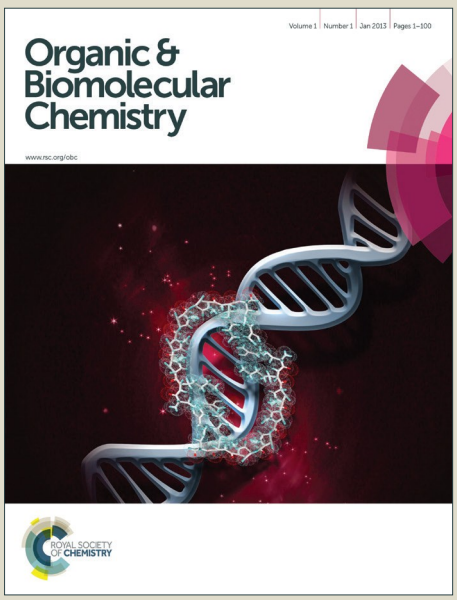
Organic & Biomolecular Chemistry

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

ARTICLE

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] Javier Rojo[a]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

α(1,2)mannobiosides with different substituents at the reducing end have been synthesized by a common strategy using benzoyls as permanent protecting groups and an acetyl as orthogonal protecting group at position C2 of the glycosyl acceptor. The new synthetic strategy has been performed reducing remarkably the number of purification steps, the time of the synthesis (less than 72 hours) and improving the overall yield at least three times 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 the Cu catalyzed azide alkyne cicloaddiction (CuAAC) also called "click chemistry" to conjugate 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 at the surface of many pathogenic microorganisms as viruses, bacteria, fungi and parasites, and they are the target of the immune system cells, including macrophages and dendritic cells.[2] The interaction 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 Cells Specific ICAM-3 Grabbing Non-integrin (DC-SIGN), defensins and macrophages mannose receptors (MR).[3] Therefore, the glycan structures on pathogen glycoproteins present in viral envelopes or bacterial cell walls help to escape 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 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 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-, α,1,6-, and β1,4-linkages. (Figure 1) Multiple copies of this glycan are present in several pathogen glycoproteins and specifically in the gp120 envelope protein of HIV.

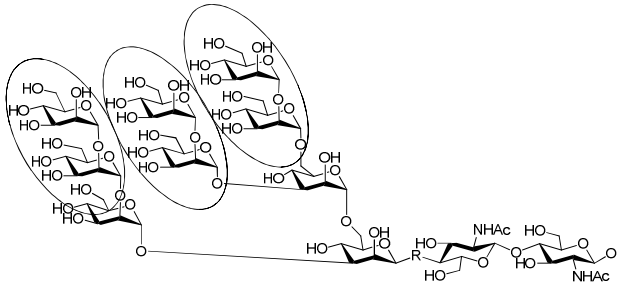


Figure 1. Structure of High-mannose type glycans

The total synthesis of Man_9 or $(Man)_9(GlcNAc)_2$ has been explored for the past two decades;[6] however, the complexity of this kind of complex glycan structures prevent the accessibility to 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 10 years ago.[7] The resolved structure shows that the Manα1-2Man residues make 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 to construct 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

[a] Dr. J.J. Reina, A. Di Maio, J. Ramos-Soriano, Dr. J. Rojo
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] Dr. R.C. Figueiredo
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

† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

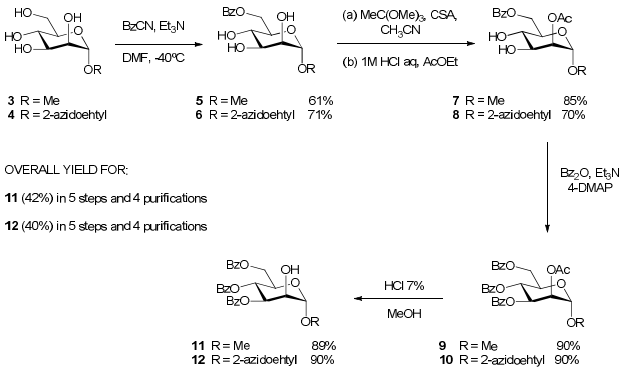
is of remarkable interest. The previously described approaches to prepare α(1-2) mannobioside derivatives involved many reaction steps, including the classical protection-deprotection pathway to prepare oligosaccharides, with several purifications of the intermediate products. These syntheses mean large time consume, high synthetic cost, and rend 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 reducting terminus is an alcohol with a particular length and substituents implying an important decrease of versatility of the synthesis. These disadvantages make difficult the current application of Manα1,2Man and compromise its use to prepare 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 permanent protecting groups and anacetate as orthogonal protecting group at positon C2 of the glycosyl acceptor. The use of this protecting group strategy is compatible with the presence of azido groups and the use of the CuAAC (Cu catalyzed azide alkyne cycloaddition) also called "click chemistry" to conjugate 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 compatibles with the methodology selected to the multivalent presentation of the final oligosaccharides. For 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 -40ºC and a catalytic amount of Et_3N to selectively protect the C6 hydroxyl group.[10] This reaction was regioselective and the 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**), only 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 done previously. The selective protection of primary alcohols in the presence of secondary alcohols has been often addressed by the use of high hindrance protecting groups 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 in 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 1M HCl implied the 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 orthogonal protecting group at position C2. Finally, selective deprotection of this acetyl group at position C2 using 7% of HCl in methanol afforded mannoses **11** and **12** in good yields.[13] The use of 7% of HCl in methanol were the best conditions 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)

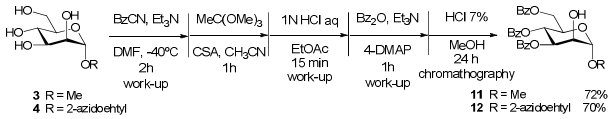


Scheme 1. Synthesis of Mannose derivatives **11** and **12**.

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**. In the literature has been described many different strategies to afford this kind 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 and overall yield of 25% in the best case.

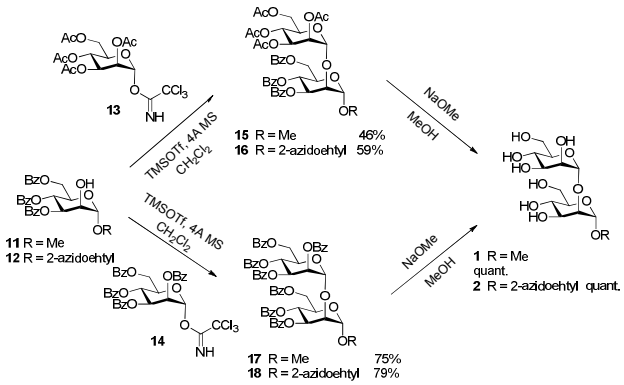
It is important to highlight that the synthetic approach described in scheme 1 to obtain the glycosyl acceptors **11** and **12** presents an important advantage: the conditions of the protection reactions are all compatible to be carried out sequentially simply by removal of the reaction solvent and a work up without chromatographic purification of intermediate products. For these reason, we afforded the sequence synthesis of **11** and **12** as described in scheme 2. The preparation of intermediate **11** and **12** were 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 time, allowing the preparation of these derivatives in a gram scale very easily in less than two days. Moreover, this versatile approach allows different modifications to generate a large number of mannose monosaccharides, for example, the benzoyl groups could be substituted by benzyls or other kind of protecting groups.



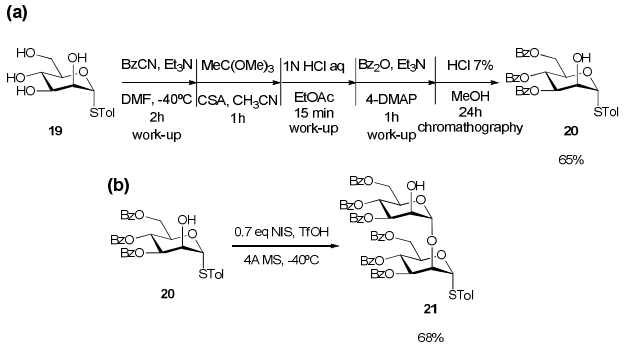
Scheme 2. Consecutive synthetic procedure to prepare **11** and **12**.

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 in the C2 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 promotor at 0 ºC 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 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 deprotection of acetyl and benzoyl groups using classical Zempler conditions (NaOMe/MeOH) to afford the final compounds **1** and **2** in quantitative yields.



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

To explore the scope of the methodology described in this work as an straightforward strategy to addressed 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 describes 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% of yield using only one chromatographic purification. Then, applying the methodology describe by Wong and co-workers,[17] compound **20** was used simultaneously as a glycosyl donor and acceptor to afford a self-glycosidation with *N*-Iodo succinimide (NIS) and triflic acid (TfOH) at -40ºC providing the dimannoside **21** with 68% of yield. The dimannoside **21** is an excellent synthetic intermediate that could be used as donor or acceptor to synthesize more complex oligosaccharides.



