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Rapid assembly of branched mannose oligosaccharides through consecutive regioselective glycosylation: A convergent and efficient strategy

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Abstract

A convergent and efficient strategy for the synthesis of high-mannose oligosaccharides is described wherein regioselective glycosylations between trichloroacetimidate donors and partially protected acceptors are employed to reduce the number of protection–deprotection steps. Two representative branched mannose oligosaccharides, a mannose heptasaccharide (Man₇) and a mannose nonasaccharide (Man₉) were constructed via (4+3) and (5+4) glycosylations, respectively. These mannose-containing oligosaccharides were obtained in nine steps in ~25% overall yield and >98% purity on 60–70 mg scales to demonstrate the effectiveness of the strategy.

1. Introduction

High-mannose *N*-glycans appended to *N*-linked glycoproteins play important roles in many normal and aberrant biological processes.¹ For example, the high-mannose *N*-glycans displayed on the outer surfaces of many pathogenic microorganisms are recognized by macrophages and dendritic cells, leading to the triggering of immune responses.² In general, the biological properties and functions of *N*-glycans are modulated by post-translational modification, that is, by glycosylation and hydrolysis events that occur in the Golgi and lead to structurally diverse *N*-glycans *in vivo*.³ In many diseases including cancer, aberrant glycosylation patterns and/or levels of high-mannose *N*-glycan expression are often observed. For example, in the blood sera of breast cancer patients, concentrations of a nonamannoside (Man₉) glycan increase while the sera of normal individuals contain mostly complex- and hybrid-type *N*-glycans.⁴ In another example, mice implanted with head and neck tumors display high concentrations of Man₅–Man₇ *N*-glycans in their sera compared to the sera of healthy mice.⁵ Access to structurally diverse and chemically pure samples of

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Appendix A. Supplementary Data

NMR data for compounds 1–4, 8–9, 12–13, 15, 17 and 19–20 are provided in the supplementary data.

high-mannose *N*-glycans is critical for immunological studies and for the development of vaccines.

Several synthetic strategies have been reported to prepare high-mannose oligosaccharides,⁶ including tri- to octa-mannosides, but many are situation-specific. Generalized synthetic protocols are still needed. Chemical syntheses of building blocks, including donors and acceptors, often require elaborate design and preparation to allow regio- and stereoselective control of each *O*-glycosidic linkage formed during assembly. Since there is little theoretical guidance in the design of building blocks, this work is often highly empirical and challenging. One way to simplify these syntheses is to reduce the number of protection–deprotection steps by partially protecting the hydroxyl groups in the building blocks, especially in acceptors, and applying them in regioselective glycosylation. Successful application of lightly protected acceptors exploits intrinsic differences in the regioselectivities and/or relative reactivities of the free hydroxyl groups in the acceptor. Fortunately, significant advances in this understanding have been made over the past few decades.⁷

In this report, we describe a convergent and efficient chemical strategy for the rapid assembly of high-mannose oligosaccharides, illustrated with the syntheses of two representative oligomannoses, heptasaccharide **1** and nonasaccharide **2** (Scheme 1). The strategy takes advantage of regioselective glycosylation and the repetitive use of several building blocks with common protecting groups. For example, heptasaccharide **1** was assembled from tetrasaccharide donor **3** and partially protected trisaccharide acceptor **4** through regioselective glycosylation. Donor **3** was prepared from monosaccharide donor **5** and partially protected acceptor **4**. Acceptor **4** was constructed from disaccharide donor **6** and lightly protected monosaccharide acceptor **7**. In a similar fashion, nonasaccharide **2** was prepared by a straightforward route enabled by the common α Man1 \rightarrow 2 α Man motifs present on the 1 \rightarrow 3 and 1 \rightarrow 6 arms of donor **8**. This strategy streamlined the syntheses of **1** and **2** by significantly reducing the number of synthetic steps and improving overall yield. Over 50 branched high mannose oligosaccharides have been prepared in high purity and in 20–100 mg quantities using this efficient strategy.

2. Results and Discussion

The synthetic strategy started with the preparation of basic building blocks. Elementary mannosyl donors, including mannose monosaccharide donor **5**,⁸ and the α -1,2-linked di- and trisaccharide donors **6** and **11**,^{9,10} were synthesized using methods reported previously. The partially protected triol acceptor **7** was obtained by silylation of allyl α -D-mannopyranoside with *tert*-butyl(chloride)diphenylsilane (TBDPSCI).¹¹

Previous investigations of the regioselective mannosylation of a 2,3,4-triol mannoside¹² showed that the 3-OH exhibits much greater reactivity than 2-OH and 4-OH. Glycosylation of allyl 6-*O*-TBDPS- α -D-mannopyranoside (**7**) with Schmidt's trichloroacetimidate donors in dichloromethane occurred nearly exclusively at the 3-OH position and in good yield with either TMSOTf or BF₃·OEt₂ as the catalyst. Subsequent regioselective glycosylations were performed between acceptor **7** with donors **6** and **11** upon activation with TMSOTf at

–35 °C, affording compounds **12** and **13**, respectively, in good yields (Scheme 2). This strategy simplified the need for protective group manipulations, and avoided the use of other specific catalysts.¹³

The newly formed linkages in compounds **12** and **13** were confirmed from analyses of 1D ¹H and 2D ¹H-¹H-gCOSY spectra. For **12**, two cross-peaks observed at 3.01 ppm / 3.94 ppm and 2.33 ppm / 3.98 ppm in the 2D ¹H-¹H gCOSY spectrum (see Supplementary Data) indicated that ¹H signals associated with two free (non-glycosylated) hydroxyl hydrogens with chemical shifts at 3.01 and 2.33 ppm correlated with ¹H signals at 3.94 and 3.98 ppm, respectively. Inspection of the *J*-coupling patterns in the latter signals (see Supplementary Data) led to their assignments to H4 and H2, respectively, since the former appears as a pseudo-triplet (the H4 signal is split by large ³*J*_{H3,H4} and ³*J*_{H4,H5} values) and the latter appears as a broadened signal containing two small splittings (the H2 signal is split by small ³*J*_{H1,H2} and ³*J*_{H2,H3} values). These signal multiplicities differ from that expected for H3, which would appear as a doublet of doublets containing a small ³*J*_{H2,H3} and a large ³*J*_{H3,H4}. In the same manner, cross-peaks at 3.29 ppm / 3.93 ppm and 2.45 ppm / 3.99 ppm in the 2D ¹H-¹H gCOSY spectrum of **13** indicated that H2 and H4 correlate with the free hydroxyl hydrogens, thus confirming glycosylation at OH3. The anomeric configurations of the (1→3)-glycosidic linkages in **12** and **13** were confirmed using the chemical shift of H5, which is typically observed downfield (>3.8 ppm) in α-Man residues relative to that in β-Man residues (~3.4 ppm).¹⁴ Having confirmed the presence of α-(1→3) linkages, compounds **12** and **13** were desilylated with *tert*-butyl ammonium fluoride (TBAF) to give acceptors **4** and **9** in almost quantitative yields (Scheme 2).

