Accessing 2-substituted piperidine iminosugars by organometallic addition/intramolecular reductive amination: aldehyde vs nitrone route

Stefania Mirabella, a Giulia Fibbi, a Camilla Matassini, a,b Cristina Faggi, a Andrea Goti a,b and Francesca Cardona a,b*

a Department of Chemistry “Ugo Schiff”, University of Firenze, Via della Lastruccia 3-13, 50019 Sesto Fiorentino (FI), Italy.
b Associated with CNR-INO, Via N. Carrara 1, Sesto Fiorentino (FI), Italy.

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Crystal structure determination for compounds \textbf{12a} and \textbf{21a} S50-S51
**General methods:** Commercial reagents were used as received. All reactions were carried out under magnetic stirring and monitored by TLC on 0.25 mm silica gel plates (Merck F254). Column chromatographies were carried out on Silica Gel 60 (32–63 μm) or on silica gel (230–400 mesh, Merck). Yields refer to spectroscopically and analytically pure compounds unless otherwise stated. $^1$H NMR spectra were recorded on a Varian Mercury-400 or on a Varian INOVA 400 instruments at 25 °C. $^{13}$C NMR spectra were recorded on a Varian Gemini-200 or on a Varian Gemini-300 spectrometer. Chemical shifts are reported relative to TMS ($^1$H: δ = 0.00 ppm) and CDCl3 ($^{13}$C: δ = 77.0 ppm). Integrals are in accordance with assignments, coupling constants are given in Hz. For detailed peak assignments 2D spectra were measured (COSY, HSQC, NOESY, and NOE as necessary). Small scale microwave assisted syntheses were carried out in a microwave apparatus for synthesis (CEM Discover) with an open reaction vessel and external surface sensor. IR spectra were recorded with a BX FTIR Perkin-Elmer system spectrophotometer. ESIMS spectra were recorded with a Thermo Scientific™ LCQ fleet ion trap mass spectrometer. Elemental analyses were performed with a Perkin-Elmer 2400 analyzer. Optical rotation measurements were performed on a JASCO DIP-370 polarimeter.
Synthesis of benzyl 2,3-\(\text{O-}(1\text{-methylethylidene})\)-5-deoxy-\(\text{N-benzyl-d-lyxofuranosylamine}\) \(\text{N-oxide}\) (11).

To a solution of 10\(^1\)(310 mg, 1.11 mmol) in dry CH\(\text{2Cl}_2\) (5.7 mL), Na\(\text{2SO}_4\) anhydrous (791 mg, 5.57 mmol) was added under nitrogen atmosphere. The suspension was stirred at room temperature for 30 minutes and then triethylamine (201 μL) and \(\text{N-benzylhydroxylamine hydrochloride}\) (267 mg, 1.67 mmol) were added. The mixture was stirred for 20 h at room temperature, when a TLC check (PET/AcOEt 2:1) attested the disappearance of the starting material 10. The mixture was cooled at 0°C and a saturated solution of NH\(\text{4Cl}\) (6 mL) was added, stirring for 10 minutes. The two layers were separated and the aqueous layer was extracted with CH\(\text{2Cl}_2\) (3×5 mL). The combined organic layers were washed with brine (2×10 mL) and concentrated after drying with Na\(\text{2SO}_4\). The residue was purified by gradient eluent silica gel flash column chromatography (PET/AcOEt from 2:1 to 1:1) to afford 360 mg of pure 11 (\(R_t = 0.09\), PET/AcOEt 2:1, 0.94 mmol, 85%) as a white solid. M.p. = 126-128 °C. \([\alpha]_D^{28} = -19.00\) (\(c = 1.01\), CHCl\(\text{3}\)). \(^1\)H-NMR (400 MHz, CDCl\(\text{3}\)) \(\delta\) ppm = 7.37-7.19 (m, 10 H, Ar), 6.75 (dd, \(J = 4.4\), 2.4 Hz, 1H, H-5), 5.11-5.07 (m, 2H, H-4, H-3), 5.04 (s, 1H, H-1), 4.89 (s, 2H, NBn), 4.61- 4.58 (m, 2H, OBn, H-2), 4.37 (d, \(J = 11.7\) Hz, 1H, OBn), 1.30 (s, 3H, Me), 1.21 (s, 3H, Me). \(^{13}\)C-NMR (50 MHz, CDCl\(\text{3}\)) \(\delta\) ppm = 137.0, 135.6 (s, 2 C, Ar), 132.4 (d, C-5), 129.4-127.9 (d, 10 C, Ar), 112.6 (s, acetone), 105.0 (d, C-1), 84.5 (d, C-2), 79.7 (d, C-4), 76.7 (d, C-3), 69.1 (t, NBn), 68.9 (t, OBn), 26.0 (q, Me), 24.7 (q, Me). IR (KBr): \(\nu = 3084, 3032, 2980, 2881, 2359, 1616, 1497, 1456, 1163, 1103\) cm\(^{-1}\). MS (ESI): \(m/z\) 406.17 ([M+Na]+; 100). Elemental analysis calcd (%) for C\(_{22}\)H\(_{25}\)NO\(_5\) (383.44): C 68.91, H 6.57, N 3.65; found: C 68.85, H 6.53, N 3.46.

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Figure S1: $^1$H NMR spectrum of 11 (400 MHz, CDCl$_3$)

Figure S2: $^{13}$C NMR spectrum of 11 (50 MHz, CDCl$_3$)
Synthesis of benzyl 6-deoxy-2,3-O-(1-methylethylidene)-α-D-mannofuranoside (12a) and of benzyl 6-deoxy-2,3-O-(1-methylethylidene)-β-L-gulofuranoside (12b).

A solution of 10 (110 mg, 0.39 mmol) in dry THF (5.2 mL) was stirred at -78°C under nitrogen atmosphere and a solution of MeMgBr 3M in Et₂O (0.72 mmol) was added. The mixture was stirred for 4 h at -78°C, when the disappearance of the aldehyde was observed, checking by ¹H-NMR spectroscopy. A saturated solution of NaHCO₃ was added at the mixture at 0°C and the mixture was stirred for 15 minutes. The two layers were separated and the aqueous layer was washed with Et₂O (3x 5 mL). The combined organic layers were washed with brine (3x5 mL), dried with Na₂SO₄, and concentrated under reduced pressure to give a mixture of 12a and 12b (a : b ratio 5:1, as attested by integrating the signals in the ¹H-NMR spectrum of the crude). The residue was purified by silica gel flash chromatography (PEt/AcOEt 5:1) to give 106 mg of a mixture of pure 12a and 12b impossible to be separated (0.36 mmol, 92%).

Figure S3: ¹H NMR spectrum of the crude reaction mixture (400 MHz, CDCl₃)

A small amount of this mixture was further purified by FCC (PEt/AcOEt 5:1, Rf = 0.28) to give a sample of isolated 12a, sufficient to be completely characterized. [α]D²⁹ = + 70.0 (c = 0.85, CHCl₃). ¹H-NMR (400 MHz, CDCl₃):
MHz, CDCl₃) δ ppm = 7.36-7.25 (m, 5H, Ar), 5.12 (s, 1H, H-1), 4.86 (dd, J =5.8, 3.5 Hz, 1H, H-3), 4.66-4.63 (m, 2H, H-2, Ha-Bn), 4.49 (d, J =11.7 Hz, 1H, Hb-Bn), 4.08 (sext, J =6.6 Hz, 1H, H-5), 3.77 (dd, J =7.3, 3.8Hz, 1H, H-4), 2.56 (d, J =5.9 Hz, 1H, OH), 1.47 (s, 3H, Me), 1.34 (s, 3H, H-6), 1.31 (s, 3H, Me).

¹³C-NMR (50 MHz, CDCl₃) δ ppm = 137.5 (s, 1C, Ar), 128.4-127.8 (d, 5C, Ar), 112.6 (s, acetal), 105.3 (d, C-1), 85.1 (d, C-2), 83.5 (d, C-4), 80.0 (d, C-3), 69.0 (t, Bn), 66.5 (d, C-5), 25.9 (q, Me), 24.6 (q, Me), 20.4 (q, C-6). IR (CHCl₃): ν = 3528, 3021, 2992, 2937, 1455, 1384, 1376, 1265, 1161, 1081, 1018 cm⁻¹. MS (ESI): m/z 316.81 ([M+Na]+; 100). Elemental analysis calcd (%) for C₁₆H₂₂O₅ (294.34): C 65.29, H 7.53; found: C 65.38, H 7.54.

Figure S4: ¹H NMR spectrum of 12a (400 MHz, CDCl₃)

Figure S5: ¹³C NMR spectrum of 12a (50 MHz, CDCl₃)
Compound 12a was crystallized from EtOH to give crystals for X-ray analysis. **CCDC 1545186** for 12a contains the supplementary crystallographic data that can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**Figure S6: X-ray crystal structure of 12a**
Synthesis of benzyl 6,7-dideoxy-2,3-O-(1-methylethylidene)-α-D-manno-heptofuranoside (13a) and of benzyl 6,7-dideoxy-2,3-O-(1-methylethylidene)-β-L-gulo-heptofuranoside (13b).

