_2Ph), 3.86 (m, 1H, H-5), 3.93 (s, 3H, OMe), 3.52 (m, 1H, H-6a), 3.44 (m, 1H, H-6b); ^{13}C NMR ($CDCl_3$): δ 158.2 (C=N), 138.5 (Cq_{Ar}), 138.3 (Cq_{Ar}), 137.9 (Cq_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 81.7 (C-3), 79.9 (C-1), 75.8 (*C*H_2Ph), 73.8 (*C*H_2Ph), 72.7 (*C*H_2Ph), 71.1 (C-4), 70.8 (C-5), 62.8 (OMe), 61.5 (C-6).

IR (neat) ν_{max}: 3448, 3063, 3031, 2934, 2866, 1496, 1454, 1396, 1360, 1262, 1210, 1048, 899, 827, 736, 698 cm^{-1}; HRMS (*m/z*, ESI) calculated for $C_{28}H_{34}NO_6Na$: (M+Na) = 480.2386 (calculated), 480.2387 (found).

4.8. 3,4,6-Tri-*O*-benzyl-L-*xylo*-Hex-2-ulose tertiobutyldiphenyl silyloxime (10b)

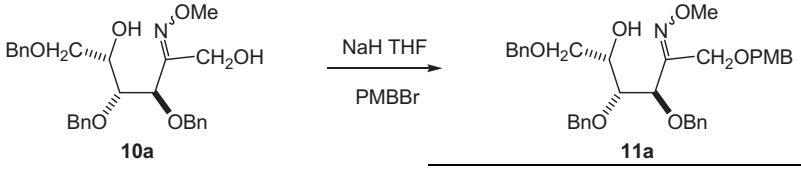
5 **10b**

To a solution of **5** (4.62 g, 10.1 mmol) in toluene (46 mL) under argon was added anhydrous magnesium sulfate (1.09 g, 4.2 mmol). After stirring for 20 min, were successively added tertiobutyldiphenylsilyloxylamine (4.25 g, 15.7 mmol) and pyridinium paratoluenesulfonate (3 × 20 mg, 3 × 366 μmol). After reflux for 48 h, the reaction mixture was directly subjected to column chromatography to give **10b** (4.98 g, 70%) as a slightly yellow oil, unseparable

mixture of *E* and *Z* stereoisomers (ratio approximately 2:1 in each case).

