Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2016, **14**, 2873

Rapid and efficient synthesis of α(1–2) mannobiosides†

José J. Reina,*[a] Antonio Di Maio,[a] Javier Ramos-Soriano,[a] Rute C. Figueiredo[b] and Javier Rojo[a]

Received 12th January 2016,
Accepted 2nd February 2016

DOI: 10.1039/c6ob00083e

www.rsc.org/obc

α(1,2)mannobiosides with different substituents at the reducing end have been synthesized by a common strategy using benzoyls as the permanent protecting groups and an acetyl as the orthogonal protecting group at position C2 of the glycosyl acceptor. The new synthetic strategy has been performed remarkably reducing the number of purification steps, the time of synthesis (less than 72 hours) and improving the overall yield at least three times with respect to the best procedure described in the literature at the moment. Additionally, this protecting group strategy is compatible with the presence of azido groups and the use of Cu catalyzed azide alkyne cycloaddition (CuAAC) also called "click chemistry" for conjugating the α(1–2)mannobiosides to different scaffolds for the preparation of mannosyl multivalent systems.

Introduction

High-mannose oligosaccharides are ubiquitous biologically important molecules. They are known to participate in quality control and intracellular transportation of glycoproteins.[1] Furthermore, they are present on the surface of many pathogenic microorganisms such as viruses, bacteria, fungi and parasites, and they are the target of immune system cells, including macrophages and dendritic cells.[2] The interactions of high-mannose oligosaccharides with animal lectins are of crucial importance for the efficient operation of the innate immune system. Examples include the mannose-binding lectin (MBL), Dendritic Cell Specific ICAM-3 Grabbing Non-integrin (DC-SIGN), defensins and macrophage mannose receptors (MRs).[3] Therefore, the glycan structures on pathogen glycoproteins present in viral envelopes or bacterial cell walls help in escaping recognition by the immune system, and the subsequent elimination or neutralization of the pathogen.[2] In particular, the group of van Kooyk in 2000 highlighted the relevance of DC-SIGN reporting the role that this lectin plays in the pathogenesis of HIV-1.[4] This virus targets DC-SIGN, but escapes degradation in lytic compartments, thus using the DCs as a Trojan Horse to invade the host organism.[4] In this context, inhibition of DC-SIGN is currently considered as an interesting new target for the design of anti-infective agents.[5] Information at the molecular level concerning the mechanism by which this receptor operates is scarce, thus effective modulators of DC-SIGN are also required to clarify the different biological pathways in which this receptor is involved. The main carbohydrate ligand recognized by DC-SIGN is the high mannose glycan, $(Man)_9(GlcNAc)_2$, a branched oligosaccharide containing mannose with α1,2-, α1,3-, α1,6-, and β1,4-linkages (Fig. 1). Multiple copies of this glycan are present in several pathogen glycoproteins and specifically in the gp120 envelope protein of HIV.

The total synthesis of Man_9 or $(Man)_9(GlcNAc)_2$ has been explored for the past two decades;[6] however, the complexity of these kinds of complex glycan structures prevent accessibility to the large amounts required to address biological studies. Thus synthetic glycan mimetics can be of great value for interrogating these relevant biological interactions. The crystal structure of a complex containing a Fab fragment of the gp120 antibody 2G12 and $(Man)_9(GlcNAc)_2$ was published more than

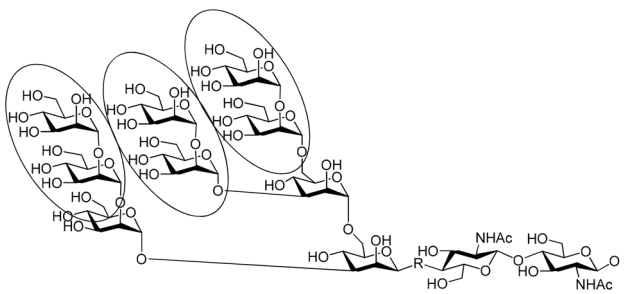


Fig. 1 Structure of high-mannose type glycans.

[a]*Glycosystems Laboratory, Instituto de Investigaciones Químicas (IIQ), CSIC – Universidad de Sevilla, Américo Vespucio, 49, 41092 Sevilla, Spain. E-mail: jose.juan@iiq.csic.es*
[b]*Departamento de Química, Instituto de Ciencias Exactas e Biológicas, Universidade Federal de Ouro Preto, Rua Costa Sena, 171, Centro, 35400-000 Ouro Preto, Minas Gerais, Brazil*

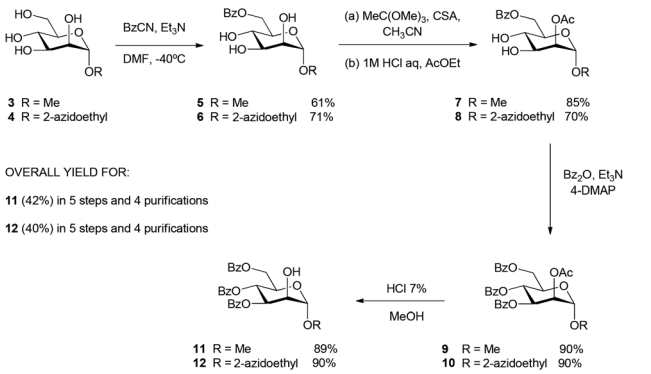
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c6ob00083e

10 years ago.[7] The resolved structure shows that the Manα1–2Man residues constitute 85% of the protein contacts. Additionally, it is known that high density arrays of unbranched Manα(1,2)Man bind to DC-SIGN almost as effectively as the entire Man_9 oligosaccharide.[8] Based on this, Manα1–2Man can be considered as an interesting fragment for constructing multivalent systems mimicking high-mannose interactions. For this reason, a rapid and straightforward synthesis of Manα1,2Man disaccharide conveniently functionalized in the reducing end to facilitate their conjugation to multivalent scaffolds is of remarkable interest. The previously described approaches to prepare α(1–2) mannobioside derivatives involved many reaction steps, including the classical protection–deprotection pathway to prepare oligosaccharides, with several purifications of the intermediate products. These syntheses imply large time consumption, high synthetic cost, and render a low overall yield of the final product. A recent example describes an efficient one-step synthesis of α(1–2) mannobioside using a polymerization-type strategy.[9] This approach provides an excellent overall yield only when the linker used in the reducing terminus is an alcohol with a particular length and substituents, implying an important decrease in the versatility of the synthesis. These disadvantages make the current application of Manα1,2Man difficult and compromise its use in preparing multivalent glycoconjugates with potential anti-infective properties.

Here, we present a very rapid, straightforward, versatile and high yield synthesis of Manα1,2Man derivatives with –OMe, 2-azidoethyl and *S*-tolyl functionalization in the reducing end. To achieve this objective, a common orthogonal protection strategy was designed employing benzoates as the permanent protecting groups and an acetate as the orthogonal protecting group at position C2 of the glycosyl acceptor. The use of this protecting group strategy is compatible with the presence of azido groups and the use of CuAAC (Cu catalyzed azide alkyne cycloaddition) also called "click chemistry" for conjugating the α(1–2)mannobiosides to different scaffolds.

Results and discussion

An efficient synthesis of α(1–2)mannobiosides can provide the required materials to facilitate a gram scale preparation of multivalent systems opening the door to explore their biological applications. The key step for a straightforward synthesis of these disaccharides is a rapid and efficient strategy to obtain large amounts of glycosyl donors and acceptors compatible with the methodology selected for the multivalent presentation of the final oligosaccharides. With this aim, we selected as glycosyl donors the per-acetylated and per-benzoylated mannose trichloroacetimidate **13** and **14** (Scheme 3) and as glycosyl acceptors the mannoside derivatives **11** and **12** (Scheme 1). Our strategy starts from the methyl and 2-azidoethyl mannopyranoside (**3** and **4**) that were treated with BzCN at −40 °C and a catalytic amount of Et_3N to selectively protect the C6 hydroxyl group.[10] This reaction was regioselective and the



Scheme 1 Synthesis of mannose derivatives **11** and **12**.

primary alcohols of both mannose derivatives **3** and **4** were selectively benzoylated with good yield after chromatographic purification (61% for **5** and 71% for **6**), and only a small amount (less than 10%) of 2,6- and 3,6-benzoyl derivatives were observed by TLC and verified by NMR spectroscopy. The monobenzoylation step could be considered one of the key steps of this synthetic strategy. The regioselective benzoylation of the primary alcohol using fully deprotected mannose has not been performed previously. The selective protection of primary alcohols in the presence of secondary alcohols has often been addressed by the use of high hindrance protecting groups such as *tert*-butyldiphenylsilyl ether (TBDPS).[11] In our strategy, the use of silylethers is incompatible with the deprotection conditions of the orthogonal acetyl group at position C2 of the glycosyl donor.

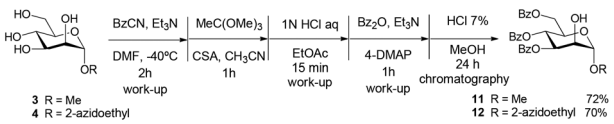
Then, compounds **5** and **6** were treated with trimethyl orthoacetate and a catalytic amount of camphorsulphonic acid (CSA) to form the acetyl orthoester with the hydroxyl groups at positions C2 and C3. This orthoester was impossible to isolate due to the partial hydrolysis of the orthoester functionality during the chromatographic purification. The treatment of the orthoester intermediates with 1 M HCl implied partial hydrolysis to obtain the hydroxyl groups at position C2 orthogonally protected with an acetate group and with the hydroxyl groups in C3 and C4 unprotected (**7** and **8**).[12] These compounds were finally benzoylated with Bz_2O, Et_3N and a catalytic amount of 4-dimethylaminopyridine (DMAP) to generate the fully protective mannose derivatives **9** and **10** with an acetyl group as the orthogonal protecting group at position C2. Finally, selective deprotection of this acetyl group at position C2 using 7% HCl in methanol afforded the mannoses **11** and **12** in good yields.[13] The use of 7% HCl in methanol was the best condition found to achieve the compromise of completing the reaction in less than 24 hours and avoiding the partial hydrolysis of benzoyl esters present in the mannose derivatives. Both intermediates **11** and **12** were used as acceptors for the synthesis of the α(1,2)mannobiosides (Scheme 3).

