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

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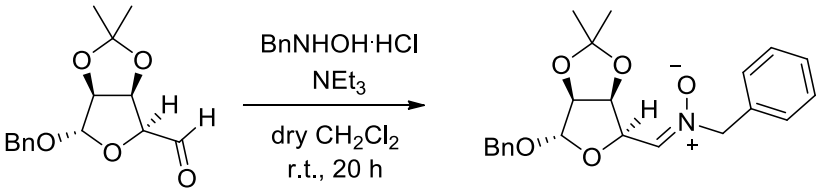
General methods: Commercial reagents were used as received. All reactions were carried out under magnetic stirring and monitored by TLC on 0.25 mm silica gel plates (Merck F254). Column chromatographies were carried out on Silica Gel 60 (32–63 μm) or on silica gel (230–400 mesh, Merck). Yields refer 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-*O*-(1-methylethylidene)-5-deoxy-*N*-benzyl-D-lyxofuranosylamine *N*-oxide (11).



To a solution of **10**[1](310 mg, 1.11 mmol) in dry CH_2Cl_2 (5.7 mL), Na_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 *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_4Cl (6 mL) was added, stirring for 10 minutes. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were washed with brine (2x10 mL) and concentrated after drying with Na_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_f = 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, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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, *N*Bn), 4.61- 4.58 (m, 2H, *O*Bn, H-2), 4.37 (d, *J* =11.7 Hz, 1H, *O*Bn), 1.30 (s, 3H, Me), 1.21 (s, 3H, Me). ^{13}C-NMR (50 MHz, $CDCl_3$) δ 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, acetonide), 105.0 (d, C-1), 84.5 (d, C-2), 79.7 (d, C-4), 76.7 (d, C-3), 69.1 (t, *N*Bn), 68.9 (t, *O*Bn), 26.0 (q, Me), 24.7 (q, Me). IR (KBr): ν = 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.

[1] C. Matassini, S. Mirabella, A. Goti, F. Cardona, *Eur. J. Org. Chem.* **2012**, 3920-3924.

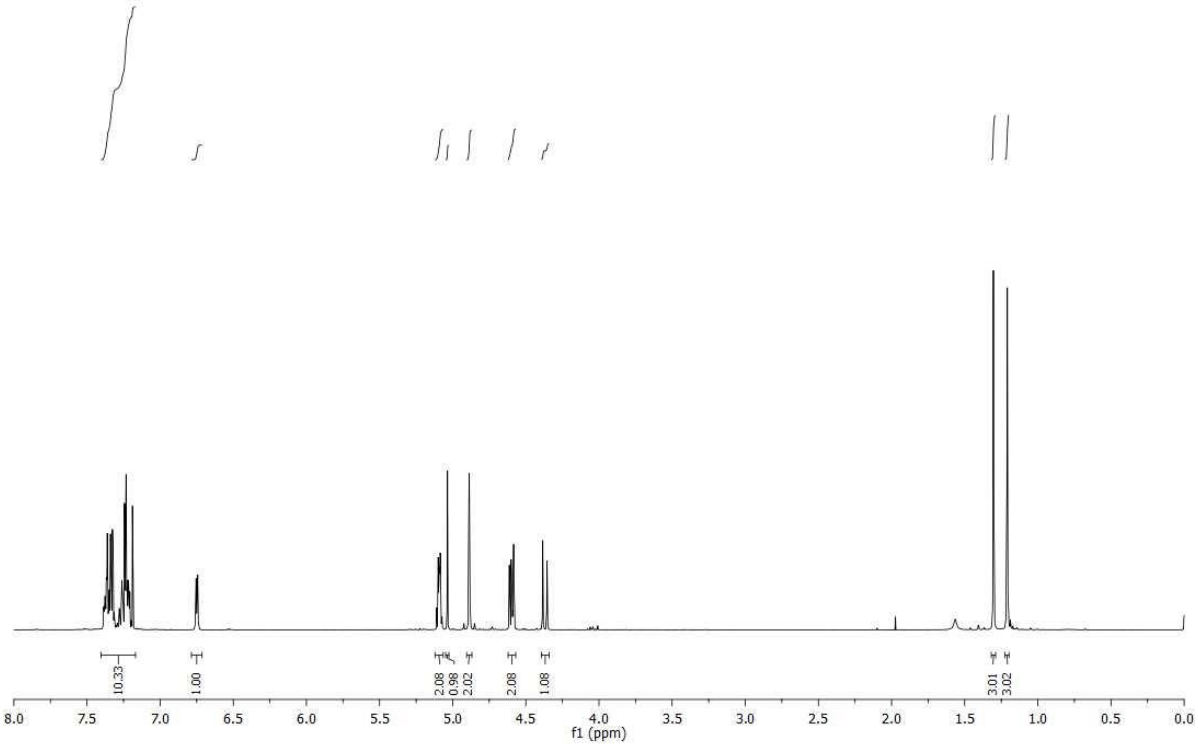


Figure S1: ^{1}H NMR spectrum of 11 (400 MHz, $CDCl_3$)

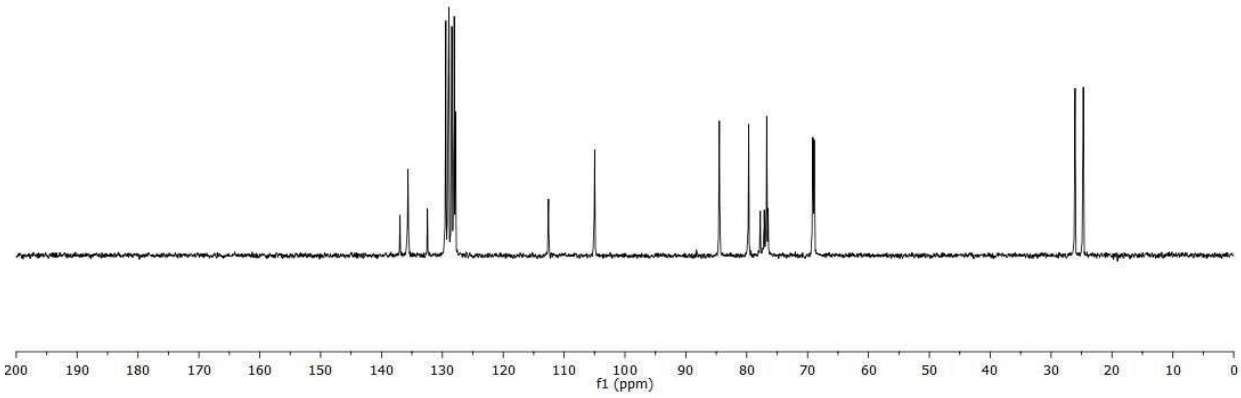
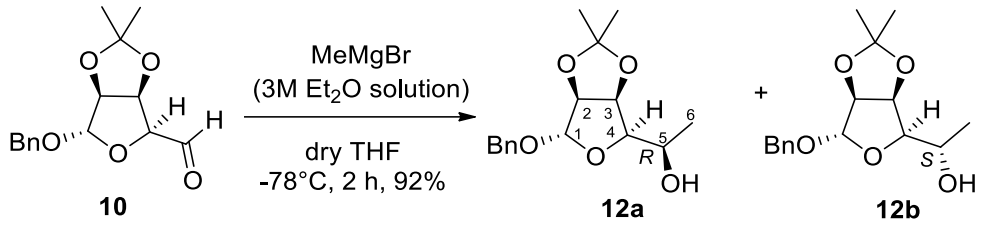


Figure S2: ^{13}C NMR spectrum of 11 (50 MHz, $CDCl_3$)

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 Et_2O (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 ^{1}H-NMR spectroscopy. A saturated solution of $NaHCO_3$ 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 Et_2O (3x 5 mL). The combined organic layers were washed with brine (3x5 mL), dried with Na_2SO_4, 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 ^{1}H-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%).

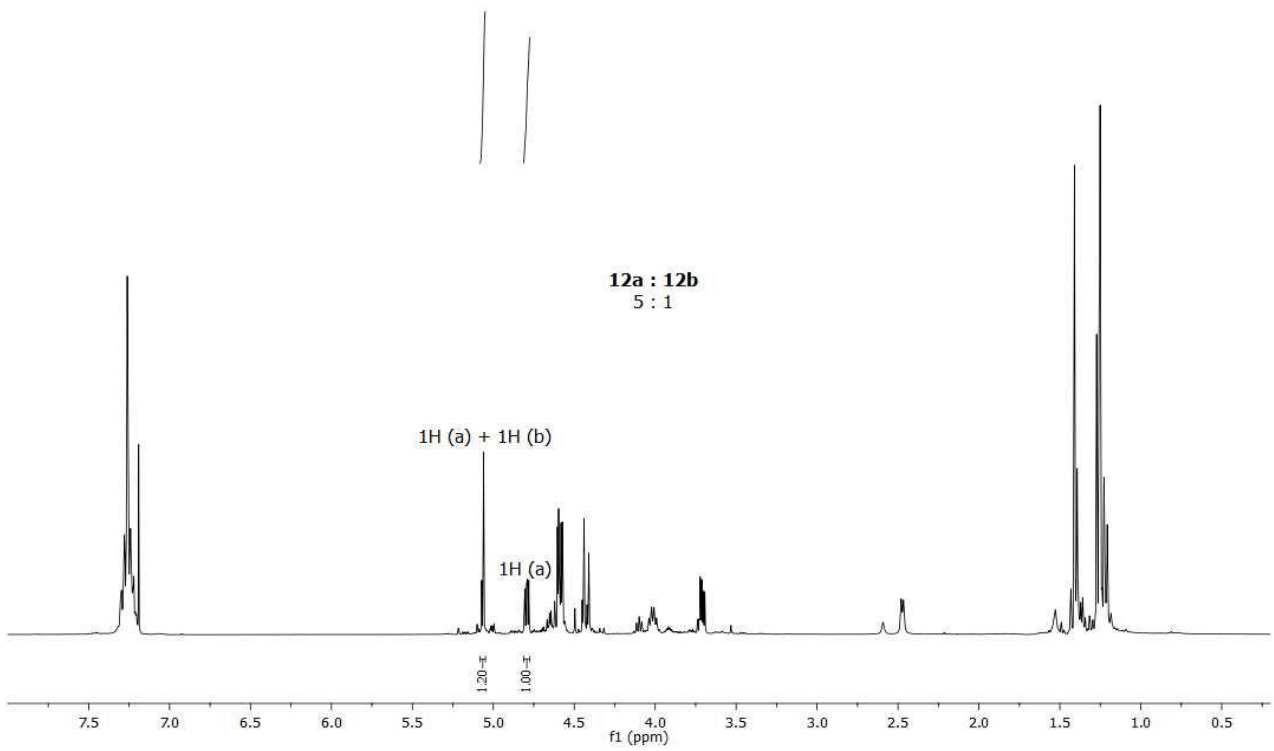


Figure S3: ^{1}H NMR spectrum of the crude reaction mixture (400 MHz, $CDCl_3$)

A small amount of this mixture was further purified by FCC (PEt/AcOEt 5:1, R_f = 0.28) to give a sample of isolated **12a**, sufficient to be completely characterized. $[\alpha]_D^{29}$ = + 70.0 (*c* = 0.85, $CHCl_3$). ^{1}H-NMR (400

MHz, $CDCl_3$) 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, O*H*), 1.47 (s, 3H, Me), 1.34 (s, 3H, H-6), 1.31 (s, 3H, Me). ^{13}C-NMR (50 MHz, $CDCl_3$) 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 ($CHCl_3$): 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 $C_{16}H_{22}O_5$ (294.34): C 65.29, H 7.53; found: C 65.38, H 7.54.

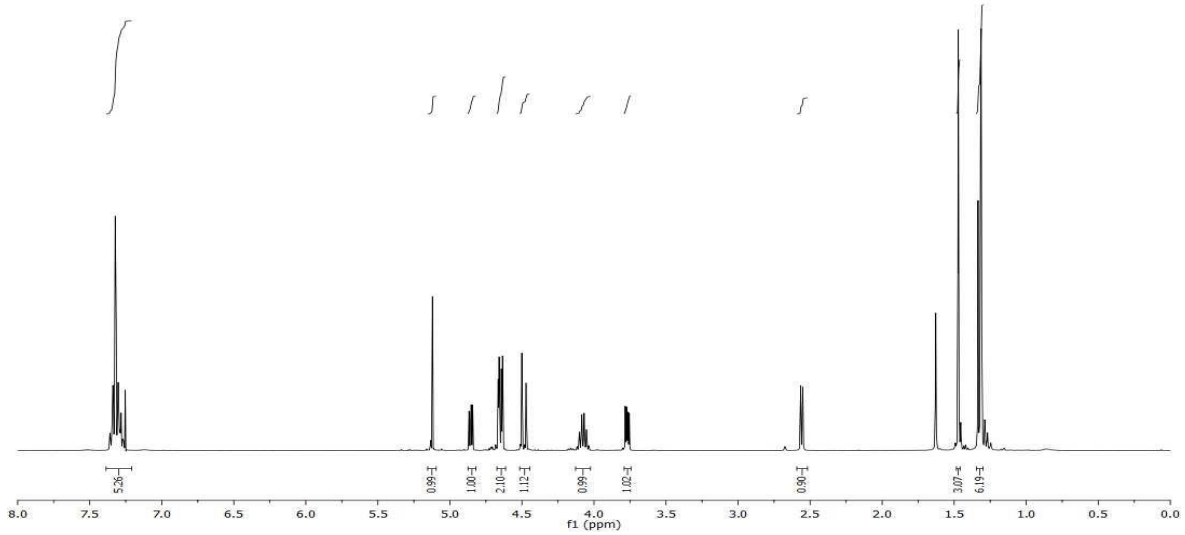


Figure S4: ^{1}H NMR spectrum of 12a (400 MHz, $CDCl_3$)

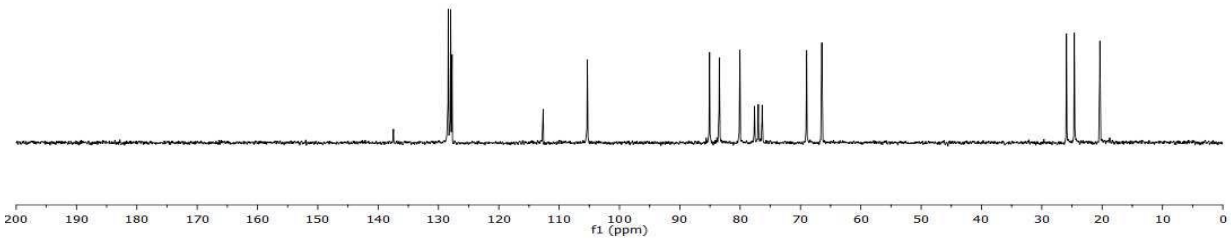


Figure S5: ^{13}C NMR spectrum of 12a (50 MHz, $CDCl_3$)

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.

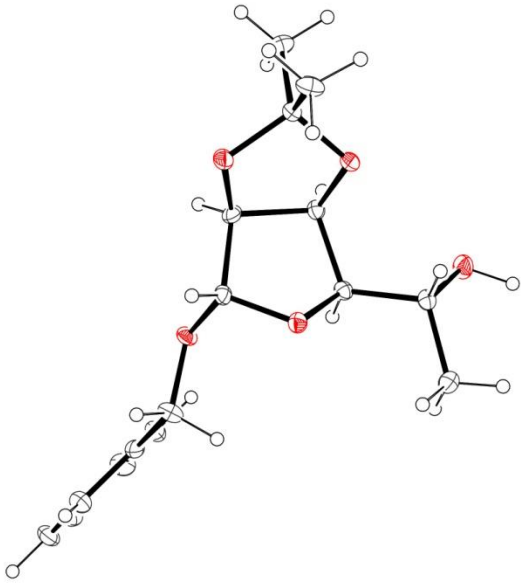
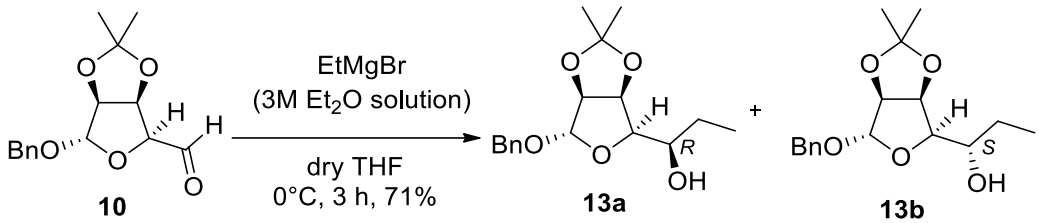


Figure S6: X-ray crystal structure of 12a

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 Et_2O (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 (PEt/AcOEt 2:1). A saturated solution of $NaHCO_3$ (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 Et_2O (3x10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give a mixture of **13a** e **13b** (**a** : **b** ratio 1.6 : 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/Et_2O 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 (R_f = 0.31, PEt/Et_2O 3:1): $[\alpha]_D^{25}$ = + 76.4 (*c* = 1.14, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) 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). ^{13}C-NMR (50 MHz, $CDCl_3$) δ ppm = 137.4 (s, Ar), 128.4-127.8 (d, 5C, Ar), 112.5 (s, acetal), 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 ($CDCl_3$)): 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 $C_{17}H_{24}O_5$ (308.37): C, 66.21; H, 7.84; found: C, 65.92, H, 7.76.