E stereoisomer: ^{1}H NMR ($CDCl_3$): δ 7.71–7.67 (m, 6H, H_{Ar}), 7.45–7.19 (m, 19H, H_{Ar}), 5.28 (d, 1H, $J_{3/4}$ 5.3 Hz, H-3 min), 4.78 (d, 1H, J_{gem} 10.9 Hz, CH_2Ph maj), 4.66 (d, 1H, J_{gem} 10.9 Hz, CH_2Ph min), 4.62 (large d, 2H, 2 H-1 maj), 4.55 (d, 1H, J_{gem} 10.9 Hz, CH_2Ph maj), 4.54 (d, 1H, J_{gem} 10.9 Hz, CH_2Ph min), 4.54 (d, 1H, J_{gem} 11.5 Hz, CH_2Ph maj), 4.54 (m, 2H, CH_2Ph maj + CH_2Ph min), 4.37 (m, 2H, CH_2Ph maj + CH_2Ph min), 4.40 (collapsed d, 1H, H-1a min), 4.40 (m, 1H, CH_2Ph min), 4.36 (m, 1H, CH_2Ph min), 4.36 (d, 1H, H-3 maj), 4.35 (d, 1H, J_{gem} 11.5 Hz, CH_2Ph maj), 4.33 (collapsed d, 1H, H-1b min), 4.05 (dd, 1H, $J_{4/5}$ 4.7 Hz, H-4 min), 3.95 (m, H-5 min), 3.88 (dd, 1H, $J_{4/3}$ 7.3 Hz, $J_{4/5}$ 2.6 Hz, H-4 maj), 3.80 (m, H-5 maj), 3.43 (m, 2H, $J_{6a/6b}$ 9.6 Hz, 2 H-6 min), 3.39 (dd, 1H, $J_{6a/6b}$ 9.5 Hz, $J_{6a/5}$ 5.5 Hz, H-6a maj), 3.35 (dd, 1H, $J_{6b/5}$ 5.9 Hz, H-6b maj), 2.75 (m, 1H, OH), 2.28 (d, 1H, *J* 5.6 Hz, OH), 1.13 (s, 9H, *t*Bu); ^{13}C NMR ($CDCl_3$): δ 163.6 (C=N maj), 163.2 (C=N min), 138.0 (Cq_{Ar} maj), 137.9 (Cq_{Ar} maj), 137.8 (Cq_{Ar} min), 137.6 (Cq_{Ar} min), 137.2 (Cq_{Ar} maj), 136.7 (Cq_{Ar} min), 135.5, 135.4, 132.9, 132.8, 132.7, 130.0, 129.9, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9 (C_{Ar}), 81.0 (C-3 maj), 79.4 (C-4 maj), 79.1 (C-4 min), 75.7 (*C*H_2Ph min), 75.3 (C-3 min), 75.0 (*C*H_2Ph maj), 73.3 (*C*H_2Ph min), 73.2 (*C*H_2Ph maj), 72.0 (*C*H_2Ph maj), 70.7 (C-6 maj), 70.6 (C-6 min), 70.5 (C-5 min), 70.0 (C-5 maj), 61.3 (C-1 min), 58.2 (C-1 maj), 27.2 (*C*(Me)$_3$ min), 27.1 ((*C*(Me)$_3$ maj); IR (neat) ν_{max}: 3443, 3069, 3030, 2931, 2859, 1496, 1472, 1454, 1428, 1392, 1362, 1217, 1115, 1028, 923, 822, 755, 699, 667, 611 cm^{-1}; HRMS (*m/z*, ESI) calculated for $C_{43}H_{49}NO_6NaSi$: (M+Na) = 726.3227 (calculated), 726.3227 (found).

4.9. 3,4,6-Tri-*O*-benzyl-1-*O*-(4-methoxybenzyl)-L-*xylo*-Hex-2-ulose methyloxime (11a)

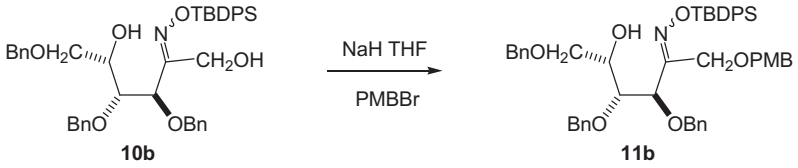


10a **11a**

To a suspension of sodium hydride 60% in mineral oil (734 mg, 18.3 mmol) in anhydrous THF (50 mL) at 0 °C was added dropwise a solution of **10a** (8 g, 16.68 mmol) in THF (100 mL). After addition of tetra-*n*-butylammonium iodide (416 mg, 1.1 mmol), 4-methoxybenzyl bromide (2.43 mL, 16.68 mmol) was added dropwise and then the yellow suspension was stirred overnight at room temperature. The reaction was quenched by the addition of methanol (10 mL) at 0 °C and after addition of water (10 mL), reaction mixture has been extracted with ethyl acetate (3 × 200 mL). Combined organic phases have been dried with $MgSO_4$, and after filtration and evaporation to dryness, the residue was purified by column chromatography to give **11a** (7.1 g, 11.84 mmol, 71%) as a colourless oil.