This synthetic strategy to prepare mannose acceptors **11** and **12** implied 5 reaction steps and 4 purifications using silica gel flash chromatography with an overall yield of 42% in the case of the OMe derivative **11** and 40% for the 2-azidoethyl

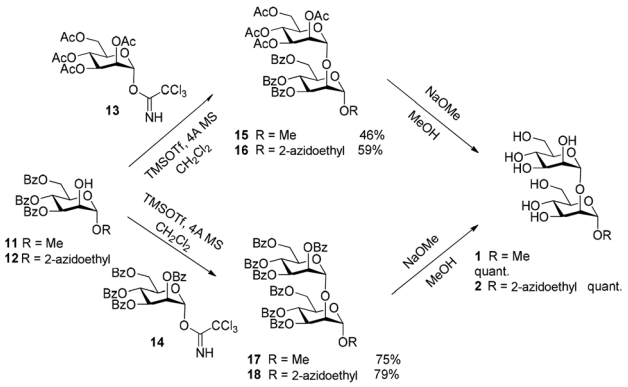
derivative **12**. Many different strategies have been described in the literature to afford these kinds of intermediates, using 1,2-*O*-ethylidene-β-D-mannopyranosides and other approaches like benzyl/acetyl or benzyl/Fmoc strategies.[13,14] All these alternatives mean at least the same number of reactions and purifications steps with an overall yield of 25% in the best case.

It is important to highlight that the synthetic approach described in Scheme 1 to obtain the glycosyl acceptors **11** and **12** presents an important advantage: the conditions of the protection reactions are all compatible for being carried out sequentially simply by the removal of the reaction solvent and a work up without chromatographic purification of the intermediate products. For these reasons, we afforded the sequence synthesis of **11** and **12** as described in Scheme 2. The preparation of intermediates **11** and **12** was performed in only 28 hours with a single final chromatographic purification with 72% and 70% overall yields, respectively. This consecutive strategy means a 30% increase in the yield over the step-wise traditional synthetic strategy demonstrating that limiting the number of purification steps produces an improvement in the final overall yield. Additionally, the consecutive strategy also introduces a significant reduction of the total cost and time of the synthesis of these key intermediates to achieve the preparation of the target molecule, the mannobioside. In fact, we have obtained a decrease of about 80% of the time, allowing the preparation of these derivatives in the gram scale in less than two days very easily. Moreover, this versatile approach allows different modifications for generating a large number of mannose monosaccharides, for example, the benzoyl groups could be substituted by benzyls or other kinds of protecting groups.

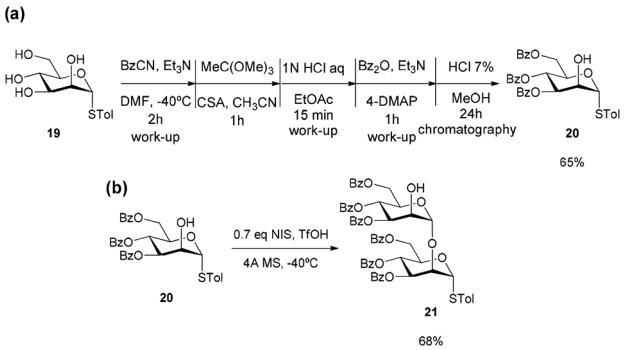
At this stage, only the preparation of the glycosyl donors is necessary to complete the synthesis of the disaccharides. α-1,2-Linked dimannosides **1** and **2** were synthesized with the α linkage typically controlled by a participating neighboring group at the C2 position of the glycosyl donor. Two different glycosyl donors were selected, per-acetylated and per-benzoylated trichloroacetimidates **13** and **14** (Scheme 3). The disaccharides **15** and **16** were prepared by reaction of the glycosyl donor **13** with the glycosyl acceptors **11** and **12** using trimethylsilyl triflate (TMSOTf) as the promoter at 0 °C with moderate yields (46% and 59%, respectively). The moderate yield of these glycosylations was due to the orthoester formation during the reaction. In order to avoid this problem and to increase the yield of the glycosylation step, per-benzoylated mannose **14** was used as the glycosyl donor.[15] Using the same conditions (0.2 eq. of TMSOTf), disaccharides **17** and **18** were obtained in good yields (75% and 78%, respectively). Finally, the disaccharides **1** and **2** were prepared by the deprotection of acetyl and benzoyl groups using classical Zempler conditions (NaOMe/MeOH) to afford the final compounds **1** and **2** in quantitative yields.



Scheme 2 Consecutive synthetic procedures to prepare **11** and **12**.



Scheme 3 Synthetic strategies to prepare the α(1,2)mannobiosides **1** and **2**.



Scheme 4 (a) Consecutive synthesis of donor/acceptor **20**; (b) self-glycosidation of **20** to obtain the disaccharide **21**.

To explore the scope of the methodology described in this work as a straightforward strategy to address the preparation of more complex oligosaccharides that present Manα1,2Man units in their structure, the *S*-tolyl mannose derivative **21** was prepared following the consecutive synthetic procedure described for compounds **11** and **12** and starting from the *S*-tolyl derivative **19** (Scheme 4). Compound **20** was prepared from the *S*-tolyl derivative **19**[16] in less than 36 hours with 65% yield using only one chromatographic purification. Then, applying the methodology described by Wong and co-workers,[17] compound **20** was used simultaneously as a glycosyl donor and acceptor to afford self-glycosidation with *N*-iodo succinimide (NIS) and triflic acid (TfOH) at −40 °C providing the dimannoside **21** with 68% yield. The dimannoside **21** is an excellent synthetic intermediate that could be used as a donor or acceptor to synthesize more complex oligosaccharides.

Conclusions

In summary, we have completed the consecutive synthesis of three α(1,2)mannobiosides, the methyl derivative **1**, the

2-azidoethyl derivative **2** and the *S*-tolyl derivative **21**. The preparation of these molecules has been achieved using a common strategy based on benzoyls as the permanent protecting groups and an acetyl as the orthogonal protecting group at the C2 position of the glycosyl acceptor. Following this strategy, the purification steps have been reduced to only two silica gel column chromatographies for every disaccharide, minimizing the time spent to perform the synthesis of these final compounds to less than 72 hours and improving the overall yield at least three times with respect to the best procedure described in the literature. This synthetic strategy allows the preparation of α(1,2)dimannosides in the gram scale reducing the cost of the synthesis a lot. Additionally, the use of the ester strategy (benzoyl/acetyl) makes the synthesis compatible with the 2-azidoethyl spacer in the case of compound **2**. This is fundamental for the preparation of glycoconjugates by click chemistry reactions using multivalent scaffolds. On the basis of this development, we are preparing multivalent Manα1,2Man conjugates using compound **1** as the ligand and we are synthesizing more complex mannose oligosaccharides using the *S*-tolyl **21** derivative as the synthetic intermediate.

Experimental

Materials and methods

All chemicals were obtained from Sigma-Aldrich and used without further purification, unless otherwise noted. ^{1}H and ^{13}C NMR were recorded on Bruker Advance DPX 300 and DRX 400 MHz spectrometers. Chemical shifts are in ppm with respect to tetramethylsilane (TMS) using the manufacturer's indirect referencing method. 2D experiments (COSY and HSQC) were performed when necessary to assign the oligosaccharide spectra. Mass spectra were recorded with an Esquire 6000 ESI-Ion Trap from Bruker Daltonics.

Synthetic procedures

Synthesis of methyl-6-*O*-benzoyl-α-D-mannopyranoside (5). To a solution of methyl-α-D-mannopyranoside (**3**) (300 mg, 1.55 mmol) in DMF (10 mL) at −40 °C were added dropwise a solution of BzCN 1 M in DMF (2 mL) and a catalytic amount of Et_3N and the reaction was stirred for 2 hours. After that, MeOH (4 mL) was added to quench excess BzCN and the reaction was warmed up to room temperature. Then, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (CH_2Cl_2 : MeOH, 40 : 1) to give compound **5** as a colorless oil (280 mg, 61%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 8.4, 1.3 Hz, 2H, $2H_{Bz}$), 7.60 (tt, J = 7.6, 1.3 Hz, 1H, $1H_{Bz}$), 7.47 (dd, J = 8.4, 1.3 Hz, 2H, $2H_{Bz}$), 4.82 (dd, J = 12.2, 4.8 Hz, 1H, H_{6Man}), 4.79 (d, J = 1.5 Hz, 1H, H_{1Man}), 4.54 (dd, J = 12.1, 2.2 Hz, 1H, H_{6Man}), 3.99 (dd, J = 3.4, 1.6 Hz, 1H, H_{2Man}), 3.89 (dd, J = 9.1, 3.3 Hz, 1H, H_{3Man}), 3.87–3.83 (m, 1H, H_{5Man}), 3.73 (t, J = 9.5 Hz, 1H, H_{4Man}), 3.42 (s, 3H, –OCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.2 (C═O_{Bz}), 133.2 (CH_{Bz}), 129.7 (CH_{Bz}), 128.4 (CH_{Bz}), 100.9 (C_{1Man}), 71.6 (C_{5Man}), 70.6 (C_{3Man}), 70.5 (C_{2Man}), 67.9 (C_{4Man}), 64.6 (C_{6Man}), 54.9 (OCH_3). **ESI-MS** for $C_{14}H_{18}O_7$; calcd: 298.1 M^+; found: 321.2 $[M + Na]^+$; **ESI-HRMS** for $C_{14}H_{18}O_7$; calcd: 321.0950 $[M + Na]^+$; found: 321.0943 $[M + Na]^+$.