Acceptor **4** was used directly in the following donor constructions. Donors **3** and **8** contain two branches at C3 and C6 of the activated α-Man residue. Donor **3** contains an α-(1→2)-linked Man disaccharide at C3 and an α-Man monosaccharide at C6, while donor **8** contains α-(1→2)-linked Man disaccharides at both sites. Although donors **3** and **8** could be prepared by regioselective glycosylation of acceptor **4** with either monosaccharide donor **5** or disaccharide donor **6**, respectively, two strategies were applied for their preparation as shown in Scheme 3. A regioselective glycosylation was performed between donor **5** and acceptor **4**, and the product **14** was acetylated to give tetrasaccharide **15** as the donor precursor. Formation of the 1→6 linkage was confirmed from the ¹³C{¹H} NMR spectrum of compound **15**, in which only three signals at ~62 ppm were observed, indicating that one of the four C6 carbons of **15** was glycosylated (glycosylation shifts the C6 signal downfield). Synthesis of donor **8** involved a one-step glycosylation of acceptor **10** with 2 equivalents of disaccharide donor **6**¹⁵ to give pentasaccharide **17** in acceptable yield. Compounds **15** and **17** were treated with palladium chloride (PdCl₂) to remove the allyl group, and the products were activated with trichloroacetonitrile to furnish trichloroacetimidate donors **3** and **8**, respectively.

With the required donors and acceptors in hand, the target oligosaccharides **1** and **2** were assembled (Scheme 4). Regioselective glycosylations at C6 were performed between donor **3** and acceptor **4**, and between donor **8** and acceptor **9**, with activation afforded by TMSOTf at –35 °C to give compounds **19** and **20**, respectively. The latter products were characterized

by NMR; confirmation of the newly introduced α Man-1,6- α Man linkage was confirmed by observing the downfield shift of the C6 signals upon glycosylation. Compounds **19** and **20** were then deacetylated with sodium methoxide in methanolic solution, deallylated with palladium chloride (PdCl₂), and purified by chromatography on a Bio-Gel P-2 column to give 60–70 mg of oligosaccharides **1** and **2** in >98% purity (Scheme 4).

3. Conclusion

A convergent and efficient chemical strategy has been developed to prepare tri-antennary mannose oligosaccharides in >20% overall yields. Regioselective glycosylation with partially protected acceptors was employed to reduce the number of protection–deprotection steps, thus improving the overall efficiency of the syntheses. The strategy significantly improves access to these important oligosaccharides on milligram–gram scales, which will promote their use in chemical, biochemical, structural, and biomedical studies.

4. Experimental Section

4.1. General Methods

All chemicals were purchased as anhydrous reagent grade and were used without further purification unless otherwise noted. All reactions were performed under anhydrous conditions. Reactions were monitored by thin-layer chromatography (TLC) on silica gel precoated aluminum plates. Zones were detected by heat/charring with a *p*-anisaldehyde–sulfuric acid visualization reagent.¹⁶ Flash column chromatography on silica gel (preparative scale) was performed on the Reveleris[®] X2 flash chromatography system. ¹H and ¹³C{¹H} NMR spectra were recorded at 22 °C on a Bruker Avance III HD 500-MHz or Varian DirectDrive 600-MHz spectrometer. Chemical shifts are reported in δ -units (ppm) relative to the ¹H signal of residual CHCl₃ at δ 7.24 ppm and the ¹³C signal at δ 77.23 ppm. Abbreviations for multiplicities and descriptors are: s = singlet; d = doublet; t = triplet; dd = doublet of doublets; dt = doublet of triplets; td = triplet of doublets; q = quartet; m = multiplet. Two-dimensional ¹H-¹H gCOSY and ¹H-¹³C gHSQC NMR spectra were recorded on the same instruments using Bruker or Varian software. Mass spectrometric analyses were performed on a Bruker microTOF-Q II quadrupole time-of-flight (QTOF) mass spectrometer with an ESI source.

4.2. General Experimental Procedures

4.2.1. Glycosylation—Donor and acceptor were dissolved in anhydrous CH₂Cl₂, and 4Å molecular sieves were added to the solution. The solution was cooled to –35 °C (dry ice/acetone bath) and was treated with TMSOTf under N₂. The reaction mixture was stirred for 2 h and then quenched with the addition of triethylamine. The mixture was filtered through Celite[®], the solution was concentrated *in vacuo*, and the residue was purified by flash chromatography on a silica gel column.

4.2.2. Desilylation—The compound was dissolved in anhydrous THF, and AcOH and TBAF were added to the solution. The solution was stirred at room temperature for 2 h,

concentrated *in vacuo*, and the residue was purified by flash chromatography on a silica gel column.

4.2.3. Acetylation—The compound was dissolved in anhydrous pyridine, and 4-(dimethylamino)pyridine (DMAP) and Ac₂O were added to the solution. The solution was stirred for 1 h at room temperature, and then concentrated under high vacuum. The residue was partitioned between EtOAc and water, and the organic layer was washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel column.

4.2.4. Deallylation—The compound was dissolved in anhydrous methanol, and PdCl₂ was added to the solution. The reaction mixture was stirred at room temperature for 7 h in the dark. The PdCl₂ was then removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purified by either flash chromatography on a silica gel column (compounds **16** and **18**), or by chromatography on a Bio-Gel P-2 column (compounds **1** and **2**).

4.2.5. Trichloroacetimidation—The compound was dissolved in anhydrous CH₂Cl₂, the solution was cooled to 0 °C, and trichloroacetonitrile and DBU were added to the solution. The reaction mixture was stirred for 3 h at room temperature and then concentrated *in vacuo*. The residue was purified by flash chromatography on a silica gel column.

4.2.6. Deacetylation—The compound was dissolved in anhydrous methanol and a small amount of NaOMe was added to the solution until the pH reached 9 (pH was determined using pH paper). The reaction solution was stirred at room temperature overnight, and then neutralized with batch addition of Dowex[®] HCR W2 ion-exchange resin in the H⁺ form (16–40 mesh). The resin was removed by filtration, and the filtrate was concentrated *in vacuo*.