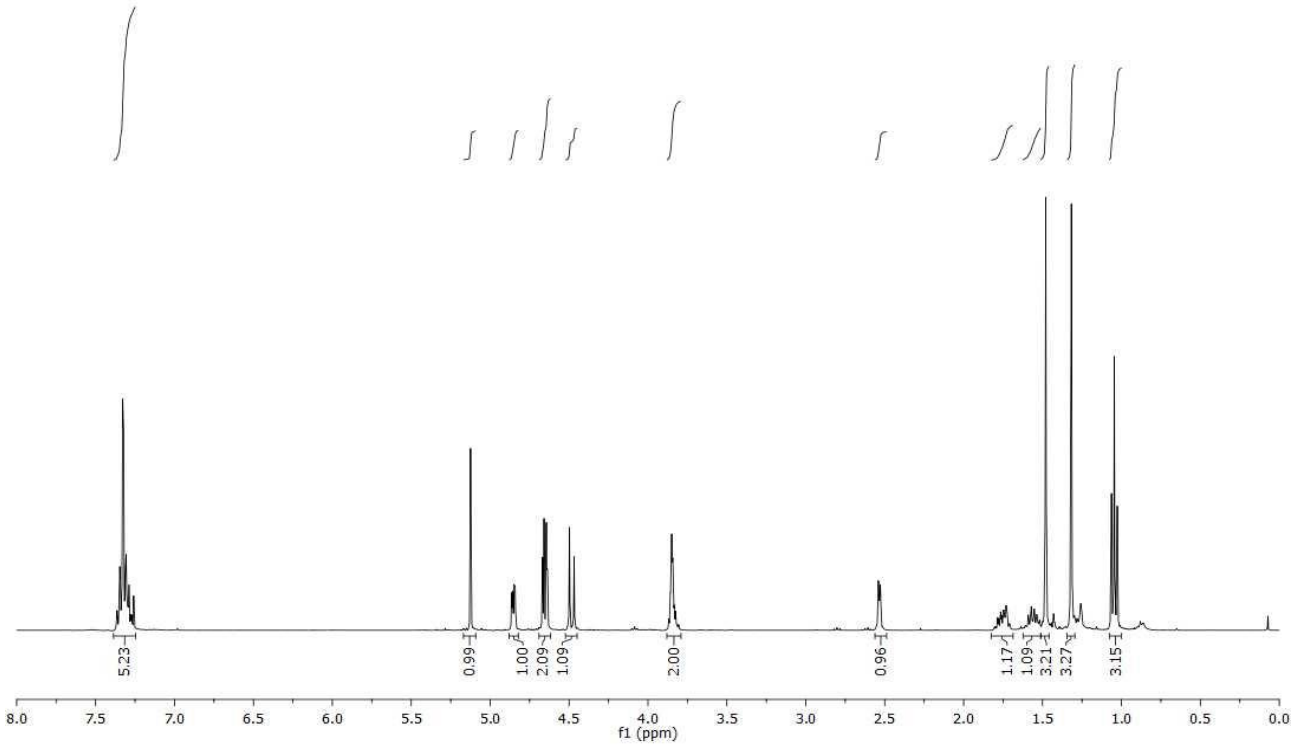


Figure S7: ^{1}H NMR spectrum of 13a (400 MHz, $CDCl_3$)

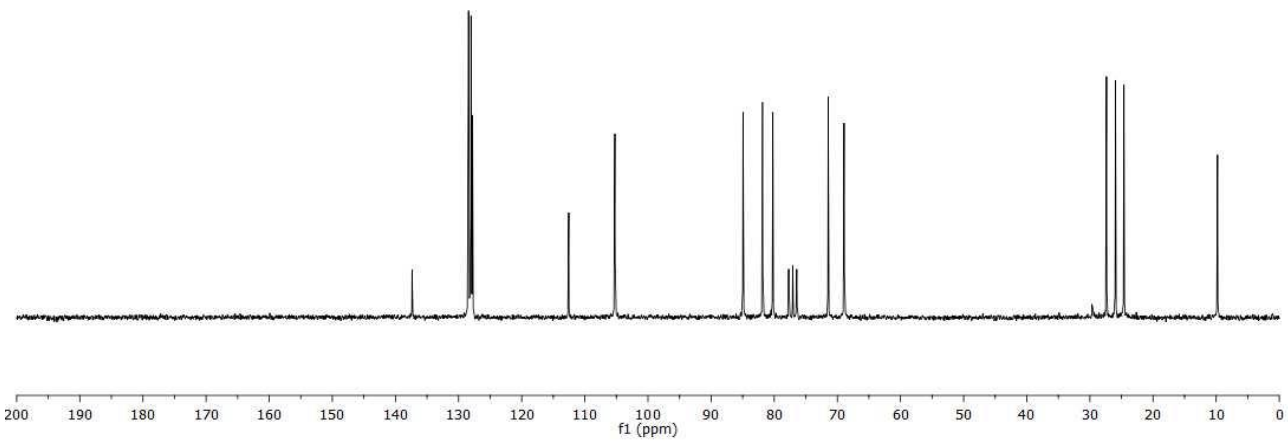


Figure S8: ^{13}C NMR spectrum of 13a (50 MHz, $CDCl_3$)

13b (R_f = 0.22, Eluente PEt/Et_2O 3:2): M.p. = 53.6-55.4 °C. $[\alpha]_D^{25}$ = + 84.0 (*c* = 0.99, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) 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_a-Bn), 4.66 (d, *J* =6.1 Hz,1H, H-2) 4.50 (d, *J* =11.6 Hz, 1H, H_b-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).^{13}C-NMR (50 MHz, $CDCl_3$) 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, 1103, 1078, 1066, 1014 cm^{-1}. MS (ESI): m/z = 331.14 ([M+Na]+; 100). Elemental analysis calcd (%) for $C_{17}H_{24}O_5$ (308.37): C, 66.21; H, 7.84; found: C, 66.27, H, 8.19.

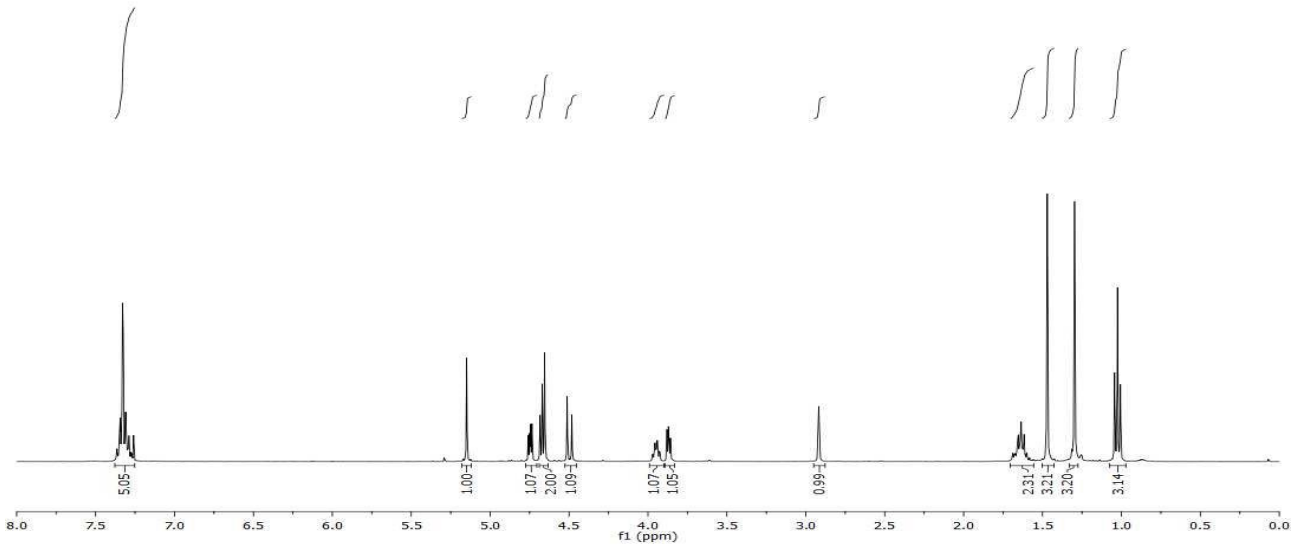


Figure S9: ^{1}H NMR spectrum of 13b (400 MHz, $CDCl_3$)

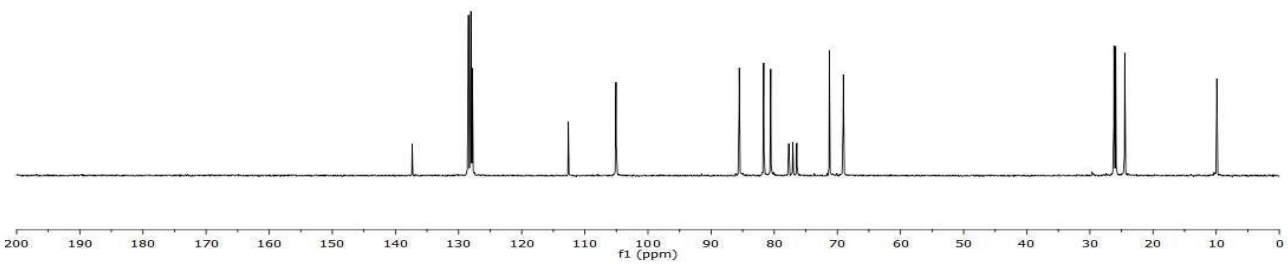
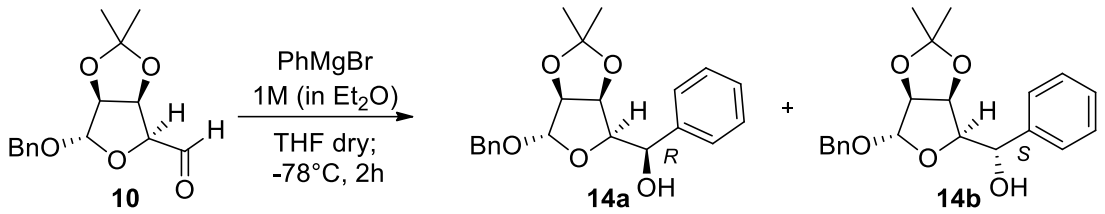


Figure S10: ^{13}C NMR spectrum of 13b (50 MHz, $CDCl_3$)

Synthesis of benzyl (5*R*)-2,3-*O*-(1-methylethylidene)-5-*C*-phenyl-α-D-lyxofuranoside (14a) and of benzyl (5*S*)-2,3-*O*-(1-methylethylidene)-5-*C*-phenyl-α-D-lyxofuranoside (14b).



A solution of **10** (207 mg, 0.74 mmol) in dry THF (10 mL) was stirred at −78°C under nitrogen atmosphere and a solution of PhMgBr in Et_2O (1 M, 1.34 mmol) was slowly added. The mixture was stirred for 2 h at −78°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_2O (3x5 mL). The combined organic layers were dried with Na_2SO_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, $CDCl_3$) δ ppm = 7.48-7.22 (m, 10 H, Ar), 5.15 (s, 1H, H-1), 5.02 (*p*t, *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_a-Bn), 4.40 (d, *J* =12.0 Hz, 1H, H_a-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, $CDCl_3$) δ 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 ($CHCl_3$): ν = 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 $C_{21}H_{24}O_5$ (356.41): C, 70.77; H, 6.79; found: C, 70.93, H, 6.98.

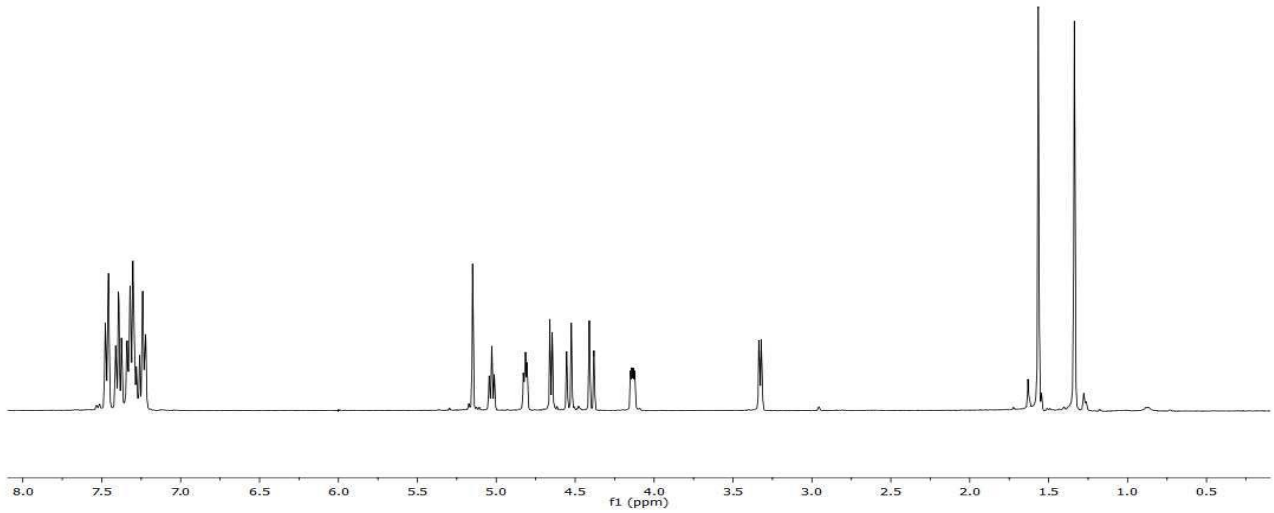


Figure S11: ^{1}H NMR spectrum of 14a (400 MHz, $CDCl_3$)

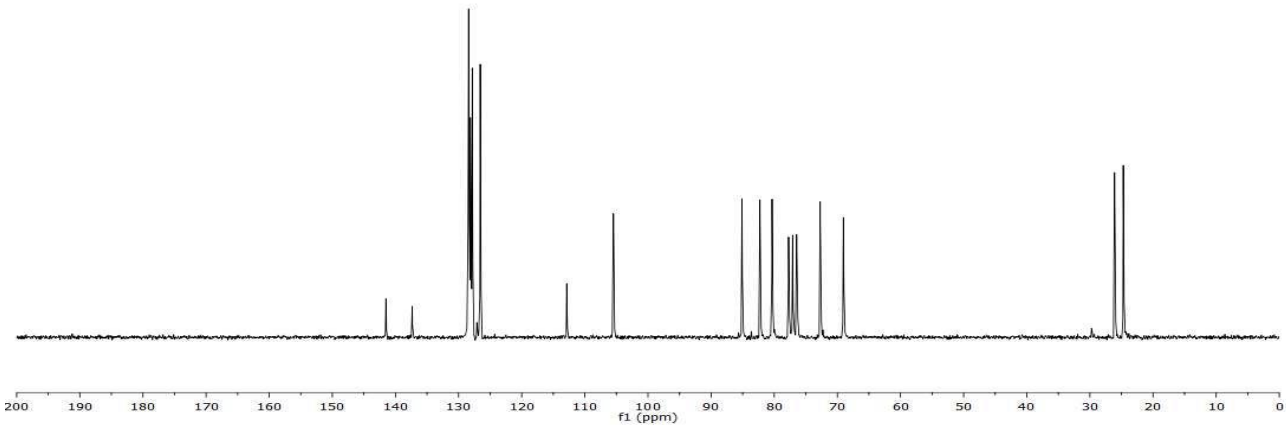


Figure S12: ^{13}C NMR spectrum of 14a (50 MHz, $CDCl_3$)

14b (R_f= 0.31, PEt/AcOEt 6:1): $[\alpha]_D^{29}$ = + 98.3 (*c* = 0.65, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) 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). ^{13}C-NMR (50 MHz, $CDCl_3$) 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 ($CHCl_3$): 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 $C_{21}H_{24}O_5$ (356.41): C, 70.77; H, 6.79; found: C, 70.84, H, 7.09.

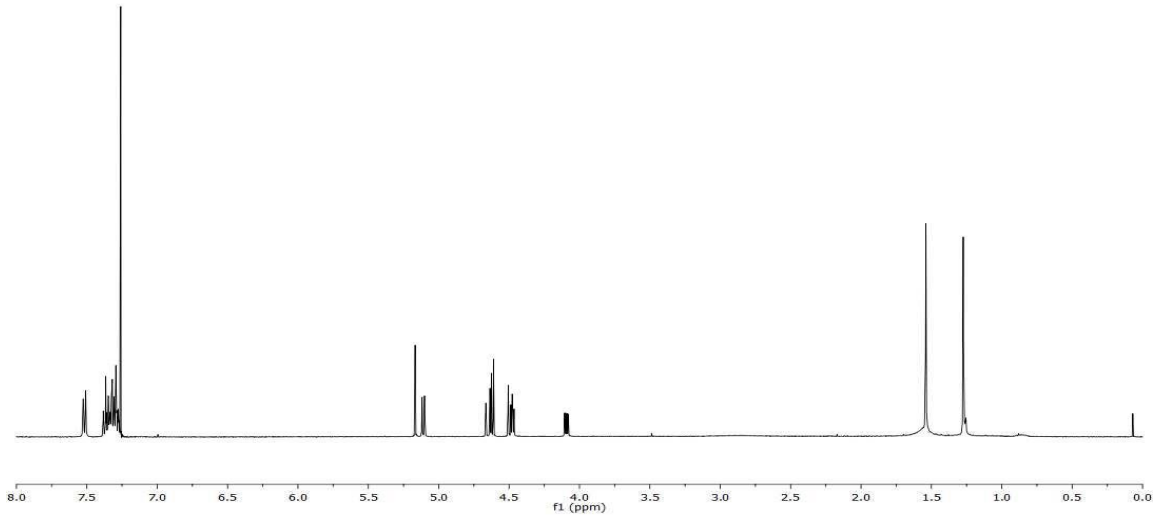


Figure S13: ^{1}H NMR spectrum of 14b (400 MHz, $CDCl_3$)

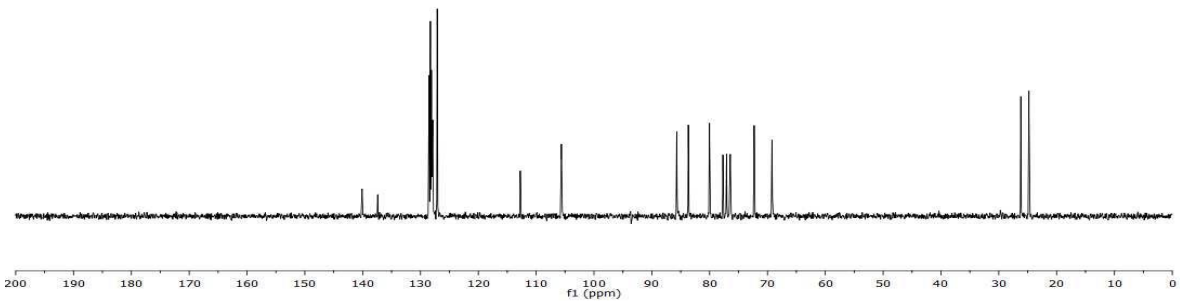
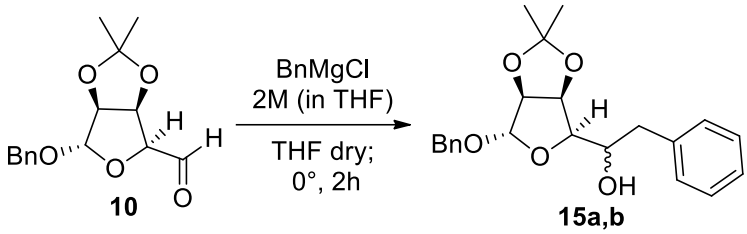


Figure S14: ^{13}C NMR spectrum of 14b (50 MHz, $CDCl_3$)

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 $NaHCO_3$ (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_2O (3x5 mL). The combined organic layers were dried with Na_2SO_4 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 ^{1}H-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).

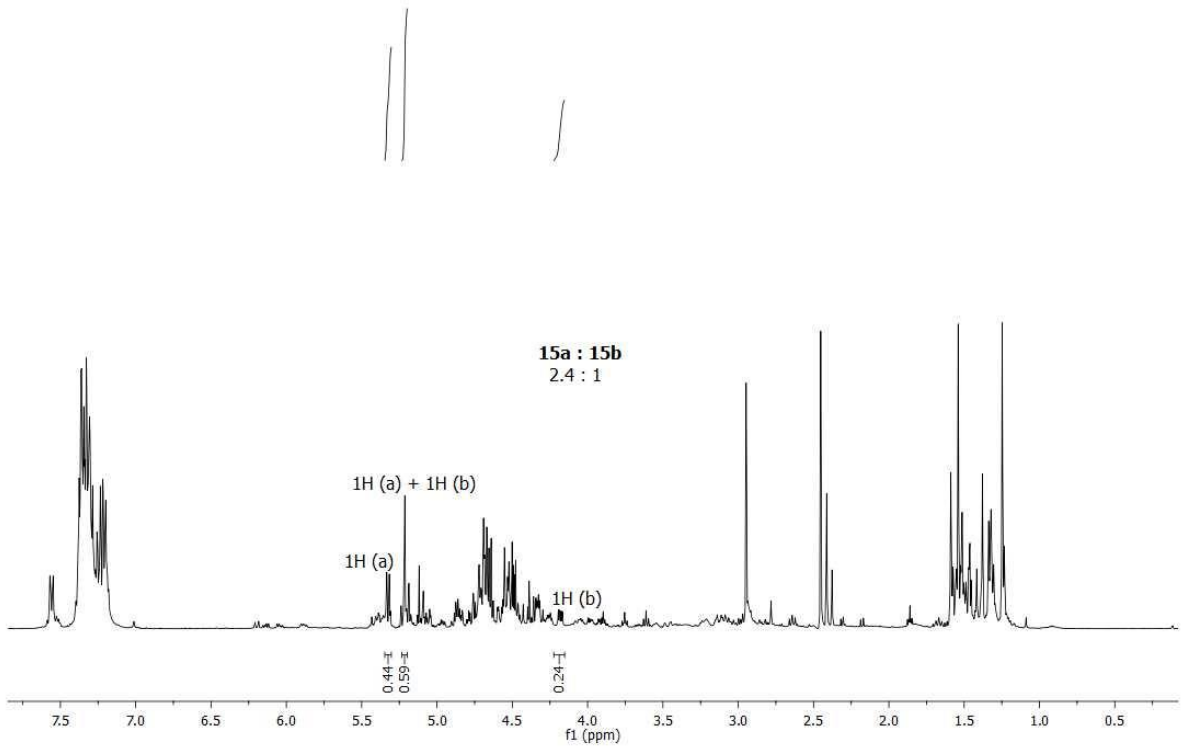


Figure S15: ^{1}H NMR spectrum of the crude reaction mixture (400 MHz, $CDCl_3$)

15a (R_f = 0.23, hexane/AcOEt 4:1): $[\alpha]_D^{23}$ = + 117.2 (*c* = 1.26, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) 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, H_a-Bn), 4.63 (d, *J* =4.0 Hz, 1H, H-2), 4.52 (d, *J* =11.8 Hz, 1H, H_b-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, O*H*), 2.42 (s, 2H, H-6), 1.51 (s, 3H, Me), 1.23 (s, 3H, Me). ^{13}C-NMR (50 MHz, $CDCl_3$) 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 ($CHCl_3$): 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 $C_{22}H_{26}O_5$ (370.44): C, 71.33; H, 7.07; found: C, 70.88, H, 6.76.