Synthesis of 2-azidoethyl-6-*O*-benzoyl-α-D-mannopyranoside (6). To a solution of 2-azidoethyl-α-D-mannopyranose (**4**) (100 mg, 0.40 mmol) in DMF (4 mL) at −40 °C were added a solution of BzCN 1 M in DMF (480 μL) and a catalytic amount of Et_3N and the reaction was stirred for 2 hours. After that, MeOH (1 mL) was added to quench excess BzCN and the reaction was warmed up to room temperature. Then, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (CH_2Cl_2 : MeOH, 20 : 1) to give compound **6** as a colorless oil (99 mg, 71%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.2 Hz, 2H, $2H_{Bz}$), 7.58 (t, J = 7.8 Hz, H_{Bz}), 7.44 (t, J = 7.7 Hz, $2H_{Bz}$), 4.91(d, J = 1.6 Hz, 1H, H_{1Man}) 4.75 (ddd, J = 12.2, 5.8, 2.9 Hz, 1H, H_{6Man}), 4.58 (dt, J = 12.2, 1.8 Hz, 1H, H_{6Man}), 4.04 (dd, J = 3.4, 1.6 Hz, 1H, H_{2Man}), 3.97–3.84 (m, 3H, H_{3Man} + H_{5Man} + H_7) 3.80 (t, J = 9.4 Hz, 1H, H_{4Man}), 3.67–3.59 (m, 1H, H_7), 3.45–3.34 (m, 2H, $2H_8$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.1 (C═O_{Bz}), 133.2 (C_{Bz}), 129.7 (CH_{Bz}), 128.4 (CH_{Bz}), 100.0 (C_{1Man}), 71.4 (C_{3Man} or C_{5Man}), 71.0 (C_{3Man} or C_{5Man}), 70.5 (C_{2Man}), 67.8 (C_{4Man}), 66.5(C_7), 64.6 (C_{6Man}), 50.4 (C_8). **ESI-MS** for $C_{15}H_{19}N_3O_7$; calcd: 353.1 M^+; found: 376.2 $[M + Na]^+$; **ESI-HRMS** for $C_{15}H_{19}N_3O_7$; calcd: 376.1121 $[M + Na]^+$; found: 376.1113 $[M + Na]^+$.

Synthesis of methyl-2-*O*-acetyl-6-*O*-benzoyl-α-D-mannopyranoside (7). To a solution of methyl-6-*O*-benzoyl-α-D-mannopyranoside (**5**) (220 mg, 0.74 mmol) and CSA (35 mg, 0.15 mmol) in CH_3CN (7 mL) was added trimethyl orthoacetate (285 μL, 2.22 mmol) and the reaction was stirred at room temperature for 1 hour. After that, the reaction was quenched with Et_3N (100 μL) and the solvent was evaporated. Then, the residue was dissolved in EtOAc (25 mL) and washed with 1 M HCl (25 mL), the organic phase was dried with anh. $MgSO_4$ and the solvent was evaporated. Finally, the residue was purified by flash chromatography on silica gel (CH_2Cl_2 : MeOH, 50 : 1) to give compound **7** as a colorless oil (215 mg, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (d, J = 7.6 Hz, 2H, $2H_{Bz}$), 7.62 (t, J = 7.4 Hz, 1H, H_{Bz}), 7.48 (t, J = 7.6 Hz, 1H, $2H_{Bz}$), 5.13 (dd, J = 3.5, 1.6 Hz, 1H, H_{2Man}), 4.81 (dd, J = 12.2, 4.6 Hz, 1H, H_{6Man}), 4.78 (d, J = 1.6 Hz, 1H, H_{1Man}), 4.56 (dd, J = 12.3, 2.1 Hz, 1H, H_{6Man}), 4.08 (dd, J = 9.7, 3.4 Hz, 1H, H_{3Man}), 3.96 (m, 1H, H_{5Man}), 3.77 (t, J = 9.6 Hz, 1H, H_{4Man}), 3.43 (s, 3H, OCH_3), 2.11 (s, 3H, –$OCOCH_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.7 (C═O_{Ac}), 167.3 (C═O_{Bz}), 133.4 (CH_{Bz}), 129.8 (CH_{Bz}), 129.7 (C_{Bz}), 128.4 (CH_{Bz}), 98.7 (C_{1Man}), 71.8 (C_{2Man}), 70.6 (C_{5Man}), 69.9 (C_{5Man}), 67.9 (C_{3Man}), 63.8 (C_{6Man}), 55.2 (–OCH_3), 20.9 (–$OCOCH_3$). **ESI-MS** for $C_{16}H_{20}O_8$; calcd: 340.1 M^+; found: 363.2 $[M + Na]^+$; **ESI-HRMS** for $C_{16}H_{20}O_8$; calcd: 363.1056 $[M + Na]^+$; found: 363.1045 $[M + Na]^+$.

Synthesis of 2-azidoethyl-2-*O*-acetyl-6-*O*-benzoyl-α-D-mannopyranoside (8). To a solution of 2-azidoethyl-6-*O*-benzoyl-α-D-mannopyranoside (**6**) (80 mg, 0.23 mmol) and CSA (5 mg, 0.02 mmol) in CH_3CN (4 mL) was added trimethyl orthoacetate (86 mL, 0.68 mmol) and the reaction was stirred at room temperature for 1 hour. After that, the reaction was quenched with

Et_3N (50 μL) and the solvent was evaporated. Then, the residue was dissolved in EtOAc (25 mL) and washed with 1 M HCl (25 mL), the organic phase was dried with anh. $MgSO_4$ and the solvent was evaporated. Finally, the residue was purified by flash chromatography on silica gel (CH_2Cl_2 : MeOH, 100 : 3) to give compound **8** as a colorless oil (63 mg, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 8.3, 1.4 Hz, 2H, $2H_{Bz}$), 7.61 (t, J = 7.2 Hz, 1H, H_{Bz}), 7.47 (t, J = 7.6 Hz, 1H, $2H_{Bz}$), 5.16 (dd, J = 3.5, 1.6 Hz, 1H, H_{2Man}), 4.91 (d, J = 1.6 Hz, 1H, H_{1Man}), 4.78 (dd, J = 12.1, 4.7 Hz, 1H, H_{6Man}), 4.59 (dd, J = 12.2, 2.2 Hz, 1H, H_{6Man}), 4.12 (dd, J = 9.5, 3.5 Hz, 1H, H_{3Man}), 3.96 (ddd, J = 9.9, 4.7, 2.2 Hz, 1H, H_{5Man}), 3.91 (ddd, J = 10.6, 7.0, 3.6 Hz, 1H, H_7), 3.82 (t, J = 9.7 Hz, 1H, H_{4Man}), 3.66 (ddd, J = 10.5, 6.0, 3.4 Hz, 1H, H_7), 3.44 (qdd, J = 13.3, 6.5, 3.5 Hz, 2H, $2H_8$), 2.11 (s, 3H, –$OCOCH_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.8 (C═O_{Ac}), 167.1 (C═O_{Bz}), 133.4 (CH_{Bz}), 129.8 (CH_{Bz}), 129.7 (C_{Bz}), 128.5 (CH_{Bz}), 97.8 (C_{1Man}), 76.7 (C_{2Man}), 71.7 (C_{2Man}), 71.1 (C_{5Man}), 69.6 (C_{3Man}), 67.7 (C_{4Man}), 66.8 (C_7), 63.8 (C_{6Man}), 50.5 (C_8), 20.9 (–OCO$\underline{C}H_3$). **ESI-MS** for $C_{17}H_{21}N_3O_8$; calcd: 395.1 M^+; found: 418.2 $[M + Na]^+$; **ESI-HRMS** for $C_{17}H_{21}N_3O_8$; calcd: 418.1226 $[M + Na]^+$; found: 418.1219 $[M + Na]^+$.

Synthesis of methyl-2-*O*-acetyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (9). To a solution of methyl-6-*O*-benzoyl-α-D-mannopyranoside (**7**) (177 mg, 0.52 mmol) in CH_2Cl_2 (10 mL) were subsequently added Bz_2O (350 mg, 1.56 mmol), Et_3N (220 μL, 1.56 mmol) and 4-dimethylaminopyridine (4-DMAP) (7 mg, 0.01 mmol) and the reaction was stirred at room temperature for 1 hour. Then, the solvent was evaporated and the residue was dissolved in EtOAc (25 mL). The solution was washed with 1 M HCl (25 mL), sat. $NaHCO_3$ (25 mL) and water (25 mL), the organic phase was dried over anh. $MgSO_4$ and the solvent was evaporated. Finally, the residue was purified by flash chromatography on silica gel (hexane : EtOAc, 2 : 1) to give compound **9** as a colorless oil (255 mg, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.5, 2H, $2H_{Bz}$), 7.97 (d, J = 7.5 Hz, 1H, $2H_{Bz}$), 7.91 (d, J = 7.5, 2H, $2H_{Bz}$), 7.60–7.29 (m, 9H, $9H_{Bz}$), 5.92 (t, J = 10.0 Hz, 1H, H_{4Man}), 5.81 (dd, J = 10.0, 3.2 Hz, 1H, H_{3Man}), 5.52 (dd, J = 3.2, 1.6 Hz, 1H, H_{2Man}), 4.88 (d, J = 1.6 Hz, 1H, H_{1Man}), 4.65 (dd, J = 12.2, 3.0 Hz, 1H, H_{6Man}), 4.52 (dd, J = 12.0, 5.2 Hz, 1H, H_{6Man}), 4.41–4.37 (m, 1H, H_{5Man}), 3.53 (s, 3H, –OCH_3), 2.17 (s, 3H, –$OCOCH_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.9 (C═O_{Ac}), 166.2 (C═O_{Bz}), 165.6 (C═O_{Bz}), 165.4 (C═O_{Bz}), 133.5 (C═O_{Bz}), 133.2(CH_{Bz}), 133.1 (CH_{Bz}), 129.8 (CH_{Bz}), 129.7 (CH_{Bz}), 129.2 (C_{Bz}), 129.0, (CH_{Bz}) 128.5 (CH_{Bz}), 128.4 (CH_{Bz}), 98.6 (C_{1Man}), 69.9 (C_{2Man}), 69.8 (C_{3Man}), 68.7 (C_{5Man}), 67.1 (C_{4Man}), 63.4 (C_{6Man}), 50.5 (–OCH_3), 20.8 (–OCO$\underline{C}H_3$). **ESI-MS** for $C_{30}H_{28}O_{10}$; calcd: 548.2 M^+; found: 571.3 $[M + Na]^+$; **ESI-HRMS** for $C_{30}H_{28}O_{10}$; calcd: 571.1780 $[M + Na]^+$; found: 571.1771 $[M + Na]^+$.

