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Synthesis of polynitrogenated analogues of glucopyranoses from levoglucosan

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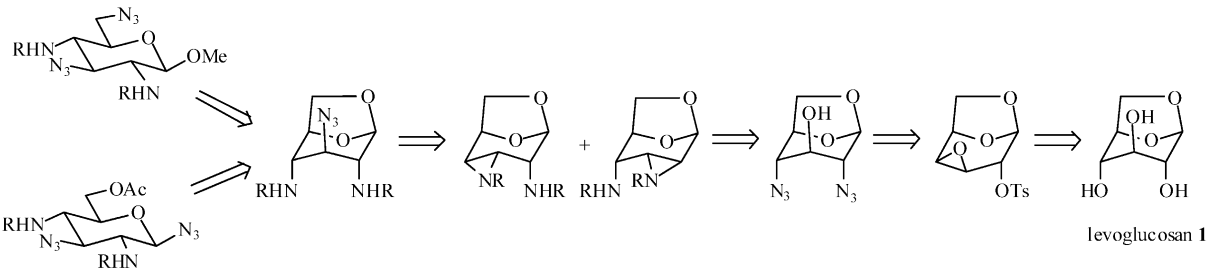
Abstract—Polynitrogenated analogues of glucopyranoses were synthesised from levoglucosan. These compounds are useful intermediates for the synthesis of new aminoglycoside mimetics.

1. Introduction

A large class of aminoglycosides (such as Kanamycin, Neomycin, Tobramycin, Gentamicin) has been known over 50 years for their antibacterial activities.[1] Their mechanism of action has also been elucidated.[2] These natural products bind to ribosomal RNA of bacteria, thereby interfering with the protein biosynthesis. Despite the established bactericidal properties of aminoglycoside antibiotics, their therapeutic use is limited; their internal administration at high doses results in clinical side effects.[1] More recently, these substances have attracted attention for their antiviral applications by interacting with the viral RNA molecules.[3] The development of new antiviral agents is necessary for fighting these diseases owing to the appearance of resistant mutant strains. The aminoglycosides have been synthetically modified in ongoing efforts to discover new antiviral and antitumor agents.[4,5] Wong and co-workers have also synthesised new aminoglycoside mimetics containing motifs that recognize viral RNA.[5] We have been interested in finding an easy access to di-, tri- and tetranitrogenated analogues of glucopyranose. These compounds will be used as building blocks for the synthesis of new aminoglycoside mimetics. A number of syntheses of tetranitrogenated compounds has been reported starting from a variety of carbohydrate derivates, but they are often lengthy and yields are unsatisfactory.[6] Moreover, they could also be very interesting for the synthesis of LPA[7] analogues and for the elaboration of macromolecular organised dendrimers.[8]

2. Results and discussion

As illustrated in Scheme 1, a retrosynthetic scheme was planned starting from levoglucosan **1**, readily available on multi-gram scale using our recently easy preparation of by a solid-supported, solvent-free, microwave assisted procedure.[9] The preparation of these polynitrogenated compounds was considered via opening of epoxides and aziridines with azide ions. The preparation of 2,3,4-trinitrogenated glucopyranoside could be carried out via the formation 2,3 or 3,4-aziridine intermediates. According to Fürst–Plattner rules,[10] these two types of aziridines might



Scheme 1. Retrosynthetic scheme.

Keywords: Levoglucosan; Aziridine; Azidolysis.
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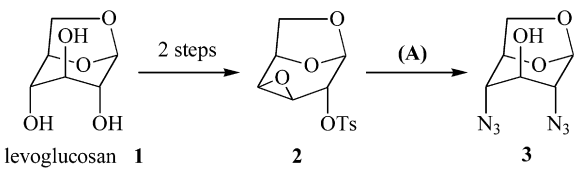
be opened by a nucleophile (azide ions in our case) in C-3 position leading to the same product.

Starting from levoglucosan **1**, the epoxide **2** is readily obtained in two steps (61% overall yield) using the Grindley procedure.[11] Conversion of epoxide **2** to diazido compound **3** has been previously described by Paulsen and co-workers[12] but requires three steps in 40–60% overall yield. We anticipated that **3** could be obtained in one step using a microwave assisted reaction with azide nucleophiles. It has been shown that microwave heating provided improvement (better yields and decrease in reaction times) in many synthetic reactions.[13] However, to the best of our knowledge, the use of azide ions under microwave irradiation has never been reported. Preliminary attempts to open epoxide **2** with NaN_3 in the presence of various Lewis acids were disappointing. However, using an excess[14] of LiN_3 (4 equiv.), in the presence of alumina, in DMF/toluene concentrated medium, the compound **3** resulting by successive trans diaxial attack at C-4 and then C-2 positions was obtained in a gratifying 90% yield (Scheme 2).



Scheme 2. *Reagents and conditions*: (A) LiN_3 (4 equiv.), Al_2O_3 (3 equiv. in weight), DMF/toluene, MW, 20 min, 90%.

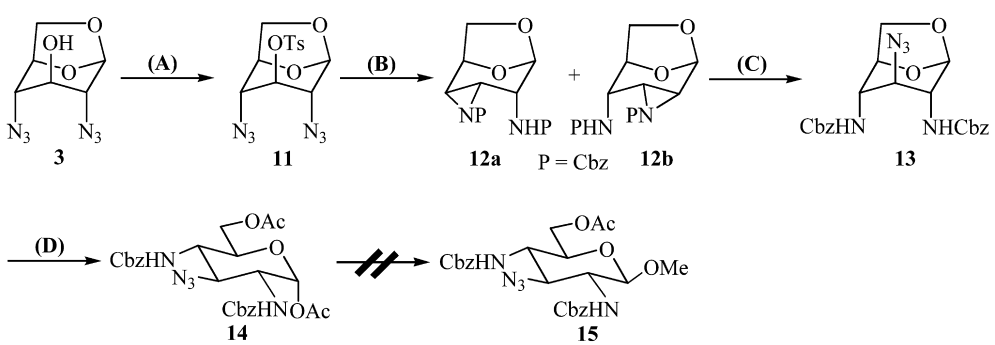
Table 1.

