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Sequential One-Pot Glycosidations Catalytically Promoted: Unprecedented Strategy in Oligosaccharide Synthesis for the Straightforward Assemblage of the Antitumor PI-88 Pentasaccharide

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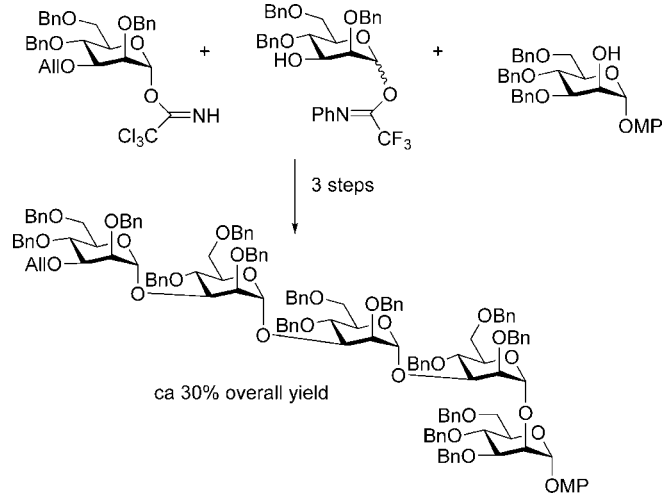

The pentasaccharide sequence of the most active components of the antitumor drug PI-88, currently in phase II clinical trial, has been rapidly assembled in high overall yield and in only three steps starting from three monosaccharide building blocks. The procedure takes advantage of the first reported strategy of sequential one-pot glycosidations conducted exclusively under catalytic activation. In addition, the procedure relies only on shelf-stable and mild promoters such as $Yb(OTf)_3$ and $Bi(OTf)_3$.

Introduction

Over the past years the therapeutic impact of oligosaccharides has been widely recognized by the scientific community as demonstrated by the increasing number of biomedical applications.[1] Consequently, the ever-growing need of pure and homogeneous oligosaccharide probes has elicited formidable progress in the field of oligosaccharide synthesis so that even some examples of automated syntheses via a solid-phase approach have been reported.[2] Concurrently, solution synthesis of oligosaccharides has reached an important stage of maturity with the advent of one-pot strategies that enable the construction of oligosaccharide fragments by means of sequential multiple glycosidations.[3] In this regard, several approaches have been usefully exploited. An option is represented by the use of the orthogonal strategy, which exploits for each coupling the selective activation of one leaving group over another, the two groups being chemically different.[4] Another opportunity is offered by a chemoselective approach, which takes advantage of the feasible reactivity tuning of donors bearing similar anomeric groups by exploiting the arming−disarming[5] effect

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of the functional groups present on the saccharide scaffold. This latter concept has been broadly elaborated by Wong and co-workers, who developed a computer-assisted protocol for choosing the best set of glycosyl donors to assemble a given target sequence.[6,7] Very recently, another ingenious one-pot approach has been proposed. It is based on a preactivation stage for every coupling in which a thioglycoside donor is converted to a highly reactive glycosylating species at low temperature upon exposure to a suitable stochiometric promoter. Subsequent addition of a thioglycoside acceptor yields a glycosidation product that can be preactivated in situ for a further elongation with a further acceptor.[8] This latter strategy is advantageous because it is independent of the relative reactivity of the employed donors. A common drawback of all one-pot sequential glycosidation procedures so far described is the required activation of glycosyl donors with stoichiometric or excess amounts of costly and/or sensitive reagents such as NIS, triflic anhydride, silver triflate, or sterically encumbered pyridines.[3]

Recently, we have communicated the first examples of catalytic procedures for the sequential construction of two glycosidic bonds in a one-pot approach.[9] Such protocols were inspired by the recognition of the well-differentiated activation conditions of similarly protected glycosyl-trichloroacetimidates[10] and (*N*-phenyl)trifluoroacetimidates[11] under the agency of catalytic ytterbium(III) triflate.[12,13] More recently, we have also disclosed that bismuth(III) triflate is a novel activator of glycosyl trihaloacetimidates endowed of exceptional reactivity so that