Synthesis of 2-azidoethyl-2-*O*-acetyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (10). To a solution of 2-azidoethyl-6-*O*-benzoyl-α-D-mannopyranoside (**8**) (60 mg, 0.15 mmol) in CH_2Cl_2 (4 mL) were subsequently added Bz_2O (138 mg, 0.61 mmol), Et_3N (85 μL, 0.61 mmol) and 4-DMAP (3 mg, 0.02 mmol) and the reaction was stirred at room temperature for 1 hour. Then, the solvent was evaporated and the residue was dissolved in EtOAc (20 mL). The solution was washed with 1 M HCl (20 mL), sat. $NaHCO_3$ (20 mL) and water, the organic phase was dried over anh. $MgSO_4$ and the solvent was evaporated. Finally, the residue was purified by flash chromatography on silica gel (hexane : EtOAc, 2 : 1) to give compound **10** as a colorless oil (81 mg, 90%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (d, J = 7.5, 2H, $2H_{Bz}$), 7.97 (dd, J = 8.3, 1.4 Hz, 1H, $2H_{Bz}$), 7.92 (d, J = 7.5, 2H, $2H_{Bz}$), 7.69–7.31 (m, 9H, $9H_{Bz}$), 5.96 (t, J = 9.9 Hz, 1H, H_{4Man}), 5.83 (dd, J = 10.1, 3.3 Hz, 1H, H_{3Man}), 5.52 (dd, J = 3.3, 1.8 Hz, 1H, H_{2Man}), 5.02 (d, J = 2.0 Hz, 1H, H_{1Man}), 4.65 (dd, J = 12.0, 2.4 Hz, 1H, H_{6Man}), 4.60–4.39 (m, 2H, H_{5Man} + H_{6Man}), 3.99 (ddd, J = 10.7, 7.2, 3.6 Hz, 1H, H_7), 3.75 (ddd, J = 10.2, 5.9, 3.5 Hz, 1H, H_7), 3.58 (ddd, J = 9.8, 6.5, 2.9 Hz, 1H, H_8), 3.47 (ddd, J = 9.8, 6.5, 2.9 Hz, 1H, H_8), 2.14 (s, 3H, –$OCOCH_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.8 (C═O_{Ac}), 166.0 (C═O_{Bz}), 165.4 (C═O_{Bz}), 165.3 (C═O_{Bz}), 133.4 (CH_{Bz}), 133.2 (CH_{Bz}), 133.0 (CH_{Bz}), 129.8 (CH_{Bz}), 129.7 (C_{Bz}), 129.7 (CH_{Bz}), 129.6 (CH_{Bz}), 129.6 (CH_{Bz}), 129.5 (C_{Bz}), 129.0 (C_{Bz}), 128.8 (CH_{Bz}), 128.4 (CH_{Bz}), 128.3 (CH_{Bz}), 128.2 (CH_{Bz}), 97.5 (C_{1Man}), 69.7 (C_{2Man}), 69.5 (C_{4Man}), 69.1 (C_{5Man}), 67.1 (C_7), 66.8 (C_{3Man}), 63.1 (C_{6Man}), 50.3 (C_8), 20.7 (–OCO$\underline{C}H_3$). **ESI-MS** for $C_{31}H_{29}N_3O_{10}$; calcd: 603.2 M^+; found: 626.2 $[M + Na]^+$; **ESI-HRMS** for $C_{31}H_{29}N_3O_{10}$; calcd: 626.1751 $[M + Na]^+$; found: 626.1740 $[M + Na]^+$.

Synthesis of methyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (11). To a solution of methyl-2-*O*-acetyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (**9**) (244 mg, 0.445 mmol) in CH_3CN (5 mL) was added a solution of 7% HCl in MeOH (10 mL) and the reaction was stirred at room temperature for 24 hours. Then, the solvent was evaporated and the residue was dissolved in EtOAc (25 mL). The solution was washed with a solution of sat. $NaHCO_3$ (2 × 50 mL) and water (50 mL). The organic phase was dried over anh. $MgSO_4$ and the solvent was evaporated to obtain compound **11** as a colorless oil (200 mg, 89%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, J = 6.9 Hz, 1H, $2H_{Bz}$), 8.00 (d, J = 8.3, 1.6 Hz, 1H, $2H_{Bz}$), 7.97 (d, J = 8.3, 1.6 Hz, 1H, $2H_{Bz}$), 7.63–7.47 (m, 2H, 3 H_{Bz}), 7.48–7.34 (m, 6H, $6H_{Bz}$), 5.96 (t, J = 10.0 Hz, 1H, H_{4Man}), 5.70 (dd, J = 10.0, 3.1 Hz, 1H, H_{3Man}), 4.92 (d, J = 1.8 Hz, 1H, H_{1Man}), 4.63 (dd, J = 12.0, 3.0 Hz, 1H, H_{6Man}), 4.52 (dd, J = 12.0, 5.5 Hz, 1H, H_{6Man}), 4.42–4.33 (m, 1H, H_{2Man} + H_{5Man}), 3.54 (s, 3H, –OCH_3), 2.26 (d, J = 4.7 Hz, 1H, –OH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.2 (C═O_{Bz}), 165.6 (C═O_{Bz}), 165.5 (C═O_{Bz}), 133.4 (CH_{Bz}), 133.3 (CH_{Bz}), 133.1 (CH_{Bz}), 129.8 (CH_{Bz}), 129.8 (CH_{Bz}), 129.7 (CH_{Bz}), 129.2 (CH_{Bz}), 129.1 (CH_{Bz}), 128.4 (CH_{Bz}), 128.4 (CH_{Bz}), 128.3 (CH_{Bz}), 100.7 (C_{1Man}), 72.6 (C_{3Man}), 69.41 (C_{2Man} or C_{5Man}), 68.6 (C_{2Man} or C_{5Man}), 67.0 (C_{4Man}), 63.6 (C_{6Man}), 55.38 (C-$_{OCH_3}$). **ESI-MS** for $C_{28}H_{26}O_9$; calcd: 506.2 M^+; found: 529.3 $[M + Na]^+$; **ESI-HRMS** for $C_{28}H_{26}O_9$; calcd: 529.1469 $[M + Na]^+$; found: 529.1452 $[M + Na]^+$.

Synthesis of 2-azidoethyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (12). To a solution of 2-azidoethyl-2-*O*-acetyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (**10**) (64 mg, 0.114 mmol) in CH_3CN (1 mL) was added a solution of 7% HCl in MeOH (2 mL) and the reaction was stirred at room temperature for 24 hours. Then the solvent was evaporated and the residue was dissolved

in EtOAc (25 mL). The solution was washed with a solution of sat. $NaHCO_3$ (2 × 25 mL) and water (25 mL). The organic phase was dried over anh. $MgSO_4$ and the solvent was evaporated to obtain compound **12** as a colorless oil (49 mg, 90%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.03 (d, J = 6.9 Hz, 1H, $2H_{Bz}$), 7.97 (d, J = 7.0 Hz, 2H, $2H_{Bz}$), 7.94 (d, J = 7.0 Hz, 2H, $2H_{Bz}$), 5.98 (t, J = 10.0 Hz, 1H, H_{4Man}), 5.71 (dd, J = 10.0, 3.1 Hz, 1H, H_{3Man}), 5.04 (d, J = 1.9 Hz, 1H, H_{1Man}), 4.60 (dd, J = 12.0, 3.1 Hz, 1H, H_{6Man}), 4.52 (dd, J = 12.0, 5.2 Hz, 1H, H_{6Man}), 4.47–4.33 (m, 2H, H_{2Man} + H_{4Man}), 4.00 (ddd, J = 10.4, 6.2, 3.9 Hz, 1H, H_7), 3.74 (ddd, J = 10.4, 6.0, 3.7 Hz, 1H, H_7), 3.61–3.39 (m, 2H, H_8). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.6 ($C{=}O_{Bz}$), 166.0 ($C{=}O_{Bz}$), 133.7 (CH_{Bz}), 133.4 (CH_{Bz}), 130.2 (CH_{Bz}), 130.1 (CH_{Bz}), 130.0 (CH_{Bz}), 129.5 (C_{Bz}), 129.4 (C_{Bz}), 128.8 (CH_{Bz}), 128.8 (CH_{Bz}), 128.7 (CH_{Bz}), 100.2 (C_{1Man}), 72.8 (C_{3Man}), 69.5 (C_{2Man} or C_{5Man}), 69.4 (C_{2Man} or C_{5Man}), 67.4 (C_{4Man} or C_7), 67.3 (C_{4Man} or C_7), 63.9 (C_{6Man}), 50.8 (C_8). **ESI-MS** for $C_{29}H_{27}N_3O_9$; calcd: 561.2 M^+; found: 583.2 $[M + Na]^+$; **ESI-HRMS** for $C_{29}H_{27}N_3O_9$; calcd: 584.1645 $[M + Na]^+$; found: 583.1636 $[M + Na]^+$.

