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One-Pot Catalytic Glycosidation/Fmoc Removal – An Iterable Sequence for Straightforward Assembly of Oligosaccharides Related to HIV gp120[‡]

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The removal of a transient Fmoc protecting group can be simply performed by the addition of excess Et_3N just after the accomplishment of a $Bi(OTf)_3$-promoted glycosidation reaction. The obtained oligosaccharide can be directly employed as a glycosyl acceptor for further elongation of the saccharide. The preparation of biologically important, linear and branched mannans incorporated into HIV gp120 demonstrates that the iteration of this one-pot sequence leads to a very straightforward oligosaccharide assembly.

Introduction

In recent years, the ever-expanding interest in the applicative potential of oligosaccharides in biochemical and pharmacological studies has elicited a massive effort towards the development of efficient approaches to gain complex sequences in relatively short times.[1] Typical procedures in oligosaccharide synthesis often suffer from lengthy experimental operations; numerous steps are required for both preparing the requisite saccharide precursors from commercially available compounds and assembling the oligomeric target through a sequence of coupling reactions alternated with protection/deprotection steps. Most of these synthetic steps also entail lengthy chromatographic procedures.

Despite the recent exceptional advancements in oligosaccharide solid-phase synthesis,[2] a wide effort is currently underway to streamline solution-phase procedures, which are more cost-effective to scale up.[3] To this end, several strategies have been developed for assembling oligosaccharides exclusively through sequential glycosidations.[4] An advantage of these approaches lies in suppressing the protection/deprotection steps interposed between glycosidations. These schemes rely on either orthogonally activatable glycosyl donors or the reactivity tuning of glycosyl donors of the same class by the proper choice of their protecting groups.[4] More recently, a preactivation strategy emerged as an alternative, useful tool for performing sequential glycosidations.[5] Further progress in all these strategies has been attained through the implementation of sequential glycosidations in a one-pot fashion.[6] In this regard, we have very recently reported the first examples of one-pot, multiple glycosidations exclusively relying on catalytic conditions for donor activation as well as on the use of experimentally convenient, moisture-stable promoters.[7,8] With few exceptions, the sequential glycosidations so far described involve the elongation of the oligomer starting from the nonreducing terminus of the target. However, with the exception of the above-mentioned preactivation strategy, the success of the elongation is critically dependent on the availability of a set of glycosyl donors displaying well-differentiated reactivities.

In this paper, we follow the less common approach of sequential glycosidations featuring the opposite elongation direction.[9] In general terms, this can be pursued by first coupling a glycosyl donor with a glycosyl acceptor and then removing in the same reaction vessel a transient protecting group from the in-situ-generated di- or oligosaccharide. In this way, after a single purification process, a potential glycosyl acceptor, ready for a further glycosidation step, is directly obtained. Apart from the reduced overall number of synthetic operations, this strategy is advantageous because it is independent of the anomeric reactivity of the involved components since, in each glycosidation step, there is no competition between two potential glycosyl donors. So far, only a few sparse examples of this tactic have been reported.[10] Almost all of them exploit the acidic conditions required in the glycosidation step for performing, upon adjustment of the experimental conditions, the subsequent removal of the transient protecting group. A much less exploited synthetic route is, instead, the removal of a base-labile protecting group immediately after an acid-promoted glycosidation. In this regard, the fluorenylmethoxycarbonyl (Fmoc) group was recently applied as a transient protecting

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group[11] in the synthesis of β-(1→6) gluco oligosaccharides conducted in microreactors.[12] The group survived the acidic activation (with 2–3 equiv. of TMSOTf) of glycosyl phosphate donors and was removed by the simple addition of on excess of a mild base (piperidine/DMF, 1:4) to the glycosidation medium. The excess promoter caused partial trimethylsilylation of the liberated alcohol, a process which required the addition of desilylation agents in the deprotection mixture. By a similar approach, Fmoc was removed in situ from oligosaccharide intermediates generated by electrochemical glycosidations.[13]

In this paper, we wish to describe the effective application of Fmoc as a transient group in an iterable sequence for solution oligosaccharide synthesis based on the $Bi(OTf)_3$-catalyzed activation[8,14] of glycosyl trihaloacetimidates. The devised strategy has been targeted to the rapid assembly of two biologically relevant targets, the protected mannose tetrasaccharide **1** and the branched pentasaccharide **2**, both corresponding to moieties incorporated into HIV glycoprotein gp120 (Figure 1).

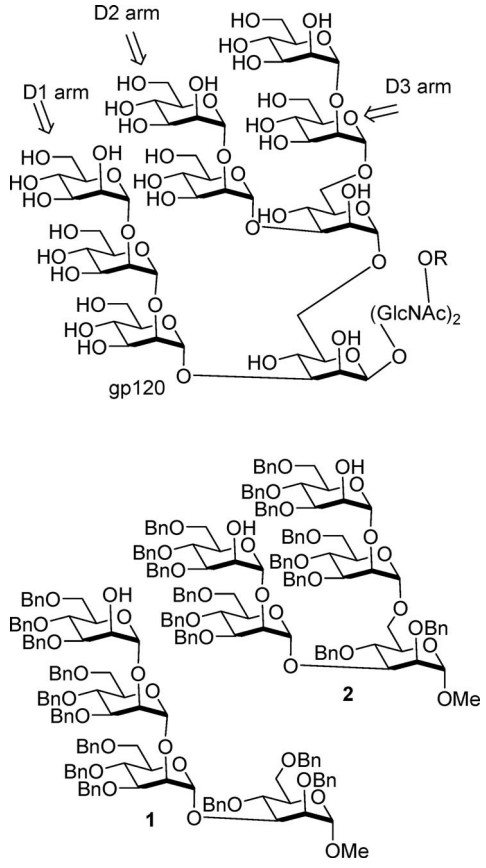


Figure 1. Structures of the gp120 glycan and the synthetic targets of the present work.