Mixture of two ketoxime stereoisomers (one of each designed by *): ^{1}H NMR ($CDCl_3$): δ 7.36–7.23 (m, 34H, H_{Ar}), 6.85 (2 d, 4H, *J* 8.7 Hz, *J* 8.7 Hz, 4$H_{Ar\ ortho/OMe}$), 5.12 (d, 1H, $J_{3,4}$ 7.3 Hz, C-3), 4.91 (d, 1H, J_{gem} 11.2 Hz, CH_2Ph on C-4*), 4.85 (d, 1H, J_{gem} 11.2 Hz, CH_2Ph on C-4), 4.66 (d, 1H, J_{gem} 11.6 Hz, CH_2Ph on C-1*), 4.60 and 4.57 (2 d, 2H, J_{gem} 11.2 Hz, J_{gem} 10.0 Hz, 2 CH_2Ph on C-4 and C-4*), 4.55 (d, 1H, $J_{3,4}$ 5.0 Hz, C-3*), 4.55 (s, 2H, CH_2Ph on C-3), 4.49 (m, 2H, CH_2Ph on C-1), 4.46 (s, 1H, OH), 4.43 (large s, 2H, CH_2Ph on C-3*), 4.36 (d, 1H, J_{gem} 13.2 Hz, C-1a*), 4.31 (d, 1H, J_{gem} 11.6 Hz, C-1a), 4.16 (d, 1H, C-1b*), 4.06 (d, 1H, C-1b), 4.04 (dd, 1H, $J_{4,5}$ 8.2 Hz, C-4*), 4.01 (dd, 1H, $J_{4,5}$ 7.2 Hz, C-4), 3.95 (s, 3H, NOMe), 3.94 (s, 3H, NOMe), 3.92 (m, 1H, C-5*), 3.90 (m, 1H, C-5), 3.81 (s, 3H, PhOMe), 3.80 (s, 3H, PhOMe), 3.50 (dd, 1H, $J_{6a,5}$ 6.6 Hz, $J_{6a,6b}$ 9.6 Hz, C-6a*), 3.45 (dd, 1H, $J_{6b,5}$ 6.2 Hz, C-6b*), 3.40 (dd, 1H, $J_{6a,5}$ 5.7 Hz, $J_{6a,6b}$ 9.6 Hz, C-6a), 3.37 (dd, 1H, $J_{6b,5}$ 5.7 Hz, C-6b); ^{13}C NMR ($CDCl_3$): δ 159.5 (Cq_{ArOMe}), 156.4 (C=N), 155.4 (C=N), 138.6 (Cq_{Ar}), 138.4 (Cq_{Ar}), 138.2 (Cq_{Ar}), 137.6 (Cq_{Ar}), 129.6 (C_{Ar}), 129.5 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 128.1 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 113.7 ($C_{Ar\ ortho/OMe}$), 80.6 (C-3*), 79.3 (C-4*), 79.1 (C-4), 76.0 (C-3), 75.3 (CH_2Ph on C-4), 75.2 (2 CH_2Ph on C-4 and C-4*), 75.0 (CH_2Ph on C-4*), 73.1 (CH_2Ph on C-3), 73.0 (CH_2Ph on C-3), 72.6 (CH_2Ph on C-1), 72.2 (CH_2Ph on C-1*), 71.4 (C-6*), 70.9 (C-6), 69.9 (C-5), 69.7 (C-5*), 67.1 (C-1), 62.3 (NOMe), 62.2 (NOMe), 62.2 (C-1*), 55.2 (PhOMe); IR (neat) ν_{max}: 3512, 3489, 3454, 3066, 3033, 3006, 2938, 2864, 1613, 1514, 1457, 1396, 1358, 1303, 1248, 1211, 1177, 1093, 1044, 902, 821, 738, 698 cm^{-1}; HRMS (*m/z*, ESI) calculated for $C_{36}H_{42}NO_7Na$: (M+Na) = 600.2961 (calculated), 600.2962 (found).

