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Diastereoselective syntheses of 1-deoxyhomonojirimycin and two new 1,5,6-trideoxy-1,5-iminoheptitols with D-*allo*- and L-*talo*-configuration

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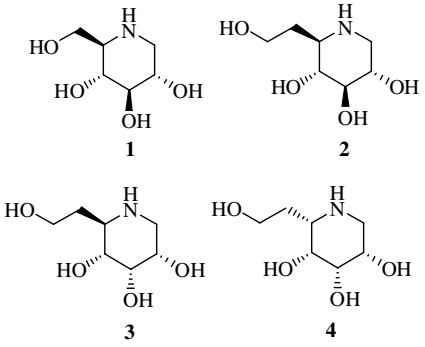
Abstract—The synthesis of 1-deoxyhomonojirimycin **2**, as well as two new diastereomers, namely 1,5,6-trideoxy-1,5-imino-D-*allo*-heptitol **3** and 1,5,6-trideoxy-1,5-imino-L-*talo*-heptitol **4**, is described. Compound **2** was obtained from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose—while **3** and **4** were obtained from 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose. These compounds were transformed in a few steps to the corresponding β-ketoesters **12** and **18**, respectively, which were hydrogenated diastereoselectively in the presence of chiral ruthenium complexes with total control of the C-5 stereogenic centre. The resulting β-hydroxyesters **13**, **19a** and **19b** are key intermediates for the syntheses of the 1,5,6-trideoxy-1,5-iminoheptitols **2**, **3** and **4**, respectively.

1. Introduction

The importance of polyhydroxylated piperidines is mostly due to their powerful activity as competitive inhibitors of glycosidases. They have several applications as potential therapeutics and in agrochemistry, and are notably used for the treatment of human diseases, such as diabetes, cancer or viral infections.[1] The number of derivatives prepared in the literature[2] since the elucidation of the structure of the first natural iminosugar nojirimycin in 1968[3] is a reflection of the interest of such compounds. Especially, the inhibition mechanism is still under study[4] and could help to understand the interactions in the sugar/enzyme complex.[5] Several modifications of the natural inhibitors have been reported and tested in order to examine the structure–activity relationship. In particular, iminosugars bearing a functionalised chain at the C-5 position have been prepared over the last few years, such as carbonyl analogues of 1-deoxynojirimycin[6] and 1,5-dideoxy-1,5-iminoalditols.[7] Several syntheses of the C-6 homologue **2** of the known 1-deoxynojirimycin **1** have been described.[8] Biological evaluations have shown that the *N*-hydroxyethyl derivative of **2** is a potent inhibitor towards β-glucosidase and β-galactosidase.[8e] Preparations of other 1,5,6-trideoxy-1,5-iminoheptitols with L-*ido*,[8a–e,9] D-*galacto*,[10] D-*talo* and L-*allo*[11] configuration have been reported.

In a previous report, we proposed the obtention of 1-deoxyhomonojirimycin **2** from the β-ketoester **7**.[8f] Herein we report, the total synthesis of compound **2** from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **8** and the first diastereoselective syntheses of 1-deoxyhomoiminosugars **3** and **4** with D-*allo* and L-*talo* configuration, respectively, from 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose **9** (Scheme 1).



Scheme 1.

The configuration of every asymmetric carbon atom is central to the activity of the inhibitor. In particular, the

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three contiguous centres C-2, C-3 and C-4 of the homoiminosugars could be obtained from the parent carbohydrate derivative. The 1,5,6-trideoxy-1,5-iminoheptitols **2**, **3** and **4** could be obtained by the cyclisation of azide **5** by acidic hydrolysis and reductive amination.[8f]Azide **5** could be obtained from alcohol **6** via an activation–nucleophilic substitution with inversion of configuration. The ester function of **6** is a precursor of the primary alcohol of **5**. The control of the C-5 hydroxylated stereogenic centre is essential, in the way that it will induce the stereochemistry of the C-5 carbon atom of the piperidine ring. β-Ketoester **7** bearing a furanose moiety is a direct precursor of β-hydroxyester **6**, which could be obtained as a single diastereomer by hydrogenation in the presence of a chiral ruthenium catalyst.[12] Compound **7** can be derived from the protected furanoses **8** or **9** (Scheme 2).

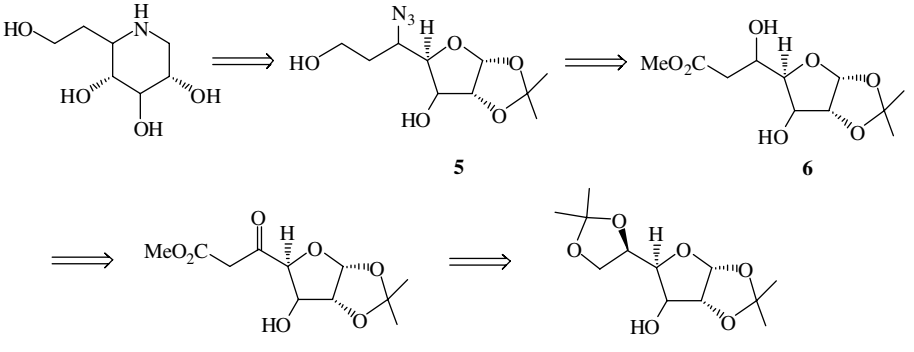
2. Results and discussion

The synthesis of 1-deoxyhomonojirimycin **2** was developed using diol **10** as the starting material (Scheme 3). Compound **10** was obtained in two steps from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **8** by protection of the hydroxyl function as a *tert*-butyldimethylsilyl ether and selective deprotection of the cyclic ketal at the 5,6-position.[13] Metaperiodate oxidation of **10** led to the corresponding aldehyde, which was not isolated, and was directly oxidised into carboxylic acid **11**. Treatment of **11** with carbonyl diimidazole and with the magnesium salt of monomethylmalonate, using the Masamune procedure,[14] afforded β-ketoester **12** without epimerisation at C-4. Hydrogenation of **12** at an atmospheric pressure, in the presence of the (*R*)-BinapRuBr$_2$ catalyst[15] gave (5*S*)-hydroxy derivative **13** in 99% yield. We have previously described the important role played by the *tert*-butyldimethylsilyl protecting group at C-3 leading to an excellent diastereomeric excess higher than 99% in favour of the (5*S*) diastereomer.[12]