In particular, tetrasaccharide **1** represents the so-called D1 arm of the highly mannosylated ensemble, whereas **2** embodies both the D2 and D3 arms. Both sequences were found to exhibit high affinity to human antibody 2G12[15] and are currently under investigation for immunogenic applications.[16]

Results and Discussion

A retrosynthetic analysis of the target **1**[17] (Figure 2) entailed the availability of only two mannose building blocks, **3** and **4**, the latter being the precursor of the reducing terminal residue.

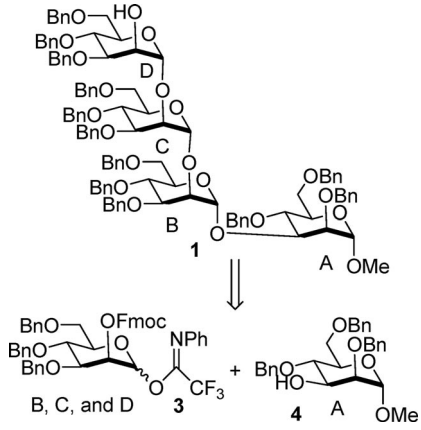
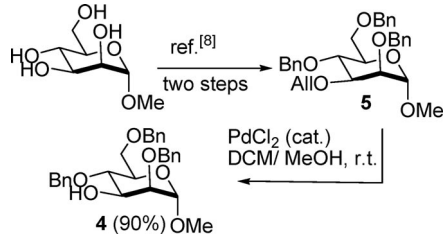


Figure 2. Retrosynthesis of **1**.

We synthesized acceptor **4** (Scheme 1) starting from commercially available methyl α-D-mannopyranoside. This we initially allylated at *O*-3 and per-*O*-benzylated to give **5** as previously reported.[8] Deallylation of **5** smoothly afforded acceptor **4** (Scheme 1).



Scheme 1. Synthesis of acceptor **4**.

We prepared **3** from intermediate **6** (Scheme 2), obtained by a previously described one-pot sequence.[8,18] We submitted ortho ester **6** to an acid-promoted rearrangement in the presence of allyl alcohol to give **7**, which we directly submitted to 2-*O* deacetylation and Fmoc protection to give **8** in 62% yield over three steps. Sequential anomeric deallylation and installation of the trifluoroacetimidate[19] leaving group completed the preparation of **3** (90% yield over two steps).

With the appropriate building blocks in hand, we examined the sequence of $Bi(OTf)_3$-promoted coupling of **3** with **4** and the addition of Et_3N (for Fmoc removal; Scheme 3).[20] We investigated the solvent mixtures (DCE/dioxane or toluene/Et_2O/dioxane) previously found compatible with the mild $Bi(OTf)_3$ activation of trifluoroacetimidate donors.[8,14] In a preliminary screening, the use of the former binary mixture for the coupling of **3** with a variety of secondary acceptors provided significant amounts of β-linked glycosides, in spite of the expected participation effect of the 2-*O*-Fmoc group. Instead, we observed the best result with the ternary solvent mixture (toluene/Et_2O/diox-

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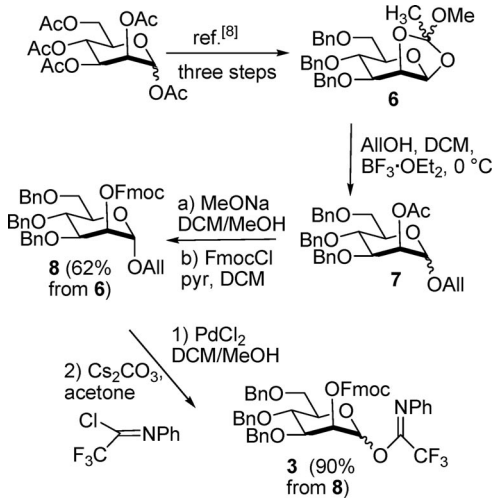
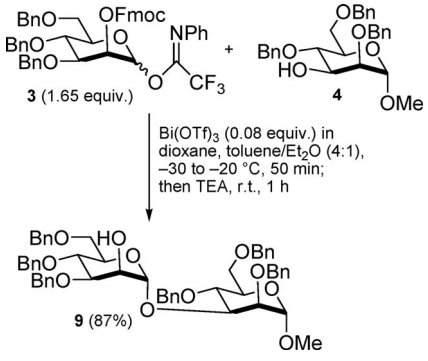


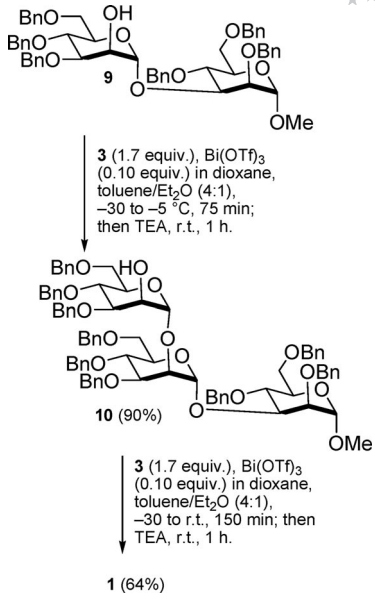
Scheme 2. Synthesis of donor **3**.

ane), and the one-pot sequence in Scheme 3 afforded essentially pure **9** in almost 90% yield after chromatographic purification. Notably, at this stage, the whole glycosidation/Fmoc removal sequence took less than 2 h.



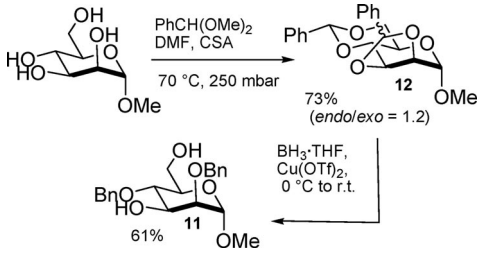
Scheme 3. Synthesis of disaccharide **9**.