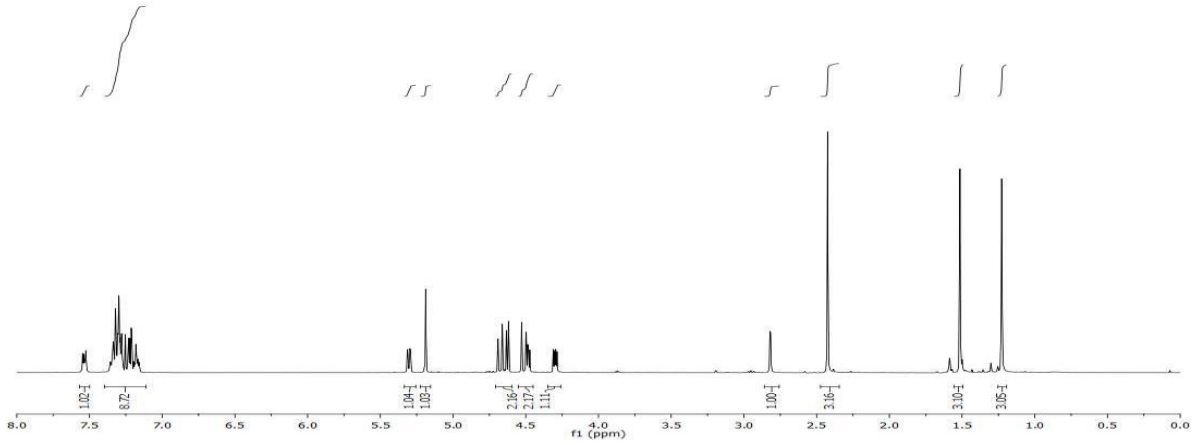


Figure S16: ^{1}H NMR spectrum of 15a (400 MHz, $CDCl_3$)

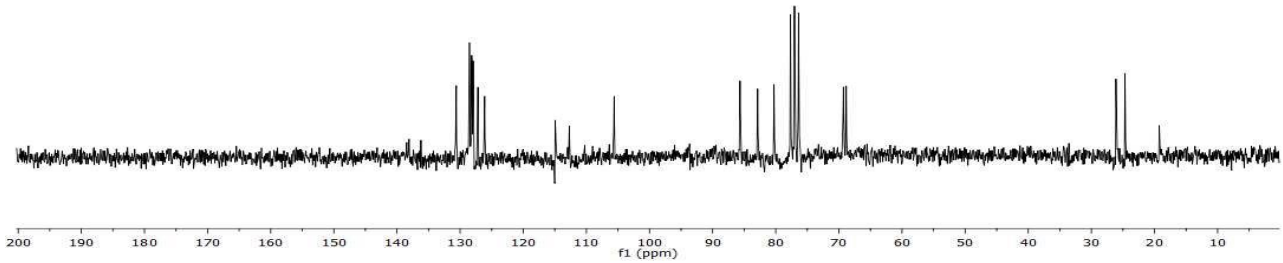


Figure 17: ^{13}C NMR spectrum of 15a (50 MHz, $CDCl_3$)

15b (partially characterized): R_f = 0.31, hexane/AcOEt 4:1). ^{1}H-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_a-Bn), 4.65 (d, *J* =5.9 Hz, 1H, H-2), 4.52 (d, *J* =11.8 Hz, 1H, H_b-Bn), 4.31-4.26 (m, 1H, H-5), 3.87 (*p*t, *J* =3.9 Hz, 1H, H-4), 2.98 (dd, *J* =13.6, 6.1 Hz, 1H, H_a-6), 2.92 (dd, *J* =13.6, 7.6 Hz, 1H, H_b-6), 1.50 (s, 3H, Me), 1.30 (s, 3H, Me). ^{13}C-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, 2938, 2360, 1603, 1496, 1456, 1376, 1088 cm^{-1}. MS (ESI): m/z 393.37 ([M+Na]+; 100).

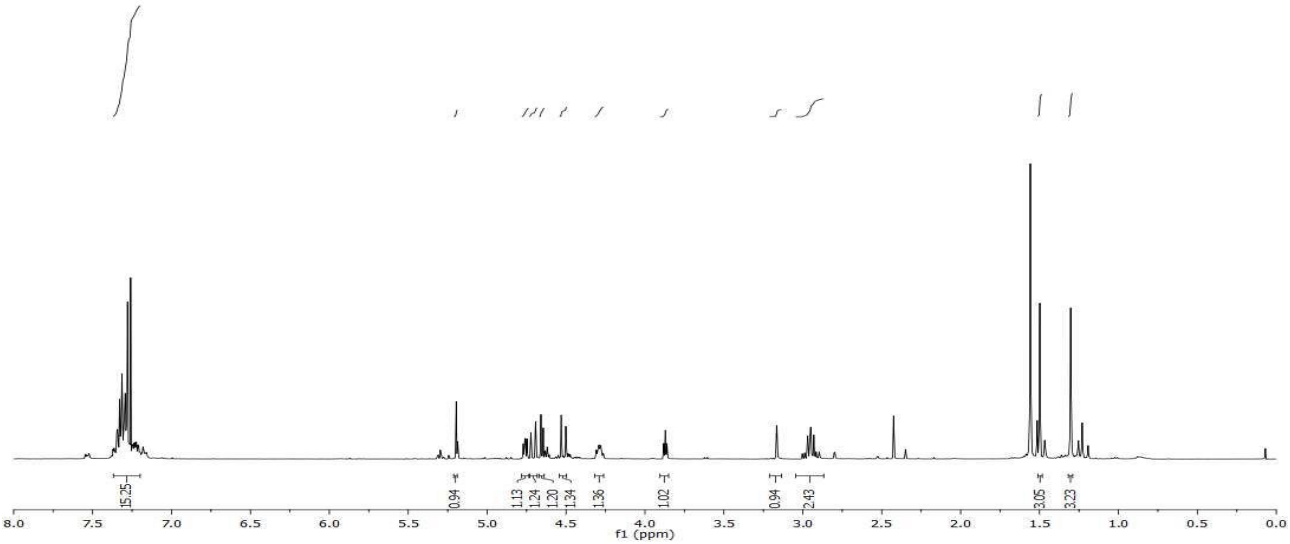


Figure S18: ^{1}H NMR spectrum of 15b (400 MHz, $CDCl_3$)

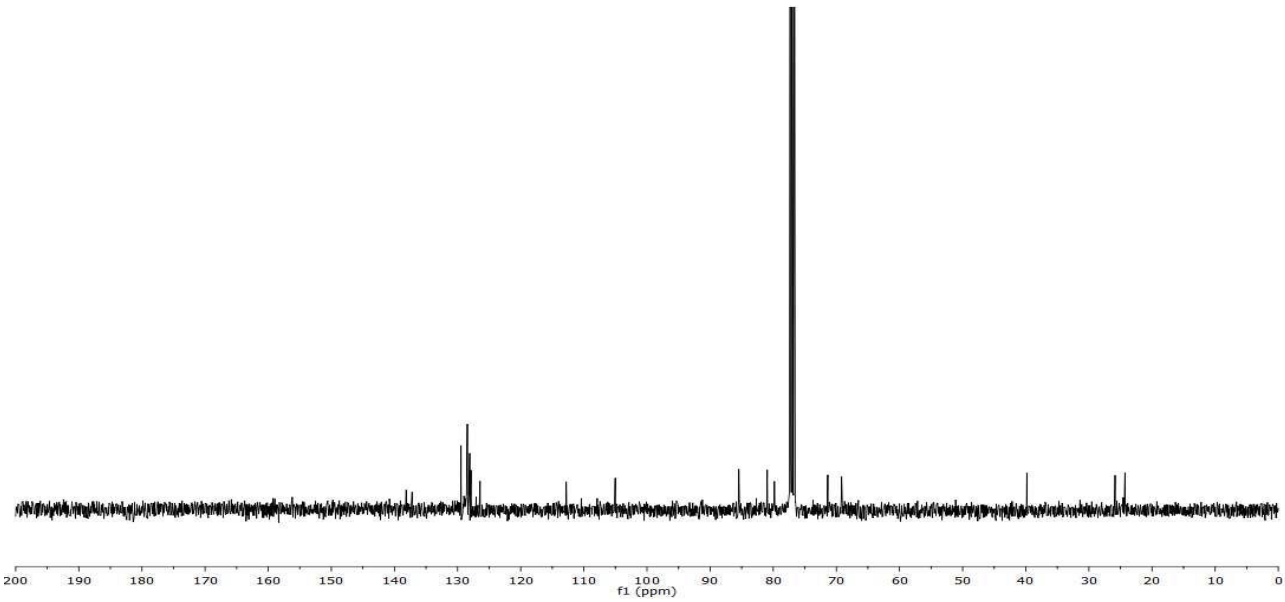
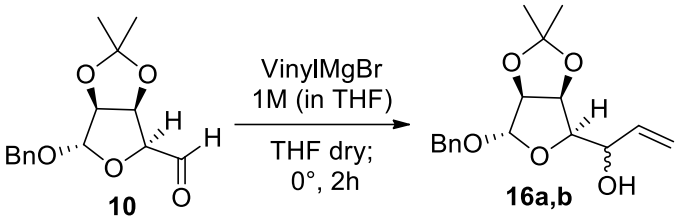


Figure S19: ^{13}C NMR spectrum of 15b (50 MHz, $CDCl_3$)

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 $NaHCO_3$ (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_2O (3x5 mL). The combined organic layers were dried with Na_2SO_4 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 ^{1}H-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).

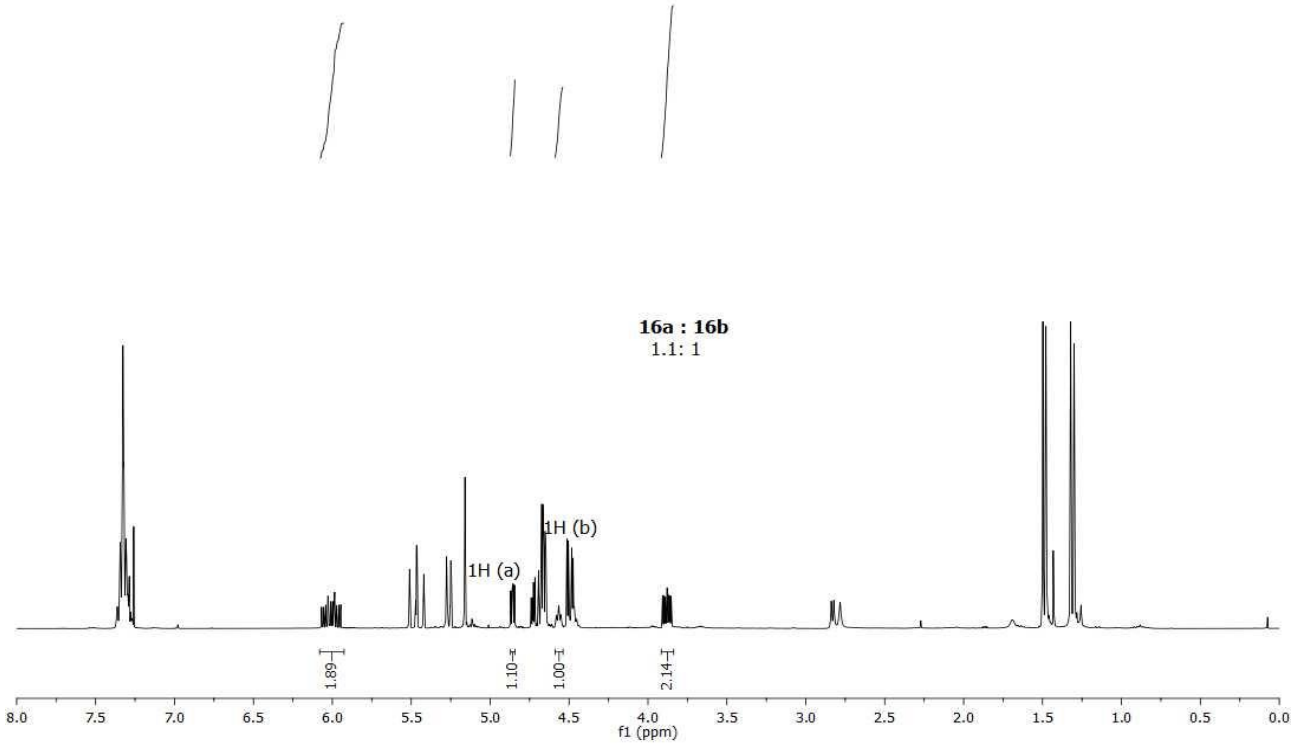


Figure S20: ^{1}H NMR spectrum of the crude reaction mixture (400 MHz, $CDCl_3$)

16a (R_f = 0.26, hexane/AcOEt 5:1): $[\alpha]_D^{22}$ = + 81.6 (*c* = 0.74, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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 H_a-Bn), 4.66 (d, *J* =6.4 Hz, 1H, H-2), 4.49 (d, *J* =11.2 Hz, 1H, H_b-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, O*H*), 1.50 (s, 3H, Me), 1.32 (s, 3H, Me). ^{13}C-NMR (50 MHz, $CDCl_3$) δ 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 ($CHCl_3$): ν = 2676, 3630, 3508, 2990, 2942, 1715, 1601, 1498, 1456, 1385, 1376, 1270, 1080 cm^{-1}. MS (ESI): m/z 329.30 ([M+Na]+; 100). Elemental analysis calcd (%) for $C_{17}H_{22}O_5$ (306.35): C, 66.65; H, 7.24, found: C, 67.00, H, 6.95.

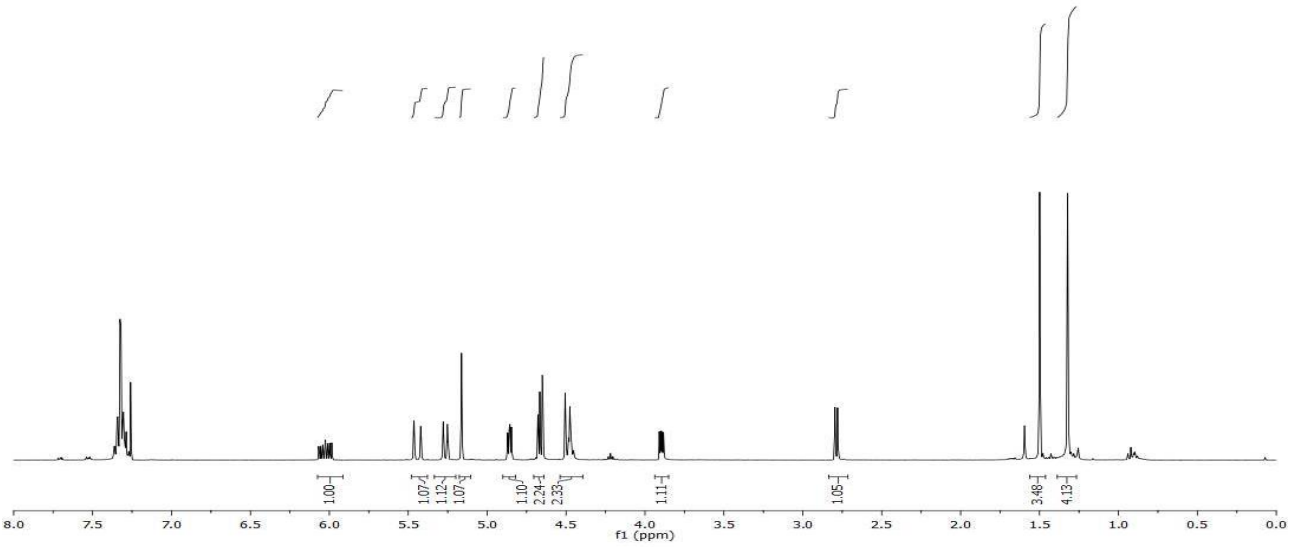


Figure S21: ^{1}H NMR spectrum of 16a (400 MHz, $CDCl_3$)

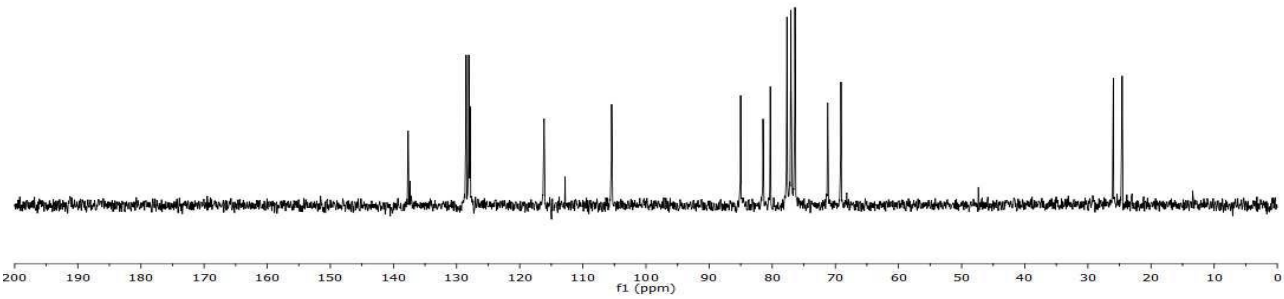


Figure S22: ^{13}C NMR spectrum of 16a (50 MHz, $CDCl_3$)

16b (R_f = 0.33, hexane/AcOEt 5:1): $[\alpha]_D^{21}$ = + 56.9 (*c* = 0.90, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm = 7.37-7.26 (m, 5H, Ar), 5.99 (ddd, *J* =17.3, 10.5, 5.3 Hz, 1H, H-6), 5.49 (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 H_a-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, H_b-Bn), 3.87 (dd, *J* =6.4, 3.6 Hz, 1H, H-4), 2.79 (d, *J* =2.4 Hz 1H, O*H*), 1.48 (s, 3H, Me), 1.30 (s, 3H, Me). ^{13}C-NMR (100 MHz, $CDCl_3$) 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 ($CHCl_3$): 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 $C_{17}H_{22}O_5$ (306.15): C, 66.65; H, 7.24, found: C, 66.84, H, 7.33.