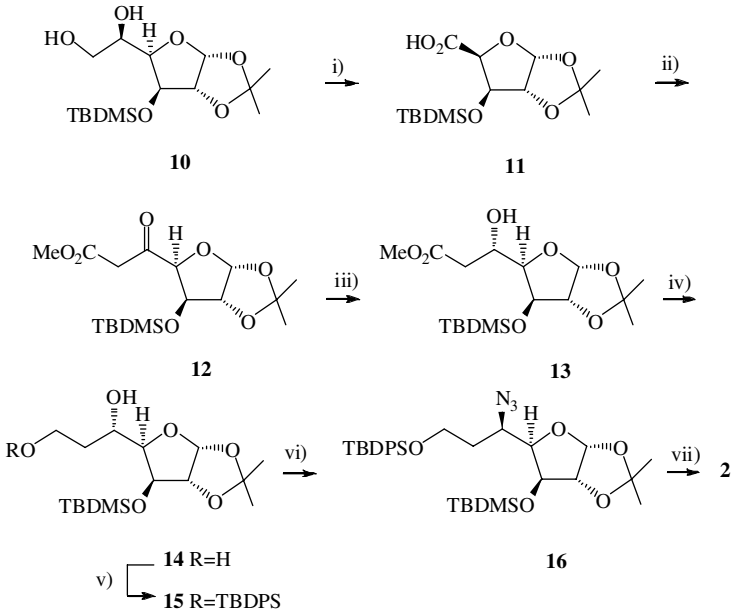
Reduction of the ester functionality in **13** with lithium aluminium hydride in tetrahydrofuran, led to diol **14** in 66% yield. A side product corresponding to the cleavage of the silyl ether at C-3 was identified in low yield. Selective silylation of the primary alcohol function of **14** with *tert*-butyldiphenylsilyl chloride in pyridine in the presence of 4-dimethylaminopyridine as a catalyst, led to silyl ether **15** in 68% yield while the starting material was recovered in 26% yield. The secondary alcohol at C-5 was then activated as the corresponding methyl sulfonate ester, which was too unstable to be purified and hence was used as the crude product for the next step. Nucleophilic displacement with sodium azide led to azide **16** with inversion of configuration at the C-5 stereogenic centre, giving the (5*R*) diastereomer. Tentative hydrolysis of **16** in a mixture of TFA–H_2O (3/2), followed by hydrogenolysis at 5 or 10 atm did not lead to the corresponding piperidine. Prior treatment with tetrabutylammonium fluoride, in order to remove the silyl groups, was necessary. Acidic treatment of the obtained diol followed by the action of hydrogen at room temperature and under atmospheric pressure in the presence of platinum oxide led to a crude product whose further purification over Amberlyst A-26 (OH^-) exchange resin afforded 1-deoxyhomonojirimycin **2** in 75% yield for the three steps. The structure of the homologated iminosugar was confirmed by the transformation into its hydrochloride form by treatment with a methanolic solution of chlorhydric acid, and then comparison with the NMR data and specific rotation given in the literature.[8a]

Following a similar synthetic route, the ribosyl acid **17**, derived from commercial 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose **9** in four steps,[16] was used as starting material for the preparation of piperidines **3** and **4**. The Masamune protocol was applied to this acid and the formation of the β-ketoester **18** with a yield of 58% was allowed. Catalytic hydrogenations under an atmospheric pressure allowed us to obtain the two β-hydroxyester epimers at C-5 in good yields: the use of the (*R*)-BinapRuBr$_2$ complex gave **19a** in excellent diastereoisomeric excess (>99%), whereas the use of the enantiomeric catalyst (*S*)-BinapRuBr$_2$ produced **19b** with 99% de (Scheme 4).

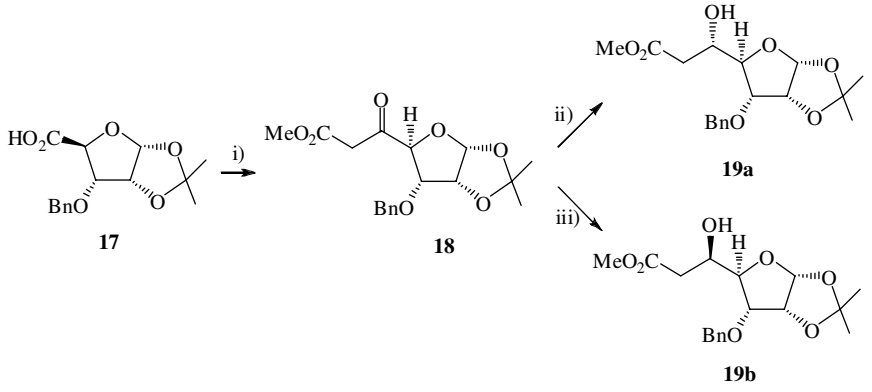
No substrate induction operated in this case, contrary to what we had observed for the hydrogenation of **14**, when the C-3 *tert*-butyldimethylsilyl ether and the β-ketoester side chain were in a *cis* relationship.



Scheme 2. Retrosynthetic analysis of piperidines **2**–**4**.

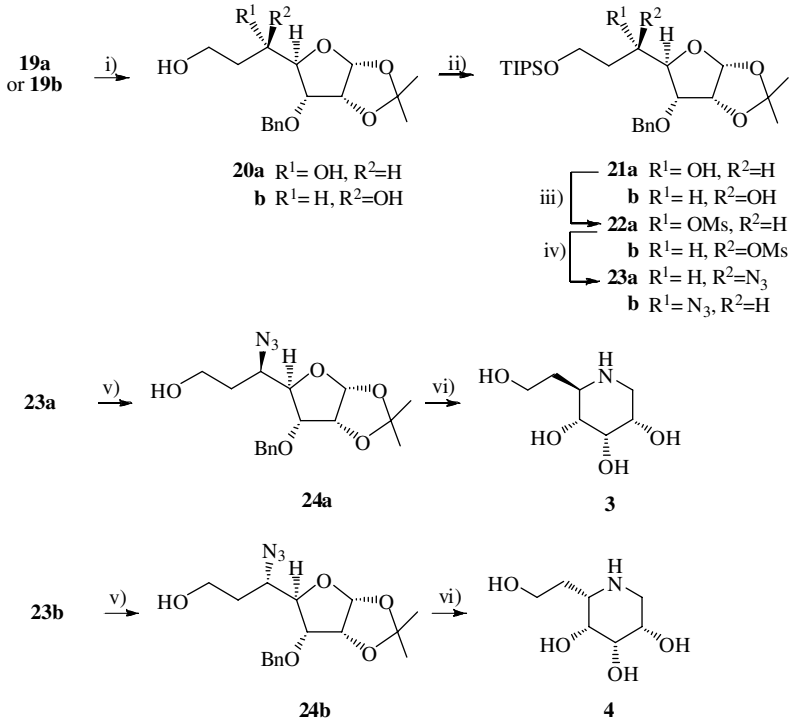


Scheme 3. Reagents and conditions: (i) $NaIO_4$, H_2O/EtOH, 16 h, rt then CrO_3, H_2SO_4, 16 h, rt, 77%; (iv) Im_2CO, THF, 8 h, rt then $(MeO_2C–CH_2–CO_2–)_2Mg^{2+}$, 24 h, rt, 51%; (iii) H_2, [(*R*)-BinapRuBr$_2$], 1 atm, 24 h, 40 °C, 99%, de >99%; (iv) 5.0 equiv $LiAlH_4$, THF, 2 h, rt, 66%; (v) 2.0 equiv TBDPSCl, 4-DMAP, py, 12 h, rt, 68%; (vi) (a) MsCl, DCM/py, 3 h, 45 °C, 100%; (b) NaN_3, DMF, 12 h, 130 °C, 77%; (vii) (a) TBAF, THF, 1 h, rt; (b) TFA, H_2O, 2 h, rt; (c) H_2, PtO_2, 1 atm, 12 h, rt; (d) Amberlyst A-26 (OH^-); 75%.



Scheme 4. Reagents and conditions: (i) Im_2CO, THF, 16 h, rt then $(MeO_2C–CH_2–CO_2–)_2Mg^{2+}$, 24 h, rt, 58%; (ii) H_2, [(*R*)-BinapRuBr$_2$], 1 atm, 24 h, 45 °C, 88%, de >99%; (iii) H_2, [(*S*)-BinapRuBr$_2$], 1 atm, 24 h, 45 °C, 80%, de >99%.