Starting material	Product	Yield (%)
4	**3**	70
5	**8**	85
6	**9**	90
7	**10**	85

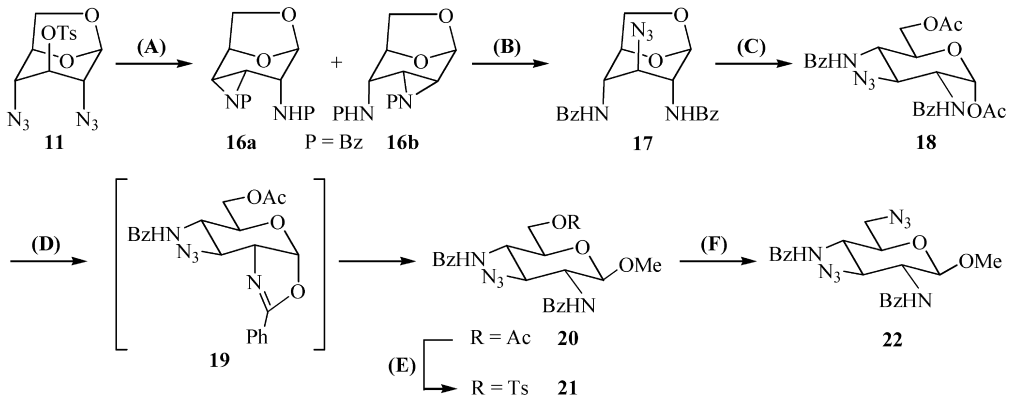
Such experimental conditions (LiN_3 (3 equiv.), Al_2O_3 (3 equiv. in weight), DMF/toluene) were also successfully applied onto dianhydropyranoses **5**, **6**, **7** according to Fürst–Plattner rules (see Table 1). Starting from the dianhydropyranose **4**, the diazide **3** can be also obtained in the same conditions in 70% yield.

With diazide **3** in hands, the access to 2,3,4-trinitrogenated glucopyranoside via the formation 2,3 or 3,4-aziridine intermediates was envisaged. From **3**, tosylate **11** was obtained in nearly quantitative yield by reaction with *N*-tosylimidazole in the presence of sodium methoxide. Catalytic hydrogenation of **11** on Pd/C led to the expected mixture of the two 2,3 and 3,4-aziridines which was directly treated with benzyl chloroformate, to give the corresponding carbamates **12a** and **12b** (65% yield; two steps) as an inseparable mixture. Azidolysis (LiN_3 2 equiv., Al_2O_3 in DMF/toluene, microwave irradiation for 12 min at 120 °C) of **12a** and **12b** mixture led, as anticipated and according to Fürst–Plattner rules, to one compound (55% yield) having the D-gluco configuration **13**. Acetolysis of **13** was done in CF_3COOH/Ac_2O medium giving the diacetate **14**. Unfortunately, several attempts for the transformation into methyl glucoside **15** were unsuccessful (Scheme 3).

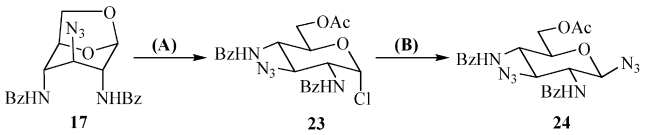
Another protecting group was then considered for obtaining the tetranitrogenated compound: after reduction of **11**, the mixture of aziridines was benzoylated giving **16a** and **16b** (Scheme 4). Azidolysis of the mixture led to the trinitrogenated compound **17** (88% yield), which was in turn acetolysed to give diacetate **18** in 90% yield. By treatment with trimethylsilyl triflate for 40 min, the oxazolidine **19** was formed and directly converted in one pot, by addition of methanol, into methyl 6-*O*-acetyl-3-azido-2,4-benzamido-2,3,4-trideoxy-β-D-glucopyranoside **20** in 80% yield. The β configuration was ascertained by a large coupling constant between H-1 and H-2 ($J_{1,2}$=8 Hz). The tetrasubstituted nitrogen compound **22** was finally obtained, from **20**, in 3 steps: MeONa catalytic deacetylation of the 6 position followed by tosylation gave the



Scheme 3. *Reagents and conditions*: (A) TsIm (1.5 equiv.), MeONa (2 equiv.), CH_3CN, 0 °C to rt, 12 h, 90%; (B) (i) Pd/C, H_2, EtOAc/EtOH (1:1), rt, 6 h; (ii) CbzCl (3 equiv.), Et_3N, CH_2Cl_2, 0 °C to rt, 15 h, 65% in two steps; (C) LiN_3 (2 equiv.), Al_2O_3 (3 equiv. in weight), DMF/toluene (1:1), MW, 120 °C, 12 min, 55%; (D) CF_3COOH, Ac_2O, 0 °C to rt, 2 days, 90%.