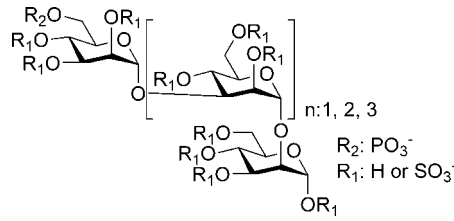

FIGURE 1. Components of PI-88.

reactions can be performed under relevantly milder conditions in terms of temperature and catalyst loading than when using $Yb(OTf)_3$.[14] The capability of $Bi(OTf)_3$ of promoting high-yielding glycosidations in short times appeared a good fit with our attempts to develop ever more efficient catalytic multiglycosidation processes to achieve biologically useful oligosaccharides.

In this paper, we wish to report on the sequential one-pot glycosidations performed exclusively under catalytic activation that led us to a very straightforward and flexible approach for preparing the pentasaccharide component of the antitumor agent PI-88 (Figure 1). This drug is currently in phase II clinical trial[15] and is constituted by a mixture of randomly sulfated tri-, tetra-, and penta-mannans bearing a phosphate functionality at the primary site of the nonreducing terminal residue. This phosphate can be replaced by a sulfate group without appreciable loss of biological activity.[16,17] The drug is obtained by the yeast *Pichia (Hansenula) holstii* NRRL Y-2448 as a mixture of phosphorylated mannans that are subsequently randomly sulfated via a chemical approach.[18]

The antitumor properties of PI-88 are believed to be connected with its ability to act as inhibitor of both heparanases and angiogenic growth factors.[19] The pentasaccharide fraction is the most abundant and is considered the most active component of the drug. To date, only two examples of chemical syntheses of this pentasaccharide have been reported, including a very recent paper by Ferro and co-workers.[17,20] Both of these schemes are providing good overall yields, but a large number of synthetic steps renders them rather laborious. In this paper we wish to report the feasible assemblage of the penta-mannose sequence **1** (Scheme 1) by an alternative strategy based on only three steps (two one-pot multiglycosidations and a single intermedi-

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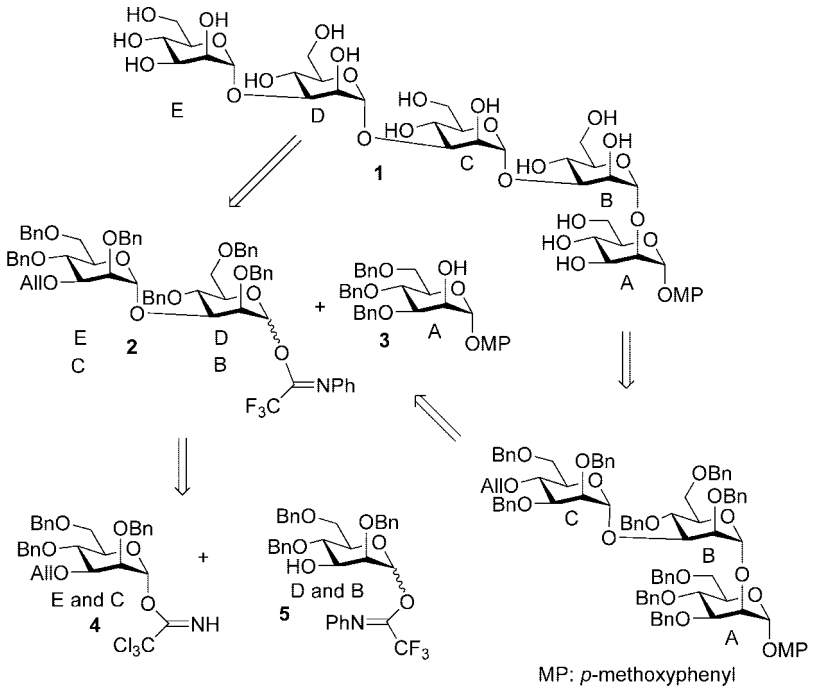
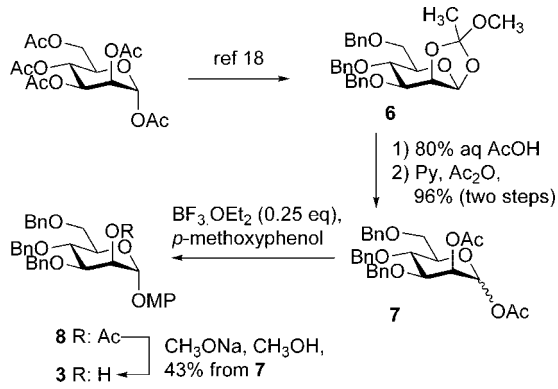
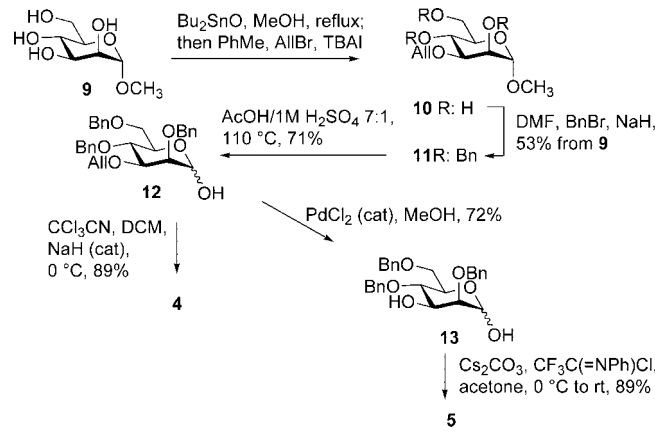
SCHEME 1. Retrosynthetic Scheme of the PI-88 Pentasaccharide