4.10. 3,4,6-Tri-*O*-benzyl-1-*O*-(4-methoxybenzyl)-L-*xylo*-Hex-2-ulose tertiobutyldiphenylsilyloxime (11b)

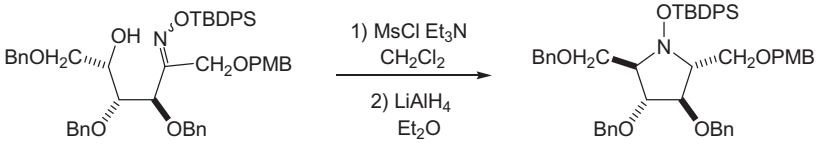


10b **11b**

To a suspension of sodium hydride 60% in mineral oil (255 mg, 6.3 mmol) in anhydrous THF (17 mL) at 0 °C was added dropwise a solution of **10b** (4 g, 5.69 mmol) in THF (35 mL). After addition of tetra-*n*-butylammonium iodide (143 mg, 379 μmol), 4-methoxybenzyl bromide (838 μL, 5.69 mmol) was added dropwise and then the yellow suspension was stirred overnight at room temperature. The reaction was quenched by the addition of methanol (4 mL) at 0 °C and after addition of water (4 mL), reaction mixture has been extracted with ethyl acetate (3 × 70 mL). Combined organic phases have been dried with $MgSO_4$, and after filtration and evaporation to dryness, the residue was purified by column chromatography to give **11b** (3.09 g, 2.78 mmol, 66%) as a colourless oil.

Mixture of two ketoxime stereoisomers (the major being designed by *): ^{1}H NMR ($CDCl_3$): δ 7.75–7.65 (m, 8H, H_{Ar}), 7.47–7.18 (m, 34H, H_{Ar}), 6.87 (d, 2H, *J* 8.7 Hz, 2$H_{Ar\ ortho/OMe}$), 6.85 (d, 2H, *J* 8.7 Hz, 2$H_{Ar\ ortho/OMe}$*), 5.16 (d, 1H, $J_{3,4}$ 7.8 Hz, C-3), 5.12 (d, 1H, J_{gem} 11.4 Hz, CH_2Ph), 5.03 (s+d, 3H, CH_2Ph + 2CH_2Ph*), 4.92 (d, 1H, J_{gem} 11.1 Hz, CH_2Ph*), 4.85 (d, 1H, J_{gem} 11.3 Hz, CH_2Ph), 4.66 (d, 1H,