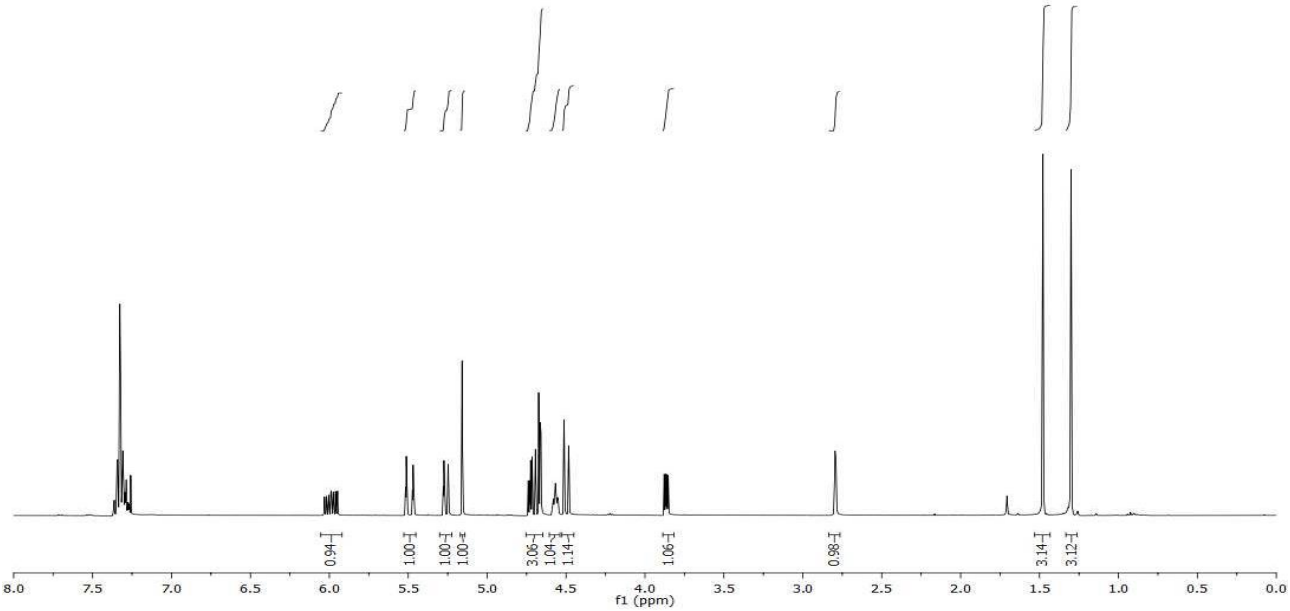


Figure S23: ^{1}H NMR spectrum of 16b (400 MHz, $CDCl_3$)

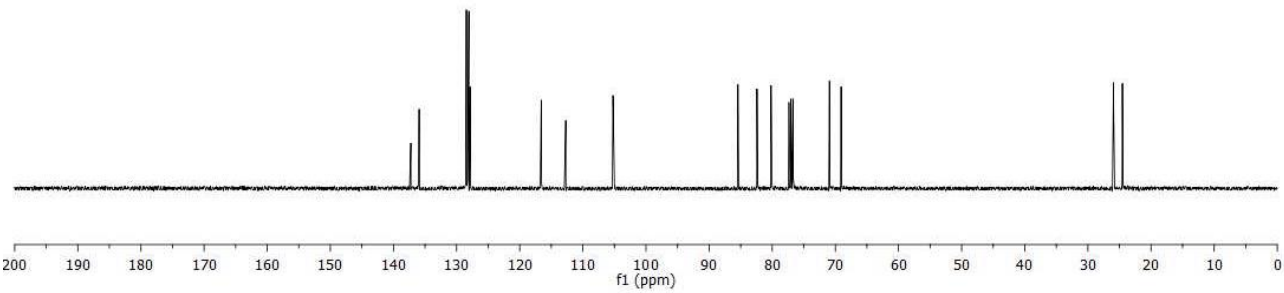
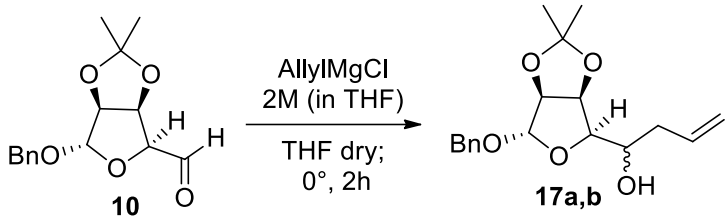


Figure S24: ^{13}C NMR spectrum of 16b (100 MHz, $CDCl_3$)

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_2O (3x5 mL). The combined organic layers were dried with Na_2SO_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).

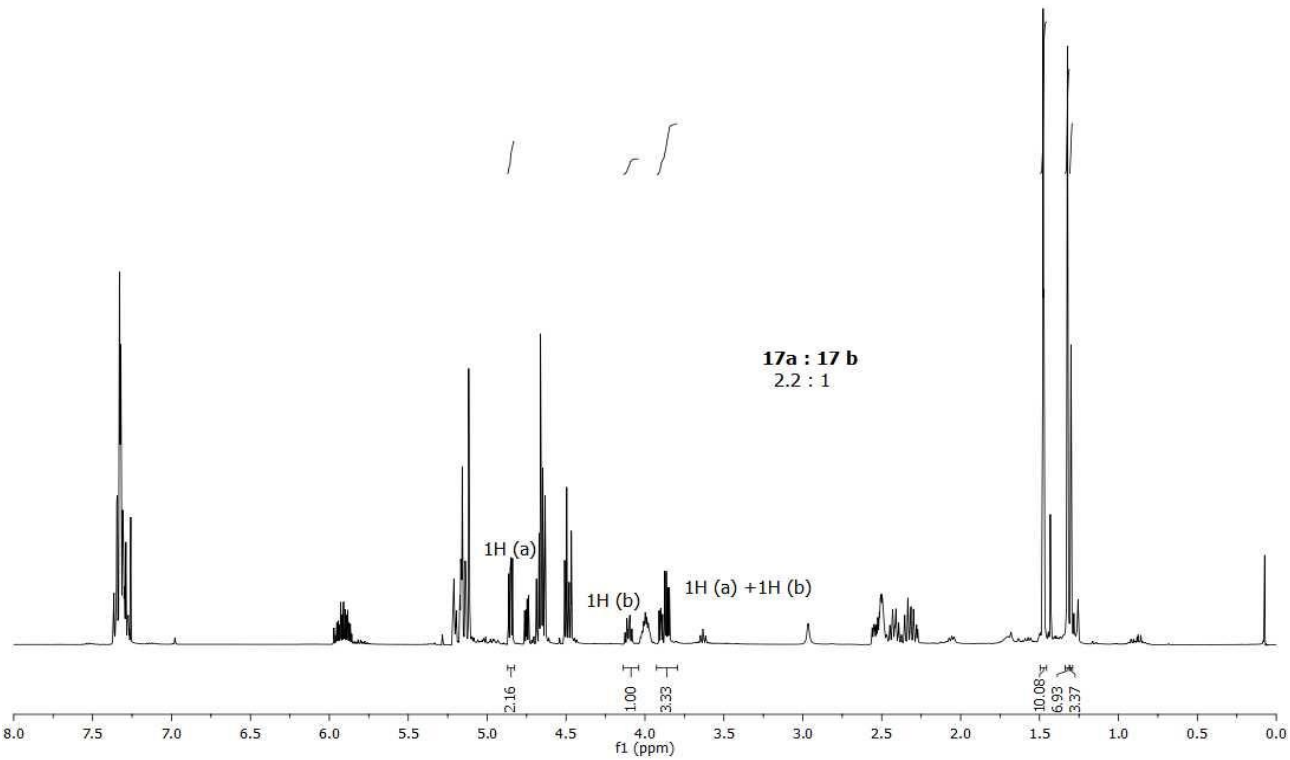


Figure S25: ^{1}H NMR spectrum of the crude reaction mixture (400 MHz, $CDCl_3$)

17a (R_f = 0.28, hexane/AcOEt 5:1): $[\alpha]_D^{25}$ = + 64.7 (*c* = 0.92, $CHCl_3$).). ^{1}H-NMR (400 MHz, $CDCl_3$) 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-Bn), 4.48 (d, *J* =11.6 Hz, 1H, H_b-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, Ha-6), 2.49 (d, *J* =5.6 Hz 1H, O*H*), 2.36-2.28 (m, 1H, Hb-6), 1.48 (s, 3H, Me), 1.33 (s, 3H, Me). ^{13}C-NMR (100 MHz, $CDCl_3$) 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 ($CHCl_3$): 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 $C_{18}H_{24}O_5$ (320.38): C, 67.48; H, 7.55, found: C, 66.95, H, 7.18.

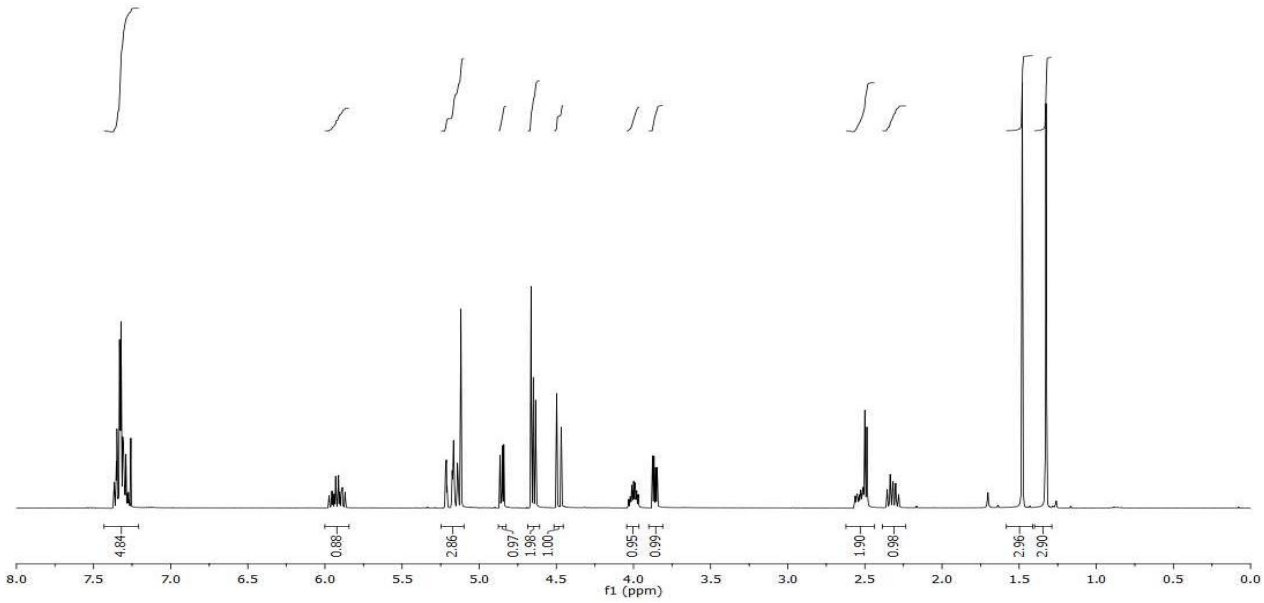


Figure S26: ^{1}H NMR spectrum of 17a (400 MHz, $CDCl_3$)

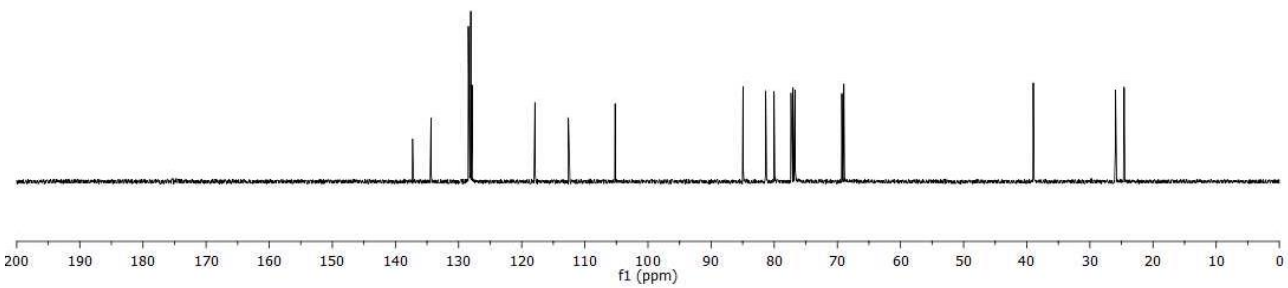


Figure S27: ^{13}C NMR spectrum of 17a (100 MHz, $CDCl_3$)

17b (R_f = 0.34, hexane/AcOEt 5:1): $[\alpha]_D^{24}$ = + 78.6 (*c* = 0.80, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) 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, H_a-Bn), 4.66 (d, *J* =5.8 Hz, 1H, H-2), 4.49 (d, *J* =12.0 Hz, 1H, H_b-Bn), 4.10 (*p*q, *J* =5.6 Hz, 1H, H-5), 3.90 (dd, *J* =4.4, 3.6 Hz, 1H, H-4), 2.96 (s, 1H, O*H*), 2.48-2.36 (m, 2H, H-6), 1.47 (s, 3H, Me), 1.30(s, 3H, Me). ^{13}C-NMR (100 MHz, $CDCl_3$) 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 ($CHCl_3$): 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 $C_{18}H_{24}O_5$ (320.38): C, 67.48; H, 7.55, found: C, 67.15, H, 7.66.

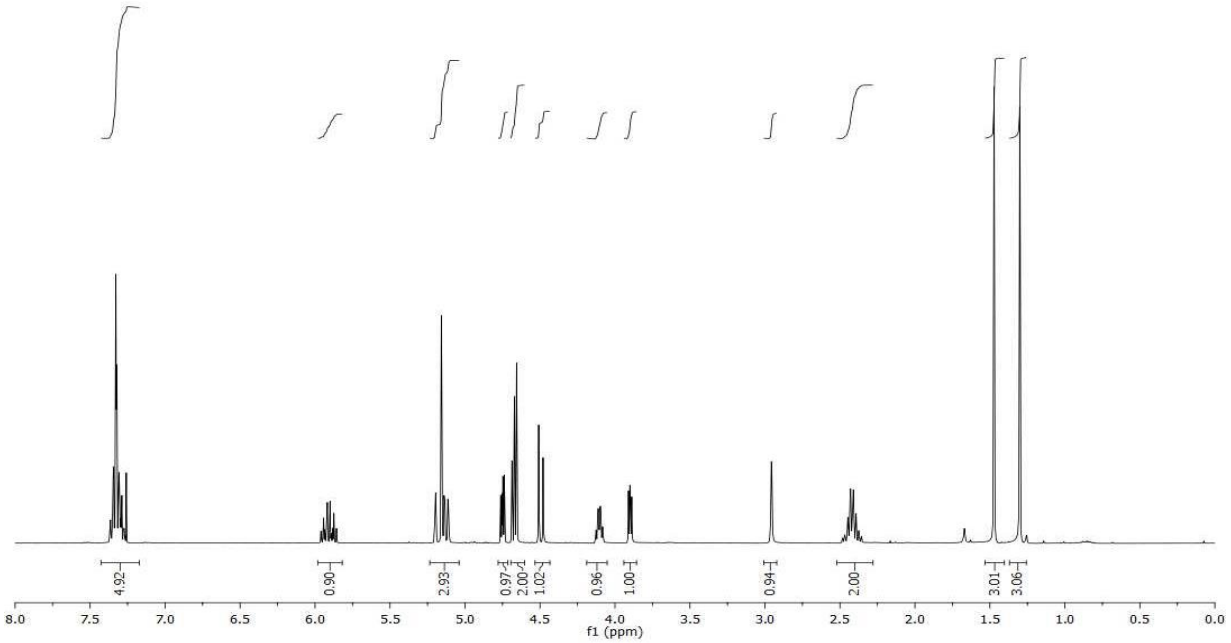


Figure S28: ^{1}H NMR spectrum of 17b (400 MHz, $CDCl_3$)

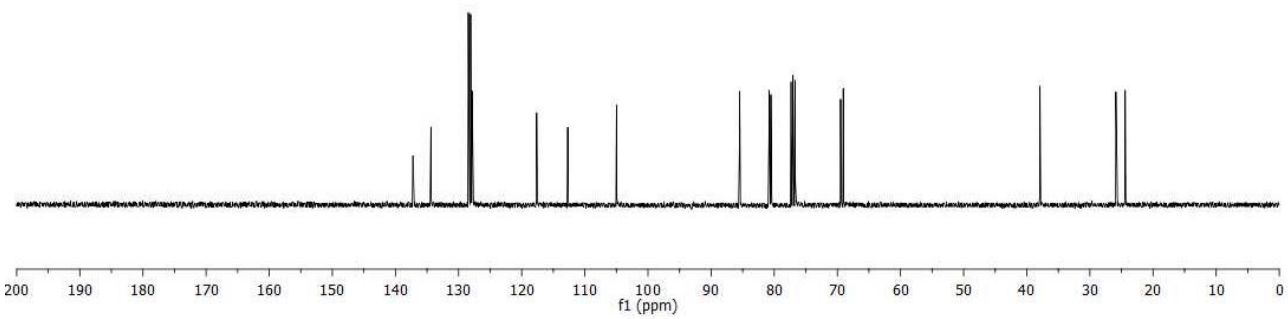
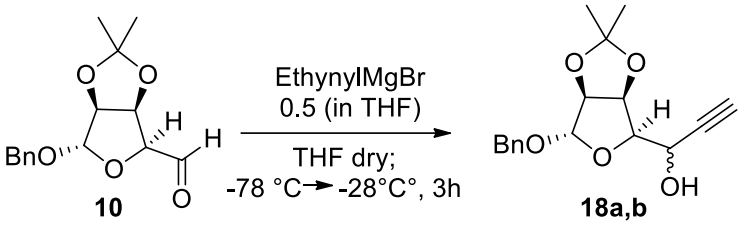


Figure S29: ^{13}C NMR spectrum of 17b (100 MHz, $CDCl_3$)

Synthesis of compounds 18a,b



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/Et_2O 2:1). A saturated solution of $NaHCO_3$ (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 Et_2O (3x5 mL). The combined organic layers were dried with Na_2SO_4 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 ^{1}H-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.