4.3 Experimental Data

4.3.1. Allyl 2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 3)-6-O-(tert-butylidiphenylsilyl)- α -D-mannopyranoside **12**—Compound **12** was prepared using the general glycosylation method above with donor **6** (6.38 g, 8.17 mmol), acceptor **7** (5.61 g, 12.25 mmol), CH₂Cl₂ (300 mL), 4Å molecular sieves (7 g), and TMSOTf (300 μ L, 1.63 mmol). The product was obtained as a white amorphous foam (6.68 g, 6.21 mmol, 76%). $[\alpha]_D^{20} +53.2$ (c 0.47, MeOH); ¹H NMR (600 MHz, Chloroform-*d*) δ 7.66 (m, 4H), 7.42 – 7.35 (m, 6H), 5.81 (dddd, *J* = 16.9, 10.4, 6.3, 5.3 Hz, 1H), 5.37 (dd, *J* = 10.0, 3.4 Hz, 1H), 5.31 (m, 2H), 5.25 – 5.20 (m, 4H), 5.16 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.93 (d, *J* = 1.9 Hz, 1H), 4.79 (d, *J* = 1.8 Hz, 1H), 4.23 (dd, *J* = 12.2, 5.3 Hz, 1H), 4.17 – 4.05 (m, 7H), 3.98 – 3.84 (m, 6H), 3.62 (dt, *J* = 9.7, 5.0 Hz, 1H), 3.01 (s, 1H), 2.33 (s, 1H), 2.12, 2.08, 2.06, 2.04, 2.01, 1.99, 1.98 (7s, 7 \times 3H), 1.03 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 171.0 (\times 2), 170.6, 170.0, 169.9, 169.7 (\times 2), 135.8 (\times 2), 133.7, 133.1, 132.9, 130.1 (\times 2), 128.0 (\times 2), 118.1, 100.1, 99.0, 98.7, 79.9, 76.4, 71.6, 70.5, 70.3, 69.9, 69.2 (\times 2), 69.0, 68.6, 68.2, 66.9, 66.6, 65.2, 62.8, 62.7, 27.0, 21.1, 21.0, 20.9 (\times 3), 20.8, 19.3. HRESIMS: (*m/z*) calcd for C₅₁H₆₈O₂₃SiNa⁺ (M+Na)⁺ 1099.3823; found 1099.3828.

4.3.2. Allyl 2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 3)- α -D-mannopyranoside 4—Compound **4** was synthesized using the general desilylation method with **12** (6.68 g, 6.21 mmol), THF (100 mL), AcOH (1.07 mL, 18.63 mmol) and TBAF (12.42 mL, 12.42 mmol). The product was obtained as a white amorphous foam (5.10 g, 6.09 mmol, 98%). $[\alpha]_{\text{D}}^{20} +55.6$ (c 0.42, MeOH); $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 5.82 (dddd, $J=17.2, 10.4, 6.2, 5.3$ Hz, 1H), 5.37 (m, 1H), 5.35–5.32 (m, 2H), 5.28 (m, 1H), 5.24 (m, 1H), 5.22–5.19 (m, 2H), 5.16 (dq, $J=10.4, 1.3$ Hz, 1H), 4.92 (d, $J=1.9$ Hz, 1H), 4.81 (d, $J=1.6$ Hz, 1H), 4.21 (m, 2H), 4.15–4.08 (m, 9H), 3.95–3.90 (m, 3H), 3.88 (m, 2H), 3.77 (dd, $J=12.0, 2.6$ Hz, 1H), 3.54 (dt, $J=9.9, 2.6$ Hz, 1H), 2.11, 2.08, 2.06, 2.05, 2.01, 2.01, 1.97 (7s, 7 \times 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 171.7, 171.2, 171.1, 170.1, 170.0, 169.7, 169.6, 133.7, 118.0, 100.4, 99.3, 99.1, 80.3, 77.1, 72.5, 71.0, 70.8, 70.0, 69.4, 69.0, 68.6, 68.3, 66.6, 66.5, 65.8, 62.8 ($\times 2$), 61.3, 21.1 ($\times 3$), 20.9 ($\times 3$). HRESIMS: (m/z) calcd for $\text{C}_{35}\text{H}_{50}\text{O}_{23}\text{Na}^+$ ($\text{M}+\text{Na}$) $^+$ 861.2645; found 861.2650.

4.3.3. Allyl 2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl (1 \rightarrow 3)-6-O-(*tert*-butyldiphenylsilyl)- α -D-mannopyranoside 13—Compound **13** was prepared using the general glycosylation method with donor **11** (1.07 g, 1.00 mmol), acceptor **7** (690 mg, 1.51 mmol), 4 \AA molecular sieves (1.5 g), and TMSOTf (36 μL , 0.20 mmol). The product was obtained as a white amorphous foam (1.06 g, 0.78 mmol, 78%). $[\alpha]_{\text{D}}^{20} +37.1$ (c 0.44, MeOH); $^1\text{H NMR}$ (600 MHz, Chloroform-*d*) δ 7.67–7.65 (m, 4H), 7.40–7.34 (m, 6H), 5.83 (dddd, $J=16.9, 10.4, 6.3, 5.3$ Hz, 1H), 5.36 (dd, $J=10.0, 3.4$ Hz, 1H), 5.32–5.29 (m, 2H), 5.27–5.24 (m, 4H), 5.21–5.13 (m, 3H), 5.10 (d, $J=2.1$ Hz, 1H), 4.92 (d, $J=1.8$ Hz, 1H), 4.81 (d, $J=1.7$ Hz, 1H), 4.22 (d, $J=4.4$ Hz, 1H), 4.18–4.06 (m, 10H), 4.05 (t, $J=2.3$ Hz, 1H), 3.99 (t, $J=2.2$ Hz, 1H), 3.95–3.89 (m, 4H), 3.86 (dd, $J=10.8, 5.1$ Hz, 1H), 3.65 (dt, $J=9.1, 4.8$ Hz, 1H), 3.29 (s, 1H), 2.45 (s, 1H), 2.12, 2.09, 2.08, 2.05, 2.04, 2.03, 2.02, 2.01, 1.98, 1.94 (10s, 10 \times 3H), 1.03 (s, 9H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 171.2, 171.0 ($\times 2$), 170.3 ($\times 2$), 170.0, 169.9, 169.7 ($\times 2$), 169.6, 135.8 ($\times 2$), 133.7, 133.3, 133.1, 130.0 ($\times 2$), 127.9 ($\times 2$), 118.1, 99.9, 99.4, 99.0, 98.7, 80.0, 75.6, 72.1, 70.6, 70.0 ($\times 2$), 69.8, 69.4, 69.3, 68.6 ($\times 2$), 68.1, 67.3, 66.7, 66.5, 65.0, 62.8, 62.7, 62.5, 27.0, 21.1, 20.9 ($\times 5$), 20.8 ($\times 2$), 19.4. HRESIMS: (m/z) calcd for $\text{C}_{63}\text{H}_{84}\text{O}_{31}\text{SiNa}^+$ ($\text{M}+\text{Na}$) $^+$ 1387.4662; found 1387.4658.