SCHEME 2



SCHEME 3



ate deprotection step) and entailing only three monosaccharide building blocks for the whole task.

Results and Discussion

The proposed strategy (Scheme 1) relies on the feasible in situ generation of disaccharide **2** as the precursor of both the BC and DE fragments, whereas readily obtainable acceptor **3** represents the precursor of the reducing terminus A. Disaccharide **2** was expected to be accessible by the key chemoselective coupling of trichoroacetimidate donor **4** and the partially protected trifluoroacetimidate **5** acting as an acceptor at this stage.

Acceptor **3** was efficiently obtained starting from penta-*O*-acetyl-D-mannose (Scheme 2), which was initially converted into orthoester **6** through a rapid sequence of three reactions and without any chromatographical purification of intermediates (50−55% overall yield).[21] Compound **6** was submitted to sequential acid-mediated cyclic orthoester opening and acetylation to yield almost quantitatively the diacetylated intermediate **7**. This latter was in turn directly converted into the corresponding 4-*O*-methoxy phenyl glycoside **8** under the agency of $BF_3 \cdot OEt_2$ and then 2-*O*-deacetylated to yield the desired building block **3**.

Compounds **4** and **5** were prepared through synthetic pathways sharing a large number of steps (Scheme 3). Methyl mannoside **9** was regioselectively 3-*O*-allylated via a stannylidene intermediate,[22] and the resulting triol **10** was then perbenzylated under standard conditions. Derivative **11** was hydrolyzed under acidic conditions to yield hemiacetal **12**, which was the last common intermediate of the routes leading to **4** and **5**. The former was prepared in high yield (ca. 90%) with only an additional standard 1-*O*-trichloroacetimidation step. Alternatively, **12** was deallylated with $PdCl_2$ in methanol in 72% yield, and the resulting diol **13** was then selectively converted into trifluoroacetimidate **5** (α:β ca. 4:1) adopting Cs_2CO_3[13d] as the base.

