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1-Methyl 1′-cyclopropylmethyl (MCPM) as an anomeric protecting group

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ABSTRACT

A pragmatic approach for preparing glycoconjugates of complex oligosaccharides is to prepare the oligosaccharide as a building block with most of its protecting groups exchanged to protecting groups whose cleavage and other manipulations are highly compatible with the functional groups of complex aglycones. For such an approach the reducing end sugar of the building bloc must be protected with a cleavable protecting group during the oligosaccharide synthesis. We demonstrate that the acid labile 1-methyl 1′-cyclopropylmethyl (MCPM) can be effectively used for this purpose. A trisaccharide glycolipid and a disaccharide glycoamino acid are prepared. The absolute chirality of the MCPM in one key acceptor is determined by a combination of NMR NOE measurements, DFT molecular modeling and Noyori catalyst catalyzed asymmetric reduction.

1. Introduction

In order to meet the increasing demand for oligosaccharides and their related glycoconjugates it is often advantageous to prepare oligosaccharide building blocks that can be subsequently converted into oligosaccharide donors.[1] Such donors can be reacted with an array of aglycones. Since the aglycones in many glycoconjugates are often expensive or sensitive to the reagents used in functional group manipulations it is often practical to minimize functional group transformations post glycosylation.[2] Our research group is involved in the preparation of various glycoconjugates including glycolipids and glycopeptides. For example, we recently synthesized a series of Man(α1→2)$_n$Man(α1→O)Arch (n=0–4) where Arch is a glycerol derived diether lipid from the domain *archaea* named archaeol. Immunological experiments showed that the trisaccharide and tetrasaccharides were the most active giving both major histocompatibility complex type I and type II activation. The initial studies were done by sequential glycosylations with donor **1**,[4] see Fig. 1. Thus, the relatively expensive archaeol lipid had to be carried through multiple glycosylation, deprotection steps followed by overall deprotection. We reasoned that synthesizing a trisaccharide donor with only *O*-acetyl groups could be more efficient due to minimizing the steps with the lipid. Since this trisaccharide is frequently found in cell surface oligosaccharides a number of syntheses of similar oligosaccharide donors have been reported.[5] Consequently, a mannose derivative that could be chain extended at O-2 and subsequently converted into an anomeric leaving group such as trichloroacetimidate, was needed.

For another synthetic project we wanted to make the disaccharide GlcNAc(β1→2)Man α-linked to Serine in sufficient quantities to be made into a glycopeptide that could be used to study enzyme specificities. A few syntheses of similar building blocks have been reported.[6] Such glycopeptides are found in the glycoprotein α-dystroglycan and defects in the related glycosyltransferases are correlated with a variety of neuromuscular disease states.[7] Thus, we needed a temporary anomeric protecting group that is stable to hydrogenation conditions. Although the 2-trimethylsilylethanol group[8] likely would work we reasoned that the 1-methyl 1′-cyclopropylmethyl (MCPM) protecting group that was introduced by us could be an attractive alternative. It is an acid

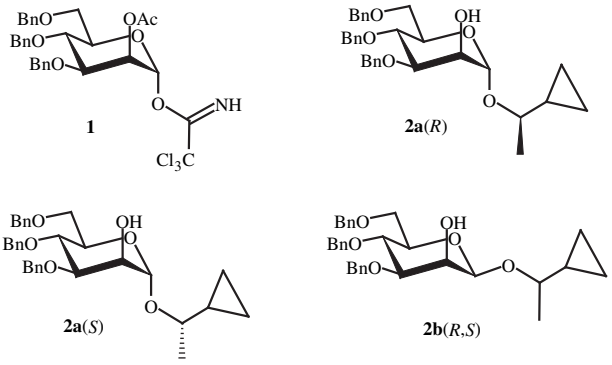

Fig. 1. Structures of donor **1** and target 2-OH glycosides **2a**(*R*,*S*) and **2b**(*R*,*S*).

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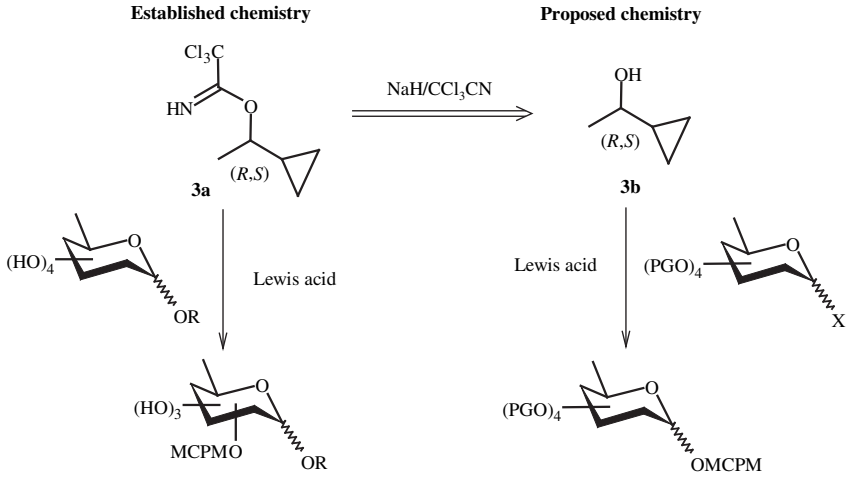
cleavable protecting group orthogonal to many common protecting groups.[9] As well, since it is an ether and relatively small it can be considered an activating protecting group. Its use as an anomeric protecting group was not tested in the previous study. Combining these two synthetic objectives led to a desire to synthesize the anomerically protected 2-OH free glycoside **2ab**, see Fig. 1. The expectation was that the anomeric MCPM group would allow both for functional group transformations and activate the adjacent hydroxyl for glycosylation due to its electron donating potential.[9]

In a previous study, the MCPM group was introduced as an electrophile via trichloroacetimidate **3a**, see Scheme 1.[9] Mild Lewis acids like silver triflate and boron trifluoride etherate were used as activators. Attachment to the anomeric position by glycosylation chemistry requires that alcohol **3b**, which is the synthetic precursor to **3a**, act as a nucleophile. Previous reports from our group with an electronically similar alcohol namely **4** had shown that glycosylation chemistry led to styrene **5** as the major by-product, see Scheme 2.[10] We reasoned that styrene **5** was generated by elimination from the corresponding resonance-stabilized carbenium ion derived from **4**. Since the MCPM is cleaved by Lewis acids or Bronstead acids in the presence of nucleophiles, glycosylation with alcohol **3b** was previously deemed difficult and had never been explored. In addition, we have determined that the MCPM is stable to 5% TFA in CH_2Cl_2 but partly labile to 7.5% and completely labile to 10% TFA, which contrasts with methoxybenzyl protecting group, which is labile to 5% TFA in CH_2Cl_2.[9]

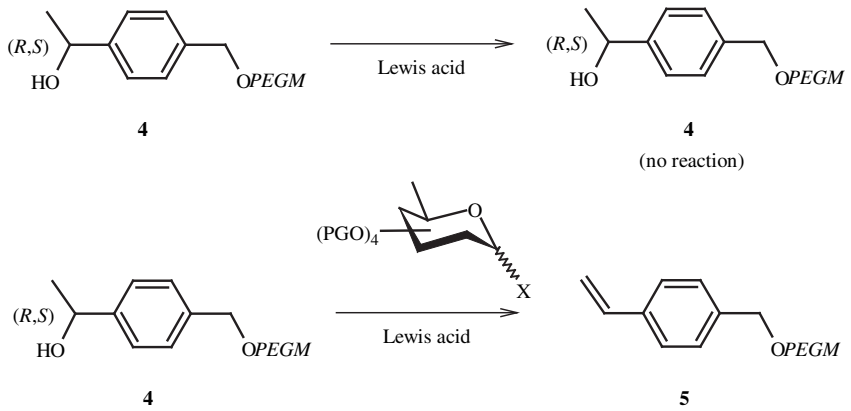
2. Results and discussion

To implement this strategy we reacted well known donor **1** with the commercially available racemic alcohol 1-methyl 1′-cyclopropylmethanol under standard glycosylation conditions with triethylsilyl trifluoromethanesulfonate to yield an inseparable α/β (85/15) of the (*R*/*S*)-MCPM glycosides **6a** and **6b**, respectively, see Scheme 3. The yield was only 65% possibly reflecting the anticipated reactivity difficulties but still sufficient to continue the synthesis. The acetates in **6a** and **6b** were readily removed under Zemplen conditions to give the desired acceptor mixture **2ab**. This mixture could be glycosylated with donor **1** to **7ab**, deacetylated to **8ab**, glycosylated again with donor **1** to trisaccharide **9ab**. All transformations proceeded smoothly indicating the stability of the anomeric MCPM group to glycosylation conditions. Since the MCPM group is orthogonal to most hydrogenation conditions the *O*-benzyl groups were removed at this stage by standard Pd catalyzed hydrogenation. Subsequent acetylation led to peracetyl trisaccharides **10ab** in 50% yield for two steps. Then the MCPM group was cleaved with 10% TFA in CH_2Cl_2 to yield the α/β-hemiacetal **11ab**, which was readily transformed into known α/β-trichloracetimodyl donor **12ab**.[11]

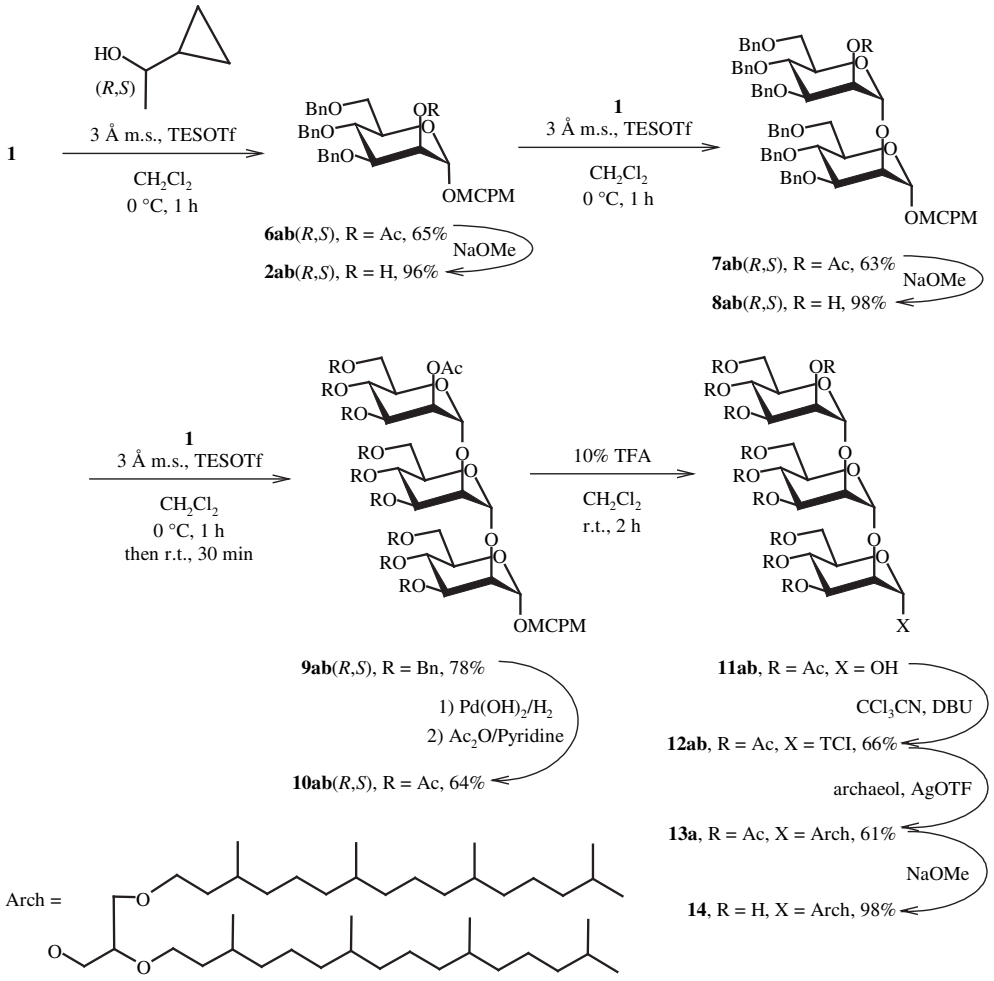
The lipid archaeol could then be glycosylated with the promoter silver trifluormethanesulfonate (AgOTf)[12] to give in 61% isolated yield pure α-glycoside **13a** after separation from traces of β-glycoside **13b** by careful silica gel chromatography. After Zemplen



Scheme 1. Switching of reactivity to introduce the MCPM group from the established electrophilic route to a nucleophilic route.



Scheme 2. Glycosylation dependent elimination reaction of an alcohol (**4**) that can form a resonance-stabilized carbenium ion.



