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Glycal-mediated syntheses of enantiomerically pure 3-azido-2,3-dideoxy-hexopyranosides and 3-amino-2,3-dideoxy-hexopyranolactones

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Abstract—Methodology for the conversion of two commercially available glycals, D-galactal and D-glucal, into 3-azido-2,3-dideoxy-hexopyranosides and 3-amino-2,3-dideoxy-hexopyranolactones is reported. Using this strategy, templates suitable in combinatorial chemistry for the construction of a number of interesting biologically active molecules have been prepared. Key features of this strategy include the development of an efficient and original reaction sequence for the differential protection of the oxygen functionalities, the regio- and stereoselective introduction of the azido group, and the chemoselective oxidation of the acetal group.

1. Introduction

3-Azido-2,3-dideoxy carbohydrate derivatives are important precursors of bio-active compounds, such as glycosidic antibiotics,[1] antitumoural agents[2] and nucleosides against HIV.[3] A common method for synthesis of these sugars is based on the use of acyclic intermediates, with a significant advantage of this strategy being that the need for protective groups is minimized.[3,4] However, the majority of the syntheses of these sugars have been achieved from other carbohydrates, even though removal and manipulation of functionality from the starting carbohydrates were necessary and the reaction sequences rather long.[1a] Within this context, the use of glycals as synthons is appealing thanks to the lower density of functionalities.

Furthermore, the investigation is limited to the transformation of the glycals into α,β-unsaturated aldehydes, which are then employed as Michael acceptors in the conjugate addition of hydrazoic acid: as reported, such methods lead to a C1 and C3 isomeric mixture of compounds which need to be separated by chromatography.[5]

Herein we report the use of D-galactal **1a** and D-glucal **1b** in the synthesis of stereochemically pure 3-azido-2,3-dideoxy-methyl-hexopyranosides **5a** and **5b** and their conversion into 3-amino-δ-lactones **7a** and **7b**.

2. Results and discussion

We needed a mild and efficient protocol for the preparation of carbohydrate intermediates, such as **3** and **4**, equipped at the 3-position with a free hydroxyl group, suitable for the introduction of an azide function (Scheme 1). Kirsching et al. described the shortest route to 3-*O*-unprotected D-galactal **2a** by an oxidation–reduction sequence on the perbenzylated derivative mediated by iodine(III) reagents [PhI(OH)OTs]:[6] following a modified procedure in the oxidation step, we obtained compound **2a** in good yield (53%).[7] As this strategy on the D-*arabino* configuration leads to a C3 epimeric mixture,[7] a direct regioselective protection–deprotection sequence of the hydroxylic groups on D-glucal scaffold **1b** was required.

The best results have been achieved using TBDPSCl for the primary alcohol in excellent yield and BzCl for the allylic position, both highly selective and easy to remove. As previous attempts to introduce a benzylic group on C4 were unsuccessful due to steric effects (using benzylic bromide with potassium hydride or silver oxide as bases), we employed 2-methoxyethoxy-methyl-chloride with good results. Finally, treatment with

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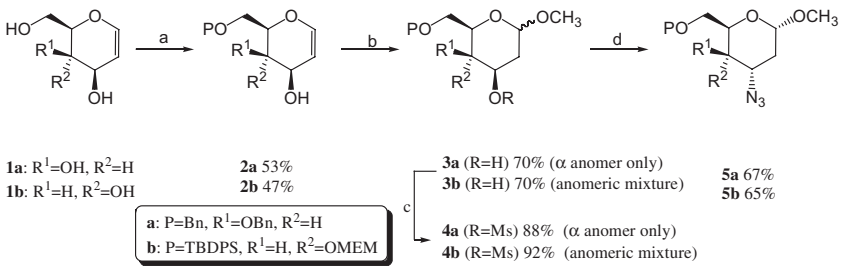


Scheme 1. Synthesis of **5a** and **b**. Reagents and conditions: (a) (i) 1.1 equiv TBDPSCl, 2.5 equiv imidazole, DMF, $T = 0\,^{\circ}C$ to rt, 1 h, (ii) 1 equiv BzCl, pyr., $T = -40\,^{\circ}C$ to rt, 1 h, 67% for two steps, (iii) 4 equiv MEMCl, 2.7 equiv DIPEA, CH_2Cl_2, rt, overnight, (iv) 5 equiv MeONa, MeOH, rt, 3 h, 70% for two steps; (b) 1.5 equiv MeOH, $PPh_3{\cdot}HBr$ cat., CH_2Cl_2, rt, 45 min; (c) 5 equiv MsCl, 5 equiv pyr., CH_2Cl_2, $T = 0\,^{\circ}C$ to rt, 24 h; (d) 3 equiv Bu_4NCl, 3.5 equiv NaN_3, toluene, reflux, 24 h.