Two diastereomers **19a** and **19b** have been used separately for the transformation into iminosugars derivatives **3** and **4**, respectively (Scheme 5). Reduction in the presence of 1.5 equiv of lithium aluminium hydride led to diols **20a** or **20b**, whose primary alcohol function was selectively protected as a triisopropylsilyl ether. Activation of the remaining hydroxyl with methanesulfonyl chloride gave **22a** or **22b**, both stable enough to be isolated as oily compounds. These sulfonates have been used directly in the substitution step, leading to the azides **23a** or **23b**, respectively, with inversion of configuration at the C-5 centres. As the preliminary attempts at direct cyclisation of **23** have failed, we decided to remove first the triisopropylsilyl ether. Treatment of **23a** with tetrabutylammonium fluoride led to alcohol **24a** in 80% yield. In our first attempt, the hydrolysis of the isopropylidene acetal of **24a** was run in aqueous TFA and the reaction mixture containing the hemiacetal was directly subjected to hydrogenation using platinum oxide. Under these conditions, reduction of the azide, cleavage of the benzyl ether and cyclisation occurred simultaneously. However the major product isolated was the *N*-trifluoroacetamide of **3**. To avoid its formation, the solvents of the reaction mixture were evaporated after the acidic hydrolysis of **24a**, while the crude product was treated under a hydrogen atmosphere in the presence of platinum oxide at 20 bar. The expected homoiminosugar **3** was obtained together with a small amount of the C-3 benzylated piperidine. The crude mixture was hydrogenolysed in the presence of catalytic palladium on carbon under acidic conditions. The purification over Amberlyst A-26 (OH^-) gave the iminosugar derivative **3**, via alcohol **24a**. The application of a similar method to **23b** produced homoiminosugar **4**, through a transformation to the alcohol **24b**.



Scheme 5. Reagents and conditions: (i) 1.5 equiv $LiAlH_4$, THF, 1 h, 0 °C to rt, **20a**: 92%, **20b**: 78%; (ii) 1.2 equiv TIPSCl, Im., DMF, 1 h, rt, **21a**: 90%, **21b**: 85%; (iii) MsCl, DCM/py, 2.5 h, 45 °C, **22a**: 92%, **22b**: 73%; (iv) NaN_3, DMF, 3 h, 110 °C, **23a**: 77%, **23b**: 76%; TBAF, THF, 1 h 30 min, rt, **24a**: 80%, **24b**: 100%; (vi) (a) TFA, H_2O, 2 h, 40 °C; (b) H_2, PtO_2, 20 bar, 12 h, rt; (c) H_2, Pd/C, 5 bar, 24 h, rt; (d) Amberlyst A-26 (OH^-); **3**: 80%, **4**: 51%.

The structures of iminosugars **3** and **4** have been confirmed by transformation into their hydrochloride forms by treatment with a methanolic solution of hydrochloride acid, and then comparison with the NMR data and specific rotation given in the literature.[11]

3. Conclusion

In conclusion, we have prepared homologated 1-deoxynojirimycin **2** from the protected α-D-*xylo*-furanuronic acid **11** in 10 steps with an overall yield of 13%, and the two 1,5,6-trideoxy-1,5-iminoheptitols **3** and **4** from the protected α-D-*ribo*-furanuronic acid **17**, with overall yields of 19% and 9%, respectively. In particular, the catalytic hydrogenation of β-ketoesters bearing sugar moieties, led to the corresponding β-hydroxyesters with excellent diastereoselectivities, allowing the control of the configuration at C-5 of the homoiminosugars.

4. Experimental

4.1. General

Solvents were distilled according to Ref. 17. The bis-(2-methylallyl)-cycloocta-1,5-diene–ruthenium(II) complex and (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl are from Acros. Flash chromatography was performed on silica gel chromagel 60 ACC 35–70 μm. Analytical TLC: aluminium-backed silica gel Merck 60 F_{254}. Optical rotations were measured at 25 °C on a Perkin–Elmer 241 polarimeter (1 dm cell). NMR spectra were recorded on a Brucker AC 200 or Avance 300 apparatus with chemical shift values (δ) in parts per million downfield from tetramethylsilane. Microanalyses were performed by the Service de Microanalyse of University Pierre et Marie Curie, Paris, France or by the ICSN, Gif-sur-Yvette, France.

4.2. 3-*O*-*tert*-Butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanuronic acid 11

A solution of imidazole (3.5 g) in dry DMF (30 mL) was added to commercial 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (5.0 g, 19.2 mmol). *tert*-Butyldimethylsilyl chloride (3.5 g, 23.0 mmol) was then added. The reaction mixture was stirred under argon for 16 h. The reaction was diluted with water (10 mL) and extracted with Et_2O (5×8 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvents were evaporated. Purification by column chromatography (SiO_2, AcOEt/pentane 3:7) gave the silylated intermediate (7.0 g, 98%) whose NMR data were similar with those of the literature;[13a] $[\alpha]_D^{25} = -17$ (*c* 1.3, DCM). This intermediate was retaken with an aqueous solution of AcOH (80%, 100 mL). The mixture was stirred for 16 h at room temperature. The solvent was then removed. Purification by column chromatography (SiO_2, AcOEt/pentane 3:7) gave **10** (5.1 g, 81%) whose NMR data are similar to those in the literature;[13b] $[\alpha]_D^{25} = -19$ (*c* 1.0, DCM).

A solution of $NaIO_4$ (13.0 g, 60.8 mmol) in H_2O/EtOH (170 mL/85 mL) was added dropwise to a solution of **10** (15.5 g, 46.4 mmol) in H_2O (44 mL). The reaction mixture

was stirred at room temperature for 16 h. The solvents were then evaporated. The crude aldehyde was obtained as a white oil and then dissolved in acetone (345 mL). The solution was then cooled to 0 °C. Jones reagent, prepared with CrO_3 (7.1 g, 71.1 mmol) in H_2O (19 mL) and H_2SO_4 95% (6.4 mL), was added dropwise to the solution. The reaction mixture was stirred at room temperature for 16 h. Isopropanol (16 mL) was then added. The solution was filtered and neutralised by the addition of a saturated aqueous solution of $NaHCO_3$ (150 mL). The solvents were then evaporated. The aqueous layer was washed with AcOEt (50 mL), acidified to pH 1 with an aqueous solution of HCl (2 M, 70 mL) and extracted with AcOEt (2×100 mL, 4×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvents evaporated. Purification by column chromatography (SiO_2, AcOEt/pentane 3:7) gave **11** (11.3 g, 77%); $[\alpha]_D^{25} = -48$ (*c* 0.8, DCM); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.08$ (s, 3H, Me), 0.12 (s, 3H, Me), 0.86 (s, 9H, *t*Bu), 1.34 (s, 3H, Me), 1.49 (s, 3H, Me), 4.41 (d, 1H, $J = 3.5$ Hz, H-2), 4.53 (d, 1H, $J = 3.1$ Hz, H-3), 4.81 (d, 1H, $J = 3.1$ Hz, H-4), 6.08 (d, 1H, $J = 3.3$ Hz, H-1), 7.30–8.20 (broad signal, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = -5.32$ (SiMe), -4.98 (SiMe), 17.84 (*C*Me$_3$), 25.48, 26.42, 27.09 (C*Me*$_2$ and C*Me*$_3$), 76.36 (C-3), 81.01 (C-4), 84.87 (C-2), 105.85 (C-1), 113.02 (*C*Me$_2$), 171.14 (CO). Anal. Calcd for $C_{14}H_{26}O_6Si$: C, 52.80; H, 8.23. Found: C, 52.68; H, 8.42.