A solution of 10 (203 mg, 0.73 mmol) in dry THF (9.6 mL) was stirred at 0°C under nitrogen atmosphere and a 3 M solution of EtMgBr in Et₂O (1.31 mmol) was slowly added; the mixture was stirred for 3 h at 0°C, when the disappearance of the aldehyde was attested by a TLC control (PET₃/acetone 2:1). A saturated solution of NaHCO₃ (10 mL) was added to the mixture at 0°C and the salts were removed by filtration. The two layers were separated and the aqueous layer was washed with Et₂O (3x10 mL). The combined organic layers were dried with Na₂SO₄ and concentrated under reduced pressure to give a mixture of 13a and 13b (a : b ratio 1.6 : 1, as attested by integrating the signals in the ¹H-NMR spectrum of the crude). The residue was purified by silica gel flash chromatography (PEt₃/Et₂O 3:1) to give 55 mg (0.18 mmol, 25%) of 13b as a white solid, 68 mg (0.22 mmol, 30%) of 13a and 37 mg of a mixture of 13a and 13b impossible to be separated (total yield 71%).

13a (Rᵣ = 0.31, PEt₃/Et₂O 3:1): [α]D²⁵ = +76.4 (c = 1.14, CHCl₃). ¹H-NMR (400 MHz, CDCl₃) δ ppm = 7.37-7.26 (m, 5H, Ar), 5.12 (s, 1H, H-1), 4.85 (dd, J = 4.0, 3.2 Hz, 1H, H-3), 4.67 (d, J = 11.8 Hz, 1H, H-a-Bn), 4.65 (d, J = 11.8 Hz, 1H, H-b-Bn), 4.65 (d, J = 6.0 Hz, 1H, H-2), 3.87-3.82 (m, 2H, H-4, H-5), 1.78-1.49 (m, 2H, H-6), 1.48 (s, 3H, Me), 1.32 (s, 3H, Me), 1.05 (t, J = 7.4 Hz, 3H, H-7). ¹³C-NMR (50 MHz, CDCl₃) δ ppm = 137.4 (s, Ar), 128.4-127.8 (d, 5C, Ar), 112.5 (s, acetale), 105.2 (d, C-1), 84.9 (d, C-2), 81.9 (d, C-4), 80.2 (d, C-3), 71.4 (d, C-5), 68.9 (t, Bn), 27.4 (t, C-6), 25.9, 24.6 (q, 2C, Me), 9.77 (q, C-7). IR (CDCl₃): ν = 2977, 2937, 2879, 2260, 1454, 1384, 1211, 1078, 1020, 898 cm⁻¹. MS (ESI): m/z 331.08 ([M+Na]⁺; 100). Elemental analysis calcd (%) for C₁₇H₂₃O₅ (308.37): C, 66.21; H, 7.84; found: C, 65.92, H, 7.76.
Figure S7: $^1$H NMR spectrum of 13a (400 MHz, CDCl$_3$)

Figure S8: $^{13}$C NMR spectrum of 13a (50 MHz, CDCl$_3$)
13b (Rf = 0.22, Eluente PEt/Et2O 3:2): M.p. = 53.6-55.4 °C. [α]D25 = + 84.0 (c = 0.99, CHCl3). 1H-NMR (400 MHz, CDCl3) δ ppm = 7.36-7.25 (m, 5H, Ar), 5.15 (s, 1H, H-1), 4.75 (dd, J = 4.0, 3.6 Hz, 1H, H-3), 4.67 (d, J = 11.6 Hz, 1H, H-Bn), 4.66 (d, J = 6.1 Hz, 1H, H-2) 4.50 (d, J = 11.6 Hz, 1H, H-Bn), 3.97-3.93 (m, 1H, H-5), 3.88-3.86 (m, 1H, H-4), 1.66-1.60 (m, 2H, H-6), 1.47 (s, 3H, Me), 1.30 (s, 3H, Me), 1.03 (t, J = 7.4 Hz, 3H, H-7). 13C-NMR (50 MHz, CDCl3) δ ppm = 137.4 (s, Ar), 128.5-127.8 (d, 5C, Ar), 112.6 (s, acetal), 105.1 (d, C-1), 85.5 (d, C-2), 81.7 (d, C-4), 80.6 (d, C-3), 71.3 (d, C-5), 69.1 (t, Bn), 26.2, 25.9 (q, 2C, Me), 24.5 (t, C-6), 9.89 (q, C-7). IR (KBr): ν = 3458, 2929, 1375, 1209, 1078, 1066, 1014 cm⁻¹. MS (ESI): m/z = 331.14 ([M+Na]+; 100). Elemental analysis calcd (%) for C17H24O5 (308.37): C, 66.21; H, 7.84; found: C, 66.27, H, 8.19.

Figure S9: 1H NMR spectrum of 13b (400 MHz, CDCl3)

Figure S10: 13C NMR spectrum of 13b (50 MHz, CDCl3)
Synthesis of benzyl \((5R)-2,3-O-(1\text{-methylethylidene})-5-C\text{-phenyl-\text{-D-lyxofuranoside}}\) (14a) and of benzyl \((5S)-2,3-O-(1\text{-methylethylidene})-5-C\text{-phenyl-\text{-D-lyxofuranoside}}\) (14b).

A solution of 10 (207 mg, 0.74 mmol) in dry THF (10 mL) was stirred at \(-78^\circ C\) under nitrogen atmosphere and a solution of PhMgBr in Et\(_2\)O (1 M, 1.34 mmol) was slowly added. The mixture was stirred for 2 h at \(-78^\circ C\), when the disappearance of the aldehyde was attested by a TLC control (EtPe : AcOEt 2:1). A saturated solution of NaHCO\(_3\) (8 mL) was added at 0°C and the salts were removed by filtration. The two layers were separated and the aqueous layer was washed with Et\(_2\)O (3x5 mL). The combined organic layers were dried with Na\(_2\)SO\(_4\) and concentrated under reduced pressure to give a mixture of 14a and 14b (a : b ratio 1.3 : 1, as attested by integrating the signals in the \(^1\)H-NMR spectrum of the crude). The residue was purified by silica gel flash chromatography (PEt/AcOEt 6:1) to give 101 mg (0.29 mmol, \(R_f = 0.19\), 38%) of 14a and 66 mg (0.19 mmol, \(R_f = 0.31\), 25%) of 14b, and 16 mg (0.04 mmol) of a mixture of the two diastereoisomers, impossible to be separated, for a total yield of 69%.

\(14a\) (\(R_f = 0.19\), PEt/AcOEt 6:1): \([\alpha]_D^{24} = + 57.3\) (c = 0.90, CHCl\(_3\)). \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm = 7.48-7.22 (m, 10 H, Ar), 5.15 (s, 1H, H-1), 5.02 (pt, J =8.0 Hz, 1H, H-5), 4.83-4.81 (m, 1H, H-3), 4.66 (d, J = 4.0 Hz, 1H, H-2), 4.54 (d, J =12.0 Hz, 1H, H-Bn), 4.40 (d, J =12.0 Hz, 1H, H-Bn), 4.14 (dd, J =8.0, 4.0 Hz, 1H, H-4), 3.34-3.32 (m, 1H, OH), 1.57 (s, 3H, Me), 1.34 (s, 3H, Me). \(^{13}\)C-NMR (50 MHz, CDCl\(_3\)) \(\delta\) ppm = 141.5 (s, Ar), 137.3 (s, Ar), 128.5-127.8 (d, 10C, Ar), 112.9 (s, acetal), 105.5 (d, C-1), 85.1 (d, C-2), 82.3 (d, C-4), 80.3 (d, C-3), 72.7 (d, C-5), 69.0 (t, Bn), 26.1 (q, Me), 24.7 (q, Me). IR (CHCl\(_3\)) \(\nu = 3591, 3498, 3014, 2995, 2939, 2879, 1454, 1375, 1269, 1207, 1058\) cm\(^{-1}\). MS (ESI): m/z = 378.95 ([M+Na]+; 100).

