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Stereoselective synthesis of β-D-GlcNAc-(1 → 4)-D-Glc disaccharide starting from lactose ☆

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ABSTRACT

The stereoselective preparation of the β-D-GlcNAc-(1 → 4)-D-Glc disaccharide starting from known 4-*O*-[6-*O*-(1-methoxy-1-methylethyl)-3,4-*O*-isopropylidene-β-D-talopyranosyl]-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (**2**), in turn easily obtained from lactose, is reported. Key steps of this new procedure, that avoids the glycosylation reaction, are (a) a first epimerization at C-4′ through an unusual procedure involving a completely stereospecific hydroboration–oxidation of the enol ether group of the hex-4-enopyranoside **4**, obtained from **3** by base promoted acetone elimination, (b) an amination with inversion by S_N2 reaction on an imidazylate intermediate, and, finally, (c) N-acetylation followed by complete deprotection.

1. Introduction

N-Acetylhexosamines are an important class of monosaccharides found in many types of natural bioactive compounds.[1] They are present in different types of glycoconjugates (glycolipids, lipopolysaccharides, and proteins),[2] glycosaminoglycans (heparin, dermatan, chondroitin, and hyaluronic acid),[3] blood group determinants,[4] and in the antigenic determinant of various pathogens.[5] Owing to the difficulties in the stereoselective chemical formation of 1,2-*cis*-hexosaminyl bonds (β-D-manno and β-D-talo series),[6] we have directed our attention to an approach involving regio- and stereoselective manipulations of β-D-galactopyranosides.[7] Lactose is a cheap and naturally abundant disaccharide which can be transformed into a number of useful analogues such as β-D-ManNAc-(1 → 4)-D-Glc, and β-D-TalNAc-(1 → 4)-D-Glc.[7a] Recently, the synthesis of β-D-GalNAc-(1 → 4)-D-Glc disaccharide from lactose has also been performed.[8] The preparation of a further hexosaminyl analogue of the series, that contains the β-D-GlcNAc unit, is reported here, starting from an intermediate obtained in our previous work.[7,8] This approach avoids the glycosylation step, while previous syntheses of the β-D-GalNAc-(1 → 4)-D-Glc disaccharide all involved the coupling of a suitably protected glucosamine donor with a glucopyranoside acceptor selectively deprotected on OH-4.[9b–d] Interestingly, some derivatives of this disaccharide have been considered recently for their aphicidal activity.[9a]

The synthesis of the target disaccharide started from the mixed tetra-acetonide β-D-talopyranosyl disaccharide **2**, easily obtained in high yield by C-2′ epimerization of corresponding lactose derivative **1** (Fig. 1).[10]

The planned approach utilizes two stereocontrolled procedures: epimerization of C-4′ and amination with inversion of configuration at C-2′, as outlined in Chart 1.

2. Results and discussion

The first transformation involves as key step the regio- and stereoselective hydroboration–oxidation of the intermediate vinyl ether **4** (Scheme 1). Compound **2** was transformed into the completely protected derivative **3** by Williamson *p*-methoxybenzylation of 2′-OH followed by selective and mild acidic hydrolysis (5% aq HCl) of the 6′-*O*-methoxyisopropyl acetal and finally 6′-O-benzylation. Compound **3** was obtained in good overall yield (83%) with only one purification step.

The acetone elimination reaction was carried out according to the conditions previously optimised for the *talo* series.[11] Treatment of compound **3** with *t*-BuOK in THF at reflux gave the corresponding vinyl ether in high yield which was directly subjected to a standard benzylation reaction to afford **4** in 77% yield over two steps. The elimination reaction required milder conditions with respect to those used for 3,4-*O*-isopropylidene-D-galactopyranoside analogues.[12] The enhanced reactivity of the *talo* series is probably related to the unfavourable *syn* interaction between the axial

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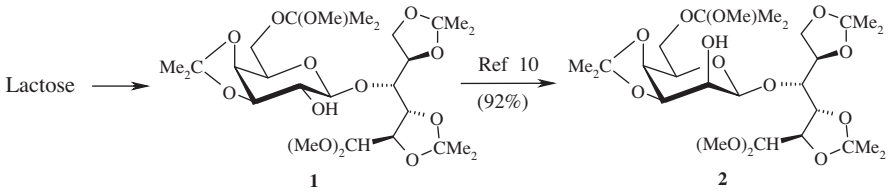


Figure 1. Transformation of lactose into talopyranosyl derivative **2**.

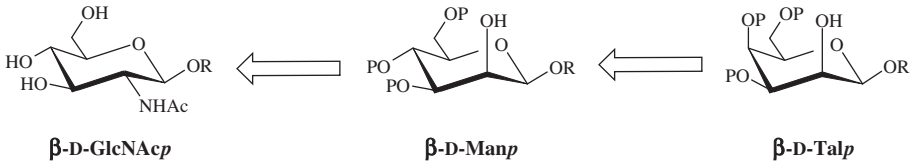


Chart 1. Retrosynthetic approach to a β-D-*N*-acetylglucosamine glycosyl unit starting from a β-D-talopyranoside.

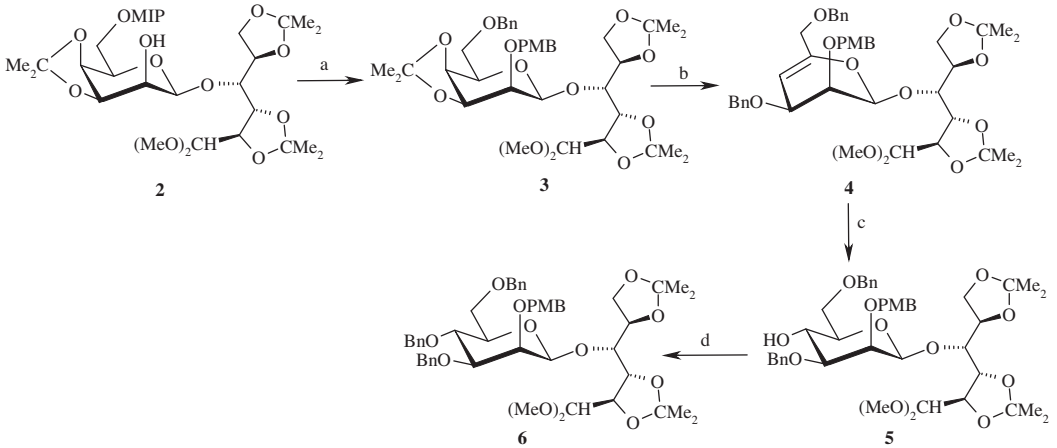
2-OR group and the 3,4-*O*-isopropylidene ring. The high strain release is presumably the reason for the observed complete regioselective elimination of acetone. It is also interesting to pinpoint that starting from the *talo* series, the regioselective preparation of hexenopyranosides can now be achieved by two complementary routes. We recently reported the high yielding NaH/Im_2SO_2 mediated preparation of 4-deoxy-D-*threo*-hex-3-enopyranosides,[10,13] while here an approach to the 4-deoxy-D-*erythro*-hex-4-enopyranoside is described.

