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Synthesis of Branched Man5 Oligosaccharides and an Unusual Stereochemical Observation

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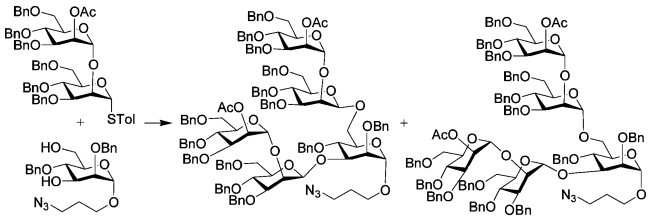

Branched mannopentaoses were synthesized through two routes. While assembly from the nonreducing end to the reducing end was more convergent with fewer intermediate steps, two diastereomers were obtained. On the other hand, synthesis from the reducing end to the nonreducing end yielded the mannopentaose with the desired stereochemistry as a single isomer. Our results suggest that it is still challenging to reliably predict stereochemical outcome of a glycosylation reaction. It is necessary to thoroughly characterize anomeric configurations of newly formed glycosidic linkages in complex oligosaccharide synthesis.

HIV is one of the most devastating modern diseases. The availability of an effective anti-HIV vaccine may be a good approach to prevent this worldwide epidemic.[1−4] One of the promising targets for immunogen design is the carbohydrate moieties on HIV-1 envelop protein gp120,[5−9] as validated by a potent neutralizing human monoclonal antibody 2G12.[10−13]

The epitope structures of 2G12 have recently being characterized to be a series of branched oligomannose residues, as represented by mannopentaose (Man5) **1**.[11−13] Oligomannoses are also primary targets for cyanovirin-N (CVN),[14−16] an example of HIV envelop binding lectins.[17] Besides their relationship to HIV, branched oligomannoses are integral structural components of asparagine-linked glycan (N-glycan), one of the major types of postsynthetic protein modifications.[18] N-Glycans are involved in many fundamental biological processes such as cell differentiation, viral infection, nascent protein processing, and tumor migration.[18−23] Therefore, efficient syntheses of branched oligomannoses can provide much needed materials to facilitate their biological studies.

There are two general approaches to assemble branched oligomannoses such as Man5 **1**. With the first approach, synthesis is carried out from the nonreducing end to the reducing end (route a in Figure 1).[9,23−28] α-1,2-Linked dimannoside **4** will be synthesized first with the α linkage typically controlled by a participating neighboring group. The dimannoside will then be used in glycosylation of a diol acceptor **5** to produce pentasaccharide **8**. With a mannosyl moiety already installed on the axially oriented O-2 of mannoside **4**, one cannot rely on neighboring group participation to control stereochemistries of the two newly formed linkages in **8**. The α linkages should be favored due to the anomeric effect as well as steric hindrance posed by the mannoside moiety on the axial O-2. As an alternative, Man5 can be assembled from the reducing end to the nonreducing end (route b in Figure 1).[8,29−34] For this approach, a selectively removable protective (PG) group such as acetate must be installed on O-2 of the mannosyl donor **2**. Upon formation of branched trisaccharide **6**, the protective group will be removed to generate a diol trisaccharide acceptor **7**. Repeating the double glycosylation with mannosyl donor **2** will lead to pentasaccharide **8**. Stereochemical outcome of the glycosylations can be controlled by neighboring group participa-

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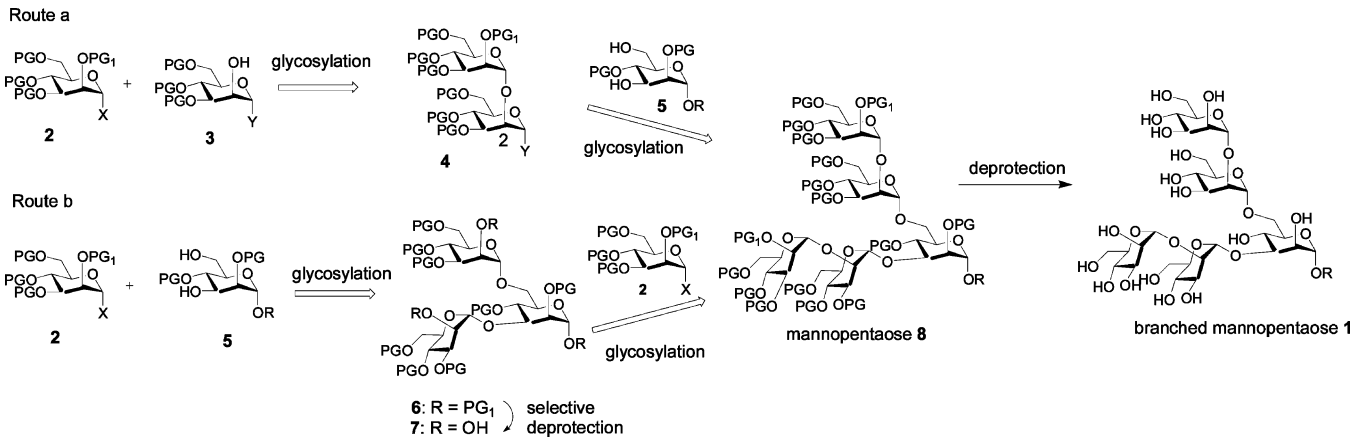
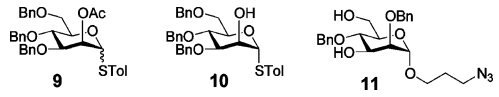