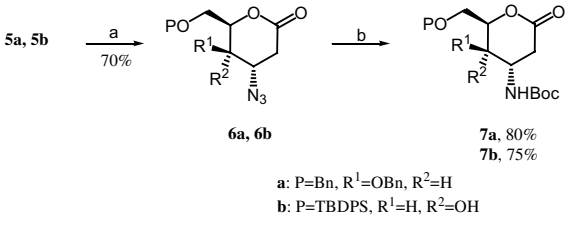
CH_3ONa led to the 3-*O*-unprotected D-*arabino*-configurated glycal **2b**. So far this procedure is the simplest and the highest yielding method to this scaffold.

On the protected glycals we investigated the stereoselective introduction of a masked amino functionality at C3. We reckoned that a Mitsunobu-type reaction[8] would be the transformation for this purpose, but Kirsching et al. obtained 3-azide-L-fucal with a yield far from satisfactory (only 15%).[6] Furthermore, efforts to convert the allylic hydroxy group into a better leaving group, such as mesylate or triflate, to employ in a substitution with NaN_3, failed.

To circumvent these problems, glycals **2a** and **2b** were first converted into 2-deoxy-methylpyranosides **3a** and **3b** by the addition of MeOH catalyzed by triphenylphosphine hydrobromide (TPHB),[9] leading to the predominant formation of an α-anomer in good yields. Subsequent treatment with MsCl in CH_2Cl_2 and S_N2 substitution with sodium azide gave successfully the stereochemically pure azides **5a** and **5b**: interestingly, the thermodynamically more stable α-anomer was selected under the azidation conditions.

The stereochemistry of **5a** and **5b** was established on the basis of ^1H NMR data: only one weak coupling of H-1 proton with axially oriented H-2 ($J_{1,2ax}$ 4.4 Hz) is diagnostic of the α-anomeric centre; $J_{2ax,3}$ 4.4 Hz is characteristic for equatorially oriented H-3 proton in D-*xylo* **5a** and D-*ribo* **5b** configurations.[5]

As a further synthetic application, **5a** and **5b** were converted into 3-amino-δ-lactones **7a** and **7b**, chiral synthons of hydroxy amino acids[10] and β-lactams:[1b] Under the oxidation conditions with *m*CPBA and $BF_3{\cdot}O(C_2H_5)_2$, cleavage of the MEM group in **6b** occurred (Scheme 2).[11]



Scheme 2. Synthesis of **7a** and **b**. Reagents and conditions: (a) 3 equiv *m*CPBA, 3 equiv $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 45 min; (b) 1.5 equiv Boc_2O, H_2, Pd/C, AcOEt, rt, 4 h.

3. Conclusion

In conclusion, an efficient synthesis of enantiomerically pure 3-azido-2,3-dideoxy-hexopyranosides, useful precursors of bioactive compounds, has been accomplished starting from D-galactal and D-glucal. Furthermore, this short sequence provides an access to 3-amino-2,3-dideoxy-hexopyranolactones, intermediates of biologically interesting hydroxy amino acids and β-lactams.

4. Experimental

4.1. General

^1H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) spectra were recorded on a Varian Gemini 200 spectrometer with $CDCl_3$ as the solvent and as the internal standard. IR spectra were recorded on a Shimadzu IR-470 infrared spectrophotometer. HRMS spectra were recorded with a Micromass Q-TOF *micro* mass spectrometer (Waters). Optical rotations were measured using a sodium D line on a DIP 370 Jasco digital polarimeter. Yields are given for isolated products after column chromatography showing a single spot on TLC and no detectable impurities in ^1H NMR spectrum. All reactions were performed under an inert atmosphere of argon in flame-dried glassware. All solvents and commercially available reagents were used without purification unless otherwise noted. All reactions were monitored by thin-layer chromatography (TLC) carried out on Merck F-254 silica glass plates visualized with UV/light and heat-gun treatment with a 2 M H_2SO_4 solution. Column chromatography was performed with Merck silica gel 60 (230–400 mesh). Compound **2a** was prepared according to the literature.[7]

4.2. 1,5-Anhydro-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-4-*O*-(2-methoxyethoxymetyl)-D-*arabino*-hex-1-enitol 2b