Scheme 4. *Reagents and conditions*: (A) (i) Pd/C, H_2, EtOAc/EtOH (1:1), rt, 6 h; (ii) Bz_2O (3 equiv.), DMAP cat., pyridine/CH_2Cl_2 (1:1), rt, 16 h, 83% in two steps; (B) LiN_3 (2 equiv.), Al_2O_3 (3 equiv. in weight), DMF/toluene (1:1), MW, 10 min, 88%; (C) CF_3COOH, Ac_2O, 0 °C to rt, 3 days, 90%; (D) TMSOTf (1.1 equiv.), $ClCH_2CH_2Cl$, 50 °C, 30 min, then MS 4 Å, rt, 1 h, then MeOH (10 equiv.), rt, 2 h, 80%; (E) (i) MeONa (0.1 equiv.), MeOH/toluene (1:1), rt, 12 h; (ii) TsCl (2 equiv.), DMAP, CH_2Cl_2/Et_3N (1:1), rt, 12 h, 62% in two steps; (F) LiN_3 (1.5 equiv.), DMF, 80 °C, 3 h, 82%.



Scheme 5. *Reagents and conditions*: (A) AcCl, MeOH, 0 °C, rt, 36 h, 80%; (B) LiN_3 (2 equiv.), DMF, 80 °C, 2 h, 77%.

crystalline ester **21** which was heated in DMF with LiN_3. Methyl 3,6-diazido-2,4-dibenzamido-2,3,4,6-tetradeoxy-β-D-glucopyranoside **22** was isolated in 51% overall yield from **20** (and 13% from levoglucosan **1** in 12 steps).

The tetrasubstituted analogue **24** was also synthesised from **17**. By treatment in Veyrieres conditions[15] (AcCl, MeOH, 0 °C, 36 h), chloride **23** was easily formed in 80% yield; the azidolysis of anomeric chloride by LiN_3 in DMF led to crystalline diazide **24** in 77% yield (Scheme 5).

In conclusion, the syntheses of tetranitrogenated analogues of glucopyranoses **22** and **24** were achieved in 12 and 9 steps, respectively, from levoglucosan **1** via a common intermediate **17** in satisfactory overall yields.

3. Experimental

3.1. General methods

The microwave reactor was a monomode system (Synthewave 402 from Prolabo Society) with focused waves. All reactions were performed in a cylindrical pyrex vessel. A continuous mechanical stirring provided a good homogeneity of the materials. The temperature was controlled all along the reaction and evaluated by an infrared detector which indicated the surface temperature. Automatic control of the irradiation (power or temperature) as well as data processing was followed by a computer system. Lithium azide was prepared by the protocol described in the literature.[16] Aluminium oxide (90 active, neutral, activity I) was used in microwave reactions. Methanol was distilled from magnesium/iodine. 1,2-Dichloroethane and acetonitrile were distilled over CaH_2 prior to use. Flash column chromatography was performed using 35–70 μ silica gel (60) purchased from S.D.S. Company. ^1H et ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively, or at 300 and 75 MHz, or 400 and 100 MHz. Chemical shifts are reported in ppm relative to TMS as internal standard. Optical rotations were determined operating at the sodium D line with a Perkin–Elmer 241C polarimeter. Melting points were measured on Büchi b-450 and are uncorrected. IR spectra were recorded with an FTIR spectrometer. Mass spectra were recorded by navigator LC/MS (source AQA) for electrospray ionisation. Elemental analyses were carried out by Laboratoire de Micro-Analyse ICSN-Gif sur Yvette.

3.1.1. 1,6-Anhydro-2,4-diazido-2,4-dideoxy-β-D-glucopyranose (3). Lithium azide (1.3 g, 26.92 mmol) and aluminium oxide (6 g, 3 equiv. in weight) were added to a solution of **2** (2 g, 6.73 mmol) in DMF/toluene (12 mL, 3:1). This mixture was submitted to microwave irradiation for 20 min (*P*: 120–240 W, *T*: 125 °C). After cooling, the reaction mixture was diluted with EtOAc, filtered through a pad of silica gel and the filtrate concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, EtOAc/heptane 1:1) to afford the compound **3** (1.323 g, 90%) as pale yellow oil: R_f 0.45 (EtOAc/heptane 1:1), IR ν_3)=2100 cm^{-1}, ^1H NMR δ (250 MHz, $CDCl_3$): 5.51 (s, 1H, H-1), 4.62 (d, 1H, H-5, *J*=5 Hz), 4.14 (d, 1H, H-6, *J*=8 Hz), 3.78–3.86 (m, 2H, H-6′, H-3), 3.5 (d, 1H, H-4), 3.4 (d, 1H, H-2), ^{13}C NMR δ (62.5 MHz, $CDCl_3$): 101 (C-1), 74.6 (C-5), 70.8 (C-3), 67.0 (C-6), 62.8, 62.7 (C-2, C-4). ESI-MS *m/z* 235 $[M+Na]^+$, 273 $[M-H+Na+K]^+$, 447 $[2M+Na]^+$.

3.1.2. 1,6-Anhydro-3-azido-3-deoxy-β-D-mannopyranose (9). Lithium azide (81 mg, 1.66 mmol) and aluminium oxide (0.36 g, 3 equiv. in weight) were added to a solution of **6** (120 mg, 0.83 mmol) in DMF/toluene (4 mL, 1:1). This mixture was submitted to microwave irradiation for 20 min (*P*: 120–240 W, *T*: 125 °C). After cooling, the reaction mixture was filtered through a pad of silica gel with a mixture of CH_2Cl_2/MeOH (9:1) and the filtrate concentrated under vacuum to afford the compound **9** (140 mg, 90%) as pale yellow oil: R_f 0.32 (CH_2Cl_2/MeOH 9:1), ^1H NMR δ (250 MHz, CD_3OD): 5.28 (s, 1H, H-1), 4.81 (sl, 1H, OH, H echangeable), 4.41 (d, H-5, *J*=5 Hz), 4.10 (d, 1H, H-6, *J*=7 Hz), 3.95 (d, H-6′, *J*=7 Hz), 3.86 (m, 1H, H-4), 3.77

(m, 1H, H-2), 3.67 (dd, 1H, H-3, J=7, 5 Hz). ^{13}C NMR δ (62.5 MHz, CD_3OD): 101.0 (C-1), 75.2 (C-5), 69.3 (C-4), 66.8 (C-2), 63.9 (C-6), 63.2 (C-3). ESI-MS m/z 210 $[M+Na]^+$; 248 $[M-H+Na+K]^+$.