FIGURE 1. Two general approaches for the synthesis of branched mannopentaoses.

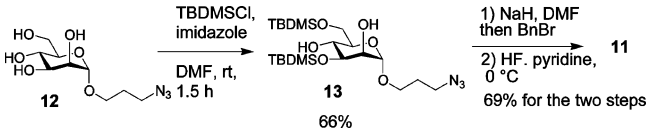
tion through this route. Although both of these approaches have been applied to the assembly of branched oligomannosides, except for a few examples,[28−31] stereochemical proofs of the newly formed glycosidic linkages are often not presented.[8,9,23−27,32−34]

The majority of glycosylation reactions were performed by adding a promoter to a mixture of glycosyl donor and acceptor.[35] Alternatively, a glycosyl donor can be preactivated in the absence of an acceptor.[36−42] This can often lead to unique stereochemical outcomes[36,41] and chemoselectivities.[37−40] Recently, we adapted the preactivation scheme into a chemoselective glycosylation method, where a thioglycosyl donor is preactivated in the absence of the acceptor.[43−46] Upon adding a thioglycosyl acceptor, nucleophilic addition of the acceptor to the activated donor yields a disaccharide product containing a thioaryl aglycon, which can be directly activated for the next round of glycosylation. Because donor activation and addition of acceptor are performed in two distinct steps, the anomeric reactivity of the donor does not need to be higher than that of the acceptor[37,38,43−47] as required by the traditional reactivity-based armed−disarmed chemoselective glycosylation.[48] We envision that we can apply our preactivation-based method to convergently assemble Man5 using building blocks **9**,[43] **10**,[43] and **11**.



Synthesis of the diol acceptor **11** started from the known azidopropyl α-mannoside **12**[49,50] (Scheme 1). Selective protection of the 3 and 6 hydroxyl groups led to disilyl ether **13** in 66% yield.[11] Benzylation of **13** followed by removal of the *tert*-butyldimethylsilyl (TBDMS) ethers gave acceptor **11**. The presence of free 3 and 6-OH in **11** was ascertained by NMR analysis of its acetylation product.

SCHEME 1. Synthesis of Diol Acceptor 11



Preactivation of thiomannosyl donor **9** by promoter *p*-TolSOTf,[41,43,51] formed in situ through reaction of *p*-TolSCl and AgOTf, was followed by addition of acceptor **10** and a sterically bulky base 2,4,6-tri-*tert*-butylpyrimidine (TTBP),[52] leading to disaccharide **14** in 63% yield (Scheme 2). The structure of **14** was confirmed by one-bond coupling constants between the anomeric carbon and hydrogen atoms ($^1J_{CH}$ = 172.5 and 171.5 Hz).[53,54] In addition, the presence of carbonyl groups in **14** was determined by ^{13}C NMR (δ = 170.4 ppm). The anomeric reactivity of donor **9** is lower than that of acceptor **10** due to the presence of acetate on O-2 of **9**. With the traditional armed−disarmed chemoselective glycosylation approach,[48] direct glycosylation of acceptor **10** by donor **9** was not possible.[9,11] Instead, the thioglycosyl donor had to be hydrolyzed into a hemiacetal followed by conversion into trichloroacetimidate donor.[11] Selective activation of the imidate donor over the thioglycosyl acceptor then gave thioglycosyl disaccharide. The usage of the preactivation procedure enables us to bypass the