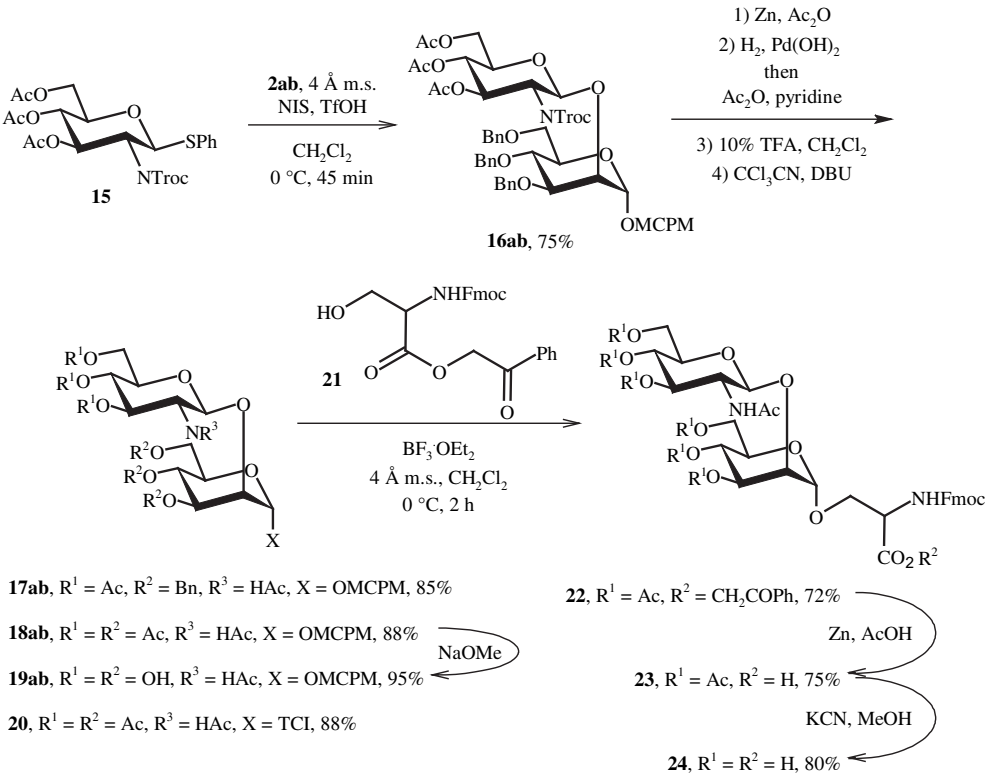
Scheme 3. Synthesis of trisaccharide glycolipid **14** via monosaccharide donor **1**.

deacetylation **13a** was turned into the previously synthesized **14** in high purity after silica gel chromatography. Glycolipid **14** is being used in ongoing immunological experiments.

Similarly the mixture of alcohols **2a** and **2b** could be glycosylated with known trichloroethoxycarbonyl (Troc) protected glucosamine donor **15**[13] in an acceptable yield of 70% to give β-linked disaccharides **16ab**, see Scheme 4. The Troc could be transformed into the *N*-acetyl of the target by treatment with Zn powder in acetic anhydride to yield **17ab** in good yield.[14] Subsequent hydrogenation and acetylation led to peracetyl disaccharides **18ab**. For characterization purposes a small portion of disaccharides **18ab** was deacetylated to **19ab**. The main portion of **18ab** had the anomeric MCPM group cleaved by 10% TFA in CH_2Cl_2 to yield the hemiacetal, which was readily transformed into the trichloracetimidate donor **20**. Thus, the MCPM allowed for an efficient synthesis of this disaccharide donor **20**.

Donor **20** could be reacted with commercially available fluorenylmethoxycarbonyl (Fmoc) *N*-protected and phenylacetyl (PhAc) CO-protected serine derivative **21** to give α-linked glycoamino acid **22** in a good yield with no detectable β-isomer formed in the presence of the promoter $BF_3 \cdot Et_2O$. The PhAc group was cleaved by treatment with Zn powder in ethyl acetate in the presence of a small amount of acetic acid to yield glycoamino acid building block **23**. For characterization a small amount of **23** had the *O*-acetates selectively removed in the presence of the Fmoc protecting group using KCN in methanol to yield **24**. Glycoamino acid **23** is being used to synthesize glycopeptides.

In none of the steps above with the chiral MCPM protecting group at the anomeric center was there any evidence for diastereoselectivity for either (*R*)- or (*S*)-glycosides. In some case during silica gel chromatography detailed TLC analysis of the separated fractions suggested some slight polarity difference between diastereomers. Frequently, the chromatography fractions chosen for concentration based on eliminating all non-product contaminants led to enrichment in one isomer over the other but the ratio's rarely exceed 55/45. The absolute chirality of none of the isomers was known. In one case during reaction optimization of the formation of disaccharides **16ab**, it proved possible to separate unreacted **2ab** into two samples with one predominantly as diastereomer **2a** and the other as diastereomer **2a** along with traces of the (*R*,*S*)-β-mannosides **2b**. This result emphasizes that there appears to be no major reactivity difference but only slight polarity differences between the diastereomers. With these partially purified samples we performed ^{1}H NMR NOE analyses to see if any conformational preferences existed which could in turn be used to assign the absolute chirality, see Supplementary data for further NOE experiments. As shown in Fig. 2a and b the NOE interactions between the anomeric proton and the MCPM protons were markedly different for the two diastereomers. In both isomers the expected strong NOE interaction with Man H-2 is observed along with a strong NOE to the MCPM ether methine. But, in one isomer (Fig. 2a) the predominant long range interactions are between Man H-1 and three of the cyclopropyl protons whereas for the other isomer (Fig. 2b) the predominant long range interaction is between Man H-1 and



Scheme 4. Synthesis of glycoamino acid building block **23** via disaccharide **16ab**.

the MCPM methyl. These results strongly suggest a conformational difference between the two diastereomers.

Computational-based conformational analysis (see Supplementary data) was performed on the (*R*)- and (*S*)-(1-methyl cyclopropylmethyl) 3,4,6-tri-*O*-methyl-α-D-mannopyranosides **25**(*R*) and **25**(*S*) (Figs. 3 and 4), which are analogues of (*R*,*S*)-**2a** where the *O*-methyl simplifies the multiple minima problem created by the *O*-benzyl groups.[15] Initial computational studies used semi-empirical calculations to exhaustively search the four most likely bonds to exhibit conformational flexibility: phi (ϕ_H=CH-1–C-1···O-1–CH), xsi (ψ=C-1–O-1···CH–Ccp), omega (ω_H=CH–5-C–5···C-6–O-6) and χ1=O-1–CH(CH_3)···CHcp–CcpH_2. This analysis revealed that phi strongly favored the *exo*-anomeric position of approximately −50° for both isomers and for most values of the remaining torsion angles. Rotation about χ1 showed limited barriers such that all three rotamers were all populated for any combination of the three other torsions. When feasible, due to lack of spectral overlap, coupling constant analysis between the two methines shows a similar value for all compounds determined to be near 9 Hz suggesting a predominant but not exclusive population of the trans isomer with respect to the methines torsion. The experimental value for **2a**(*R*) and **2a**(*S*) is 8.2 Hz. Similarly omega showed the 'normal' preferences for values of −60° (gt) and 180° (gg) with a slight preference for conformations near 180° for any combination of the other three torsions. The torsion ψ, however, essentially sorted the conformers into two families, see Fig. 4. The ψ value for Family 1 and 2 are about 60° and 180°, respectively. Based on strictly steric arguments it has been suggested that glycosides with chiral centers at the aglycone carbon of α-D-mannopyranosides should have ψ equal to 180° for both isomers (with ψ defined with the highest priority carbon replacing Ccp).[16] In our case this torsion likely depends on a combination of steric and hyper-conjugative effects as well as sigma donation from the cyclopropyl ring. The magnitude of the last effect being particularly difficult to predict. Consequently, it was decided to investigate this torsion by Density Functional Theory (DFT) calculations using a relatively large for this size of molecule TZP basis set. Experimentation showed that a relatively small rotation step size of 3° was necessary to avoid discontinuities, which are still apparent in Fig. 3a and b but minimized. The results shown in Fig. 3a and b indicate a remarkable diastereoselective dependence with the (*R*)-isomer favoring Family 1 and the *S*-isomer favoring Family 2. Fig. 4a and b show molecular models of the two minimum energy conformers for the two families of the (*R*)- and (*S*)-isomers. It is readily apparent that the calculated minimum energy conformation for the (*R*)-isomer fits the NOE data in Fig. 2a whereas the calculated conformation of the (*S*)-isomer fits the data in Fig. 2b providing a plausible assignment of the absolute stereochemistry.

To further corroborate the assignments we undertook a stereoselective synthesis of 1-methyl 1′-cyclopropylmethanol by asymmetric reduction of cyclopropylmethyl ketone. To this end the ketone was reduced using the Noyori catalyst ((*R*)-Ru(η^6-mesitylene)-(*R*,*R*)-TsDPEN) with formic acid as the hydrogen source.[17] This gave an approximately 90/10 mixture of epimers, see Supplementary data. To assign the major isomer the Mosher esters derived from both commercially available chlorides were prepared.[18] The NMR parameters suggest an absolute stereochemistry of (*R*) for the major isomer, see Supplementary data for details.[19] A previous report of Noyori hydrogenation of cyclopropylmethyl ketone also led to predominant formation of the (*R*)-isomer but using different experimental conditions.[20] After purification of a small amount of the alcohol from the reduction mixture the glycoside mixture **6a** and **6b** was produced by reaction with donor **1**. Purification by preparative TLC followed by deacetylation and further preparative TLC led to a small amount of slightly impure **2a**(*R*). Significant NMR resonances and NOE patterns after irradiation of H-1 strongly corroborated the (*R*)-assignment from molecular modeling by computation.

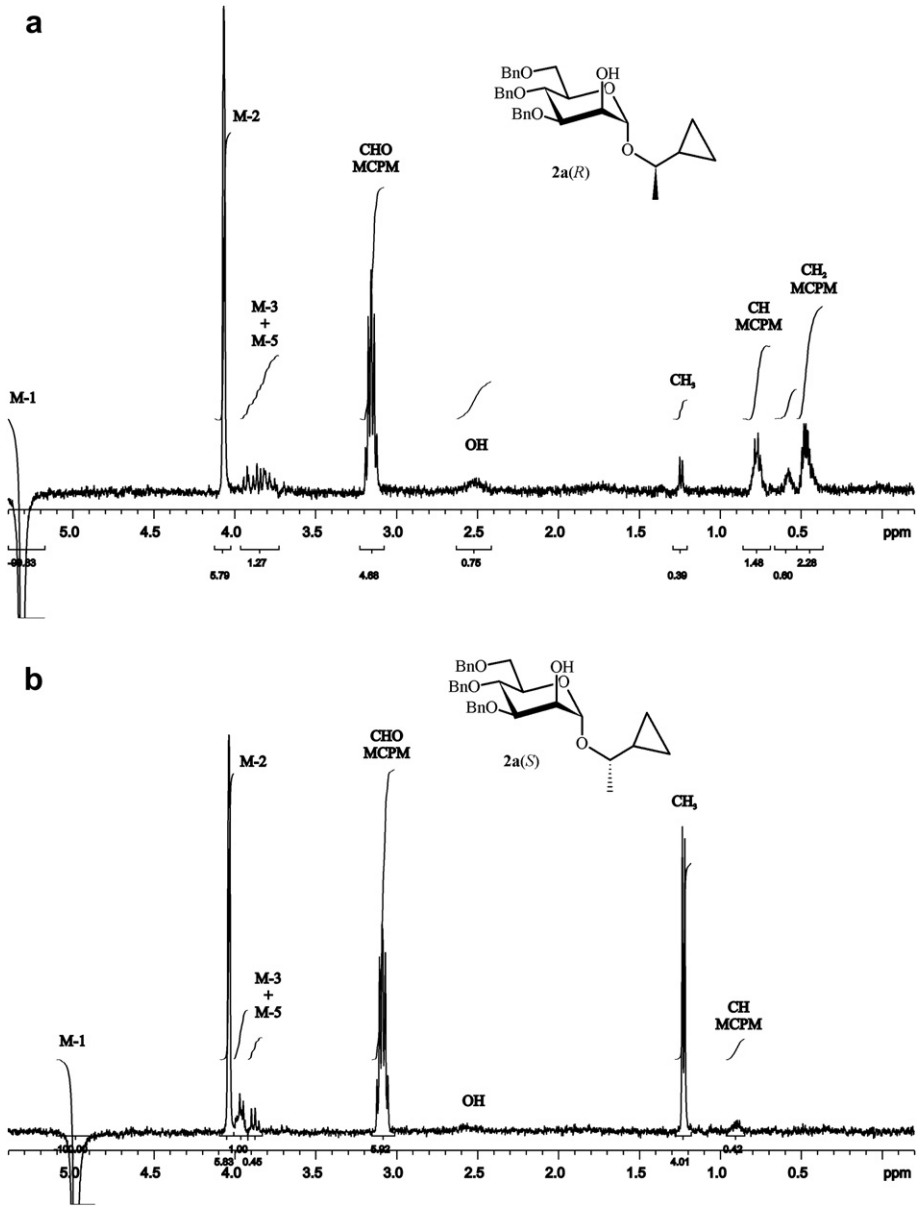


Fig. 2. Partial ^{1}H NMR (400 MHz) 1D difference NOE spectra. (a) Single isomer **2a** (probably *R*) irradiated on Man H-1: note small NOE to CH_3 and medium to cyclopropyl CH's. (b) The other single isomer **2a** (probably *S*) irradiated on Man H-1: note large NOE to CH_3 and very small to cyclopropyl CH's. M-1, M-2, M-3 and M-5 refer to mannose H-1, H-2, H-3, and H-5, respectively.