Consecutive synthesis of methyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (11). To a solution of methyl α-D-mannopyranose (**3**) (1.5 g, 7.72 mmol) in DMF (80 mL) at −40 °C were added dropwise a solution of BzCN (1.21 g, 9.26 mmol) in DMF (20 mL) and a catalytic amount of Et_3N and the reaction was stirred for 2 hours. After that, MeOH (40 mL) was added to quench excess BzCN and the reaction was warmed until room temperature. Then, the solvent was evaporated. After being dissolved in CH_3CN (80 mL), to the resulting mixture containing the methyl 6-*O*-benzoyl-α-D-mannopyranoside (**5**) were added CSA (361 mg, 1.55 mmol) and trimethyl orthoacetate (2.95 mL, 23.16 mmol) and the reaction was stirred at room temperature 1 hour. After that, the reaction was quenched with Et_3N (1.5 mL) and the solvent was evaporated. Then, the residue was dissolved in EtOAc (200 mL) and washed with 1 M HCl (200 mL), the organic phase was dried with anh. $MgSO_4$ and the solvent was evaporated. To the resulting mixture containing 2-methyl 2-*O*-acetyl-6-*O*-benzoyl-α-D-mannopyranoside (**7**) in CH_2Cl_2 (100 mL) were subsequently added Bz_2O (7.0 g, 30.88 mmol), Et_3N (4.3 mL, 30.88 mmol) and 4-DMAP (104 mg, 0.80 mmol) and the reaction was stirred at room temperature for 1 hour. Then, the solvent was evaporated and the residue was dissolved in EtOAc (200 mL). The solution was washed with 1 M HCl (250 mL), sat. $NaHCO_3$ (250 mL) and water (250 mL), the organic phase was dried over anh. $MgSO_4$ and the solvent was evaporated. Finally, to the residue containing methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (**9**) in CH_3CN (40 mL) was added a solution of 7% HCl in MeOH (200 mL) and the reaction was stirred at room temperature for 24 hours. Then the solvent was evaporated and the residue was dissolved in EtOAc (250 mL). The solution was washed with a solution of sat. $NaHCO_3$ (2 × 500 mL) and water (500 mL). The organic phase was dried over anh. $MgSO_4$ and the solvent was evaporated. The residue was purified by flash chromatography on silica gel (hexane : EtOAc, 3 : 1) to obtain compound **11** as a colorless oil (2.81 g, 72%).

Consecutive synthesis of 2-azidoethyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (12). To a solution of 2-azidoethyl-α-D-mannose (**4**) (1.8 g, 7.23 mmol) in DMF (80 mL) at −40 °C were added dropwise a solution of BzCN (1.14 g, 8.68 mmol) in DMF (20 mL) and a catalytic amount of Et_3N and the reaction was stirred for 2 hours. After that, MeOH (40 mL) was added to quench excess BzCN and the reaction was warmed until room temperature. Then, the solvent was evaporated. After being dissolved in CH_3CN (80 mL), to the resulting mixture containing 2-azidoethyl-6-*O*-benzoyl-α-D-mannopyranoside (**6**) were added CSA (335 mg, 1.45 mmol) and trimethyl orthoacetate (2.60 mL, 21.63 mmol) and the reaction was stirred at room temperature for 1 hour. After that, the reaction was quenched with Et_3N (1 mL) and the solvent was evaporated. Then, the residue was dissolved in EtOAc (200 mL) and washed with 1 M HCl (200 mL), the organic phase was dried with anh. $MgSO_4$ and the solvent was evaporated. To the resulting mixture containing 2-azidoethyl 2-*O*-acetyl-6-*O*-benzoyl-α-D-mannopyranoside (**8**) in CH_2Cl_2 (100 mL) were subsequently added Bz_2O (6.5 g, 28.92 mmol), Et_3N (4 mL, 28.92 mmol) and 4-DMAP (104 mg, 0.80 mmol) and the reaction was stirred at room temperature for 1 hour. Then, the solvent was evaporated and the residue was purified with EtOAc (200 mL). The solution was washed with 1 M HCl (250 mL), sat. $NaHCO_3$ (250 mL) and water (250 mL), the organic phase was dried over anh. $MgSO_4$ and the solvent was evaporated. Finally, to the residue containing 2-azidoethyl 2-*O*-acetyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (**10**) in CH_3CN (40 mL) was added a solution of 7% HCl in MeOH (200 mL) and the reaction was stirred at room temperature for 24 hours. Then the solvent was evaporated and the residue was dissolved in EtOAc (250 mL). The solution was washed with a solution of sat. $NaHCO_3$ (2 × 500 mL) and water (500 mL). The organic phase was dried over anh. $MgSO_4$ and the solvent was evaporated. The residue was purified by flash chromatography on silica gel (hexane : EtOAc, 3 : 1) to obtain compound **12** as a transparent oil (2.84 g, 70%).

Synthesis of methyl *O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-(1 → 2)-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (15). A mixture of the acceptor **11** (150 mg, 0.296 mmol) and the donor **13** (219 mg, 0.445 mmol) was co-evaporated from toluene three times. Powdered and activated 4 Å molecular sieves were added, and the mixture was kept under vacuum for few hours and then dissolved in CH_2Cl_2 (10 mL). The mixture was cooled to −0 °C for 15 min, followed by the addition of TMSOTf (13 μL, 0.059 mmol), and stirred for 30 min at 0 °C. The reaction was quenched by the addition of Et_3N, filtered over a pad of Celite and dried under vacuum. The crude was purified by flash column chromatography on silica gel (CH_2Cl_2–MeOH, 100 : 1) to obtain **15** as an white solid (114 mg, 46%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15–8.07 (m, 4H, $4H_{Bz}$), 8.04 (d, J = 7.0 Hz, 2H, $2H_{Bz}$), 8.02 (d, J = 7.0 Hz, 2H, $2H_{Bz}$), 8.00–7.95 (m, 4H, $4H_{Bz}$), 7.90 (d, J = 6.9 Hz, 2H, $2H_{Bz}$), 7.65–7.30 (m, 21H, $21H_{Bz}$), 6.12–6.05 (m, 2H, H_{3ManB} + H_{4ManB}), 6.02 (t, J = 9.9 Hz, 1H, H_{4ManA}), 5.94 (dd, J = 2.3, 1.8 Hz, 1H, H_{2ManB}), 5.91 (dd, J = 9.9, 3.2 Hz, 1H, H_{3ManA}), 5.29 (d, J = 1.8 Hz, 1H, H_{1ManB}), 5.09 (d, J = 1.8 Hz, 1H, H_{1ManA}),

4.73–4.64 (m, 3H, H_{5ManB} + H_{6ManB} + H_{6ManA}), 4.60 (dd, J = 12.2, 5.5 Hz, 1H, H_{6ManA}), 4.50 (dd, J = 12.0, 5.3 Hz, 1H, H_{6ManB}), 4.41 (dd, J = 2.6, 1.8 Hz, H_{2ManA}), 4.41–4.35(m, 1H, H_{5ManA}), 3.42 (s, 3H, –OMe). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.4 ($C{=}O_{Bz}$), 166.1 ($C{=}O_{Bz}$), 165.6 ($C{=}O_{Bz}$), 165.3 ($C{=}O_{Bz}$), 165.0 ($C{=}O_{Bz}$), 165.0 ($C{=}O_{Bz}$), 133.5 (CH_{Bz}), 133.4 (CH_{Bz}), 133.3 (CH_{Bz}), 133.3 (CH_{Bz}), 133.1 (CH_{Bz}), 133.0 (CH_{Bz}), 130.0 (CH_{Bz}), 130.0 (CH_{Bz}), 129.9 (CH_{Bz}), 129.8 (CH_{Bz}), 129.8 (CH_{Bz}), 129.7 (CH_{Bz}), 129.2 (C_{Bz}), 129.1 (C_{Bz}), 128.9 (C_{Bz}), 128.8 (C_{Bz}), 128.5 (CH_{Bz}), 128.5 (CH_{Bz}), 128.4 (CH_{Bz}), 128.4 (CH_{Bz}), 128.3 (CH_{Bz}), 99.6 (C_{1ManA}), 99.6 (C_{1ManB}), 76.9 (C_{2ManA}), 70.8, 70.1, 69.8, 69.7, 68.8, 67.6, 67.0, 63.8 (C_{6ManA}), 63.1 (C_{6ManB}), 55.2($C\text{-}_{OCH_3}$). **ESI-MS** for $C_{42}H_{44}O_{18}$; calcd: 836.2 M^+; found: 859.3 $[M + Na]^+$; **ESI-HRMS** for $C_{42}H_{44}O_{18}$; calcd: 859.2425 $[M + Na]^+$; found: 859.2413 $[M + Na]^+$.

Synthesis of 2-azidoethyl *O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-(1 → 2)-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (16). A mixture of the acceptor **12** (120 mg, 0.214 mmol) and the donor **13** (158 mg, 0.321 mmol) was co-evaporated from toluene three times. Powdered and activated 4 Å molecular sieves were added, and the mixture was kept under vacuum for few hours and then dissolved in CH_2Cl_2 (8 mL). The mixture was cooled to 0 °C for 15 min, followed by the addition of TMSOTf (8.5 μL, 0.040 mmol), and stirred for 30 min at 0 °C. The reaction was quenched by the addition of Et_3N, filtered over a pad of Celite and dried under vacuum. The crude was purified by flash column chromatography on silica gel (CH_2Cl_2–MeOH, 100 : 1) to obtain **16** as a white solid (112 mg, 59%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.1 Hz, 2H, $2H_{Bz}$), 7.98 (d, J = 7.1 Hz, 2H, $2H_{Bz}$), 7.95 (d, J = 7.0 Hz, 2H, $2H_{Bz}$), 7.68–6.99 (m, 9H, $9H_{Bz}$), 5.94 (t, J = 9.9 Hz, 1H, H_{4ManA}), 5.84 (dd, J = 9.9, 3.2 Hz, 1H, H_{4ManA}), 5.49–5.43 (m, 2H, H_{2ManB} + H_{3ManB}), 5.26 (t, J = 9.5 Hz, 1H, H_{4ManB}), 5.15 (d, J = 1.9 Hz, 1H, H_{1ManA}), 4.98 (d, J = 1.5 Hz, 1H, H_{1ManB}), 4.63 (dd, J = 12.2, 3.0 Hz, 1H, H_{6ManA}), 4.52 (dd, J = 12.1, 5.4 Hz, 1H, H_{6ManA}), 4.41 (ddd, J = 10.1, 5.4, 2.9 Hz, 1H, H_{5ManA}), 4.34 (dd, J = 3.2, 1.9 Hz, 1H, H_{2ManA}), 4.25 (dd, J = 11.9, 5.4 Hz, 1H, H_{6ManB}), 4.17 (ddd, J = 12.1, 7.4, 3.3 Hz, 1H, H_{5ManB}), 4.11 (dd, J = 11.9, 2.5 Hz, 1H, H_{6ManB}), 4.01 (dt, J = 10.3, 4.7 Hz, 1H, H_7), 3.82–3.72 (m, 1H, H_7), 3.54 (t, J = 5.0 Hz, 2H, H_8), 2.10 (s, 3H, $-OCOCH_3$), 2.06 (s, 3H, $-OCOCH_3$), 2.04 (s, 3H, $-OCOCH_3$), 2.01 (s, 3H, $-OCOCH_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.51 ($C{=}O_{Ac}$), 169.80 ($C{=}O_{Ac}$), 169.48 ($C{=}O_{Ac}$), 169.42 ($C{=}O_{Ac}$), 166.22 ($C{=}O_{Bz}$), 165.50 ($C{=}O_{Bz}$), 165.19 ($C{=}O_{Bz}$), 133.43 (CH_{Bz}), 133.32 (CH_{Bz}), 133.02 (CH_{Bz}), 129.92 (CH_{Bz}), 129.86 (CH_{Bz}), 129.70 (CH_{Bz}), 128.97 (C_{Bz}), 128.82 (C_{Bz}), 128.55 (CH_{Bz}), 128.47 (CH_{Bz}), 128.36 (CH_{Bz}), 99.46 (C_{1ManB}), 98.65 (C_{1ManA}), 76.50 (C_{2ManA}), 70.62 (C_{3ManA}), 69.30 (C_{2ManB}), 69.2 (C_{5ManB}), 69.1 (C_{5ManA}), 68.8 (C_{3ManB}), 67.2 (C_7), 67.1 (C_{4ManA}), 66.3 (C_{4ManB}), 63.6 (C_{6ManA}), 62.6 (C_{6ManB}), 50.4 (C_8), 20.70 ($-OCO\underline{C}H_3$), 20.67 ($-OCO\underline{C}H_3$). **ESI-MS** for $C_{43}H_{45}N_3O_{18}$; calcd: 891.3 M^+; found: 914.3 $[M + Na]^+$; **ESI-HRMS** for $C_{43}H_{45}N_3O_{18}$; calcd: 914.2596 $[M + Na]^+$; found: 914.2590 $[M + Na]^+$.