The C-4′ epimerization was accomplished with the hydroboration–oxidation reaction ((a) BH_3SMe_2 in THF; (b) H_2O_2/NaOH/H_2O; 80% yield). The subsequent benzylation reaction of **5** afforded **6** in 93% yield and the coupling constant pattern confirmed the *manno* configuration ($J_{3',4'}$ 9.4 Hz, $J_{4',5'}$ 9.6 Hz). The regioselectivity of the hydroboration step is not surprising in light of the polarity of the vinyl ether double bond. The complete stereoselectivity obtained is attributed to the orientation of the substituents, and in particular the axial 2′-OR group, which all shield the *beta* face from the borane coordination.

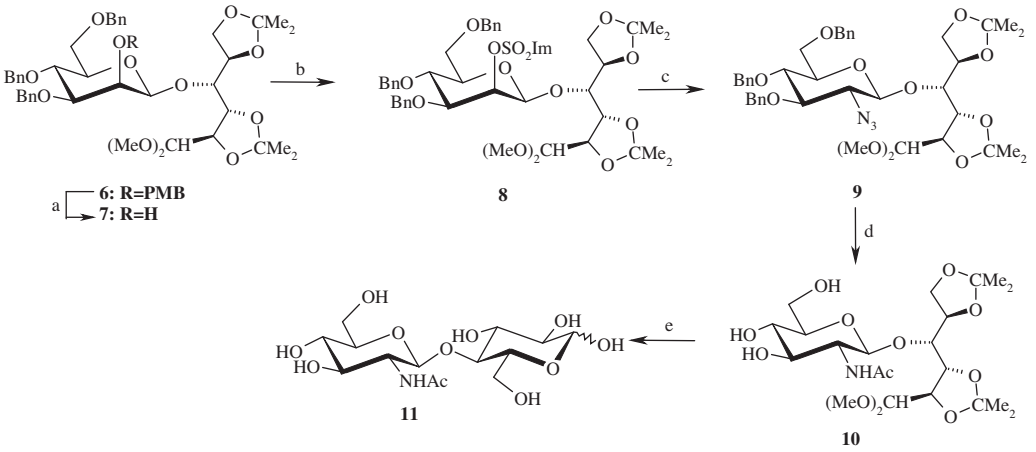
The orthogonal *p*-methoxybenzyl group was removed using DDQ in a mixture of CH_2Cl_2–H_2O (76% yield) and the leaving group was then introduced by treating **7** with imidazyl sulfate (Im_2SO_2) and NaH in DMF at −30 °C (Scheme 2). The corresponding imidazylate **8**, isolated pure by flash chromatography in 83% yield, was then subjected to a S_N2 displacement with NaN_3 in DMF at 100 °C, and afforded the azido derivative **9** in 92% yield ($J_{1',2'}$ 7.8 Hz, $J_{2',3'}$ 9.1 Hz). This result confirms the usefulness of the imidazylate leaving group in comparison with other aryl and alkyl sulfonates[14] for performing efficient substitution in position 2 of a pyranoside. The first step of the deprotection strategy consisted of a hydrogenolysis (H_2, Pd/C) in the presence of Ac_2O. These conditions allowed for benzyl group removal, reduction of the azido function, and direct N-acetylation.

The target compound **11** was finally obtained by complete deprotection of **10** via acidic hydrolysis of all acetals using 80% aq AcOH at 80 °C: this exposes the C-1 aldehyde group and thus a concomitant six-membered ring closure occurs. The structure of **11** as well as its anomeric composition (α/β ratio about 2:3) was established on the basis of its NMR spectra. The ^{13}C NMR signals (see Table 1) were assigned by comparison with those of α-, β-cellobiose[15] and with those of methyl 2-acetamido-2-deoxy-β-D-glucopyranoside.[16]

In conclusion, we reported an easy access to the β-D-GlcNAc-(1 → 4)-D-Glc disaccharide starting from lactose. This approach is based on high yielding and stereoselective manipulations of the natural disaccharide skeleton and avoids the time consuming classical preparation of protected monosaccharide donor and acceptor. In addition, it bypasses the difficulties previously encountered in



Scheme 1. Stereoselective synthesis of 4'-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-*p*-methoxybenzyl-β-D-mannopyranosyl)-2,3:5,6-di-*O*-isopropylidene*aldehydo*-D-glucose dimethyl acetal (**6**). Reagents and conditions: (a) (1) PMBCl, NaH, DMF, room temp, 2 h; (2) CH_2Cl_2 and 5% aq HCl; (3) BnBr, NaH, DMF, room temp, 12 h, (83%); (b) (1) *t*-BuOK, THF, reflux, 20 min; (2) BnBr, NaH, DMF, room temp, 12 h (77%); (c) BH_3 Me_2S (5 M, Et_2O), THF, room temp, 5 h, then H_2O, 10% NaOH, 35% aq H_2O_2, room temp, 2 h (80%); (d) BnBr, NaH, DMF, room temp, 12 h (93%).