Once we established the optimized reaction conditions, we attempted the elongation of the disaccharide with the glycosidation of the sterically encumbered, axial 2-OH (Scheme 4). The application of the optimized protocol with slight modifications gave acceptor trisaccharide **10** in an excellent overall yield (90%), comparable with that of the previous one-pot sequence. Further coupling with **3** under analogous conditions gave tetrasaccharide **1** in a rewarding, albeit lower overall yield (64%). The whole sequence of the three synthetic operations gave the D1 tetrasaccharide **1** in about 50% overall yield over six steps, corresponding to an almost 90% average yield for each step. Additionally, this scheme required only three chromatographic purifications. A comparison of NMR spectroscopic data with those reported for a differently synthesized tetrasaccharide **1**[17a] confirmed the identity of the obtained product, with the anomeric linkages all being α-configured.



Scheme 4. Assembly of tetrasaccharide **1**.

We then applied the strategy illustrated above to the more demanding target mannan pentasaccharide **2** (Figure 1). This sequence required diol **11** (Scheme 5) as the precursor of the reducing terminus. During the screening of several known preparations of this target based on three synthetic steps,[21,22] we found a practical two-step procedure. In the first step, we submitted methyl mannopyranoside to a double benzylidenation by slightly modifying a previously reported procedure described by Liptak and co-workers.[23] We obtained product **12** after chromatographic purification as an almost equimolar diasteroisomeric mixture (*endo*/*exo* = 1.2:1). It is well established by several precedents[24,25] that the reductive opening of five-membered benzylidenes displays complementary regioselectivity according to the configuration of the starting material. However, we have observed that when the *exo*/*endo* mixture of **12** was directly submitted to the reductive opening conditions reported by Hung and co-workers [excess BH_3·THF and 0.3 equiv. of copper(II) triflate][26] the desired 3,6-diol **11** largely prevailed. Curiously, we also isolated minor amounts (ca. 10%) of the unexpected 3,4-diol and characterized it in its acetylated form.



Scheme 5. Synthesis of diol acceptor **11**.

Having established straightforward access to the reducing terminus precursor **2**, we attempted its direct double glycosidation. The simultaneous attachment of two mannose resi-

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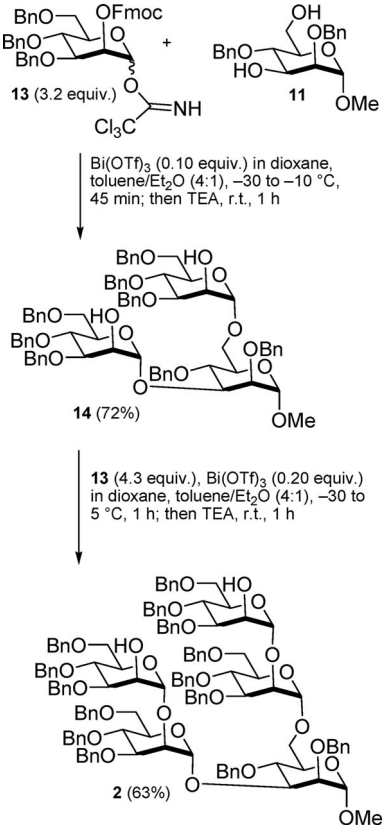
dues to acceptor diol **11** is not a trivial task (Scheme 6). As a matter of fact, in some cases, the assembly of this trisaccharide structure entails long sequences, in which the mannose residues are added to the branching unit at different stages.[27] Additionally, a literature survey[28] revealed that the removal of poorly accessible 2-*O*-substituted protecting groups from the inserted mannoses did not frequently proceed in yields higher than 90%. After a preliminary screening, for this application (Scheme 6) trichloroacetimidate **13**[29] proved more efficient than the trifluoro counterpart **3** at providing trisaccharide **14**. Indeed, with the latter donor, we detected higher amounts of intermediate dimannosides; with donor **13**, we instead satisfyingly carried out the sequence of bis(glycosylation) and bis(deprotection) under very mild conditions, in short times, and in a very high overall yield (72% over four synthetic steps, Scheme 6). We then exposed trisaccharide diol **14** to trichloroacetimidate **13** under $Bi(OTf)_3$ activation to afford pentasaccharide **2** in 63% overall yield. We performed the whole synthesis in only two synthetic operations, and the overall yield (ca. 45%) of its eight synthetic steps corresponded once again to an approximate average yield of 90% for each step.



Scheme 6. Assembly of pentasaccharide **2**.

A comparison of NMR spectroscopic data of the obtained pentasaccharide with those of close analogues of **2** (differentiated exclusively for the aglycon)[22,24] confirmed the identity of the structure and the lack of β-mannosidic linkages.[22] We note that we obtained oligosaccharides **1** and **2** in partially protected forms, which can be exploited for further elaborations.

Conclusions

In this paper, we have shown that the Fmoc protecting group can be simply removed in the same vessel where a $Bi(OTf)_3$-promoted glycosidation is conducted. The iteration of this one-pot sequence leads to biologically useful mannose oligosaccharides related to HIV gp120 by performing a smaller number of synthetic operations than required in other reported procedures towards similar sequences. As to yields, the effectiveness of the present approach often compares favourably with most of the synthetic schemes so far described,[15,16a,17,21,22,27,28] with exceptions being found in a few examples of especially high-yielding synthetic routes.[24,28h,28p–28r] Nevertheless, the actual merit of the strategy resides in the combination, rather unusual in other schemes, of simultaneous advantages such as the reduced experimental work (also because of the minimal number of required precursors), the attainment of high yields and the exclusive use of a catalytic and moisture-stable glycosidation promoter. Furthermore, the present, iterable, one-pot scheme is anticipated to be of broad applicability, thus adding a further useful complement to the recent strategic advances in oligosaccharide synthesis.