3. Conclusion

As exemplified by the synthesis of trisaccharide donor **12ab** and disaccharide donor **20**, the MCPM protecting group can be used as a temporary anomeric protecting group. The MCPM group was shown to be stable to hydrogenation and reduction with Zn metal, which often used in carbohydrate protecting group manipulations and can compromise the selection of anomeric protecting groups such as allyl, benzyl, trichloroethyl and related derivatives. The successful glycosylation at O-2 adjacent to the anomeric MCPM of **2ab** also suggests that this protecting group is activating for glycosylations. The absolute chirality of the MCPM group in key acceptor **2a** was established by a combination of asymmetric synthesis, ^{1}H NMR NOE experiments and DFT calculations. These computational studies also show that the conformational bias of the MCPM group about ψ is different from that expected on solely steric grounds. Thus, the use of the MCPM protecting group has been successfully extended to temporary anomeric protection in oligosaccharide synthesis.

4. Experimental

4.1. Materials and general methods

The ^{1}H NMR spectra were obtained on a Varian VXR-500 (500 MHz) or Varian-400 (400 MHz) with tetramethylsilane or the residual signal of the solvent as the internal standard. The ^{13}C NMR spectra were recorded at Varian-400 (100 MHz). Optical rotations were measured at 20 °C in a 1 dm cell on a Perkin–Elmer 343 polarimeter with a Na/Hal lamp at 589 nm. Thin-layer chromatography was performed on precoated plates of silica gel (60-F_{254}, E. Merck, Darmstadt) and visualized with H_2SO_4/H_2O (1:20 v/v) followed by heating. Unless otherwise stated, flash column chromatography was performed on silica gel 60 (230–400 mesh,

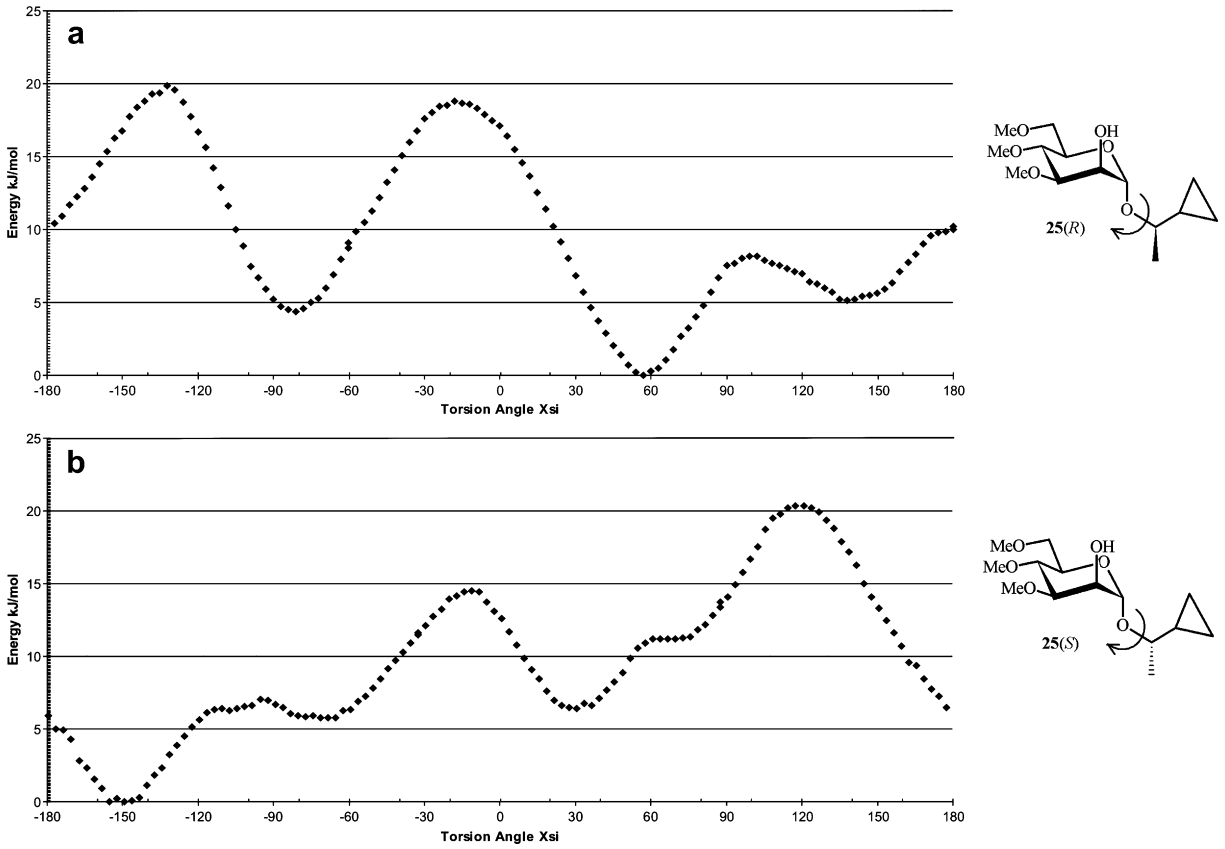


Fig. 3. Rotational profiles for rotation about ψ for (a) **25**(*R*) and (b) **25**(*S*) based on DFT Calculations (ADF-TPZ basis set), see Supplementary data for computational details.

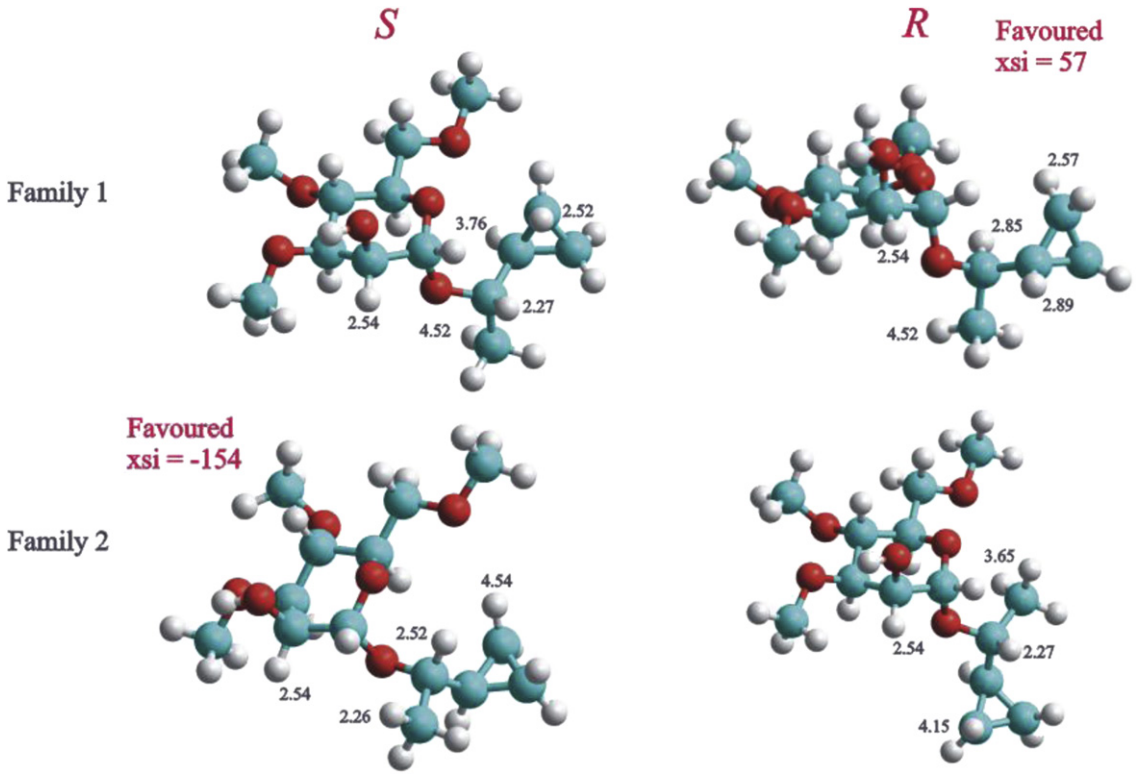


Fig. 4. Ball and stick representations of the two minima for each diastereomer of **25**(*R*) and **25**(*S*) based on DFT Calculations (ADF-TPZ basis set). The numbers written on the structures are distances from Man H-1 in angstroms.

Merck). Medium pressure liquid chromatography (MPLC) was performed in self packed glass silica columns with a flow rate of 8–10 mL/min delivered using high performance liquid chromatography pumps. All solvents and reagents were purified and dried according to standard procedures. 3,4,6-Tri-*O*-benzyl-β-D-mannopyranose-1,2-(methylorthoacetate) was obtained from Toronto Research Chemicals, Toronto, ON, Canada. Phenylacetyl, Fmoc-Ser (**21**) was obtained from Sussex Research Laboratories, Ottawa, ON, Canada.

*4.1.1. 2-O-Acetyl-3,4,6-tri-O-benzyl-α/β-D-mannopyranosyl trichloroacetimidate **1**.* 3,4,6-Tri-*O*-benzyl-β-D-mannopyranose-1,2-(methylorthoacetate) (5.0 g, 9.87 mmol) was dissolved in 95% acetic acid (15 mL) and stirred at room temperature for 1.5 h. After solvent removal, co-evaporation with toluene (5×) and further drying under high vacuum, the resulting crude was redissolved in anhydrous CH_2Cl_2 (22 mL) and cooled to 0 °C. Trichloroacetonitrile (11.2 mL, 108.6 mmol) and $CsCO_3$ (0.365 g, 1.08 mmol) were added sequentially. Stirring continued for 16 h under an atmosphere of Ar with the temperature gradually rising up to room temperature. Silica gel flash chromatography using 7.5:2:0.5 hexanes/EtOAc/CH_2Cl_2 as eluent yielded the desired product **1** (5.42 g, 86%).

*4.1.2. (R,S)-Methyl cyclopropylmethyl 2-O-acetyl-3,4,6-tri-O-benzyl-α/β-D-mannopyranoside **6ab**.* Trichloroacetimidate (**1**, 2.04 g, 3.20 mmol) was dissolved in anhydrous CH_2Cl_2 (36 mL) followed by the addition of 3 Å molecular sieve (3.6 g) and racemic 1-methyl 1′-cyclopropylmethanol (0.625 mL, 6.40 mmol). The resulting suspension was stirred at room temperature under an atmosphere of Ar for 30 min. The mixture was then cooled to 0 °C followed by the addition of TESOTf (80 μL, 0.35 mmol). Stirring continued at 0 °C for 1 h and the reaction was quenched with diisopropylethylamine (DIPEA, 0.4 mL) followed by gravity filtration with filter paper and solvent removal. Silica gel flash chromatography using 7.5:1.5:1 hexanes/EtOAc/CH_2Cl_2 as eluent yielded the desired product **6ab** (1.16 g, 65%, α/β about 85:15). Compound **6a** ^{1}H NMR $CDCl_3$: δ 7.42–7.19 (m, 30H, BnAr*H*), 5.45 and 5.40 (2×dd, 2H, $J_{2,3}$=3.2, H-2(*R*,*S*)), 5.31 and 4.98 (2×d, 2H, $J_{1,2}$=1.8, H-1(*R*,*S*)), 5.02–4.51 (m, 12H, BnC*H*$_2$), 4.11–3.69 (m, 10H, H-3, H-4, H-5, H-6, H-6′(*R*,*S*)), 3.17 and 3.10 (2×dq, 2H, $J_{CH-CHcp}$=8.2, J_{CH-CH3}=6.2), MCPM−C*H*(*R*,*S*), 2.203 and 2.192 (2×s, Ac C*H*$_3$(*R*,*S*)), 1.287 and 1.268 (2×d, 6H, MCPM−C*H*$_3$(*R*,*S*)), 0.94 and 0.82 (2×m, 2H, MCPM−cpC*H*(*R*,*S*)), 0.66–0.36 (m, 6H, MCPM−cpC*H*$_2$(*R*,*S*)), 0.17 and 0.10 (m, 2H, MCPM−cpC*H*$_2$(*R*,*S*)); ^{13}C NMR $CDCl_3$: δ 170.44 and 170.43 (Ac*C*=O(*R*,*S*)), 138.3, 138.2 and 138.1 (BnAr*C*$_{ipso}$), 128.3–127.4 (BnAr*C*H), 95.6 and 95.1 (C-1(*R*,*S*)), 78.3 (C-3(*R*,*S*)), 78.3 and 78.2 (MCPM−*C*H(*R*,*S*)), 76.6 (BnCH$_2$), 75.1 (C-4(*R*,*S*)), 74.4 (BnCH$_2$), 71.7 (BnCH$_2$), 71.3 and 71.2 (C-5(*R*,*S*)), 69.4 and 69.1 (C-2(*R*,*S*)), 68.83 and 68.81 (C-6(*R*,*S*)), 21.11 (Ac*C*H$_3$), 21.07 and 19.19 (MCPM−*C*H$_3$(*R*,*S*)), 16.95 and 15.35 (MCPM−cp*C*H(*R*,*S*)), 4.53 and 4.35 (MCPM−cpCH$_2$(*R*,*S*)), 2.22 and 0.29 (MCPM−cpCH$_2$(*R*,*S*)). Compound **6b** partial ^{1}H NMR $CDCl_3$: δ 5.68 and 5.62 (2×dd, 2H, $J_{2,3}$=2.6, H-2(*R*,*S*)), 5.02 and 4.63 (2×d, 2H, $J_{1,2}$=0.6, H-1(*R*,*S*)), 3.51 (m, 2H, H-5(*R*,*S*)), 3.32 and 3.29 (2×m, 2H, MCPM−C*H*(*R*,*S*)), 2.245 (1×s, Ac C*H*$_3$(*R* or *S*)); partial ^{13}C NMR $CDCl_3$: δ 170.66 and 170.64 (Ac*C*=O(*R*,*S*)), 96.5 and 95.5 (C-1(*R*,*S*)), 80.7 and 80.5 (C-3(*R*,*S*)), 78.7 and 77.8 (MCPM−*C*H(*R*,*S*)), 68.6 and 68.5 (C-2(*R*,*S*)); HRMS obsd 583.2695 calcd $C_{34}H_{40}O_7Na_1$ $(M+Na)^+$ 583.2672.