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

Conclusions

In summary, we have completed a 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 have been achieved using a common strategy based on benzoyls as permanent protecting groups and an acetyl as an orthogonal protecting group at the C2 of the glycosyl acceptor. Following this strategy, it has been reduced the purification steps up 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 respect to the best procedure describe in the literature. This synthetic strategy allows the preparation of α(1,2)dimannosides in gram scale reducing a lot the cost of the synthesis. Additionally, the used of the ester strategy (Benzoyl/acetyl) make 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 the compound **1** as ligand and we are synthetizing more complex mannose oligosaccharides using the *S*-tolyl **21** derivative as 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 indirect referencing method. 2D experiments (COSY and HSQC) were done when necessary to assign the oligosaccharide spectra. Mass spectra were carried out 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 ºC were added dropwise a solution of BzCN 1M 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 the excess of 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%). **1H 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, $-OCH_3$). **13C 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 ºC were added a solution of BzCN 1M 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 the excess of 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%). **1H 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, $2H_8$). **13C NMR** (101 MHz, CDCl3) 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 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 HCl 1M (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%). **1H 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, $-OCOCH_3$). **13C 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 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 HCl 1M (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%). **1H 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, $-OCOCH_3$). **13C 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<u>C</u>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) was 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 dissolved in EtOAc (25 mL). The solution was washed with HCl 1M (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%). **1H 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, -$OCOCH_3$). **13C 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<u>C</u>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) was 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 dissolved in EtOAc (20 mL). The solution was washed with HCl 1M (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%). **1H 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, $2H_{Bz}$), 7.9 2 (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, -$OCOCH_3$). **13C 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<u>C</u>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 HCl 7 % in MeOH (10 mL) and the reaction was stirred at room temperature for 24 hours. Then, the solvent was evaporated and the residue dissolved in EtOAc (25 mL). The solution was washed with a solution of sat. $NaHCO_3$ (2 x 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%). **1H 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). **13C 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 ($C_{\text{-}OCH3}$). **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, mmol) in CH_3CN (1 mL) was added a solution of HCl 7 % in MeOH (2 mL) and the reaction was stirred at room temperature for 24 hours. Then the solvent was evaporated and the residue dissolved in EtOAc (25 mL). The solution was washed with a solution of sat. $NaHCO_3$ (2 x 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%). **1H 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). **13C 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 ºC 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 the excess of 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 HCl 1M (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) was 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 dissolved EtOAc (200 mL). The solution was washed with HCl 1M (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 the Methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (**9**) in CH_3CN (40 mL) was added a solution of HCl 7 % in MeOH (200 mL) and the reaction was stirred at room temperature for 24 hours. Then the solvent was evaporated and the residue dissolved in EtOAc (250 mL). The solution was washed with a solution sat. $NaHCO_3$ (2 x 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 ºC 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 the excess of 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 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 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 HCl 1M (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) was 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 pure with EtOAc (200 mL). The solution was washed with HCl 1M (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 the 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 HCl 7 % in MeOH (200 mL) and the reaction was stirred at room temperature for 24 hours. Then the solvent was evaporated and the residue dissolved in EtOAc (250 mL). The solution was washed with a solution of sat. $NaHCO_3$ (2 x 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 ºC for 15 min, followed by the addition of TMSOTf (13 μL, mmol, 0.059 mmol), and stirred for 30 min at 0 ºC. 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%). **1H 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). **13C 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_{-OCH3}). **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 ºC for 15 min, followed by the addition of TMSOTf (8,5 μL, mmol, 0.040 mmol), and stirred for 30 min at 0 ºC. 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%). **1H 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, -$OCOCH_3$). **13C 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 few hours and then dissolved in CH_2Cl_2 (5 mL). The mixture was cooled to 0 ºC for 15 min, followed by the addition of TMSOTf (4,5 μL, mmol, 0.024 mmol), and stirred for 30 min at 0 ºC. 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 an white solid (97 mg, 75 %). **1H 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). **13C 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_{-OCH3}). **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 ºC for 15 min, followed by the addition of TMSOTf (20 μL, mmol, 0.088 mmol), and stirred for 30 min at 0 ºC. 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 an white solid (396 mg, 79%). **1H 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) **13C 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 1M 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 reduce 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 1M 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 reduce 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.)