4.3.4. Allyl 2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl (1 \rightarrow 3)- α -D-mannopyranoside 9—Compound **9** was synthesized using the general desilylation method with compound **13** (1.06 g, 0.78 mmol), THF (50 mL), AcOH (134 μL , 2.34 mmol) and TBAF (1.56 mL, 1.56 mmol). The product was obtained as a white amorphous foam (0.87 g, 0.77 mmol, 99%). $[\alpha]_{\text{D}}^{20} +46.4$ (c 0.50, MeOH); $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 5.82 (dddd, $J=17.3, 10.4, 6.2, 5.3$ Hz, 1H), 5.34–5.30 (m, 3H), 5.29–5.18 (m, 6H), 5.16 (dq, $J=10.4, 1.3$ Hz, 1H), 5.06 (d, $J=2.1$ Hz, 1H), 4.91 (d, $J=1.8$ Hz, 1H), 4.81 (d, $J=1.7$ Hz, 1H), 4.21–4.03 (m, 13H), 3.94 (m, 1H), 3.90–3.86 (m, 2H), 3.79 (m, 1H), 3.67 (s, 1H), 3.56 (dt, $J=9.8, 2.9$ Hz, 1H), 3.13 (s, 1H), 2.47 (s, 2H), 2.11, 2.09, 2.06, 2.04, 2.04, 2.04, 2.00, 2.00, 2.00, 1.96 (10s, 10 \times 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 171.4, 171.2,

171.0 (×2), 170.4, 170.0, 169.9, 169.7, 169.6 (×2), 133.7, 117.9, 100.1, 99.3, 99.1 (×2), 80.1, 76.9, 75.8, 72.6, 71.0, 70.4, 69.9, 69.8, 69.3 (×2), 69.2, 68.6, 68.3, 66.9, 66.6, 66.5, 66.0, 62.7, 62.6, 62.6, 61.6, 21.0 (×2), 20.9 (×4), 20.8 (×2). HRESIMS: (*m/z*) calcd for C₄₇H₆₆O₃₁Na⁺ (M+Na)⁺ 1149.3446; found 1149.3440.

4.3.5. Allyl 2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 6)-[2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 3)]-2,4-di-O-acetyl- α -D-mannopyranoside 15—Compound **14** was prepared according using the general glycosylation method with donor **5** (1.48 g, 3.00 mmol), acceptor **4** (2.51 g, 3.00 mmol), CH₂Cl₂ (100 mL), 4Å molecular sieves (2 g), and TMSOTf (108 μ L, 0.60 mmol). The afforded product **14** was acetylated with pyridine (100 mL), DMAP (catalytic amt.), and Ac₂O (1.1 mL, 12 mmol). Compound **15** was obtained as a white amorphous foam (2.22 g, 1.77 mmol, 59% over two steps). ¹H NMR (600 MHz, Chloroform-*d*) δ 5.83 (ddt, *J* = 16.6, 10.5, 5.9 Hz, 1H), 5.32 (dd, *J* = 10.0, 3.4 Hz, 1H), 5.29 – 5.17 (m, 9H), 5.12 (t, *J* = 10.0 Hz, 1H), 5.09 (d, *J* = 2.0 Hz, 1H), 5.06 (dd, *J* = 9.9, 3.1 Hz, 1H), 4.79 (d, *J* = 1.7 Hz, 1H), 4.76 (2d, *J* = 2.2 Hz, 2H), 4.19 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.16 – 4.01 (m, 9H), 3.99 – 3.93 (m, 2H), 3.84 (dd, *J* = 3.1, 2.0 Hz, 1H), 3.80 (ddd, *J* = 9.7, 6.5, 2.5 Hz, 1H), 3.70 (dd, *J* = 10.7, 6.6 Hz, 1H), 3.45 (dd, *J* = 10.7, 2.5 Hz, 1H), 2.13, 2.09, 2.09, 2.08, 2.06, 2.06, 2.04, 2.00, 1.99, 1.98 (×2), 1.94, 1.92 (13s, 13×3H). ¹³C NMR (151 MHz, CDCl₃) δ 170.9, 170.7, 170.5 (×2), 170.3, 170.1, 170.0, 169.9 (×2), 169.8 (×2), 169.5 (×2), 133.0, 118.9, 99.9, 99.8, 97.3, 96.2, 78.3, 74.8, 70.9, 69.7 (×3), 69.6, 69.5 (×2), 69.0, 68.7, 68.6, 68.6, 68.5, 66.8, 66.3, 66.1, 65.7, 62.7, 62.5, 62.2, 21.0 (×3), 20.9 (×3), 20.8 (×6), 20.7. HRESIMS: (*m/z*) calcd for C₅₃H₇₂O₃₄Na⁺ (M+Na)⁺ 1275.3744; found 1275.3740.

4.3.6. 2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 6)-[2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 3)]-2,4-di-O-acetyl- α -D-mannopyranosyl trichloroacetimidate 3—Compound **16** was prepared using the general deallylation method with compound **15** (2.22 g, 1.77 mmol), methanol (100 mL), and PdCl₂ (20 mg). The afforded product (1.57 g, 1.29 mmol, 73%) was activated using the general acetimidation method with CH₂Cl₂ (50 mL), trichloroacetonitrile (0.52 mL, 5.16 mmol) and DBU (29 μ L, 0.19 mmol). Compound **3** was afforded as a white amorphous foam (1.64 g, 1.21 mmol, 94%). ¹H NMR (600 MHz, Chloroform-*d*) δ 8.84 (s, 1H), 6.17 (d, *J* = 1.9 Hz, 1H), 5.36 (dd, *J* = 3.5, 1.9 Hz, 1H), 5.32 – 5.28 (m, 2H), 5.27 – 5.20 (m, 3H), 5.18 (m, 2H), 5.14 (m, 2H), 5.07 (dd, *J* = 9.9, 3.0 Hz, 1H), 4.78 (d, *J* = 1.9 Hz, 1H), 4.73 (d, *J* = 1.7 Hz, 1H), 4.22 – 4.19 (m, 2H), 4.14 (dd, *J* = 12.4, 3.7 Hz, 1H), 4.10 (m, 3H), 4.05 – 4.02 (m, 2H), 4.01 – 3.97 (m, 2H), 3.94 (m, 1H), 3.86 (t, *J* = 2.5 Hz, 1H), 3.70 (dd, *J* = 11.0, 6.1 Hz, 1H), 3.52 (dd, *J* = 11.0, 2.5 Hz, 1H), 2.18, 2.08, 2.07, 2.07, 2.06, 2.05, 2.03, 2.00, 1.98, 1.97, 1.97, 1.93, 1.90 (13s, 13×3H). ¹³C NMR (151 MHz, CDCl₃) δ 170.9, 170.7, 170.4, 170.3, 170.2, 170.1, 169.9, 169.8 (×3), 169.7, 169.5 (×2), 159.5, 99.7, 97.4, 94.1, 90.6, 78.1, 77.0, 73.8, 71.9, 69.8, 69.7, 69.6, 69.5, 69.4, 69.3, 69.0, 68.6, 68.4, 68.1, 66.4, 66.3, 66.0, 65.5, 62.6, 62.3, 61.9, 60.5, 21.1, 21.0 (×3), 20.9, 20.8 (×4), 20.74 (×3). HRESIMS: (*m/z*) calcd for C₅₂H₆₈O₃₄NCl₃Na⁺ (M+Na)⁺ 1378.2590; found 1378.2594.