Synthesis of methyl *O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-(1 → 2)-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (17). A mixture of the acceptor **11** (60 mg, 0.119 mmol) and the donor **14** (105 mg, 0.142 mmol) was co-evaporated from toluene three times. Powdered and activated 4 Å molecular sieves were added, and the mixture was kept under vacuum for a few hours and then dissolved in CH_2Cl_2 (5 mL). The mixture was cooled to 0 °C for 15 min, followed by the addition of TMSOTf (4.5 μL, 0.024 mmol), and stirred for 30 min at 0 °C. The reaction was quenched by the addition of Et_3N, filtered over a pad of Celite and dried under vacuum. The crude was purified by flash column chromatography on silica gel (CH_2Cl_2–MeOH, 100 : 1) to obtain **17** as a white solid (97 mg, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15–8.07 (m, 4H, $4H_{Bz}$), 8.04 (d, J = 7.0 Hz, 2H, $2H_{Bz}$), 8.02 (d, J = 7.0 Hz, 2H, $2H_{Bz}$) δ 8.00–7.95 (m, 4H, $4H_{Bz}$), 7.90 (d, J = 6.9 Hz, 2H, $2H_{Bz}$), 7.65–7.30 (m, 21H, $21H_{Bz}$), 6.12–6.05 (m, 2H, H_{3ManB} + H_{4ManB}), 6.02 (t, J = 9.9 Hz, 1H, H_{4ManA}), 5.94 (dd, J = 2.3, 1.8 Hz, 1H, H_{2ManB}), 5.91 (dd, J = 9.9, 3.2 Hz, 1H, H_{3ManA}), 5.29 (d, J = 1.8 Hz, 1H, H_{1ManB}), 5.09 (d, J = 1.8 Hz, 1H, H_{1ManA}), 4.73–4.64 (m, 3H, H_{5ManB} + H_{6ManB} + H_{6ManA}), 4.60 (dd, J = 12.2, 5.5 Hz, 1H, H_{6ManA}), 4.50 (dd, J = 12.0, 5.3 Hz, 1H, H_{6ManB}), 4.41 (dd, J = 2.6, 1.8 Hz, H_{2ManA}), 4.41–4.35(m, 1H, H_{5ManA}), 3.42 (s, 3H, –OMe). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.4 ($C{=}O_{Bz}$), 166.1 ($C{=}O_{Bz}$), 165.6 ($C{=}O_{Bz}$), 165.3 ($C{=}O_{Bz}$), 165.0 ($C{=}O_{Bz}$), 165.0 ($C{=}O_{Bz}$), 133.5 (CH_{Bz}), 133.4 (CH_{Bz}), 133.3 (CH_{Bz}), 133.3 (CH_{Bz}), 133.1 (CH_{Bz}), 133.0 (CH_{Bz}), 130.0 (CH_{Bz}), 130.0 (CH_{Bz}), 129.9 (CH_{Bz}), 129.8 (CH_{Bz}), 129.8 (CH_{Bz}), 129.7 (CH_{Bz}), 129.2 (C_{Bz}), 129.1 (C_{Bz}), 128.9 (C_{Bz}), 128.8 (C_{Bz}), 128.5 (CH_{Bz}), 128.5 (CH_{Bz}), 128.4 (CH_{Bz}), 128.4 (CH_{Bz}), 128.3 (CH_{Bz}), 99.6 (C_{1ManA}), 99.6 (C_{1ManB}), 76.9 (C_{2ManA}), 70.8, 70.1, 69.8, 69.7, 68.8, 67.6, 67.0, 63.8 (C_{6ManA}), 63.1 (C_{6ManB}), 55.2 ($C\text{-}_{OCH_3}$). **ESI-MS** for $C_{62}H_{52}O_{18}$; calcd: 1084.3 M^+; found: 1107.3 $[M + Na]^+$; **ESI-HRMS** for $C_{62}H_{52}O_{18}$; calcd: 1107.3051 $[M + Na]^+$; found: 1107.3039 $[M + Na]^+$.

Synthesis of 2-azidoethyl *O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-(1 → 2)-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (18). A mixture of the acceptor **12** (250 mg, 0.440 mmol) and the donor **14** (494 mg, 0.670 mmol) was co-evaporated from toluene three times. Powdered and activated 4 Å molecular sieves were added, and the mixture was kept under vacuum for few hours and then dissolved in CH_2Cl_2 (12 mL). The mixture was cooled to 0 °C for 15 min, followed by the addition of TMSOTf (20 μL, 0.088 mmol), and stirred for 30 min at 0 °C. The reaction was quenched by the addition of Et_3N, filtered over a pad of Celite and dried under vacuum. The crude was purified by flash column chromatography on silica gel (CH_2Cl_2–MeOH, 100 : 1) to obtain **18** as a white solid (396 mg, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (d, J = 7.3 Hz, 2H, $2H_{Bz}$), 8.09 (d, J = 7.3 Hz, 2H, $2H_{Bz}$), 8.06 (d, J = 7.3 Hz, 2H, $2H_{Bz}$) δ 8.03–7.95 (m, 6H, $4H_{Bz}$), 7.91 (d, J = 7.6 Hz, 2H, $2H_{Bz}$), 7.65–7.29 (m, 21H, $21H_{Bz}$), 6.15–6.02 (m, 3H, H_{4ManA} + H_{3ManB} + H_{4ManB}), 5.97–5.90 (m, 2H, H_{2ManB} + H_{3ManA}), 5.31 (d, J = 1.8 Hz, 1H, H_{1ManB}), 5.24 (d, J = 1.8 Hz, 1H, H_{1ManA}), 4.74–4.60 (m, 3H, H_{5ManB} + H_{6ManB} + H_{6ManA}), 4.53 (dd, J = 12.0, 4.9 Hz, 1H, H_{6ManA}), 4.49 (m, 2H, H_{2ManA} + H_{6ManB}), 3.91 (ddd, J = 10.5, 6.7, 3.8 Hz 1H, H_7), 3.59 (ddd, J = 10.2, 6.0, 3.5 Hz 1H, H_7), 3.52–3.37 (m, 2H, H_8). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 ($C{=}O_{Bz}$), 166.1 ($C{=}O_{Bz}$), 165.6 ($C{=}O_{Bz}$), 165.3 ($C{=}O_{Bz}$), 165.1

($C{=}O_{Bz}$), 164.9 ($C{=}O_{Bz}$), 133.5 (CH_{Bz}), 133.4 (CH_{Bz}), 133.3 (CH_{Bz}), 133.3 (CH_{Bz}), 133.1 (CH_{Bz}), 133.1 (CH_{Bz}), 130.0 (CH_{Bz}), 130.0 (CH_{Bz}), 129.9 (CH_{Bz}), 129.8 (CH_{Bz}), 129.8 (CH_{Bz}), 129.7 (CH_{Bz}), 129.2 (C_{Bz}), 129.0 (C_{Bz}), 128.8 (C_{Bz}), 128.6 (C_{Bz}), 128.5 (CH_{Bz}), 128.5 (CH_{Bz}), 128.4 (CH_{Bz}), 128.4 (CH_{Bz}), 128.3 (CH_{Bz}), 99.7 (C_{1ManA}), 98.7 (C_{1ManB}), 76.9 (C_{2ManA}), 70.6, 70.1, 69.8, 69.7, 69.2, 67.5, 67.0, 66.9, 63.7 (C_{6ManA}), 63.1 (C_{6ManB}), 50.3 (C_8). **ESI-MS** for $C_{63}H_{53}N_3O_{18}$; calcd: 1139.3 M^+; found: 1162.5 $[M + Na]^+$; **ESI-HRMS** for $C_{63}H_{53}N_3O_{18}$; calcd: 1162.3222 $[M + Na]^+$; found: 1139.3212 $[M + Na]^+$.

Synthesis of methyl α-D-mannopyranosyl-(1 → 2)-α-D-mannopyranoside (1)

*From **15**.* To a solution of **15** (100 mg, 0.119 mmol) in dry methanol, under nitrogen at room temperature, was added a 1 M solution of sodium methoxide in MeOH (2 equiv.) and the reaction was stirred for 1 hour. Then, the reaction mixture was neutralized with Amberlite IRA 120-H^+ resin. The resin was filtered off and the filtrate was concentrated under reduced pressure. The crude was diluted in H_2O (10 mL), washed with CH_2Cl_2 (10 mL) and the aqueous phase was lyophilized to obtain **1** as a white solid (42 mg, quant.).

