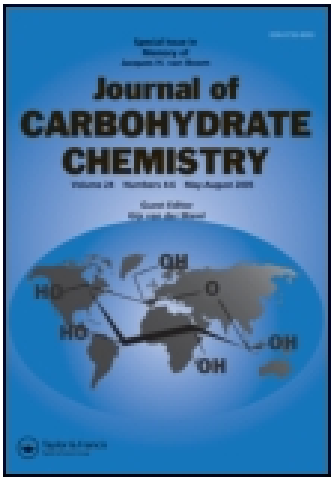

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A New Preparation of the Disaccharide β-D-ManNAcp-(1 → 4)-D-Glc from Lactose Through a Highly Stereoselective β-D-Galp to β-D-ManNAcp Transformation

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A New Preparation of the Disaccharide β-D-ManNAc*p*-(1 → 4)-D-Glc from Lactose Through a Highly Stereoselective β-D-Gal*p* to β-D-ManNAc*p* Transformation[#]

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CONTENTS

[#]Part 19 of the series, "Chemical Valorisation of Milk-Derived Carbohydrates"; for part 18, see Ref. [26].

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ABSTRACT

A new method for the construction of the β-D-ManNAc*p*-(1 → 4)-D-Glc framework from lactose avoiding the β-mannosaminylation step was developed starting from 4-*O*-(2-acetamido-2-deoxy-3,4-*O*-isopropylidene-6-*O*-trityl-β-D-talopyranosyl)-2,3 : 5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal **2**, obtained from 6′-*O*-trityl-triacetonelactose dimethyl acetal, as previously reported [Barili, P.L.; Berti, G.; Catelani, G.; D'Andrea, F.; Puccioni, L. Stereoselective synthesis of 4-*O*-(2-acetamido-2-deoxy-β-D-talopyranosyl)-D-glucose derivatives from lactose. J. Carbohydr. Chem. **2000**, *19*, 79–81.] After a preliminary modification of the protecting groups on the β-D-talosamine unit into the 3′,6′-di-*O*-benzyl derivative **6**, a new stereoselective protocol of *C*-4′ epimerization was applied using (a) a regioselective dehydration providing the 4′-deoxy-hex-3′-eno derivative **7** through a simultaneous activation–elimination reaction with NaH-sulfuryldiimidazole system, (b) its regio- and stereoselective hydroboration–oxidation to give the protected β-D-mannosamine disaccharide **8**, with an overall 64% yield. The completely deprotected β-D-ManNAc*p*-(1 → 4)-D-Glc disaccharide was, finally, obtained with high yield, as an about 45 : 55 mixture of α- and β-pyranose forms, through catalytic debenzylation followed by acid hydrolysis of **8**.

Key Words: Mannosamine; Talosamine; Epimerization; 2-Acetamido-2-deoxy-β-D-mannopyranosides; Lactose; Hex-3-enopyranosides.

INTRODUCTION

One of the more biologically relevant members of the 2-amino-2-deoxyhexose family[1] is 2-acetamido-2-deoxy-D-mannose (D-mannosamine, ManNAc), frequently occurring in its pyranose form in the capsular polysaccharide repeating unit of some pathogens, including *Haemophilus influenzae* and *Pneumococcus* strains.[2,3] The β-D-ManNAc*p* residue is a component of the natural spacer unit linking teichoic acids to the peptidoglycan chain in some Gram-positive bacteria.[4] More recently, Kren and co-workers[5] demonstrated that ManNAc is the strongest 2-acetamido-2-deoxyhexose ligand for the natural killer cell activating protein (NKR-P1).[5] Furthermore, disaccharides containing ManNAc unit at the reducing end were proved to have the highest affinity for the NKR-P1 receptors.[5] Syntheses of β-D-GlcNAc*p*- and β-D-GalNAc*p*-(1 → 4)-D-ManNAc disaccharides were performed[6,7] by the Lobry de Bruyn–Alberda van Ekenstein epimerization[8] of the GlcNAc unit of pertinent disaccharide, followed by separation of the resulting disaccharide mixtures by chromatographic[6] or enzymatic means.[7] The synthesis of disaccharides having a β-D-ManNAc*p* unit at the non-reducing end, potentially active as NKR-P1 ligands,[5] has constituted until now one of the most challenging problems in synthetic carbohydrate chemistry.[9,10] Only one[11] of the five reported syntheses[12–15] of β-D-ManNAc*p*-(1 → 4)-D-Glc*p* disaccharide derivatives employed a direct glycosylation between a 2-azido-2-deoxy-D-mannopyranosyl donor and a glucopyranosyl acceptor leading to a β-enriched mixture of diastereoisomeric disaccharides.[11] Other constructions of the β-D-ManNAc*p*-(1 → 4)-D-Glc*p* framework[12–15] were made indirectly by amination with inversion at C-2 of β-D-Glc*p* units[12,14] or by reduction of a 2′-oximino group of disaccharides obtained by glycosylation with 2-deoxy-2-oximino-α-D-*arabino*-hexopyranosyl

donors.[15,16] In one case[11] the complete deprotection leading to β-D-ManNAc*p*-(1 → 4)-D-Glc*p* (**1**), has been described.