4.3. Methyl 3-*O*-*tert*-butyldimethylsilyl-6-deoxy-1,2-*O*-isopropylidene-5-oxo-α-D-*xylo*-heptofuranuronate 12

Carbonyldiimidazole (9.6 g, 59.3 mmol) was added to a solution of **11** (15.7 g, 49.4 mmol) in dry THF (330 mL). The reaction mixture was stirred at room temperature for 8 h. The magnesium salt of monomethylmalonate (14.3 g, 55.4 mmol) was added and the reaction mixture and stirred over 24 h. The solvents were evaporated and the residue was treated with an aqueous solution of HCl (2 M) to obtain pH 1. The aqueous layer was extracted with DCM (4×80 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and the solvents evaporated. Purification by column chromatography (SiO_2, Et_2O/pentane 1:5) gave **12** as white crystals (9.4 g, 51%); mp 78.5 °C; $[\alpha]_D^{25} = -104$ (*c* 1.4, DCM); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.04$ (s, 3H, Me), 0.10 (s, 3H, Me), 0.86 (s, 9H, *t*Bu), 1.33 (s, 3H, Me), 1.47 (s, 3H, Me), 3.47 (d, 1H, $J = 17.1$ Hz, H-6), 3.72 (s, 3H, COO*Me*), 3.81 (d, 1H, $J = 17.1$ Hz, H-6′), 4.37 (d, 1H, $J = 3.6$ Hz, H-2), 4.49 (d, 1H, $J = 3.3$ Hz, H-3), 4.63 (d, 1H, $J = 3.3$ Hz, H-4), 6.06 (d, 1H, $J = 3.3$ Hz, H-1); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = -5.30$ (SiMe), -5.16 (SiMe), 17.91 (*C*Me$_3$), 25.48, 25.62, 26.46, 27.04 (C*Me*$_2$ and C*Me*$_3$), 47.70 (C-6), 52.08 (OMe), 77.98 (C-3), 84.95 (C-2), 85.98 (C-4), 105.97 (C-1), 112.63 (*C*Me$_2$), 167.52 (*C*OOMe), 202.26 (CO). Anal. Calcd for $C_{17}H_{30}O_7Si$: C, 54.52; H, 8.07. Found: C, 54.43; H, 8.24.

4.4. Methyl 3-*O*-*tert*-butyldimethylsilyl-6-deoxy-1,2-*O*-isopropylidene-β-L-*ido*-heptofuranuronate 13

The catalyst was prepared under argon according to the following procedure: To bis-(2-methylallyl)-cycloocta-1,5-diene–ruthenium(II) complex (0.02 equiv, 1.6 mg) and (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (0.02 equiv, 3.4 mg) in degassed acetone (0.3 mL) was added a methanolic solution of hydrogen bromide (0.15–0.18 M, 0.04 equiv). The reaction mixture was stirred for 1 h. The solvents were evaporated and the β-ketoester **12** (100 mg, 0.3 mmol) in freshly distilled degassed MeOH (0.6 mL) cannulated to the catalyst. The reaction mixture was stirred for 24 h at 40 °C under a hydrogen atmosphere. The solvents were evaporated and a purification by column chromatography (SiO_2, Et_2O/pentane 1:3) gave **13** (100 mg, 99%, de >99%); $[\alpha]_D^{25} = -18$ (*c* 1.6, DCM); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.14$ (s, 3H, Me), 0.17 (s, 3H, Me), 0.90 (s, 9H, *t*Bu), 1.32 (s, 3H, Me), 1.47 (s, 3H, Me), 2.60 (m, 2H, H-6 and H-6′), 3.26 (d, 1H, $J = 2.3$ Hz, OH), 3.70 (s, 3H, COO*Me*), 4.12 (dd, 1H, $J = 6.9$ and 4.9 Hz, H-4), 4.26 (d, 1H, $J = 4.9$ Hz, H-3), 4.37 (m, 2H, H-2 and H-5), 5.97 (d, 1H, $J = 5.3$ Hz, H-1); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = -5.19$ (SiMe), -4.52 (SiMe), 17.80 (*C*Me$_3$), 25.57, 26.44, 26.92 (C*Me*$_2$ and C*Me*$_3$), 38.05 (C-6), 51.71 (OMe), 67.10 (C-5), 77.63 (C-3), 81.56 (C-4), 85.86 (C-2), 104.74 (C-1), 111.99 (*C*Me$_2$), 171.76 (CO). Anal. Calcd for $C_{17}H_{32}O_7Si$: C, 54.23; H, 8.57. Found: C, 54.14; H, 8.67.

4.5. 3-*O*-*tert*-Butyldimethylsilyl-6-deoxy-1,2-*O*-isopropylidene-β-L-*ido*-hepto-1,4-furanose 14

A solution of $LiAlH_4$ (5.0 equiv, 2.4 mmol, 92 mg) in dry THF (2.5 mL) was added slowly (period over 5–10 min) to a mixture of **13** (0.5 mmol, 183 mg) in dry THF (2.5 mL) at 0 °C under argon. The reaction mixture was stirred for 2 h at room temperature. MeOH (1 mL) was added slowly, followed by a saturated aqueous solution of NH_4Cl (10 mL). The crude was extracted with AcOEt (4×5 mL), the organic layer dried over $MgSO_4$, filtered and the solvents evaporated. Purification by column chromatography (SiO_2, Et_2O/pentane 3:1) gave diol **14** (111 mg, 66%); $[\alpha]_D^{25} = -28$ (*c* 1.1, DCM); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.14$ (s, 3H, Me), 0.17 (s, 3H, Me), 0.90 (s, 9H, *t*Bu), 1.32 (s, 3H, Me), 1.49 (s, 3H, Me), 1.80 (m, 2H, H-6 and H-6′), 2.69 (broad s, 1H, OH), 3.21 (broad s, 1H, OH), 3.86 (m, 2H, H-7 and H-7′), 4.04 (dd, 1H, $J = 4.8$ and 3.0 Hz, H-4), 4.14 (m, 1H, H-5), 4.23 (d, 1H, $J = 3.1$ Hz, H-3), 4.38 (d, 1H, $J = 3.7$ Hz, H-2), 5.97 (d, 1H, $J = 3.7$ Hz, H-1); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.50$ (SiMe), -4.00 (SiMe), 17.43 (*C*Me$_3$), 25.20, 25.29, 25.99, 26.49, 29.90 (C*Me*$_2$ and C*Me*$_3$), 34.63 (C-6), 60.38 (C-7), 69.56 (C-5), 76.77 (C-3), 82.36 (C-4), 85.33 (C-2), 104.25 (C-1), 111.55 (*C*Me$_2$). Anal. Calcd for $C_{16}H_{32}O_6Si$: C, 55.14; H, 9.25. Found: C, 55.23; H, 9.63.