A solution of **1b** (200.0 mg, 1.37 mmol) in DMF (2.5 mL) was treated with imidazole (233 mg, 3.42 mmol) followed by TBDPSCl (0.39 mL, 1.51 mmol), under argon at 0 °C. The reaction was allowed to warm up to room

temperature over a period of 1 h until no starting material was detected on TLC. The reaction mixture was diluted with Et_2O (20 mL) and washed with a saturated aqueous $NaHCO_3$ solution (2×5 mL) and water (3×5 mL). The organic phase was dried over Na_2SO_4 and then concentrated in vacuo. The crude product was dissolved, under argon, in dry pyridine (3 mL) and BzCl (0.16 mL, 1.37 mmol) then added dropwise at −40 °C. The reaction was allowed to warm up to room temperature and stirred for 1 h, then diluted with Et_2O (20 mL), washed with a saturated aqueous $CuSO_4$ solution (2×10 mL) and water (2×10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in dry CH_2Cl_2 (5 mL) and treated with DIPEA (0.21 mL) and MEMCl (0.19 mL, 1.72 mmol). The reaction was stirred at room temperature overnight until no starting material was detected on TLC, then diluted with CH_2Cl_2 (15 mL), washed with water (3×5 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in MeOH (5 mL) and treated with MeONa (69 mg, 2.15 mmol) for 3 h at room temperature. The solvent was removed in vacuo, the residue diluted with AcOEt (20 mL) and washed with water (3×5 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, hexane/EtOAc 30:1) to give **2b** as a colourless oil (0.64 mmol, 303 mg, 47%). $[\alpha]_D = -17.0$ (*c* 1.2, $CHCl_3$). IR ν_{max} ($CHCl_3$)/cm^{-1}: 3290 (OH). ^{1}H NMR (δ, $CDCl_3$): 7.80–7.66 (m, 4H, Ar*H*), 7.51–7.27 (m, 6H, Ar*H*), 6.24 (dd, 1H, $J_{1,2} = 5.8$ Hz, $J_{1,3} = 1.5$ Hz, H-1), 4.93 (d, 1H, $J = 7.3$ Hz, OCH_2O), 4.83 (d, 1H, $J = 7.3$ Hz, OCH_2O), 4.79 (dd, 1H, $J_{1,2} = 5.8$ Hz, $J_{2,3} = 2.2$ Hz, H-2), 4.54–4.42 (br s, 1H, O*H*, disappears after D_2O addition), 4.05–3.55 (m, 9H, OCH_2CH_2O, 2H-6, H-5, H-4, H-3), 3.41 (s, 3H, CH_3O), 1.15 (s, 9H, 3CH_3). ^{13}C NMR (δ, $CDCl_3$): 144.1 (*C*-1), 135.7, 135.5, 133.6, 133.2, 129.6, 128.7, 127.6, 127.5 (Ar), 102.2 (*C*-2), 97.0 (OCH_2O), 80.0 (*C*-4), 77.1 (*C*-3), 71.4 (OCH_2), 68.5 (*C*-5), 67.6 (OCH_2), 62.3 (*C*-6), 59.0 (CH_3O), 26.8 (CH_3), 19.3 (C_{quat}). Anal. Calcd for $C_{26}H_{36}O_6Si$: C, 66.07; H, 7.68. Found: C, 66.02; H, 7.73.