As shown in the retrosynthetic analysis (Scheme 1), the successful assemblage of the target pentasaccharide is critically

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SCHEME 4. Chemoselective Coupling of 14 and 5

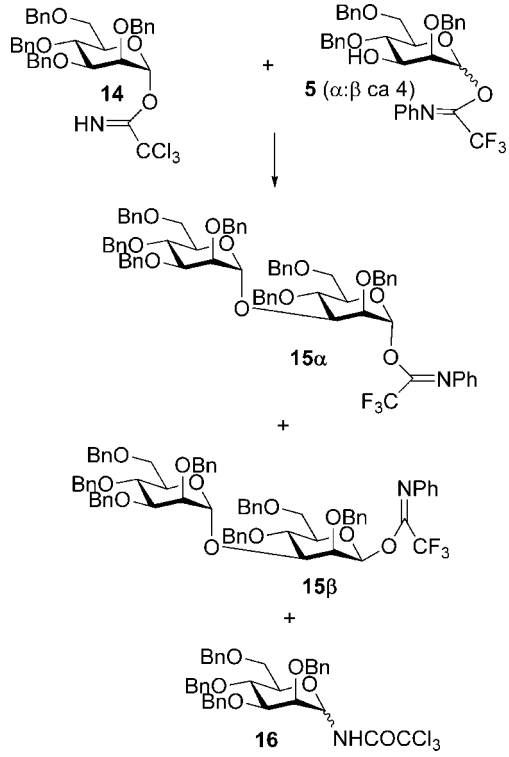


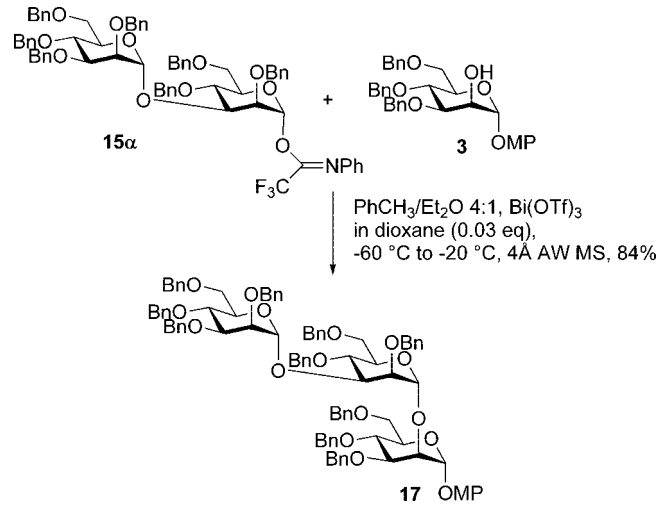
TABLE 1[a]

entry	promoter (equiv)	*T* (°C)	time (min)	isolated yield of **15α**[b]
1	$Bi(OTf)_3$ (0.10)	−60 to −55	30	42
2	$Bi(OTf)_3$ (0.05)	−70 to −60	60	47
3	$Yb(OTf)_3$ (0.03)	−10	30	58

[a] General conditions: **14** (1.4−1.7 equiv), **5** (1 equiv), $PhCH_3/Et_2O$ 4/1, $Yb(OTf)_3$ or $Bi(OTf)_3$ (16−20 mg/mL in dioxane), 4Å AW MS. [b] Calculated with respect to the overall amount (α and *β* anomers) of **5**.

dependent on the coupling between the fully protected trichloroacetimidate **4** and the partially protected trifluoroacetimidate **5**. Indeed, this reaction should provide in high yield and stereocontrol the desired glycosidic bond while leaving intact the activatable trifluoroacetimidate functionality to allow the subsequent glycosidation. To optimize this delicate step, acceptor **5** and the model trichloroacetimidate **14**, easier to obtain than **4**,[10] were coupled under a variety conditions aimed at achieving exclusive activation of the trichloroacetimidate component (Scheme 4). The reactions were quenched at low temperature with pyridine to minimize any deterioration of the trifluoroacetimidate functionality. After a preliminary screening, a toluene/diethyl ether mixture was found as the best serving reaction solvent. Reactions conducted under $Bi(OTf)_3$ activation at very low temperature produced the desired disaccharide trifluoroacetimidate **15α** in a satisfying isolated yield (Table 1, entries 1 and 2) together with minor amounts of the anomer ***15β*** (equally useful for our purposes in the planned one-pot application). This latter could not be isolated pure because it coeluted with the byproduct **16** derived from rearrangement of the trichloroacetimidate **14**. To the best of our knowledge, these are the first examples of isolated glycosylation products in which an anomeric (*N*-phenyl)trifluoroacetimidate group is designed to act as a temporary protecting group. Interestingly, the milder promoter $Yb(OTf)_3$ furnished **15α** in a higher yield than