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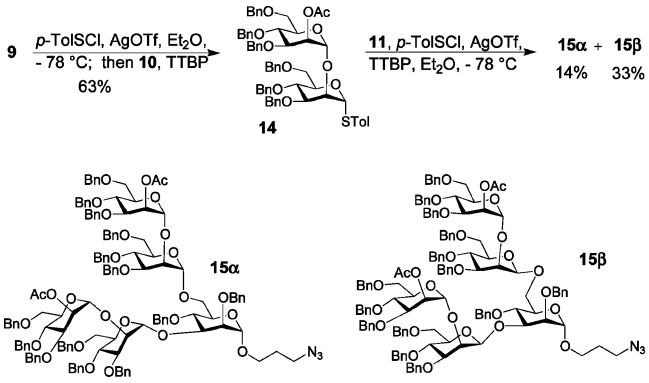
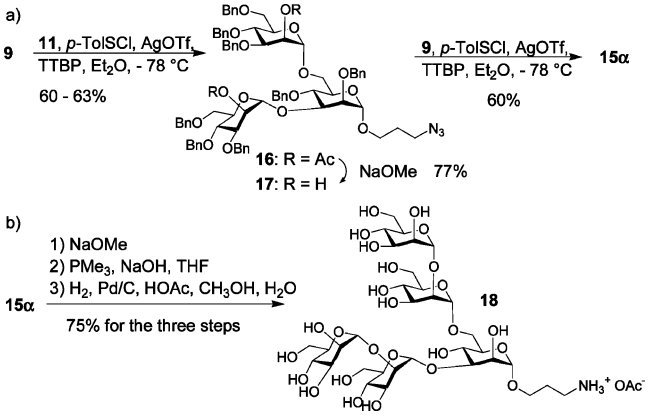
SCHEME 2. Synthesis of Man5 from the Nonreducing End to the Reducing End



SCHEME 3. Synthesis of Man5 from the Reducing End to the Nonreducing End



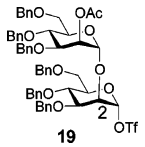
need for aglycon transformation, thus simplifying synthetic designs and improving overall synthetic efficiencies.

With disaccharide **14** prepared, double glycosylation of diol acceptor **11** by **14** was performed with the *p*-TolSCl/AgOTf promoter system (Scheme 2). Two compounds were formed in a ratio of 3:7 with slight polarity difference shown by TLC. After careful silica gel chromatography separation, to our surprise, the two products were found to have identical molecular weights corresponding to pentamannoside, indicating that they are diastereomers. The less polar minor component **15**α was obtained in 14% yield with $^1J_{CH}$ between anomeric carbons and hydrogens determined to be 169.9, 170.7, 170.9, 171.6, and 171.6 Hz, confirming that all five glycosidic linkages are α.[53,54] The more polar major products **15**β (33%) have $^1J_{CH}$ between anomeric carbons and hydrogens of 162.4, 162.9, 172.8, 173.6, and 173.6 Hz, suggesting that both of the newly formed glycosidic linkages are β! Glycosylation of acceptor **11** by **14** using *N*-iodosuccinimide and triflic acid as the promoter[11] failed to yield any pentamannosides in our hands. Instead, multiple decomposition products were observed presumably due to acid sensitivity of the oligosaccharide products.

In order to confirm our structure assignment, we investigated the alternative route for Man5 construction (Scheme 3a). Double glycosylation of diol **11** by donor **9** provided trimannan **16** in 60−63% yield. ^{13}C NMR of **16** has two resonances at 170.4 and 170.6 ppm, and $^1J_{CH}$ values between anomeric protons and carbons are 169.5, 172.1, and 172.1 Hz, proving it is not an orthoester and both new glycosidic linkages are α. Removal of the acetates with NaOMe produced trisaccharide diol **17** in 77% yield. Double glycosylation of diol **17** by donor **9** led to pentamannoside **15**α in 60% yield, which was found to have identical polarity, NMR, and molecular weight as **15**α synthesized from the nonreducing end to the reducing end (Scheme 2). No **15**β was obtained through this route, demonstrating that anomeric configurations of **15**α are stable under the reaction conditions.

Deprotection of pentamannoside **15**α was quite straightforward (Scheme 3b). Removal of the two acetates by sodium methoxide followed by Staudinger reduction of the azido moiety and catalytic hydrogenation[46] produced fully deprotected Man5 **18** in 75% overall yield for the three steps. The aminopropyl moiety at the reducing end can be utilized for future bioconjugation and the development of anti-HIV vaccine studies.