4.3. Methyl 4,6-di-*O*-benzyl-2-deoxy-α-D-*lyxo*-hexopyranoside 3a

A solution of **2a** (179 mg, 0.55 mmol) in dry CH_2Cl_2 (4 mL) was treated with PPh_3·HBr (14 mg, 0.041 mmol) and MeOH (0.03 mL, 0.82 mmol). The reaction was stirred for 45 min at room temperature until no starting material was detected on TLC. The mixture was diluted with CH_2Cl_2 (20 mL), washed with a saturated aqueous $NaHCO_3$ solution (3×5 mL) and brine (3×5 mL), then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, hexane/EtOAc 10:1) to give **3a** as a colourless oil (136 mg, 0.38 mmol, 70%). $[\alpha]_D = +73.0$ (*c* 1.3, $CHCl_3$). IR ν_{max} ($CHCl_3$)/cm^{-1}: 3360 (OH). ^{1}H NMR (δ, $CDCl_3$): 7.43–7.27 (m, 10H, Ar*H*), 4.84 (d 1H, $J_{1,2} = 2.2$ Hz, H-1), 4.79–4.49 (m, 4H, $2 \times$ CH_2Ph), 4.08–3.94 (m, 2H, H-3, H-5), 3.82 (d, 1H, $J_{3,4} = 2.9$ Hz, H-4), 3.69 (dd, 1H, $J_{6,6'} = 8.8$ Hz, $J_{5,6} = 7.3$ Hz, H-6), 3.65 (dd, 1H, $J_{6,6'} = 8.8$ Hz, $J_{5,6'} = 6.6$ Hz, H-6′), 3.35 (s, 3H, CH_3O), 1.91 (dd, 2H, $J_{2,3} = 8.4$ Hz, $J_{1,2} = 2.2$ Hz, 2H-2), 1.72 (br s, 1H, O*H* disappears after D_2O addition). ^{13}C NMR (δ, $CDCl_3$): 138.4, 137.9, 128.5, 128.4, 127.9, 127.9, 127.8, 127.7 (Ar), 98.8 (*C*-1), 76.4 (*C*-4), 75.1, 73.5 (CH_2Ph), 69.3 (*C*-3), 69.2 (*C*-6), 65.7 (*C*-5), 54.8 (OCH_3), 34.4 (*C*-2). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.42; H, 7.37.

4.4. Methyl 6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-4-*O*-(2-methoxyethoxymetyl)-D-*arabino*-hexopyranoside 3b, as an inseparable α,β-anomeric mixture

Compound **3b** (112 mg, 0.22 mmol, 70%) was obtained from **2b** (150 mg, 0.32 mmol) following the procedure described for **3a**. IR ν_{max} ($CHCl_3$)/cm^{-1}: 3120 (OH). ^{1}H NMR (δ, $CDCl_3$): (α,β mixture 3:1) 7.82–7.68 (m, Ar*H*), 7.48–7.35 (m, Ar*H*), 4.87–4.71 (m, OCH_2O, H1$_\alpha$), 4.61–4.50 (br s, O*H*, disappears after D_2O addition), 4.44 (dd, $J_{1,2eq} = 2.2$ Hz, $J_{1,2ax} = 10.2$ Hz, H-1$_\beta$), 4.06–3.32, 3.75–3.46 (2m, H-3, H-4, H-5, 2H-6, OCH_2CH_2O), 3.41 (s, OCH_3), 3.33 (s, CH_3O), 2.32 (ddd, $J_{2ax,2\ eq} = 9.5$ Hz, $J_{1,2eq} = 2.2$ Hz, $J_{3,2eq} = 5.8$ Hz, H-2$_{\alpha eq}$), 2.22 (dd, $J_{2ax,2eq} = 13.2$ Hz, $J_{3,2eq} = 5.1$ Hz, H-2$_{\beta eq}$), 1.78–1.51 (m, H2$_{\alpha ax}$, H2$_{\beta ax}$), 1.08 (s, CH_3). ^{13}C NMR (δ, $CDCl_3$): (α anomer) 135.8, 134.5, 129.9, 129.8, 128.6, 128.5, 128.3, 127.9 (Ar), 98.3 (*C*-1), 100.7 (OCH_2O), 83.1 (*C*-4), 75.4 (*C*-3), 71.4 (OCH_2), 67.8 (*C*-5), 66.5 (OCH_2), 63.1 (*C*-6), 58.9 (CH_3O), 54.4 (OCH_3), 36.7 (*C*-2), 26.8 (CH_3), 19.3 (C_{quat}). Anal. Calcd for $C_{27}H_{40}O_7Si$: C, 64.26; H, 7.99. Found: C, 64.22; H, 8.02.