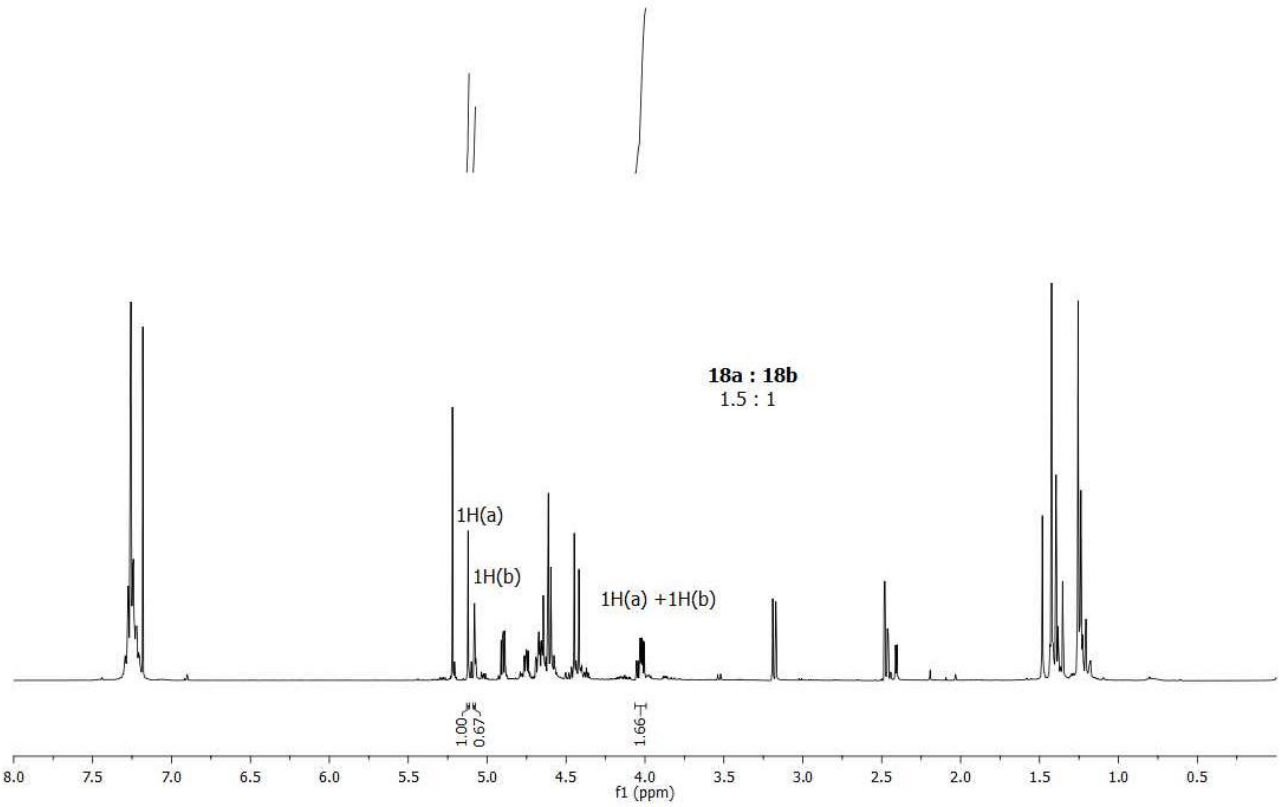


Figure S30: ^{1}H NMR spectrum of the crude reaction mixture (400 MHz, $CDCl_3$)

18a/18b (R_f = 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), O*H*), 2.70 (d, *J* =1.8 Hz, 1H(b), O*H*), 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).

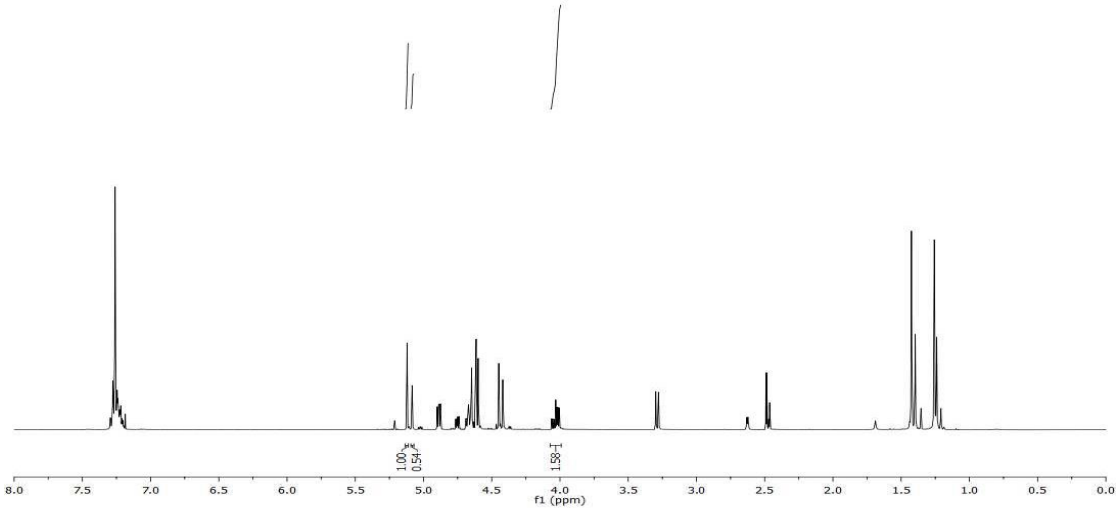


Figure S31: ^{1}H NMR spectrum of the mixture 18a/18b (400 MHz, $CDCl_3$)

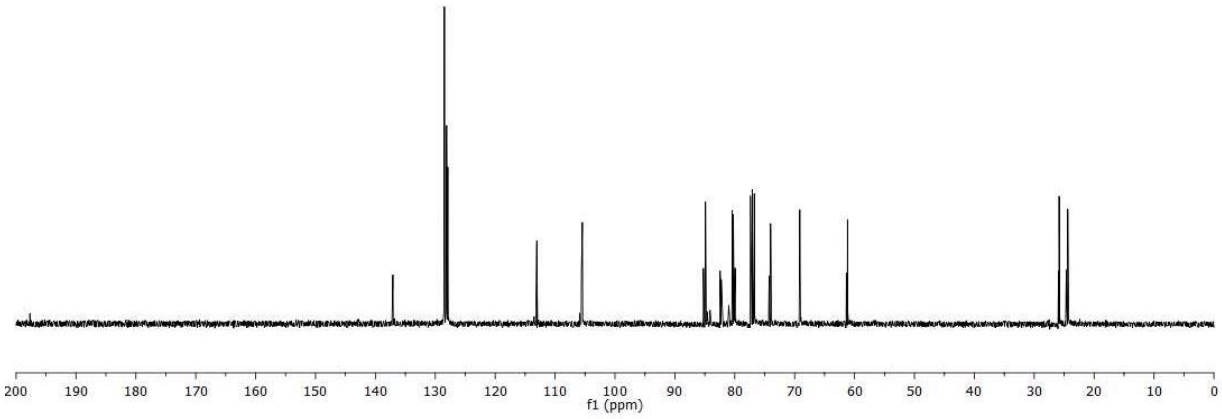
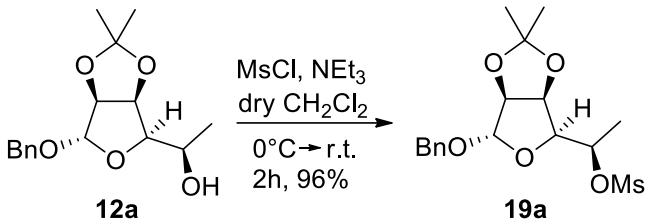


Figure S32: ^{13}C NMR spectrum of the mixture 18a/18b (100 MHz, $CDCl_3$)

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 CH_2Cl_2 (2.4 mL) at 0°C, NEt_3 (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 CH_2Cl_2 (3x2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified on silica gel by FCC (PEt/AcOEt 5:1) to afford 50 mg of **19a** (R_f= 0.30, 0.13 mmol, 96%) as a waxy white solid. $[\alpha]_D^{23}$ = + 48.4 (*c* = 0.72, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) 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, -C*H*$_3$ mesylate), 1.58-1.51 (m, 3H, H-6), 1.45 (s, 3H, Me), 1.30 (s, 3H, Me). ^{13}C-NMR (50 MHz, $CDCl_3$) 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, *C*H$_3$ mesylate), 26.0 (q, Me), 24.9 (q, Me), 19.2 (q, C-6). IR ($CDCl_3$): 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 $C_{17}H_{24}O_7S$ (372.43): C, 54.82; H, 6.50; found: C, 54.93, H, 6.22.

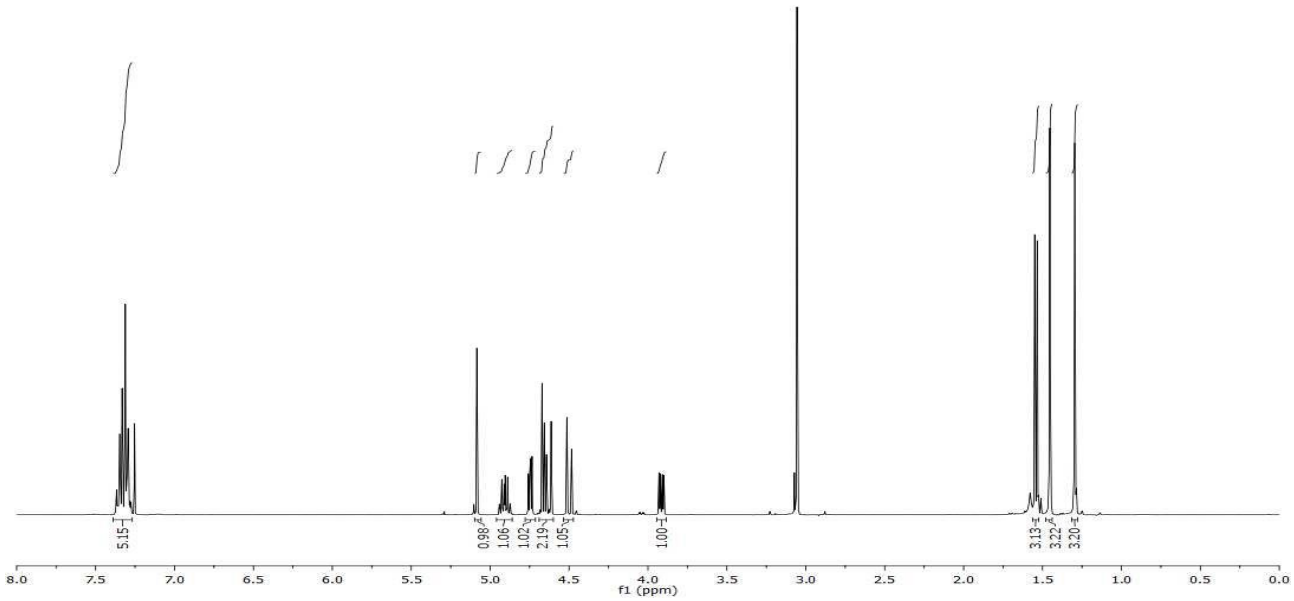


Figure S33: ^{1}H NMR spectrum of 19a (400 MHz, $CDCl_3$)

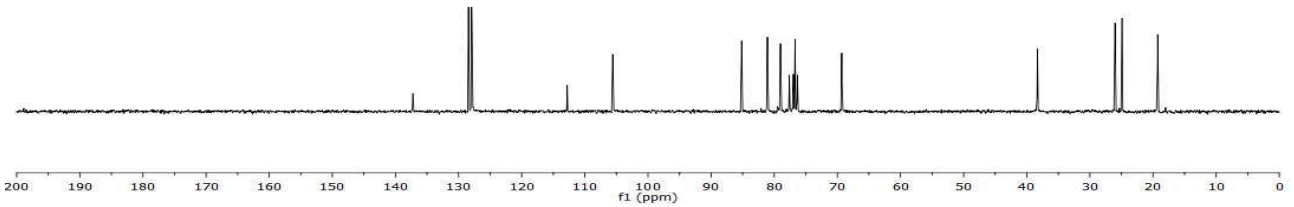
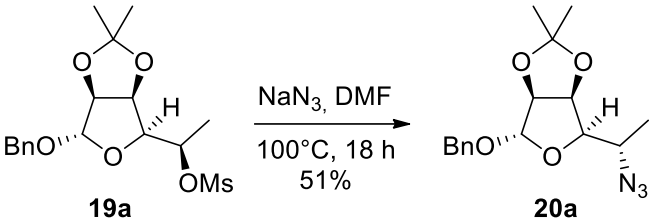


Figure S34: ^{13}C NMR spectrum of 19a (50 MHz, $CDCl_3$)

Synthesis of benzyl 5-azido-5,6-dideoxy-2,3-*O*-(1-methylethylidene)-β-L-gulofuranoside (20a)



To a solution of **19a** (91 mg, 0.24 mmol) in dry DMF (4.8 mL), NaN_3 (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 (R_f= 0.38) together with a newly form product (R_f= 0.85). Therefore, 3 more equivalents of NaN_3 (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** (R_f= 0.21 in PEt/AcOEt 15:1, 0.12 mmol, 51%) as a waxy solid. $[\alpha]_D^{23}$ = + 82.6 (*c* = 1.35, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) 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). ^{13}C-NMR (50 MHz, $CDCl_3$) 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 ($CHCl_3$): ν = 3619, 3448, 3020, 2401, 2125, 1384, 1224. MS (ESI): m/z 341.91 ([M+Na]+; 100). Elemental analysis calcd (%) for $C_{16}H_{21}N_3O_4$ (319.36): C, 60.17; H, 6.63, N, 13.16; found: C, 60.11, H, 7.01, N, 13.51.

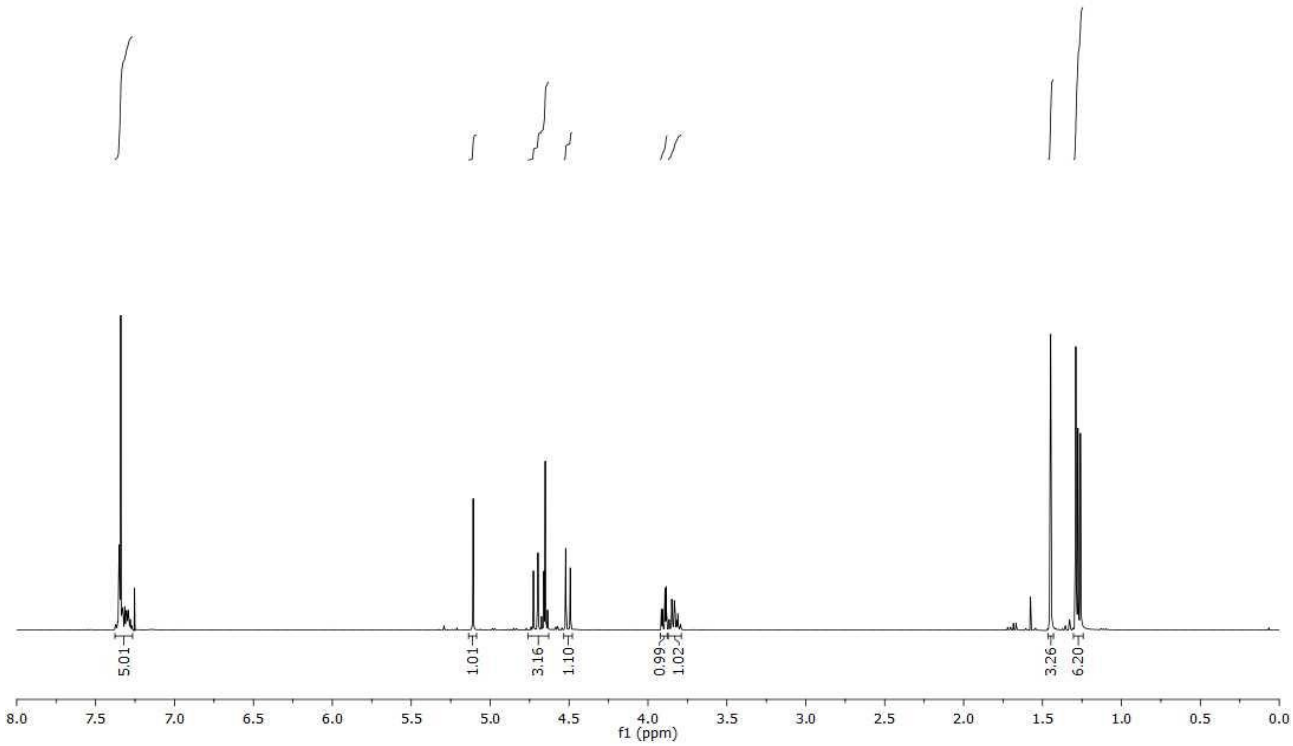


Figure S35: ^{1}H NMR spectrum of 20a (400 MHz, $CDCl_3$)

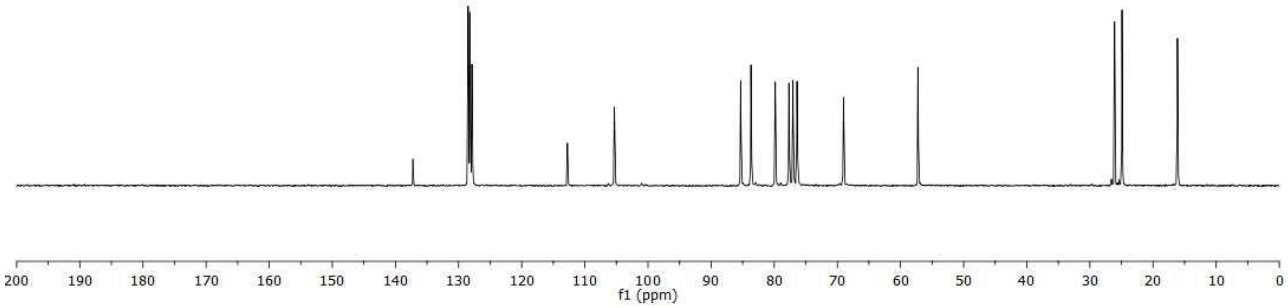
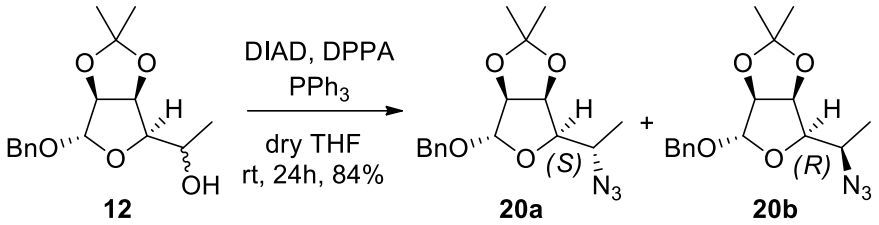


Figure S36: ^{13}C NMR spectrum of 20a (50 MHz, $CDCl_3$)

Synthesis of benzyl 5-azido-5,6-dideoxy-2,3-*O*-(1-methylethylidene)-β-L-gulofuranoside (20a) and of benzyl 5-azido-5,6-dideoxy-2,3-*O*-(1-methylethylidene)-α-D-mannofuranoside (20b).



To a 4.5:1 mixture of **12a** and **12b** (53 mg, 0.18 mmol) in dry THF (5 mL), PPh_3 (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/Et_2O 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): ^{1}H-NMR (400 MHz, $CDCl_3$) 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). ^{13}C-NMR (50 MHz, $CDCl_3$) 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 ($CHCl_3$): ν = 3689, 2938, 2250, 2099, 1455, 1384, 1376, 1080 cm^{-1}. MS (ESI): m/z 342.06 ([M+Na]+; 100).