$J_{3,4}$ 4.4 Hz, C-3*), 4.64 (d, 1H, J_{gem} 14.3 Hz, C-1a*), 4.62 (d, 1H, J_{gem} 11.1 Hz, CH_2Ph*), 4.60 (d, 1H, J_{gem} 11.1 Hz, CH_2Ph*), 4.56 (d, 1H, J_{gem} 11.3 Hz, CH_2Ph), 4.54 (d, 1H, J_{gem} 12.2 Hz, C-1a), 4.52 (d, 1H, J_{gem} 11.1 Hz, CH_2Ph*), 4.47 (m, 2H, J_{gem} 11.1 Hz, CH_2Ph* + CH_2Ph), 4.42 (m, 2H, CH_2Ph* + CH_2Ph), 4.36 (s, 2H, CH_2Ph), 4.33 (d, 1H, C-1b*), 4.20 (d, 1H, C-1b), 4.17 (dd, 1H, $J_{4,5}$ 7.8 Hz, C-4*), 4.10 (dd, 1H, $J_{4,5}$ 2.2 Hz, C-4), 3.94 (m, 1H, C-5*), 3.94 (m, 1H, C-5), 3.80 (s, 3H, PhOMe), 3.79 (s, 3H, PhOMe*), 3.51 (dd, 1H, $J_{6a,5}$ 6.9 Hz, $J_{6a,6b}$ 9.5 Hz, C-6a*), 3.46 (dd, 1H, $J_{6a,5}$ 6.8 Hz, $J_{6a,6b}$ 9.5 Hz, C-6a), 3.42 (dd, 1H, $J_{6b,5}$ 5.7 Hz, C-6b*), 3.34 (dd, 1H, $J_{6b,5}$ 5.0 Hz, C-6b), 1.05 (s, 9H, *t*Bu), 1.03 (s, 9H, *t*Bu*); ^{13}C NMR ($CDCl_3$): δ 159.6 (Cq_{ArOMe}), 159.2 (Cq_{ArOMe}*), 158.1 (C=N), 157.1 (C=N*), 138.5 (2Cq_{Ar}), 138.1 (3Cq_{Ar}), 137.5 (Cq_{Ar}), 135.8–135.7 (C_{Ar}), 132.9 (Cq_{Ar}), 132.8 (Cq_{Ar}), 132.7 (Cq_{Ar}*), 132.6 (Cq_{Ar}*), 128.4 (C_{Ar}), 128.3 (3C_{Ar}), 128.2 (2C_{Ar}), 128.1 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (2C_{Ar}), 127.7 (2C_{Ar}), 127.6 (2C_{Ar}), 127.5 (C_{Ar}), 113.9 ($C_{Ar\ ortho/OMe}$), 113.7 ($C_{Ar\ ortho/OMe}$*), 81.0 (C-3*), 80.0 (C-4), 79.3 (C-4*), 76.7 (C-3), 75.1 (CH_2Ph*), 76.5 (CH_2Ph), 76.0 (CH_2Ph*), 75.4 (CH_2Ph), 73.4 (CH_2Ph* + CH_2Ph), 72.9 (CH_2Ph), 72.1 (CH_2Ph*), 71.5 (C-6*), 71.3 (C-6), 70.3 (C-5), 70.3 (C-5*), 62.4 (C-1), 62.2 (NOMe), 57.4 (C-1*), 55.3 (2PhO*Me*), 26.8 (C*Me*$_3$* + C*Me*$_3$), 19.2 (C*Me*$_3$), 19.1 (C*Me*$_3$*); IR (neat) ν_{max}: 3508, 3030, 2931, 2061, 1959, 1886, 1813, 1776, 1612, 1587, 1514, 1497, 1454, 1428, 1361, 1303, 1248, 1175, 1112, 823, 738, 700,
613 cm^{-1}; HRMS (*m/z*, ESI) calculated for $C_{51}H_{57}NO_7NaSi$: (M+Na) = 846.3802 (calculated), 846.3810 (found).



4.11. (2*S*,3*S*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-2-(4-methoxybenzylmethyl)-1-methoxypyrrolidine (2a)

To a solution of compound **11a** (7.7 g, 12.85 mmol) in methylene chloride (150 mL) at 0 °C, were added dropwise triethylamine (3.6 mL, 25.7 mmol) and then methanesulfonyl chloride (1.32 mL, 17 mmol). After stirring for 15 min at room temperature, the mixture was washed with water (3 × 30 mL). The organic phase was dried with $MgSO_4$, and after filtration and evaporation to dryness (with a cold bath), dry diethyl ether (150 mL) was added. After cooling down to 0 °C, a solution of lithium aluminum hydride 4 M in diethyl ether (6.4 mL, 25.7 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. At 0 °C, a Rochelle salt solution was slowly added to the reaction mixture and after stirring for 15 min, the reaction mixture was washed with water (3 × 25 mL). The combined organic phases have been dried with $MgSO_4$, and after filtration and evaporation to dryness, the residue was purified by column chromatography to give **2a** (4.64 g, 7.97 mmol, 62%) as a colourless oil (mixture of two stereoisomers in ratio 4.6:1).