4.5. Methyl 4,6-di-*O*-benzyl-2-deoxy-3-*O*-mesyl-α-D-*lyxo*-hexopyranoside 4a

MsCl (1.8 mmol, 0.14 mL) was added dropwise to a solution of **3a** (129 mg, 0.36 mmol) in dry CH_2Cl_2 (3 mL) and dry pyridine (0.15 mL), under argon at 0 °C. The reaction was allowed to warm up to room temperature and stirred overnight until no starting material was detected on TLC. The reaction mixture was diluted with CH_2Cl_2 (15 mL), then washed with a saturated aqueous $CuSO_4$ solution (5 mL), brine (3×5 mL) and water (3×5 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, hexane/EtOAc 8:1) to give **4a** as a colourless oil (138 mg, 0.31 mmol, 88%). $[\alpha]_D = +66.0$ (*c* 1.2, $CHCl_3$). ^{1}H NMR (δ, $CDCl_3$): 7.45–7.26 (m, 10H, Ar*H*), 5.13 (ddd, 1H, $J_{3,2ax} = 12.4$ Hz, $J_{3,2eq} = 5.1$ Hz, $J_{3,4} = 2.9$ Hz, H-3), 4.87 (d, 1H, $J_{1,2ax} = 3.6$ Hz, H-1), 4.70–4.40 (m, 4H, $2 \times$ CH_2Ph), 4.09–3.93 (m, 2H, H-4, H-5), 3.59 (d, 2H, $J_{5,6} = 5.9$ Hz, 2H-6), 3.36 (s, 3H, OCH_3), 2.99 (s, 3H, CH_3), 2.43 (td, 1H, $J_{2eq,2ax} = J_{3,2ax} = 12.4$ Hz, $J_{1,2ax} = 3.6$ Hz, H-2$_{ax}$), 2.05 (dd, 1H, $J_{2eq,2ax} = 12.4$ Hz, $J_{3,2eq} = 5.1$ Hz, H-2$_{eq}$). ^{13}C NMR (δ, $CDCl_3$): 138.1, 137.7, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6 (Ar), 98.2 (*C*-1), 76.3 (*C*-3), 74.8 (CH_2Bn), 74.1 (*C*-4), 73.34 (CH_2Ph), 69.2, 68.7 (*C*-5, *C*-6), 54.7 (OCH_3), 38.3 (CH_3), 31.5 (*C*-2). Anal. Calcd for $C_{22}H_{28}O_7S$: C, 60.53; H, 6.47; S, 7.35. Found: C, 60.50; H, 6.52; S, 7.31.

4.6. Methyl 6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-3-*O*-mesyl-4-*O*-(2-methoxyethoxymetyl)-D-*arabino*-hexopyranoside 4b, as an inseparable α,β-anomeric mixture

Compound **4b** (100 mg, 0.18 mmol, 92%) was obtained from **3b** (100 mg, 0.2m·mol) following the procedure described for **4a**. ^{1}H NMR (δ, $CDCl_3$): (3:1 α,β-anomeric mixture) 7.79–7.69 (m, Ar*H*), 7.51–7.33 (m, Ar*H*), 5.04–4.60 (m, OCH_2O, H-1$_\alpha$, H-3), 4.44 (dd, $J_{1,2eq}$ = 2.2 Hz, $J_{1,2ax}$ = 9.5 Hz, H-1$_\beta$), 3.98–3.38 (m, H-4, H-5, 2H-6, OCH_2CH_2O), 3.53 (s, OCH_3), 3.34 (s, CH_3O), 3.32 (s, CH_3O), 3.30 (s, OCH_3), 3.11 (s, CH_3SO$_2$), 3.01 (s, CH_3SO$_2$), 2.54 (ddd, $J_{2ax,2eq}$ = 10.2 Hz, $J_{1,2eq}$ = 2.2 Hz, $J_{3,2eq}$ = 5.1 Hz, H-2$_{\beta eq}$), 2.46 (ddd, $J_{2ax,2eq}$ = 12.4 Hz, $J_{1,2eq}$ = 1.4 Hz, $J_{3,2eq}$ = 5.1 Hz, H-2$_{\alpha eq}$), 1.99 (dd, $J_{2ax,2eq}$ = 12.4 Hz, $J_{1,2ax}$ = 3.7 Hz, H-2$_{\alpha ax}$), 1.89 (m, H-2$_{\beta ax}$), 1.08 (s, CH_3). ^{13}C NMR (δ, $CDCl_3$): 135.8, 135.7, 135.5, 133.4, 133.2, 129.6, 127.6, 127.5 (Ar), 103.6 (*C*-1$_\beta$), 99.7, 97.4 (O*C*H$_2$O), 97.2 (*C*-1$_\alpha$), 80.5, 79.7, 75.6, 75.1, 74.6, 73.9, 71.8, 71.5, 68.2, 67.5, 63.1 (*C*-6$_\alpha$), 62.8 (*C*-6$_\beta$), 58.8 (*C*H$_3$O$_\alpha$), 56.5 (*C*H$_3$O$_\beta$), 54.5 (O*C*H$_{3\alpha}$), 51.5 (O*C*H$_{3\beta}$), 38.7 (O$_2$S*C*H$_{3\beta}$), 38.3 (O$_2$S*C*H$_{3\alpha}$), 37.8 (*C*-2$_\beta$), 36.7 (*C*-2$_\alpha$), 26.7 (*C*H$_3$), 19.3 (C_{quat}). Anal. Calcd for $C_{28}H_{42}O_9SSi$: C, 57.71; H, 7.26; S, 5.50. Found: C, 57.64; H, 7.30; S, 5.45.