Scheme 2. Synthesis of β-D-GlcNAc*p*-(1 → 4)-D-Glc*p* disaccharide from derivative **6**. Reagents and conditions: (a) DDQ, 18:1 CH_2Cl_2–H_2O, room temp, 1 h (76%); (b) Im_2SO_2, NaH, DMF, −30 °C, 1 h (83%); (c) NaN_3, DMF, 100 °C, 45 min (92%); (d) H_2, 10% Pd/C, 1:3 EtOAc–EtOH, Ac_2O, room temp, 48 h (53%); (e) 80% aq AcOH, 80 °C, 3 h (87%).

Table 1
^{13}C NMR chemical shifts of **α**- and **β-11** and related compounds

Compound	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	C-1	C-2	C-3	C-4	C-5	C-6
α-Cellobiose[a]	103.3	74.1	76.5	70.4	76.8	61.6	92.7	72.3	72.3	79.6	71.0	61.1
β-Cellobiose[a]	103.3	74.1	76.5	70.4	76.8	61.6	96.6	74.9	75.3	79.5	75.6	61.1
Me β-D-GlcNAc*p*[b]	102.8	57.9	74.8	70.8	76.8	61.6						
α-**11**[c]	102.3	56.4	74.3	70.6	76.7	61.4	92.5	72.3	72.3	80.7	71.5	60.9
β-**11**[c]	102.3	56.4	74.3	70.6	76.7	61.4	96.5	74.5	75.3[d]	80.3	75.2[d]	61.0

[a] Spectra taken in D_2O with 1,4-dioxane (δ 67.40) as internal reference (Ref. 15).
[b] Spectra taken in D_2O with acetone (δ 30.89) as internal reference (Ref. 16).
[c] Spectra taken in D_2O with TMSP as internal reference.
[d] Assignments may be reversed.

the optimization of the glycosylation reaction with glucosamine donors.[9a–d]

An undeniable role, in the reaction pathway here reported, is played by the axial 2′-OR group which is involved both in the regioselective hex-4-enopyranoside formation as well as in the stereoselective C-4′ epimerization.

3. Experimental

3.1. General methods

General methods are those reported in Ref. 7b. Compound **2** was prepared according to the reported procedures.[10]

3.2. 4-*O*-(6-*O*-Benzyl-3,4-*O*-isopropylidene-2-*O*-*p*-methoxybenzyl-β-D-talopyranosyl)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (3)

A suspension of pre-washed (hexane) NaH (60% in mineral oil, 345 mg, 8.61 mmol) in dry DMF (10 mL) was cooled to 0 °C and treated under argon atmosphere with a solution of **2**[10] (2.50 g, 4.31 mmol) in dry DMF (25 mL). The mixture was warmed to room temperature and stirred for 30 min, cooled again to 0 °C and then treated with PMBCl (0.70 mL, 5.17 mmol). The mixture was allowed to reach room temperature and further stirred until the starting material was consumed (2 h, TLC, 3:7 hexane–EtOAc). Excess of NaH was destroyed by dropwise addition of MeOH (1 mL) followed by 10 min stirring at 0 °C. After removal of the solvents under diminished pressure, the crude residue was dissolved in CH_2Cl_2 (50 mL) and treated with 5% aq HCl (50 mL) until TLC analysis (3:7 hexane–EtOAc) revealed the complete disappearance of the product at R_f 0.57 and the formation of a slower moving product (R_f 0.32). The two phases were separated, the aqueous phase was further extracted with CH_2Cl_2 (20 mL) and the collected organic extracts were neutralized with satd aq $NaHCO_3$ (30 mL). The organic phases were dried, filtered and concentrated under diminished pressure. The crude residue was dissolved in dry DMF (25 mL) and added to a suspension of pre-washed (hexane) NaH (60% in mineral oil, 318 mg, 7.95 mmol) in dry DMF (10 mL) cooled to 0 °C. The mixture was warmed to room temperature and stirred for 20 min, cooled again to 0 °C and then treated with BnBr (0.57 mL, 4.7 mmol). The mixture was allowed to reach room temperature and further stirred until the starting material (R_f 0.32) was consumed (12 h, TLC, 3:7 hexane–EtOAc). MeOH (1 mL) and water (20 mL) were slowly added at 0 °C, and the mixture was extracted with CH_2Cl_2 (4 × 20 mL). The collected organic layers were dried, filtered, and concentrated under diminished pressure. The residue was purified by flash chromatography over silica gel, eluting with 7:3 hexane–EtOAc, to give **3** (2.37 g, 83% yield) as a clear syrup; R_f 0.18 (7:3 hexane–EtOAc); $[\alpha]_D$ −7.41 (*c* 1.08; $CHCl_3$); ^1H NMR (CD_3CN): δ 7.36–7.30 (m, 7H, Ar-*H*), 6.88–6.82 (m, 2H, Ar-*H*), 4.65 (d, 1H, $J_{1',2'}$ 1.3 Hz, H-1′), 4.63 (s, 2H, CH_2PMB), 4.56, 4.51 (AB system, 2H, $J_{A,B}$ 12.0 Hz, CH_2Ph), 4.43 (dd, 1H, $J_{1,2}$ 6.0 Hz, $J_{2,3}$ 7.5 Hz, H-2), 4.34 (d, 1H, H-1), 4.25 (dd, 1H, $J_{2',3'}$ 5.6 Hz, $J_{3',4'}$ 6.3 Hz, H-3′), 4.21 (dt, 1H, $J_{5,6a}$=$J_{5,6b}$ 6.5 Hz, $J_{4,5}$ 2.0 Hz, H-5), 4.05 (dd, 1H, $J_{3,4}$ 1.6 Hz, H-3), 4.03 (dd, 1H, $J_{4',5'}$ 2.6 Hz, H-4′), 3.96 (dd, 1H, $J_{6a,6b}$ 8.5 Hz, H-6b), 3.91 (dd, 1H, H-6a), 3.88 (dd, 1H, H-4), 3.86 (ddd, 1H, $J_{5',6'a}$ 6.7 Hz, $J_{5',6'b}$ 5.7 Hz, H-5′), 3.76 (s, 3H, OMe-PMB), 3.67 (dd, 1H, $J_{6'a,6'b}$ 10.0 Hz, H-6′b), 3.61 (dd, 1H, H-6′a), 3.63 (dd, 1H, H-2′), 3.32, 3.31 (2s, each 3H, 2 × OMe-1), 1.39, 1.35, 1.31, 1.30, 1.27, 1.26 (6s, each 3H, 3 × CMe_2); ^{13}C NMR (CD_3CN): δ 160.0, 131.7 (2 × Ar-*C* PMB), 139.6 (Ar-*C*, Bn), 131.0, 114.3 (Ar-*C*H PMB), 129.3-128.5 (Ar-*C*H, Bn), 110.5, 110.4, 108.9 (3 × CMe_2), 106.2 (C-1), 102.5 (C-1′), 78.4 (C-3), 78.2 (C-5), 77.4