4.6. 3-*O*-*tert*-Butyldimethylsilyl-7-*O*-*tert*-butyldiphenylsilyl-6-deoxy-1,2-*O*-isopropylidene-β-L-*ido*-hepto-1,4-furanose 15

tert-Butyldiphenylsilyl chloride (2.0 equiv, 726 μL) and 4-DMAP (catalytic amount) were added to a solution of **14** (490 mg, 1.4 mmol) in pyridine (10 mL). The reaction mixture was stirred for 3 h under argon. The overall was retaken with water (15 mL) and extracted with Et_2O (4×10 mL). The organic layer was washed with an aqueous solution of $CuSO_4$ (5%, 3×10 mL), water (15 mL),

then dried over $MgSO_4$, filtered and the solvents were evaporated. A purification by column chromatography (SiO_2, Et_2O/pentane 1:4) gave the expected product **15** (560 mg, 68%) and the unreacted starting material (127 mg, 26%); mp 69.3 °C; $[\alpha]_D^{25} = -18$ (*c* 1.0, DCM); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.14$ (s, 3H, Me), 0.18 (s, 3H, Me), 0.91 (s, 9H, *t*Bu), 1.05 (s, 9H, *t*Bu), 1.33 (s, 3H, Me), 1.49 (s, 3H, Me), 1.82 (m, 2H, H-6 and H-6′), 3.30 (s, 1H, OH), 3.87 (m, 2H, H-7 and H-7′), 4.09 (m, 1H, H-4), 4.25 (m, 2H, H-5 and H-3), 4.38 (d, 1H, $J = 5.6$ Hz, H-2), 5.99 (d, 1H, $J = 5.6$ Hz, H-1), 7.38–7.67 (m, 10H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = -5.11$ (SiMe), −4.52 (SiMe), 17.86 (*C*Me_3), 19.15 (*C*Me_3), 25.65, 26.43, 26.54, 26.82, 26.95 (C*Me*$_2$ and C*Me*$_3$), 35.78 (C-6), 60.98 (C-7), 67.62 (C-5), 77.49 (C-3), 82.75 (C-4), 85.90 (C-2), 104.75 (C-1), 111.78 (*C*Me_2), 127.64–133.66 (Ar). Anal. Calcd for $C_{32}H_{50}O_6Si_2$: C, 65.49; H, 8.59. Found: C, 65.67; H, 8.72.

4.7. 5-Azido-3-*O*-*tert*-butyldimethylsilyl-7-*O*-*tert*-butyldiphenylsilyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-hepto-1,4-furanose 16

Methanesulfonyl chloride (3.2 mmol, 245 μL) was added to a solution of **15** (528 mg, 0.9 mmol) in a mixture of pyridine/DCM (1/2, 20 mL). The overall mixture was then warmed at 45 °C for 3 h. Then a saturated aqueous solution of $NaHCO_3$ was added until neutrality, and the aqueous layer was extracted with Et_2O (5 × 15 mL). The organic layer was washed with an aqueous solution of $CuSO_4$ (5%, 2 × 25 mL), water (30 mL), dried over $MgSO_4$, filtered and the solvents evaporated. The crude product has been introduced directly into the next step.

The mesylate was retaken in DMF (15 mL) under argon. Sodium azide (1.2 equiv, 70 mg) was added and the reaction mixture was warmed at 130 °C for 12 h. After cooling, water (15 mL) was added. The aqueous layer was extracted with Et_2O (4 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvents were evaporated. Purification by column chromatography (SiO_2, Et_2O/pentane 1:9) gave **16** (424.0 mg, 77%); $[\alpha]_D^{25} = -6$ (*c* 1.6, DCM); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.19$ (s, 6H, 2 Me), 0.94 (s, 9H, *t*Bu), 1.06 (s, 9H, *t*Bu), 1.33 (s, 3H, Me), 1.48 (s, 3H, Me), 1.76 (m, 1H, H-6), 2.29 (m, 1H, H-6′), 3.85 (m, 4H, H-4, H-5, H-7 and H-7′), 4.29 (d, 1H, $J = 2.0$ Hz, H-3), 4.39 (d, 1H, $J = 3.7$ Hz, H-2), 5.89 (d, 1H, $J = 3.5$ Hz, H-1), 7.39–7.70 (m, 10H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = -5.21$ (SiMe), −4.52 (SiMe), 17.99 (*C*Me_3), 19.15 (*C*Me_3), 25.81, 26.34, 26.79, 26.89 (C*Me*$_2$ and C*Me*$_3$), 34.92 (C-6), 55.80 (C-5), 60.16 (C-7), 75.22 (C-3), 82.32 (C-4), 85.11 (C-2), 104.95 (C-1), 111.81 (*C*Me_2), 127.64–135.60 (Ar). Anal. Calcd for $C_{32}H_{49}N_3O_5Si_2$: C, 62.81; H, 8.07. Found: C, 62.24; H, 8.30.

4.8. 1,5,6-Trideoxy-1,5-imino-D-*gluco*-heptitol 2

Tetra-*N*-butyl ammonium fluoride (TBAF) 1 M in THF (1.1 mL) was added to a solution of **16** (329 mg, 0.5 mmol) in THF (2.3 mL). The reaction mixture was stirred for 1 h. A saturated aqueous solution of NH_4Cl was added and the mixture was extracted with Et_2O (4 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvents were evaporated. Purification by column chromatography (SiO_2, AcOEt) led to the expected diol (121 mg, 88%). This diol (121 mg, 0.46 mmol) was stirred in a solution of TFA in water (3/2, 5 mL) at 40 °C for 2 h. PtO_2 (10.6 mg, 0.046 mmol) was added under hydrogen atmosphere. The reaction was stirred at room temperature for 12 h. The catalyst was filtered over Celite and washed with MeOH. The solvents were evaporated. The crude product was dissolved in water (5 mL), washed with DCM (2 mL) then the solvents were evaporated. Purification over Amberlyst A-26 (OH^-) eluting with an aqueous solution of NH_4OH (2.5%) gave the expected piperidine **2** (70 mg, 75% from **16**). The specific rotation was measured on the hydrochloride form of the piperidine after treatment with a methanolic solution of HCl; $[\alpha]_D^{25} = +33$ (*c* 0.8, MeOH) {lit.[8a] $[\alpha]_D^{25} = +30$ (*c* 0.55, MeOH)}.

4.9. Methyl 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-5-oxo-α-D-*ribo*-heptofuranuronate 18

Compound **17** (10 g, 25.5 mmol) was treated according to the same procedure as for **12** with a reaction time of 16 h for the formation of the intermediate acylimidazolide. Purification by column chromatography (SiO_2, AcOEt/pentane 1:3) gave **18** (5.2 g, 58%) as a colourless oil; $[\alpha]_D^{25} = +76$ (*c* 1.3, DCM); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$ (s, 3H, C*Me*$_2$), 1.60 (s, 3H, C*Me*$_2$), 3.54 (d, 1H, $J = 16.2$ Hz, H-6), 3.65 (d, 1H, $J = 16.2$ Hz, H-6′), 3.71 (s, 3H, O*Me*), 3.94 (dd, 1H, $J = 4.3$ and 8.9 Hz, H-3), 4.53–4.72 (m, 3H, H-2, H-4, CH*H*Ar), 4.77 (d, 1H, $J = 12.1$ Hz, CH*H*Ar), 5.79 (d, 1H, $J = 3.5$ Hz, H-1), 7.3–7.4 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.57$, 26.96 (C*Me*$_2$), 45.75 (C-6), 52.34 (O*Me*), 72.48 (*C*H_2Ar), 78.04 (C-2), 79.08 (C-3), 82.58 (C-4), 104.36 (C-1), 113.79 (*C*Me_2), 128.14, 128.51, 136.96 (Ar), 167.40 (C-7), 200.62 (C-5). Anal. Calcd for $C_{18}H_{22}O_7$: C, 61.71; H, 6.33. Found: C, 61.42; H, 6.26.