4.7. Methyl 3-azido-4,6-di-*O*-benzyl-2-deoxy-α-D-*xylo*-hexopyranoside 5a

A solution of **4a** (287 mg, 0.66 mmol) in dry toluene (7 mL) was treated with Bu_4NCl (550 mg, 1.98 mmol) and then with NaN_3 (150 mg, 2.31 mmol). The reaction was stirred at reflux for 24 h until no starting material was detected on TLC. The reaction mixture was diluted with AcOEt (20 mL), then washed with brine (3 × 5 mL) and water (3 × 5 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, hexane/EtOAc 50:1) to give **5a** as a colourless oil (169 mg, 0.44 mmol, 67%). $[\alpha]_D$ = +94.0 (*c* 1.5, $CHCl_3$). IR ν_{max} ($CHCl_3$)/cm^{-1}: 2130 (N_3). ^{1}H NMR (δ, $CDCl_3$): 1.87 (dd, 1H, $J_{2eq,2ax}$ = 14.6 Hz, $J_{3,2eq}$ = 1.5 Hz, H-2$_{eq}$); 2.26 (td, 1H, $J_{2eq,2ax}$ = 14.6 Hz, $J_{2ax,3}$ = 4.4 Hz, $J_{1,2ax}$ = 4.4 Hz, H-2$_{ax}$); 3.42 (s, 3H, OCH_3); 3.65 (d, 2H, $J_{5,6}$ = 6.6 Hz, 2H-6); 3.84–3.91 (m, 1H, H-3); 4.27 (dd, 1H, $J_{5,6}$ = 6.6 Hz, $J_{4,5}$ = 1.5 Hz, H-5); 4.46–4.63 (m, 4H, 2 × CH_2Ph); 4.67 (dd, 1H, $J_{4,5}$ = 1.5 Hz, $J_{4,3}$ = 3.7 Hz, H-4); 4.80 (br d, 1H, $J_{1,2ax}$ = 4.4 Hz, H-1); 7.27–7.44 (m, 10H, Ar*H*). ^{13}C NMR (δ, $CDCl_3$): 29.1 (*C*-2); 54.4, 55.1 (O*C*H$_3$, *C*-3); 65.2 (*C*-6); 69.1 (*C*-5); 72.8, 73.2, (*C*H$_2$Ph); 73.3 (*C*-4); 96.7 (*C*-1); 127.4, 127.6, 127.9, 128.0, 128.2, 128.3, 137.8, 138.1 (Ar). Anal. Calcd for $C_{21}H_{25}N_3O_4$: C, 65.78; H, 6.57; N, 10.96. Found: C, 65.75; H, 6.61; N, 11.01.

4.8. Methyl 3-azido-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-4-*O*-(2-methoxyethoxymetyl)-α-D-*ribo*-hexopyranoside 5b

Compound **5b** (144 mg, 0.27 mmol, 65%) was obtained from **4b** (245 mg, 0.42 mmol) following the procedure described for **5a**. $[\alpha]_D$ = −35.0 (*c* 1.3, $CHCl_3$). IR ν_{max} ($CHCl_3$)/cm^{-1}: 2120 (N_3). ^{1}H NMR (δ, $CDCl_3$): 1.08 (s, 9H, 3 × CH_3) 2.05 (td, 1H, $J_{2eq,2ax}$ = 15.4 Hz, $J_{3,2ax}$ = $J_{1,2ax}$ 4.4 Hz, H-2$_{ax}$); 2.15 (dd, 1H, $J_{2eq,2ax}$ = 15.4 Hz, $J_{2eq,3}$ = 2.2 Hz, H-2$_{eq}$); 3.37, 3.38 (2s, 6H, OCH_3, CH_3O); 3.43–3.69, 3.78–4.10 (2m, 8H, H-4, H-5, 2H-6, OCH_2CH_2O); 4.21 (m, 1H, $J_{3,4}$ = 2.9 Hz, H-3); 4.74 (d, 1H, $J_{1,2ax}$ = 4.4 Hz, H-1); 4.81, 4.88 (2d, 2H, *J* = 7.3 Hz, OCH_2O), 7.32–7.50 (m, 6H, Ar*H*); 7.68–7.82 (m, 4H, Ar*H*). ^{13}C NMR (δ, $CDCl_3$): 19.2 (C_{quat}); 26.7 (*C*H$_3$); 32.7 (*C*-2); 54.9, 57.1, 58.82 (*C*H$_3$O, O*C*H$_3$, *C*-3); 63.2 (*C*-6); 67.5 (*C*-5); 67.5 (O*C*H$_2$-*C*H$_2$O); 71.5; 73.6 (*C*-4); 95.5 (O*C*H$_2$O); 96.5 (*C*-1); 127.4, 127.5, 128.3, 129.4, 133.1, 133.5, 135.4, 135.7 (Ar). Anal. Calcd for $C_{27}H_{39}N_3O_6Si$: C, 61.22; H, 7.42; N, 7.93. Found: C, 61.18; H, 7.50; N, 7.95.