Elemental analysis calcd (%) for C\(_{21}\)H\(_{25}\)O\(_5\) (356.41): C, 70.77; H, 6.79; found: C, 70.93, H, 6.98.
Figure S11: $^1$H NMR spectrum of 14a (400 MHz, CDCl$_3$)

Figure S12: $^{13}$C NMR spectrum of 14a (50 MHz, CDCl$_3$)
14b (R = 0.31, PEt/ACOEt 6:1): [α]D20 = +98.3 (c = 0.65, CHCl3). 1H-NMR (400 MHz, CDCl3) δ ppm = 7.53-7.51 (m, 2H, Ar), 7.39-7.27 (m, 8H, Ar), 5.17 (s, 1H, H-1), 5.11 (d, J =8.0 Hz, 1H, H-5), 4.65 (d, J =11.8 Hz, 1H, H-a-Bn), 4.61 (d, J =5.8 Hz, 1H, H-2), 4.51-4.46 (m, 2H, H-3, H-b-Bn), 4.10 (dd, J =8.0, 4.0 Hz, 1H, H-4), 1.54 (s, 3H, Me), 1.27 (s, 3H, Me). 13C-NMR (50 MHz, CDCl3) δ ppm = 140.6 (s, Ar), 137.3 (s, Ar), 128.6-127.1 (d, 10C, Ar), 112.7 (s, acetal), 105.6 (d, C-1), 85.7 (d, C-2), 83.7 (d, C-4), 80.0 (d, C-3), 72.3 (d, C-5), 69.2 (t, Bn), 26.2 (q, Me), 24.8 (q, Me). IR (CHCl3): ν = 3502, 2985, 2920, 2358, 2341, 1452, 1380, 1269, 1207, 1163, 1064 cm⁻¹. MS (ESI): m/z = 378.95 ([M+Na]+; 100). Elemental analysis calcd (%) for C21H24O5 (356.41): C, 70.77; H, 6.79; found: C, 70.84, H, 7.09.

Figure S13: 1H NMR spectrum of 14b (400 MHz, CDCl3)

Figure S14: 13C NMR spectrum of 14b (50 MHz, CDCl3)
Synthesis of compounds 15a,b.

A solution of 10 (200 mg, 0.72 mmol) in dry THF (10 mL) was stirred at 0°C under nitrogen atmosphere and a solution of BnMgCl in THF (2 M, 2.16 mmol, 3 equiv.) was slowly added. The mixture was stirred for 2 h at 0°C, when the disappearance of the aldehyde was attested by a TLC control (hexane/AcOEt 2:1). A saturated solution of NaHCO₃ (8 mL) was added at 0°C and the salts were removed by filtration. The two layers were separated and the aqueous layer was washed with Et₂O (3x5 mL). The combined organic layers were dried with Na₂SO₄ and concentrated under reduced pressure to give a mixture of 15a and 15b (a : b ratio 2.4 : 1, as attested by integrating the signals in the ¹H-NMR spectrum of the crude). The residue was purified by silica gel flash chromatography (hexane/AcOEt 4:1) to give 32 mg (0.09 mmol, 11%) of 15a and 7 mg (0.02 mmol, 3%) of 15b, and 46 mg (0.12 mmol) of a mixture of the two diastereoisomers, impossible to be separated, for a total yield of 32% (85 mg, 0.23 mmol).

Figure S15: ¹H NMR spectrum of the crude reaction mixture (400 MHz, CDCl₃)
15a (Rf = 0.23, hexane/AcOEt 4:1): [α]D23 = + 117.2 (c = 1.26, CHCl3). 1H-NMR (400 MHz, CDCl3) δ ppm = 7.55-7.52 (m, 2H, Ar), 7.36-7.16 (m, 8H, Ar), 5.30 (dd, J = 4.8, 1.8 Hz, 1H, H-5), 5.19 (s, 1H, H-1), 4.68 (d, J = 11.8 Hz, 1H, Hα-Bn), 4.63 (d, J = 4.0 Hz, 1H, H-2), 4.52 (d, J = 11.8 Hz, 1H, Hβ-Bn), 4.49-4.47 (m, 1H, H-3), 4.30 (dd, J = 6.8, 3.6 Hz, 1H, H-4), 2.82 (s, 1H, OH), 2.42 (s, 2H, H-6), 1.51 (s, 3H, Me), 1.23 (s, 3H, Me). 13C-NMR (50 MHz, CDCl3) δ ppm = 138.1, 136.2 (s, 2C, Ar), 130.6-126.1 (d, 10C, Ar), 112.7 (s, acetal), 105.6 (d, C-1), 85.6 (d, C-2), 82.8 (d, C-4), 80.3 (d, C-3), 69.3 (t, Bn), 68.9 (d, C-5), 26.1 (q, Me), 24.7 (q, Me), 19.1 (t, C-6). IR (CHCl3): ν = 3580, 3510, 3067, 3026, 3011, 2939, 1497, 1375, 1227, 1217, 1180 cm⁻¹. MS (ESI): m/z 393.30 ([M+Na]+; 100). Elemental analysis calcd (%) for C22H26O5 (370.44): C, 71.33; H, 7.07; found: C, 70.88, H, 6.76.

Figure S16: 1H NMR spectrum of 15a (400 MHz, CDCl3)

Figure 17: 13C NMR spectrum of 15a (50 MHz, CDCl3)
15b (partially characterized): R f = 0.31, hexane/AcOEt 4:1. 1H-NMR (400 MHz, CDCl 3 ) δ ppm = 7.33-7.25 (m, 10H, Ar), 5.20 (s, 1H, H-1), 4.76 (dd, J = 5.9, 3.7 Hz, 1H, H-3), 4.71 (d, J = 11.8 Hz, 1H, H 2 -Bn), 4.65 (d, J = 5.9 Hz, 1H, H-2), 4.52 (d, J = 11.8 Hz, 1H, H 2 -Bn), 4.31-4.26 (m, 1H, H-5), 3.87 (pt, J = 3.9 Hz, 1H, H-4), 2.98 (dd, J = 13.6, 6.1 Hz, 1H, H 5 -6), 2.92 (dd, J = 13.6, 7.6 Hz, 1H, H 6 -6), 1.50 (s, 3H, Me), 1.30 (s, 3H, Me). 13C-NMR (100 MHz, CDCl 3 ) δ ppm = 138.2, 137.2 (s, 2C, Ar), 129.5-126.5 (d, 10C, Ar), 112.8 (s, acetal), 105.0 (d, C-1), 85.5 (d, C-2), 81.0 (d, C-3), 79.8 (d, C-4), 71.4 (d, C-5), 69.2 (t, Bn), 39.8 (t, C-6), 25.9 (q, Me), 24.3 (q, Me). IR (CHCl 3 ): ν = 3685, 3496, 3008, 2948, 2360, 1603, 1496, 1456, 1376, 1088 cm -1 . MS (ESI): m/z 393.37 ([M+Na]+; 100).

Figure S18: 1H NMR spectrum of 15b (400 MHz, CDCl 3 )

Figure S19: 13C NMR spectrum of 15b (50 MHz, CDCl 3 )
Synthesis of compounds 16a,b.

A solution of 10 (99 mg, 0.36 mmol) in dry THF (5 mL) was stirred at 0°C under nitrogen atmosphere and a solution of VinylMgBr in THF (1 M, 0.64 mmol, 1.8 equiv.) was slowly added. The mixture was stirred for 2 h at 0°C, when the disappearance of the aldehyde was attested by a TLC control (hexane/AcOEt 2:1). A saturated solution of NaHCO₃ (5 mL) was added at 0°C and the salts were removed by filtration. The two layers were separated and the aqueous layer was washed with Et₂O (3x5 mL). The combined organic layers were dried with Na₂SO₄ and concentrated under reduced pressure to give a mixture of 16a and 16b (a : b ratio 1.1 : 1, as attested by integrating the signals in the ¹H-NMR spectrum of the crude). The residue was purified by silica gel flash chromatography (hexane/AcOEt 5:1) to give 34 mg (0.11 mmol, 31%) of 16a as a white waxy solid and 8 mg (0.03 mmol, 8%) of 16b as a colourless oil, and 44 mg (0.14 mmol) of a mixture of the two diastereoisomers, impossible to be separated, for a total yield of 79% (86 mg, 0.28 mmol).

Figure S20: ¹H NMR spectrum of the crude reaction mixture (400 MHz, CDCl₃)
16a \( (R_f = 0.26, \text{hexane}/\text{AcOEt 5:1}) \): \([\alpha]_D^{22} = +81.6 \ (c = 0.74, \text{CHCl}_3) \). ¹H-NMR (400 MHz, CDCl₃) \( \delta \) ppm = 7.36-7.26 (m, 5H, Ar), 6.02 (ddd, \( J =17.0, 10.6, 5.3 \) Hz, 1H, H-6), 5.44 (dt, \( J =17.2, 1.2 \) Hz, 1H, Ha-7), 5.27 (dt, \( J =10.6, 1.2 \) Hz, 1H, Hb-7), 5.16 (s, 1H, H-1), 4.86 (dd, \( J =6.4, 3.6 \) Hz, 1H, H-3), 4.67 (d, \( J =11.2 \) Hz, 1H H₂-Bn), 4.66 (d, \( J =6.4 \) Hz, 1H, H-2), 4.49 (d, \( J =11.2 \) Hz, 1H, Hb-Bn), 4.48-4.45 (m, 1H, H-5), 3.90 (dd, \( J =7.2, 3.6 \) Hz, 1H, H-4), 2.79 (d, \( J =6.8 \) Hz 1H, OH), 1.50 (s, 3H, Me), 1.32 (s, 3H, Me). ¹³C-NMR (50 MHz, CDCl₃) \( \delta \) ppm = 137.7 (d, C-6), 137.4 (s, Ar), 128.5-127.9 (d, 5C, Ar), 116.1 (t, C-7), 112.8 (s, acetal), 105.5 (d, C-1), 85.0 (d, C-2), 81.5 (d, C-4), 80.3 (d, C-3), 71.2 (d, C-5), 69.1 (t, Bn), 26.0 (q, Me), 24.6 (q, Me). IR (CHCl₃): \( \nu = 2676, 3630, 3508, 2990, 2942, 1715, 1601, 1498, 1456, 1385, 1376, 1270, 1080 \text{ cm}^{-1} \). MS (ESI): \( m/z \) 329.30 ([M+Na]+; 100). Elemental analysis calcd (%) for \( \text{C}_{17}\text{H}_{22}\text{O}_5 \): C, 66.65; H, 7.24, found: C, 67.00, H, 6.95.