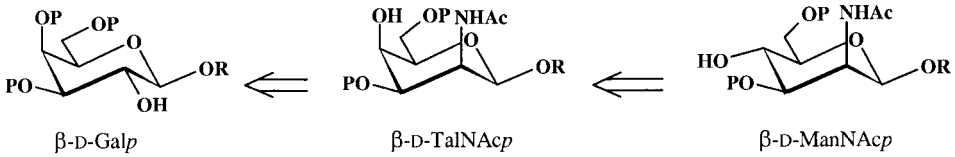
Owing to the biological interest of **1**[5] and its rather complicated reported preparation,[11] we have envisaged a new synthetic way to **1** starting from lactose through a recently disclosed stereoselective protocol for the transformation of β-D-Gal*p* into β-D-ManNAc*p* units[17] based (Sch. 1) on the first amination with configurational inversion at C-2 followed by an epimerization at C-4, thus avoiding the difficult β-mannosaminylation step. Described here is the synthesis of **1** starting from 4-*O*-(2-acetamido-2-deoxy-3,4-*O*-isopropylidene-6-*O*-trityl-β-D-talopyranosyl)-2,3 : 5,6-di-*O*-isopropylidene-*aldheydo*-D-glucose dimethyl acetal (**2**) (Sch. 2), previously obtained by us in overall 32% yield from lactose.[18]

RESULTS AND DISCUSSION

In order to realize the TalNAc*p* → ManNAc*p* epimerization we needed a talosamino derivative having exclusively the 4-OH group in the free form,[17] and, consequently, a preliminary procedure to perform a regioselective 3′,4′-de-*O*-isopropylidenation of **2**. This task, however, is not directly obtainable. We have, in fact, previously found[18] that a partial de-*O*-isopropylidenation of **2** through mild acid hydrolysis with 80% aqueous AcOH determined the contemporary removal of 6′-*O*-trityl protecting group.[18] Any attempt to operate a more selective deprotection by acting on the AcOH concentration as well as other reaction parameters (temperature and time) gave only mixtures of partially deprotected derivatives not viable for preparative purposes. This problem could be circumvented by a change of protection of the OH-6′ group from the acid labile trityl ether to the more acid stable benzyl ether. The de-*O*-tritylation step, however, turned to be more complicated than expected; catalytic removal of trityl group, in fact, failed under different reaction conditions with several lots of Pd/C and $Pd(OH)_2/C$ catalysts. A satisfactory selective de-*O*-tritylation was made in an acceptable yield (77%) taking advantage of the Kong's methodology employing $FeCl_3 \cdot 6H_2O$ as acid catalyst in CH_2Cl_2.[19] The known[18] intermediate alcohol **3**, previously obtained as side product isolated in minute amounts during the synthesis of **2**,[18] was then 6′-*O*-benzylated (BnBr, KOH, 18-crown-6, wet THF, room temperature, 1.5 hr, 87% yield) to give derivative **4**.

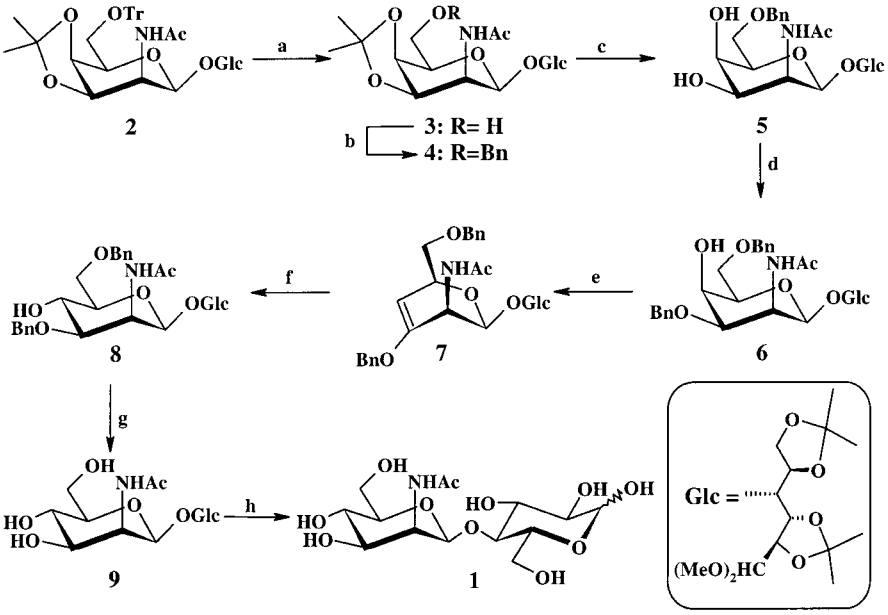
The following de-*O*-isopropylidenation step with 80% aq. AcOH gave, as expected,[18] the tetraol **10** with good yield (79%). As previously found for the same reaction of **2**,[18] the 5,6- and the 3′,4′-*O*-isopropylidene groups, involving respectively a primary hydroxyl group and an annular strain, showed a relative reactivity very similar to each other and much higher with respect to the remaining 2,3-*O*-isopropylidene group.

A highly regioselective re-acetonation of the 5,6-diol function of **10** was performed by treatment with one equivalent of 2-methoxypropene (2-MP) under mild acid catalysis



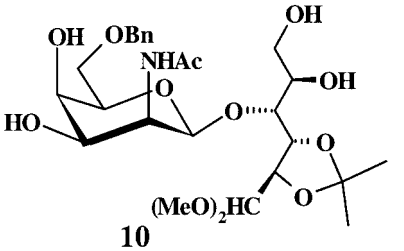
β-D-Gal*p* β-D-TalNAc*p* β-D-ManNAc*p*

Scheme 1. Retrosynthetic approach for the β-D-Gal*p* to β-D-ManNAc*p* transformation.