4.10. Methyl 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-β-L-*talo*-heptofuranuronate 19a and methyl 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*allo*-heptofuranuronate 19b

Following the procedure described for **12**, β-ketoester **18** (100 mg, 0.3 mmol) was reacted with the catalyst prepared with either (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl or (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl to give, respectively, after purification by column chromatography (SiO_2, AcOEt/pentane 1:1), **19a** or **19b**.

Compound **19a**: colourless oil (88 mg, 88%), de >99%; $[\alpha]_D^{25} = +72$ (*c* 0.8, DCM); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.36$ (s, 3H, C*Me*$_2$), 1.59 (s, 3H, C*Me*$_2$), 2.52–2.78 (m, 3H, H-6, H-6′, OH), 3.71 (s, 3H, O*Me*), 3.96 (m, 2H, H-3, H-4), 4.16 (m, 1H, H-5), 4.59 (m, 2H, H-2, CH*H*Ar), 4.77 (d, 1H, $J = 11.8$ Hz, CH*H*Ar), 5.75 (d, 1H, $J = 3.6$ Hz, H-1), 7.30–7.42 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.46$, 26.79 (C*Me*$_2$), 38.73 (C-6), 51.80 (O*Me*), 66.23 (C-5), 72.31 (*C*H_2Ar), 77.28 (C-3), 77.57 (C-2), 80.42 (C-4), 104.19 (C-1), 113.08 (*C*Me_2), 128.01, 128.42, 137.41 (Ar), 172.63 (C-7). Anal. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86. Found: C, 61.38; H, 6.87.

Compound **19b**: pale yellow oil (80 mg, 80%), de >99%; $[\alpha]_D^{25} = +110$ (*c* 0.6, DCM); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.36$ (s, 3H, C*Me*$_2$), 1.59 (s, 3H, C*Me*$_2$), 2.56 (m, 2H, H-6, H-6′), 2.79 (br, 1H, OH), 3.70 (s, 3H, O*Me*), 3.92 (dd, 1H, $J = 4.4$ and 8.8 Hz, H-3), 4.07 (m, 1H, H-4), 4.34 (m, 1H, H-5), 4.58 (m, 2H, H-2, CH*H*Ar), 4.77 (d, 1H, $J = 11.5$ Hz, CH*H*Ar), 5.74 (d, 1H, $J = 3.7$ Hz, H-1), 7.35 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.60$, 26.87 (C*Me*$_2$), 36.90 (C-6), 51.84 (O*Me*), 67.34 (C-5), 72.08 (*C*H$_2$Ar), 77.23 (C-3), 77.67 (C-2), 79.92 (C-4), 104.10 (C-1), 113.11 (*C*Me$_2$), 128.05, 128.08 128.46, 137.23 (Ar), 172.38 (C-7). Anal. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86. Found: C, 60.93; H, 7.01.

4.11. 3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-β-L-*talo*-hepto-1,4-furanose 20a and 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*allo*-hepto-1,4-furanose 20b

A mixture of **19a** (1.1 g, 3.1 mmol) in dry THF (16.2 mL) was slowly added via cannula to a solution of $LiAlH_4$ (176.3 mg, 4.6 mmol) in dry THF (10.5 mL) at 0 °C under argon. The reaction was stirred for 1 h at room temperature. The mixture was quenched by dropwise addition of aqueous solution of HCl (2 M) until neutrality. The crude product was extracted with DCM (4 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and the solvents evaporated. Purification by column chromatography (SiO_2, AcOEt) gave **20a** as white crystals (924 mg, 92%); mp 104.1 °C; $[\alpha]_D^{25} = +101$ (*c* 0.9, DCM); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$ (s, 3H, C*Me*$_2$), 1.60 (s, 3H, C*Me*$_2$), 1.84 (m, 2H, H-6, H-6′), 2.22 (br s, 2H, 2OH), 3.87 (m, 4H, H-3, H-5, H-7, H-7′), 4.00 (dd, 1H, $J = 2.7$ and 8.8 Hz, H-4), 4.59 (m, 2H, H-2, CH*H*Ar), 4.78 (d, 1H, $J = 11.9$ Hz, CH*H*Ar), 5.75 (d, 1H, $J = 3.6$ Hz, H-1), 7.32–7.38 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.55$, 26.85 (C*Me*$_2$), 36.20 (C-6), 60.91 (C-7), 69.46 (C-5), 72.34 (*C*H$_2$Ar), 77.58, 77.60 (C-2, C-3), 80.98 (C-4), 104.18 (C-1), 113.21 (*C*Me$_2$), 128.10, 128.49, 137.44 (Ar). Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 63.15; H, 7.76.

The same procedure with **19b** gave **20b**: white crystals (783 mg, 78%); mp 83.6 °C; $[\alpha]_D^{25} = +113$ (*c* 1.0, DCM); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.35$ (s, 3H, C*Me*$_2$), 1.58 (s, 3H, C*Me*$_2$), 1.78 (m, 2H, H-6, H-6′), 2.84 (br s, 2H, 2OH), 3.78 (dd, 2H, $J = 5.3$–5.9 Hz, H-7, H-7′), 3.94 (dd, 1H, $J = 16$ Hz, H-3), 4.07 (m, 2H, H-4, H-5), 4.57 (m, 2H, H-2, CH*H*Ar), 4.74 (d, 1H, $J = 11.4$ Hz, CH*H*Ar), 5.72 (d, 1H, $J = 3.5$ Hz, H-1), 7.29 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.60$, 26.85 (C*Me*$_2$), 33.75 (C-6), 61.49 (C-7), 71.00 (C-5), 72.10 (*C*H$_2$Ar), 77.28 (C-3), 77.68 (C-2), 80.35 (C-4), 104.01 (C-1), 113.15 (*C*Me$_2$), 128.14, 128.50, 137.20 (Ar). Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 63.12; H, 7.69.

4.12. 3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-7-*O*-triisopropylsilyl-β-L-*talo*-hepto-1,4-furanose 21a and 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-7-*O*-triisopropylsilyl-α-D-*allo*-hepto-1,4-furanose 21b

A solution of imidazole (142.3 mg, 2.1 mmol) in dry DMF (1.2 mL) was added to **20a** (252.8 mg; 0.8 mmol) under argon. Triisopropylsilyl chloride (180.4 mg, 0.9 mmol) was added. The reaction solution was stirred for 1 h. The reaction mixture was retaken with water (1 mL) and extracted with Et_2O (3 × 3 mL). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$, filtered and the solvents evaporated. Purification by column chromatography (SiO_2, Et_2O/pentane 1:1) gave **21a** as a colourless oil (337 mg, 90%); $[\alpha]_D^{25} = +67$ (*c* 1.0, DCM); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.07$ (m, 21H, *i*-Pr$_3$Si), 1.37 (s, 3H, C*Me*$_2$), 1.59 (s, 3H, C*Me*$_2$), 1.76 (m, 1H, H-6), 1.94 (m, 1H, H-6′), 3.02 (br s, 1H, OH), 3.88 (m, 1H, H-7 or H-5), 3.99 (m, 4H, H-3, H-4, H-5 or H-7, H-7′), 4.57 (m, 1H, H-2), 4.62 (d, 1H, $J = 11.8$ Hz, CH*H*Ar), 4.78 (d, 1H, $J = 11.7$ Hz, CH*H*Ar), 5.77 (d, 1H, $J = 3.8$ Hz, H-1), 7.36 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.82$ (Si(*C*HMe$_2$)$_3$), 17.96 (Si(CH*Me*$_2$)$_3$), 26.57, 26.86 (C*Me*$_2$), 36.30 (C-6), 62.32 (C-7), 68.80 (C-5), 72.33 (*C*H$_2$Ar), 77.44 (C-3), 77.64 (C-2), 81.39 (C-4), 104.29 (C-1), 112.88 (*C*Me$_2$), 127.88, 127.99, 128.38, 137,77 (Ar). Anal. Calcd for $C_{26}H_{44}O_6Si$: C, 64.96; H, 9.23. Found: C, 64.91; H, 9.21.