Major stereoisomer (R): $[\alpha]_D^{20}$ −4° (*c* 2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.27–7.08 (m, 17H, H_{Ar}), 6.74 (d, 2H, J_{gem} 10 Hz, 2 $H_{Ar\ ortho/OMe}$), 4.47–4.30 (m, 8H, 4 CH_2Ph), 3.89 (m, 2H, C-3 and C-4), 3.64 (m, 5H, C-2 and C-5, NOMe), 3.43 (m, 7H, C-1 and C-6, PhOMe); ^{13}C NMR ($CDCl_3$): δ 159.1 (Cq_{ArOMe}), 138.2 (Cq_{Ar}), 130.3 (C_{Ar}), 129.4 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.8 (C_{Ar}), 127.6 (C_{Ar}), 113.7 ($C_{Ar\ ortho/OMe}$), 84.5 (C-3 and C-4), 73.3 (CH_2Ph), 72.9 (CH_2Ph), 71.6 (CH_2Ph), 68.7 (C-2 and C-5), 68.1 and 67.7 (CH_2OBn and CH_2OPMB), 61.4 (NOMe), 55.2 (PhOMe); IR (neat) ν_{max}: 3451, 3090, 3065, 3033, 2934, 2869, 2813, 1955, 1876, 1812, 1605, 1497, 1455, 1397, 1364, 1310, 1257, 1208, 1099, 911, 815, 740, 699 cm^{-1}; HRMS (*m/z*, ESI) calculated for $C_{36}H_{42}NO_6Na$: (M+Na) = 584.3012 (calculated), 584.3008 (found).

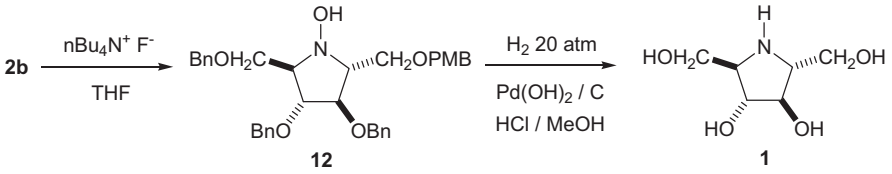
Minor stereoisomer (S): ^{1}H NMR ($CDCl_3$): 7.36–7.17 (m, 17H, H_{Ar}), 6.85 (d, 2H, J_{gem} 10 Hz, 2 $H_{Ar\ ortho/OMe}$), 4.55, 4.48 and 4.37 (m, 8H, 4 CH_2Ph), 3.93 (m, 2H, C-3 and C-4), 3.78 (s, 3H, NOMe), 3.71 (m, 3H, C-2, C-5 and CH_2OPMB), 3.55 (m, 4H, CH_2OPMB and PhOMe), 3.46 (m, 1H, CH_2OBn), 3.22 (m, 1H, CH_2OBn); ^{13}C NMR ($CDCl_3$): δ 159.2 (Cq_{ArOMe}), 138.3 (Cq_{Ar}), 138.2 (Cq_{Ar}), 130.5 (C_{Ar}), 129.5 (C_{Ar}), 128.4 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.7 (C_{Ar}), 113.8 ($C_{Ar\ ortho/OMe}$), 84.7 and 82.5 (C-3 and C-4), 73.3 (CH_2Ph), 73.2 and 69.9 (C-2 and C-5), 72.8 (CH_2Ph), 72.0 (CH_2Ph), 71.2 (CH_2Ph), 70.3 and 67.2 (CH_2OBn and CH_2OPMB), 63.3 (NOMe), 55.3 (PhOMe).

4.12. (2*S*,3*S*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-2-(4-methoxybenzylmethyl)-1-tertiobutyldiphenylsilyloxy pyrrolidine (2b)