*From **17**.* To a solution of **17** (90 mg, 0.081) in dry methanol, under nitrogen at room temperature, was added a 1 M solution of sodium methoxide in MeOH (2 equiv.) and the reaction was stirred for 1 hour. Then, the reaction mixture was neutralized with Amberlite IRA 120-H^+ resin. The resin was filtered off and the filtrate was concentrated under reduced pressure. The crude was diluted in H_2O (10 mL), washed with CH_2Cl_2 (10 mL) and the aqueous phase was lyophilized to obtain **1** as a white solid (29 mg, quant.).

^{1}H NMR (400 MHz, D_2O) δ 4.95 (d, J = 1.8 Hz, 1H, H_{1ManB}), 4.92 (d, J = 2.0 Hz, 1H, H_{1ManB}), 3.99 (dd, J = 3.3, 1.8 Hz, 1H, H_{2ManB}), 3.88 (dd, J = 3.3, 1.8 Hz, 1H, H_{2ManA}), 3,85–375 (m, 4H, H_{3ManA} + H_{3ManB} + H_{6ManA} + H_{4ManA}), 3.74–3.50 (m, 6H, H_{4ManB} + H_{5ManA} + H_{5ManB} + H_{6ManA} + $2H_{6ManB}$), 3,33 (s, 3H, –OMe); **^{13}C NMR** (101 MHz, D_2O) δ 102.3 (C_{1ManB}), 99.3 (C_{6ManA}), 78.5 (C_{2ManB}), 73.2 (C_{5ManB}), 72.5 (C_{5ManA}), 70.3 (C_{3ManB}), 70.3 (C_{3ManA}), 69.9 (C_{2ManB}), 66.9 (C_{4ManB}), 66.8 (C_{4ManA}), 61.1(C_{6ManA}), 60.9 (C_{6ManB}), 54.8 ($C\text{-}_{OCH_3}$); **ESI-MS** for $C_{13}H_{24}O_{11}$; calcd: 356.1 M^+; found: 379.2 $[M + Na]^+$; **ESI-HRMS** for $C_{13}H_{24}O_{11}$; calcd: 379.1211 $[M + Na]^+$; found: 379.1204 $[M + Na]^+$.

Synthesis of 2-azidoethyl α-D-mannopyranosyl-(1 → 2)-α-D-mannopyranoside (2)

*From **16**.* To a solution of **16** (100 mg, 0.112 mmol) in dry methanol, under nitrogen at room temperature, was added a 1 M solution of sodium methoxide in MeOH (2 equiv.) and the reaction was stirred for 1 hour. Then, the reaction mixture was neutralized with Amberlite IRA 120-H^+ resin. The resin was filtered off and the filtrate was concentrated under reduced pressure. The crude was diluted in H_2O (10 mL), washed with CH_2Cl_2 (10 mL) and the aqueous phase was lyophilized to obtain **2** as a white solid (46 mg, quant.).

*From **18**.* To a solution of **18** (390 mg, 0.342 mmol) in dry methanol, under nitrogen at room temperature, was added a 1 M solution of sodium methoxide in MeOH (2 equiv.) and the reaction was stirred for 1 hour. Then, the reaction mixture was neutralized with Amberlite IRA 120-H^+ resin. The resin was filtered off and the filtrate was concentrated under reduced pressure. The crude was diluted in H_2O (10 mL), washed with CH_2Cl_2 (10 mL) and the aqueous phase was lyophilized to obtain **2** as a white solid (140 mg, quant.).

^{1}H NMR (400 MHz, D_2O) δ 5.08 (d, J = 1.8 Hz, 1H, H_{1ManB}), 4.95 (d, J = 1.9 Hz, 1H, H_{1ManA}), 3.99 (dd, J = 3.4, 1.8 Hz, 1H, H_{2ManB}), 3.92 (dd, J = 3.3, 1.8 Hz, 1H, H_{2ManA}), 3.89–3.74 (m, 4H, H_{3ManA} + H_{3ManB} + H_{6ManA} + H_{4ManA} + H_7), 3.73–3.50 (m, 7H, H_{4ManB} + H_{5ManA} + H_{5ManB} + H_{6ManA} + $2H_{6ManB}$ + H_7), 3.49–3.35 (m, 2H, H_8); **^{13}C NMR** (101 MHz, D_2O) δ 102.3 (C_{1ManB}), 98.2 (C_{6ManA}), 78.6 (C_{2ManB}), 73.3 (C_{5ManB}), 72.9 (C_{5ManA}), 70.3 (C_{3ManB}), 70.0 (C_{3ManA}), 69.9 (C_{2ManB}), 66.9 (C_{4ManB}), 66.9 (C_{4ManA}), 66.4 (C_7), 61.1(C_{6ManA}), 60.9 (C_{6ManB}), 50.2 (C_8); **ESI-MS** for $C_{14}H_{25}N_3O_{11}$; calcd: 411.1 M^+; found: 434.2 $[M + Na]^+$; **ESI-HRMS** for $C_{14}H_{25}O_{11}N_3$; calcd: 434.1381 $[M + Na]^+$; found: 434.1372 $[M + Na]^+$.

Consecutive synthesis of *S*-tolyl 3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (20). To a solution of *S*-tolyl α-D-mannopyranose (**19**)[14] (1.5 g, 5.24 mmol) in DMF (50 mL) at −40 °C were added dropwise a solution of BzCN (0.9 g, 8.68 mmol) in DMF (20 mL) and a catalytic amount of Et_3N and the reaction was stirred for 2 hours. After that, MeOH (30 mL) was added to quench excess BzCN and the reaction was warmed up to room temperature. Then, the solvent was evaporated. After being dissolved in CH_3CN (50 mL), to the resulting mixture containing the 6-*O*-benzoyl derivative were added CSA (364 mg, 1.57 mmol) and trimethyl orthoacetate (2.0 mL, 15.7 mmol) and the reaction was stirred at room temperature for 1 hour. After that, the reaction was quenched with Et_3N (1 mL) and the solvent was evaporated. Then, the residue was dissolved in EtOAc (200 mL) and washed with 1 M HCl (200 mL), the organic phase was dried with anh. $MgSO_4$ and the solvent was evaporated. To the resulting mixture containing the 2-*O*-acetyl-6-*O*-benzoyl derivative in CH_2Cl_2 (60 mL) weres subsequently added Bz_2O (4.75 g, 20.96 mmol), Et_3N (3 mL, 20.96 mmol) and 4-DMAP (104 mg, 0.80 mmol) and the reaction was stirred at room temperature for 1 hour. Then, the solvent was evaporated and the residue was purified with EtOAc (150 mL). The solution was washed with 1 M HCl (200 mL), sat. $NaHCO_3$ (200 mL) and water (200 mL), the organic phase was dried over anh. $MgSO_4$ and the solvent was evaporated. Finally, to the residue containing the 2-*O*-acetyl-3,4,6-tri-*O*-benzoyl derivative in CH_3CN (40 mL) was added a solution of 7% HCl in MeOH (150 mL) and the reaction was stirred at room temperature for 24 hours. Then the solvent was evaporated and the residue was dissolved in EtOAc (200 mL). The solution was washed with a solution of sat. $NaHCO_3$ (2 × 300 mL) and water (300 mL). The organic phase was dried over anh. $MgSO_4$ and the solvent was evaporated. The residue was purified by flash chromatography on silica gel (hexane : EtOAc, 4 : 1) to obtain compound **20** as a white solid (2.04 g, 65%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04–7.99 (m, 6H, $6H_{Bz}$), 7.62–7.52 (m, 3H, $3H_{Bz}$), 7.50–7.37 (m, 8H, $6H_{Bz}$ + $2H_{Tolyl}$), 5.98 (t, J = 10.0 Hz, 1H, H_{4Man}), 5.69 (dd, J = 9.9, 3.0 Hz, 1H, H_{3Man}), 5.64 (d, J = 1.6 Hz, 1H, H_{1Man}),

4.98 (ddd, J = 9.6, 6.0, 3.0 Hz, 1H, H_{5Man}), 4.65–4.55 (m, 3H, H_{2Man} + $2H_{6Man}$), 2.54 (s, 3H, CH_{3Tolyl}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.2 ($C{=}O_{Bz}$), 165.6 ($C{=}O_{Bz}$),138.1(C_{Tolyl}) 133.5 (CH_{Bz}), 133.4 (CH_{Bz}), 133.0 (CH_{Bz}), 132.3 (CH_{Tolyl}), 130.0 (CH_{Tolyl}), 129.9 (CH_{Bz}), 129.8 (CH_{Bz}), 129.7 (CH_{Bz}) 129.1 (CH_{Bz}), 129.0 (CH_{Bz}), 129. (C_{Tol}) 128.5 (CH_{Bz}), 128.4 (CH_{Bz}), 128.4 (CH_{Bz}), 128.3 (CH_{Bz}), 88.0 (C_{1Man}), 72.8 (C_{3Man}), 70.7 (C_{5Man}), 69.7 (C_{2Man}), 67.2 (C_{4Man}), 63.5 (C_{6Man}), 21.15 (CH_{3Tolyl}). **ESI-MS** for $C_{34}H_{30}O_8$; calcd: 598.2 M^+; found: 621.2 $[M + Na]^+$. **ESI-HRMS** for $C_{34}H_{30}O_8S$; calcd: 621.1559 $[M + Na]^+$; found: 621.1551 $[M + Na]^+$.