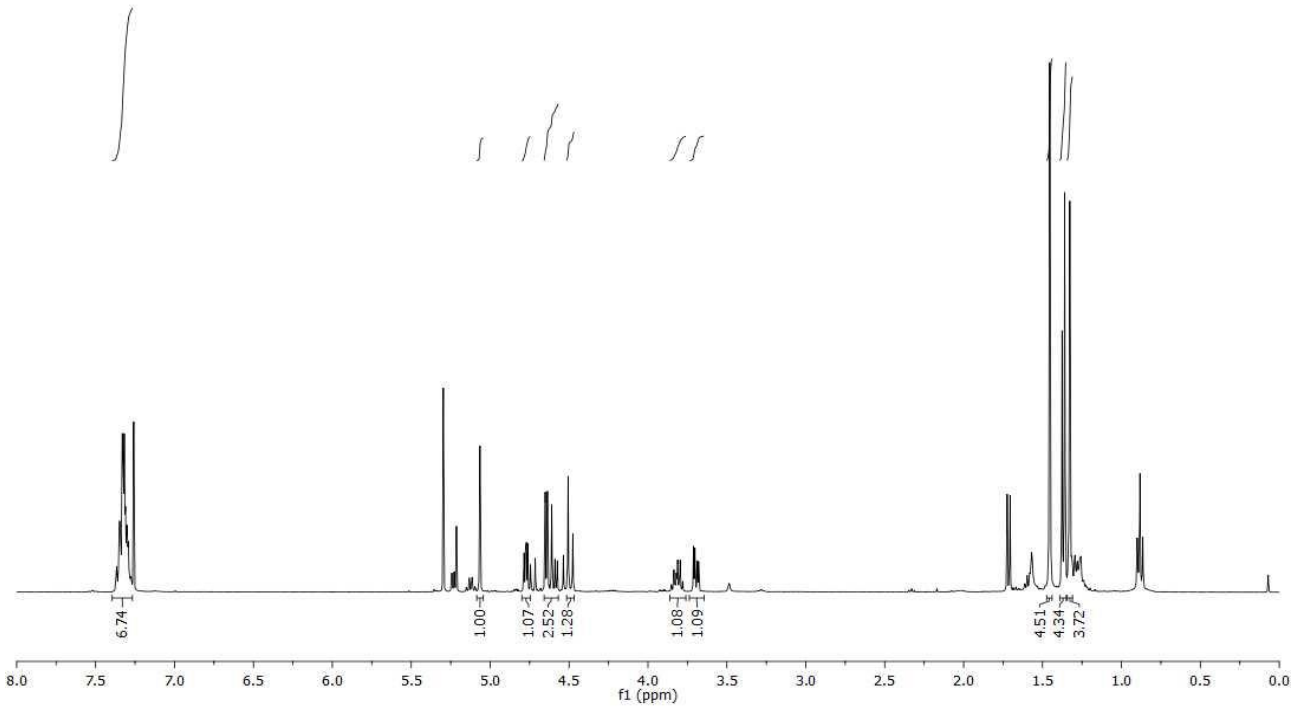


Figure S37: ^{1}H NMR spectrum of 20b (400 MHz, $CDCl_3$)

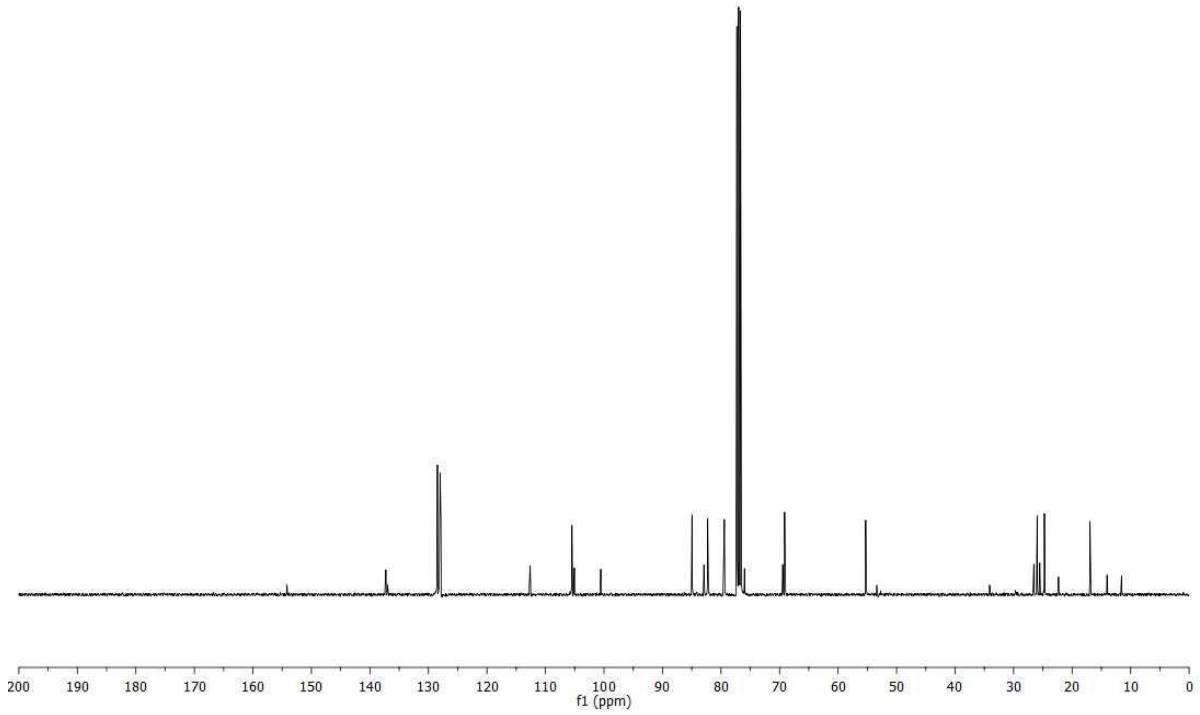
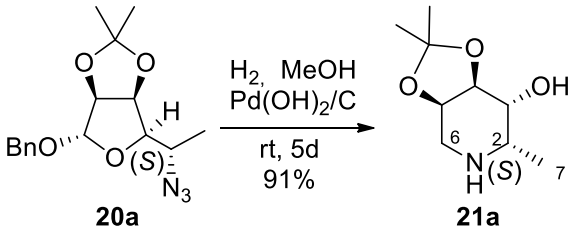


Figure S38: ^{13}C NMR spectrum of 20b (50 MHz, $CDCl_3$)

Synthesis of (2*S*,3*R*,4*S*,5*R*)-3-hydroxy-4,5-*O*-(1-methylethylidene)-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 mixtute was filtered through Celite® and the solvent was removed under reduced pressure. The crude was purified on silica gel by FCC (CH_2Cl_2/MeOH/NH_4OH (6%) 15:1:0.1) to afford 33 mg of **21a** (R_f= 0.11, 0.18 mmol, 91%). $[\alpha]_D^{21}$ = + 8.6 (*c* = 1.11, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ 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 (*p*t, *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_3OD_3) δ 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_2Cl_2): ν = 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 $C_9H_{17}NO_3$ (187.24): C, 57.73; H, 9.15, N, 7.48; found: C, 57.64, H, 9.55, N, 7.14.

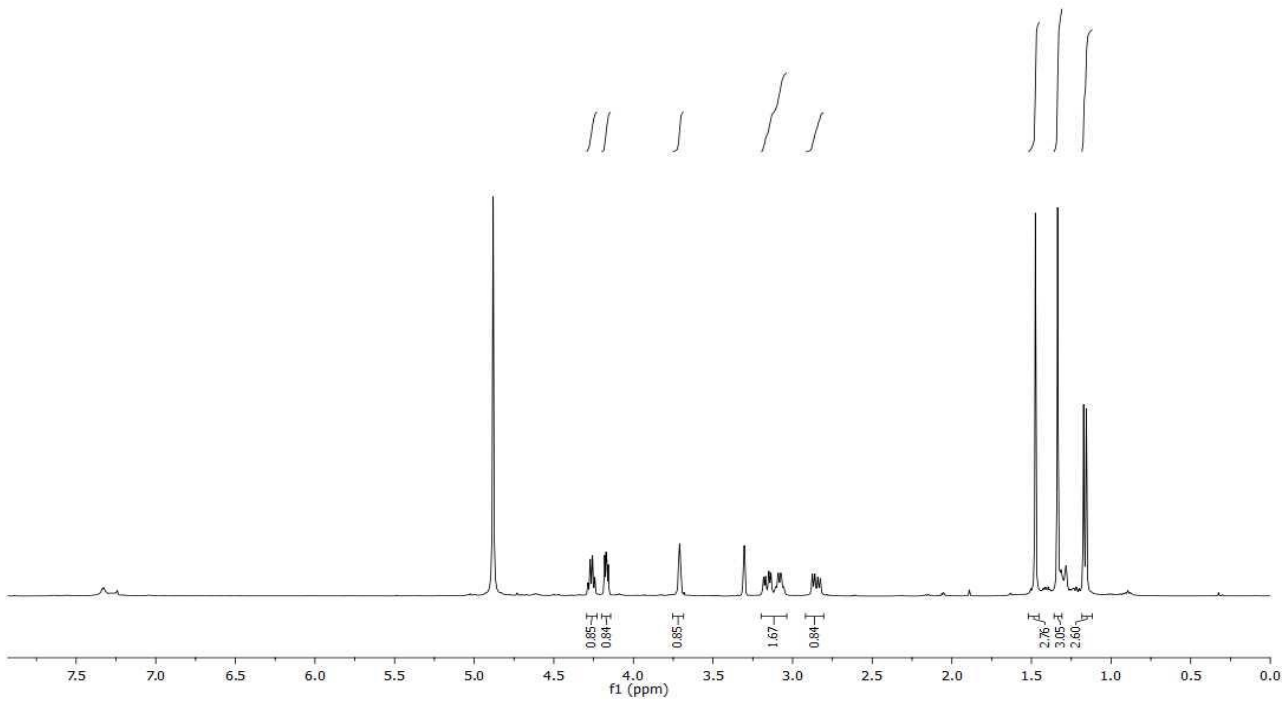


Figure S39: ^{1}H NMR spectrum of 21a (400 MHz, CD_3OD)

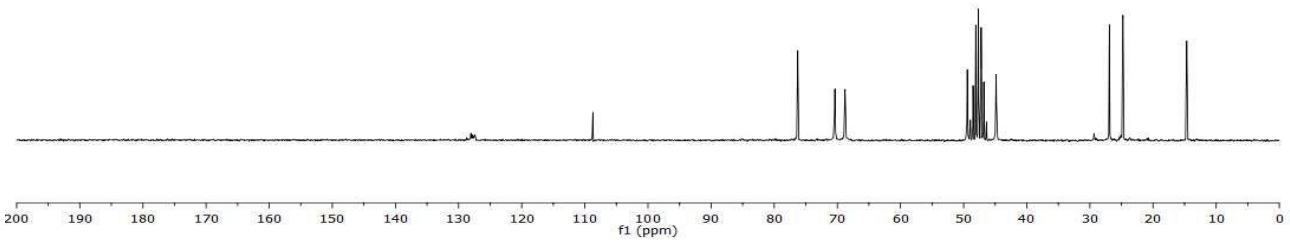


Figure S40: ^{13}C NMR spectrum of 21a (400 MHz, CD_3OD)

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.

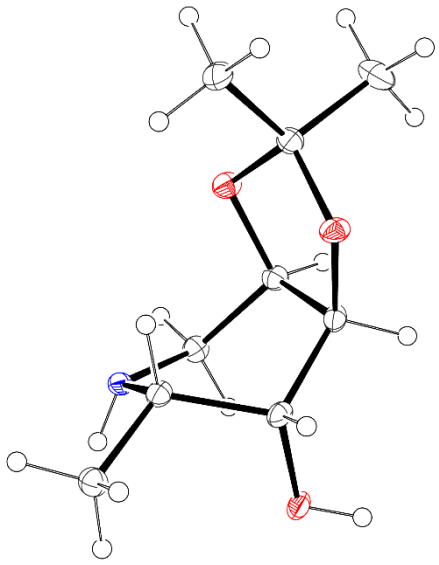
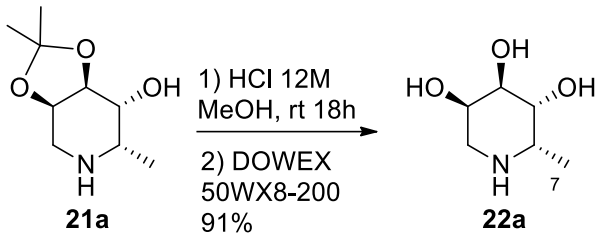


Figure S41: X-ray crystal structure of 21a

Synthesis of (2*S*, 3*R*, 4*R*, 5*R*)-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® 50XW8-100 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 H_2O). ^{1}H-NMR (400 MHz, D_2O) δ 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, D_2O) δ 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 $C_6H_{13}NO_3$ (147.17): C, 48.97; H, 8.90, N, 9.52; found: C, 48.44, H, 9.26, N, 9.72.

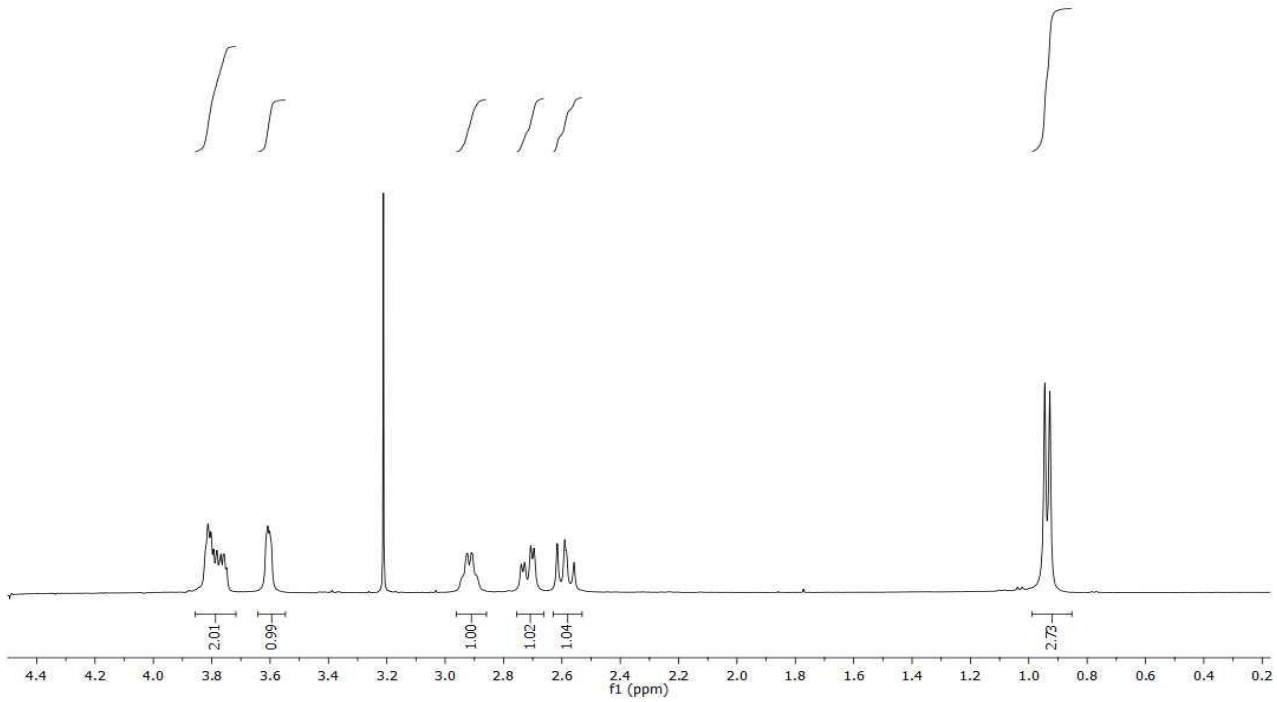


Figure S42: ^{1}H NMR spectrum of 22a (400 MHz, D_2O)

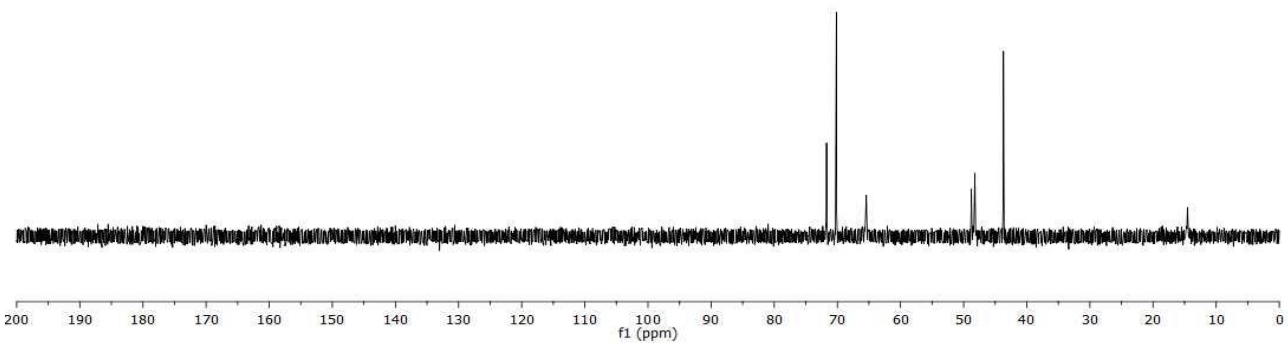
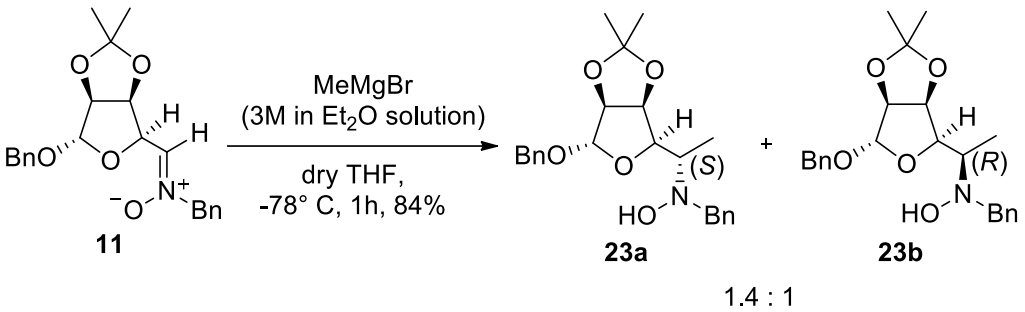


Figure S43: ^{13}C NMR spectrum of 22a (100 MHz, D_2O)

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 Et_2O (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 $NaHCO_3$ (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 Et_2O (3x8 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a mixture of **23a** e **23b** (**a** : **b** ratio 1.4 : 1, as attested by integrating the signals in the ^{1}H-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** (R_f= 0.4, PE/AcOEt 7:1). A further purification of **23a/23b** (Hex/AcOEt 10:1, R_f= 0.15) allowed to characterize the hydroxylamine as a mixture.

^{1}HNMR (400 MHz, $CDCl_3$) 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)). **^{13}C-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, *N*Bn (a)), 69.7 (t, *N*Bn (b)), 69.1 (t, *O*Bn (b)), 68.8 (t, *O*Bn (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 $C_{23}H_{29}NO_5$ (399.48): C, 69.15; H, 7.32, N, 3.51; found: C, 69.48, H, 7.02, N, 3.89.