Scheme 2. (a) $FeCl_3 \cdot 6H_2O$, CH_2Cl_2, 3 hr, 77%; (b) KOH, 18-crown-6, BnBr, THF, 1.5 hr, 87%; (c) i. 80% aq. AcOH, 40°C, 1.45 hr; ii. 2-MP, PyHOTs, CH_2Cl_2, 1.5 hr, 82% for two steps; (d) Bu_2SnO, toluene, reflux, overnight then BnBr, Bu_4NBr, reflux, 5.5 hr, 95%; (e) NaH, Im_2SO_2, DMF, $-30°C \rightarrow$ rt, 4 hr; (f) $BH_3 \cdot Me_2S$, Et_2O, 5 hr then NaOH, H_2O_2, 2 hr, 64% from **6**; (g) $Pd(OH)_2/CH_2$, 5 hr; 93%; (h) 80% aq. AcOH, 80°C, 3.5 hr, 89%.

(PyHOTs) in dry CH_2Cl_2 leading in good yield (92%) to the diol **5**. The overall result of this two-steps de-acetonation/re-acetonation procedure was, thus, the selective deprotection of the 3′,4′diol function. A closely similar result, taking advantage of the higher reactivity of the primary hydroxyl function compared to the secondary ones,[20] had been used for the preparation of 2′,6′-di-*O*-benzyl-2,3 : 5,6-di-*O*-isopropylidenelactose dimethyl acetal from its relative triacetonide.[21] The efficiency of the two step 3′,4′-de-*O*-isopropylidenation of **4** was further improved, raising to an overall 82% yield, avoiding the chromatographic purification of **10** and subjecting the crude product obtained by acid hydrolysis of **4** to the acetonation with 2-MP.



10

The protection of the 3′-OH group of **5** was efficiently achieved through a regioselective stannylidene acetal mediated benzylation[22] (Bu_2SnO/toluene under azeotropic

anhydrification followed by BnBr and Bu_4NBr) leading with excellent yield (95%) to the derivative **6** as the sole reaction product. Although we have not found previous reports on the opening of 3,4-*O*-stannylidene acetals of the talo series, the complete regioselectivity observed is quite expected on the basis of the well known results for analogous galacto derivatives, in which the electrophilic attack was inferred exclusively at the equatorial *O*-3 of the intermediate 3,4-*O*-stannylidene acetal.[22]

The C-4′ epimerization of the derivative **6** was based on a two step procedure,[17] requiring first its regioselective dehydration to the hex-3′-enopyranoside **7** through an activation–elimination reaction by treatment with sulfuryldiimidazole and an excess NaH. The complete regioselectivity in the elimination of the putative intermediate 4′-*O*-imidazole-1-sulfonate (4′-*O*-imidazylate) was ascribed[23] to the stereoelectronic assistance of the C-2′ axial substituent favoring the anti elimination of the axial H-3′ to a greater extent than to the axial H-5′. The specific role of the axial orientation of the C-2′ substituent of the talo derivatives, was demonstrated by the complete lack of regioselectivity observed in the same reaction of galacto derivatives.[23] The second step of the epimerization procedure was the regio- and stereoselective hydroboration–oxidation ($BH_3 \cdot Me_2S/Et_2O$, room temperature 5 hr, followed by aq. H_2O_2, room temperature 2 hr) of the enol ether **7** leading to the β-D-mannosamine derivative **8**, in which the equatorial position of the 4′-OH was nicely demonstrated by the NMR signal of H-4′ at δ 3.88 with vicinal coupling constants ($J_{3',4'} = 9.4$ Hz, $J_{4',5'} = 9.6$ Hz) compatible only with a trans-diaxial disposition of H-3′, H-4′, and H-5′. The exclusive formation of the manno derivative **8** was attributed to the polarization of the enol ether double bond ensuring the complete regioselective attack at C-4′ of the electrophilic boron atom while the complete diastereoselection of the reaction was evidently due to the steric shielding of the β face exerted by the three substituents at C-1′, C-2′, and C-5′. The application of this new protocol for the C-4′ epimerization of a β-D-TalNAc*p* derivative to compound **6** was directly performed without purification of the intermediate enol ether **7** leading with good overall yield (64%) to the mannosamine derivative **8**.

The complete deprotection of **8** was finally made with high yield by classical procedures providing for its catalytic debenzylation (H_2, 5% $Pd(OH)_2$/C-EtOAc, room temperature, 5 hr, 93%) followed by hydrolysis of the triol **9** (80% aq. AcOH, 80°C 3.5 hr, 89% yield) involving de-*O*-isopropylidenation, exposition of the C-1 aldehyde group and its spontaneous pyranylization to **1**.

The structure of **1** and its anomeric composition as an about 45 : 55 α- and β-pyranose mixture were easily established on the basis of ^{13}C spectra. The chemical shift of the β-mannosamine carbons were, in fact, coincident for the two anomers (see Experimental) and strictly similar to those reported for other 2-acetamido-2-deoxy-β-D-mannopyranose units.[24] Furthermore the D-glucosyl reducing unit of **1** showed two well separated sets of signals very closely correspondent to those of α- and β-4-*O*-glycosyl-D-glucopyranose anomers.[25]

In conclusion, we have usefully applied our recently disclosed stereoselective procedure for the β-D-Gal*p* to β-D-ManNAc*p* transformation[17] to the definition of a new simple and effective synthesis of the biologically relevant disaccharide **1** starting from lactose, a readily available and cheap natural reducing disaccharide. Further studies directed to the utilization of some protected derivatives of **1** for the synthesis of more complex biologically active glycides are now planned.