(C-4), 76.4 (C-2), 74.9 (CH_2Ph), 74.7 (C-3′), 74.1 (C-2′), 73.8 (CH_2-PMB), 72.9 (C-5′), 72.2 (C-4′), 70.0 (C-6′), 66.2 (C-6), 56.1, 54.5 (OMe-1), 55.8 (OMe-PMB), 27.4, 27.2, 26.9, 26.1, 26.0, 25.3 (3 × CMe_2). Anal. Calcd for $C_{38}H_{54}O_{13}$: C, 63.49; H, 7.57. Found: C, 63.59; H, 7.67.

3.3. 4-*O*-(3,6-Di-*O*-benzyl-4-deoxy-2-*O*-*p*-methoxybenzyl-β-D-*erhytro*-hex-4-enopyranosyl)- 2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (4)

A soln of **3** (2.37 g, 3.29 mmol) in dry THF (56 mL) was warmed to reflux and treated with solid *t*-BuOK (3.70 g, 33.0 mmol). After 20 min, TLC analysis (1:1 hexane–EtOAc) showed the complete disappearance of the starting material, and satd aq $NaHCO_3$ (50 mL) was then added. The aq phase was extracted with CH_2Cl_2 (3 × 75 mL) and the organic extracts were dried, filtered, and concentrated under diminished pressure. The crude enol ether was dissolved in dry DMF (25 mL) and added to a suspension of pre-washed (hexane) NaH (60% in mineral oil, 264 mg, 6.59 mmol) in dry DMF (10 mL) cooled to 0 °C. The mixture was warmed to room temperature and stirred for 20 min, cooled again to 0 °C and then treated with BnBr (0.50 mL, 3.95 mmol). The mixture was allowed to reach room temperature and further stirred until the starting material was consumed (12 h, TLC, 6:4 hexane–EtOAc). MeOH (1 mL) and water (30 mL) were slowly added at 0 °C, and the mixture was extracted with CH_2Cl_2 (4 × 20 mL). The collected organic layers were dried, filtered and concentrated under diminished pressure. The residue (2.21 g) was subjected to flash chromatography (7:3 hexane–EtOAc + 0.1% Et_3N) to give **4** (1.91 g, 77% yield) as a clear syrup; R_f 0.46 (6:4 hexane–EtOAc); $[\alpha]_D$ −38.9 (*c* 1.04, $CHCl_3$); ^{1}H NMR (CD_3CN): δ 7.38–7.25 (m, 12H, Ar-*H*), 6.86–6.80 (m, 2H, Ar-*H*), 5.29 (t, 1H, $J_{1',2'} = J_{1',3'}$ 1.1 Hz, H-1′), 4.90 (dd, 1H, $J_{3',4'}$ 2.8 Hz, $J_{4',6'a} = J_{4',6'b}$ 0.9 Hz, H-4′), 4.78, 4.66 (AB system, 2H, $J_{A,B}$ 11.1 Hz, CH_2Ph), 4.53, 4.45 (AB system, 2H, $J_{A,B}$ 11.8 Hz, CH_2Ph), 4.51 (s, 2H, CH_2PMB), 4.42 (dd, 1H, $J_{2,3}$ 7.1 Hz, $J_{1,2}$ 6.2 Hz, H-2), 4.33 (d, 1H, H-1), 4.26 (dt, 1H, $J_{4,5}$ 6.7 Hz, $J_{5,6a} = J_{5,6b}$ 3.7 Hz, H-5), 4.22 (ddd, 1H, $J_{2',3'}$ 6.0 Hz, H-3'), 4.10 (dd, 1H, $J_{3,4}$ 1.5 Hz, H-4), 4.05 (dd, 1H, H-3), 4.03 (dd, 1H, $J_{6a,6b}$ 10.1 Hz, H-6b), 3.98 (dd, 1H, H-6a), 3.94 (dd, 1H, H-2′), 3.89 (m, 2H, H-6′a, H-6′b), 3.75 (s, 3H, OMe-PMB), 3.35, 3.33 (2s, each 3H, 2 × OMe-1), 1.33, 1.29 (2s, each 3H, CMe_2), 1.31 (s, 6H, CMe_2); ^{13}C NMR (CD_3CN): δ 160.2, 131.8 (2 × Ar-*C*, PMB), 150.5 (C-5′), 139.9, 139.6 (2 × Ar-*C*, Bn), 130.6, 114.5 (Ar-*C*H, PMB), 129.2–128.4 (Ar-*C*H, Bn), 110.6, 108.7 (2 × CMe_2), 106.3 (C-1),101.2 (C-1′), 100.5 (C-4′), 78.7 (C-4), 78.5 (C-5), 77.0 (C-3), 76.1 (C-2), 73.6, 73.2 (2 × CH_2Ph), 73.2 (C-2′), 71.5 (CH_2PMB), 71.4 (C-3′), 69.9 (C-6′), 65.9 (C-6), 55.8 (OMe-PMB), 56.2, 53.9 (2 × OMe-1), 27.4, 27.2, 26.9, 25.6 (2 × CMe_2). Anal. Calcd for $C_{42}H_{54}O_{12}$: C, 67.18; H, 7.25. Found: C, 67.20; H, 7.26.