SCHEME 5



$Bi(OTf)_3$, although a remarkably higher temperature (−10 versus −60 °C) was required for reactions to proceed within comparable times (Table 1, entry 3).

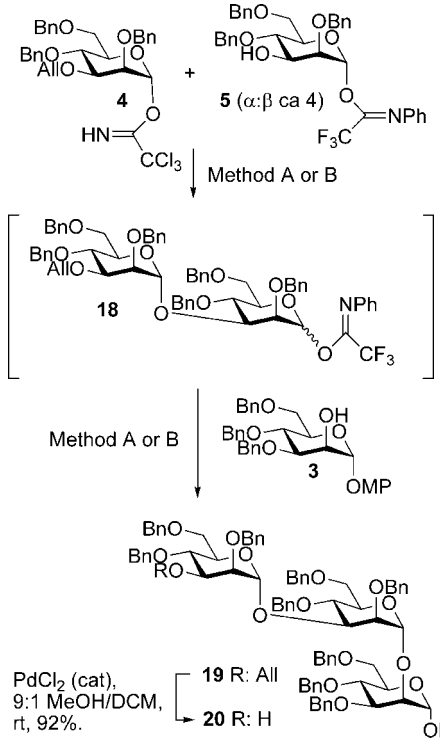
The donor ability of disaccharide **15α** under $Bi(OTf)_3$ activation was then examined in the coupling with acceptor **3** to quickly provide in excellent yield the trisaccharide **17** (Scheme 5), which corresponds to the ABC fragment of the target pentasaccharide and is itself biologically interesting, being related to an antiallergenic sequence.[23]

Having established the optimized conditions for generating and activating the requisite mannose disaccharide trifluoroacetimidate, their application was targeted toward the assemblage of the desired pentasaccharide via sequences of one-pot double glycosidations.

The extensible precursor **19** of the ABC fragment was prepared by initial coupling of **5** and the 3-*O*-allylated trichloroacetimidate **4**, the subsequent addition of acceptor **3** to the mixture, and the adjustment of the experimental conditions for activating the trifluroacetimidate leaving group (Scheme 6). The one-pot synthesis was examined by using either $Bi(OTf)_3$ or $Yb(OTf)_3$ for the initial coupling. In the former case (Scheme 6, Method A), the first glycosidation step occurred at a very low temperature (from −70 to −60 °C), and the second coupling was accomplished without any further amount of promoter by the simple addition of acceptor **3** and the spontaneous warming of the mixture. Alternatively (Scheme 6, Method B), $Yb(OTf)_3$ promoted the first coupling between **4** and **5** at −10 °C for 30 min, and then, after cooling to −60 °C, acceptor **3** and $Bi(OTf)_3$ (0.03 equiv) were sequentially added, and the mixture was allowed to warm spontaneously. As expected from the results of preliminary experiments shown in Table 1, use of a different promoter for each glycosidation (Route B) provided an improved yield, the results being in any way quite satisfying by the means of both methods (yields in the range of 43−60%). It is worthy of note that in both cases a very low amount of promoter(s) was needed for accomplishing the sequential double glycosidation and the whole process took less than 3 h, with a sensible acceleration in comparison with the previously reported catalytic procedure based on the sole $Yb(OTf)_3$.[8] Trisaccharide **19** was smoothly deallylated to yield **20** (Scheme 6), the requisite acceptor for the final one-pot sequence leading to pentasaccha-