*4.1.3. (R,S)-Methyl cyclopropylmethyl 3,4,6-tri-O-benzyl-α/β-D-mannopyranoside **2ab**.* Acetates **6ab** (0.99 g, 1.76 mmol) were dissolved in 1:2 MeOH/CH_2Cl_2 (30 mL) followed by the addition of 1 M methanolic NaOMe (1.4 mL). The reaction was stirred at room temperature under an atmosphere of Ar for 16 h and then quenched by adding Rexyn 101(H) resin until acidic pH (~4). Water-aspirator filtration with 1:1 MeOH/CH_2Cl_2 rinse followed by solvent removal yielded alcohol **2ab** (0.87 g, 96%). Compound **2a** ^{1}H NMR $CDCl_3$: δ 7.43–7.22 (m, 30H, BnAr*H*), 5.36 (d, $J_{1,2}$=<1, H-1(*R*)), 5.03 (d, $J_{1,2}$=<1, H-1(*S*)), 4.95–4.55 (m, 12H, BnC*H*$_2$), 4.11 (br d, $J_{2,3}$=3.2, H-2(*R*)), 4.03 (br d, $J_{2,3}$=3.2, H-2(*S*)), 3.99 (dd, $J_{3,4}$=9.4, H-3(*S*)), 3.97 (dd, $J_{3,4}$=8.8, H-3(*R*)), 3.91 (dd, $J_{4,5}$=9.4, H-4(*S*)), 3.91 (dd, $J_{4,5}$=9.4, H-4(*R*)), 4.01 (m, H-5(*S*)), 3.86 (dd, $J_{5,6}$=4.5, $J_{6,6'}$=11.6, H-6(*S*)), 3.84 (m, H-5(*R*)), 3.81 (br d, H-6(*R*)), 3.78 (dd, $J_{5,6'}$=1.7, H-6′(*S*)), 3.73 (br d, H-6′(*R*)), 3.02 (dq, $J_{CH-CHcp}$=8.2, J_{CH-CH3}=6.2, MCPM−C*H*(*R*)), 3.13 (dq, $J_{CH-CHcp}$=8.2, J_{CH-CH3}=6.2, MCPM−C*H*(*S*)), 2.55 (br d, 2H, OH), 1.29 (d, 3H, MCPM−C*H*$_3$(*R*)), 1.26 (d, 3H, MCPM−C*H*$_3$(*S*)), 0.94 (m, 1H, MCPM−cpC*H*(*S*)), 0.82 (m, 1H, MCPM−cpC*H*(*R*)), 0.59 (m, 1H, MCPM−cpC*H*$_2$(*R*)), 0.52 (m, 2H, MCPM−cpC*H*$_2$(*S*)), 0.50 (m, 2H, MCPM−cpC*H*$_2$(*R*)), 0.41 (m, 1H, MCPM−cpC*H*$_2$(*S*)), 0.18 (m, 1H, MCPM−cpC*H*$_2$(*S*)), 0.06 (m, 1H, MCPM−cpC*H*$_2$(*R*)); ^{13}C NMR $CDCl_3$: δ 138.3 and 138.0 (BnAr*C*$_{ipso}$), 128.4–127.4 (BnAr*C*H), 96.7 (C-1(*R*)), 96.6 (C-1(*S*)), 80.32 and 80.27 (C-3(*R*,*S*)), 77.3 (MCPM−*C*H(*S*)), 76.3 (MCPM−*C*H(*R*)), 75.1 (BnCH$_2$), 74.45 and 74.44 (C-4(*R*,*S*)), 73.34 and 73.28 (BnCH$_2$), 71.82 and 71.80 (BnCH$_2$), 70.98 and 70.93 (C-5(*R*,*S*)), 68.93 (C-6(*R*,*S*)), 68.8 (C-2(*R*)), 68.7 (C-2(*S*)), 21.2 (MCPM−*C*H$_3$(*S*)), 18.9 (MCPM−*C*H$_3$(*R*)), 17.0 (MCPM−cp*C*H(*R*)), 15.5 (MCPM−cp*C*H(*S*)), 4.4 (MCPM−cpCH$_2$(*R*)), 4.2 (MCPM−cpCH$_2$(*S*)), 2.2 (MCPM−cpCH$_2$(*R*)), 0.3 (MCPM−cpCH$_2$(*S*)). Compound **2b** partial ^{1}H NMR $CDCl_3$: δ 4.95 and 4.52 (2×br s, 2H, $J_{1,2}$=<1, H-1(*R*,*S*)), 4.16 and 4.03 (2×br dd, 2H, H-2(*R*,*S*)), 3.63 (m, 2H, H-3(*R*,*S*)), 3.45 (m, 2H, H-5(*R*,*S*)), 3.32 and 3.29 (2×m, 2H, MCPM−C*H*(*R*,*S*)), 1.370 (d, J_{CH-CH3}=6.2, MCPM−C*H*$_3$(*R* or *S*)); partial ^{13}C NMR $CDCl_3$: δ 97.1 and 96.3 (C-1(*R*,*S*)), 81.76 and 81.71 (C-3(*R*,*S*)), 78.9 and 77.7 (MCPM−*C*H(*R*,*S*)), 21.3 and 19.4 (MCPM−*C*H$_3$(*R*,*S*)), 16.9 and 15.0 (MCPM−cp*C*H(*R*,*S*)), 4.6 and 4.1 (MCPM−cpCH$_2$(*R*,*S*)), 2.3 and 0.4 (MCPM−cpCH$_2$(*R*,*S*)); HRMS obsd 541.2605, calcd $C_{32}H_{38}O_6Na_1$ $(M+Na)^+$ 541.2566.

*4.1.4. (R,S)-Methyl cyclopropylmethyl-2-O-(2-O-acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-3,4,6-tri-O-benzyl-α/β-D-mannopyranoside **7ab**.* Alcohol (**2ab**, 0.87 g, 1.68 mmol) was dissolved in anhydrous CH_2Cl_2 (17 mL) followed by the addition of 3 Å molecular sieve (4.5 g). Trichloroacetimidate (**1**, 1.63 g, 2.56 mmol) was added via cannulation with anhydrous CH_2Cl_2 (6 mL). The resulting suspension was stirred at room temperature under an atmosphere of Ar for 45 min. The mixture was then cooled to 0 °C followed by the dropwise addition of TESOTf (30.3 μL, 0.134 mmol). Stirring continued at 0 °C for 1 h and the reaction was quenched with DIPEA (120 μL) followed by gravity filtration with filter paper and solvent removal. Silica gel flash chromatography using 7.5:1.5:1 hexanes/EtOAc/CH_2Cl_2 as eluent yielded the desired product (**7ab**, 1.04 g, 63%). ^{1}H NMR $CDCl_3$: δ 7.39–7.16 (m, 60H, BnAr*H*), 5.58 (m, 2H, H-2(*R*,*S*)^{II}), 5.23 (d, 1H, $J_{1,2}$=1.5, H-1(*R*)^{I}), 5.13 and 5.12 (2×d, 2H, $J_{1,2}$=1.28, H-1(*R*,*S*)^{II}), 4.97 (s, 1H, H-1(*S*)^{I}), 4.88 and 4.86 (2×d, 4H, *J*=2.7, BnC*H*$_2$), 4.71–4.41 (m, 20H, BnC*H*$_2$), 4.05–3.70 (m, 22H, H-2(*R*,*S*)^{I}, H-3(*R*,*S*)^{I,II}, H-4(*R*,*S*)^{I,II}, H-5(*R*,*S*)^{I,II}, H-6(*R*,*S*)^{I,II}, H-6′(*R*,*S*)^{I,II}), 3.11 (dq, 1H, $J_{CH-CHcp}$=7.8, J_{CH-CH3}=6.3, MCPM−C*H*(*R* or *S*)), 3.00 (dq, 1H, $J_{CH-CHcp}$=8.2, J_{CH-CH3}=6.1, MCPM−C*H*(*R* or *S*)), 2.143 and 2.140 (2×s, 6H, Ac*CH*$_3$(*R*,*S*)), 1.22 and 1.14 (2×d, 6H, *J*=6.3, MCPM−C*H*$_3$(*R*,*S*)), 0.88 and 0.72 (2×m, 2H, MCPM−cpC*H*(*R*,*S*)), 0.52–0.32 (m, 6H, MCPM−cpC*H*$_2$(*R*,*S*)), 0.09 and −0.01 (2×m, 2H, MCPM−cpC*H*$_2$(*R*,*S*)); ^{13}C NMR $CDCl_3$: δ 170.13 and 170.11 (Ac*C*=O(*R*,*S*)), 138.6–138.0 (BnAr*C*$_{ipso}$), 128.3–127.3 (BnAr*C*H), 99.6 (C-1^{II}), 96.5 and 96.4 (C-1(*R*,*S*)^{I}), 79.84 and 79.80 (C-2(*R*,*S*)^{I}), 78.2 (C-3^{II}), 77.6 and 76.6 (MCPM−*C*H(*R*,*S*)), 75.5 (C-3^{I}), 75.2–75.0 (2×BnCH$_2$), 74.8, 74.4 and 74.3 (C-4(*R*,*S*)^{I,II}), 73.4–73.2 (2×BnCH$_2$), 72.0–71.8 (2×BnCH$_2$, C-5(*R*,*S*)^{I,II}), 69.3, 69.1 and 68.9 (C-6(*R*,*S*)^{I,II}), 68.7 (C-2^{II}), 21.2 (MCPM−*C*H$_3$(*R*)), 21.14 and 21.12 (Ac*CH*$_3$(*R*,*S*)), 19.1 (MCPM−*C*H$_3$(*S*)), 17.0 and 15.7 (MCPM−cp*C*H(*R*,*S*)), 4.27, 4.18,

2.28 and 0.46 (MCPM–cpCH_2(*R*,*S*)); HRMS obsd 1010.4990, calcd $C_{61}H_{72}NO_{12}$ $(M+NH_4)^+$ 1010.5054.

4.1.5. (R,S)-Methyl cyclopropylmethyl-2-O-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-3,4,6-tri-O-benzyl-α/β-D-mannopyranoside ***8ab****.* Acetates (**7ab**, 1.04 g, 1.05 mmol) were dissolved in 1:2 MeOH/CH_2Cl_2 (30 mL) followed by the addition of 1 M methanolic NaOMe (1.4 mL). The reaction was stirred at room temperature under an atmosphere of Ar for 16 h and then quenched by adding Rexyn 101(H) resin until acidic pH (~4). Water-aspirator filtration with 1:1 MeOH/CH_2Cl_2 rinse followed by solvent removal yielded alcohol (**8ab**, 0.98 g, 98%). ^{1}H NMR $CDCl_3$: δ 7.44–7.25 (m, 30H, BnAr*H*), 5.31 (d, 1H, $J_{1,2}$=1.4, H-1^{I}), 5.27 (s, 1H, H-1^{II}), 4.92 and 4.89 (2×d, 2H, *J*=6.5, BnCH_2), 4.81–4.56 (m, 10H, BnCH_2), 4.22 (s, 1H, H-2^{II}), 4.13 (m, 1H, H-2^{I}), 4.05–3.75 (m, 10H, H-3^{I,II}, H-4^{I,II}, H-5^{I,II}, H-6^{I,II}, H-6′^{I,II}), 3.16 (dq, 1H, $J_{CH-CHcp}$=7.8, J_{CH-CH3}=6.6, MCPM–C*H*), 2.51 (s, 1H, OH), 1.27 (d, 3H, *J*=6.4, MCPM–CH_3), 0.77 (m, 1H, MCPM–cpC*H*), 0.57–0.37 (m, 3H, MCPM–cpCH_2), 0.04 (m, 1H, MCPM–cpCH_2); ^{13}C NMR $CDCl_3$: δ 138.6–138.0 (BnArC_{ipso}), 128.4–127.3 (BnArCH), 101.0 (C-1^{II}), 96.6 (C-1^{I}), 80.0 and 79.9 (C-3^{I,II}), 76.6 (MCPM–*C*H), 75.1 (C-2^{I}), 75.1–75.0 (2×BnCH_2 and C-4^{II}), 74.3 (C-4^{I}), 73.4 and 73.2 (2×BnCH_2), 72.2 and 72.1 (2×BnCH_2), 71.8 and 71.6 (C-5^{I,II}), 69.4 and 69.0 (C-6^{I,II}), 68.5 (C-2^{II}), 21.2 (MCPM–CH_3), 15.7 (MCPM–cpCH), 4.14 and 0.47 (MCPM–cpCH_2(*R*,*S*)). HRMS obsd 973.4495, calcd $C_{59}H_{66}O_{11}Na$ $(M+Na)^+$ 973.4502.