The same procedure with **20b** gave **21b** as a colourless oil (318 mg, 85%); $[\alpha]_D^{25} = +64$ (*c* 2.0, DCM); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.07$ (m, 21H, *i*-Pr$_3$Si), 1.36 (s, 3H, C*Me*$_2$), 1.60 (s, 3H, C*Me*$_2$), 1.77 (m, 2H, H-6, H-6′), 3.33 (br s, 1H, OH), 3.95 (m, 4H, H-3, H-4, H-7, H-7′), 4.18 (m, 1H, H-5), 4.59 (m, 2H, H-2, CH*H*Ar), 4.77 (d, 1H, $J = 11.9$ Hz, CH*H*Ar), 5.75 (d, 1H, $J = 3.7$ Hz, H-1), 7.31–7.35 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.77$ (Si(*C*HMe$_2$)$_3$), 17.95 (Si(CH*Me*$_2$)$_3$), 26.63, 26.89 (C*Me*$_2$), 34.16 (C-6), 62.45 (C-7), 69.88 (C-5), 72.06 (*C*H$_2$Ar), 76.84 (C-3), 77.91 (C-2), 81.25 (C-4), 104.02 (C-1), 112.82 (*C*Me$_2$), 127.87, 128.07, 128.35, 137.65 (Ar). Anal. Calcd for $C_{26}H_{44}O_6Si$: C, 64.96; H, 9.23. Found: C, 64.96; H, 9.51.

4.13. 3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-7-*O*-triisopropylsilyl-β-L-*talo*-hepto-1,4-furanose 22a and 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-7-*O*-triisopropylsilyl-α-D-*allo*-hepto-1,4-furanose 22b

Methanesulfonyl chloride (0.2 mL, 2.3 mmol) was added to a solution of **21a** or **21b** (318.6 mg, 0.7 mmol) in a mixture of pyridine/DCM (1/2, 14 mL). The reaction mixture was warmed to 45 °C for 2.5 h for **21a** or 1.5 h for **21b**. A saturated aqueous solution of $NaHCO_3$ was added until neutrality. The overall solution was extracted with Et_2O (4 × 10 mL). The combined organic layers were washed with an aqueous solution of $CuSO_4$ (5%, 4 × 15 mL), water (15 mL), dried over $MgSO_4$, filtered and the solvents were evaporated. Compound **22** (**a** or **b**) has been introduced directly into the next step. Purification by column chromatography (SiO_2, DCM) has allowed us to obtain the pure compounds for analysis.

Compound **22a**: pale yellow oil (341 mg, 92%); $[\alpha]_D^{25} = +41$ (*c* 0.8, DCM); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.07$ (m, 21H, *i*-Pr$_3$Si), 1.36 (s, 3H, C*Me*$_2$), 1.58 (s, 3H, C*Me*$_2$), 2.08 (m, 2H, H-6, H-6′), 3.07 (s, 3H, SO$_2$*Me*), 3.84 (m, 3H, H-3, H-7, H-7′), 4.16 (dd, 1H, $J = 3.7$ and 8.8 Hz,

H-4), 4.57 (m, 1H, $J = 3.9$–4.1 Hz, H-2), 4.62 (d, 1H, $J = 11.1$ Hz, CH*H*Ar), 4.74 (d, 1H, $J = 11.1$ Hz, CH*H*Ar), 5.06 (m, 1H, H-5), 5.77 (d, 1H, $J = 3.6$ Hz, H-1), 7.29–7.38 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.93$ (Si(*C*HMe$_2$)$_3$), 17.99 (Si(CH*Me*$_2$)$_3$), 26.56, 26.88 (C*Me*$_2$), 34.95 (C-6), 38.62 (SO$_2$*Me*), 58.9 (C-7), 72.34 (*C*H$_2$Ar), 77.44 (C-2), 78.41 (C-3), 78.65 (C-5), 79.17 (C-4), 104.05 (C-1), 113.14 (*C*Me$_2$), 127.97, 128.29, 128.35, 137.38 (Ar). Anal. Calcd for $C_{27}H_{46}O_8SSi$: C, 58.03; H, 8.30. Found: C, 58.51; H, 8.13.

Compound **22b**: pale yellow oil (270 mg, 73%); $[\alpha]_D^{25} = +61$ (*c* 1.7, DCM); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.06$ (m, 21H, *i*-Pr$_3$Si), 1.36 (s, 3H, C*Me*$_2$), 1.59 (s, 3H, C*Me*$_2$), 2.03 (m, 2H, H-6, H-6′), 3.00 (s, 3H, SO$_2$*Me*), 3.83 (m, 2H, H-7, H-7′), 3.99 (dd, 1H, $J = 4.4$ and 8.8 Hz, H-3), 4.27 (dd, 1H, $J = 2.2$, 8.8 Hz, H-4), 4.58 (m, 2H, H-2, CH*H*Ar), 4.75 (d, 1H, $J = 11.4$ Hz, CH*H*Ar), 5.13 (m, 1H, H-5), 5.73 (d, 1H, $J = 3.7$ Hz, H-1), 7.29–7.36 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.88$ (Si(*C*HMe$_2$)$_3$), 17.96 (Si(CH*Me*$_2$)$_3$), 26.57, 26.89 (C*Me*$_2$), 34.16 (C-6), 38.18 (SO$_2$*Me*), 59.12 (C-7), 72.14 (*C*H$_2$Ar), 77.27 (C-3), 77.52 (C-2), 79.05, 79.12 (C-5, C-4), 103.81 (C-1), 113.32 (*C*Me$_2$), 128.01, 128.43, 137.17 (Ar). Anal. Calcd for $C_{27}H_{46}O_8SSi$: C, 58.03; H, 8.30. Found: C, 57.94; H, 8.17.

4.14. 5-Azido-3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-7-*O*-triisopropylsilyl-α-D-*allo*-hepto-1,4-furanose 23a and 5-azido-3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-7-*O*-triisopropylsilyl-β-L-*talo*-hepto-1,4-furanose 23b

Sodium azide (74.2 mg, 1.1 mmol) was added to a solution of **22a** (177.3 mg, 0.3 mmol) in DMF (5 mL) under argon. The reaction mixture was warmed to 110 °C for 3 h. After cooling, water (5 mL) was added. The aqueous layer was extracted with Et_2O (4 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvents evaporated. Purification by column chromatography (SiO_2, DCM) gave **23a**.