3.1.3. 1,6-Anhydro-2-azido-4-*O*-benzyl-2-deoxy-β-D-gluco-pyranose (10). Compound **10** was obtained from **7** by the same experimental protocol than compound **3**. 3 equiv. of lithium azide were used. Compound **10**: pale yellow oil, 85% yield. R_f 0.4 (EtOAc/heptane 1:1), IR ν_3)=2100 cm^{-1}, ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.3–7.5 (m, 5H, H-Ar), 5.48 (s, 1H, H-1), 4.70 (s, 2H, CH_2Ph), 4.62 (d, H-5, J=5.5 Hz), 3.95 (d, H-6, J=7.5 Hz), 3.91 (m, 1H, H-4), 3.70 (dd, H-6′, J=7.5, 5.5 Hz), 3.38 (m, 1H, H-3), 3.24 (d, 1H, H-2, J=3 Hz), 2.52 (sl, 1H, OH, H echangeable). ^{13}C NMR δ (62.5 MHz, $CDCl_3$): 136.0, 128.6, 128.4, 128.3 (C-Ar), 101.1 (C-1), 78.7 (C-4), 75.1 (C-5), 71.9 (*C*H_2Ph), 70.4 (C-3), 66.3 (C-6), 62.8 (C-2). MS (ESI) m/z 300 $[M+Na]^+$; 316 $[M+K]^+$.

3.1.4. 1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-*O*-tosyl-β-D-glucopyranose (11). To a solution of **3** (6.7 g, 31.9 mmol) in dry CH_3CN (150 mL) was added *N*-tosyl-imidazole (10.5 g, 47.85 mmol). The mixture was stirred at 0 °C and then sodium methoxide (3.5 g, 63.8 mmol) was added. After 12 h at rt, the reaction was neutralised with 1 N HCl. The material was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, EtOAc/heptane 1:1) and recrystallized from ethanol to afford the compound **11** (10.45 g, 90%) as white crystals: mp 61–62 °C, R_f 0.55 (EtOAc/heptane 1:1), $[\alpha]_D^{25}$=−3 (*c* 1, $CHCl_3$), ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.83 (d, 2H, H-Ar, J=8 Hz), 7.42 (d, 2H, H-Ar, J=8 Hz), 5.47 (s, 1H, H-1), 4.65 (d, 1H, H-3, J=5 Hz), 4.42 (m, 1H, H-5), 4.13 (d, 1H, H-6, J=8 Hz), 3.84 (dd, 1H, H-6′, J=8, 5 Hz), 3.57 (s, 1H, H-4), 3.27 (s, 1H, H-2), 2.48 (s, 3H, CH_3 Ts), ^{13}C NMR δ (50 MHz, $CDCl_3$): 146.2, 132.5, 130.5, 128.0, (C-Ar), 99.8 (C-1), 76.2 (C-3), 73.6 (C-5), 65.9 (C-6), 59.4 (C-4), 59.1 (C-2), 21.8 (CH_3 Ts). ESI-MS m/z 427 $[M-H+Na+K]^+$; 755 $[2M+Na]^+$. Anal. calcd for $C_{13}H_{14}N_6O_5S$: C, 42.62, H, 3.85, N, 22.94, S, 8.75. Found: C, 42.89, H, 3.71, N, 23.04, S, 8.66.

3.1.5. 1,6-Anhydro-3,4-benzyloxycarbonylepimino-2-benzyl-oxycarboxamido-2,3,4-trideoxy-β-D-allopyranose (12a) and 1,6-anhydro-2,3-benzyloxycarbonyl-epimino-4-benzyloxycarboxamido-2,3,4-trideoxy-β-D-allopyranose (12b). Pd/C (0.85 g) was added to a solution of **11** (8.05 g, 22.055 mmol) in EtOAc/EtOH (60 mL, 1:1). The mixture was stirred under hydrogen atmosphere (4 bar) during 6 h. The reaction mixture was filtered through a pad of celite with EtOH and the filtrate concentrated under vacuum. The resulting crude material was dissolved in CH_2Cl_2 (45 mL); DMAP (0.8 g, 6.56 mmol) and triethylamine (20 mL) were added. After being stirred at 0 °C, benzyl chloroformate (10 mL, 70 mmol) was added dropwise. After 20 h at rt, the reaction was extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$, filtered, concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, EtOAc/heptane 1:1) and recrystallized from ethanol to afford a mixture of the compound **12a/12b** (5.88 g, 65%) as white crystals: R_f 0.39 (EtOAc/heptane 1:1), ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.20–7.45 (m, 10H, H-Ar), 5.63, 5.81 (m, 2NH), 5.59 (d, H-1a, J=9 Hz), 5.17 (s, H-1b), 5.04–5.15 (m, 4H, 2CH_2Ph Cbz), 4.71 (d, H-5a), 4.36 (d, H-5b), 3.82–4.04 (m, H-6, H-4b, H-2a), 3.63–3.82 (m, H-6′), 2.84–3.05 (m, H-2b, H-3a), 2.67–2.82 (m, H-3b, H-4a), ^{13}C NMR δ (62.5 MHz, $CDCl_3$): 155.8, 161.9 (C=O), 136.4, 135.4, 128.7, 128.6, 128.3, 128.1 (C-Ar), 101.5 (C-1b), 96.8 (C-1a), 76.1 (C-5b), 69.3 (C-5a), 68.8, 67.1 (2OCH_2Ph Cbz), 66.4 (C-6), 47.6 (C-4b), 47.4 (C-2a), 36.7 (C-4a), 36.2 (C-2b), 35.2 (C-3b), 34.7 (C-3a). ESI-MS m/z 433 $[M+Na]^+$; 449 $[M+K]^+$; 471 $[M-H+Na+K]^+$; 843 $[2M+Na]^+$. Anal. calcd for $C_{22}H_{22}N_2O_6$: C, 64.38, H, 5.40, N, 6.83. Found: C, 64.42, H, 5.31, N, 6.66.