4.1.6. (R,S)-Methyl cyclopropylmethyl-2-O-(2-O-acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-2-O-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-3,4,6-tri-O-benzyl-α/β-D-mannopyranoside ***9ab****.* To a round-bottom flask containing alcohol (**8ab**, 0.98 g, 1.03 mmol) and 3 Å molecular sieve (3 g), trichloroacetimidate (**1**, 1.29 g, 2.02 mmol) was added via cannulation with anhydrous CH_2Cl_2 (4×4 mL). The resulting suspension was stirred at room temperature under an atmosphere of Ar for 30 min. The mixture was then cooled to 0 °C followed by the dropwise addition of TESOTf (18.7 μL, 0.082 mmol). Stirring continued at 0 °C for 1 h and an additional 30 min at room temperature. The reaction was quenched with DIPEA (80 μL) followed by gravity filtration with filter paper and solvent removal. The desired product (**9ab**, 1.15 g, 78%) was obtained from silica gel flash chromatography (7.5:1.5:1 hexanes/EtOAc/CH_2Cl_2) followed by Sephadex LH-20 chromatography (4:3 $CHCl_3$/MeOH). ^{1}H NMR $CDCl_3$: δ 7.42–7.21 (m, 90H, BnAr*H*), 5.62 (m, 2H, H-2(*R*,*S*)^{III}), 5.30 (s, 1H, H-1(*R*)^{I}), 5.29 and 5.26 (2×s, 2H, H-1(*R*,*S*)^{II}), 5.15 and 5.14 (2×s, 2H, H-1(*R*,*S*)^{III}), 5.06 (s, 1H, H-1(*S*)^{I}), 4.93 and 4.88 (m, 6H, BnCH_2), 4.78–4.36 (m, 30H, BnCH_2), 4.19 (m, 2H, H-2(*R*,*S*)^{II}), 4.08–3.71 (m, 30H, H-2(*R*,*S*)^{I}, H-3(*R*,*S*)^{I,II,III}, H-4(*R*,*S*)^{I,II,III}, H-5(*R*,*S*)^{I,II,III}, H-6(*R*,*S*)^{I,II,III}, H-6′(*R*,*S*)^{I,II}), 3.60 and 3.58 (2×d, 2H, $J_{5,6'}$=3.4, H-6′(*R*,*S*)^{III}), 3.15 (dq, 1H, $J_{CH-CHcp}$=7.8, J_{CH-CH3}=6.4, MCPM–*CH*(*R* or *S*)), 3.03 (dq, 1H, $J_{CH-CHcp}$=7.8, J_{CH-CH3}=6.4, MCPM–*CH*(*R* or *S*)), 2.20 (s, 6H, AcCH_3(*R*,*S*)), 1.26 and 1.18 (2×d, 6H, *J*=6.3, MCPM–CH_3(*R*,*S*)), 0.94 and 0.77 (2×m, 2H, MCPM–cpC*H*(*R*,*S*)), 0.56–0.32 (m, 6H, MCPM–cpCH_2(*R*,*S*)), 0.12 and 0.02 (2×m, 2H, MCPM–cpCH_2(*R*,*S*)); ^{13}C NMR $CDCl_3$: δ 170.1 (Ac*C*=O(*R*,*S*)), 138.6–137.7 (BnArC_{ipso}), 128.4–127.3 (BnArCH), 100.6 and 100.5 (C-1(*R*,*S*)^{II}), 99.3 (C-1^{III}), 96.7 and 96.5 (C-1(*R*,*S*)^{I}), 79.70 and 79.67 (C-3(*R*,*S*)^{III}), 78.2 and 78.1 (C-3(*R*,*S*)^{I,II}), 77.6 and 76.7 (MCPM–*CH*(*R*,*S*)), 75.6 (C-2^{I}), 75.3–74.7 (3×BnCH_2, C-2^{II} and C-4^{I,II}), 74.2 (C-4^{III}), 73.3–73.2 (3×BnCH_2), 72.3–71.8 (3×BnCH_2 and C-5^{I,II,III}), 69.5, 69.4, and 69.3 (C-6^{I,II,III}), 68.7 (C-2^{III}), 21.2 and 21.1 (MCPM–CH_3(*R* or *S*), AcCH_3(*R*,*S*)), 19.1 (MCPM–CH_3(*R* or *S*)), 17.0 and 15.7 (MCPM–cpCH(*R*,*S*)), 4.25, 4.10, 2.23, and 0.50 (MCPM–cpCH_2(*R*,*S*)); HRMS obsd 1442.6790, calcd $C_{88}H_{100}NO_{17}$ $(M+NH_4)^+$ 1442.6991.

4.1.7. (R,S)-Methyl cyclopropylmethyl-2-O-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-2-O-(3,4,6-tri-O-acetyl-α-D-mannopyranosyl)-3,4,6-tri-O-acetyl-α/β-D-mannopyranoside ***10ab****.* Benzyl ether (**9ab**, 1.15 g, 0.807 mmol) was dissolved in EtOAc (80 mL) and hydrogenated at 50 psi. at room temperature in the presence of 20% $Pd(OH)_2$/C (2.2 g) for 48 h. The resulting mixture was filtered through a bed of Celite with 1:1 MeOH/EtOAc rinse. After solvent evaporation under reduced pressure, the crude deprotected intermediate was redissolved in anhydrous pyridine (10 mL) and cooled to 0 °C. Acetic anhydride (5 mL) was added through a dropping funnel. Stirring continued for 16 h under an atmosphere of Ar with the temperature gradually rising up to room temperature. After solvent removal and co-evaporation with toluene (4×), the desired product (**10ab**, 0.51 g, 64% overall) was obtained from silica gel flash chromatography using 1:2 hexanes/EtOAc as eluent. ^{1}H NMR $CDCl_3$: δ 5.41–5.22 (m, 14H, H-2(*R*,*S*)^{III}, H-3(*R*,*S*)^{I,II,III}, H-4(*R*,*S*)^{I,II,III}), 5.24 (s, 1H, H-1(*R*)^{I}), 5.12 and 5.10 (2×d, 2H, $J_{1,2}$=1.8, H-1(*R*,*S*)^{II}), 4.97 (d, 1H, $J_{1,2}$=2.1, H-1(*S*)^{I}), 4.95 (m, 2H, H-1(*R*,*S*)^{III}), 4.23–3.92 (m, 20H, H-2(*R*,*S*)^{I,II}, H-5(*R*,*S*)^{II,III}, H-6(*R*,*S*)^{I,II,III}, H-6′(*R*,*S*)^{I,II,III}), 4.00 and 3.97 (2×m, 2H, H-5(*R*,*S*)^{I}), 3.14 (dq, 1H, $J_{CH-CHcp}$=8.0, J_{CH-CH3}=6.6, MCPM–*CH*(*R* or *S*)), 3.03 (dq, 1H, $J_{CH-CHcp}$=8.0, J_{CH-CH3}=6.6, MCPM–*CH*(*R* or *S*)), 2.14–2.00 (m, 60H, AcCH_3(*R*,*S*)), 1.28 and 1.24 (2×d, 6H, *J*=6.4, MCPM–CH_3(*R*,*S*)), 0.94 and 0.81 (2×m, 3H, MCPM–cpC*H*(*R*,*S*)), 0.61–0.37 (m, 4H, MCPM–cpCH_2(*R*,*S*)), 0.30 (m, 1H, MCPM–cpCH_2(*R*,*S*)), 0.14 and 0.06 (2×m, 2H, MCPM–cpCH_2(*R*,*S*)); ^{13}C NMR $CDCl_3$: δ 170.9–169.3 (Ac*C*=O(*R*,*S*)), 99.65 and 99.56 (C-1(*R*,*S*)^{II}), 99.36 and 99.33 (C-1(*R*,*S*)^{III}), 96.4 and 96.3 (C-1(*R*,*S*)^{I}), 79.4 and 78.1 (MCPM–*CH*(*R*,*S*)), 77.2–76.7 (C-2 ^{I,II}), 70.5, 70.4, 69.7, and 69.6 (C-3(*R*,*S*)^{I,II,III}), 69.4, 69.2, and 68.5 (C-5(*R*,*S*)^{I,II,III}), 68.4 (C-2(*R*,*S*)^{III}), 66.7, 66.6, 66.2, 66.1, and 66.0 (C-4(*R*,*S*)^{I,II,III}), 62.5, 62.3, and 62.0 (C-6(*R*,*S*)^{I,II,III}), 21.2 (MCPM–CH_3(*R* or *S*)), 20.8, 20.7, and 20.6 (AcCH_3(*R*,*S*)), 19.5 (MCPM–CH_3(*R* or *S*)), 17.0 and 15.8 (MCPM–cpCH(*R*,*S*)), 4.44, 4.20, 2.46, and 0.71 (MCPM–cpCH_2(*R*,*S*)); HRMS obsd 993.3436, calcd $C_{43}H_{61}O_{26}$ $(M+H)^+$ 993.3451.

4.1.8. Trichloroacetimidoyl-2-O-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-2-O-(3,4,6-tri-O-acetyl-α-D-mannopyranosyl)-3,4,6-tri-O-acetyl-α/β-D-mannopyranoside ***12ab****.* Product (**10ab**, 0.51 g, 0.51 mmol) was dissolved in CH_2Cl_2 (11 mL) followed by the addition of trifluoroacetic acid (3 mL). The resulting solution was stirred at room temperature for 2 h. Upon cooling to 0 °C, saturated aqueous $NaHCO_3$ (50 mL) was added followed by the addition of solid $NaHCO_3$ until basic pH (~9). The mixture was diluted with CH_2Cl_2 and the resulting layers were separated through a separatory funnel. The organic phase was further washed with saturated aqueous $NaHCO_3$ (3×) and the combined aqueous phase was re-extracted with CH_2Cl_2 (3×). The combined organic phase was dried with anhydrous Na_2SO_4, filtered, concentrated, and dried overnight under high vacuum. The crude intermediate **11ab** was then redissolved in anhydrous CH_2Cl_2 (14 mL) and cooled to 0 °C. Trichloroacetonitrile (0.6 mL, 5.98 mmol) and DBU (10 drops) were added sequentially. Stirring continued under an atmosphere of Ar for 1 h at 0 °C and 1 h at room temperature followed by solvent removal. Silica gel flash chromatography using basified (0.1% Et_3N) 3.5:6.5 hexanes/EtOAc as eluent yielded the desired product (**12ab**, 363 mg, 66%). ^{1}H NMR $CDCl_3$: δ 8.74 (s, 1H, NH), 6.41 (d, 1H, *J*=2.1, H-1^{I}), 5.41–5.24 (m, 7H, H-2^{III}, H-3^{I,II,III}, H-4^{I,II,III}), 5.18 (d, 1H, *J*=1.5, H-1^{II}), 4.95 (s, 1H, H-1^{III}), 4.29 (m, 1H, H2^{I}), 4.25–4.08 (m, 10H, H-2^{II}, H-5^{I,II,III}, H-6^{I,II,III}, H-6′^{I,II,III}), 2.14–1.99 (m, 30H, Ac-CH_3); ^{13}C NMR $CDCl_3$: δ 170.8–169.3 (Ac*C*=O), 160.1 (*C*=N), 99.6 (C-1^{II}), 99.3 (C-1^{III}), 95.6 (C-1^{I}), 90.5 (*C*Cl_3), 77.1 (C-2^{II}), 74.3 (C-2^{I}), 71.2 (C-5^{I}), 69.8 (C-3), 69.6–69.5 (C-3 and C-5^{II,III}), 68.3 (C-3), 66.2 and 65.9 (C-4^{I,II,III}), 65.5 (C-2^{III}), 62.4, 62.0 and 61.6 (C-6^{I,II,III}), 20.8–20.6 (AcCH_3).

4.1.9. (2R)-2,3-Bis[(3R,7R,11R)-3,7,11,15-tetramethylhexadecyloxy] propan-1-yl-2-O-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-2-O-(3,4,6-tri-O-acetyl-α-D-mannopyranosyl)-3,4,6-tri-O-acetyl-α-D-

mannopyranoside ***13a***. (a) To a round-bottom flask containing trichloroacetimidate (**12ab**, 363 mg, 0.34 mmol) and 3 Å molecular sieve (0.7 g), archaeol (130 mg, 0.20 mmol) was added via cannulation with anhydrous CH_2Cl_2 (4×1.8 mL). The resulting suspension was stirred at room temperature under an atmosphere of Ar for 30 min. The mixture was then cooled to 0 °C followed by the dropwise addition of TESOTf (3.6 μL, 0.016 mmol). Stirring continued at 0 °C for 1 h and an additional 30 min at room temperature. The reaction was quenched with DIPEA (15 μL) followed by gravity filtration with filter paper and solvent removal. The desired α glycoside (**13a**, 110 mg, 35%) was isolated from a series of gradient silica gel MPLC (hexanes/EtOAc, 2:1→1:1→1:2).