4.9. 3-Azido-4,6-di-*O*-benzyl-2,3-dideoxy-D-idonolactone 6a

To a solution of **5a** (165 mg, 0.43 mmol) in dry CH_2Cl_2 (5 mL) MCPBA (225 mg, 1.31 mmol) and BF_3·OEt_2 (0.16 mL, 1.31 mmol) were added at room temperature. The reaction was stirred for 45 min until no starting material was detected on TLC. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and then washed with a saturated aqueous $NaHCO_3$ solution (3 × 5 mL), brine (3 × 5 mL) and water (3 × 5 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, hexane/EtOAc 10:1) to give **6a** as a colourless oil (110 mg, 0.30 mmol, 70%). $[\alpha]_D$ = +65.0 (*c* 1.1, $CHCl_3$). IR ν_{max} ($CHCl_3$)/cm^{-1}: 2120 (N_3), 1750 (CO). ^{1}H NMR (δ, $CDCl_3$): 7.48–7.28 (m, 10H, Ar*H*), 4.75–4.47 (m, 5H, 2 × CH_2Ph, H-5), 4.16 (m, 1H, H-3), 3.85–3.80 (m, 1H, H-4), 3.83 (dd, 1H, $J_{6,6'}$ = 9.7 Hz, $J_{6,5}$ = 5.4 Hz, H-6), 3.75 (dd, 1H, $J_{6,6'}$ = 9.7 Hz, $J_{6',5}$ = 4.5 Hz, H-6′), 3.01 (dd, 1H, $J_{2\ eq,2ax}$ = 18.0 Hz, $J_{2eq,3}$ = 6.1 Hz, H-2$_{eq}$), 2.54 (dd, 1H, $J_{2eq,2ax}$ = 18.0 Hz, $J_{2ax,3}$ = 5.4 Hz, H-2$_{ax}$). ^{13}C NMR (δ, $CDCl_3$): 167.4 (*C*-1), 137.3, 136.8, 128.7, 128.5, 128.4, 128.2, 127.9, 127.8 (Ar), 75.9 (*C*-4), 73.7 (*C*H$_2$Ph), 73.0 (*C*-5), 67.3 (*C*-6), 56.4 (*C*-3), 32.9 (*C*-2). Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.35; H, 5.80; N, 11.42.

4.10. 3-Azido-6-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-D-altronolactone 6b

Compound **6b** (64 mg, 0.15 mmol, 70%) was obtained from **5b** (115 mg, 0.21 mmol) following the procedure described for **6a**. $[\alpha]_D$ = −42 (*c* 1.0, $CHCl_3$). IR ν_{max} ($CHCl_3$)/cm^{-1}: 3300 (OH), 2140 (N_3), 1760 (CO). ^{1}H NMR (δ, $CDCl_3$): 7.66–7.44 (m, 4 H, Ar*H*), 7.40–7.24 (m, 6 H, Ar*H*), 4.55–4.38 (m, 2H, H-3, H-5), 3.84–3.73 (m, 3H, H-4, 2H-6), 3.06 (br s, O*H*, disappears after D_2O addition), 2.95 (dd, 1H, $J_{2,2'}$ = 18.3 Hz, $J_{2,3}$ = 7.9 Hz, H-2), 2.55 (dd, 1H, $J_{2,2'}$ = 18.3 Hz, $J_{2,3}$ = 4.0 Hz, H-2), 1.1 (s, 9H, CH_3). ^{13}C NMR (δ, $CDCl_3$): 173.6 (C-1), 135.6, 133.7, 132.5, 132.4, 130.2, 129.8, 128.3, 127.9 (Ar), 83.8 (C-4), 71.3 (C-5), 64.0 (C-6), 57.9 (C-3), 34.6 (C-2), 26.9 (*C*H$_3$), 19.3 (Si*C*CH$_3$). Anal. Calcd for $C_{22}H_{27}N_3O_4Si$: C, 62.09; H, 6.40; N, 9.87. Found: C, 62.03; H, 6.48; N, 9.84.