4.3.7. Allyl 2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 6)-[2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-

(1→2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1→3)]-2,4-di-O-acetyl- α -D-mannopyranoside 17—Compound **17** was synthesized using the general glycosylation method with donor **6** (3.2 g, 4.10 mmol), acceptor **10** (500 mg, 1.64 mmol), 4Å molecular sieves (4.0 g), CH₂Cl₂ (50 mL), and TMSOTf (148 μ L, 0.82 mmol). The product was afforded as a white amorphous foam (1.64 g, 1.06 mmol, 65%). ¹H NMR (600 MHz, Chloroform-*d*) δ 5.83 (dddd, *J* = 17.3, 10.4, 6.3, 5.4 Hz, 1H), 5.35 (dd, *J* = 10.0, 3.4 Hz, 1H), 5.32 (dd, *J* = 10.0, 3.4 Hz, 1H), 5.29 (m, 1H), 5.27 – 5.23 (m, 3H), 5.22 – 5.18 (m, 6H), 5.12 (t, *J* = 10.0 Hz, 1H), 5.09 (d, *J* = 2.0 Hz, 1H), 5.06 (dd, *J* = 10.0, 3.0 Hz, 1H), 4.91 (d, *J* = 1.9 Hz, 1H), 4.85 (d, *J* = 1.8 Hz, 1H), 4.78 (d, *J* = 1.7 Hz, 1H), 4.77 (d, *J* = 1.9 Hz, 1H), 4.18 – 4.03 (m, 12H), 4.00 – 3.93 (m, 4H), 3.84 (dd, *J* = 3.1, 2.0 Hz, 1H), 3.81 (ddd, *J* = 10.6, 6.5, 2.5 Hz, 1H), 3.72 (dd, *J* = 10.5, 6.6 Hz, 1H), 3.45 (dd, *J* = 10.5, 2.6 Hz, 1H), 2.14, 2.10, 2.10, 2.09, 2.09, 2.06, 2.05, 2.03, 2.01, 2.01, 1.99, 1.99, 1.99, 1.97, 1.96, 1.94 (16s, 16 \times 3H). HRESIMS: (*m/z*) calcd for C₆₅H₈₈O₄₂Na⁺ (M+Na)⁺ 1563.4632; found 1563.4630.

4.3.8. 2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1→2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1→6)-[2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1→2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1→3)]-2,4-di-O-acetyl- α -D-mannopyranosyl trichloroacetimidate 8—Compound **18** was synthesized using the general deallylation method with compound **17** (1.64 g, 1.06 mmol), methanol (50 mL), and PdCl₂ (20 mg). The afforded product (1.30 g, 0.87 mmol, 82%) was activated to the trichloroacetimidate using the general acetimidation method with trichloroacetonitrile (0.35 mL, 3.48 mmol), DBU (19 μ L, 0.13 mmol) and CH₂Cl₂ (50 mL) to afford product **8** (1.32 g, 0.80 mmol, 92%) as a white amorphous foam. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.87 (s, 1H), 6.21 (d, *J* = 1.9 Hz, 1H), 5.41 (dd, *J* = 3.6, 2.0 Hz, 1H), 5.39 – 5.31 (m, 4H), 5.29 – 5.25 (m, 2H), 5.23 (m, 3H), 5.18 (d, *J* = 2.1 Hz, 1H), 5.15 (dd, *J* = 10.0, 3.2 Hz, 1H), 5.12 (dd, *J* = 9.9, 3.1 Hz, 1H), 4.91 (d, *J* = 1.9 Hz, 1H), 4.86 (d, *J* = 1.9 Hz, 1H), 4.82 (d, *J* = 1.9 Hz, 1H), 4.24 (dd, *J* = 9.6, 3.5 Hz, 1H), 4.21 – 4.17 (m, 3H), 4.14 – 4.09 (m, 6H), 4.03 – 3.96 (m, 5H), 3.90 (dd, *J* = 3.0, 2.1 Hz, 1H), 3.75 (dd, *J* = 10.9, 5.9 Hz, 1H), 3.56 (dd, *J* = 10.9, 2.6 Hz, 1H), 2.23, 2.13, 2.13, 2.12, 2.11, 2.10, 2.09, 2.05, 2.05, 2.04, 2.02, 2.02 (\times 2), 2.01, 1.98, 1.98 (16s, 16 \times 3H). HRESIMS: (*m/z*) calcd for C₆₄H₈₄O₄₂NCl₃Na⁺ (M+Na)⁺ 1666.3456; found 1666.3453.

4.3.9. Allyl 2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1→6)-[2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1→2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1→3)]-2,4-di-O-acetyl- α -D-mannopyranosyl-(1→6)-[2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1→2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1→3)]- α -D-mannopyranoside 19—Compound **19** was synthesized using the general glycosylation method with donor **3** (110 mg, 0.08 mmol), acceptor **4** (90 mg, 0.11 mmol), CH₂Cl₂ (50 mL), 4Å molecular sieves (200 mg) and TMSOTf (4.3 μ L, 0.024 mmol). The product was obtained as a white amorphous foam (114 mg, 0.056 mmol, 69%). ¹H NMR (600 MHz, Chloroform-*d*) δ 5.83 (ddt, *J* = 16.5, 10.7, 5.8 Hz, 1H), 5.36 – 5.15 (m, 16H), 5.10 (m, 2H), 5.07 (dd, *J* = 9.8, 3.0 Hz, 1H), 4.89 (d, *J* = 1.9 Hz, 1H), 4.88 (d, *J* = 1.7 Hz, 1H), 4.79 (d, *J* = 1.8 Hz, 1H), 4.78 (d, *J* = 1.9 Hz, 1H), 4.78 (d, *J* = 2.0 Hz, 1H), 4.24 (td, *J* = 5.0, 2.6 Hz, 1H), 4.19 – 4.01 (m, 17H), 3.96 – 3.91 (m, 4H), 3.86 – 3.80 (m, 3H), 3.73 – 3.67 (m, 3H), 3.46 (dd, *J* = 10.9, 2.2 Hz, 1H), 3.17 (d, *J* = 4.8 Hz, 1H), 2.99 (d, *J* = 6.6 Hz, 1H), 2.14 (s, 3H),

2.10 (s, 6H), 2.09 (s, 9H), 2.08 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.99 (s, 9H), 1.98 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.94 (s, 3H). ¹³C NMR (151 MHz, CDCl₃) δ 171.3, 171.0 (×2), 170.9 (×2), 170.8, 170.5 (×2), 170.4 (×2), 170.1, 170.0 (×2), 169.9 (×3), 169.6 (×2), 169.5 (×2), 133.7, 118.1, 100.8, 99.7, 99.6, 99.3, 99.2, 97.0 (×2), 82.0, 78.0, 77.0, 74.5, 71.6, 71.0, 70.6, 70.4, 69.9, 69.8, 69.7, 69.6 (×2), 69.5, 69.3 (×2), 69.1, 68.8 (×2), 68.6, 68.5 (×2), 68.4, 66.8, 66.7, 66.5, 66.4, 66.3, 66.1, 65.8, 65.7, 63.0, 62.7, 62.6, 62.5, 61.9, 21.2 – 20.7.