Experimental Section

General Methods: ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (internal standard, for ^1H: $CHCl_3$ at $\delta = 7.26$ ppm; for ^{13}C: $CDCl_3$ at $\delta = 77.0$ ppm). ^1H NMR assignments were based on homo-decoupling experiments. MALDI mass spectra were recorded in the positive mode; compounds were dissolved in CH_3CN at a concentration of 0.1 mg/mL, and 1 μL of these solutions was mixed with 1 μL of a 20 mg/mL solution of 2,5-dihydroxybenzoic acid in CH_3CN/H_2O (7:3) or, in the case of trifluoroacetimidate derivatives, with a 10 mg/mL solution of trihyroxyacetophenone in $MeOH/H_2O$ (1:1). Analytical thin layer chromatography (TLC) was performed on aluminium plates precoated with Silica Gel 60 F_{254} as the adsorbent. The plates were developed with the application of 5% H_2SO_4 ethanolic solution followed by heating to 130 °C. Column chromatography was performed on silica gel (63–200 mesh). $[\alpha]_D^{29}$ values are given in 10^{-1} deg cm^2 g^{-1}. Glycosidations were performed with commercially available, anhydrous solvents. $Bi(OTf)_3$ was coevaporated three times in toluene and dried under vacuum for 30–45 min and then dissolved in dioxane in the presence of freshly activated molecular sieves (4 Å).

Methyl 2,4,6-Tri-*O*-benzyl-α-D-mannopyranoside (4): To a solution of **5**[8] (260 mg, 0.515 mmol) in MeOH/DCM (2.5:1, 3.5 mL) was added at room temp. palladium chloride (10 mg, 0.056 mmol). The mixture was stirred overnight and then concentrated under vacuum. The residue was then filtered through a short plug of silica gel (eluent: DCM/MeOH, 95:5), concentrated and purified by silica-gel flash chromatography (eluent: petroleum ether/EtOAc from 8:2 to 7:3) to provide **4** as an oil (215 mg, 90%). $[\alpha]_D^{29} = +15.6$ ($c = 1.0$, in $CHCl_3$), (ref.[30] $[\alpha]_D^{29} = +14.5$ ($c = 1.0$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.40–7.15$ (Ar), 4.87 (br. s, 1 H, 1-H), 4.90–

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4.50 (3 AB, 6 H, 3 CH_2Ph), 4.05–3.95 (m, 1 H, 5-H), 3.85–3.70 (overlapped signals, 4 H, 2-H, 4-H and 6-H_2), 3.37 (s, 3 H, 1-OCH_3), 2.50 (br. s, 1 H, 3-OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.3, 138.1, 137.6 (aromatic C), 128.4–127.4 (aromatic CH), 97.7 (C-1), 78.1, 76.4, 74.6, 73.2, 72.6, 71.6, 70.6, 69.0, 54.7 ppm. MALDI-TOF MS: calcd. for $[M + Na]^+$ 487.21; found 487.45. $C_{28}H_{32}O_6$ (487.21): calcd. C 72.39, H 6.94; found C 72.20, H 6.85.

Allyl 3,4,6-Tri-*O*-benzyl-2-*O*-fluorenylmethoxycarbonyl-α-D-mannopyranoside (8): Ortho ester **6**[8] (181 mg, 0.357 mmol) was coevaporated three times with toluene (3 × 2 mL) and dried under vacuum. After adding freshly activated molecular sieves (4 Å), **6** was dissolved at room temp. in dry DCM (1.6 mL), and allyl alcohol (120 μL, 1.79 mmol) was subsequently added. The mixture was then cooled to 0 °C and stirred for ca. 10 min. A solution of $BF_3{\cdot}OEt_2$ (0.4 M in DCM, 180 μL, 0.073 mmol) was then added at 0 °C under argon. After 15 min, the reaction was quenched at the same temperature with 5 drops of pyridine, and the mixture was filtered through a short plug of silica gel (eluent: DCM/MeOH/CH_3CN, 85:10:5) and concentrated in vacuo to obtain crude **7** as an oil, which was directly submitted to the following step. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.60–7.15 (Ar), 6.05–5.90 (m, 1 H, C*H*=CH_2), 5.50 (br. s, 1 H, 2-H), 5.36 (br. d, J_E = 17.4 Hz, 1 H, CH_2CH=CH_ZH_E), 5.28 (br. d, J_Z = 10.2 Hz, 1 H, CH_2CH=CH_ZH_E), 5.00 (br. s, 1 H, 1-H), 4.98–4.55 (6 H, 3 CH_2Ph), 4.26 (m, 1 H, CH_aH_bCH=CH_2), 4.15–3.98 (3 H), 3.95–3.79 (3 H), 2.23 (s, 3 H, $COCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1 (*C*OCH_3), 138.2, 138.0, 137.8 (aromatic C), 133.2 (*C*H=CH_2), 128.2–127.4 (aromatic CH), 117.5 (CH=*C*H_2), 96.7 (C-1), 78.0, 74.9, 74.2, 73.2, 71.6, 71.3, 68.7, 68.6, 67.9 ppm. Crude **7** was dissolved in MeOH/DCM (1.3:1, 6.4 mL), and the mixture was then cooled to 0 °C. At this temperature, 8 drops of a solution of MeONa (2 M in MeOH) were added, and the mixture was warmed to room temp. and stirred overnight. After the addition of Amberlist 15, the supernatant was removed and concentrated in vacuo to obtain an oil in a satisfying purity to be directly submitted to the last step of this one-pot sequence. Spectroscopic data of the 2-*O*-deacetylated intermediate:[28m] ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.10 (Ar), 6.00–5.80 (m, 1 H, C*H*=CH_2), 5.30–5.15 (2 H, CH=CH_2), 5.02 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 4.90–4.45 (6 H, 3 CH_2Ph), 4.25–4.10 (m, 1 H, CH_aH_bCH=CH_2), 4.08–3.95 (2 H, CH_aH_bCH=CH_2 and 2-H), 3.90–3.65 (4 H, 3-H, 4-H, 5-H and 6-H_2), 2.44 (d, $J_{2,OH}$ = 2.2 Hz, 1 H, 2-OH) ppm. The product from the previous step was dissolved in dry DCM (3.5 mL) at room temp., and pyridine (300 μL, 3.73 mmol) and FmocCl (120 mg, 0.464 mmol) were sequentially added under argon to the solution. The mixture was stirred for 25 min and was then diluted with EtOAc, washed three times with aqueous saturated $CuSO_4$, and the organic phase was dried with anhydrous Na_2SO_4 and concentrated in vacuo to give a residue, which was purified by silica-gel flash chromatography (eluent: petroleum ether/EtOAc from 9:1 to 8:2) to yield **8** as a yellow oil (157 mg, 62% over three steps). $[\alpha]_D^{29}$ = +19.9 (*c* = 0.6, in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.80–7.10 (Ar), 6.00–5.80 (m, 1 H, C*H*=CH_2), 5.35–5.18 (3 H, CH=CH_2 and 2-H), 5.02 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 4.95–4.25 (9 H, 3 CH_2Ph and Fmoc OCH_2CH), 4.25–4.15 (m, 1 H, CH_aH_bCH=CH_2), 4.10–3.70 (6 H, CH_aH_bCH=CH_2, 3-H, 4-H, 5-H, 6-H_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.5 (Fmoc CO_2), 143.2, 142.9, 141.0, 140.9, 138.0, 137.9, 137.7 (aromatic C), 133.1 (*C*H=CH_2), 128.0–126.9, 122.1, 124.9, 119.7 (aromatic CH), 117.5 (CH=*C*H_2), 96.3 (C-1), 78.0, 75.0, 74.1, 73.1, 72.4, 71.5, 71.3, 69.9, 68.6, 67.8, 46.3 ppm. MALDI-TOF MS: calcd. for $[M + Na]^+$ 735.30; found 735.25. $C_{45}H_{44}O_8$ (712.84): calcd. C 75.82, H 6.22; found C 75.53, H 6.15.