Compound **23a**: colourless oil (124 mg, 77%); $[\alpha]_D^{25} = +105$ (*c* 1.4, DCM); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.07$ (m, 21H, *i*-Pr$_3$Si), 1.37 (s, 3H, C*Me*$_2$), 1.60 (s, 3H, C*Me*$_2$), 1.76 (m, 2H, H-6, H-6′), 3.80 (m, 2H, H-7, H-7′), 3.93 (dd, 1H, $J = 4.4$ and 8.5 Hz, H-3), 4.11 (m, 1H, H-5), 4.22 (dd, 1H, $J = 2.9$ and 8.6 Hz, H-4), 4.56 (m, 2H, H-2, CH*H*Ar), 4.74 (d, 1H, $J = 11.6$ Hz, CH*H*Ar), 5.78 (d, 1H, $J = 3.7$ Hz, H-1), 7.37 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.93$ (Si(*C*HMe$_2$)$_3$), 17.99 (Si(CH*Me*$_2$)$_3$), 26.65, 26.93 (C*Me*$_2$), 33.05 (C-6), 59.43 (C-5), 59.54 (C-7), 72.09 (*C*H$_2$Ar), 77.51 (C-3), 77.83 (C-2), 81.09 (C-4), 103.97 (C-1), 113.14 (*C*Me$_2$), 128.00, 128.41, 137.36 (Ar). Anal. Calcd for $C_{26}H_{43}N_3O_5Si$: C, 61.75; H, 8.57. Found: C, 61.54; H, 8.41.

The same procedure with **22b** led to **23b**: colourless oil (122 mg, 76%); $[\alpha]_D^{25} = +48$ (*c* 1.1, DCM); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.08$ (m, 21H, *i*-Pr$_3$Si), 1.37 (s, 3H, C*Me*$_2$), 1.59 (s, 3H, C*Me*$_2$), 1.96 (m, 2H, H-6, H-6′), 3.66 (m, 1H, H-5), 3.87 (m, 3H, H-3, H-7,s H-7′), 4.09 (dd, 1H, $J = 2.6$ and 8.8 Hz, H-4), 4.59 (m, 2H, H-2, CH*H*Ar), 4.78 (d, 1H, $J = 12.1$ Hz, CH*H*Ar), 5.76 (d, 1H, $J = 3.5$ Hz, H-1), 7.33–7.39 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.91$ (Si(*C*HMe$_2$)$_3$), 18.00 (Si(CH*Me*$_2$)$_3$), 26.52, 26.87 (C*Me*$_2$), 34.22 (C-6), 57.40 (C-5), 59.56 (C-7), 72.26 (*C*H$_2$Ar), 76.21 (C-2), 78.26 (C-3), 80.63 (C-4), 104.05 (C-1), 113.15 (*C*Me$_2$), 127.94, 128.07, 128.48, 137.31 (Ar). Anal. Calcd for $C_{26}H_{43}N_3O_5Si$: C, 61.75; H, 8.57. Found: C, 61.59; H, 8.64.

4.15. 5-Azido-3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*allo*-hepto-1,4-furanose 24a and 5-azido-3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*talo*-hepto-1,4-furanose 24b

TBAF 1 M in THF (1.2 mL) was added to a solution of **23a** or **23b** (507.4 mg, 1.0 mmol) in THF (4.4 mL). The reaction mixture was stirred for 1.5 h. A saturated aqueous solution of NH_4Cl was added until neutrality and the mixture was extracted with Et_2O (5 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvents were evaporated. Purification by column chromatography (SiO_2, Et_2O/pentane 3:2) gave **24a** or **24b**.

Compound **24a**: 281 mg, 80%; $[\alpha]_D^{25} = +152$ (*c* 2.1, DCM); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$ (s, 3H, C*Me*$_2$), 1.60 (s, 3H, C*Me*$_2$), 1.70 (m, 3H, H-6, H-6′,OH), 3.76 (m, 2H, H-7, H-7′), 3.93 (dd, 1H, $J = 4.3$ and 8.6 Hz, H-3), 3.99 (m, 1H, H-5), 4.24 (dd, 1H, $J = 3.1$ and 8.5 Hz, H-4), 4.57 (d, 1H, $J = 11.6$ Hz, CH*H*Ar), 4.60 (m, 1H, H-2), 4.76 (d, 1H, $J = 11.6$ Hz, CH*H*Ar), 5.78 (d, 1H, $J = 3.7$ Hz, H-1), 7.34–7.38 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.62$, 26.91 (C*Me*$_2$), 32.63 (C-6), 59.62 (C-7), 60.10 (C-5), 72.13 (*C*H$_2$Ar), 77.49 (C-3), 77.69 (C-2), 80.67 (C-4), 103.89 (C-1), 113.24 (*C*Me$_2$), 128.10, 128.46, 137.15 (Ar). Anal. Calcd for $C_{17}H_{23}N_3O_5$: C, 58.44; H, 6.64; N, 12.03. Found: C, 58.34; H, 6.53; N, 11.92.

Compound **24b**: 350 mg, 100%; $[\alpha]_D^{25} = +97$ (*c* 2.0, DCM); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$ (s, 3H, C*Me*$_2$), 1.65 (s, 3H, C*Me*$_2$), 2.01 (m, 2H, H-6, H-6′), 3.57 (m, 1H, H-5), 3.80 (m, 2H, H-7, H-7′), 3.87 (dd, 1H, $J = 4.2$ and 8.8 Hz H-3), 4.12 (dd, 1H, $J = 2.9$ and 8.8 Hz, H-4), 4.60 (m, 2H, H-2, CH*H*Ar), 4.79 (d, 1H, $J = 11.8$ Hz, CH*H*Ar), 5.76 (d, 1H, $J = 3.7$ Hz, H-1), 7.34 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.52$, 26.87 (C*Me*$_2$), 33.70 (C-6), 57.84 (C-5), 59.14 (C-7), 72.33 (*C*H$_2$Ar), 77.30 (C-2), 78.23 (C-3), 80.34 (C-4), 104.00 (C-1), 113.29 (*C*Me$_2$), 128.12, 128.21, 128.54, 137.17 (Ar). Anal. Calcd for $C_{17}H_{23}N_3O_5$: C, 58.44; H, 6.64; N, 12.03. Found: C, 58.37; H, 6.62; N, 12.19.

4.16. 1,5,6-Trideoxy-1,5-imino-D-*allo*-heptitol 3

Azide **24a** (123.3 mg, 0.3 mmol) was stirred for 2 h at 40 °C in a solution of TFA in water (3/2, 3.8 mL). The solvents were eliminated and the residue retaken in MeOH (3.8 mL). PtO_2 (8.0 mg, 0.03 mmol) was added and the reaction mixture hydrogenolysed at room temperature for 12 h to 20 bar. The catalyst was filtered over Celite and washed with MeOH. The solvents were then evaporated. The crude was dissolved in EtOH (4 mL). Concentrated

HCl (3.5 mL) and Pd/C (353 mg) were then added. The mixture was stirred under a hydrogen atmosphere (5 bars) at room temperature for 24 h. Purification over Amberlyst A-26 (OH^-) eluting with an aqueous solution of NH_4OH (2.5%), gave the expected piperidine **3** (49.9 mg, 80%). The specific rotation was measured on the hydrochloride form of the piperidine after treatment with a methanolic solution of HCl; $[\alpha]_D^{25} = +19$ (*c* 0.1, MeOH) {lit.[11] $[\alpha]_D^{25} = -18$ (*c* 1.6, MeOH) for its enantiomer}.

4.17. 1,5,6-Trideoxy-1,5-imino-L-*talo*-heptitol 4

Azide **24b** (178.5 mg, 0.5 mmol) was treated as for **24a** to give **4** (46.0 mg, 51%). The specific rotation was measured on the hydrochloride form of the piperidine after treatment with a methanolic solution of HCl; $[\alpha]_D^{25} = +24$ (*c* 0.6, MeOH) {lit.[11] $[\alpha]_D^{25} = -24.1$ (*c* 0.5, MeOH) for its enantiomer}.

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