EXPERIMENTAL

General Methods

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at $20 \pm 2^{\circ}C$. ^1H NMR spectra were recorded with a Bruker AC 200 instrument at 200 MHz in the stated solvent (Me_4Si was used as the internal standard).^{13}C NMR spectra were recorded with the same spectrometer at 50 MHz. Assignments were made with the aid of DEPT and HETCOR experiments and by comparison with those of known compounds. All reactions were followed by TLC on Kieselgel 60 F_{254} with detection by UV light and/or with ethanolic 10% phosphomolybdic or sulphuric acid, and heating. Kieselgel 60 (Merck, 70–230 and 230–400 mesh, respectively) was used for column and flash chromatography. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium using benzophenone radical as an indicator, and stored under argon before use. Other solvents were distilled and stored over 4 Å molecular sieves activated at least 24 hr at 400°C. $MgSO_4$ was used as the drying agent for solutions.

4-*O*-(2-Acetamido-2-deoxy-3,4-*O*-isopropylidene-β-D-talopyranosyl)-2,3 : 5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (3). To a solution of trityl derivative **2**[18] (2.00 g, 2.52 mmol) in CH_2Cl_2 (40 mL) was added solid $FeCl_3 \cdot 6H_2O$ (140 mg, 0.50 mmol). The mixture was stirred at room temperature until the starting material was completely reacted [3 hr, TLC (EtOAc)]. The reaction mixture was treated with water (50 mL) and diluted with CH_2Cl_2 (70 mL). The organic phase was separated, the aqueous layer repeatedly extracted with CH_2Cl_2 (4 × 50 mL), and the collected organic phases, after drying, were concentrated at reduced pressure. The crude residue was subjected to a flash chromatographic purification (93 : 7 $CHCl_3$–^{i}PrOH) to give pure **3** (1.07 g, 77% yield) as a white solid having physico-chemical properties identical to those of an authentic sample previously obtained by us.[18]

4-*O*-(2-Acetamido-6-*O*-benzyl-2-deoxy-3,4-*O*-isopropylidene-β-D-talopyranosyl)-2,3 : 5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (4). A stirred solution of **3** (0.85 g, 1.55 mmol) in wet THF (10 mL) was treated at room temperature with powdered KOH (0.35 g, 6.21 mmol) followed by 18-crown-6 (4 mg, 0.8 mmol). After 0.5 hr at room temperature the mixture was treated with neat BnBr (0.37 mL, 2.15 mmol). The starting material was completely reacted (TLC, 93 : 7 CH_2Cl_2–^{i}PrOH) after 1.5 hr, the reaction mixture was treated with MeOH (3 mL) and further stirred for 10 min, concentrated at reduced pressure to give a crude residue that was partitioned between CH_2Cl_2 (50 mL) and brine (30 mL). The aqueous phase was repeatedly extracted with CH_2Cl_2 (3 × 50 mL). The organic phases were collected, dried and concentrated at reduced pressure to give, after a flash chromatography (3 : 7 hexane–EtOAc) the title compound **4** (0.870 g, 87% yield) as a syrup; R_f 0.20 (3 : 7 hexane–EtOAc); $[\alpha]_D = -6.8$ (*c* 1.1, $CHCl_3$); ^1H NMR (CD_3CN) δ 1.27, 1.28, 1.30, 1.31, 1.37, 1.43 [6s, each 3H, 3 × C(CH_3)$_2$], 1.88 (s, 3H, CH_3CO), 3.30, 3.31 (2s, each 3H, 2 × OCH_3), 3.63 (dd, 1H, $J_{6'a,6'b} = 10.1$ Hz, $J_{5',6'b} = 6.7$ Hz, H-6′b), 3.70 (dd, 1H, $J_{5',6'a} = 5.4$ Hz, H-6′a), 3.88–4.00 (m, 4H, H-5′, H-3′, H-6a, H-6b), 3.98 (dd, 1H, $J_{3,4} = 1.4$ Hz, $J_{2,3} = 7.0$ Hz, H-3), 4.20 (ddd, 1H, $J_{5,6a} = 6.1$ Hz, $J_{5,6b} = 6.6$ Hz, H-5), 4.22 (dd, 1H, $J_{3',4'} = 7.0$ Hz, $J_{4',5'} = 3.8$ Hz, H-4′), 4.30 (d, 1H, $J_{1,2} = 6.1$ Hz, H-1), 4.33 (dd, 1H, $J_{4,5} = 2.6$ Hz, H-4), 4.37 (m, 1H, H-2′), 4.43 (dd, 1H, H-2), 4.51 and 4.58 (AB system, 2H,

$J_{A,B}$ = 12.1 Hz, CH_2Ph), 4.87 (d, 1H, $J_{1',2'}$ = 2.5 Hz, H-1′), 6.36 (d, 1H, $J_{2',NH}$ = 9.0 Hz, NH), 7.28–7.39 (m, 5H, aromatic H); ^{13}C NMR (CD_3CN) δ 23.5 (*C*H_3CO), 25.3, 26.4, 26.7, 26.9, 27.7, 28.1 [3 × C(*C*H_3)$_2$], 48.6 (C-2′), 54.1, 55.9 (2 × O*C*H_3), 65.9 (C-6), 69.8 (C-6′), 72.5, 72.8, 73.7 (C-2, C-4′, C-5′), 73.7 (*C*H_2Ph), 76.2, 76.4, 78.4, 78.9 (C-3′, C-3, C-4, C-5), 100.1 (C-1′), 106.2 (C-1), 108.7, 110.0, 110.8 [3 × *C*(CH$_3$)$_2$], 128.5–129.6 (aromatic CH), 139.6 (aromatic C), 170.4 (C═O).

Anal. Calcd for $C_{32}H_{49}NO_{12}$ (639.75): C, 60.08; H, 7.72; N, 2.19; Found: C, 60.17; H, 7.73; N, 2.10.