3,4,6-Tri-*O*-benzyl-2-*O*-fluorenylmethoxycarbonyl-α,β-D-mannopyranosyl *N*-Phenyltrifluoroacetimidate (3): To a solution of **8** (474 mg, 0.67 mmol) in MeOH/DCM (1.6:1, 6.7 mL) was added at room temp. palladium chloride (12 mg, 0.068 mmol). The mixture was stirred overnight and then concentrated under vacuum. The residue was then filtered through a short plug of silica gel (eluent DCM/MeOH, 95:5) and concentrated to yield the hemiacetal intermediate in a satisfying purity to be directly submitted to the following step. Spectroscopic data: ^1H NMR (200 MHz, $CDCl_3$): significant signals at δ = 7.90–7.20 (Ar), 5.41 (br. s, 1 H, 1-H), 5.30 (br. d, 1 H, 2-H), 4.14 (dd, $J_{2,3}$ = 2.4 Hz, $J_{3,4}$ = 9.0 Hz, 1 H, 3-H), 3.90–3.70 (m, 2 H, 6-H_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.6 (Fmoc CO_2), 143.3, 143.1, 141.0, 138.1, 137.8, 137.6 (aromatic C), 128.2–127.0, 125.2, 125.0, 119.8 (aromatic CH), 91.9 (C-1), 77.6, 74.9, 74.5, 73.2, 73.0, 71.6, 70.7, 70.0, 69.4 ppm. To a solution of the hemiacetal in acetone (6 mL) were sequentially added at 0 °C Cs_2CO_3 (239 mg, 0.733 mmol) and (*N*-phenyl)trifluoroacetimidoyl chloride (230 μL, 1.82 mmol). The mixture was warmed to room temp. and, after 3 h, was diluted with DCM, filtered through Celite (eluent: EtOAc) and concentrated under vacuum. The residue was purified by silica-gel flash chromatography (eluent: petroleum ether/EtOAc from 9:1 to 8.5:1.5) to yield **3** as a yellow oil (anomeric mixture, α/β ≈ 7.6:1, 506 mg, 90% over two steps). ^1H NMR (400 MHz, $CDCl_3$): signals of α-anomer at δ = 7.90–7.00 (Ar), 6.61 (br. s, 1 H, 1-H), 5.55 (br. s, 1 H, 2-H), 5.12–4.70 (6 H, 3 CH_2Ph), 4.63–4.48 (3 H, Fmoc OCH_2CH), 4.42–4.10 (3 H, 3-H, 4-H and 5-H), 4.05–3.90 (2 H, 6-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.3 (Fmoc CO_2), 143.1, 142.9, 142.8, 141.3, 141.0, 137.8 (2 C), 137.3 (aromatic C), 128.8–125.7, 120.4, 119.8, 119.1 (aromatic CH), 93.9 (C-1), 77.3, 75.2, 74.0, 73.4, 73.2, 72.1, 71.1, 70.2, 68.3 ppm. MALDI-TOF MS: calcd. for $[M + Na]^+$ 866.30; found 866.15. $C_{50}H_{44}F_3NO_8$ (866.30): calcd. C 71.16, H 5.26; found C 71.00, H 5.35.