3.1.6. 1,6-Anhydro-3-azido-2,4-dibenzyloxycarboxamido-2,3,4-trideoxy-β-D-glucopyranose (13). In pyrex tube for MW, a mixture of aziridines **12a/12b** (3.53 g, 8.63 mmol) was dissolved in DMF/toluene (20 mL, 1:1); lithium azide (1.05 g, 17.26 mmol) and aluminium oxide (10.6 g, 3 equiv. in weight) were added. This mixture was submitted to microwave irradiation for 10 min (*P*: 60–150 W, *T*: 125 °C). After cooling, the reaction mixture was diluted with EtOAc, filtered through a pad of silica gel and the filtrate concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, EtOAc/heptane 1:1) and recrystallized from ethanol to afford the compound **13** (2.67 g, 55%) as white crystals: mp 109 °C, R_f 0.54 (EtOAc/heptane 1:1), $[\alpha]_D^{25}$=−5 (*c* 1, $CHCl_3$), ^{1}H NMR δ (400 MHz, $CDCl_3$): 7.15–7.45 (m, 10H, H-Ar), 6.10, 6.35 (m, 2NH), 5.39 (s, 1H, H-1), 5.00–5.25 (m, 4H, 2CH_2Ph Cbz), 4.44 (s, 1H, H-5), 4.23 (s, 1H, H-6), 3.50–3.95 (m, 4H, H-2, H-3, H-4, H-6′), ^{13}C NMR δ (62.5 MHz, $CDCl_3$): 156.0, 156.1 (C=O), 136.0, 129.0, 128.5, 128.3 (C-Ar), 100.5 (C-1), 75.2 (C-5), 67.3 et 68.1 (2OCH_2Ph Cbz), 66.3 (C-6), 61.8 (C-3), 51.2, 51.4 (C-2, C-4). ESI-MS m/z 476 $[M+Na]^+$; 514 $[M-H+Na+K]^+$; 929 $[2M+Na]^+$. Anal. calcd for $C_{22}H_{23}N_5O_6$: C, 58.27, H, 5.11, N, 15.44. Found: C, 58.56, H, 4.96, N, 15.56.

3.1.7. 1,6-Di-*O*-acetyl-3-azido-2,4-dibenzyloxycarboxamido-2,3,4-trideoxy-α-D-glucopyranose (14). To a solution of **13** (2.045 g, 4.514 mmol) in acetic anhydride (20 mL) was added dropwise trifluoroacetic acid (1.1 mL) at 0 °C. After 2 days at rt, the reaction was quenched by the addition of ethanol then concentrated in vacuo. The resulting crude material was purified by column chromatography (SiO_2, EtOAc/heptane 1:1) and recrystallized from ethanol to afford the compound **14** (2.255 g, 90%) as white crystals: mp 148–150 °C, R_f 0.41 (EtOAc/heptane 1:1), $[\alpha]_D^{25}$=+44 (*c* 1, acetone), ^{1}H NMR δ (400 MHz, $CDCl_3$): 7.02–7.51 (m, 10H, H-Ar), 6.12 (s, 1H, H-1), 5.80, 5.91 (m, 2NH), 4.75–5.22 (m, 4H, 2CH_2Ph Cbz), 4.35 (m, 1H, H-3), 4.00–4.24 (m, 4H, H-2, H-5, H-6, 6′), 3.64 (m, 1H, H-4), 2.00, 2.15 (s, 3H, CH_3 Ac), ^{13}C NMR δ (100 MHz, $CDCl_3$): 170.7, 169.1 (C=O Ac), 156.4 (2C=O Cbz), 136.0, 135.7, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1 (C-Ar), 91.1 (C-1), 69.9 (C-5), 67.8, 67.5 (2OCH_2Ph Cbz), 62.6 (C-6), 61.9 (C-3), 53.6, 53.0 (C-2 et C-4), 20.9, 20.7 (2CH_3 Ac). ESI-MS m/z 578 $[M+Na]^+$; 616 $[M-H+Na+K]^+$. Anal. calcd

for $C_{26}H_{29}N_5O_9$: C, 56.21, H, 5.26, N, 12.61. Found: C, 56.37, H, 5.08, N, 12.61.