4.11. 4,6-Di-*O*-benzyl-3-(*tert*-butoxycarbonyl)amino-2,3-dideoxy-D-idonolactone 7a

A solution of **6a** (80 mg, 0.22 mmol) and Boc_2O (74 mg, 0.34 mmol) in AcOEt (5 mL) was hydrogenated with H_2 in the presence of Pd/C (15 mg) for 4 h until no starting material was detected on TLC. The catalyst was filtered off through a pad of Celite and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexane/EtOAc 7:1) to give **7a** as a colourless oil (80 mg, 0.18 mmol, 80%). $[\alpha]_D = +42.0$ (*c* 1.1, $CHCl_3$). IR ν_{max} ($CHCl_3$)/cm^{-1}:1750 (CO). ^1H NMR (δ, $CDCl_3$): 7.52–7.23 (m, 10H, Ar*H*), 5.37 (d, 1H, $J_{3,NH} = 6.8$ Hz, N*H*), 4.76–4.44 (m, 5H, H-5, $2 \times CH_2Ph$), 4.23 (m, 1H, H-3), 3.95–3.75 (m, 3H, H-4, 2H-6), 3.07 (dd, 1H, $J_{2,2'} = 17.5$ Hz, $J_{2,3} = 7.6$ Hz, H-2), 2.51 (dd, 1H, $J_{2,2'} = 17.5$ Hz, $J_{2',3} = 4.2$ Hz, H-2′), 1.3 (s, 9H, $3 \times CH_3$). ^{13}C NMR (δ, $CDCl_3$): 168.4 (C-1), 154.8 (N*C*O), 137.4, 135.9, 128.7, 128.6, 128.4, 128.3, 127.9, 127.8 (Ar), 80.9 (O*C*CH_3), 73.7, 73.2, 72.7, 72.3, 68.2 (C-6), 46.7 (C-3), 33.5 (C-2), 31.8 (*C*H_3). Anal. Calcd for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N, 3.17. Found: C, 68.05; H, 7.04; N, 3.15.

4.12. 6-*O*-(*tert*-Butyldiphenylsilyl)-3-(*tert*-butoxycarbonyl)amino-2,3-dideoxy-D-altronolactone 7b

Compound **7b** (60 mg, 0.12 mmol, 75%) was obtained from **6b** (70 mg, 0.16 mmol) following the procedure described for **7a**. Colourless oil; $[\alpha]_D = -75.0$ (*c* 1.0, $CHCl_3$). IR ν_{max} ($CHCl_3$)/cm^{-1}: 3300 (OH), 1760 (CO); ^1H NMR (δ, $CDCl_3$): 7.76–7.24 (m, 10 H, Ar*H*), 5.01 (d, 1H, $J_{3,NH} = 6.1$ Hz, N*H*), 4.48–4.41 (m, 2H, H-3, H-5), 3.86–3.80 (m, 3H, H-4, 2H-6), 3.01 (dd, 1H, $J_{2,2'} = 18.1$ Hz, $J_{2,3} = 8.4$ Hz, H-2), 2.9 (br s, O*H*, disappears after D_2O addition), 2.52 (dd, 1H, $J_{2,2'} = 18.1$ Hz, $J_{2,3} = 4.6$ Hz, H-2), 1.4 (s, 9H, $3 \times CH_3$), 1.1 (s, 9H, $3 \times CH_3$). ^{13}C NMR (δ, $CDCl_3$): 174.6 (C-1), 155.0 (N*C*O), 135.4, 132.7, 130.0, 129.5, 128.7, 128.5, 127.7, 127.5 (Ar), 84.4 (C-4), 80.5 (O*C*CH_3), 71.8 (C-5), 64.0 (C-6), 48.7 (C-3), 35.6 (C-2), 28.2 (*C*H_3), 26.8 (*C*H_3), 19.2 (Si*C*CH_3). Anal. Calcd. for $C_{27}H_{37}NO_6Si$: C, 64.90; H, 7.46; N, 2.80. Found: C, 64.95; H, 7.54; N, 2.75.

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