3.4. 4-*O*-(3,6-di-*O*-Benzyl-2-*O*-*p*-methoxybenzyl-β-D-mannopyranosyl)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (5)

A soln of **4** (1.91 g, 2.54 mmol) in dry THF (101 mL) was treated at 0 °C and under argon atmosphere with a 1:10 (v/v) soln of $BH_3{\cdot}Me_2S$ in Et_2O (5 M) in dry THF (2.28 mL, 11.4 mmol) (5 M). The reaction mixture was allowed to reach to room temperature and was stirred until the disappearance of the starting material (TLC, 6:4 hexane–EtOAc, 5 h). The mixture was cooled to 0 °C, and H_2O (2.4 mL), 10% aq NaOH (7.4 mL) and 35% aq H_2O_2 (20 mL) were sequentially added. The biphasic mixture was stirred at room temperature until the TLC analysis (6:4 hexane–EtOAc) revealed the disappearance of the borane intermediate (2 h) and the formation of a single spot (R_f 0.22). Water (200 mL) was added and the aq soln was extracted with CH_2Cl_2 (4 × 20 mL). The collected organic phase was dried, filtered, and concentrated under diminished pressure. The crude residue was subjected to a flash chromatographic purification on silica gel (65:35 hexane–EtOAc) to give pure **5** (1.57 g, 80% yield) as a clear syrup; R_f 0.22 (6:4 hexane–EtOAc); $[\alpha]_D$ −61.6 (*c* 1.27, $CHCl_3$); ^{1}H NMR (CD_3CN): δ 7.36–7.26 (m, 12H, Ar-*H*), 6.84-6.78 (m, 2H, Ar-*H*), 4.82, 4.61 (AB system, 2H, $J_{A,B}$ 11.2 Hz), 4.72 (d, 1H, $J_{1',2'}$ 0.6 Hz, H-1′), 4.60, 4.50 (AB system, 2H, $J_{A,B}$ 12.2 Hz), 4.55, 4.47 (AB system, 2H, $J_{A,B}$ 11.9 Hz), (2 × CH_2Ph, CH_2PMB), 4.45 (dd, 1H, $J_{1,2}$ 6.1 Hz, $J_{2,3}$ 7.6 Hz, H-2), 4.35 (d, 1H, H-1), 4.26 (dt, 1H, $J_{4,5}$ 3.7 Hz, $J_{5,6a} = J_{5,6b}$ 6.9 Hz, H-5), 4.09 (dd, 1H, $J_{3,4}$ 1.5 Hz, H-3), 4.04 (m, 2H, H-6a, H-6b), 4.01 (dd, 1H $J_{2',3'}$ 3.4 Hz, H-2′), 3.96 (dd, 1H, H-4), 3.75 (s, 3H, OMe-PMB), 3.74 (m, 1H, H-4′), 3.71 (m, 2H, H-6′a, H-6′b), 3.31 (m, 2H, H-3′, H-5′), 3.34, 3.32 (2s, each 3H, 2 × OMe-1), 1.34, 1.33, 1.32, 1.31 (4s, each 3H, 2 × CMe_2); ^{13}C NMR (CD_3CN): δ 160.0, 132.1 (2 × Ar-*C*, PMB), 139.9, 139.7 (2 × Ar-*C*, Bn), 130.5, 114.4 (Ar-*C*H, PMB), 129.2-128.3 (Ar-*C*H, Bn), 110.6, 108.7 (2 × CMe_2), 106.2 (C-1), 103.1 (C-1′), 82.6 (C-3′), 78.6 (C-5), 78.5 (C-3), 77.1 (C-4), 77.0 (C-5′), 76.5 (C-2), 75.6 (C-2′), 74.9, 74.6, 74.1 (2 × CH_2Ph, CH_2PMB), 70.6 (C-6′), 67.5 (C-4′), 65.9 (C-6), 56.0, 54.3 (2 × OMe-1), 55.8 (OMe-PMB), 27.4, 27.3, 26.9, 25.2 (2 × CMe_2). Anal. Calcd for $C_{42}H_{56}O_{13}$: C, 65.61; H, 7.34. Found: C, 65.63; H, 7.38.

3.5. 4-*O*-(3,4,6-tri-*O*-Benzyl-2-*O*-*p*-methoxybenzyl-β-D-mannopyranosyl)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (6)

To a suspension of pre-washed (hexane, 3 × 30 mL) NaH (60% in mineral oil , 164 mg, 4.09 mmol) in dry DMF (10 mL), a soln of **5** (1.57 g, 2.05 mmol) in dry DMF (20 mL) was added at 0 °C. The mixture was stirred for 30 min at 0 °C, then BnBr (0.30 mL, 2.45 mmol) was added and the reaction mixture was further stirred at room temperature until the starting compound was completely reacted (12 h, TLC, 7:3 hexane–EtOAc). Excess of NaH was destroyed by dropwise addition of MeOH (1 mL, 30 min) at 0 °C, and then the solvents were evaporated under diminished pressure. The residue was partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL). The organic phase was separated, and the aq layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried, filtered, and concentrated under diminished pressure. Flash chromatographic purification over silica gel of the crude product (7:3 hexane–EtOAc) gave pure **6** (1.64 g, 93% yield) as a clear syrup; R_f 0.52 (6:4 hexane–EtOAc), $[\alpha]_D$ −36.3 (*c* 1.15, $CHCl_3$); ^{1}H NMR (CD_3CN): δ 7.36–7.20 (m, 17H, Ar-*H*), 6.86–6.80 (m, 2H, Ar-*H*), 4.85, 4.65 (AB system, 2H, $J_{A,B}$ 11.3 Hz), 4.81, 4.52 (AB system, 2H, $J_{A,B}$ 10.3 Hz), 4.74 (d, 1H, $J_{1',2'}$ 0.4 Hz, H-1′), 4.63, 4.48 (AB system, 2H, $J_{A,B}$ 11.9 Hz), 4.56, 4.48 (AB system, 2H, $J_{A,B}$ 11.7 Hz), (3 × CH_2Ph, CH_2PMB), 4.49 (dd, 1H, $J_{1,2}$ 6.0 Hz, $J_{2,3}$ 7.4 Hz, H-2), 4.36 (d, 1H, H-1), 4.27 (dt, 1H, $J_{4,5}$ 3.6 Hz, $J_{5,6a} = J_{5,6b}$ 6.7 Hz, H-5), 4.05 (dd, 1H, $J_{3,4}$ 1.5 Hz, H-3), 4.03 (m, 2H, H-6a, H-6b), 4.02 (dd, 1H, $J_{2',3'}$ 3.0 Hz, H-2′), 3.96 (dd, 1H, H-4), 3.80 (dd, 1H, $J_{3',4'}$ 9.4 Hz, $J_{4',5'}$ 9.6 Hz, H-4′), 3.76 (s, 3H, OMe-PMB), 3.75 (dd, 1H, $J_{5',6'b}$ 4.0 Hz, $J_{6'a,6'b}$ 11.0 Hz, H-6′b), 3.68 (dd, 1H, $J_{5',6'a}$ 1.9 Hz, H-6′a), 3.53 (dd, 1H, H-3′), 3.37, 3.35 (2s, each 3H, 2 × OMe-1), 3.32 (ddd, 1H, H-5′), 1.35, 1.34, 1.32, 1.31 (4s, each 3H, 2 × CMe_2); ^{13}C NMR (CD_3CN): δ 160.2, 132.2 (2 × Ar-C, PMB), 139.9, 139.7, 139.6 (2 × Ar-C, Bn), 130.6, 114.4 (Ar-*C*H, PMB), 129.2–128.4 (Ar-*C*H, Bn), 110.6, 108.8 (2 × CMe_2), 106.3 (C-1), 103.2 (C-1′), 83.0 (C-3′), 78.6 (C-5), 77.3 (C-4), 76.6 (C-2), 76.5 (C-5′), 75.8 (C-2′), 75.4 (C-4′), 75.5, 74.7, 74.1, 72.0 (3 × CH_2Ph, CH_2-PMB), 70.2 (C-6′), 65.9 (C-6), 55.8 (OMe-PMB), 56.1, 54.4 (2 × OMe-1), 27.4, 27.3, 27.0, 25.3 (2 × CMe_2). Anal. Calcd for $C_{49}H_{62}O_{13}$: C, 68.51; H, 7.27. Found: C, 68.49; H, 7.25.