(b) Alternative, scaled-up glycosidation with AgOTf:

To a round-bottom flask containing trichloroacetimidate (**12ab**, 1.05 g, 0.98 mmol), archaeol (0.38 g, 0.58 mmol) was added via cannulation with anhydrous CH_2Cl_2 (3×7 mL). The resulting mixture was then cooled to 0 °C followed by the addition of AgOTf (75 mg, 0.29 mmol). Stirring continued at 0 °C under Ar for 2 h. The reaction was then quenched by adding saturated $NaHCO_3$ (15 mL) and 10% $Na_2S_2O_3$ (15 mL). The resulting mixture was stirred at room temperature for 20 min followed by phase separation with a separatory funnel. The aqueous phase was further extracted with CH_2Cl_2 (3×). The combined organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The desired α-glycoside (**13a**, 556 mg, 61%) was isolated from a series of gradient silica gel MPLC (hexanes/EtOAc, 2:1 to 1:2). ^{1}H NMR $CDCl_3$: δ 5.41–5.25 (m, 7H, H-2^{III}, H-3^{I,II,III}, H-4^{I,II,III}), 5.10 (d, 1H, $J_{1,2}$=1.8, H-1^{I}), 4.97 (d, 1H, $J_{1,2}$=1.8, H-1^{II}), 4.94 (d, 1H, $J_{1,2}$ 1.5, H-1^{III}), 4.1 (m, 1H, H2^{I}), 4.05 (m, 1H, H2^{II}), 4.25–4.08 (m, 9H, H-5^{I,II,III}, H-6^{I,II,III}, H-6′^{I,II,III}), 2.151, 2.131, 2.123, 2.082, 2.067, 2.047, 2.036, 2.027, 2.011, 2.001 (10×s, 30H, AcCH_3); ^{13}C NMR $CDCl_3$: δ 170.9, 170.7, 170.4, 170.0(2), 169.8, 169.7, 169.45, 169.41, 169.3 (10×AcC=O), 99.9 (C-1^{I}), 99.4 (C-1^{III}), 98.1 (C-1^{II}), 77.5 (C-2^{II}), 77.4 (CH-gly), 76.8 (C-2^{I}), 70.6 (C-2^{III}), 70.2, 70.1 (OCH_2, arch), 69.7, 69.6 (C-4), 69.5, 69.3 (C-5), 69.2 (CH_2-gly), 68.5 (C-5), 68.4 (C-4), 68.1 (SugOCH_2-gly), 66.3, 66.2, 66.1 (C-3^{I,II,III}), 62.5, 62.2, and 61.9 (C-6^{I,II,III}), 39.6, 37.5, 37.42, 37.38, 37.3, 37.1, 36.6 (CH_2-arch), 32.8, 30.0, 29.8, 28.0 (CH, arch), 24.8, 24.5, 24.4 (CH_2, arch), 22.7, 22.6 (CH_3, arch), 20.8–20.7 (AcCH_3), 19.7, 19.6 (CH_3, arch); HRMS obsd 1576.9540, calcd $C_{81}H_{142}O_{28}N_1$ $(M+NH_4)^+$ 1576.9718.

4.1.10. (2R)-2,3-Bis[(3R,7R,11R)-3,7,11,15-tetramethylhexadecyloxy] propan-1-yl-2-O-(-α-D-mannopyranosyl)-2-O-(α-D-mannopyranosyl)-α-D-mannopyranoside ***14***. Acetate (**13a**, 110 mg, 0.070 mmol) was dissolved in 1:2 MeOH/CH_2Cl_2 (24 mL) followed by the addition of 1 M methanolic NaOMe (1.2 mL). The reaction was stirred at room temperature under an atmosphere of Ar for 16 h and then quenched by adding Rexyn 101(H) resin until acidic pH (~4). Water-aspirator filtration with 1:1 MeOH/CH_2Cl_2 rinse followed by solvent removal yielded known trimannoside (**14**, 79.2 mg, 98%).[3]

4.1.11. (R,S)-Methyl cyclopropylmethyl [3,4,6-tri-O-acetyl-2-deoxy-2-(2,2′,2″-trichloroethoxycarbonylamino)-β-D-glucopyranosyl]-(1→2)-3,4,6-tri-O-benzyl-α/β-D-mannopyranoside ***16ab***. Donor phenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,2′,2″-trichloroethoxycarbonylamino)-β-D-1-thioglucopyranoside (**15**, 732 mg, 1.28 mmol)[13] and acceptor (**2a**, 442 mg, 0.85 mmol) were dissolved in dichloromethane (4 mL) along with powdered 4Å molecular sieves (about 500 mg) and cooled in an ice salt bath to 0 °C under an atmosphere of argon. To the mixture was added solid *N*-iodosuccinimide (383 mg, 1.7 mmol) followed by trifluoromethanesulfonic acid (15 μL, 0.17 mmol) by syringe. After stirring for 45 min the reaction was quenched with DIPEA (about 100 μL). The resulting mixture was filtered by gravity directly into a separatory funnel with rinsing with dichloromethane. The organic layer was washed by a mixture of $NaHCO_3$(aq) and NaS_2O_3(aq), which was concentrated after drying with Na_2SO_4 and filtration. The residue was purified by MPLC eluting with ethyl acetate/hexanes 25:75 to 36:64 to yield a colorless oil (**16ab**, 75%): ^{1}H NMR $CDCl_3$: δ 7.41–7.21 (m, 30H, BnAr*H*), 5.62 (br t, 2H, H-3^{II}), 5.22 (br d, 2H, NH^{II}), 5.16 (d, 1H, $J_{1,2}$=1.9, H-1(*R*)^{I}), 5.09 (br d, 2H, H-1^{II}), 4.98 (t, 2H, J=9.2, H-4^{II}), 4.88 (br d, 2H, $J_{H,H}$=8.6, Troc–C*H*H), 4.83 (d, $J_{1,2}$=1.9, H-1(*S*)^{I}), 4.77–4.48 (m, 14H, BnCH_2, Troc–CH*H*), 4.25 (dd, 2H, $J_{5,6}$=5.2, $J_{6,6'}$=12.3, H-6^{II}), 4.15 (m, 2H, H-2(*R*,*S*)^{I}), 4.12 (dd, 2H, $J_{5,6'}$=<1 H-6′^{II}), 3.98–3.62 (m, 12H, H-3(*R*,*S*)^{I}, H-4(*R*,*S*)^{I}, H-5(*R*,*S*)^{I}, H-6(*R*,*S*)^{I}, H-6′(*R*,*S*)^{I}, H-5^{II}), 3.25 (m, 2H, H-2^{II}), 3.11 (dq, $J_{CH-CHcp}$=8.2, J_{CH-CH3}=6.2, MCPM–C*H*(*R*)), 3.02 (dq, $J_{CH-CHcp}$=8.2, J_{CH-CH3}=6.2, MCPM–C*H*(*S*)), 2.03, 2.022, 2.015, 2.0, 1.99 (5s, 18H, Ac-CH_3), 1.22 (d, 3H, MCPM–CH_3(*R*)), 1.19 (d, 3H, MCPM–CH_3(*S*)), 0.87 (m, 1H, MCPM–cpC*H*(*S*)), 0.76 (m, 1H, MCPM–cpC*H*(*R*)), 0.50 (m, 1H, MCPM–cpCH_2(*R*)), 0.45 (m, 4H, MCPM–cpCH_2(*R*,*S*)), 0.30 (m, 1H, MCPM–cpCH_2(*S*)), 0.12 (m, 1H, MCPM–cpCH_2(*S*)), 0.02 (m, 1H, MCPM–cpCH_2(*R*)); ^{13}C NMR $CDCl_3$: δ 170.59, 170.57, 170.1, 169.6 (Ac-*C*=O), 153.8 (Troc–*C*=O), 138.5, 138.4, and 138.0 (BnArC_{ipso}), 128.4–127.4 (BnAr*C*H), 98.1 (br, C-1^{II}), 95.5 and 95.2 (C-1(*R*,*S*)^{I}), 78.7 and 78.6 (C-3(*R*,*S*)^{I}), 77.3 (MCPM–*C*H(*S*)), 76.5 (MCPM–*C*H(*R*)), 75.14 (Troc–CH_2), 74.9 (C-4(*R*,*S*)^{I}), 74.3–74.1 (C-2(*R*,*S*)^{I}, BnCH_2), 73.27 and 73.19 (BnCH_2), 72.4–71.9 (C-5(*R*,*S*)^{I}, C-5^{II}, BnCH_2), 70.7 (C-3^{II}), 69.2 (C-6(*R*,*S*)^{I}), 69.0 (C-4^{II}), 62.4 and 62.3 (C-6^{II}), 56.1 (C-2^{II}), 21.2 (MCPM–*C*H_3(*S*)), 20.68, 20.62, 20.60 (Ac-*C*H_3), 19.1 (MCPM–*C*H_3(*R*)), 17.0 (MCPM–cp*C*H(*R*)), 15.6 (MCPM–cp*C*H(*S*)), 4.34 and 4.33 (MCPM–cp*C*H_2(*R*,*S*)), 2.3 (MCPM–cp*C*H_2(*R*)), 0.5 (MCPM–cp*C*H_2(*S*)). Compound **16b** partial ^{1}H NMR $CDCl_3$: δ 4.83 (br s, 1H, $J_{1,2}$=<1, H-1(*R* or *S*)^{I}), 3.58 (m, 2H, H-3(*R*,*S*)^{I}), 3.38 (2×m, 2H, MCPM–C*H*(*R*,*S*)), 1.39 (d, J_{CH-CH3}=6.4, MCPM–CH_3(*R* or *S*)); MS obsd 997.3104 calcd $C_{47}H_{60}Cl_3N_2O_{15}$ $(M+NH_4)^+$ 997.3059.

4.1.12. (R,S)-Methyl cyclopropylmethyl [3,4,6-tri-O-acetyl-2-deoxy-2-acetamido-β-D-glucopyranosyl]-(1→2)-3,4,6-tri-O-benzyl-α/β-D-mannopyranoside ***17ab***. Disaccharide (**16ab**, 400 mg, 0.41 mmol) was dissolved at room temperature in acetic anhydride (5.0 mL) and Zinc powder (500 mg) was added. After stirring for 6 h more acetic anhydride (5.0 mL) and Zinc (500 mg) were added. After stirring for 2 more hours the mixture was filtered by suction through a bed of Celite and rinsed with ethyl acetate (about 150 mL). The solvent was evaporated and the residue co-evaporated with toluene (2× about 100 mL). This residue was purified by flash chromatography eluting with ethyl acetate/hexanes 50:50 to 66.6:33.3 to yield a colorless oil (**17ab**, 296 mg, 85%): ^{1}H NMR $CDCl_3$: δ 7.39–7.21 (m, 30H, BnAr*H*), 5.80 (2×t, 2H, $J_{2,3}$=10.0, H-3^{II}), 5.39 (br t, 2H, NH^{II}), 5.16 (d, 1H, $J_{1,2}$=1.0, H-1(*R*)^{I}), 5.24 and 5.21 (2×d, 2H, $J_{1,2}$=8.2, H-1^{II}), 5.00 (t, 2H, $J_{4,5}$=9.4, H-4^{II}), 4.94–4.44 (m, 12H, BnCH_2), 4.82 (d, 1H, $J_{1,2}$=1.0, H-1(*S*)^{I}), 4.28 (dd, 2H, $J_{5,6}$=5.3, $J_{6,6'}$=12.6, H-6^{II}), 4.13 (m, 3H, H-6′^{II}, H-2(*R*)^{I}), 4.07 (br d, H-2(*S*)^{I}), 4.1–3.6 (m, 12H, H-3(*R*,*S*)^{I}), H-4(*R*,*S*)^{I}, H-5(*R*,*S*)^{I}, H-6(*R*,*S*)^{I}, H-6′(*R*,*S*)^{I}, (H-5^{II}), 3.21 (m, 2H, H-2^{II}), 3.09 (dq, $J_{CH-CHcp}$=8.2, J_{CH-CH3}=6.4, MCPM–C*H*(*R*)), 3.01 (dq, $J_{CH-CHcp}$=8.2, J_{CH-CH3}=6.4, MCPM–C*H*(*S*)), 2.05, 2.01, 2.00, 1.73 (4s, 24H, Ac-CH_3), 1.21 (d, 3H, MCPM–CH_3(*R*)), 1.20 (d, 3H, MCPM–CH_3(*S*)), 0.88 (m, 1H, MCPM–cpC*H*(*S*)), 0.75 (m, 1H, MCPM–cpC*H*(*R*)), 0.62 (m, 1H, MCPM–cpCH_2(*R*)), 0.44 (m, 4H, MCPM–cpCH_2(*R*,*S*)), 0.30 (m, 1H, MCPM–cpCH_2(*S*)), 0.11 (m, 1H, MCPM–cpCH_2(*S*)), −0.01 (m, 1H, MCPM–cpCH_2(*R*)); ^{13}C NMR $CDCl_3$: δ 170.7, 170.1, 170.0, 169.7 (Ac-*C*=O), 138.5, 138.4 and 138.2 (BnArC_{ipso}), 128.4–127.5 (BnAr*C*H), 97.5 (C-1^{II}), 95.3 and 94.6 (C-1(*R*,*S*)^{I}), 78.5 and 78.4 (C-3(*R*,*S*)^{I}), 78.2 (MCPM–*C*H(*S*)), 77.2 (MCPM–*C*H(*R*)), 75.26 and 75.21 (BnCH_2), 74.54 and 74.53 (C-4(*R*,*S*)^{I}), 74.3 and 74.1 (C-2(*R*,*S*)^{I}), 73.28 and 73.24 (BnCH_2), 71.7 (m, C-5(*R*,*S*)^{I}, C-5^{II}, BnCH_2), 70.98 and 70.93 (C-3^{II}), 69.34 (C-6(*R*,*S*)^{I}), 69.29 (C-4^{II}), 62.59 and 62.52 (C-6^{II}), 56.59 and 56.52 (C-2^{II}), 23.2 (AcN–*C*H_3), 21.2 (MCPM–*C*H_3(*S*)), 20.72, 20.69 (AcO–*C*H_3), 19.4 (MCPM–*C*H_3(*R*)), 17.1 (MCPM–cp*C*H(*R*)), 15.5 (MCPM–cp*C*H(*S*)), 4.6 and 4.4 (MCPM–cp*C*H_2(*R*,*S*)), 2.3 (MCPM–cp*C*H_2(*R*)), 0.5 (MCPM–cp*C*H_2(*S*)). Compound **17b** partial ^{1}H NMR $CDCl_3$: δ 3.58 (m, 2H, H-3(*R*,*S*)^{I}), 3.4 (2×m, 2H, MCPM–C*H*(*R*,*S*)), 1.39 (d, J_{CH-CH3}=6.4,

MCPM−CH_3(*R* or *S*)); HRMS obsd 870.3789 calcd $C_{46}H_{57}N_1O_{14}Na_1$ $(M+Na)^+$ 870.3777.