To a solution of compound **11b** (1 g, 1.21 mmol) in methylene chloride (14 mL) at 0 °C, were added dropwise triethylamine (340 μL, 2.4 mmol) and then methanesulfonyl chloride (124 μL, 1.6 mmol). After stirring for 15 min at room temperature, the mixture was washed with water (3 × 3 mL). The organic phase was dried with $MgSO_4$, and after filtration and evaporation to dryness (with a cold bath), dry diethyl ether (15 mL) was added. After cooling down to 0 °C, a solution of lithium aluminum hydride 4 M in diethyl ether (600 μL, 2.4 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. At 0 °C, a Rochelle salt solution was slowly added to the reaction mixture and after stirring for 15 min, the reaction mixture was washed with water (3 × 3 mL). The combined organic phases have been dried with $MgSO_4$, and after filtration and evaporation to dryness, the residue was purified by column chromatography to give **2b** (588 mg, 728 μmol, 60%) as a colourless oil. $[\alpha]_D^{20}$ −16.3° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.70 (d, 4H, $H_{Ar\ from\ PhSi}$), 7.46–7.27 (m, 21H, H_{Ar}), 7.11 (d, 2H, J_{gem} 10 Hz, 2 $H_{Ar\ meta/OMe}$), 6.79 (d, 2H, 2 $H_{Ar\ orthoOMe}$), 4.57 (d, 1H, J_{gem} 12.0 Hz, CH_2Ph on C-4), 4.56 (overlapped d, 2H, CH_2Ph on C-1), 4.55 (overlapped d, 2H, CH_2Ph on C-3), 4.54 (overlapped d, 2H, CH_2Ph on C-6), 4.47 (d, 1H, CH_2Ph on C-4), 4.15 (m, 1H, $J_{4,3}$ 3.2 Hz, C-4), 4.06 (dd, 1H, $J_{3,2}$ 5.9 Hz, C-3), 3.95 (dd, 1H, $J_{1a,1b}$ 10.5 Hz, $J_{6a,5}$ 4.6 Hz, C-6a), 3.82 (m, 1H, C-6b), 3.80 (s, 3H, PhOMe), 3.77 (m, 1H, C-1a),

3.61 (dd, 1H, $J_{1b,1a}$ 9.8 Hz, $J_{1b,2}$ 5.9 Hz,C-1b), 3.52 (m, 1H, C-5), 3.50 (m, 1H, C-2), 1.08 (s, 9H, *t*Bu); ^{13}C NMR ($CDCl_3$): δ 159.4 (Cq_{ArOMe}), 138.4 (2 Cq_{Ar}), 135.7 (Cq_{Ar}), 133.4 (C_{Ar}), 130.5 ($C_{Ar\ meta/OMe}$), 129.7 (C_{Ar}), 129.6 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 127.5 (C_{Ar}), 113.5 ($C_{Ar\ ortho/OMe}$), 84.5 (C-4), 84.2 (C-3), 75.6 (CH_2Ph), 73.2 (CH_2Ph), 71.6 (2 CH_2Ph), 68.5 (C-2), 68.5 (C-5), 68.0 (C-1), 62.0 (C-6), 55.2 (PhOMe), 26.8 (CMe_3), 19.1 (CMe_3); IR (neat) ν_{max}: 3067, 3030, 2930, 2857, 1611, 1513, 1496, 1454, 1428, 1390, 1362, 1302, 1249, 1209, 1174, 1112, 1029, 823, 739, 700, 612 cm^{-1}; HRMS (*m/z*, ESI) calculated for $C_{51}H_{57}NO_6K$: (M+K) = 846.3802 (calculated), 846.3810 (found).

4.13. (2*S*,3*S*,4*R*,5*S*)-3,4-Dihydroxy-2,5-dihydroxymethyl pyrrolidine (1)



To a solution of **2b** (520 mg, 640 μmol) in dry THF (20 mL) at 0 °C was added a solution of tetra-*n*-butylammonium fluoride 1 M in THF (1.2 mL). After stirring for 1 h at room temperature, the mixture was evaporated to dryness, and then the residue was dissolved in methanol (6 mL), was treated with $Pd(OH)_2$ on C (15 mg) and a solution of HCl in methanol (100 μL, 1 M). The resulting mixture was stirred under hydrogen (20 atm) for 6 h. The catalyst was eliminated by filtration through a pad of Celite, the filtrate was treated with HCl (1 mL, 3 M) in methanol, and the resulting solution was stirred at room temperature for an additional 10 min. The solvent was eliminated under reduced pressure to afford pure **1** (94 mg, 90%) as a white solid.

Acknowledgments

S. Balieu thanks the 'Region Champagne-Ardenne' and FEDER for financial support. We would like to thank Dr. K. Plé for helpful discussions.

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