**Figure S21:** ¹H NMR spectrum of 16a (400 MHz, CDCl₃)

**Figure S22:** ¹³C NMR spectrum of 16a (50 MHz, CDCl₃)
16b (Rf = 0.33, hexane/AcOEt 5:1): [α]D21 = + 56.9 (c = 0.90, CHCl3). ¹H-NMR (400 MHz, CDCl3) δ ppm = 7.37-7.26 (m, 5H, Ar), 5.99 (ddd, J =17.3, 10.5, 5.3 Hz, 1H, H-6), 5.54 (dt, J =17.3, 1.8 Hz, 1H, Ha-7), 5.26 (dt, J =10.5, 1.80 Hz, 1H, Hb-7), 5.16 (s, 1H, H-1), 4.73 (dd, J =6.0, 3.6 Hz, 1H, H-3), 4.68 (d, J =11.6 Hz, 1H Ha-Bn), 4.67 (d, J =6.0 Hz, 1H, H-2), 4.53 (td, J =5.8, 1.5 Hz, 1H, H-5), 4.50 (d, J =11.6 Hz, 1H, Hb-Bn), 3.87 (dd, J =6.4, 3.6 Hz, 1H, H-4), 2.79 (d, J =2.4 Hz 1H, OH), 1.48 (s, 3H, Me), 1.30 (s, 3H, Me). ¹³C-NMR (100 MHz, CDCl3) δ ppm = 137.3 (s, Ar), 136.0 (d, C-6), 128.5-127.9 (d, 5C, Ar), 116.6 (t, C-7), 112.7 (s, acetal), 105.2 (d, C-1), 85.4 (d, C-2), 82.4 (d, C-4), 80.2 (d, C-3), 70.9 (d, C-5), 69.1 (t, Bn), 26.0 (q, Me), 24.5 (q, Me). IR (CHCl3): ν = 3688, 3691, 3519, 2990, 2941, 1602, 1384, 1376, 1161, 1106, 1079 cm⁻¹. MS (ESI): m/z 329.34 ([M+Na]+; 100). Elemental analysis calcd (%) for C₁₇H₂₂O₅ (306.15): C, 66.65; H, 7.24, found: C, 66.84, H, 7.33.

Figure S23: ¹H NMR spectrum of 16b (400 MHz, CDCl₃)

Figure S24: ¹³C NMR spectrum of 16b (100 MHz, CDCl₃)
Synthesis of compounds 17a,b

A solution of 10 (100 mg, 0.36 mmol) in dry THF (5 mL) was stirred at 0°C under nitrogen atmosphere and a solution of AllylMgCl in THF (2M, 0.65 mmol, 1.8 equiv.) was slowly added. The mixture was stirred for 2 h at 0°C, when the disappearance of the aldehyde was attested by a TLC control (hexane/AcOEt 2:1). A saturated solution of NaHCO$_3$ (5 mL) was added at 0°C and the salts were removed by filtration. The two layers were separated and the aqueous layer was washed with Et$_2$O (3x5 mL). The combined organic layers were dried with Na$_2$SO$_4$ and concentrated under reduced pressure to give a mixture of 17a and 17b (a : b ratio 2.2 : 1, as attested by integrating the signals in the $^1$H-NMR spectrum of the crude). The residue was purified by silica gel flash chromatography (hexane/AcOEt 5:1) to give 35 mg (0.11 mmol, 31%) of 17a as a colourless oil and 27 mg (0.08 mmol, 23%) of 16b as a colourless oil, and 34 mg (0.11 mmol) of a mixture of the two diastereoisomers, impossible to be separated, for a total yield of 83% (96 mg, 0.30 mmol).

![Figure S25: $^1$H NMR spectrum of the crude reaction mixture (400 MHz, CDCl$_3$)](image-url)
17a (Rf = 0.28, hexane/AcOEt 5:1): [α]D25 = + 64.7 (c = 0.92, CHCl3). 1H-NMR (400 MHz, CDCl3) δ ppm = 7.37-7.26 (m, 5H, Ar), 5.92 (dddd, J = 17.0, 9.9, 7.3, 6.7 Hz 1H, H-7), 5.22-5.14 (m, 2H, H-8), 5.12 (s, 1H, H-1), 4.85 (dd, J = 6.0, 3.6 Hz, 1H, H-3), 4.66 (d, J = 6.0 Hz, 1H, H-2), 4.65 (d, J = 11.6 Hz, 1H H-A), 4.48 (d, J = 11.6 Hz, 1H, Hb-Bn), 4.03-4.97 (m, 1H, H-5), 3.86 (dd, J = 7.6, 3.6 Hz, 1H, H-4), 2.56-2.51 (m, 1H, H-A), 2.49 (d, J = 5.6 Hz 1H, O/H), 2.36-2.28 (m, 1H, Hb-Bn), 1.48 (s, 3H, Me), 1.33 (s, 3H, Me). 13C-NMR (100 MHz, CDCl3) δ ppm = 137.3 (s, Ar), 134.4 (d, C-7), 128.5-127.9 (d, 5C, Ar), 117.9 (t, C-8), 112.6 (s, acetal), 105.2 (d, C-1), 85.0 (d, C-2), 81.4 (d, C-4), 80.0 (d, C-3), 69.3 (d, C-5), 69.0 (t, Bn), 39.0 (t, C-6), 25.9 (q, Me), 24.6 (q, Me). IR (CHCl3): ν = 3674, 3573, 3521, 3069, 3004, 2940, 1642, 1601, 1497, 1455, 1435, 1384, 1376, 1270, 1163, 1085 cm⁻¹. MS (ESI): m/z 343.35 ([M+Na]+; 100). Elemental analysis calcd (%) for C18H24O5 (320.38): C, 67.48; H, 7.55, found: C, 66.95, H, 7.18.

Figure S26: 1H NMR spectrum of 17a (400 MHz, CDCl3)

Figure S27: 13C NMR spectrum of 17a (100 MHz, CDCl3)

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17b (Rf = 0.34, hexane/AcOEt 5:1): [α]D24 = + 78.6 (c = 0.80, CHCl3). 1H-NMR (400 MHz, CDCl3) δ ppm = 7.37-7.26 (m, 5H, Ar), 5.91 (ddt, 17.3, 10.3, 7.3 Hz, 1H, H-7), 5.20-5.15 (m, 1H, Ha-8), 5.16 (s, 1H, H-1), 5.13 (dd, J = 10.2, 0.9 Hz, 1H, Hb-8) 4.75 (dd, J = 5.8, 3.6 Hz, 1H, H-3), 4.67 (d, J = 12.0 Hz, 1H, Hb-Bn), 4.66 (d, J = 5.8 Hz, 1H, H-2), 4.49 (d, J = 12.0 Hz, 1H, Hb-Bn), 4.10 (p, J = 5.6 Hz, 1H, H-5), 3.90 (dd, J = 4.4, 3.6 Hz, 1H, H-4), 2.96 (s, 1H, OH), 2.48-2.36 (m, 2H, H-6), 1.47 (s, 3H, Me), 1.30 (s, 3H, Me). 13C-NMR (100 MHz, CDCl3) δ ppm = 137.3 (s, Ar), 134.4 (d, C-7), 128.5-127.9 (d, 5C, Ar), 117.7 (t, C-8), 112.7 (s, acetal), 105.0 (d, C-1), 85.5 (d, C-2), 80.8 (d, C-4), 80.5 (d, C-3), 69.5 (d, C-5), 69.1 (t, Bn), 37.9 (t, C-6), 25.9 (q, Me), 24.4 (q, Me). IR (CHCl3): ν = 3676, 3505, 3030, 2996, 2941, 1642, 1602, 1497, 1455, 1384, 1376, 1271, 1107, 1089 cm⁻¹. MS (ESI): m/z 343.37 ([M+Na]+; 100). Elemental analysis calcd (%) for C18H24O5 (320.38): C, 67.48; H, 7.55, found: C, 67.15, H, 7.66.