4-*O*-(2-Acetamido-6-*O*-benzyl-2-deoxy-β-D-talopyranosyl)-2,3-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (10). A solution of **4** (800 mg, 1.25 mmol) in 80% aq. AcOH (25 mL) was stirred at 40°C until the starting compound was completely reacted [1.45 hr, TLC (85 : 15 $CHCl_3$–CH_3OH)] with formation of a slower moving product. The reaction mixture was concentrated at reduced pressure and repeatedly co-evaporated with toluene (4 × 20 mL). The crude residue was directly applied to a flash chromatography column eluting with 85 : 15 $CHCl_3$–CH_3OH to give **10** (550 mg, 79% yield) as a solid foam; R_f = 0.24 (85 : 15 $CHCl_3$–CH_3OH); $[\alpha]_D = -67.1$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (CD_3CN–D_2O) δ 1.30, 1.31 [2s, each 3H, C(C*H*$_3$)$_2$], 1.89 (s, 3H, C*H*$_3$CO), 3.28 (s, 6H, 2 × O*C*H_3), 3.52–3.75 (m, 9H, H-3′, H-4′, H-5′, H-6′a, H-6′b, H-3, H-4, H-6a, H-6b), 4.13 (d, 1H, $J_{1,2}$ = 6.8 Hz, H-1), 4.35 (m, 3H, H-2, H-5, H-2′), 4.52 (s, 2H, C*H*$_2$Ph), 4.61 (d, 1H, $J_{1',2'}$ = 1.5 Hz, H-1′), 7.27–7.36 (m, 5H, aromatic H); ^{13}C NMR (CD_3CN–D_2O) δ 23.9 (*C*H_3CO), 26.9, 27.7 [C(*C*H_3)$_2$], 53.3 (C-2′), 53.9, 55.9 (2 × O*C*H_3), 63.4 (C-6), 68.7, 69.1 (C-4′, C-5), 69.9 (C-6′), 73.2, 74.8 (C-3′, C-5′), 73.8 (*C*H_2Ph), 76.2 (C-4), 78.2, 79.2 (C-2, C-3), 101.5 (C-1′), 105.9 (C-1), 110.5 [*C*(CH$_3$)$_2$], 128.5–129.2 (aromatic CH), 139.2 (aromatic C), 172.7 (C═O).

Anal. Calcd for $C_{26}H_{41}NO_{12}$ (559.62): C, 55.80; H, 7.38; N, 2.50. Found: C, 55.91; H, 7.40; N, 2.65.

4-*O*-(2-Acetamido-6-*O*-benzyl-2-deoxy-β-D-talopyranosyl)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (5). To a solution of **10** (500 mg, 0.89 mmol) and PyHOTs (23 mg, 0.09 mmol) in dry CH_2Cl_2 (10 mL) was dropwise added a 1 : 10 solution of 2-MP in dry CH_2Cl_2 (0.89 mL, 0.89 mmol). The reaction mixture was stirred at room temperature until **10** was completely reacted [1.5 hr, TLC (9 : 1 $CHCl_3$–CH_3OH)], diluted with CH_2Cl_2 (30 mL) and treated with saturated aq. $NaHCO_3$. The organic phase was separated, the aqueous layer repeatedly extracted with CH_2Cl_2 (3 × 20 mL) and the collected organic phases, after drying were concentrated at reduced pressure. The crude residue was subjected to a flash chromatographic purification (9 : 1 $CHCl_3$–CH_3OH) to give **5** (491 mg, 92%) as a solid foam; mp = 30–32°C; R_f 0.24 (9 : 1 $CHCl_3$–CH_3OH); $[\alpha]_D = -32.9$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (CD_3CN) δ 1.29 [s, 6H, C(C*H*$_3$)$_2$], 1.31, 1.38 [2s, each 3H, C(C*H*$_3$)$_2$], 1.84 (s, 3H, C*H*$_3$CO), 3.29, 3.31 (2s, each 3H, 2 × O*C*H_3), 3.50–3.71 (m, 6H, H-3′, H-4′, H-6′a, H-6′b, OH-3′, OH-4′), 3.73 (m, 1H, H-5′), 3.89 (dd, 1H, $J_{3,4}$ = 1.5 Hz, $J_{4,5}$ = 4.1 Hz, H-4), 3.91 (m, 2H, H-6a, H-6b), 3.98 (dd, 1H, $J_{2,3}$ = 6.6 Hz, H-3), 4.15 (ddd, 1H, $J_{5,6a}$ = 6.8 Hz, $J_{5,6b}$ = 7.1 Hz, H-5), 4.30 (d, 1H, $J_{1,2}$ = 6.2 Hz, H-1), 4.40 (m, 2H, H-2, H-2′), 4.53 (s, 2H, CH_2Ph), 4.71 (d, 1H, $J_{1',2'}$ = 1.7 Hz, H-1′), 7.32–7.38 (m, 5H, aromatic H); ^{13}C NMR (CD_3CN) δ 23.9 (*C*H_3CO), 25.7, 26.8, 26.9, 27.7 [2 × C(*C*H_3)$_2$], 52.9 (C-2′), 54.2, 55.8 (2 × O*C*H_3), 66.1 (C-6), 69.1 (C-6′), 69.4 (C-4′), 70.1 (*C*H_2Ph), 73.9, 74.8 (C-3′, C-5′), 76.4, 76.5 (C-4, C-3), 78.4, 78.8 (C-2, C-5), 101.5 (C-1′), 106.1 (C-1), 108.7, 110.9 [2 × *C*(CH$_3$)$_2$], 128.5–129.3 (aromatic CH), 139.5 (aromatic C), 171.3 (C═O).