3.6. 4-*O*-(3,4,6-tri-*O*-Benzyl-β-D-mannopyranosyl)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (7)

To a soln of **6** (1.64 g, 1.91 mmol) in 18:1 CH_2Cl_2–H_2O (50 mL), DDQ (650 mg, 2.86 mmol) was added and the resulting mixture was stirred until TLC analysis (6:4 hexane–EtOAc, 1 h) revealed the complete disappearance of the starting material. The reaction mixture was washed with satd aq $NaHCO_3$ (50 mL) and the organic phase was separated. The aqueous layer was repeatedly extracted with CH_2Cl_2 (4 × 50 mL), and the collected organic phases were dried, filtered, and concentrated under diminished pressure. Flash chromatographic purification over silica gel (6:4 hexane–EtOAc) afforded pure **7** (1.05 g, 76% yield) as a clear syrup; R_f 0.29 (6:4 hexane–EtOAc), $[\alpha]_D$ −2.57 (*c* 1.13, $CHCl_3$); ^{1}H NMR (CD_3CN): δ 7.42–7.20 (m, 15H, Ar-*H*), 4.82, 4.47 (AB system, 2H, $J_{A,B}$ 11.2 Hz, C*H*$_2$Ph), 4.73, 4.57 (AB system, 2H, $J_{A,B}$ 10.9 Hz, C*H*$_2$Ph), 4.71 (d, 1H, $J_{1',2'}$ 0.9 Hz, H-1′), 4.55, 4.46 (AB system, 2H, $J_{A,B}$ 11.8 Hz, C*H*$_2$-Ph), 4.45 (dd, 1H, $J_{1,2}$ 6.2 Hz, $J_{2,3}$ 7.0 Hz, H-2), 4.34 (d, 1H, H-1), 4.22 (dt, 1H, $J_{4,5}$ 4.3 Hz, $J_{5,6a} = J_{5,6b}$ 6.2 Hz, H- 5), 4.14 (dd, 1H, $J_{2',3'}$ 3.0 Hz, H-2′), 4.05 (dd, 1H, $J_{3,4}$ 1.5 Hz, H-3), 3.98 (m, 2H, H-6a, H-6b), 3.91 (dd, 1H, H-4), 3.74 (t, 1H, $J_{4',5'} = J_{3',4'}$ 9.4 Hz, H-4′), 3.70 (m, 2H, H-6′a, H-6′b), 3.55 (dd, 1H, H-3′), 3.35, 3.34 (2s, each 3H, 2 × OMe-1), 3.32 (m, 1H, H-5′), 2.86 (d, $J_{2',OH}$ 3.7 Hz, OH-2′), 1.38, 1.34, 1.33, 1.29 (4s, each 3H, 2 × C*Me*$_2$); ^{13}C NMR (63 MHz, CD_3-CN): δ 139.8, 139.6, 139.5 (3 × Ar-*C*), 129.2–128.4 (Ar-*C*H), 110.9, 108.8 (2 × *C*Me$_2$), 106.1 (C-1), 101.5 (C-1′), 82.6 (C-3′), 78.7 (C-3), 78.1 (C-5), 76.7 (C-4), 76.5 (C-2), 76.0 (C-5′), 75.5, 73.9, 71.4 (3 × *C*H$_2$Ph), 74.0 (C-4′), 70.2 (C-6′), 68.7 (C-2′), 66.0 (C-6), 56.0, 54.2 (2 × OMe-1), 27.7, 27.1, 26.9, 25.4 (2 × C*Me*$_2$). Anal. Calcd for $C_{41}H_{54}O_{12}$: C, 66.65; H, 7.37. Found: C, 66.61; H, 7.34.