3.1.8. 1,6-Anhydro-2-benzamido-3,4-benzoylepimino-2,3,4-tri-deoxy-β-D-allopyranose (16a) and 1,6-anhydro-4-benzamido-2,3-benzoylepimino-2,3,4-trideoxy-β-D-allo-pyranose (16b). Pd/C (0.1 g) was added to a solution of **11** (0.875 g, 2.4 mmol) in EtOAc/EtOH (8 mL, 1:1). The mixture was stirred under hydrogen atmosphere (4 bar) during 6 h. The reaction mixture was filtered through a pad of celite with EtOH and the filtrate concentrated under vacuum. The resulting crude material was dissolved in pyridine/CH_2Cl_2 (25 mL, 1:1), DMAP (30 mg, 0.24 mmol) and benzoic anhydride (1.7 g, 7.515 mmol) were added at 0 °C. After 16 h at rt, the reaction mixture was concentrated under vacuum. The resulting crude material was purified by column chromatography (SiO_2, EtOAc/heptane 7:3) and recrystallized from a mixture of ethyl acetate and heptane to afford a mixture of the compound **16a/16b** (0.7 g, 83%) as white crystals: R_f 0.49 (EtOAc/heptane 8:2), ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.95–8.10 (m, 2H, H-Ar), 7.80–7.92 (m, 2H, H-Ar), 7.37–7.55 (m, 6H, H-Ar), 7.60, 7.31 (m, 2NH), 5.73 (s, H-1a), 5.34 (s, H-1b), 4.80 (m, H-5a), 4.44–4.61 (m, H-2a, H-5b), 3.93–4.12 (m, H-6, H-4b), 3.78–3.90 (m, H-6′), 3.35 (m, H-3b), 3.29 (m, H-3a), 2.88 (m, H-4a), 2.83 (m, H-2b), ^{13}C NMR δ (75 MHz, $CDCl_3$): 167.0, 167.1, 177.5, 177.9 (C=O), 133.4, 133.3, 132.7, 131.9, 131.8, 129.0, 128.8, 128.6, 127.2 (C-Ar), 101.5 (C-1b), 96.8 (C-1a), 76.1 (C-5b), 69.3 (C-5a), 66.4 (C-6), 47.6 (C-4b), 47.4 (C-2a), 36.7 (C-4a), 36.2 (C-2b), 35.2 (C-3b), 34.7 (C-3a). ESI-MS *m/z* 373 $[M+Na]^+$; 389 $[M+K]^+$. Anal. calcd for $C_{20}H_{18}N_2O_4$: C, 68.56, H, 5.18, N, 8.00. Found: C, 68.37, H, 5.11, N, 7.85.

3.1.9. 1,6-Anhydro-3-azido-2,4-dibenzamido-2,3,4-tri-deoxy-β-D-glucopyranose (17). In pyrex tube for MW, a mixture of aziridines **16a/16b** (1 g, 2.856 mmol) was dissolved in DMF/toluene (6 mL, 1:1); lithium azide (0.3 g, 5.712 mmol) and aluminium oxide (3 g, 3 equiv. in weight) were added. This mixture was submitted to microwave irradiation for 10 min (*P*: 60–150 W, *T*: 120 °C). After cooling, the reaction mixture was diluted with EtOAc, filtered through a pad of silica gel and the filtrate concentrated under vacuum. The crude product was recrystallized from a mixture of ethyl acetate and heptane to afford the compound **17** (2.8 g, 88%) as white crystals: mp 195–197 °C, R_f 0.56 (EtOAc/heptane 8:2), $[\alpha]_D^{25}=+13$ (*c* 1, $CHCl_3$), ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.62–7.73 (m, 4H, H-Ar), 7.46–7.57 (m, 2H, H-Ar), 7.32–7.43 (m, 4H, H-Ar), 6.71, 6.44 (m, 2NH), 5.60 (s, 1H, H-1), 4.67 (d, 1H, H-5, *J*=5 Hz), 4.46 (d, 1H, H-6, *J*=8 Hz), 4.30 (d, 1H, H-2, *J*=8 Hz), 4.20 (d, 1H, H-4, *J*=7 Hz), 4.05 (m, 1H, H-3), 3.92 (dd, 1H, H-6′, *J*=5, 8 Hz), ^{13}C NMR δ (75 MHz, $CDCl_3$): 167.5, 162.7 (C=O), 133.8, 131.9, 128.6, 127.3 (C-Ar), 101.0 (C-1), 75.1 (C-5), 66.7 (C-6), 60.3 (C-3), 50.8, 50.9 (C-2, C-4). Anal. calcd for $C_{20}H_{19}N_5O_4$: C, 61.06, H, 4.87, N, 17.80. Found: C, 61.09, H, 4.89, N, 17.67.

3.1.10. 1,6-Di-*O*-acetyl-3-azido-2,4-dibenzamido-2,3,4-tri-deoxy-α-D-glucopyranose (18). To a solution of **17** (0.8 g, 2.05 mmol) in acetic anhydride (70 mL) was added dropwise trifluoroacetic acid (3 mL) at 0 °C. After 3 days at rt, the reaction was quenched by the addition of ethanol then concentrated in vacuo. The resulting white solid was recrystallized from a mixture of ethyl acetate and heptane to afford the compound **18** (0.9 g, 90%) as white crystals: mp 211 °C (decomposition), R_f 0.48 (EtOAc/heptane 8:2), $[\alpha]_D^{25}=+32$ (*c* 1, acetone), ^{1}H NMR δ (300 MHz, Acetone D): 8.23 (d, 1H, NH, *J*=9 Hz), 8.11 (d, 1H, NH, *J*=8 Hz), 7.75–7.95 (m, 4H, H-Ar), 7.35–7.60 (m, 6H, H-Ar), 6.33 (d, 1H, H-1, *J*=4 Hz), 4.69 (t, 1H, H-3, *J*=11 Hz), 4.40–4.58 (m, 2H, H-2, H-5), 4.25–4.39 (m, 2H, H-4 et H-6), 4.15 (dd, 1H, H-6′, *J*=2, 12 Hz), 2.00, 2.15 (s, 3H, CH_3 Ac), ^{13}C NMR δ (62.5 MHz, Acetone D): 169.1, 170.3 (C=O Ac), 167.6, 162.7 (C=O Bz), 134.9, 134.7, 131.9, 128.7, 128.6, 127.8, 127.6 (C-Ar), 90.6 (C-1), 70.8 (C-5), 63.1 (C-6), 60.7 (C-3), 52.2, 52.8 (C-2, C-4), 20.3, 20.5 ($2CH_3$ Ac). Anal. calcd for $C_{24}H_{25}N_5O_7$: C, 56.21, H, 5.26, N, 12.61. Found: C, 56.37, H, 5.08, N, 12.61.