3,4,6-Tri-*O*-benzyl-2-*O*-fluorenylmethoxycarbonyl-α,β-D-mannopyranosyl Trichloracetimidate (13): To a solution of **8** (318 mg, 0.447 mmol) in MeOH/DCM (1.6:1, 4.5 mL) was added at room temp. palladium chloride (8 mg, 0.045 mmol). The mixture was stirred overnight and then concentrated under vacuum. The residue was then filtered through a short plug of silica gel (eluent: DCM/MeOH, 95:5) and concentrated to yield the hemiacetal as a foam. The obtained hemiacetal was dissolved in trichloroacetonitrile (6.7 mL), and the solution was added dropwise to a reaction vessel containing sodium hydride (60% in oil, 1.9 mg) at 0 °C under magnetic stirring. After 15 min at the same temperature, the mixture was neutralized by the portion-wise addition of silica gel, and the residue was purified by silica-gel flash chromatography (eluent: toluene/acetone, 20:1) to yield **13** as a foam (anomeric mixture, α/β ≈ 8.3:1, 348 mg, 95% over two steps). ^1H NMR (400 MHz, $CDCl_3$): signals of α-anomer at δ = 8.83 (s, 1 H, NH), 8.00–7.15 (Ar), 6.57 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 5.47 (t, $J_{2,3}$ = 1.6 Hz, 1 H, 2-H), 4.55–4.35 (3 H, Fmoc $CHCH_2O$), 4.26 (t, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz,1 H, 4-H), 4.20 (dd, 1 H, 3-H), 4.20–4.13 (m, 1 H, 5-H), 3.98 (dd, $J_{5,6a}$ = 4.4, $J_{6a,6b}$ = 11.2 Hz, 1 H, 6_a-H), 3.87 (dd, $J_{5,6b}$ = 1.6 Hz, 1 H, 6_b-H) ppm. Significant signals of the β-anomer at δ = 8.78 (s, 1 H, NH), 6.05 (s, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): signals of α-anomer at δ = 160.0 (C=NH), 154.6 (OCO_2), 143.4, 143.2, 141.3 (2 C, Fmoc aromatic C), 138.1, 137.9, 137.4 (benzyl aromatic C), 128.4–127.3, 125.4, 125.3, 120.1 (aromatic CH), 95.3 (C-1), 77.5, 75.6, 74.6, 73.8, 73.5, 72.2, 71.4, 70.6, 68.6, 46.6 ppm.

Methyl 2,4-Di-*O*-benzyl-α-D-mannopyranoside (11): BH_3 (1 M in THF, 1.5 mL, 1.5 mmol) was added to **12**[23,25a] (*endo*/*exo*, 1.2:1, 55 mg, 0.15 mmol) at 0 °C under argon. To the resulting solution was added at 0 °C copper(II) triflate (0.069 M in THF, 0.65 mL,

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0.045 mmol). After 30 min, the ice bath was removed, and the reaction vessel was warmed to room temp. After a few minutes, a black precipitate appeared. After 1 h and 40 min from the start, the reaction was quenched with Et_3N (25 μL) and MeOH (0.2 mL). The mixture was concentrated in vacuo, and the residue was purified by silica-gel flash chromatography (eluent: *n*-hexane/EtOAc from 32:18 to 55:45) to yield diol **11** as a colourless oil (34 mg, 61% yield). The acetylation of a sample confirmed the presence of free hydroxy groups at O-3 and O-6, as indicated by ^{1}H NMR. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.16 (dd, $J_{2,3}$ = 3.3, $J_{3,4}$ = 9.0 Hz, 1 H, 3-H), 4.30 (dd, $J_{5,6a}$ = 3.0, $J_{6a,6b}$ = 12.4 Hz, 1 H, 6a-H), 4.22 (dd, $J_{5,6b}$ = 4.2 Hz, 1 H, 6b-H) ppm. Compound **11**: $[\alpha]_D^{28}$ = +21.5 (*c* = 1.1, in $CHCl_3$), [ref.[25a] $[\alpha]_D^{29}$ = +23.5 (*c* = 0.77, in $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.25 (Ar), 4.75 (d, $J_{1,2}$ = 1.6 Hz, 1 H, anomeric proton), 4.92–4.59 (4 H, 2 CH_2Ph), 3.99 (dd, $J_{2,3}$ = 3.2, $J_{3,4}$ = 9.6 Hz, 1 H, 3-H), 3.86 (dd, $J_{5,6a}$ = 3.2, $J_{6a,6b}$ = 11.6 Hz, 1 H, 6a-H), 3.77 (dd, $J_{5,6b}$ = 4.4 Hz, 1 H, 6b-H), 3.73 (dd, 1 H, 2-H), 3.68 (t, $J_{4,5}$ = 9.6 Hz, 1 H, 4-H), 3.60–3.55 (m, 1 H, 5-H), 3.32 (s, 3 H, OCH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.3, 137.6 (aromatic C), 128.6–127.8 (aromatic CH), 98.1 (C-1), 78.3, 74.8, 73.1, 71.7, 71.1, 62.3, 54.8 (OCH_3) ppm. MALDI-TOF MS: calcd. for $[M + Na]^+$ 397.17; found 397.25. $C_{21}H_{26}O_6$ (374.43): calcd. C 67.36, H 7.00; found C 67.05, H 7.10.