4.1.13. (R,S)-Methyl cyclopropylmethyl [3,4,6-tri-O-acetyl-2-deoxy-2-acetamido-β-D-glucopyranosyl]-(1→2)-3,4,6-tri-O-acetyl-α/β-D-mannopyranoside ***18ab****.* Disaccharide (**17ab**, 1.38 g, 1.6 mmol) was dissolved in ethyl acetate (45 mL) and hydrogenated in a Parr apparatus at room temperature at 45 p.s.i of H_2(g) in the presence of Pearlman's catalyst (10% $Pd(OH)_2$ on carbon, 1 g) overnight. The solids were removed by filtration by suction through a bed of Celite followed by rinsing extensively with alternate aliquots of ethyl acetate and methanol. The liquids were evaporated and the residue was dissolved in pyridine (20 mL). After cooling in an ice bath acetic anhydride (10 mL) was added. After stirring for 4 h the liquids were removed by evaporation. The residue was purified by flash chromatography eluting with ethyl acetate/hexanes 65:35 to 80:20 to yield a viscous oil (**18ab**, 0.99 g, 88%): ^{1}H NMR $CDCl_3$: δ 5.59 (m, 4H, $J_{2,NH}$=7.6, NH^{II}, H-3^{II}), 5.21 (m, 2H, $J_{3,4}$=10.0, H-3(*R*,*S*)^I), 5.11 (br s, 1H, H-1(*R*)^I), 5.09 (m, 2H, H-4^{II}), 5.06 (d, 2H, $J_{1,2}$=8.6, H-1^{II}), 4.99 (t, 2H, $J_{4,5}$=10.3, H-4(*R*,*S*)^I), 4.76 (br s, 1H, H-1(*S*)^I), 4.3−4.0 (m, 10H, H-6^{II}, H-6′^{II}, H-2(*R*,*S*)^I, H-6(*R*,*S*)^I, H-6′(*R*,*S*)^I), 3.87 (m, 2H, H-5(*R*,*S*)^I), 3.69 (m, 2H, H-5^{II}), 3.43 (ddd, 2H, $J_{2,3}$=10.3, H-2^{II}), 3.06 (dq, $J_{CH-CHcp}$=8.8, J_{CH-CH3}=6.2, MCPM−C*H*(*R*)), 2.99 (dq, $J_{CH-CHcp}$=8.8, J_{CH-CH3}=6.2, MCPM−C*H*(*S*)), 2.07 (s, 6H, Ac-CH_3), 2.06 (s, 3H, Ac-CH_3), 2.04 (s, 3H, Ac-CH_3), 2.033, 2.025, 2.01 2.00, 1.92 (5×s, 15H, Ac-CH_3), 1.27 (d, 3H, MCPM−CH_3(*R*)), 1.24 (d, 3H, MCPM−CH_3(*S*)), 0.95 (m, 1H, MCPM−cpC*H*(*S*)), 0.83 (m, 1H, MCPM−cpC*H*(*R*)), 0.64 (m, 1H, MCPM−cpCH_2(*R*)), 0.45 (m, 4H, MCPM−cpCH_2(*R*,*S*)), 0.31 (m, 1H, MCPM−cpCH_2(*S*)), 0.13 (m, 1H, MCPM−cpCH_2(*S*)), 0.02 (m, 1H, MCPM−cpCH_2(*R*)); ^{13}C NMR $CDCl_3$: δ 170.8−170.6, 170.4−170.3, 169.7, 169.6 (Ac-*C*═O), 98.7 (C-1^{II}), 95.5 and 94.8 (C-1(*R*,*S*)^I), 79.1 (MCPM−*C*H(*S*)), 76.3 (MCPM−*C*H(*R*)), 75.15 and 73.05 (C-2(*R*,*S*)^I), 71.8 (C-5^{II}), 71.33 and 71.26 (C-3^{II}), 70.3 (C-4^{II}), 68.95 and 68.89 (C-4(*R*,*S*)^I), 68.5 and 68.4 C-5(*R*,*S*)^I), 66.4 and 66.3 (C-3(*R*,*S*)^I), 63.15 and 63.07(C-6(*R*,*S*)^I), 62.1 (C-6^{II}), 56.16 and 56.10 (C-2^{II}), 23.3 (AcN−*C*H_3), 21.1 (MCPM−*C*H_3(*S*)), 20.78−20.66 (AcO−*C*H_3), 19.4 (MCPM−*C*H_3(*R*)), 17.0 (MCPM−cp*C*H(*R*)), 15.3 (MCPM−cp*C*H(*S*)), 4.73 and 4.47 (MCPM−cpCH_2(*R*,*S*), 2.4 (MCPM−cpCH_2(*R*)), 0.5 (MCPM−cpCH_2(*S*)). HRMS obsd 704.2819 calcd $C_{31}H_{46}N_1O_{17}$ $(M+H)^+$ 704.2766; obsd 726.2681 calcd $C_{31}H_{45}N_1O_{17}Na_1$ $(M+Na)^+$ 726.2585.

4.1.14. (R,S)-Methyl cyclopropylmethyl [2-deoxy-2-acetamido-β-D-glucopyranosyl]-(1→2)-α/β-D-mannopyranoside ***19ab****.* A small amount of (**18ab**, 20 mg, 0.03 mmol) was dissolved in dry methanol (5 mL) and 1 M NaOMe in MeOH (0.5 mL) was added and the mixture stirred overnight at room temperature under an atmosphere of Ar. The resulting solution was neutralized with Rexyn 101(H) resin, filtered and evaporated. The residue was purified by reverse phase C-18 Sepak loading in water and eluting stepwise with water, 5% v/v methanol/water, 10% methanol/water and 50% methanol/water. The product eluted predominantly in 10% methanol/water to yield a white powder (**19ab**, 13 mg, 95%). Compound **19a** ^{1}H NMR D_2O: δ 5.21 (d, 1H, $J_{1,2}$=1.6, H-1(*R*)^I), 4.95 (d, $J_{1,2}$=1.6, H-1(*S*)^I), 4.56 (d, 2H, $J_{1,2}$=8.2, H-1^{II}), 4.05 (dd, 1H, $J_{2,3}$=3.5, H-2(*R*)^I), 4.02 (dd, $J_{2,3}$=3.5, H-2(*S*)^I), 3.93−3.29 (m, 22H, H-6′^{II}, H-4^{II}, H-3^{II}, H-6^{II}, H-3(*R*,*S*)^I, H-4(*R*,*S*)^I, H-5(*R*,*S*)^I, H-6(*R*,*S*)^I, H-6′(*R*,*S*)^I, H-5^{II}, H-2^{II}), 3.27 (dq, $J_{CH-CHcp}$=8.5, J_{CH-CH3}=6.4, MCPM−C*H*(*R*)), 3.18 (dq, $J_{CH-CHcp}$=8.8, J_{CH-CH3}=6.2, MCPM−C*H*(*S*)), 2.06, 2.04 (2s, 6H, Ac-CH_3), 1.29 (d, 3H, MCPM−CH_3(*R*)), 1.26 (d, 3H, MCPM−CH_3(*S*)), 0.96 (m, 1H, MCPM−cpC*H*(*S*)), 0.87 (m, 1H, MCPM−cpC*H*(*R*)), 0.62 (m, 1H, MCPM−cpCH_2(*R*)), 0.52 (m, 6H, MCPM−cpCH_2(*R*,*S*)), 0.34 (m, 1H, MCPM−cpCH_2(*S*)), 0.29 (m, 1H, MCPM−cpCH_2(*S*)), 0.13 (m, 1H, MCPM−cpCH_2(*R*)); ^{13}C NMR D_2O: δ 174.7 (Ac-*C*═O), 99.9 and 99.7 (C-1^{II}), 94.8 and 94.0 (C-1(*R*,*S*)^I), 78.1 (MCPM−*C*H(*S*)), 78.0 (MCPM−*C*H(*R*)), 77.2 and 77.0 (C-2(*R*,*S*)^I), 75.8 (C-5^{II}), 73.3, 73.2, 73.0, 72.9 74.53 (C-4(*R*,*S*)^I), (C-5(*R*,*S*)^I), 69.9 (C-3^{II}), 69.7 (C-3(*R*,*S*)^I), 67.3 (C-4^{II}), 61.5 (C-6(*R*,*S*)^I), 60.6 (C-6^{II}), 55.43 and 55.38 (C-2^{II}), 22.3 (AcN−*C*H_3), 20.1 (MCPM−*C*H_3(*S*)), 17.6 (MCPM−*C*H_3(*R*)), 16.3 (MCPM−cp*C*H(*R*)), 15.0 (MCPM−cp*C*H(*S*)), 3.9 and 3.5 (MCPM−cpCH_2(*R*,*S*)), 1.9 and 0.0 (MCPM−cpCH_2(*R*,*S*)). Compound **19b** partial ^{1}H NMR D_2O: δ 4.91 (br s, H-1(*R*)^I), 4.89 (br s, H-1(*S*)^I), 4.23 (br d, 1H, $J_{2,3}$=3.2, H-2(*R*)^I), 4.19 (br d, $J_{2,3}$=3.0, H-2(*S*)^I) 3.33 (2×m, 2H, MCPM−C*H*(*R*,*S*)); HRMS obsd 452.2728 calcd $C_{19}H_{33}N_1O_{11}$ $(M+H)^+$ 452.2131.

4.1.15. 3,4,6-Tri-O-acetyl-2-deoxy-2-acetamido-β-D-glucopyranosyl-(1→2)-3,4,6-tri-O-acetyl-α-D-mannopyranose and 3,4,6-tri-O-acetyl-2-deoxy-2-acetamido-β-D-glucopyranosyl-(1→2)-3,4,6-tri-O-acetyl-α-D-mannopyranosyl trichloroacetimidate ***20****.* MCPM protected disaccharide (**18ab**, 0.99 g, 1.4 mmol) was dissolved at room temperature under an atmosphere of argon in dichloromethane (17 mL) and trifluoroacetic acid (3 mL) was added dropwise. After stirring for 45 min the mixture was cooled in an ice bath diluted with dichloromethane (about 40 mL) and cold $NaHCO_3$(aq) (about 100 mL) followed by addition of solid $NaHCO_3$ until effervescence ceased. The mixture was transferred to a separatory funnel, separated and the organic layer washed with $NaHCO_3$(aq) (about 100 mL). After drying over Na_2SO_4, filtration, concentration the residue was dried at high vacuum. Partial ^{1}H NMR $CDCl_3$: 5.75 (d, 1H, $J_{2,NH}$=7.9, NH^{II}), 5.56 (dd, 1H, $J_{2,3}$=10.4, H-3^{II}), 5.22 (t, 1H, $J_{4,5}$=10.0, H-4^I), 5.08 (dd, 1H, $J_{3,4}$=10.3, H-3^I), 5.00 (d, 1H, $J_{1,2}$=8.2, H-1^{II}), 4.99 (t, 1H, $J_{4,5}$=9.1, H-4^{II}), 4.70 (br s, 1H, $J_{1,2}$=1.8, H-1^I), 4.25 (dd, 1H, $J_{5,6}$=5.3, $J_{6,6'}$=12.3, H-6^{II}), 4.20 (dd, 1H, $J_{5,6}$=5.9, $J_{6,6'}$=12.3, H-6^I), 4.15 (dd, 1H, $J_{2,3}$=3.5, H-2^I), 4.05 (dd, 1H, $J_{5,6'}$=2.4, H-6′^{I}), 4.01 (dd, 1H, $J_{5,6'}$=2.1, H-6′^{II}), 3.88 (ddd, 1H, H-5^I), 3.69 (m, 1H, H-5^{II}), 3.50 (m, 1H, H-2^{II}), 2.078, 2.072, 2.034, 2.025 (4×s, 12H, AcOCH_3), 2.01 (s, 6H, AcOCH_3), 1.93 (s, 3H, AcNCH_3); HRMS obsd 636.2770 calcd $C_{26}H_{38}N_1O_{17}$ $(M+H)^+$ 636.2139. The residue was cooled in an ice bath under an atmosphere of argon and dissolved in dichloromethane (13 mL) followed by addition of trichloroacetonitrile (2.5 mL) and 1,8-diazobicyclo[5.4.0]undec-7-ene (about 80 μL). The mixture was stirred for 1 h and then concentrated. The reside was purified by flash chromatography eluting with ethyl acetate/hexanes 65:35 to 80:20 to yield a viscous oil (**20**, 0.99 g, 88%). Compound **20** ^{1}H NMR $CDCl_3$: δ 8.69 (s, 1H, N*H*), 6.17 (d, 1H, $J_{1,2}$=2.0, H-1^I), 5.68 (d, 1H, $J_{2,NH}$=7.9, NH^{II}), 5.39 (m, 2H, H-3^{II}, H-4^I), 5.10 (dd, 1H, $J_{3,4}$=10.3, H-3^I), 5.05 (t, 1H, $J_{4,5}$=10.0, H-4^{II}), 4.89 (d, 1H, $J_{1,2}$=8.4, H-1^{II}), 4.41 (dd, 1H, $J_{2,3}$=3.5, H-2^I), 4.27 (dd, 1H, $J_{5,6}$=5.1, $J_{6,6'}$=12.1, H-6^{II}), 4.23 (dd, 1H, $J_{5,6}$=5.3, $J_{6,6'}$=12.3, H-6^I), 4.12 (m, 2H, H-5^I, H-6′^{I}), 4.03 (dd, 1H, $J_{5,6'}$=2.2, H-6^{II}), 3.79 (ddd, 1H, H-2^{II}), 3.70 (ddd, 1H, H-5^{II}), 2.10, 2.07, 2.06, 2.04, 2.03, 2.01, 1.97 (7×s, 21H, Ac-CH_3); ^{13}C NMR $CDCl_3$: δ 170.8, 170.7, 170.6, 170.5, 170.4, 169.4, 169.3 (Ac-*C*═O), 160.1 (*C*═N), 99.8 (C-1^{II}), 95.1 (C-1^I), 85.5 (*C*Cl_3), 72.7 (C-2^I), 71.9 (C-5^{II}), 71.7 (C-3^{II}), 71.4 (C-5^I), 69.9 (C-3^I), 68.4 (C-4^{II}), 65.0 (C-4^I), 62.1 (C-6^I), 61.9 (C-6^{II}), 55.0 (C-2^{II}), 23.2 (AcN−*C*H_3), 20.7 (m, AcO−*C*H_3), MS obsd 636.3 calcd $C_{26}H_{38}N_1O_{17}$ $(M-TCI+H_2O)^+$ 636.2.