4.3.10. Allyl 2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 6) [2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 3)]-2,4-di-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 6)-[2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 2)-3,4,6-tri-O-acetyl- α -D-mannopyranosyl-(1 \rightarrow 3)]- α -D-mannopyranoside **20**—Compound **20** was synthesized using the general glycosylation method with donor **8** (150 mg, 0.091 mmol), acceptor **9** (120 mg, 0.11 mmol), CH₂Cl₂ (50 mL), 4Å molecular sieves (200 mg), and TMSOTf (5.0 μ L, 0.027). The product was afforded as a white amorphous foam (144 mg, 0.055 mmol, 61%). ¹H NMR (600 MHz, CD₃OD) δ 5.96 (m, 1H), 5.43 – 5.16 (m, 25H), 5.13 (d, *J* = 1.9 Hz, 1H), 5.10 (d, *J* = 1.9 Hz, 1H), 5.02 (d, *J* = 1.8 Hz, 1H), 4.99 (d, *J* = 1.8 Hz, 1H), 4.91 (d, *J* = 1.6 Hz, 1H), 4.81 (d, *J* = 1.7 Hz, 1H), 4.34 (dd, *J* = 3.1, 1.8 Hz, 1H), 4.31 – 4.13 (m, 22H), 4.07 – 4.01 (m, 5H), 3.99 (ddd, *J* = 6.4, 3.1, 1.9 Hz, 2H), 3.91 (d, *J* = 9.6 Hz, 1H), 3.88 (dd, *J* = 9.6, 3.1 Hz, 1H), 3.81 (dd, *J* = 11.1, 5.4 Hz, 1H), 3.73 (m, 1H), 3.70 (m, 1H), 3.65 (m, 1H), 2.19 (s, 3H), 2.15 (s, 3H), 2.15 (s, 3H), 2.15 (s, 3H), 2.14 (s, 3H), 2.14 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 2.08 (2s, 6H), 2.07 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.05 (s, 3H), 2.05 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 6H), 1.99 (s, 3H), 1.99 (s, 3H), 1.98 (s, 3H). ¹³C NMR (151 MHz, CD₃OD) δ 173.0, 172.8, 172.7, 172.6 (×2), 172.5, 172.3 (×2), 172.2, 171.9, 171.8 (×3), 171.7, 171.6, 171.5 (×6), 171.4 (×2), 171.3 (×2), 171.2, 135.3, 118.1, 102.0, 101.1, 100.9 (×2), 100.6 (×2), 100.5, 99.2, 98.7, 81.1, 79.8, 78.8, 78.6, 77.7, 75.2, 73.2, 72.1, 72.0, 71.6, 71.0, 70.9, 70.8, 70.7, 70.6, 70.5, 70.2, 70.1 (×2), 69.9, 69.2, 67.7, 67.5 (×2), 67.4, 67.3 (×2), 67.2, 66.8, 64.0, 63.7, 63.4, 63.3, 63.2, 63.0 (×2), 21.6 – 20.5.

4.3.11. α -D-Mannopyranosyl-(1 \rightarrow 6)-[α -D-mannopyranosyl-(1 \rightarrow 2)- α -D-mannopyranosyl-(1 \rightarrow 3)]- α -D-mannopyranosyl-(1 \rightarrow 6)-[α -D-mannopyranosyl-(1 \rightarrow 2)- α -D-mannopyranosyl-(1 \rightarrow 3)]- α / β -D-mannopyranose **1**—Compound **1** was obtained using the global deprotection and general deacetylation methods with compound **19** (114 mg, 0.056 mmol), methanol (20 mL) and a small amount of NaOMe, followed by use of the general deallylation method with PdCl₂ (10 mg). The product was obtained as a white solid (60 mg, 0.052 mmol, 92%) after purification by chromatography on a Bio-Gel P2 column (2.7 cm \times 100 cm). ¹H NMR (600 MHz, D₂O) δ 5.42 – 5.41 (d, *J* = 1.8; d, *J* = 1.7 Hz, 1H), 5.37 (d, *J* = 1.7 Hz, 1H), 5.14 (d, *J* = 1.8 Hz, 0.64H (α -H)), 5.06 (m, 1H), 5.05 (d, *J* = 1.8 Hz, 1H), 4.92 (d, *J* = 1.7 Hz, 1H), 4.90 (d, *J* = 1.7 Hz, 0.26H (β -H)), 4.87 – 4.86 (d, *J* = 1.8 Hz; d, *J* = 1.8 Hz, 1H), 4.17 – 3.54 (m, 42H). ¹³C NMR (151 MHz, D₂O) δ 102.2 (×2), 100.7, 100.6, 100.5, 99.3, 99.2, 94.1, 78.8, 78.6 (×2), 78.4, 78.3, 73.2 (×2), 73.1 (×2), 72.6, 70.7, 70.6, 70.5, 70.2 (×2), 70.0, 69.9 (×2), 69.4, 66.9, 66.8, 66.7, 66.6 (×2), 65.7, 65.6, 65.2,

61.0, 60.8. HRESIMS: (*m/z*) calcd for C₄₂H₇₂O₃₆Na⁺ (M+Na)⁺ 1175.2825; found 1175.2829.

4.3.12. α-D-Mannopyranosyl-(1→2)-α-D-mannopyranosyl-(1→6)-[α-D-mannopyranosyl-(1→2)-α-D-mannopyranosyl-(1→3)]-α-D-mannopyranosyl-(1→6)-[α-D-mannopyranosyl-(1→2)-α-D-mannopyranosyl-(1→2)-α-D-mannopyranosyl-(1→3)]-α/β-D-mannopyranose 2—Compound **2** was obtained using the global deprotection and general deacetylation methods with compound **20** (144 mg, 0.055 mmol), methanol (20 mL), and a small amount of NaOMe, followed by use of the general deallylation method with PdCl₂ (10 mg). The product was obtained as a white amorphous solid (74 mg, 0.05 mmol, 90%) after purification by chromatography on a Bio-Gel P2 column (2.7 × 100 cm). ¹H NMR (600 MHz, D₂O) δ 5.41 (d, *J* = 1.9 Hz, 1H), 5.36 (d, *J* = 1.7 Hz, 1H), 5.31 (d, *J* = 1.8 Hz, 1H), 5.15 (d, *J* = 1.8 Hz, 1H), 5.14 (d, *J* = 1.8 Hz, 0.67H (α-H)), 5.05 (m, 3H), 4.90 (d, *J* = 1.9 Hz, 0.33H (β-H)), 4.87 – 4.86 (d, *J* = 1.9 Hz; d, *J* = 1.9 Hz, 1H), 4.15 – 3.54 (m, 54H). ¹³C NMR (151 MHz, D₂O) δ 102.2, 102.1, 102.0, 100.6 (×2), 100.5, 99.3, 97.8, 94.0, 93.6, 78.8, 78.6, 78.5 (×2), 78.4, 78.3, 73.1 (×3), 73.0 (×2), 72.5, 71.0, 70.5, 70.1 (×2), 69.9 (×2), 69.8, 69.4, 66.8, 66.7 (×2), 66.6 (×2), 65.5 (×2), 65.4, 65.3, 65.2 (×2), 61.0, 60.9 (×2), 60.8 (×2). HRESIMS: (*m/z*) calcd for C₅₄H₉₂O₄₆Na⁺ (M+Na)⁺ 1499.4219; found 1499.4216.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