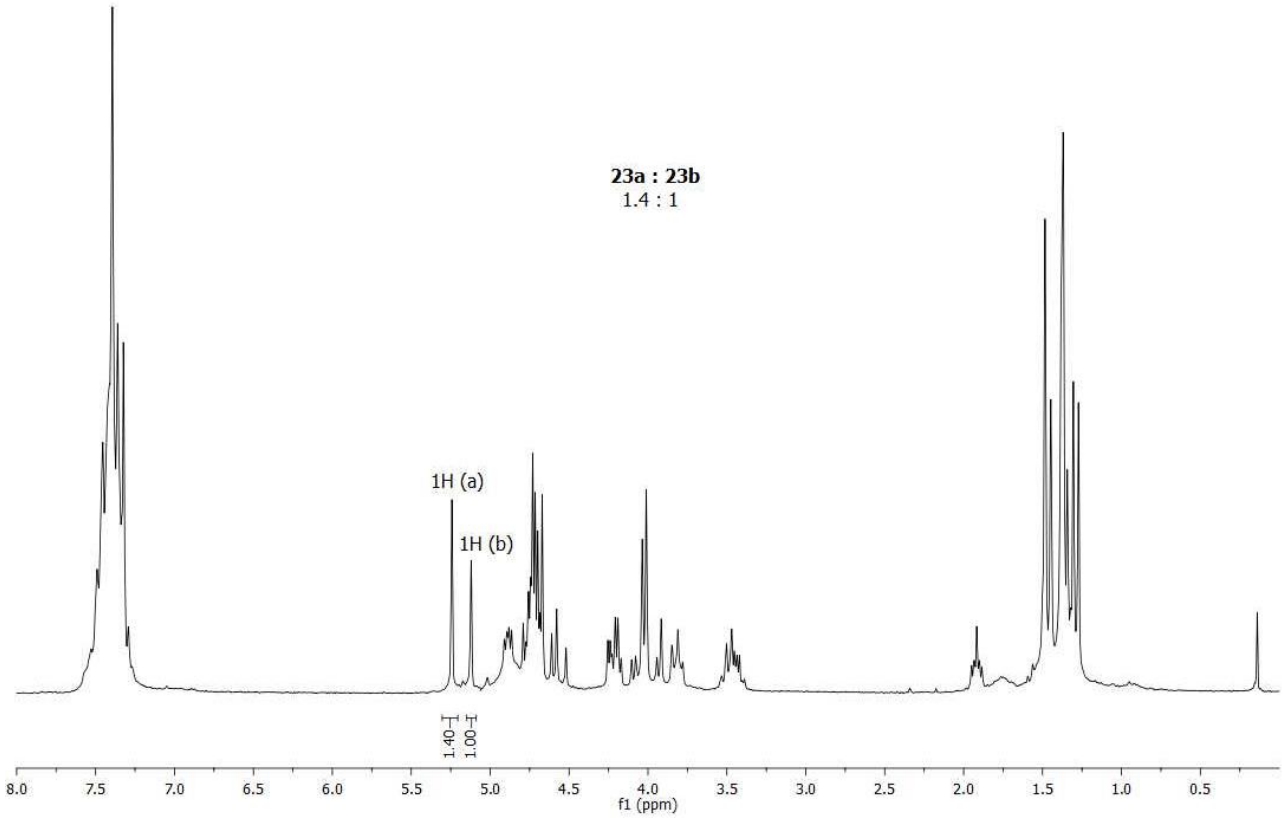


Figure S44: ^{1}H NMR spectrum of the crude reaction mixture (200 MHz, $CDCl_3$)

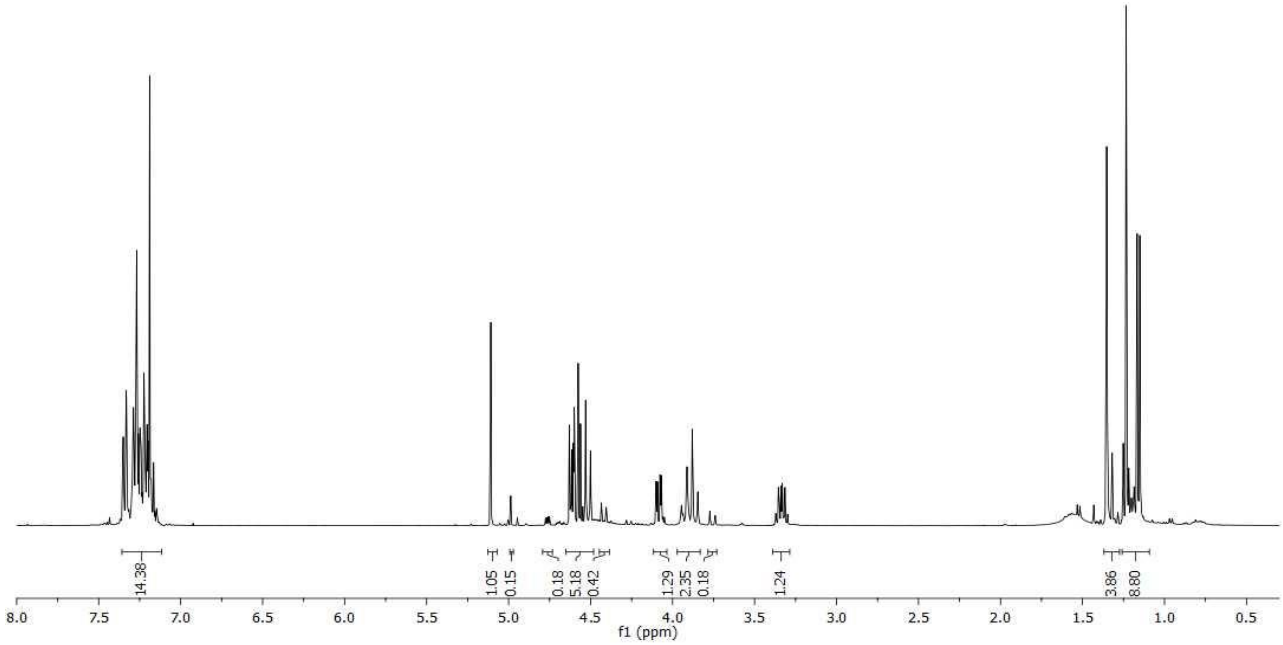


Figure S45: ^{1}H NMR spectrum of the 23a/23b mixture after FCC (400 MHz, $CDCl_3$)

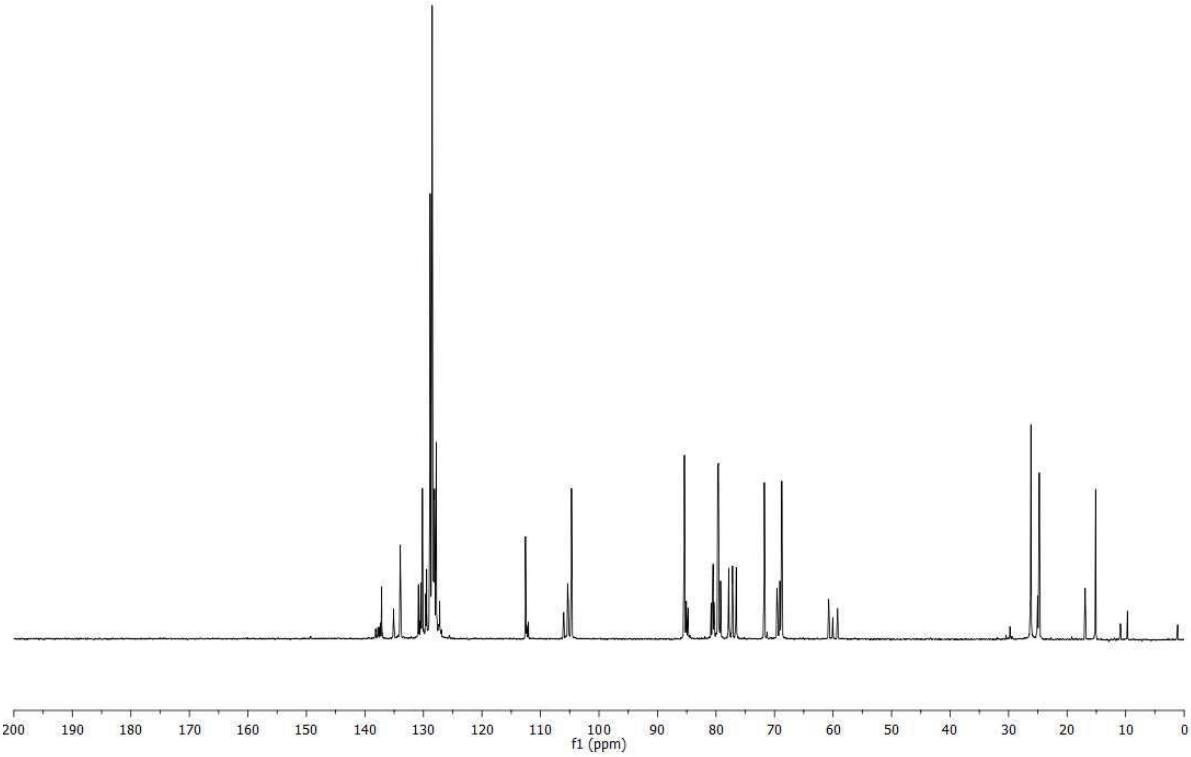
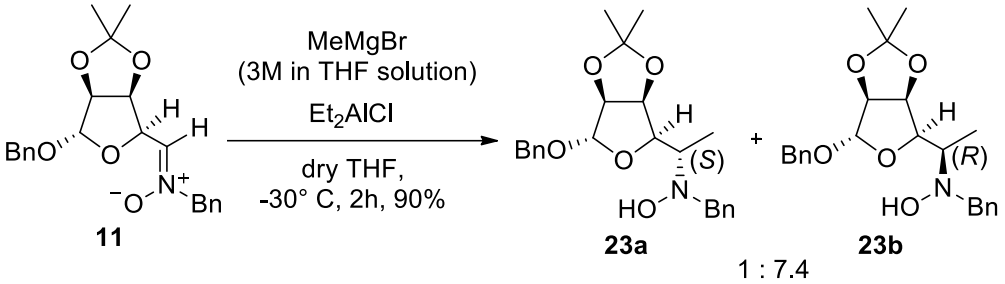


Figure S46: ^{13}C NMR spectrum of the 23a/23b mixture after FCC (100 MHz, $CDCl_3$)

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, Et_2AlCl (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 Et_2O (6 mL) and left stirring for 20 minutes. The phases were separated and the aqueous layer was extracted with Et_2O (2x10 mL). The combined organic layers were washed with brine (2x15 mL), dried with Na_2SO_4 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 ^{1}H-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** (R_f= 0.40, PEt/AcOEt 7:1).

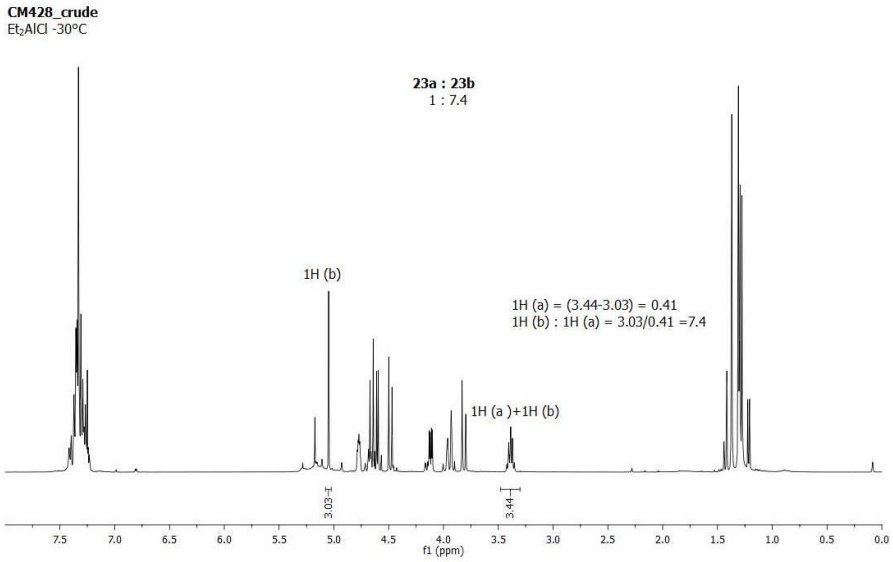
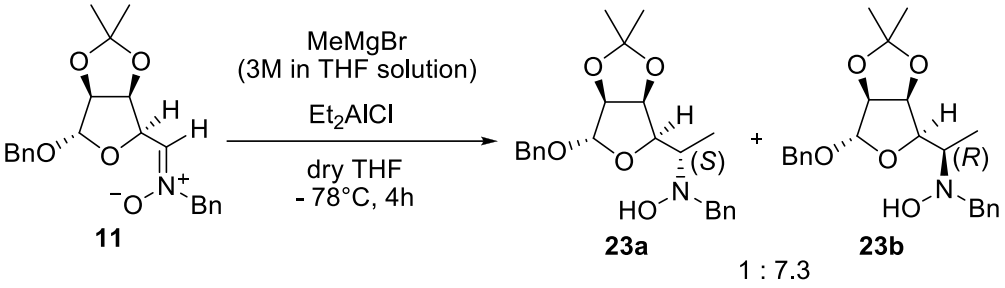


Figure S47: ^{1}H NMR spectrum of the crude reaction mixture with Lewis acid (400 MHz, $CDCl_3$)

[2] P. Merino, S. Anoro, S. Franco, J. M. Gascon, V. Martin, F. L. Merchan, J. Revuelta, T. Tejero and V. Tuñon, *Synth. Commun.* **2000**, *30*, 2989-3021.



To a stirred solution of nitrone **11** (120 mg, 0.31 mmol) in dry THF (9.3 mL) at room temperature, Et_2AlCl (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 Et_2O (6 mL) and left stirring for 20 minutes. The phases were separated and the aqueous layer was extracted with Et_2O (2x10 mL). The combined organic layers were washed with brine (2x15 mL), dried with Na_2SO_4 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 ^{1}H-NMR spectrum of the crude, Figure S48). The ^{1}H-NMR spectrum also confirmed the presence of some unreacted starting material.

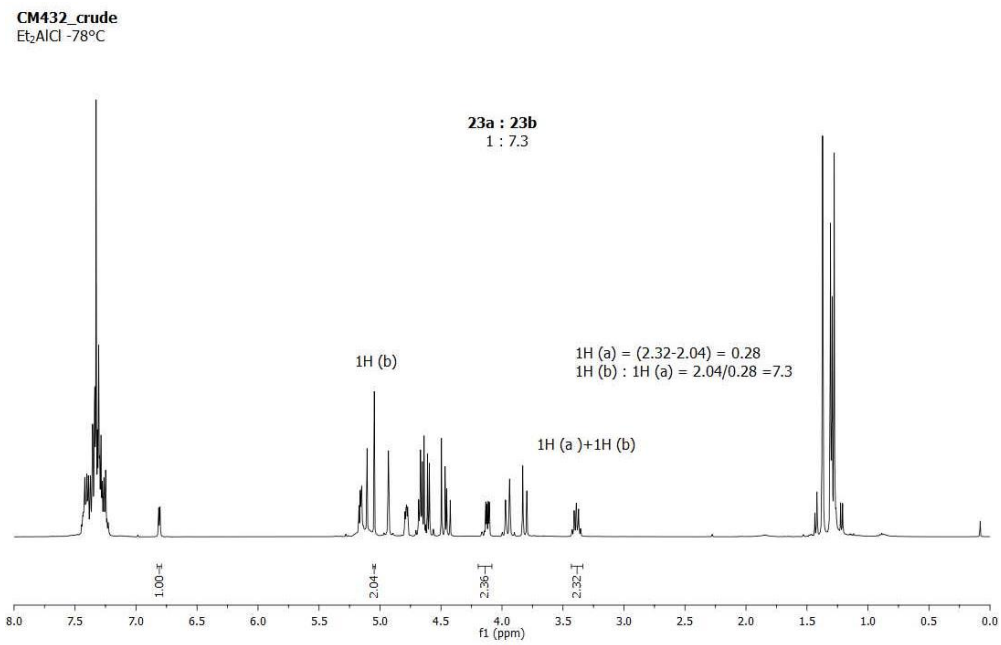
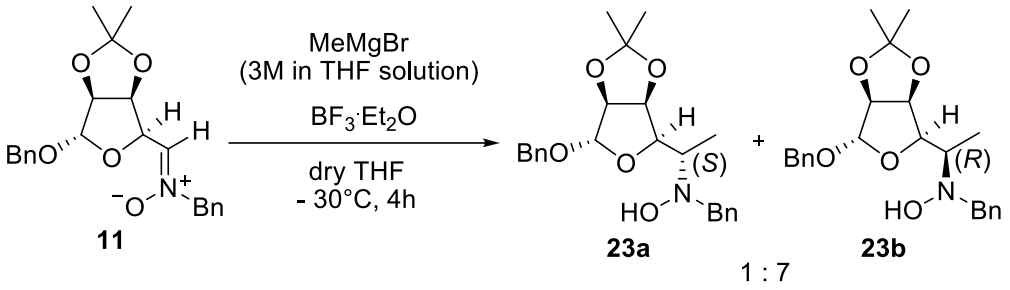


Figure S48: ^{1}H NMR spectrum of the crude reaction mixture with Lewis acid (400 MHz, $CDCl_3$)



To a stirred solution of nitrone **11** (171 mg, 0.45 mmol) in dry THF (14 mL) at room temperature, $BF_3 \cdot Et_2O$ (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_2O (6 mL) and left stirring for 20 minutes. The phases were separated and the aqueous layer was extracted with Et_2O (2x10 mL). The combined organic layers were washed with brine (2x15 mL), dried with Na_2SO_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).

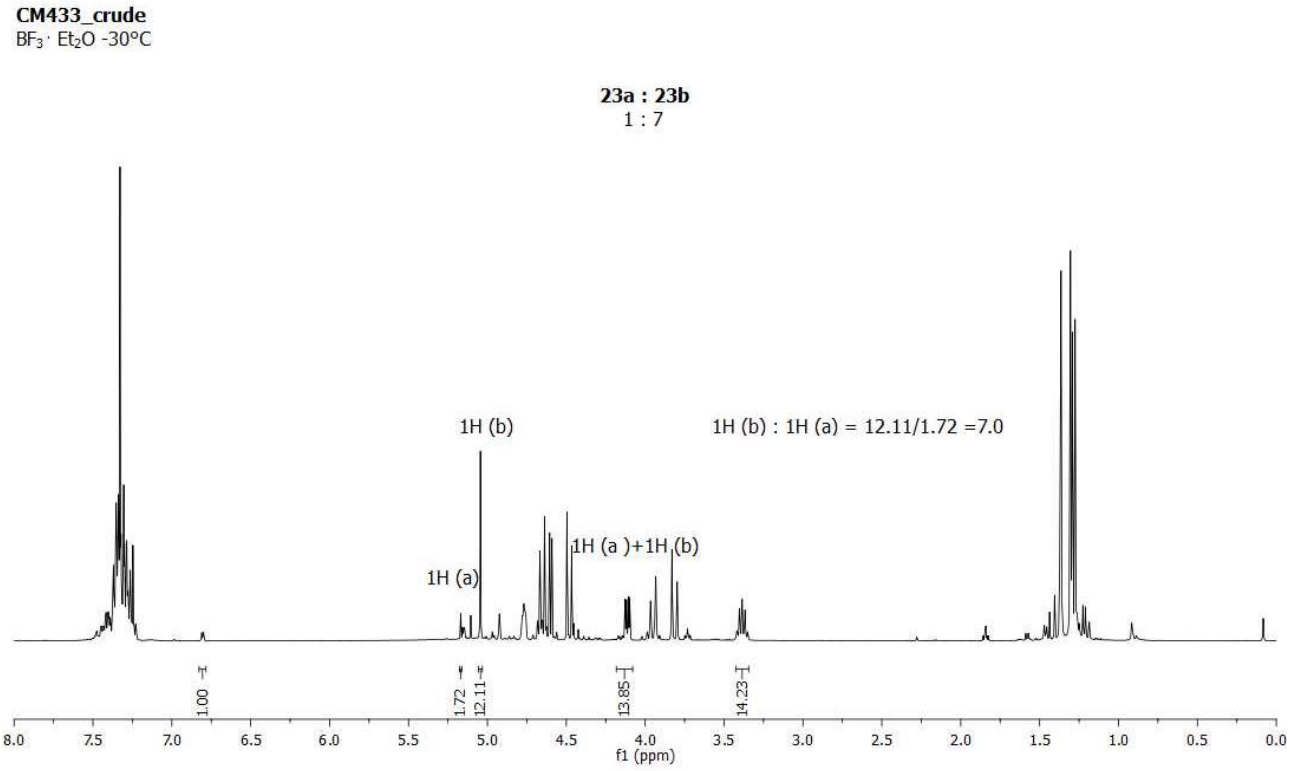
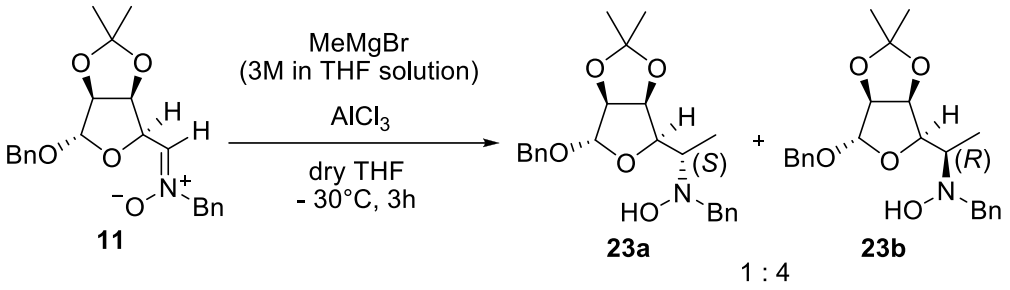


Figure S49: ^{1}H NMR spectrum of the crude reaction mixture with Lewis acid (400 MHz, $CDCl_3$)



To a stirred solution of nitrone **11** (120 mg, 0.31 mmol) in dry THF (9.3 mL) at room temperature, $AlCl_3$ (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 Et_2O (6 mL) and left stirring for 20 minutes. The phases were separated and the aqueous layer was extracted with Et_2O (2x10 mL). The combined organic layers were washed with brine (2x15 mL), dried with Na_2SO_4 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 ^{1}H-NMR spectrum of the crude, Figure S50).