3.1.11. Methyl 6-*O*-acetyl-3-azido-2,4-dibenzamido-2,3,4-tri-deoxy-β-D-glucopyranoside (20). TMSOTf (0.36 mL, 1.793 mmol) dissolved in dry 1,2-dichloroethane (8 mL) was added dropwise under argon to a solution of **18** (0.807 g, 1.63 mmol) in dry 1,2-dichloroethane (30 mL). The mixture was stirred at 50 °C until completion as monitored by TLC (30 min); the oxazolidine **19** was formed (at this stage, this compound can be isolated). Molecular sieves (0.5 g) were added. After 1 h at rt, methanol (0.7 mL, 16.3 mmol) was added. The reaction was quenched by addition of triethylamine (0.4 mL). The reaction mixture was filtered through a pad of celite with EtOAc/toluene and the filtrate concentrated under vacuum. The crude product was recrystallized from a mixture of ethyl acetate and heptane to afford the compound **20** (0.61 g, 80%) as white crystal: mp 242 °C (decomposition), R_f 0.48 (EtOAc/heptane 8:2), $[\alpha]_D^{25}=+20$ (*c* 1.09, DMSO), ^{1}H NMR δ (300 MHz, DMSO D): 8.63–8.83 (m, 2H, 2NH), 7.75–7.95 (m, 4H, H-Ar), 7.37–7.63 (m, 6H, H-Ar), 4.65 (d, 1H, H-1, *J*=9 Hz), 4.13–4.37 (m, 2H, H-5, H-6), 4.00–4.13 (m, 1H, H-6′), 3.73–4.00 (m, 3H, H-2, H-3, H-4), 3.40 (s, 3H, CH_3 OMe), 2.05 (s, 3H, CH_3 Ac), ^{13}C NMR δ (62.5 MHz, DMSO D): 170.1 (C=O Ac), 166.4, 166.7 (C=O Bz), 134.2, 134.0, 131.4, 131.3, 128.8, 127.2 (C-Ar), 101.2 (C-1), 72.8 (C-5), 63.0 (C-3), 62.9 (C-6), 55.9 (CH_3 OMe), 54.4 (C-2), 50.8 (C-4), 20.5 (CH_3 Ac). Anal. calcd for $C_{23}H_{25}N_5O_6$: C, 58.18, H, 5.09, N, 14.13. Found: C, 57.95, H, 5.17, N, 13.78.

3.1.12. Methyl 3-azido-2,4-dibenzamido-2,3,4-trideoxy-6-*O*-tosyl-β-D-glucopyranoside (21). The compound **20** (1.2 g, 2.42 mmol) was dissolved in toluene/methanol (40 mL, 1:1). A solution (2 M) of sodium methoxide in methanol (1 mL, 0.242 mmol) was added. After being stirred for 12 h at room temperature, the reaction mixture was neutralised with DOWEX AG50W-X8 (H^+) resin then filtered through a pad of celite. The filtrate was concentrated under vaccum. The crude material was dissolved in Et_3N/CH_2Cl_2 (20 mL, 1:1). DMAP (30 mg, 0.242 mmol) and *p*-toluenesulfonyl chloride (0.74 g, 3.88 mmol) were added. After being stirred for 12 h at rt, the reaction mixture was filtered through a pad of silica gel with a mixture of CH_2Cl_2/MeOH (9:1) then concentrated under reduce pressure. The crude product was recrystallized from the mixture of acetone and heptane to afford the compound **21** (0.875 g, 62%) as white crystal: mp 165 °C (decomposition), R_f 0.46

(EtOAc/heptane 6:4), $[\alpha]_D^{25}=+17$ (*c* 1, acetone), ^{1}H NMR δ (300 MHz, acetone D): 8.13 (t, 2H, 2NH, *J*=9 Hz), 7.80–7.95 (m, 4H, H-Ar), 7.76 (d, 2H, H-Ar, *J*=8 Hz), 7.45–7.60 (m, 6H, H-Ar), 7.35 (d, 2H, H-Ar, *J*=8 Hz), 4.86 (d, 1H, H-1, *J*=9 Hz), 4.59 (t, 1H, H-3, *J*=10.5 Hz), 4.28 (m, 1H, H-6), 4.06–4.21 (m, 2H, H-5, H-6), 3.94 (m, 1H, H-4), 3.82 (m, 1H, H-2), 3.41 (s, 3H, CH_3 OMe), 2.35 (s, 3H, CH_3 Ts), ^{13}C NMR δ (75 MHz, Acetone D): 167.6, 167.8 (C=O Bz), 146.0, 135.8, 135.3, 133.9, 132.6, 132.4, 131.0, 129.4, 129.0, 128.4, 128.3 (C-Ar), 102.0 (C-1), 73.8 (C-5), 70.2 (C-6), 63.2 (C-3), 56.6 (C-2), 56.4 (CH_3 OMe), 52.6 (C-4), 21.4 (CH_3 Ts). Anal. calcd for $C_{28}H_{29}N_5O_7S$: C, 58.02, H, 5.04, N, 12.08, S, 5.53. Found: C, 58.19, H, 4.92, N, 11.78, S, 5.59.