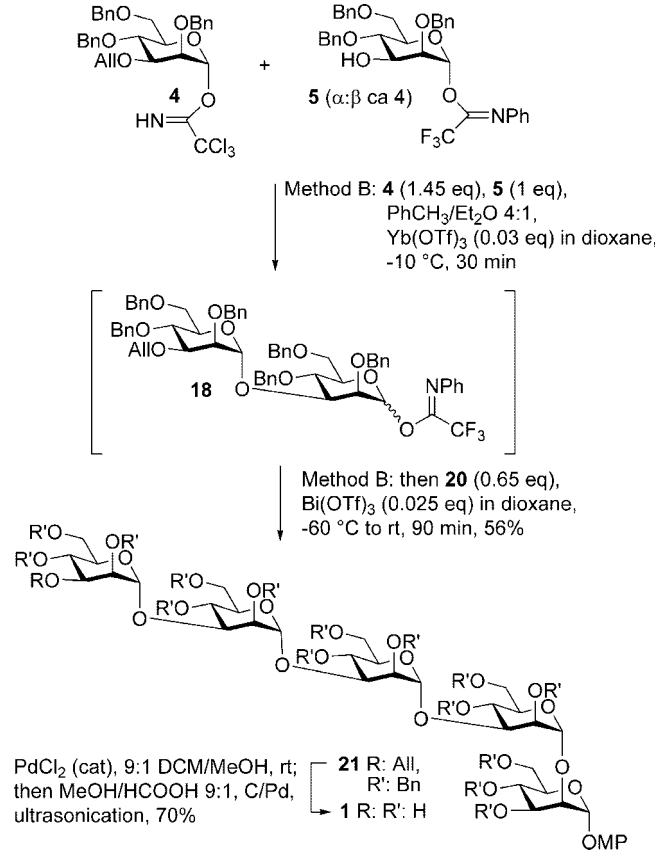
(23) Carpenter, C.; Nepogodiev, S. A. *Eur. J. Org. Chem.* **2005**, 3286–3296.

SCHEME 6[a]



[a] Method A: **4** (1.3−1.5 equiv), **5** (1 equiv), $PhCH_3/Et_2O$ 4:1, $Bi(OTf)_3$ (0.05 equiv) in dioxane, −70 to −60 °C, 45 min; then **3** (1−1.3 equiv), −60 to 0 °C, 90 min, 43−46%. Method B: **4** (1.2 equiv), **5** (1 equiv), $PhCH_3/Et_2O$ 4:1, $Yb(OTf)_3$ (0.03 equiv) in dioxane, −10 °C, 30 min; then **3** (0.8 equiv), $Bi(OTf)_3$ (0.025 equiv) in dioxane, −60 to 10 °C, 90 min, 60%.

SCHEME 7



ride **21**. Following the procedure that best served for **19** (Method B, Scheme 6), **18** was transiently formed from **4** and **5** under the agency of $Yb(OTf)_3$ and then coupled with **20** in the presence of $Bi(OTf)_3$ to give **21** in a gratifying yield of 56% (Scheme 7).

Despite the structural changes in the final acceptor (**20** rather than **3**), the yield of this sequence was somewhat similar to that leading to trisaccharide **19**. Pentasaccharide **21** was deallylated and debenzylated under standard conditions to yield the free pentasaccharide **1**, which can be submitted to the procedure of random sulfation. On the other hand, the presence in **21** of differentiated protecting groups (allyl, benzyls, and an anomeric 4-methoxy-phenyl group) renders the obtained pentasaccharide amenable to further structural elaborations.

Conclusions

In conclusion, in this paper we have shown the notable applicative potential of one-pot glycosidation of oligosaccharides conducted under exclusively catalytic conditions of activation, the pentasaccharide component of the drug PI-88 being rapidly accessed through a reduced number of synthetic steps and resorting to only three easily obtained D-mannose building blocks. Notably, inclusion of $Bi(OTf)_3$ in the activation system allows the one-pot glycosidation sequences to be accomplished in short times and high yields. Additionally, very low amounts of shelf-stable promoter(s) (about 0.10 equiv) are sufficient for the assemblage of the overall sequence, which entails the construction of four glycosidic bonds. It is also worthy of note that some model coupling experiments have shown that the trifluoroacetimidate anomeric group can play the role of a temporary anomeric protecting group in sequential multiglycosidation steps. Feasible access to a biological important target establishes a conceptually novel strategy where the catalytic activation of all sequential glycosidation steps makes it possible to overcome important drawbacks of the current strategies such as the use of costly and/or sensitive stoichiometric promoters and the production of higher amounts of side products. Elaboration of the developed protocols toward other biologically useful oligosaccharide sequences are being evaluated in our laboratory and will be reported in due course.