Synthesis of *S*-tolyl *O*-(3,4,6-tri-*O*-benzoyl-α-D-mannopyranosyl)-(1 → 2)-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (21). To a solution of compound **20** (200 mg, 0.334 mmol) in anhydrous CH_2Cl_2 (3 mL) was added 4 Å molecular sieves and the mixture was stirred at room temperature for 2 h. Then, the reaction mixture was cooled at −40 °C and NIS (53 mg, 0.241 mmol) and TfOH (4.5 mL, 0.017 mmol) were added and the reaction was stirred for 1 hour. Then it was quenched with sat. $NaHCO_3$ (aq.). The reaction mixture was diluted with CH_2Cl_2 (10 mL) and was filtered over a pad of Celite. The organic layer was washed with sat. $Na_2S_2O_3$ (aq) (10 mL × 3) and then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give a colorless oil. The oil was purified by flash column chromatography on silica gel (4 : 1 → 2 : 1 hexane : EtOAc) to give the disaccharide **21** as a white solid (243 mg, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07–7.99 (m, 12H, $10H_{Bz}$), 7.95 (d, J = 7.1 Hz, 2H, $2H_{Bz}$), 7.59–7.47 (m, 6H, $6H_{Bz}$), 7.44–7.32 (m, 14H, $12H_{Bz}$ + $2H_{Tolyl}$), 6.98 (d, J = 7.5 Hz, 2H, $2H_{Tolyl}$), 6.03 (t, J = 9.8 Hz, 1H, H_{4ManA}), 5.97 (t, J = 9.8 Hz, 1H, H_{4ManB}), 5.86 (dd, J = 9.7, 3.1 Hz, 1H, H_{3Mana}), 5.83–5.79 (m, 2H, H_{1ManA} + H_{3ManB}), 5.23 (d, J = 1.9 Hz, 1H, H_{1ManB}), 5.00 (ddd, J = 9.5, 5.9, 3.1 Hz, 1H, H_{5ManA}), 4.73 (dd, J = 3.1, 1.9 Hz, 1H, H_{2Mana}), 4.69–4.41 (m, 6H, H_{2ManB} + H_{5ManB} + $2H_{6ManB}$ + $2H_{6ManA}$), 2.29 (s, 3H, CH_{3Tolyl}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 ($C{=}O_{Bz}$), 166.2 ($C{=}O_{Bz}$), 165.6 ($C{=}O_{Bz}$), 165.4 ($C{=}O_{Bz}$), 165.2 ($C{=}O_{Bz}$), 128.3 (C_{Tolyl}), 133.6 (CH_{Bz}), 133.4 (CH_{Bz}), 133.4 (CH_{Bz}), 133.3 (CH_{Bz}), 133.0 (CH_{Bz}), 132.5 (CH_{Bz}), 130.1 (CH_{Bz}), 129.9 (CH_{Bz}), 129.9 (CH_{Bz}), 129.8 (CH_{Bz}), 129.8 (CH_{Bz}), 129.7 (CH_{Bz}), 129.6 (C_{Tolyl}), 129.2 (C_{Bz}), 129.0 (C_{Bz}), 128.8 (C_{Bz}), 128.7 (C_{Bz}), 128.6 (CH_{Bz}), 128.5 (CH_{Bz}), 128.4 (CH_{Bz}), 128.4 (CH_{Bz}), 128.3 (CH_{Bz}), 101.4 (C_{1ManB}), 87.1 (C_{1ManB}), 77.2 (C_{2ManA}), 72.1 (C_{3ManB}), 71.7 (C_{3ManA}), 69.8 (C_{5ManA}), 69.4 (C_{5ManB}), 67.6 (C_{4ManA}), 66.8 (C_{4ManB}), 63.7 (C_{6ManA}), 63.4 (C_{6ManB}), 55.2 (CH_{3Tolyl}). **ESI-MS** for $C_{61}H_{52}O_{16}S$; calcd: 1072.3 M^+; found: 1095.2 $[M + Na]^+$; **ESI-HRMS** for $C_{61}H_{52}O_{16}S$; calcd: 1095.2868 $[M + Na]^+$; found: 1095.2860 $[M + Na]^+$.

Acknowledgements

This work was supported by Ministerio de Economía y Competitividad (MINECO) project CTQ2014-52328-P, co-financed by European Regional Development Funds (ERDF) and EU H2020-MSCA-ITN-2014-642870 (Immunoshape). JJR thanks CSIC for a JAEdoc contract and JRS thanks MINECO for a FPI fellowship. RCF acknowledge Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq-CsF) and Fundación Carolina for financial support. We acknowledge support of the publication fee by the CSIC Open Access Publication Support Initiative through its Unit of Information Resources for Research (URICI).

Notes and references

1 (*a*) *Essentials in Glycobiology*, ed. A. Varki, T. Cummings, J. Esko, H. Freeze, G. Hart and J. Marth, Cold Spring Harbor Laboratory Press, Plainview, 1999. V. Wittman, in *Glycoscience*, ed. B. Fraser-Reid, K. Tatsuta and J. Thiem, Springer-Verlag, Berlin, Germany, 2008, p. 135.
2 C. G. Figdor, Y. van Kooyk and G. J. Adema, *Nat. Rev. Immunol.*, 2002, **2**, 77.
3 (*a*) R.A. Ezekowitz, *J. Infect. Dis.*, 2003, **187**, S335; (*b*) E. van Liempt, C.M.C. Bank, P. Mehta, J.J. García-Vallejo, Z.S. Kawar, R. Geyer, R.A. Alvarez, R.D. Cummings, Y. van Kooyk and I. van Die, *FEBS Lett.*, 2006, **580**, 6123; (*c*) T. L. Chang and M. E. Klotman, *AIDS Res.*, 2004, **6**, 161; (*d*) E.I. Buzás, B. György, M. Pásztói, I. Jelinek, A. Falus and H.-J. Gabius, *Autoimmunity*, 2006, **39**, 691.
4 T. B. H. Geijtenbeek, D. S. Kwon, R. Torensma, S. J. Van Vliet, van G. C. F. Duijnhoven, J. Middel, I. L. M. H. A. Cornelissen, H. S. L. M. Nottet, V. N. Kewal Ramani, D. R. Littman, C. G. Figdor and Y. van Kooyk, *Cell*, 2000, **100**, 587.
5 (*a*) J. J. Reina and A. Bernardi, *Mini–Rev. Med. Chem.*, 2012, **12**, 1434; (*b*) J. J. Reina, A. Bernardi, M. Clerici and J. Rojo, *Future Med. Chem.*, 2010, **2**, 1141; (*c*) B. Ernst and J. L. Magnani, *Nat. Rev. Drugs Discovery*, 2009, **8**, 661; (*d*) P. Cheshev and A. Bernardi, *Chem. – Eur. J.*, 2008, **14**, 7434.
6 (*a*) X. Geng, V. Y. Dudkin, M. Mandal and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2004, **43**, 2562; (*b*) D. M. Ratner, O. J. Plante and P. H. Seeberger, *Eur. J. Org. Chem.*, 2002, 826–833; (*c*) J. R. Merritt, E. Naisang and B. Fraser-Reid, *J. Org. Chem.*, 1994, **59**, 4443.
7 (*a*) D. A. Calarese, C. N. Scanlan, M. B. Zwick, S. Deechongkit, Y. Mimura, R. Kunert, P. Zhu, M. R. Wormald, R. L. Stanfield, K. H. Roux, J. W. Kelly, P. M. Rudd, R. A. Dwek, H. Katinger, D. R. Burton and I. A. Wilson, *Science*, 2003, **300**, 2065.
8 (*a*) E. W. Adams, D. M. Ratner, H. R. Bokesch, J. B. MacMahon, B. R. O'Keefe and P. H. Seeberger, *Chem. Biol.*, 2004, **11**, 875; (*b*) P. M. Enríquez-Navas, M. Marradi, D. Padro, J. Angulo and S. Penadés, *Chem. – Eur. J.*, 2011, **17**, 1547.
9 H. J. Schuster, B. Vijayakrishnan and B. G. Davis, *Carbohydr. Res.*, 2015, **403**, 135.
10 J.-L. de Paz, J. Angulo, J.-M. Lassaletta, P. M. Nieto, M. Redondo-Horcajo, R. M. Lozano, G. Giménez-Gallego and M. Martín-Lomas, *ChemBioChem*, 2001, **2**, 673.

11 (*a*) J. J. Reina and J. Rojo, *Tetrahedron Lett.*, 2006, **47**, 2475; (*b*) J. J. Reina, I. Díaz, P. M. Nieto, N. E. Campillo, J. A. Páez, G. Tabarani, F. Fieschi and J. Rojo, *Org. Biomol. Chem.*, 2008, **6**, 2743.

12 S.-M. Chang, Z. Tu, H.-M. Jan, J.-F. Pan and C.-H. Lin, *Chem. Commun*, 2013, **49**, 4265.

13 A. K. Pathak, V. Pathak, J. M. Riordan, S. S. Gurcha, G. S. Besra and R. C. Reynolds, *Carbohydr. Res.*, 2004, **339**, 683.

14 (*a*) O. Francesconi, C. Nativi, G. Gabrielli, M. Gentili, M. Palchetti, B. Bonora and S. Roelens, *Chem. – Eur. J.*, 2013, **339**, 11742; (*b*) M. Porcelot, L. Cattiaux, G. Sfini-Loualia, E. Fabre, F. Krzewinski, C. Fradin, D. Poulain, F. Delplace, Y. Guerardel and J.-M. Mallet, *RSC Adv.*, 2013, **3**, 22560; (*c*) G. Depras, R. Robert, B. Sendid, E. Machez, D. Poulain and J.-M. Mallet, *Bioorg. Med. Chem.*, 2012, **20**, 1817; (*d*) L. Heng, J. Ning and F. Kong, *J. Carbohydr. Chem.*, 2001, **20**, 285.

15 D. J. Lee, R. Kowalczyk, V. J. Muir, P. M. Rendle and M. A. Brimble, *Carbohydr. Res.*, 2007, **342**, 2628.

16 J. A. Watt and S. J. Willians, *Org. Biomol. Chem.*, 2005, **3**, 1982.

17 H.-K. Lee, C. N. Scanlan, C.-Y. Huang, A. Y. Chang, D. A. Calarese, R. A. Dwek, P. M. Rudd, D. R. Burton, I. A. Wilson P and C.-H. Wong, *Angew. Chem., Int. Ed.*, 2004, **43**, 1000.