3.1.13. Methyl 3,6-diazido-2,4-dibenzamido-2,3,4,6-tetra-deoxy-β-D-glucopyranoside (22). Lithium azide (60 mg, 1.191 mmol) was added to a solution of **21** (0.46 g, 0.794 mmol) in DMF (4 mL). After being stirred for 3 h at 80 °C, the reaction mixture was filtered through a pad of silica gel with EtOAc then concentrated under reduce pressure. The crude material was recrystallized from a mixture of acetone and heptane to afford the compound **22** (0.295 g, 82%) as white crystal: mp 241 °C (decomposition), R_f 0.56 (EtOAc/heptane 6:4), $[\alpha]_D^{25}=-49$ (*c* 1.1, DMSO), ^{1}H NMR δ (300 MHz, DMSO D): 8.60–8.90 (m, 2H, 2NH), 7.75–7.95 (m, 4H, H-Ar), 7.40–7.65 (m, 6H, H-Ar), 4.69 (d, 1H, H-1, *J*=9 Hz), 4.15–4.35 (m, 1H, H-5), 3.72–4.00 (m, 3H, H-2, H-3, H-4), 3.40–3.60 (m, 1H, H-6), 3.42 (s, 3H, CH_3 OMe), 3.20–3.40 (m, 1H, H-6′), ^{13}C NMR δ (75 MHz, DMSO D): 166.5, 166.7 (C=O Bz), 134.0, 133.8, 131.5, 131.4, 128.3, 127.3, 127.2 (C-Ar), 101.1 (C-1), 74.7 (C-5), 62.9 (C-3), 55.9 (CH_3 OMe), 54.5 (C-2), 51.8 (C-4), 51.2 (C-6). Anal. calcd for $C_{21}H_{22}N_8O_4$: C, 55.99, H, 4.92, N, 24.88. Found: C, 55.97, H, 4.97, N, 25.09.

3.1.14. 6-*O*-Acetyl-3-azido-2,4-dibenzamido-2,3,4-tri-deoxy-α-D-glucopyranosyl chloride (23). To a solution of **17** (1.224 g, 3.165 mmol) in acetyl chloride (100 mL) was added dropwise methanol (1.05 mL) at 0 °C. After 24 h at rt, methanol (1 mL) was also added dropwise. After 12 h, the mixture was evaporated under reduce pressure. The crude product as white solid was recrystallized from a mixture of acetone and heptane to afford the compound **23** (1.19 g, 80%) as white crystal: mp 147 °C (decomposition), R_f 0.73 (EtOAc/heptane 8:2), $[\alpha]_D^{25}=+78$ (*c* 1, acetone), ^{1}H NMR δ (300 MHz, acetone D): 8.10–8.40 (m, 2H, 2NH), 7.75–8.05 (m, 4H, H-Ar), 7.35–7.65 (m, 4H, H-Ar), 6.51 (d, 1H, H-1, *J*=4 Hz), 4.58–4.80 (m, 2H, H-3, H-5), 4.45–4.58 (m, 2H, H-2, H-4), 4.38 (dd, 1H, H-6, *J*=5, 12.5 Hz), 4.22 (dd, 1H, H-6′, *J*=2, 12.5 Hz), 2.05 (s, 3H, CH_3 Ac). ^{13}C NMR δ (75 MHz, Acetone D): 170.8 (C=O Ac), 168.0, 168.2 (C=O Bz), 135.3, 134.9, 132.6, 132.5, 129.2, 128.3, 128.2 (C-Ar), 95.6 (C-1), 72.5 (C-5), 63.5 (C-6), 60.5 (C-3), 55.6 (C-2), 52.4 (C-4), 20.7 (CH_3 Ac). Anal. calcd for $C_{22}H_{22}$ ClN_5O_5: C, 55.99, H, 4.70, N, 14.84, O, 16.95. Found: C, 56.21, H, 4.75, N, 14.77, O, 16.71.

3.1.15. 6-*O*-Acetyl-3-azido-2,4-dibenzamido-1,2,3,4-tetra-deoxy-β-D-glucopyranosyl azide (24). Lithium azide (0.23 g, 4.628 mmol) was added to a solution of **23** (1.09 g, 2.314 mmol) in DMF (4 mL). After being stirred for 2 h at 80 °C, the reaction mixture was filtered through a pad of silica gel with EtOAc then concentrated under vacuum. The crude material was recrystallized from acetone to afford the compound **24** (0.85 g, 77%) as white crystal: mp 178 °C (decomposition), R_f 0.62 (EtOAc/heptane 8:2), $[\alpha]_D^{25}=-59$ (*c* 1.64, DMSO), ^{1}H NMR δ (250 MHz, DMSO D): 8.90 (d, 1H, NH, *J*=8 Hz), 8.80 (m, 1H, NH), 7.75–7.97 (m, 4H, H-Ar), 7.35–7.65 (m, 6H, H-Ar), 4.98 (d, 1H, H-1, *J*=9 Hz), 3.75–4.45 (m, 6H, H-2, H-3, H-4, H-5, H-6, 6′), 2.05 (s, 3H, CH_3 Ac). ^{13}C NMR δ (62.5 MHz, DMSO D): 169.9 (C=O Ac), 166.6, 166.7 (C=O Bz), 133.9, 133.7, 131.5, 131.4, 128.2, 127.1 (C-Ar), 87.7 (C-1), 74.7 (C-5), 64.6 (C-6), 54.0 (C-2), 50.5 (C-4), 20.5 (CH_3 Ac). Anal. calcd for $C_{22}H_{22}N_8O_5$: C, 55.23, H, 4.63, N, 23.42. Found: C, 55.22, H, 4.77, N, 23.53.

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