Methyl 3,4,6-Tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (9): A mixture of donor **3** (147 mg, 0.174 mmol) and acceptor **4** (49 mg, 0.105 mmol) was coevaporated three times with anhydrous toluene (3 × 2 mL) and then dried in vacuo for 30 min. After the addition of molecular sieves (4 Å, AW 300), the mixture was dissolved under argon in toluene/Et_2O (4:1, 3.3 mL), cooled to –30 °C and stirred for 15 min. $Bi(OTf)_3$ (14.5 mg/mL in dioxane, 0.38 mL, 8.4 μmol) was then added, and the temperature was allowed to slowly rise. After 50 min (temperature at –20 °C), the glycosidation step was complete (TLC analysis, eluent: *n*-hexane/EtOAc, 7:3). Et_3N (0.8 mL) was added, and the reaction vessel was immediately warmed to room temp. After 1 h, the reaction mixture was filtered through a short plug of silica gel and repeatedly washed with DCM/MeOH/CH_3CN (85:10:5). The filtrate was concentrated, and the residue was purified by silica-gel flash chromatography (eluent: *n*-hexane/EtOAc from 3:1 to 2:1) to yield disaccharide **9** as an oil (84 mg, 87% overall yield). $[\alpha]_D^{28}$ = +29.1 (*c* = 1.0, in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.10 (Ar), 5.22 (d, $J_{1,2}$ = 1.2 Hz, 1 H, 1′-H), 4.72 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 4.85–4.46 (12 H, 6 CH_2Ph), 4.13 (dd, *J* = 3.2, 10.6 Hz, 1 H), 4.02–3.60 (11 H), 3.29 (s, 3 H, OCH_3), 2.31 (d, *J* = 2.4 Hz, 1 H, 2-OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.6, 138.3 (3 C), 138.1, 137.9 (aromatic C), 128.5–127.5 (aromatic CH), 101.2 and 98.2 (anomeric CH), 80.0, 78.4, 75.2, 75.0, 74.9, 74.4, 72.1, 72.0, 71.9, 71.7, 69.2, 69.0, 68.6, 54.8 ppm. MALDI-TOF MS: calcd. for $[M + Na]^+$ 919.40; found 919.27. $C_{55}H_{60}O_{11}$ (919.40): calcd. C 73.64, H 6.74; found C 73.50, H 6.65.

Methyl 3,4,6-Tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (10): A mixture of donor **3** (74 mg, 88 μmol) and acceptor **9** (45 mg, 49 μmol) was coevaporated three times with anhydrous toluene (3 × 1 mL) and then dried in vacuo for 30 min. After the addition of molecular sieves (4 Å, AW 300), the mixture was dissolved under argon in toluene/Et_2O (4:1, 3.3 mL), cooled to –30 °C and stirred for 1 5 min. $Bi(OTf)_3$ (14.5 mg/mL in dioxane, 0.22 mL, 4.9 μmol) was then added, and the temperature was allowed to rise to –5 °C over 75 min. Upon the completion of the glycosidation step (TLC analysis, eluent *n*-hexane/EtOAc, 7:3), Et_3N (0.83 mL) was added, and the reaction vessel was immediately warmed to room temp. After 1 h, the reaction mixture was filtered through a short plug of silica gel and repeatedly washed with DCM/MeOH/CH_3CN (85:10:5). The filtrate was concentrated, and the residue was purified by silica-gel flash chromatography (eluent: *n*-hexane/EtOAc from 3:1 to 2:1) to yield trisaccharide **10** as an oil (59 mg, 90% overall yield). $[\alpha]_D^{28}$ = +34.2 (*c* = 1.3, in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.10 (Ar), 5.31 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1′′-H), 5.13 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1′-H), 4.85 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 4.92–4.41 (18 H, 9 CH_2Ph), 4.18–4.12 (2 H), 4.10–3.80 (9 H), 3.80–3.65 (6 H), 3.55 (br. d, *J* = 10.0 Hz, 1 H), 3.33 (s, 3 H, OCH_3), 2.48 (br. s, 1 H, 2-OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 138.6, 138.55, 138.48 (2 C), 138.41 (2 C), 138.2, 138.1 (aromatic C), 128.5–127.3 (aromatic CH), 101.0 (2 C), 98.2 (anomeric CH), 79.9, 79.5, 77.7, 75.4, 75.0, 74.9, 74.7, 74.3, 73.4, 73.3, 73.2, 72.7, 72.2, 72.1, 72.0, 71.8, 69.7, 69.3, 68.6, 68.5 54.8 ppm. MALDI-TOF MS: calcd. for $[M + Na]^+$ 1351.60; found 1351.48. $C_{82}H_{88}O_{16}$ (1351.60): calcd. C 74.18, H 6.67; found C 73.95, H 6.71.

Methyl 3,4,6-Tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (1): A mixture of donor **3** (11 mg, 13 μmol) and acceptor **10** (10 mg, 7.5 μmol) was coevaporated three times with anhydrous toluene (3 × 1 mL) and then dried in vacuo for 30 min. After the addition of molecular sieves (4 Å, AW 300), the mixture was dissolved under argon in toluene/Et_2O (4:1, 0.51 mL), cooled to –30 °C and stirred for 15 min. $Bi(OTf)_3$ (14.3 mg/mL in dioxane, 34 μL, 0. 75 μmol) was then added, and the temperature was allowed to rise to room temp. over 2.5 h. Upon the completion of the glycosidation step (TLC analysis, eluent: *n*-hexane/EtOAc, 7:3), Et_3N (0.13 mL) was added. After 1 h from the addition, the reaction mixture was filtered through a short plug of silica gel and repeatedly washed with DCM/MeOH/CH_3CN (85:10:5). The filtrate was concentrated, and the residue was purified by silica-gel flash chromatography (eluent: toluene/EtOAc from 10:0 to 85:15) to yield tetrasaccharide **1** as an oil (8 mg, 64% overall yield). $[\alpha]_D^{28}$ = +28.5 (*c* = 0.8, in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.05 (Ar), 5.25 (br. s, 1 H, 1′′′-H), 5.18 (br. s, 1 H, 1′′-H), 5.14 (br. s, 1 H, 1′-H), 4.70 (d, $J_{1,2}$ = 1.5 Hz, 1 H, 1-H), 4.85–4.22 (24 H, 12 CH_2Ph), 4.12–4.08 (2 H), 4.00 (*J* = 1.5 Hz, 1 H), 3.98–3.60 (18 H), 3.55 (dd, *J* = 11.5, 3.0 Hz, 1 H), 3.47 (br. d, *J* = 11.5 Hz, 1 H), 3.43 (br. d, *J* = 10.0 Hz, 1 H), 3.26 (s, 3 H, OCH_3), 2.39 (br. s, 1 H, 2-OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8–138.1 (aromatic C), 128.5–127.2 (aromatic CH), 101.0, 100.9, 100.8 and 98.2 (anomeric CH), 80.0, 79.6, 79.4, 79.2, 79.0, 77.6, 77.2, 75.6, 75.1, 74.9, 74.7, 74.2, 73.4, 73.3, 73.0, 72.6, 72.5, 72.4, 72.1, 72.0, 71.9, 71.7, 71.6, 69.7, 69.3, 69.0, 68.7, 68.5, 54.7 ppm. MALDI-TOF MS: calcd. for $[M + Na]^+$ 1784.79; found 1784.45. $C_{109}H_{116}O_{21}$ (1784.79): calcd. C 74.30, H 6.64; found C 73.95, H 6.50.