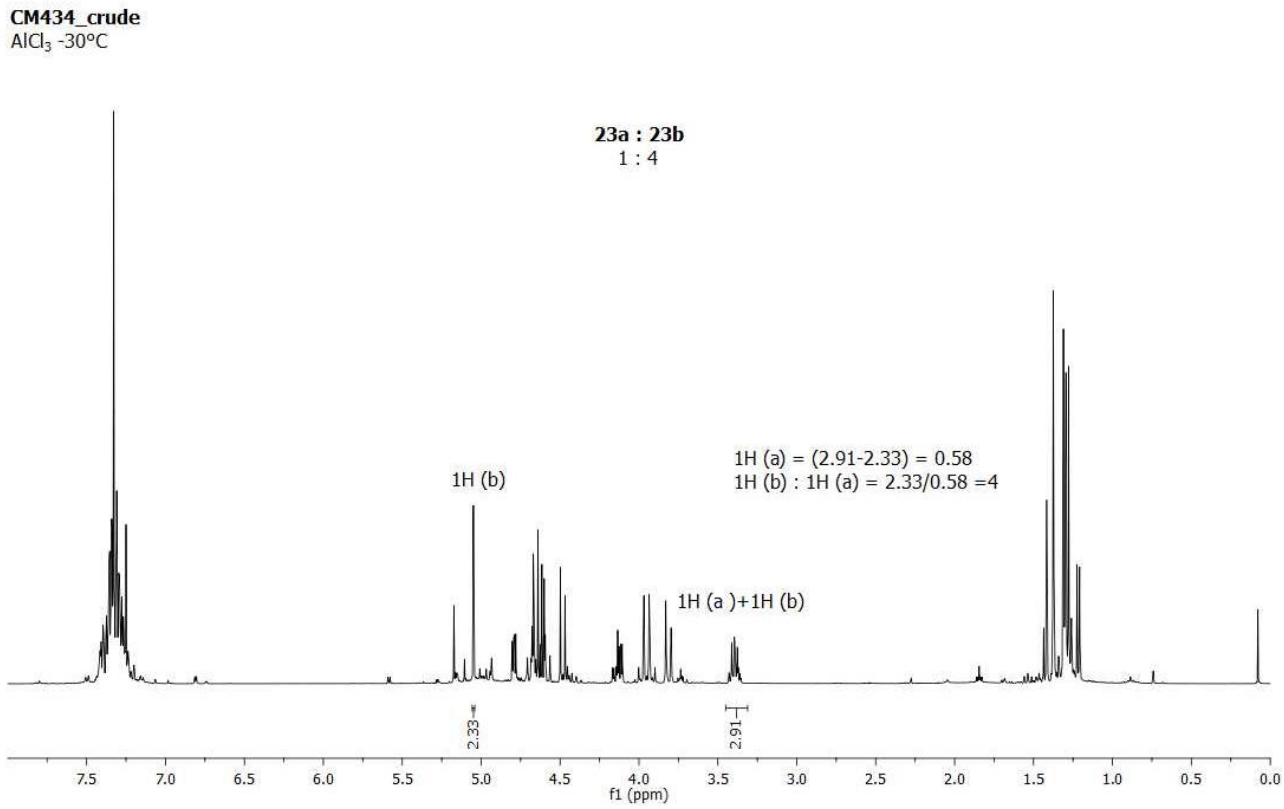
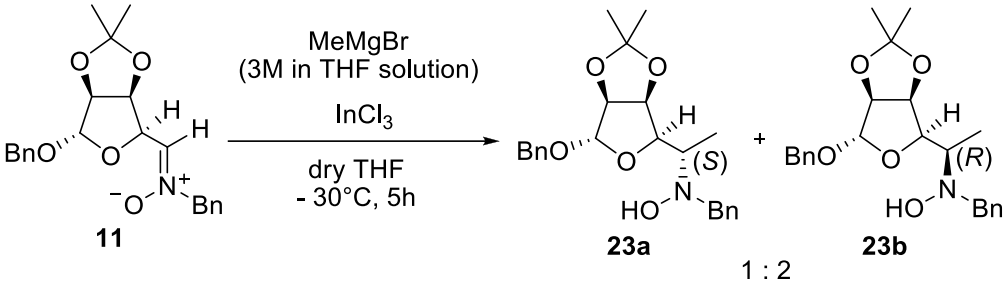


Figure S50: ^{1}H NMR spectrum of the crude reaction mixture with Lewis acid (400 MHz, $CDCl_3$)



To a stirred solution of nitrone **11** (120 mg, 0.31 mmol) in dry THF (9.3 mL) at room temperature, $InCl_3$ (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 Et_2O (6 mL) and left stirring for 20 minutes. The phases were separated and the aqueous layer was extracted with Et_2O (2x10 mL). The combined organic layers were washed with brine (2x15 mL), dried with Na_2SO_4 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 ^{1}H-NMR spectrum of the crude, Figure S51).

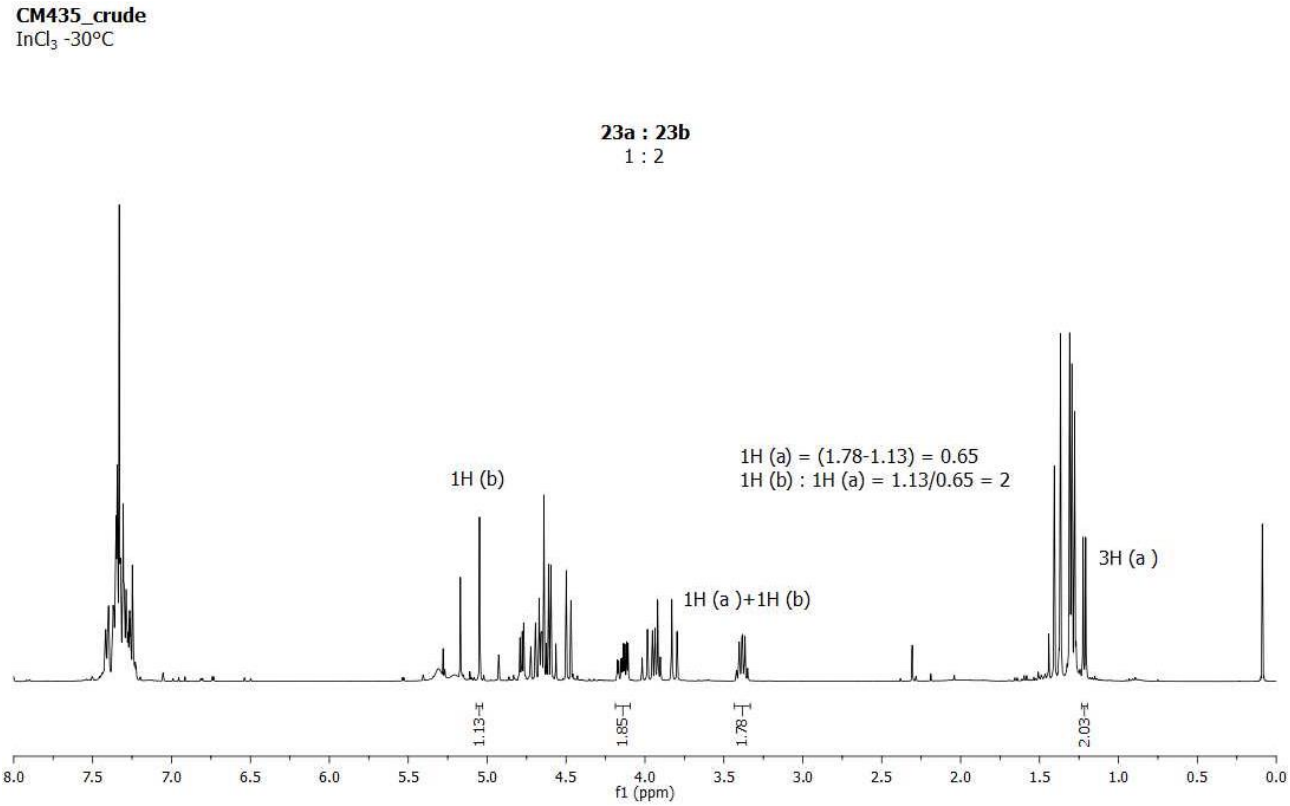
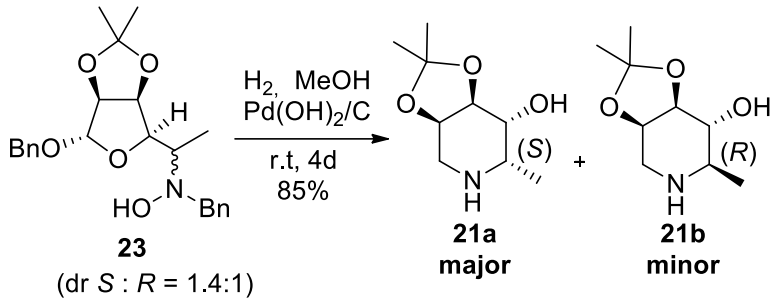


Figure S51: ^{1}H NMR spectrum of the crude reaction mixture with Lewis acid (400 MHz, $CDCl_3$)

Synthesis of (2*S*,3*R*,4*S*,5*R*)-3-hydroxy-4,5-*O*-(1-methylethylidene)-2-methyl-piperidine (21a) and (2*R*,3*R*,4*S*,5*R*)-3-hydroxy-4,5-*O*-(1-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 mixtute was filtered through Celite® and the solvent was removed under reduced pressure. The crude was purified on silica gel by FCC (CH_2Cl_2/MeOH/6% NH_3OH 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.

21b: $[\alpha]_D^{21}$ = −98.3 (*c* = 1.40, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ 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_3OD_3) δ 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 (CH_2Cl_2): ν = 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 $C_9H_{17}NO_3$ (187.24): C, 57.73; H, 9.15, N, 7.48; found: C, 57.37, H, 9.52, N, 7.78.

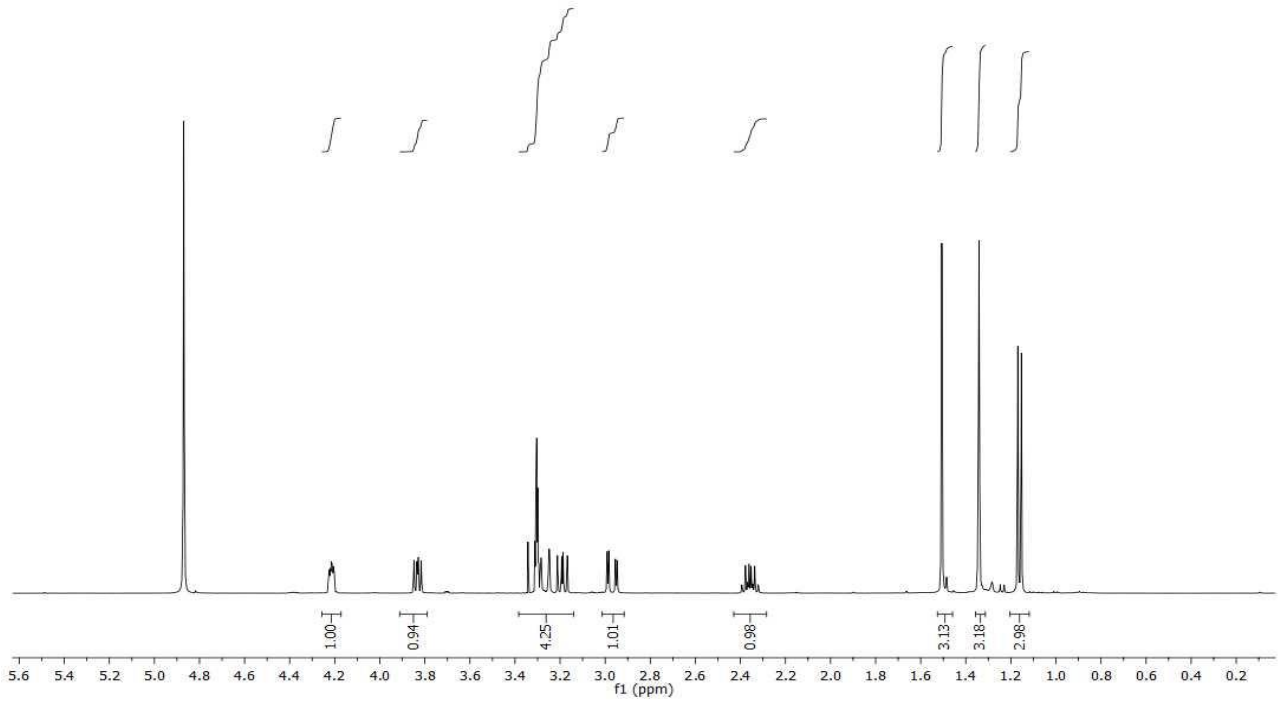


Figure S52: ^{1}H NMR spectrum of 21b (400 MHz, CD_3OD)

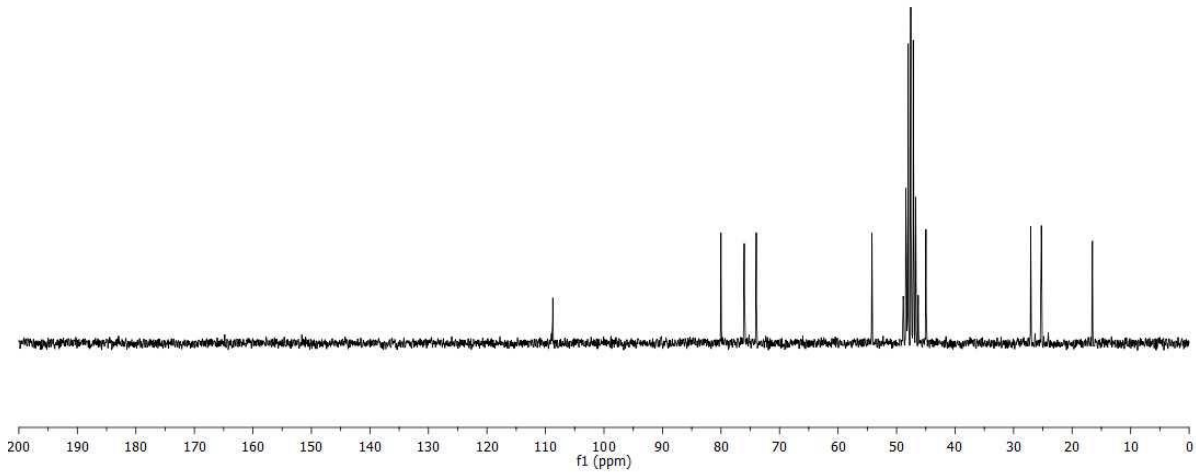
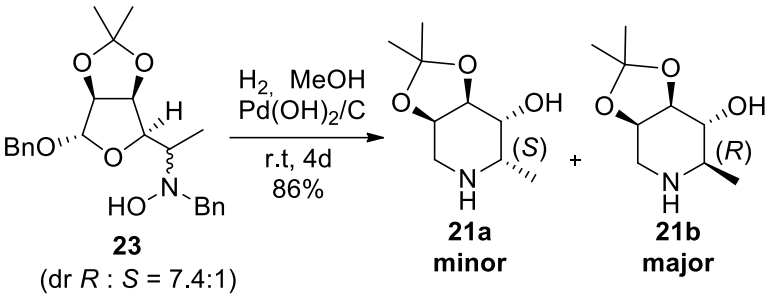


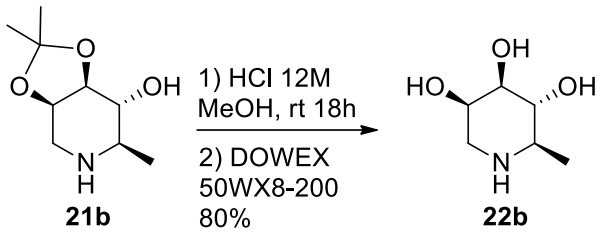
Figure S53: ^{13}C NMR spectrum of 21b (50 MHz, CD_3OD)

Synthesis of (2*S*,3*R*,4*S*,5*R*)-3-hydroxy-4,5-*O*-(1-methylethylidene)-2-methyl-piperidine (21a) and (2*R*,3*R*,4*S*,5*R*)-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}HNMR spectroscopy attested the sole presence of the final products **21**. The mixtute was filtered through Celite® and the solvent was removed under reduced pressure. The crude was purified on silica gel by FCC (CH_2Cl_2/MeOH/6% NH_3OH 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 (2*R*, 3*R*, 4*R*, 5*R*)-2-methylpiperidine-3,4,5-triol 22b[3]



A solution of **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 **22b**. The corresponding free amine was obtained by passing the hydrochloride salt through a DOWEX® 50XW8-100 ion-exchange resin. Elution with 6% ammonia afforded the free base **22b** (8 mg, 0.06 mmol, 80%).

$[\alpha]_D^{21}$ = −65.9 (*c* = 0.76 in H_2O). ^{1}H-NMR(400 MHz, CD_3OD) δ ppm = 3.86 (*b*s, 1H, H-5), 3.36 (dd, *J* =9.3, 3.4 Hz 1H, H-4), 3.27 (*p*t, *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): m/z 170.08 ([M+Na]+; 100).

[3] M. Sugiyama, Z. Hong, P. H. Liang, S. M. Dean, L. J. Whalen, W. A. Greenberg, C. H. Wong, *J. Am. Chem. Soc.* **2007**, *129*, 14811-14817.

Crystal structure determination for compounds 12a and 21a

12a:

$C_{16}H_{22}O_5$, M=294.33, Orthorhombic, space group P $2_12_12_1$, *a*=5.7984(1), *b*=7.8542(2), *c*=33.8291(8)Å, V=1540.5(3)Å^3, Z=4 D_c=1.269, μ=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:

$C_9H_{17}NO_3$, M=187.23, Orthorhombic, space group P $2_12_12_1$, *a*=5.5000(2), *b*=9.8160(3), *c*=18.5860(6)Å, V=1003.4(2)Å^3, Z=4 D_c=1.239, μ=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.

Donor-H	Donor...Acceptor	H...Acceptor	Donor-H-Acceptor
O2-H3a 0.820Å	O3-N1(1) 2.689Å	H3a-N1(1) 1.933Å	O3-H3a-N1(1) 152.87 deg

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Equivalent positions:
 ( 1)    x+1,+y,+z
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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.[4]

[4] N. Walker, D. Stuart, *Acta Cystallogr. Sect.A* **1983**, *39*, 158-166.

Direct methods of SIR2004[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,[6] by SHELXL2014.[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.

[5] M.C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G. L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, R. Spagna, *J. Appl. Cryst.* **2005**, *38*, 381-388.

[6] L. J. Farrugia, *J. Appl. Cryst.* **2012**, *45*, 849-854.

[7] G. M Sheldrick, *Acta Cryst.* **2015**, *C71*, 3-8.