3.7. 4-*O*-(3,4,6-tri-*O*-Benzyl-2-*O*-imidazoylsulfonyl-β-D-mannopyranosyl)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (8)

To a pre-washed (hexane) suspension of NaH (60% in mineral oil, 284 mg, 7.11 mmol) in dry DMF (10 mL), a soln of **7** (1.06 g, 1.42 mmol) in dry DMF (15 mL) was slowly added under argon atmosphere at 0 °C. The mixture was stirred at 0 °C for 30 min, cooled to −30 °C, treated with Im_2SO_2 (411.5 mg, 2.08 mmol) and further stirred at −30 °C. After 1 h, TLC analysis (4:6 hexane–EtOAc) revealed the complete disappearance of the starting material. The reaction mixture was then cooled to −40 °C, the excess of NaH was destroyed by addition of MeOH (0.5 mL). After 10 min, Et_2O (20 mL) and crushed iced-water were added. The organic phase was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The collected organic phases were dried, filtered, and concentrated under diminished pressure. Flash chromatographic purification over silica gel of the reaction product (6:4 hexane–EtOAc) gave pure **8** (1.02 g, 83% yield) as a clear syrup; R_f 0.37 (6:4 hexane–EtOAc), $[\alpha]_D$ −13.6 (*c* 1.16, $CHCl_3$); ^{1}H NMR (CD_3CN): δ 8.01 (dd, 1H, $J_{2,4}$ 1.3 Hz, Im-H_2), 7.46 (dd, 1H, $J_{2,5}$ 0.9 Hz, $J_{4,5}$ 1.6 Hz, Im-H_4), 7.40–7.24 (m, 15H, Ar-*H*), 7.01 (dd, 1H, Im-H_5), 5.25 (dd, 1H, $J_{1',2'}$ 0.6 Hz, $J_{2',3'}$ 2.3 Hz, H-2′), 4.94 (d, 1H, H-1′), 4.68, 4.48 (AB system, 2H, $J_{A,B}$ 10.8 Hz, C*H*$_2$Ph), 4.64, 4.49 (AB system, 2H, $J_{A,B}$ 11.8 Hz, C*H*$_2$Ph), 4.56, 4.47 (AB system, 2H, $J_{A,B}$ 11.9 Hz, C*H*$_2$Ph), 4.35 (m, 2H, H-1, H-2), 4.20 (dt, 1H, $J_{4,5}$ 4.9 Hz, $J_{5,6a} = J_{5,6b}$ 6.4 Hz, H-5), 4.03 (dd, 1H, $J_{2,3}$ 7.3 Hz, $J_{3,4}$ 1.9 Hz, H-3), 3.94 (m, 2H, H-6a, H-6b), 3.89 (dd, 1H, H-4), 3.70 (dd, 1H, $J_{3',4'}$ 10.5 Hz, H-3′), 3.68 (m, 3H, H-4′, H-6′a, H6′b), 3.39 (m, 1H, H-5′), 3.38, 3.35 (2s, each 3H, 2 × OMe-1), 1.35, 1.34, 1.32, 1.29 (4s, each 3H, 2 × C*Me*$_2$); ^{13}C NMR (CD_3CN): δ 139.3, 139.1, 138.4 (3 × Ar-*C*), 138.1 (Im-C_2), 131.2 (Im-C_4), 129.3-128.6 (Ar-*C*H), 119.7 (Im-C_5), 110.5, 109.0 (2 × *C*Me$_2$), 106.3 (C-1), 99.0 (C-1′), 84.6 (C-2′), 78.7 (C-4), 78.0 (C-3), 77.4 (C-5), 76.2 (C-2), 76.0 (C-5′), 75.6, 74.1, 73.2 (3 × *C*H$_2$-Ph), 74.8 (C-4′), 72.2 (C-3′), 69.4 (C-6′), 66.1 (C-6), 56.3, 54.4 (2 × OMe-1), 27.3, 27.2, 27.1, 25.3 (2 × C*Me*$_2$). Anal. Calcd for C_{44}-$H_{56}N_2O_{14}S$: C, 60.81; H, 6.50; N, 3.22; S, 3.69. Found: C, 60.79; H, 6.48; N, 3.20; S, 3.66.

3.8. 4-*O*-(2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (9)

A soln of **8** (954 mg, 1.09 mmol) and NaN_3 (142 mg, 2.18 mmol) in dry DMF (32 mL) was stirred at 100 °C under argon atmosphere. After 45 min, TLC analysis (1:1 hexane–EtOAc) revealed the complete disappearance of the starting material; the mixture was then cooled to room temperature and partitioned between satd aq $NaHCO_3$ (50 mL) and Et_2O (50 mL). The organic phase was separated and the aq layer extracted with Et_2O (4 × 50 mL). The organic extracts were dried, filtered, and concentrated under diminished pressure. Purification of the crude by flash chromatography over silica gel (7:3 hexane–EtOAc) afforded pure **9** (762 mg, 92% yield) as a clear syrup; R_f 0.68 (1:1 hexane–EtOAc), $[\alpha]_D$ −53.5 (*c* 1.02, $CHCl_3$); ^{1}H NMR (CD_3CN): δ 7.40–7.20 (m, 15H, Ar-*H*), 4.83, 4.78 (AB system, 2H, $J_{A,B}$ 11.1 Hz, C*H*$_2$Ph), 4.75, 4.57 (AB system, 2H, $J_{A,B}$ 10.9 Hz, C*H*$_2$Ph), 4.70 (d, 1H, $J_{1',2'}$ 7.8 Hz, H-1′), 4.56, 4.47 (AB system, 2H, $J_{A,B}$ 11.8 Hz, C*H*$_2$Ph), 4.43 (dd, 1H, $J_{1,2}$ 6.2 Hz, $J_{2,3}$ 7.0 Hz, H-2), 4.34 (d, 1H, H-1), 4.29 (dt, 1H, $J_{4,5}$ 4.7 Hz, $J_{5,6a} = J_{5,6b}$ 6.4 Hz, H- 5), 4.12 (dd, 1H, $J_{6a,6b}$ 8.4 Hz, H6b), 4.10 (dd, 1H, $J_{3,4}$ 1.4 Hz, H-3), 4.03 (dd, 1H, H-6a), 3.97 (dd, 1H, H-4), 3.74 (dd, 1H, $J_{5',6'b}$ 3.6 Hz, $J_{6'a,6'b}$ 11.1 Hz, H6′b), 3.67 (dd, 1H, $J_{5',6'a}$ 3.1 Hz, H-6′a), 3.62 (dd, 1H, $J_{2',3'}$ 9.1 Hz, $J_{3',4'}$ 8.6 Hz, H-3′), 3.48-3.35 (m, 3H, H-2′, H-4′, H-5′), 3.37, 3.35 (2s, each 3H, 2 × OMe-1), 1.46, 1.36, 1.34, 1.30 (4s, each 3H, 2 × C*Me*$_2$); ^{13}C NMR (CD_3CN): δ 139.5, 139.4, 139.3 (3 × Ar-*C*), 129.2–128.5 (Ar-*C*H), 110.9, 108.9 (2 × *C*Me$_2$), 106.4 (C-1), 102.2 (C-1′), 83.6 (C-4′), 78.6 (C-3′), 78.5 (C-3), 78.0 (C-5), 76.6 (C-2), 76.1 (C-4), 75.6 (C-5′), 75.8, 75.6, 74.1 (3 × *C*H$_2$Bn), 69.7 (C-6′), 68.1 (C-2′), 66.0 (C-6), 56.1, 54.4 (2 × OMe-1), 27.7, 27.2, 26.8, 25.3 (2 × C*Me*$_2$). Anal. Calcd for $C_{41}H_{53}N_3O_{11}$: C, 64.47; H, 6.99; N, 5.50. Found: C, 64.45; H, 6.97; N, 5.48.