Figure S28: 1H NMR spectrum of 17b (400 MHz, CDCl3)

Figure S29: 13C NMR spectrum of 17b (100 MHz, CDCl3)
A solution of 10 (201 mg, 0.72 mmol) in dry THF (10 mL) was stirred at −78°C under nitrogen atmosphere and a solution of EthynylMgBr in THF (0.5 M, 1.44 mmol, 2.0 equiv.) was slowly added. The mixture was stirred for 3 h while the temperature raised to −28°C and a TLC control attested the disappearance of the aldehyde (PEt/Et₂O 2:1). A saturated solution of NaHCO₃ (9 mL) was added at 0°C and the salts were removed by filtration. The two layers were separated and the aqueous layer was washed with Et₂O (3x5 mL). The combined organic layers were dried with Na₂SO₄ and concentrated under reduced pressure to give a mixture of 18a and 18b (a : b ratio 1.5 : 1, as attested by integrating the signals in the ¹H-NMR spectrum of the crude). The residue was purified by silica gel gradient eluent flash chromatography (hexane/AcOEt from 4:1 to 2:1) to give 167 mg (0.55 mmol, 76%) of a mixture of the two diastereoisomers 18a and 18b, impossible to be separated. The purified mixture was partially characterized.

Figure S30: ¹H NMR spectrum of the crude reaction mixture (400 MHz, CDCl₃)
18a/18b (Rf = 0.25, hexane/AcOEt 4:1): $^1$H-NMR (400 MHz, CDCl$_3$) δ ppm = 7.37-7.26 (m, 5H(a) + 5H(b), Ar), 5.19 (s, 1H, H-1(a)), 5.18 (s, 1H, H-1(b)), 4.96 (dd, J =6.0, 3.6 Hz, 1H (a)), 4.83 (dd, J =5.6, 3.6 Hz, 1H(b)), 4.77-4.67 (m, 3H(a) + 3H(b)), 4.50 (d, J =11.6 Hz, 1H(a) + 1H(b)), 4.12 (dd, J =8.0, 3.6 Hz, 1H(b)), 4.09 (dd, J =6.4, 3.8 Hz, 1H(a)), 3.36), (d, J =7.6 Hz, 1H(a), OH), 2.70 (d, J =1.8 Hz, 1H(b), OH), 2.56 (d, J =2.0 Hz, 1H, H-7(a)), 2.54 (d, J =2.0 Hz, 1H, H-7(b)), 1.50 (s, 3H(a), Me), 1.47 (s, 3H(b), Me), 1.33 (s, 3H(a), Me), 1.31 (s, 3H(b), Me). $^{13}$C-NMR (100 MHz, CDCl$_3$) δ ppm = 137.1 (s, 1C(a) + 1C(b), Ar), 128.6-127.9 (d, 5C(a) + 5C(b), Ar), 113.1 (s, acetal, C(a)), 113.0 (s, acetal, C(b)), 105.6 (d, C-1(a)), 105.5 (d, C-1(b)), 85.2 (C(b)), 84.9 (C(b)), 82.5 (C(a)), 82.3 (C(b)), 80.4 (1C(a) + 1C(b)), 80.2 (C(a)), 79.9 (C(b)), 74.2 (C(b)), 74.0 (C(a)), 69.2 (C(b)), 69.1 (C(a)), 61.4 (C(b)), 61.2 (C(a)), 25.0 (q, C(b), Me), 25.8 (q, C(a), Me), 24.7 (q, C(b), Me), 24.4 (q, C(b), Me). IR (CHCl$_3$): ν = 3677, 3590, 3067, 3502, 3306, 3036, 2992, 2941, 2875, 2119, 1731, 1601, 1455, 1376, 1086 cm$^{-1}$. MS (ESI): m/z 327.31 ([M+Na]+; 100).

Figure S31: $^1$H NMR spectrum of the mixture 18a/18b (400 MHz, CDCl$_3$)

Figure S32: $^{13}$C NMR spectrum of the mixture 18a/18b (100 MHz, CDCl$_3$)
Synthesis of benzyl 6-deoxy-2,3-O-(1-methylethylidene)-5-O-(methylsulfonyl)-α-D-mannofuranoside (19a)

To a solution of 12a (42 mg, 0.14 mmol) in dry CH₂Cl₂ (2.4 mL) at 0°C, NEt₃ (59 μL, 0.42 mmol) and MsCl (14 μL, 0.19 mmol) were added under nitrogen atmosphere. The mixture was left rise room temperature and stirred for 2 h, when the disappearance of starting material was attested by a TLC control (PEt/AcOEt 1:1). Then, 2 mL of water were added, the two layers were separated and the aqueous layer was washed with CH₂Cl₂ (3x2 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified on silica gel by FCC (PEt/AcOEt 5:1) to afford 50 mg of 19a (Rf = 0.30, 0.13 mmol, 96%) as a waxy white solid. [α]D²³ = + 48.4 (c = 0.72, CHCl₃). ¹H-NMR (400 MHz, CDCl₃) δ ppm = 7.37-7.29 (m, 5H, Ar), 5.08 (s, 1H, H-1), 4.91 (dq, J =8.4, 6.0 Hz, 1H, H-5), 4.74 (dd, J =6.6, 5.6 Hz, 1H, H-3), 4.64 (m, 2H, Ha-Bn, H-2), 4.50 (d, J =12.0 Hz, 1H, Hb-Bn), 3.92 (dd, J =8.4, 3.6 Hz, 1H, H-4), 3.05 (s, 3H, -CH₃ mesylate), 1.58-1.51 (m, 3H, H-6), 1.45 (s, 3H, Me), 1.30 (s, 3H, Me). ¹³C-NMR (50 MHz, CDCl₃) δ ppm = 137.2 (s, Ar), 128.4-127.9 (d, 5C, Ar), 112.8 (s, acetal), 105.6 (d, C-1), 85.2 (d, C-2), 81.1 (d, C-4), 79.0 (d, C-3), 76.7 (d, C-4), 69.3 (t, Bn), 38.3 (q, CH₃ mesylate), 26.0 (q, Me), 24.9 (q, Me), 19.2 (q, C-6). IR (CDCl₃): ν = 3675, 3034, 2992, 2940, 1454, 1383, 1375, 1359, 1218, 1176, 1079, 1022 cm⁻¹. MS (ESI): m/z 397.67 ([M+Na]+; 100). Elemental analysis calcd (%) for C₁₇H₂₄O₇S (372.43): C, 54.82; H, 6.50; found: C, 54.93, H, 6.22.
Figure S33: $^1$H NMR spectrum of 19a (400 MHz, CDCl$_3$)

Figure S34: $^{13}$C NMR spectrum of 19a (50 MHz, CDCl$_3$)
Synthesis of benzyl 5-azido-5,6-dideoxy-2,3-O-(1-methylethylidene)-β-L-gulofuranoside (20a)

![Chemical Reaction Diagram]

To a solution of 19a (91 mg, 0.24 mmol) in dry DMF (4.8 mL), NaN₃ (47 mg, 0.72 mmol) was slowly added and then the mixture was heated at 100 °C. The reaction mixture was stirred at 100 °C for 66 h, but a TLC control (PEt/AcOEt 5:1) showed the persistence of the starting material (Rᶠ = 0.38) together with a newly form product (Rᶠ = 0.85). Therefore, 3 more equivalents of NaN₃ (47 mg, 0.72 mmol) were added and the reaction mixture was stirred at 120 °C for further 48 h. A second TLC control showed the complete disappearance of the starting material. The reaction mixture was left rise room temperature and then concentrated under vacuum. The crude was purified on silica gel by gradient eluent FCC (PEt/AcOEt from 80:1 to 70.1) to afford 39 mg of 20a (Rᶠ = 0.21 in PEt/AcOEt 15:1, 0.12 mmol, 51%) as a waxy solid. [α]₀²³ = + 82.6 (c = 1.35, CHCl₃). ¹H-NMR (400 MHz, CDCl₃) δ ppm = 7.36-7.28 (m, 5H, Ar), 5.11 (s, 1H, H-1), 4.72 (d, J = 11.6 Hz, 1H, Ha-Bn), 4.65 (m, 2H, H-3, H-2), 4.51 (d, J = 11.6 Hz, 1H, Hb-Bn), 3.90 (dd, J = 9.2, 2.8 Hz, 1H, H-4), 3.86-3.79 (m, 1H, H-5), 1.45 (s, 3H, Me), 1.29-1.26 (m, 6H, Me, H-6). ¹³C-NMR (50 MHz, CDCl₃) δ ppm = 137.3 (s, Ar), 128.5-127.9 (d, 5C, Ar), 112.7 (s, acetal), 105.3 (d, C-1), 85.3 (d, C-2), 83.7 (d, C-4), 79.8 (d, C-3), 69.0 (t, Bn), 57.2 (d, C-5), 26.1 (q, Me), 24.9 (q, Me), 16.1 (q, C-6). IR (CHCl₃): ν = 3619, 3448, 3020, 2401, 2125, 1384, 1224. MS (ESI): m/z 341.91 ([M+Na]+; 100). Elemental analysis calcd (%) for C₁₆H₂₁N₃O₄ (319.36): C, 60.17; H, 6.63, N, 13.16; found: C, 60.11, H, 7.01, N, 13.51.
Figure S35: $^1$H NMR spectrum of 20a (400 MHz, CDCl$_3$)

Figure S36: $^{13}$C NMR spectrum of 20a (50 MHz, CDCl$_3$)
Synthesis of benzyl 5-azido-5,6-dideoxy-2,3-O-(1-methylethyldiene)-β-L-gulofuranoside (20a) and of benzyl 5-azido-5,6-dIDEOXY-2,3-O-(1-methylethyldiene)-α-D-mannofuranoside (20b).