Anal. Calcd for $C_{29}H_{45}NO_{12}$ (599.68): C, 58.08; H, 7.56; N, 2.34. Found: C, 58.13; H, 7.60; N, 2.28.

4-*O*-(2-Acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-talopyranosyl)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (6). A solution of **5** (1.35 g, 2.25 mmol) and Bu_2SnO (675 mg, 2.70 mmol) in toluene (135 mL) was refluxed in a Dean–Stark apparatus overnight. The solution was cooled to room temperature, treated with Bu_4NBr (369 mg, 1.13 mmol) and neat BnBr (0.36 mL, 3.09 mmol) and newly refluxed until the starting material was completely reacted (5.5 hr, TLC, 9 : 1 $CHCl_3$–CH_3OH). The reaction solution was concentrated at reduced pressure, and the resulting residue was directly subjected to flash chromatography, eluting in the order with hexane and 2 : 8 hexane–EtOAc, to give **6** (1.47 g, 95% yield) as a solid foam; R_f 0.23 (2 : 8 hexane–EtOAc); mp = 30–34°C; $[\alpha]_D = -59.3$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (CD_3CN) δ 1.30, 1.31, 1.33, 1.39 [4s, each 3H, 2 × C(CH_3)$_2$], 1.84(s, 3H, CH_3CO), 3.29, 3.31 (2s, each 3H, 2 × OCH_3), 3.47 (dd, 1H, $J_{2',3'} = 4.4$ Hz, $J_{3',4'} = 2.4$ Hz, H-3′), 3.54 (m, 1H, H-5′), 3.63 (dd, 1H, $J_{6'a,6'b} = 9.6$ Hz, $J_{5',6'b} = 6.1$ Hz, H-6′b), 3.70 (dd, 1H, $J_{5',6'a} = 5.4$ Hz, H-6′a), 3.92 (m, 1H, H-4), 3.94 (m, 1H, H-4′), 3.96 (m, 2H, H-6a, H-6b), 3.99 (dd, 1H, $J_{2,3} = 6.8$ Hz, $J_{3,4} = 1.5$ Hz, H-3), 4.18 (ddd, 1H, $J_{5,6a} = J_{5,6b} = 6.7$ Hz, $J_{4,5} = 3.8$ Hz, H-5), 4.31 (d, 1H, $J_{1,2} = 6.2$ Hz, H-1), 4.44 (dd, 1H, H-2), 4.50 and 4.63 (AB system, 2H, $J_{A,B} = 11.6$ Hz, CH_2Ph), 4.53 (s, 2H, CH_2Ph), 4.72 (d, 1H, $J_{1',2'} = 1.4$ Hz, H-1′), 4.76 (m, 1H, H-2′), 6.52 (d, 1H, $J_{2',NH'} = 9.5$ Hz, NH), 7.31–7.38 (m, 10H, aromatic H); ^{13}C NMR (CD_3CN) δ 23.9 (*C*H_3CO), 25.8, 26.8, 27.1, 27.8 [2 × C(*C*H_3)$_2$], 49.8 (C-2′), 54.1, 55.8 (2 × OCH_3), 66.0 (C-6), 67.6 (C-4′), 70.0 (C-6′), 70.4, 73.9 (2 × *C*H_2Ph), 74.9 (C-5′), 75.7 (C-3′); 76.4, 76.5 (C-2, C-4), 78.5 (C-5), 78.8 (C-3), 101.5 (C-1′), 106.1 (C-1), 108.6, 110.9 [2 × *C*(CH$_3$)$_2$], 128.5–129.3 (aromatic CH), 139.2, 139.5 (aromatic C), 170.5 (C═O).

Anal. Calcd for $C_{36}H_{51}NO_{12}$ (689.81): C, 62.68; H, 7.45; N, 2.03. Found: C, 62.71; H, 7.51; N, 2.10.

4-*O*-(2-Acetamido-3,6-di-*O*-benzyl-2,4-dideoxy-β-D-*threo*-hex-3-enopyranosyl)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (7). A suspension of 60% NaH in mineral oil (304 mg, 7.66 mmol) was washed with hexane under an argon atmosphere and slowly treated at room temperature with a solution of **6** (1.05 g, 1.52 mmol) in dry DMF (60 mL). The mixture was stirred at room temperature for 30 min, cooled at −30°C, treated with Im_2SO_2 (442 mg, 2.22 mmol) and was further stirred at −30°C for 1 hr. The mixture was allowed to reach room temperature and was further stirred for 3 hr when TLC analysis (2 : 8 hexane–EtOAc) revealed the complete formation of a faster moving product. The reaction mixture was cooled to 0°C, excess of NaH was destroyed by addition of MeOH (1 mL) followed by 10 min stirring, and partitioned between ethyl ether (120 mL) and crushed iced-water. The organic phase was separated, and the aqueous layer extracted with Et_2O (100 mL). The organic phases were collected, dried and concentrated at reduced pressure to give a syrup (900 mg) constituted mainly by **7**, sufficiently pure for further transformations. The flash chromatographic purification of a portion of the above crude reaction product (300 mg) eluting with 2 : 3 hexane–EtOAc + 0.1% Et_3N gave an analytically pure sample of **7** (269 mg, 79% yield) as a syrup; R_f 0.44 (1 : 4 hexane–EtOAc); $[\alpha]_D = +18.6$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (CD_3CN) δ 1.30, 1.31, 1.32, 1.39 [4s, each 3H, 2 × C(CH_3)$_2$], 1.77 (s, 3H, CH_3CO), 3.32, 3.33 (2s, each 3H, 2 × OCH_3), 3.47 (dd, 1H, $J_{6'a,6'b} = 9.9$ Hz, $J_{5',6'a} = 5.2$ Hz, H-6′a), 3.58 (dd, 1H, $J_{5',6'b} = 5.4$ Hz, H-6′b), 3.93 (dd, 1H,