3.9. 4-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (10)

A soln of **9** (123 mg, 0.16 mmol) in 1:3 EtOAc–EtOH (18 mL) containing 10% Pd on charcoal (63 mg) and Ac_2O (0.08 mL, 0.42 mmol) was stirred at room temperature under an H_2 atmosphere until TLC analysis (8:2 $CHCl_3$–MeOH, 48 h) revealed the disappearance of the starting material. The mixture was diluted with EtOH (30 mL), filtered over Celite, concentrated under diminished pressure. Purification of the residue by flash chromatography over silica gel (95:5 $CHCl_3$–MeOH + 0.01% Et_3N) gave **10** (44 mg, 53%) as a white foam; R_f 0.52 (8:2 $CHCl_3$–MeOH); $[\alpha]_D$ −48.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (CD_3CN): δ 6.79 (d, 1H, $J_{2',NH}$ 7.4 Hz, NH), 4.56 (d, 1H, $J_{1',2'}$ 8.1 Hz, H-1′), 4.43 (dd, 1H, $J_{1,2}$ 6.8 Hz, $J_{2,3}$ 7.4 Hz, H-2), 4.35 (d, 1H, H-1), 4.21 (m, 1H, H-5), 4.05-3.85 (m, 4H, H-3′, H-3, H-6a, H-6b), 3.81 (m, 1H, H-6′b), 3.73 (m, 1H, H-4), 3.59-3.45 (m, 5H, H-2′, H-6′a, 3 × OH), 3.40, 3.39 (2s, each 3H, 2 × OMe-1), 3.22 (m, 2H, H-4′, H-5′), 1.92 (s, 3H, *Me*CO), 1.42, 1.31, 1.30, 1.29 (4s, each 3H, 2 × C*Me*$_2$); ^{13}C NMR (CD_3CN): δ 172.2 (CO), 110.4, 108.9 (2 × *C*Me$_2$), 107.5 (C-1), 102.3 (C-1′), 78.9 (C-3), 77.7 (C-5), 77.2 (C-5′), 76.5 (C-4), 76.0 (C-2), 75.9 (C-3′), 72.5 (C-4′), 65.9 (C-6), 63.2 (C-6′), 57.4 (C-2′), 57.3, 54.5 (2 × OMe-1), 27.3, 26.7, 26.6, 24.6 (2 × C*Me*$_2$), 23.3 (*Me*CO). Anal. Calcd for $C_{22}H_{39}NO_{12}$: C, 51.86; H, 7.71; N, 2.75. Found: C, 52.03; H, 7.68; N, 2.84.

3.10. 4-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-α,β-D-glucopyranose (11)

A soln of **10** (73 mg, 0.14 mmol) in 80% aq. AcOH (2.7 mL) was stirred at 80 °C until TLC analysis (7:3 $CHCl_3$–MeOH, 3 h) revealed the disappearance of the starting material. The reaction mixture was concentrated under diminished pressure by coevaporation with toluene (4 × 30 ml). The crude residue was triturated with EtOAc to give an amorphous white solid (47.6 mg, 87% yield) composed by a 2:3 α/β anomeric mixture of **11**, as established on the basis of the integration of the H-1 signals at δ 5.05 and 4.57 respectively; $[\alpha]_{D\infty}$ +27 (*c*, 0.81, water); lit.[9d] $[\alpha]_D$ +30 (*c*, 0.7, water); mp 195–197 °C (MeOH–Et_2O), lit.[9d] mp 190–195 °C (MeOH–Et_2O); selected ^1H NMR (D_2O) signals: **α-11**): δ 5.05 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 4.40 (d, 1H, $J_{1',2'}$ 8.0 Hz, Hz, H-1′); 1.97 (s, 3H, MeCO), **β-11**: δ 4.47 (d, 1H, $J_{1,2}$ 8.0 Hz, H-1), 4.39 (d, 1H, $J_{1',2'}$ 8.1 Hz, Hz, H-1′); 3.80 (dd, 1H, $J_{5',6'b}$ 1.7 Hz, $J_{6'a,6'b}$ 12.1 Hz, H-6′b); 3.12 (dd, 1H, $J_{2,3}$ 9.1 Hz, H-2); 1.89 (s, 3H, MeCO); ^{13}C NMR (D_2O) signals: **α-11**: δ 175.4 (CO), 102.3 (C-1′), 92.5 (C-1), 80.7 (C-4), 76.7 (C-5′), 74.3 (C-3′), 72.3 (C-3), 72.2 (C-2), 71.5 (C-5), 70.6 (C-4′), 61.4 (C-6′), 60.9 (C-6), 56.4 (C-2′), 22.9 (*Me*CO), **β-11**: δ 175.4 (CO), 102.3 (C-1′), 96.5 (C-1), 80.3 (C-4), 73.7 (C-5′), 75.3, 75.2 (C-3, C-5), 74.5 (C-2), 74.3 (C-3′), 70.6 (C-4′), 61.4 (C-6′), 61.0 (C-6), 56.4 (C-2′), 22.9 (*Me*CO).

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