To a 4.5:1 mixture of 12a and 12b (53 mg, 0.18 mmol) in dry THF (5 mL), PPh₃ (151 mg, 0.58 mmol) was added under nitrogen atmosphere. The reaction mixture was cooled at 0°C and DIAD (113 μL, 0.58 mmol) and DPPA (141 μL, 0.63 mmol) were added. The resulting mixture was let rise room temperature and then stirred for 24 h, under nitrogen atmosphere, until a TLC control (PEt/AcOEt 5:2) showed the disappearance of the starting material and the formation of the new products. The solvent was removed under reduced pressure and the crude was purified on silica gel by FCC (PET/Et₂O 15:1), to afford 10 mg of 20b (R_f= 0.27, 0.03 mmol, 17%) and 37 mg (R_f= 0.21, 0.12 mmol, 67%) of 20a.

20b (partially characterized): ¹H-NMR (400 MHz, CDCl₃) δ ppm = 7.37-7.29 (m, 5H, Ar), 5.06 (s, 1H, H-1), 4.78 (dd, J =8.0; 4.0, 1H, H-3), 4.66-4.57 (m, 2H, Ha-Bn, H-2), 4.50 (d, J =12.0 Hz, 1H, Hb-Bn), 3.85-3.78 (m, 1H, H-5), 3.70 (dd, J =8.0, 4.0 Hz, 1H, H-4), 1.45 (s, 3H, Me), 1.37 (d, J =8.0 Hz, 3H, H-6), 1.33 (s, 3H, Me). ¹³C-NMR (50 MHz, CDCl₃) δ ppm = 137.3 (s, Ar), 128.5-127.9 (d, 5C, Ar), 112.6 (s, acetal), 105.5 (d, C-1), 85.0 (d, C-2), 82.3 (d, C-4), 79.4 (d, C-3), 69.1 (t, Bn), 55.3 (d, C-5), 26.0 (q, Me), 24.7 (q, Me), 17.0 (q, C-6). IR (CHCl₃): ν = 3689, 2938, 2250, 2099, 1455, 1384, 1376, 1080 cm⁻¹. MS (ESI): m/z 342.06 ([M+Na]+; 100).
Figure S37: $^1$H NMR spectrum of 20b (400 MHz, CDCl$_3$)

Figure S38: $^{13}$C NMR spectrum of 20b (50 MHz, CDCl$_3$)
Synthesis of (2S,3R,4S,5R)-3-hydroxy-4,5-O-(1-methyleneidene)-2-methyl-piperidine (21a).

To a solution of 20a (62 mg, 0.20 mmol) in MeOH (13 mL), Pd(OH)$_2$/C (34 mg) was added under nitrogen atmosphere. The mixture was stirred at room temperature under hydrogen atmosphere (balloon) for 5 days, until a control by $^1$HNMR spectroscopy attested the sole presence of the final product 21a. The mixture was filtered through Celite® and the solvent was removed under reduced pressure. The crude was purified on silica gel by FCC (CH$_2$Cl$_2$/MeOH/NH$_4$OH (6%) 15:1:0.1) to afford 33 mg of 21a ($R_t$= 0.11, 0.18 mmol, 91%). $[\alpha]^2_{D}$ = + 8.6 ($c$ = 1.11, MeOH). $^1$H-NMR (400 MHz, CD$_3$OD) $\delta$ ppm = 4.26 (dd, $J$ =11.4, 5.7 Hz 1H, H-5), 4.17 (dd, $J$ =5.7, 3.4 Hz, 1H, H-4), 3.73 (pt, $J$ =2.3 Hz, 1H, H-3), 3.16 (dd, $J$ =13.8, 5.0 Hz, 1H, Ha-6), 3.08 (qd, $J$ =6.8, 2.0 Hz, 1H, H-2), 2.82 (dd, $J$ =13.8, 6.3 Hz, 1H, Hb-6), 1.47 (s, 3H, Me), 1.33 (s, 3H, Me), 1.14 (d, $J$ =6.8 Hz, 3H, H-7). $^{13}$C-NMR (50 MHz, CD$_3$OD) $\delta$ ppm = 108.7 (s, acetal), 76.0 (d, C-4), 70.2 (d, C-5), 68.6 (d, C-3), 49.2 (d, C-2), 44.5 (t, C-6), 26.9 (q, Me), 24.8 (q, Me), 14.6 (q, C-7). IR (CH$_2$Cl$_2$): $\nu$ = 3604, 3483, 3360, 2988, 2937, 2854, 1732, 1606, 1458, 1382, 1218, 1060 cm$^{-1}$. MS (ESI): m/z 187.95 ([M+H]+; 100). Elemental analysis calcd (%) for C$_9$H$_{17}$NO$_3$ (187.24): C, 57.73; H, 9.15, N, 7.48; found: C, 57.64, H, 9.55, N, 7.14.
Figure S39: $^1$H NMR spectrum of 21a (400 MHz, CD$_3$OD)

Figure S40: $^{13}$C NMR spectrum of 21a (400 MHz, CD$_3$OD)
Compound 21a was crystallized from AcOEt to give crystals for X-ray analysis. **CCDC 1545187** for 21a contains the supplementary crystallographic data that can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**Figure S41: X-ray crystal structure of 21a**
Synthesis of (2S, 3R, 4R, 5R)-2-methylpiperidine-3,4,5-triol (22a)

A solution of 21a (22 mg, 0.12 mmol) in MeOH (2.0 mL) was left stirring with 12M HCl (142 µL, 1.7 mmol) at room temperature for 18 h. The crude mixture was concentrated to yield the hydrochloride salt of 22a. The corresponding free amine was obtained by passing the hydrochloride salt through a DOWEX® 50WX8-100 ion-exchange resin. Elution with 6% ammonia afforded the free base 22a (16 mg, 0.11 mmol, 91%). \([\alpha]_{D}^{23} = -5.8\) (c = 1.24 in H2O). \(^1\)H-NMR (400 MHz, D2O) \(\delta\) ppm = 3.81-3.75 (m, 2H, H-5, H-3), 3.61 (d, \(J = 2.0\) Hz, 1H, H-4), 2.92 (q, \(J = 2.4\) Hz, 1H, H-2), 2.72 (dd, \(J = 12.7, 4.3\) Hz, 1H, Ha-6), 2.59 (dd, \(J = 12.7, 10.2\) Hz, 1H, Hb-6), 0.94 (d, \(J = 6.8\) Hz, 3H, H-7). \(^{13}\)C-NMR (100 MHz, D2O) \(\delta\) ppm = 71.7 (d, C-4), 70.2 (d, C-5), 65.4 (d, C-3), 48.2 (d, C-2), 43.7 (t, C-6), 14.6 (q, C-7). MS (ESI): m/z 170.08 ([M+Na]+; 100). Elemental analysis calcd (%) for C6H13NO3 (147.17): C, 48.97; H, 8.90, N, 9.52; found: C, 48.44, H, 9.26, N, 9.72.
Figure S42: $^1$H NMR spectrum of 22a (400 MHz, D$_2$O)

Figure S43: $^{13}$C NMR spectrum of 22a (100 MHz, D$_2$O)
Synthesis of benzyl 5,6-dideoxy-5-(hydroxyamino)-2,3-O-(1-methylethylidene)-β-L-gulofuranoside (23a) and benzyl 5,6-dideoxy-5-(hydroxyamino)-2,3-O-(1-methylethylidene)-α-D-mannofuranoside (23b).

Method A (without Lewis acid)

A solution of 11 (172 mg, 0.45 mmol) in dry THF (6 mL) was stirred at −78 °C under nitrogen atmosphere and a 3 M solution of MeMgBr in Et2O (0.99 mmol, 2.2 equiv.) was slowly added. The reaction mixture was stirred for 2 h, when a TLC control (PEt/AcOEt 1:1) attested the disappearance of the starting material. A saturated solution of NaHCO3 (6 mL) was added to the mixture at 0°C and left stirring for 1 h. The two layers were separated and the aqueous layer was extracted with Et2O (3x8 mL). The combined organic layers were dried over Na2SO4 and concentrated under reduced pressure to give a mixture of 23a and 23b (a : b ratio 1.4 : 1, as attested by integrating the signals in the 1H-NMR spectrum of the crude, Figure S43). The crude was purified by silica gel flash column chromatography (gradient eluent from Pet/AcOEt 7:1 to 5:1) to give 151 mg (0.30 mmol, 84%) of pure mixed 23a and 23b (Rf = 0.4, Pet/AcOEt 10:1). A further purification of 23a/23b (Hex/AcOEt 10:1, Rf = 0.15) allowed to characterize the hydroxylamine as a mixture.