$J_{3,4} = 1.4$ Hz, $J_{4,5} = 4.3$ Hz, H-4), 4.01 (dd, 1H, $J_{2,3} = 6.9$ Hz, H-3), 4.05 (m, 2H, H-6a, H-6b), 4.16 (ddd, 1H, $J_{5,6a} = J_{5,6b} = 7.5$ Hz, H-5), 4.32 (d, 1H, $J_{1,2} = 6.2$ Hz, H-1), 4.37 (m, 1H, H-5′), 4.48 (dd, 1H, H-2), 4.55 (s, 2H, CH_2Ph); 4.72 and 4.80 (AB system, 2H, $J_{A,B} = 12.0$ Hz, CH_2Ph), 4.67 (ddd, 1H, $J_{2',NH'} = 9.8$ Hz, $J_{2',5'} = 1.5$ Hz, H-2′), 4.89 (d, 1H, $J_{4',5'} = 1.7$ Hz, H-4′), 4.91 (d, 1H, $J_{1',2'} = 2.3$ Hz, H-1′), 6.45 (d, 1H, NH), 7.30–7.39 (m, 10H, aromatic H); ^{13}C NMR (CD_3CN)δ 23.2 (CH_3CO), 25.9, 26.9, 27.0, 27.7 [2 × C(CH_3)$_2$], 49.3 (C-2′), 54.4, 55.7 (2 × OCH_3), 66.0 (C-6), 70.1 (C-6′), 72.9 (C-5′), 73.7, 73.9 (2 × CH_2Ph), 76.3, 76.4 (C-2, C-4); 78.5, 78.6 (C-3, C-5), 98.8 (C-4′), 100.3 (C-1′), 106.2 (C-1), 108.7, 110.9 [2 × C(CH_3)$_2$], 128.4–129.4 (aromatic CH), 137.8, 139.6 (aromatic C), 153.5 (C-3′), 170.4 (C═O).

Anal. Calcd for $C_{36}H_{49}NO_{11}$ (671.79): C, 64.37; H, 7.35; N, 2.08. Found: C, 64.41; H, 7.31; N, 2.12.

4-*O*-(2-Acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-mannopyranosyl)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (8). A solution of crude **7** (600 mg) in dry Et_2O (19 mL) was treated at 0°C with a 96% solution of borane dimethylsulfide complex (0.14 mL, 1.33 mmol), warmed to room temperature and stirred until the starting material was completely reacted [TLC (1 : 4 hexane–EtOAc), 5 hr]. The mixture was cooled to 0°C and treated in the order with H_2O (2.5 mL), 10% aq. NaOH (5 mL) and, finally, 35% aq. H_2O_2 (10 mL). The biphasic mixture was stirred for 2 hr, diluted with Et_2O (10 mL), and the organic phase was separated. The aqueous layer was repeatedly extracted with Et_2O (4 × 40 mL), and the collected organic phases, after drying, were concentrated at reduced pressure. The crude residue was subjected to a flash chromatographic purification (1 : 4 hexane–EtOAc) to give pure **8** (447 mg, 64% yield over two steps from **6**) as a white solid; R_f 0.18 (1 : 4 hexane–EtOAc); mp = 187–190°C (dec.); $[\alpha]_D = -50.1$ (c 1.5, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 1.33, 1.38, 1.40, 1.51 [4s, each 3H, 2 × C(CH_3)$_2$], 1.74 (s, 3H, CH_3CO), 3.20, 3.28 (2s, each 3H, 2 × OCH_3), 3.14 (m, 1H, H-5′), 3.38 (dd, 1H, $J_{3',4'} = 9.4$ Hz, $J_{2',3'} = 4.0$ Hz, H-3′), 3.70 (dd, 1H, $J_{6'a,6'b} = 10.6$ Hz, $J_{5',6'a} = 2.3$ Hz, H-6′a), 3.80 (dd, 1H, $J_{5',6'b} = 3.9$ Hz, H-6′b), 3.88 (dd, 1H, $J_{4',5'} = 9.6$ Hz, $J_{3',4'} = 9.4$ Hz, H-4′), 4.07–4.27 (m, 5H, H-3, H-4, H-5, H-6a, H-6b), 4.31 (d, 1H, $J_{1,2} = 6.1$ Hz, H-1), 4.45 (s, 2H, CH_2Ph), 4.47, and 5.07 (AB system, 2H, $J_{A,B} = 11.1$ Hz, CH_2Ph), 4.73 (t, 1H, $J_{2,3} = 6.1$ Hz, H-2), 4.96 (d, 1H, $J_{1',2'} = 1.0$ Hz, H-1′), 5.18 (m, 1H, H-2′), 6.32 (d, 1H, $J_{2',NH'} = 9.8$ Hz, NH), 7.08–7.46 (m, 10H, aromatic H); ^{13}C NMR (C_6D_6) δ 22.9 (CH_3CO), 25.7, 26.6, 26.9, 27.9 [2 × C(CH_3)$_2$], 49.3 (C-2′), 54.2, 55.3 (2 × OCH_3), 65.5 (C-6), 67.0 (C-4′), 69.7 (C-6′), 70.9, 73.8 (2 × CH_2Ph), 75.9, 76.1, 76.4 (C-4, C-5, C-5′), 78.4, 78.6 (C-2, C-3), 80.6 (C-3′), 100.7 (C-1′), 106.0 (C-1), 108.0, 110.8 [2 × C(CH_3)$_2$], 128.0–128.8 (aromatic CH), 138.7, 138.9 (aromatic C); 170.0 (C═O).