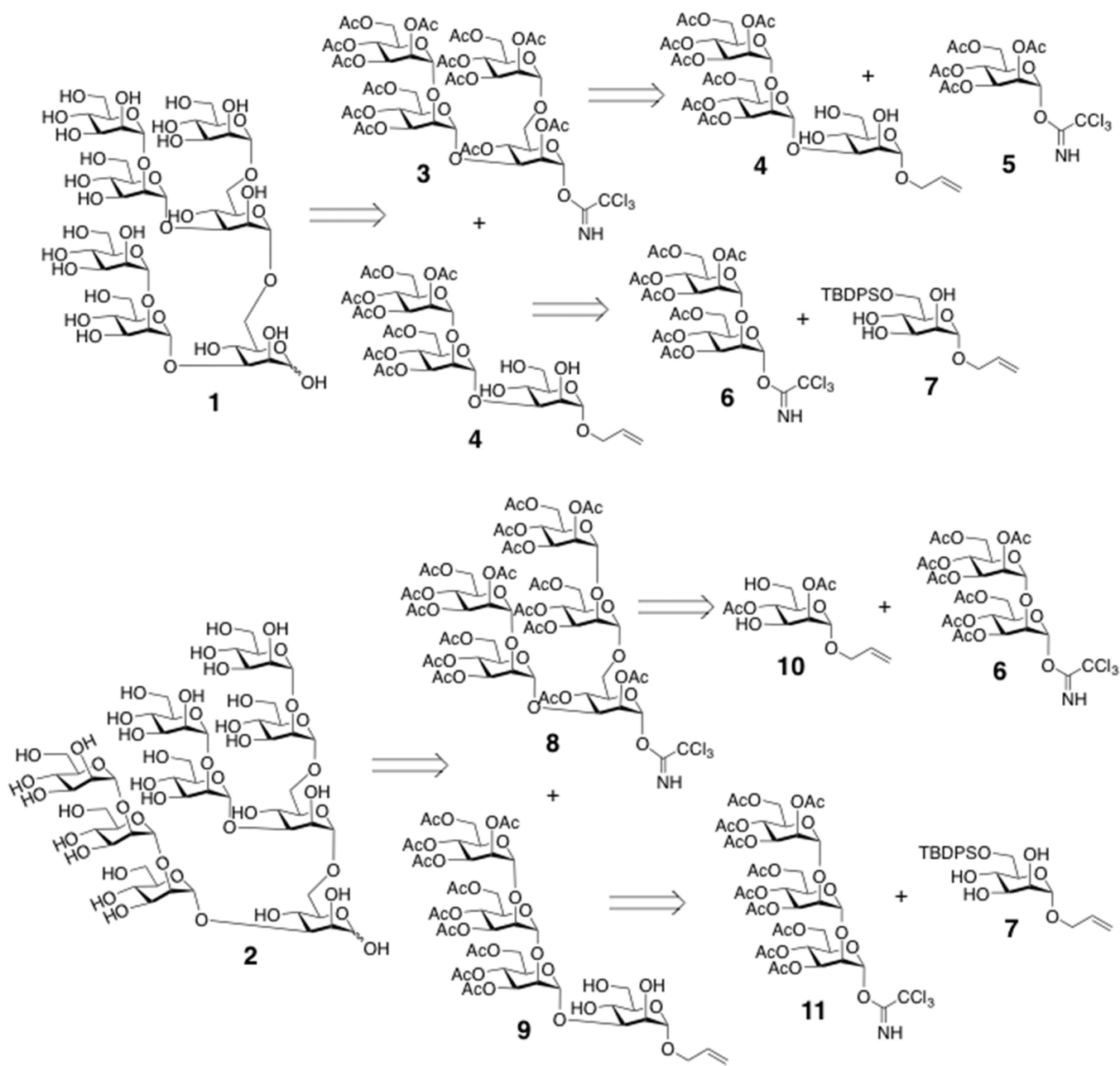
Acknowledgments

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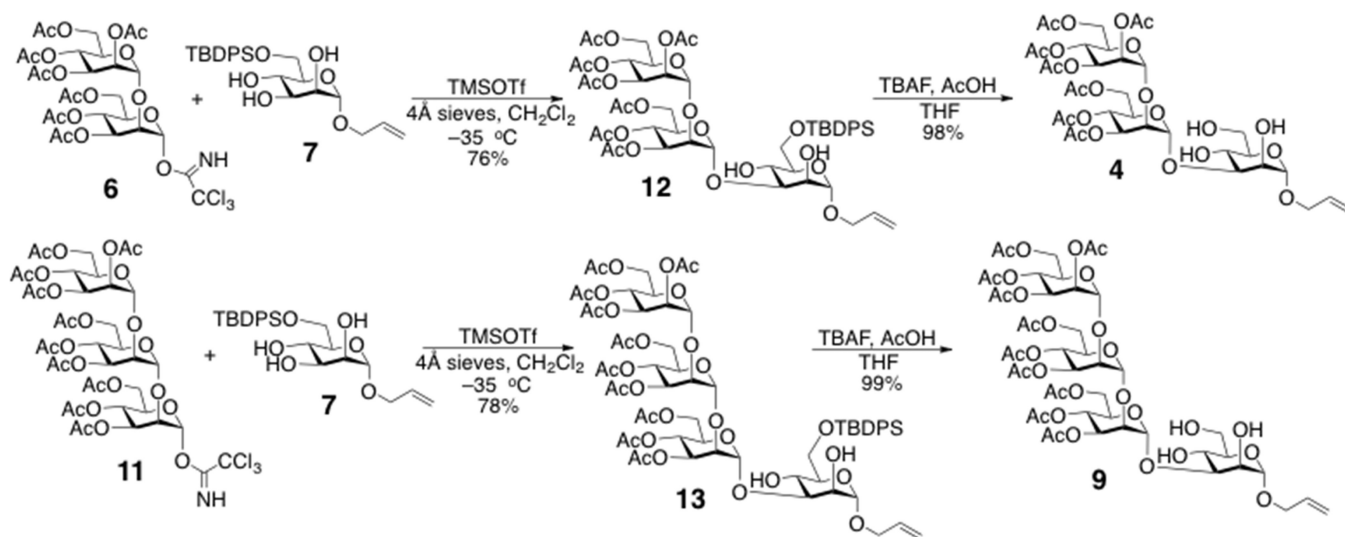
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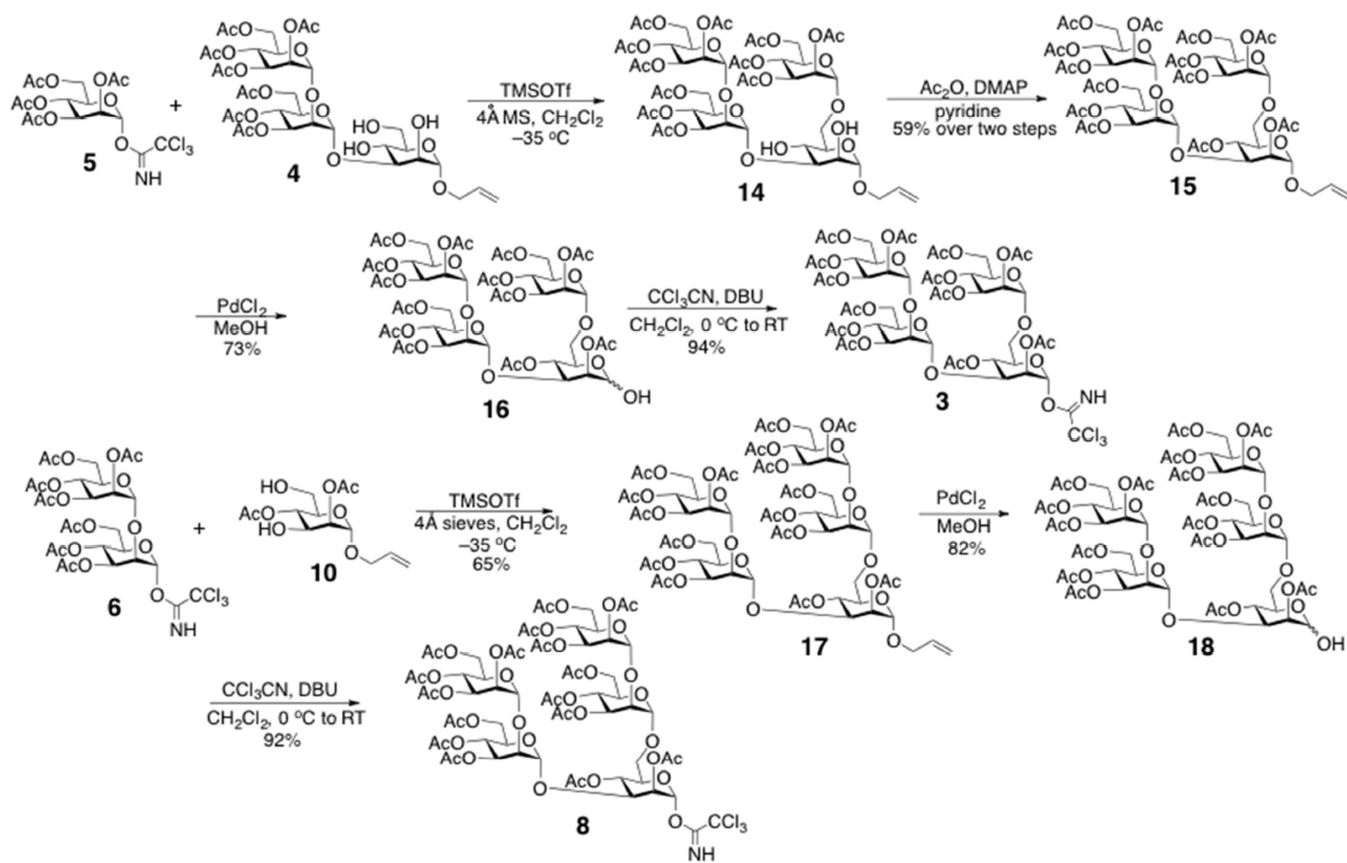
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**Scheme 1.**