The fact that the major product synthesized from the nonreducing end to the reducing end direction is **15**β is surprising considering that (1) reaction is carried out in diethyl ether, an ethereal solvent well-known to favor the generation of thermodynamically more stable, axial glycoside product,[55−57] and (2) the anomeric effect and the steric hindrance posed by the bulky mannoside moiety on the axial O-2 of disaccharide **14** should disfavor the equatorial glycoside. Crich and coworkers have developed a powerful methodology for β-mannoside formation using 4,6-benzylidene-protected mannosyl donors.[41,47] α-Mannosyl triflate was identified as the resting state of the reactive intermediate,[58] with S_N2-like displacement of the anomeric triflate through an exploded transition state leading to the β product.[59] Benzylidene moiety was found to be crucial to conformationally lock the pyranoside ring into chair conformation, disfavoring oxacarbenium ion formation, while electron-withdrawing protective groups on O-2 were shown to have a similar effect.[60] The generation of Man5 **15**β in our synthesis may be rationalized by the formation of α-mannosyl triflate intermediate **19** upon activation of disaccharide **14**. With the presence of the carbohydrate moiety on O-2, which can be viewed as an electron-withdrawing[61] nonparticipating group, the α-mannosyl triflate intermediate **19** may be stabilized. The O-2 mannosyl unit on **19** can rotate around the O-2 and C-2 bond, with the large pyranoside ring pointing away from the anomeric position. This can reduce the steric hindrance of the β face posed by the pyranoside ring, allowing formation of the β linkage. The formation of α linkage may be disfavored due to the mismatch[62] of **19** with the acceptor at the transition state.[63]



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Our results suggest that factors controlling stereochemistry of glycosylation especially in the absence of neighboring group

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participation are still not well understood. Although assembly of branched oligomannosides from the direction of the nonreducing end to the reducing end is a popular approach, caution needs to be taken regarding stereochemical outcome of the reaction. Anomeric effect and steric hindrance are not dependable control of stereochemistry. For the development of a reliable and general automated glycosylation method, stereochemical control remains a significant challenge.