1H-NMR (400 MHz, CDCl3) δ ppm: 7.37-7.14 (m, 20H, 10H (a) + 10H (b)), 5.11 (s, 1H, H-1 (b)), 4.99 (s, 1H, H-1 (a)), 4.76 (dd, J = 5.9, 3.4 Hz, 1H (a)), 4.63-4.50 (m, 6H, 2H (a) + 4H (b)), 4.27 (d, J = 11.8 Hz, 1H (a)), 4.08 (dd, J = 9.5, 3.3 Hz, 1H (b)), 4.06 (dd, J = 7.0, 3.5, Hz, 1H (a)), 3.95-3.85 (m, 3H, 1H (a) + 2H (b)), 3.76 (d, J = 13.3 Hz, 1H (a)), 3.37-3.30 (m, 2H, 1H (a) + 1H 8b)), 1.35 (s, 3H (b)), 1.32 (s, 3H (a)), 1.25 (s, 3H (a)), 1.23 (s, 3H (b)), 1.19 (d, J = 6.6, Hz, 3H, Me (a)), 1.16 (d, J = 6.6, Hz, 3H, Me (b)). 13C-NMR (100 MHz, CDCl3) δ = 137.4, 137.0, 135.1, 134.0, 130.8, 130.1, 127.9, 127.2 (24C, 12 Ar (a) + 12 Ar (b)), 112.5 (s, acetal (a)), 112.1 (s, acetal (b)), 105.4 (d, C-1 (b)), 104.7 (d, C-1 (a)), 85.4 (d, C-2 (a)), 85.1 (d, C-2 (b)), 85.1 (d, C-4 (b)), 79.7 (d, C-4 (a)), 79.6 (d, C-3 (a)), 79.2 (d, C-3 (b)), 72.0 (t, NBn (a)), 69.7 (t, NBn (b)), 69.1 (t, OBN (b)), 68.8 (t, OBN (a)), 60.8 (d, C-5 (a)), 59.2 (d, C-5 (b)), 26.2 (q, Me (a)), 26.2 (q, Me (b)), 24.9 (q, Me (b)), 24.7 (q, Me (a)), 16.9 (q, C-7 (b)), 15.1 (q, C-7 (a)). MS (ESI): m/z 421.94 ([M+K]+; 100). Elemental analysis calcd (%) for C23H29NO5 (399.48): C, 69.15; H, 7.32, N, 3.51; found: C, 69.48, H, 7.02, N, 3.89.
Figure S44: $^1$H NMR spectrum of the crude reaction mixture (200 MHz, CDCl$_3$)

Figure S45: $^1$H NMR spectrum of the 23a/23b mixture after FCC (400 MHz, CDCl$_3$)
Figure S46: $^{13}$C NMR spectrum of the 23a/23b mixture after FCC (100 MHz, CDCl$_3$)
Method B (with Lewis acid)²

To a stirred solution of nitrone 11 (120 mg, 0.31 mmol) in dry THF (9.3 mL) at room temperature, Et₂AlCl (310 μL of a 1 M solution in hexane, 0.31 mmol) was added and the resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was cooled at −30 °C and treated with MeMgBr (190 μL of a 3 M solution in THF, 0.56 mmol, 1.8 equiv.) dropwise. The resulting suspension was stirred at −30 °C for 2 h, when a TLC control (PEt/AcOEt 1:1) attested the disappearance of the starting material. The reaction mixture was diluted with 1 N NaOH (6 mL) and Et₂O (6 mL) and left stirring for 20 minutes. The phases were separated and the aqueous layer was extracted with Et₂O (2x10 mL). The combined organic layers were washed with brine (2x15 mL), dried with Na₂SO₄ and concentrated under reduced pressure to give a mixture of 23a and 23b (a : b ratio 1 : 7.4, as attested by integrating the signals in the ¹H-NMR spectrum of the crude, Figure S47). The crude was purified by silica gel flash column chromatography (gradient eluent from PEt/AcOEt 7:1 to 5:1) to give 111 mg (0.28 mmol, 90%) of pure mixed 23a and 23b (Rf = 0.40, PEt/AcOEt 7:1).

Figure S47: ¹H NMR spectrum of the crude reaction mixture with Lewis acid (400 MHz, CDCl₃)

To a stirred solution of nitrone 11 (120 mg, 0.31 mmol) in dry THF (9.3 mL) at room temperature, Et₂AlCl (310 μL of a 1 M solution in hexane, 0.31 mmol) was added and the resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was cooled at −78 °C and treated with MeMgBr (190 μL of a 3 M solution in THF, 0.56 mmol, 1.8 equiv.) dropwise. The resulting suspension was stirred at −78 °C for 2 h, when a TLC control (PEt/AcOEt 1:1) still attested the presence of the starting material. Further 0.5 equivalents of MeMgBr (53 μL, 0.16 mmol) were added and the reaction mixture was stirred at −78 °C for further 2 h and was stopped, even if the TLC control (PEt/AcOEt 1:1) did not attested the complete disappearance of the starting material. The reaction mixture was diluted with 1 N NaOH (6 mL) and Et₂O (6 mL) and left stirring for 20 minutes. The phases were separated and the aqueous layer was extracted with Et₂O (2x10 mL). The combined organic layers were washed with brine (2x15 mL), dried with Na₂SO₄ and concentrated under reduced pressure to give a mixture of 23a and 23b (a : b ratio 1 : 7.3, as attested by integrating the signals in the ¹H-NMR spectrum of the crude, Figure S48). The ¹H-NMR spectrum also confirmed the presence of some unreacted starting material.

Figure S48: ¹H NMR spectrum of the crude reaction mixture with Lewis acid (400 MHz, CDCl₃)
To a stirred solution of nitrone 11 (171 mg, 0.45 mmol) in dry THF (14 mL) at room temperature, BF$_3$·Et$_2$O (56 µL, 0.45 mmol) was added and the resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was cooled at −30 °C and treated with MeMgBr (270 µL of a 3 M solution in THF, 0.81 mmol, 1.8 equiv.) dropwise. The resulting suspension was stirred at −30 °C for 4 h, when a TLC control (PEt/AcOEt 1:1) attested the disappearance of the starting material. The reaction mixture was diluted with 1 N NaOH (6 mL) and Et$_2$O (6 mL) and left stirring for 20 minutes. The phases were separated and the aqueous layer was extracted with Et$_2$O (2×10 mL). The combined organic layers were washed with brine (2×15 mL), dried with Na$_2$SO$_4$ and concentrated under reduced pressure to give a mixture of 23a and 23b (a : b ratio 1 : 7, as attested by integrating the signals in the $^1$H-NMR spectrum of the crude, Figure S49).
To a stirred solution of nitrone 11 (120 mg, 0.31 mmol) in dry THF (9.3 mL) at room temperature, AlCl₃ (41 mg, 0.31 mmol) was added and the resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was cooled at –30 °C and treated with MeMgBr (190 µL of a 3 M solution in THF, 0.56 mmol, 1.8 equiv.) dropwise. The resulting suspension was stirred at –30 °C for 3 h, when a TLC control (PEt/AcOEt 1:1) attested the disappearance of the starting material. The reaction mixture was diluted with 1 N NaOH (6 mL) and Et₂O (6 mL) and left stirring for 20 minutes. The phases were separated and the aqueous layer was extracted with Et₂O (2x10 mL). The combined organic layers were washed with brine (2x15 mL), dried with Na₂SO₄ and concentrated under reduced pressure to give a mixture of 23a and 23b (a : b ratio 1 : 4, as attested by integrating the signals in the ¹H-NMR spectrum of the crude, Figure S50).

Figure S50: ¹H NMR spectrum of the crude reaction mixture with Lewis acid (400 MHz, CDCl₃)
To a stirred solution of nitrone 11 (120 mg, 0.31 mmol) in dry THF (9.3 mL) at room temperature, InCl₃ (69 mg, 0.31 mmol) was added and the resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was cooled at −30 °C and treated with MeMgBr (190 µL of a 3 M solution in THF, 0.56 mmol, 1.8 equiv.) dropwise. The resulting suspension was stirred at −30 °C for 3 h, when a TLC control (PEt/AcOEt 1:1) still attested the presence of the starting material. Further 1.8 equivalents of MeMgBr (190 µL, 0.56 mmol) were added and the reaction mixture was stirred at −30 °C for further 2 h when a second TLC control attested the disappearance of the starting material. The reaction mixture was diluted with 1 N NaOH (6 mL) and Et₂O (6 mL) and left stirring for 20 minutes. The phases were separated and the aqueous layer was extracted with Et₂O (2x10 mL). The combined organic layers were washed with brine (2x15 mL), dried with Na₂SO₄ and concentrated under reduced pressure to give a mixture of 23a and 23b (a : b ratio 1 : 2, as attested by integrating the signals in the ¹H-NMR spectrum of the crude, Figure S51).