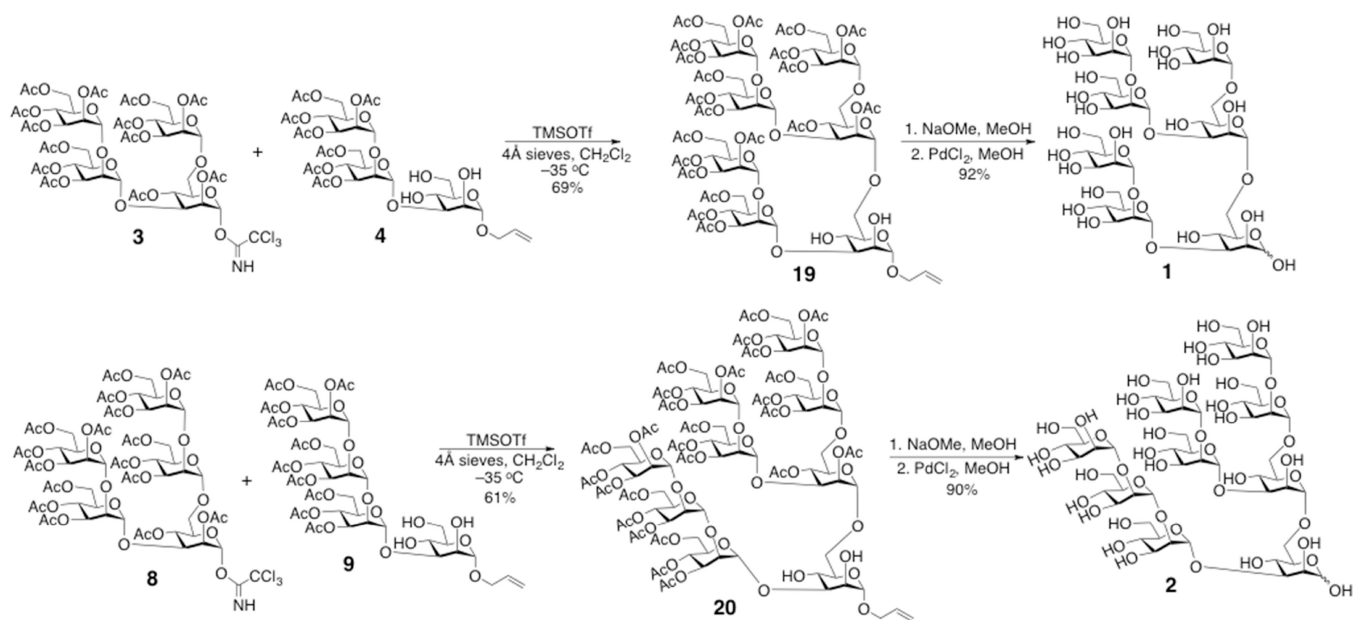
Structures of heptasaccharide **1** and nonasaccharide **2**, and their retrosynthetic analyses.



Scheme 2.
Regioselective syntheses of acceptors **4** and **9**.



Scheme 3.
Syntheses of trichloroacetimidate donors **3** and **8**.



Scheme 4.
Assembly of mannose oligosaccharides **1** and **2**.