Anal. Calcd for $C_{36}H_{51}NO_{12}$ (689.81): C, 62.68; H, 7.45; N, 2.03. Found: C, 62.71; H, 7.42; N, 2.09.

4-*O*-(2-Acetamido-2-deoxy-β-D-mannopyranosyl)-2,3 : 5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (9). A solution of **8** (396 mg, 0.57 mmol) in EtOAc (40 mL) containing 5% $Pd(OH)_2$ on charcoal (260 mg) was stirred at room temperature under an H_2 atmosphere for 5 hr. The solution was diluted with MeOH (30 mL), filtered over celite, washed with MeOH, and the combined organic phases were concentrated at reduced pressure. The crude residue was subjected to a chromatographic purification (85 : 15 $CHCl_3$–MeOH) to give pure **9** (272 mg, 93% yield) as a white solid; R_f 0.31 (85 : 15 $CHCl_3$–MeOH); mp = 222–225°C (dec.); $[\alpha]_D = 0$ (c 1.0, $CHCl_3$); ^{1}H NMR

(CD_3CN-D_2O) δ 1.28, 1.29, 1.30, 1.37 [4s, each 3H, 2 × $C(CH_3)_2$], 1.89 (s, 3H, CH_3CO), 3.22 (m, 1H, H-5′), 3.33 (dd, 1H, $J_{4',5'} = 9.5$ Hz, $J_{3',4'} = 9.3$ Hz, H-4′), 3.40, 3.41 (2s, each 3H, 2 × OCH_3), 3.59 (dd, 1H, $J_{2',3'} = 4.2$ Hz, H-3′), 3.67–4.04 (m, 6H, H-3, H-4, H6a, H-6b, H-6′a, H-6′b), 4.20 (m, 1H, H-5), 4.35 (d, 1H, $J_{1,2} = 6.8$ Hz, H-1), 4.39 (m, 1H, H-2′), 4.43 (dd, 1H, $J_{2,3} = 7.0$ Hz, H-2), 4.76 (d, 1H, $J_{1',2'} = 1.1$ Hz, H-1′); ^{13}C NMR (CD_3CN-D_2O) δ 23.1 (CH_3CO), 25.4, 26.5, 26.7, 27.4 [2 × $C(CH_3)_2$], 53.8 (C-2′), 55.1, 57.3 (2 × OCH_3), 62.1 (C-6′), 65.7 (C-6), 68.0 (C-4′), 73.5 (C-3′), 75.9, 76.3 (C-4, C-5), 77.5 (C-5′), 78.1, 78.7 (C-2, C-3), 100.5 (C-1′), 107.2 (C-1), 109.2, 111.1 [2 × $C(CH_3)_2$], 174.1 (C═O).

Anal. Calcd for $C_{22}H_{39}NO_{12}$ (509.56): C, 51.86; H, 7.71; N, 2.75. Found: C, 51.91; H, 7.74; N, 2.80.

4-*O*-(2-Acetamido-2-deoxy-β-D-mannopyranosyl)-α,β-D-glucopyranose (1). A solution of **9** (211 mg, 0.41 mmol) in 80% aq. AcOH (7 mL) was stirred at 80°C for 3.5 hr, then concentrated at reduced pressure and coevaporated with toluene (3 × 10 mL). The residue was tritured with EtOAc to give an amorphous white solid (140 mg, 89% yield) constituted (^{13}C NMR, D_2O) exclusively by a 45 : 55 α/β anomeric mixture of **1**, as established on the basis of the integration of the anomeric carbon signals; R_f 0.09 (7 : 3 EtOAc–MeOH); $[\alpha]_D = -4.8$ (*c* 1.0, H_2O); lit.[11] $[\alpha]_D$ − 7.3 (*c* 1.0, H_2O); NMR data for **α − 1**: ^{1}H NMR (CD_3OD) δ 2.02 (s, 3H, CH_3CO), 4.52 (m, 1H, H-2′), 4.78 (m, 1H, H-1′), 5.08 (d, 1H, $J_{1,2} = 4.0$ Hz, H-1); ^{13}C NMR (D_2O) δ 23.2 (CH_3CO), 54.4 (C-2′), 61.3 (C-6), 61.5 (C-6′), 67.8 (C-4′), 71.0 (C-5), 72.5 (C-3′), 73.2 (C-2, C-3), 77.7 (C-5′), 80.1 (C-4), 93.0 (C-1), 100.5 (C-1′), 176.6 (C═O). NMR data for **β-1**:^{1}H NMR (CD_3OD) δ 2.02 (s, 3H, CH_3CO), 3.18 (dd, 1H, $J_{1,2} = 7.9$ Hz, $J_{2,3} = 8.7$ Hz, H-2), 4.48 (d, 1H, H-1), 4.52 (m, 1H, H-2′), 4.78 (m, 1H, H-1′); ^{13}C NMR (D_2O) δ 23.2 (CH_3CO), 54.4 (C-2′), 61.3 (C-6), 61.5 (C-6′), 67.8 (C-4′), 72.5 (C-3′), 75.1, 75.4, 75.7 (C-2, C-3, C-5), 77.7 (C-5′), 79.9 (C-4), 97.0 (C-1), 100.5 (C-1′), 176.6 (C═O).

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