4.1.16. N-(9-Fluorenylmethoxycarbonyl)-O-[3,4,6-tri-O-acetyl-2-deoxy-2-acetamido-β-D-glucopyranosyl]-(1→2)-3,4,6-tri-O-acetyl-α-D-mannopyranosyl]-L-serine phenylacyl ester ***22****.* Disaccharide donor (**20**, 0.315 g, 0.41 mmol), protected serine (**21**, 0.12 g, 0.27 mmol), and 4 Å molecular sieves (about 400 mg) were dried overnight at high vacuum. To this mixture was added CH_2Cl_2 (4 mL) and the flask was cooled in an ice bath under an atmosphere of argon. Subsequently boron trifluoride etherate (20 μL, 0.59 equiv) was added by syringe and after 1 h at the same T another aliquot (10 μL) was added. After further stirring for 1 h the reaction was quenched with DIPEA (30 μL) and after filtration and concentration the residue was purified by flash chromatography eluting with hexanes/ethyl acetate:CH_2Cl_2 6:3:1 to yield a viscous oil (**22**, 207 mg, 72%). ^{1}H NMR $CDCl_3$: δ 7.95 (d, 2H, $J_{o,m}$=7.3, Fmoc−CH*o*),

7.77 (d, 2H, $J_{o,m}$=7.3, Fmoc–CH*o*), 7.65 (m, 3H, PhAc), 7.58 (t, 2H, $J_{p,m}$=7.3, Fmoc–CH*m*), 7.40 (t, 2H, $J_{p,m}$=7.6, Fmoc–CH*m*), 7.33 (m, 2H, PhAc), 6.21 (d, 1H, $J_{2,NH}$=9.0, NH^{II}), 5.95 (d, 1H, $J_{\alpha,NH}$=8.8, NH^{S}), 5.76 (d, 1H $J_{H,H}$=16.6, PhAc–C*H*H), 5.26 (m, 4H, H-3^{II},H-1^{I}, H-4^{I}, PhAc–CH*H*), 5.09 (dd, 1H, $J_{2,3}$=3.7, $J_{3,4}$=9.6, H-3^{I}), 5.03 (t, 1H, $J_{4,5}$=9.9, H-4^{II}), 4.71 (m, 2H, $J_{1,2}$=8.6, H-1^{II}, H-α^{S}), 4.42 (m, 2H, Fmoc–CH_2), 4.22 (m, 6H, H-6^{II}, H-2^{I}, H-6^{I}, H-$6'^{I}$, H-β^{S}, Fmoc–C*H*), 4.02 (m, 3H, H-2^{II}, H-$6'^{II}$, H-β'^{S}), 3.90 (m, 1H, H-5^{I}), 3.54 (ddd, 1H, $J_{5,6}$=2.2, $J_{5,6'}$=4.9, H-5^{II}), 2.11, 2.07, 2.04 (3×s, 9H, Ac-CH_3), 2.03 (s, 6H, Ac-CH_3), 1.98, 1.89 (2×s, 6H, Ac-CH_3); ^{13}C NMR $CDCl_3$: δ 193.7 (PhAc–*C*O), 170.9, 170.69, 170.65, 170.5, 169.8, 169.3 (Ac-*C*=O, S-*C*O), 156.1 (Fmoc–*C*O), 143.7, 141.3 (Fmoc$_{ipso}$), 134.7 (PhAc$_p$), 133.7 (PhAc$_{ipso}$), 129.4 (Fmoc$_m$), 127.8 (Fmoc$_o$), 127.7 (Fmoc$_m$), 127.1 (PhAc$_m$), 125.2 (PhAc$_o$), 120.0 (Fmoc$_o$), 100.3 (C-1^{II}), 98.7 (C-1^{I}), 74.6 (C-2^{I}), 72.5 (C-3^{II}), 71.7 (C-5^{II}), 70.1 (C-3^{I}), 69.3 (C-5^{I}), 68.5 (C-4^{II}), 67.5 (S-β, FmocCH_2), 66.8 (PhAc–CH_2), 65.9 (C-4^{I}), 62.3 (C-6^{I}), 61.9 (C-6^{II}), 54.2 (C-2^{II}, S-α), 47.1 (FmocCH), 23.0 (AcN–CH_3), 20.74, 20.71, 20.65, 20.56 (AcO-CH_3); HRMS obsd 1063.3550 calcd $C_{52}H_{59}N_2O_{22}$ $(M+H)^+$ 1063.3559.

4.1.17. N-(9-Fluorenylmethoxycarbonyl)-O-[3,4,6-tri-O-acetyl-2-deoxy-2-acetamido-β-D-glucopyranosyl]-(1→2)-3,4,6-tri-O-acetyl-α-D-mannopyranosyl]-L-serine ***23****.* Phenylacyl ester (**22**, 200 mg, 0.19 mmol) was dissolved in acetic acid (8 mL) and ethyl acetate (2 mL). To this solution at room temperature under an atmosphere of argon was added Zinc powder (1 g). After stirring for 15 min the reaction was filtered through a bed of Celite and rinsed well with ethyl acetate. The liquids were removed by evaporation followed by co-evaporation with toluene. The residue was purified by flash chromatography eluting with CH_2Cl_2 followed by ethyl acetate/CH_2Cl_2 3:1, 10% v/v methanol/ethyl acetate and 20% v/v methanol/ethyl acetate to yield a viscous oil (**23**, 133 mg, 75%). ^{1}H NMR $CDCl_3$+five drops CD_3OD: δ 7.71 (d, 2H, $J_{o,m}$=7.1, Fmoc–CH*o*), 7.61 (d, 2H, $J_{o,m}$=7.1, Fmoc–CH*o*), 7.35 (t, 2H, $J_{p,m}$=7.3, Fmoc–CH*m*), 7.27 (t, 2H, $J_{p,m}$=7.3, Fmoc–CH*m*), 6.29 (d, 1H, $J_{2,NH}$=7.4, NH^{II}), 5.62 (br t, 1H, $J_{2,3}$=10.0, $J_{3,4}$=10.0, H-3^{II}), 5.10 (d+t, 2H, $J_{1,2}$=8.1, $J_{3,4}$=10.0 $J_{4,5}$=10.0, H-1^{II}, H-4^{I}), 5.01 (dd, 1H, $J_{2,3}$=3.4, $J_{3,4}$=10.0, H-3^{I}), 4.92 (t, 1H, $J_{4,5}$=10.5, H-4^{II}), 4.71 (br s, 1H, H-1^{I}), 4.38 (m, 1H, Fmoc–C*H*H), 4.2–4.15 (m, 5H, Fmoc–CH*H*, H-6^{II}, H-6^{I}, H-α^{S}, Fmoc–C*H*, H-2^{I}), 4.0 (m, 3H, H-$6'^{I}$, H-$6'^{II}$, H-β^{S}), 3.89–3.85 (m, 2H, H-5^{I}, H-β'^{S}), 3.76 (m, 1H, H-5^{II}), 3.21 (br t, $J_{2,3}$ 10.0, H-2^{II}), 2.03, 2.00, 1.982 (3×s, 9H, Ac-CH_3), 1.977 (s, 6H, Ac-CH_3), 1.96, 1.90 (2×s, 6H, Ac-CH_3); ^{13}C NMR $CDCl_3$: δ 175.7 (S-COOH), 173.2 (CO-NH^{II}) 171.1, 171.0, 170.8, 170.6 (2), 169.8 (Ac-*C*=O), 156.0 (Fmoc–*C*O), 143.8, 141.1 (Fmoc$_{ipso}$), 127.6 (Fmoc$_o$), 127.0 (Fmoc$_m$), 125.0 (Fmoc$_o$), 119.8 (Fmoc$_m$), 98.4 (C-1^{II}), 98.1 (C-1^{I}), 74.7 (C-2^{I}), 71.3 (C-3^{II}, C-5^{II}), 70.8 (C-4^{I}), 68.9 (C-4^{II}), 68.5 (C-5^{I}), 68.2 (S-β), 66.9 (FmocCH_2), 66.0 (C-3^{I}), 62.6 (C-6^{I}), 61.9 (C-6^{II}), 55.7 (C-2^{II}, S-α), 47.1 (FmocCH), 22.3 (AcN–CH_3), 20.51, 20.40 (AcO–CH_3). MS obsd 967.4 calcd $C_{44}H_{52}N_2O_{21}Na$ $(M+Na)^+$ 967.3.

4.1.18. N-(9-Fluorenylmethoxycarbonyl)-O-[2-deoxy-2-acetamido-β-D-glucopyranosyl]-(1→2)-α-D-mannopyranosyl]-L-serine ***24****.* An aliquot of glycoamino acid (**23**, 76 mg, 0.08 mmol) was dissolved in dry methanol (5 mL) under an atmosphere of argon at room temperature. KCN[21] (63 mg, 12 equiv) was added and the reaction monitored by TLC using ethyl actetate/methanol/acetic acid 80:15:5 v/v/v as eluent. The reaction was quenched with a small amount of Rexyn 101(H) resin, filtered and evaporated. The residue was purified by reverse phase C-18 Sepak loading in water and eluting stepwise with water, 5% v/v methanol/water, 10% methanol/water, 50% methanol/water and methanol. The product eluted in 50% methanol/water to yield a white powder (**24**, 44 mg, 80%) ^{1}H NMR CD_3OD: δ 7.79 (d, 2H, $J_{o,m}$=7.6, Fmoc–CH*o*), 7.69 (d, 2H, $J_{o,m}$=7.3, Fmoc–CH*o*), 7.39 (t, 2H, $J_{p,m}$=7.3, Fmoc–CH*m*), 7.32 (t, 2H, $J_{p,m}$=7.6, Fmoc–CH*m*), 4.81 (br s, 1H, H-1^{I}), 4.44 (d, 1H, $J_{1,2}$ 8.1, H-1^{II}), 4.34 (br d, 2H, Fmoc–C*HH*), 4.23 (m, 2H, Fmoc–C*H*, H-α^{S}), 3.99, 3.92 (2×br d, $J_{H\beta,H\beta}$ 10.5, H-$\beta\beta'^{S}$), 3.91 (br d, 1H, H-2^{I}), 3.86 (dd, 1H, $J_{5,6}$ 2.0, $J_{6,6'}$ 12.0, H-6^{II}), 3.77 (m, 1H, H-6^{I}), 3.74 (m, 1H, H-4^{I}), 3.69 (dd, 1H, $J_{5,6'}$ 5.4, H-$6'^{II}$), 3.62 (m, 2H, H-$6'^{I}$, H-2^{II}), 3.55 (m, 2H, H-5^{I}, H-3^{I}), 3.49 (m, 1H, H-3^{II}), 3.34 (m, 1H, H-4^{II}), 3.31 (m, 1H, H-5^{II}), 2.02 (s, 3H, Ac-CH_3); ^{13}C NMR CD_3OD: δ 174.7 (S-COOH, CO-NH^{II}), 158.3 (Fmoc–*C*O), 145.5, 142.7 (Fmoc$_{ipso}$), 128.9 (Fmoc$_o$), 128.4 (Fmoc$_m$), 126.4 (Fmoc$_o$), 121.0 (Fmoc$_m$), 102.1 (C-1^{II}), 99.5 (C-1^{I}), 79.2 (C-2^{I}), 78.0 (C-5^{II}), 75.5 (C-3^{II}), 75.2 (C-5^{I}), 72.0 (C-4^{I}), 71.6 (C-4^{II}), 69.6 (S-β), 69.1 (C-3^{I}), 68.2 (FmocCH_2), 63.4 (C-6^{I}), 62.6 (C-6^{II}), 57.3 (C-2^{II}, S-α), 48.2 (FmocCH), 23.5 (AcN–CH_3); HRMS obsd 693.2486 calcd $C_{32}H_{41}N_2O_{15}$ $(M+H)^+$ 693.2506.

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Supplementary data

Supplementary data for this article can be found in the online version. It contains experimental procedures for the Mosher esters, computational details and representative NMR spectra. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.05.133.

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