Figure S51: ¹H NMR spectrum of the crude reaction mixture with Lewis acid (400 MHz, CDCl₃)
Synthesis of \((2S,3R,4S,5R)\)-3-hydroxy-4,5-\(\text{O}-\text{methylethylidene}\)-2-methyl-piperidine (21a) and \((2R,3R,4S,5R)\)-3-hydroxy-4,5-\(\text{O}-\text{methylethylidene}\)-2-methyl-piperidine (21b).

To a 1.4:1 mixture of 23a (S) and 23b (R) (151 mg, 0.38 mmol) in MeOH (25 mL), Pd(OH)\(_2\)/C (76 mg) was added under nitrogen atmosphere. The mixture was stirred at room temperature under hydrogen atmosphere (balloon) for 4 days, until a control by \(^1\)HNMR spectroscopy attested the sole presence of the final products 21. The mixture was filtered through Celite\(^\circledR\) and the solvent was removed under reduced pressure. The crude was purified on silica gel by FCC (\(\text{CH}_2\text{Cl}_2/\text{MeOH/6\% NH}_3\text{OH}\) 8:1:0.1) to afford 35 mg (0.19 mmol) of 21a and 25 mg (0.13 mmol) of 21b, with a 85\% (0.32 mmol) total yield.

\(21\text{b}: [\alpha]_D^{21} = -98.3 (c = 1.40, \text{MeOH}). \)\(^1\)H-NMR (400 MHz, CD\(_3\)OD) \(\delta\) ppm = 4.21 (tt, \(J = 4.8, 1.3\) Hz, 1H, H-5), 4.83 (dd, \(J = 7.5, 5.3\) Hz, 1H, H-4), 3.27 (dd, \(J = 14.8, 1.2\) Hz, 1H, Ha-6), 3.19 (dd, \(J = 10.1, 7.5\) Hz, 1H, H-3), 2.97 (dd, \(J = 14.8, 3.0\) Hz, 1H, Hb-6), 2.36 (dq, H=10.1, 6.4 Hz, 1H, H-2), 1.51 (s, 3H, Me), 1.34 (s, 3H, Me), 1.14 (d, \(J = 6.4\) Hz, 3H, H-7). \(^13\)C-NMR (50 MHz, CD\(_3\)OD) \(\delta\) ppm = 108.8 (s, acetal), 80.0 (d, C-4), 76.0 (d, C-3), 74.0 (d, C-5), 54.2 (d, C-2), 44.0 (t, C-6), 27.1 (q, Me), 25.3 (q, Me), 16.5 (q, C-7). IR (\(\text{CH}_2\text{Cl}_2\)); \(\nu = 3433, 3282, 3125, 2991, 2872, 2679, 2352, 2317, 1448, 1221, 1162, 1011\) cm\(^{-1}\). MS (ESI): m/z 187.78 ([M+H]+; 100). Elemental analysis calcd (%) for C\(_9\)H\(_{17}\)NO\(_3\) (187.24): C, 57.73; H, 9.15, N, 7.48; found: C, 57.37, H, 9.52, N, 7.78.
Figure S52: $^1$H NMR spectrum of 21b (400 MHz, CD$_3$OD)

Figure S53: $^{13}$C NMR spectrum of 21b (50 MHz, CD$_3$OD)
Synthesis of (2S,3R,4S,5R)-3-hydroxy-4,5-O-(1-methylethylidene)-2-methyl-piperidine (21a) and (2R,3R,4S,5R)-3-hydroxy-4,5-O-(1-methylethylidene)-2-methyl-piperidine (21b).

To a 7.4:1 mixture of 23b (R) and 23a (S) (111 mg, 0.28 mmol) in MeOH (16 mL), Pd(OH)$_2$/C (56 mg) was added under nitrogen atmosphere. The mixture was stirred at room temperature under hydrogen atmosphere (balloon) for 4 days, until a control by $^1$H NMR spectroscopy attested the sole presence of the final products 21. The mixture was filtered through Celite® and the solvent was removed under reduced pressure. The crude was purified on silica gel by FCC (CH$_2$Cl$_2$/MeOH/6% NH$_3$OH 8:1:0.1) to afford 39 mg (0.21 mmol, 75%) of 21b and 6 mg (0.13 mmol, 11%) of 21a, with a 86% (0.24 mmol) total yield.
Synthesis of \((2R, 3R, 4R, 5R)-2\text{-methylpiperidine-3,4,5-triol} \text{ 22b}\)

A solution of \textbf{21b} (13 mg, 0.07 mmol) in MeOH (2.0 mL) was left stirring with 12 M HCl (142 µL, 1.0 mmol) at room temperature for 18 h. The crude mixture was concentrated to yield the hydrochloride salt of \textbf{22b}. The corresponding free amine was obtained by passing the hydrochloride salt through a DOWEX\textsuperscript{®} 50WX8-100 ion-exchange resin. Elution with 6% ammonia afforded the free base \textbf{22b} (8 mg, 0.06 mmol, 80%).

\(\left[\alpha\right]_D^{21} = -65.9 \) (c = 0.76 in \(\text{H}_2\text{O}\)). \(\textsuperscript{1}H\)-NMR (400 MHz, CD\textsubscript{3}OD) \(\delta\) ppm = 3.86 (bs, 1H, H-5), 3.36 (dd, \(J = 9.3, 3.4\) Hz 1H, H-4), 3.27 (pt, \(J = 9.3\) Hz, 1H, H-3), 2.94 (dd, \(J = 14.2, 3.0\) Hz, 1H, Ha-6), 2.72 (d, \(J = 14.2\) Hz, 1H, Hb-6), 2.41 (dq, \(J = 12.7, 6.3\) Hz, 1H, H-2), 1.20 (d, \(J = 6.3\) Hz, 3H, H-7). MS (ESI): \textit{m/z} 170.08 ([M+Na]+; 100).

Crystal structure determination for compounds 12a and 21a

12a:
C_{16}H_{22}O_{5}, M=294.33, Orthorhombic, space group P 2_{1}2_{1}2_{1}, \( a=5.7984(1) \), \( b=7.8542(2) \), \( c=33.8291(8) \)Å, \( V=1540.5(3) \)Å³, \( Z=4 \). \( D_{c}=1.269, \mu=0.772 \) mm⁻¹, \( F(000)= 632. \)

4627 reflections were collected with a 5.230<θ< 72.397 range with a completeness to theta 99.2%; 2724 were unique, the parameters were 194 and the final R index was 0.0497 for reflections having I>2σI, and 0.0576 for all data.

A colourless prismatic crystal (0.08x0.06x0.05) was used for collection and RX-analysis was carried out with a Goniometer Oxford Diffraction KM4 Xcalibur2 at 100°K.

Hydrogen atoms were all assigned in calculated positions.

No significant intra or intermolecular interactions have been detected.

21a:
C_{9}H_{17}NO_{3}, M=187.23, Orthorhombic, space group P 2_{1}2_{1}2_{1}, \( a=5.5000(2) \), \( b=9.8160(3) \), \( c=18.5860(6) \)Å, \( V=1003.4(2) \)Å³, \( Z=4 \). \( D_{c}=1.239, \mu=0.759 \) mm⁻¹, \( F(000)= 408. \)

2631 reflections were collected with a 4.758<θ< 70.649 range with a completeness to theta 93.0%; 1516 were unique, the parameters were 122 and the final R index was 0.0384 for reflections having I>2σI, and 0.0541 for all data.

A colourless needle shaped crystal (0.09x0.04x0.03) was used for collection and RX-analysis was carried out with a Goniometer Oxford Diffraction KM4 Xcalibur2 at 100°K.

Hydrogen atoms were all assigned in calculated positions, except for hydrogen on N-H group which was find in F.D. analysis.

A significant intermolecular H-bond is reported below.

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Equivalent positions:
( 1) x+1, y, z

Cu/Kα radiation (40mA/-40KV), monochromated by an Oxford Diffraction Enhance ULTRA assembly, and an Oxford Diffraction Excalibur PX Ultra CCD were used for cells parameters determination and data collection.

The integrated intensities, measured using the ω scan mode, were corrected for Lorentz and polarization effects.

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Direct methods of SIR2004\textsuperscript{5} were used in solving the structure and the refinement was performed using the full-matrix least squares on $F^2$ provided, within WinGX v.2013.3 routine,\textsuperscript{6} by SHELXL2014.\textsuperscript{7} Multi-scan symmetry-related measurement was used as experimental absorption correction type. The non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were refined as isotropic.