Methyl [3,4,6-Tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)]-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→6)-2,4-di-*O*-benzyl-α-D-mannopyranoside (14): A mixture of donor **13** (78 mg, 95 μmol) and diol **11** (12 mg, 29 μmol) was coevaporated three times with anhydrous toluene (3 × 2 mL) and then dried in vacuo for 30 min. After the addition of molecular sieves (4 Å, AW 300), the mixture was dissolved under argon in toluene/Et_2O (4:1, 2.8 mL), cooled to –30 °C and stirred for 15 min. $Bi(OTf)_3$ (14.5 mg/mL in dioxane, 135 μL, 0.29 μmol) was then added, and the temperature was allowed to rise to –10 °C over 45 min. Upon the completion of the glycosidation step (TLC analysis, eluent: petroleum ether/EtOAc, 7:3), Et_3N (0.70 mL) was added, and the reaction vessel was immediately warmed to room temp. After 1 h, the reaction mixture was filtered through a short plug of silica gel and repeatedly washed with DCM/MeOH/CH_3CN (85:10:5). The filtrate was concentrated, and

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the residue was purified by silica-gel flash chromatography (eluent: *n*-hexane/acetone/DCM from 3:1:0.5 to 2:1:0.5) to yield trisaccharide **14** as an oil (26 mg, 72% overall yield). $[\alpha]_D^{26}$ = +25.9 (*c* = 0.77, in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.10 (Ar), 5.23 (d, $J_{1,2}$ = 1.2 Hz, 1 H, 1′^{3}-H), 5.09 (d, $J_{1,2}$ = 1.2 Hz, 1 H, 1′^{6}-H), 4.66 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 4.87–4.46 (16 H, 8 CH_2Ph), 4.15–4.10 (2 H), 4.05–3.95 (2 H), 3.95–3.80 (8 H), 3.80–3.60 (6 H), 3.25 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 138.4, 138.3 (2 C), 138.2, 138.1, 137.9 (2 C, aromatic C), 128.6–127.5 (aromatic CH), 101.4, 98.7, and 98.2 (anomeric CH), 80.1, 79.5, 78.9, 77.7, 75.0, 74.9, 74.8, 74.4, 74.2, 73.6, 73.3, 72.3, 72.0, 71.9, 71.4, 71.1, 69.4, 68.8, 68.7, 68.0, 66.1, 54.7 ppm. MALDI-TOF MS: calcd. for $[M + Na]^+$ 1261.55; found 1261.15. $C_{75}H_{82}O_{16}$ (1261.55): calcd. C 72.68, H 6.67; found C 72.35, H 6.50.

Methyl [3,4,6-Tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)]-[3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→6)]-2,4-di-*O*-benzyl-α-D-mannopyranoside (2): A mixture of donor **13** (40 mg, 49 μmol) and diol **14** (14 mg, 11 μmol) was coevaporated three times with anhydrous toluene (3 × 1 mL) and then dried in vacuo for 30 min. After the addition of molecular sieves (4 Å, AW 300), the mixture was dissolved under argon in toluene/Et_2O (4:1, 2.1 mL), cooled to –30 °C and stirred for 15 min. $Bi(OTf)_3$ (14.5 mg/mL in dioxane, 100 μL, 2.2 μmol) was then added, and the temperature was allowed to rise to 5 °C over 1 h. Upon the completion of the glycosidation step (TLC analysis, eluent petroleum ether/EtOAc, 7:3), Et_3N (0.35 mL) was added, and the reaction mixture immediately warmed to room temp. The reaction mixture was then filtered through a short plug of silica gel and repeatedly washed with DCM/MeOH/CH_3CN (85:10:5). The filtrate was concentrated, and the residue was purified by silica-gel flash chromatography (eluent: *n*-hexane/acetone/DCM 3:1:0.5) to yield pentasaccharide **2** as an oil (15 mg, 63% overall yield). $[\alpha]_D^{28}$ = +34.7 (*c* = 0.7, in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.10 (Ar), 5.25, 5.11 and 5.05 (3 d, $J_{1,2}$ = 1.6 Hz, 3 H, 2 1′′-H and 1′^{3}-H), 4.97 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1′^{6}-H), 4.64 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 4.98–4.30 (28 H, 14 CH_2Ph), 4.15–4.05 (4 H), 4.05–3.95 (3 H), 3.95–3.75 (13 H), 3.75–3.63 (6 H), 3.60–3.40 (4 H), 3.16 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7–138.0 (aromatic C), 128.6–127.0 (aromatic CH), 101.1 (3 C), 99.1, and 97.9 (anomeric CH), 80.3, 80.0, 79.9, 79.6, 78.9, 77.8, 75.3, 75.0, 74.9, 74.8, 74.7, 74.6, 74.5, 74.3, 74.2, 73.4, 73.3, 72.7, 72.1, 72.0, 71.8, 71.6, 71.5, 71.0, 69.7, 69.1, 68.9, 68.6, 68.5, 66.5, 54.6 ppm. MALDI-TOF MS: calcd. for $[M + Na]^+$ 2126.94; found 2126.11. $C_{129}H_{138}O_{26}$ (2126.94): calcd. C 73.62, H 6.61; found C 73.35, H 6.70.

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