1H 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); **13C 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_{-OCH3}); **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 1M 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 reduce 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 1M 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 reduce 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.)

1H 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); **13C 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 ºC 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 the excess of 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 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 HCl 1M (200 mL), the organic phase was dried with anh. $MgSO_4$ and the solvent was evaporated. To the resulting mixture containing 2-*O*-acetyl-6-*O*-benzoyl derivative in CH_2Cl_2 (60 mL) was 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 pure with EtOAc (150 mL). The solution was washed with HCl 1M (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 HCl 7 % in MeOH (150 mL) and the reaction was stirred at room temperature for 24 hours. Then the solvent was evaporated and the residue dissolved in EtOAc (200 mL). The solution was washed with a solution of sat. $NaHCO_3$ (2 x 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%). **1H 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}), **13C 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 2h. Then, reaction mixture was cooled at -40ºC 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 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 x 3) and then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give 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%). **1H 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, *2*H, 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}). **13C 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 to CSIC for a JAEdoc contract and JRS thanks MINECO for a FPI fellowship. RCF acknowledge Fundación Carolina for financial support.

Notes and references

1 (a) Essentials in Glycobiology, (Eds.: A. Varki, T. Cummings, J. Esko, H. Freeze, G. Hart and J. Marth), Cold Spring Harbor Laboratory Press, Plainview, 1999; V. Wittman, in Glycoscience (Eds.: B. Fraser-Reid, K. Tatsuta and J. Thiem), Springer-Verlag, Berlin, Germany, 2008, pp. 135

2 C. G. Figdor, Y. van Kooyk, 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, I. van Die *FEBS Lett.*, 2006, **580**, 6123; (c) T. L. Chang, M. E. Klotman *AIDS Res.*, 2004, **6**, 161; (d) E.I. Buzás, B. György, M. Pásztói, I. Jelinek, A. Falus, 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, Y. van Kooyk *Cell*, 2000, **100**, 587.

5 (a) J. J. Reina, A. Bernardi, *Mini Rev. Med. Chem.*, 2012, **12**, 1434; (b) J. J. Reina, A. Bernardi, M. Clerici, J. Rojo, *Fut. Med. Chem.*, 2010, **2**, 1141; (c) B. Ernst, J. L. Magnani *Nat. Rev. Drugs Discovery*, 2009, **8**, 661; (d) P. Cheshev, A. Bernardi *Chem. Eur. J.*, 2008, **14**, 7434.

6 (a) X. Geng, V. Y. Dudkin, M. Mandal, S. J. Danishefsky *Angew. Chem. Int. Ed.* 2004, **43**, 2562; (b) D. M. Ratner, O. J. Plante, P. H. Seeberger, *Eur. J. Org. Chem.*, 2002, 826-833; (c) J. R. Merritt, E. Naisang, B. Fraser-Reid, 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, I. A. Wilson, *Science,* 2003, **300**, 2065;

8 E. W. Adams, D. M. Ratner, H. R., Bokesch, J. B. MacMahon, B. R. O'Keefe, P. H. Seeberger *Chem. Biol.*, 2004, **11**, 875. (b) P. M. Enríquez-Navas, M. Marradi, D. Padro, J. Angulo, S. Penadés, *Chem. Eur. J.*, 2011, **17**, 1547.

9 H. J. Schuster, B. Vijayakrishnan, 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, M. Martín-Lomas, *ChemBioChem*, 2001, **2**, 673.

11 (a) J. J. Reina, 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, J. Rojo, *Org. Biomol. Chem.*, 2008, **6**, 2743.

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

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

14 (a) O. Francesconi, C. Nativi, G. Gabrielli, M. Gentili, M. Palchetti, B. Bonora, 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, J.-M. Mallet, *RSC Adv.*, 2013, **3**, 22560; (c) G. Depras, R. Robert, B. Sendid, E. Machez, D. Poulain, J.-M. Mallet, *Bioorg. Med. Chem.*, 2012, **20**, 1817; (d) L. Heng, J. Ning, F. Kong, *J. Carbohydr. Chem.*, 2001, **20**, 285.

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

16 J. A. Watt, 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, C.-H. Wong *Angew. Chem. Int. Ed.*, 2004, **43**, 1000.