Experimental Section

3-Azidopropyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-mannopyranosyl-α-(1→2)-3,4,6-tri-*O*-benzyl-D-mannopyranosyl-α-(1→3)-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-mannopyranosyl-α-(1→2)-3,4,6-tri-*O*-benzyl-D-mannopyranosyl-α-(1→6))-2,4-di-*O*-benzyl-α-D-mannopyranoside (15α) and 3-Azidopropyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-mannopyranosyl-α-(1→2)-3,4,6-tri-*O*-benzyl-D-mannopyranosyl-*β*-(1→3)-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-mannopyranosyl-α-(1→2)-3,4,6-tri-*O*-benzyl-D-mannopyranosyl-*β*-(1→6))-2,4-di-*O*-benzyl-α-D-mannopyranoside (15*β*). Donor **14** (0.180 g, 0.175 mmol) and acceptor **11** (0.4 equiv, 0.033 g, 0.070 mmol) were azeotropically dried over toluene together three times and mixed with freshly activated molecular sieves (MS 4 Å) (200 mg) in diethyl ether (5 mL). The mixture was stirred at room temperature for 30 min and cooled to −78 °C, which was followed by addition of TTBP (0.043 g, 0.175 mmol) and a solution of AgOTf (0.135 g, 0.53 mmol, 3 equiv) dissolved in Et_2O (2 mL) without touching the wall of the flask. After 5 min, orange colored *p*-TolSCl (25 μL, 0.175 mmol) was added through a microsyringe. Since the reaction temperature was lower than the freezing point of *p*-TolSCl, *p*-TolSCl was added directly into the reaction mixture to prevent it from freezing on the flask wall. The characteristic yellow color of *p*-TolSCl in the reaction dissipated rapidly within a few seconds, indicating depletion of *p*-TolSCl. The reaction mixture was warmed to −20 °C under stirring over 90 min. The reaction was quenched with triethylamine, diluted with CH_2Cl_2 (30 mL), and filtered over Celite. The Celite was further washed with CH_2Cl_2 until no organic compounds were observed in the filtrate by TLC. All CH_2Cl_2 solutions were combined and washed twice with saturated aqueous solution of $NaHCO_3$ (20 mL) and twice with water (10 mL). The organic layer was collected and dried over Na_2SO_4. After removal of the solvent, the yellowish residue was purified by silica gel chromatography (toluene/CH_2Cl_2/acetone = 1.5:0.02:0.02) to give pentasaccharides **15**α (22 mg) and **15***β* (51.5 mg) in 47% yield. **15***β*: $[\alpha]^{25}_D$ +16 (c = 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.20−1.24 (m, 3H), 1.51−1.52 (m, 2H), 2.07 (s, 3H), 2.09 (s, 3H), 3.30−3.34 (m, 2H), 3.42−3.44 (m, 1H), 3.49−3.61 (m, 7H), 3.65−3.72 (m, 4H), 3.78−3.84 (m, 6H), 3.87−3.94 (m, 5H), 3.97−4.03 (m, 4H), 4.21−4.26 (m, 3H), 4.32−4.43 (m, 7H), 4.44−4.65 (m, 15H), 4.66−4.75 (m, 2H), 4.77−4.85 (m, 4H), 5.06 (s, 1H), 5.13−5.15 (m, 1H), 5.50 (s, 1H), 5.57 (d, J = 1.8 Hz, 1H), 7.08−7.34 (m, 70H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.40, 21.43, 22.9, 28.8, 29.9, 30.5, 48.5, 64.5, 68.5, 68.8, 69.0, 69.07, 69.09, 69.5, 69.7, 71.5, 72.0, 72.08, 72.14, 72.21, 72.28, 72.33, 72.5, 72.8, 73.4, 73.52, 73.55, 74.2, 73.6, 74.5, 74.84, 74.87, 74.93, 75.04, 75.24, 75.26, 75.32, 75.9, 76.0, 77.0, 77.2, 77.5, 77.7, 78.3, 78.8, 82.5, 97.0 ($^1J_{H1,C1}$ = 162.4 Hz), 99.1 ($^1J_{H1,C1}$ = 173.6 Hz), 99.5 ($^1J_{H1,C1}$ = 173.6 Hz), 100.9 ($^1J_{H1,C1}$ = 162.9 Hz), 101.1 ($^1J_{H1,C1}$ = 172.8 Hz), 127.26, 127.36, 127.39, 127.55, 127.61, 127.65, 127.67, 127.69, 127.72, 127.76, 127.82, 127.86, 127.89, 127.94, 127.97, 128.09, 128.11, 128.18, 128.20, 128.25, 128.28, 128.32, 128.34, 128.38, 128.39, 128.44, 128.48, 128.49, 128.50, 128.54, 128.56, 128.58, 128.61, 128.63, 128.66, 128.69, 128.75, 128.82, 128.86, 138.17, 138.23, 138.35, 138.38, 138.42, 138.45, 138.57, 138.61, 138.7, 138.8, 139.1, 170.3, 170.4. MS (ESI) m/z calcd for $C_{135}H_{145}N_3NaO_{28}$ $[M + Na]^+$ 2279.0; found 2279.8. HRMS: m/z calcd for $C_{135}H_{145}N_3NaO_{28}$ $[M + Na]^+$ 2278.9912; found 2278.9900. **15**α: $[\alpha]^{25}_D$ +17 (c = 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.64−1.66 (m, 2H), 2.10 (s, 6H), 3.18−3.34 (m, 4H), 3.45−3.49 (t, J = 11.4 Hz, 2H), 3.58−3.67 (m, 8H), 3.77−3.81 (m, 4H), 3.84−3.85 (m, 2H), 3.88−4.07 (m, 12H), 4.24−4.27 (d, J = 10.8 Hz, 1H), 4.34−4.47 (m, 8H), 4.50−4.69 (m, 15H), 4.73 (s, 1H), 4.78−4.87 (m, 4H), 4.93 (s, 1H), 5.06−5.06 (m, 2H), 5.16 (s, 1H), 5.51 (s, 2H), 7.09−7.32 (m, 70H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 29.0, 48.5, 64.5, 66.7, 68.4, 68.8, 69.0, 69.1, 69.8, 71.6, 72.0, 72.11, 72.19, 72.25, 72.9, 73.4, 73.56, 73.60, 74.2, 74.4, 74.6, 74.7, 74.8, 74.9, 75.1, 75.3, 75.4, 77.0, 77.3, 77.6, 77.8, 78.0, 78.3, 78.4, 79.4, 79.9, 97.2 ($^1J_{H1,C1}$ = 169.9 Hz), 99.3 ($^1J_{H1,C1}$ = 170.9 Hz), 99.5 ($^1J_{H1,C1}$ = 171.6 Hz), 99.8 ($^1J_{H1,C1}$ = 171.6 Hz), 101.4 ($^1J_{H1,C1}$ = 170.7 Hz), 127.2, 127.5, 127.70, 127.78, 127.84, 127.95, 127.99, 128.02, 128.29, 128.42, 128.47, 128.49, 128.55, 128.59, 128.71, 138.24, 138.27, 138.37, 138.44, 138.46, 138.51, 138.63, 138.72, 138.78, 138.80, 170.37, 170.40. HRMS: m/z calcd for $C_{135}H_{145}N_3NaO_{28}$ $[M + Na]^+$ 2278.9912; found 2278.9949.

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Supporting Information Available: Experimental procedures for synthesis of compounds **11**, **14**, **15**α, **16**, **17**, and **18**. Selected ^{1}H, ^{13}C, and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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