Experimental Section

1,2-Di-*O*-acetyl-3,4,6-tri-*O*-benzyl-α,*β*-D-mannopyranoside (7). Orthoester **6** (3.895 g, 7.9 mmol) was dissolved at room temperature in 80% aqueous AcOH (20 mL). After 30 min, the mixture was diluted with DCM and the organic phase washed with water, and then with aqueous Na_2CO_3. The aqueous phases were then re-extracted with DCM and the collected organic phases dried and concentrated under vacuum. The residue was dissolved in pyridine (5 mL) and acetic anhydride (2.5 mL). After 2.5 h the mixture was treated with MeOH and diluted with DCM. The organic phase was washed with water, dried and concentrated to yield syrupy **7** in a satisfying purity (3.960 g, α/*β* ca. 4, yield 96%) to be directly submitted to the following step. ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.50−7.00 (aromatic protons), 6.15 (1H, d, $J_{1,2}$ = 2.1 Hz, H-1), 5.39 (1H, bd, H-2), 4.90−4.50 (6H, 3 × AB, 3 × benzyl CH_2), 4.00 (1H, bd, $J_{3,4}$ = 9.3 Hz, H-3), 3.95−3.75 (3H, H-5, H-6a, H-6b), 3.72 (1H, t, $J_{4,5}$ = 9.3 Hz, H-4), 2.17, 2.08 (6H, 2 × s, 2 × $-COCH_3$). ^{13}C NMR ($CDCl_3$, 50 MHz): *δ* 170.8, 170.0, 138.1 (×2), 137.6, 128.9−127.5, 91.3, 75.3, 73.7, 73.6, 73.5, 71.9, 68.5, 67.5, 20.9. Anal. Calcd for $C_{31}H_{34}O_8$: C, 69.65, H, 6.41. Found: C, 69.93; H, 6.52.

***p*-Methoxyphenyl 3,4,6-Tri-*O*-benzyl-α-D-mannopyranoside (3).** To a solution of compound **7** (1.234 g, 2.31 mmol) and *p*-methoxyphenol (436 mg, 3.51 mmol) in dry DCM (7 mL) were added freshly activated 4Å molecular sieves and $BF_3 \cdot OEt_2$ (75 μL, 0.59 mmol) at 0 °C under argon. After removing the ice bath, the mixture was stirred at room temperature for 3 h and then pyridine (6 drops) was added to quench the reaction. The mixture was concentrated in vacuo and the residue submitted to silica gel flash chromatography to yield **8** slightly contaminated with unreacted *p*-methoxyphenol. To this impure material dissolved in methanol (4 mL) was added dropwise a solution of MeONa (2 M in MeOH) until completion of the reaction (TLC). The mixture was then diluted with DCM and washed with 0.1 M aqueous NaOH and water. Aqueous phases were re-extracted with DCM and the collected organic phases were dried and concentrated. The residue was applied to a short silica gel column eluted with petroleum ether/acetone 6:4 to yield **3** as a yellow oil (556 mg, 43% over two steps). $[\alpha]^{25}_D$ +86.4° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.44−6.70 (aromatic protons), 5.50 (1H, d, $J_{1,2}$ = 1.8 Hz, H-1), 4.84−4.40 (6H, 3 × AB, 3 × benzyl CH_2), 4.19 (1H, m, H-2), 4.06 (1H, dd, $J_{2,3}$ = 3.3 Hz, H-3), 3.94 (1H, t, $J_{3,4} = J_{4,5}$ = 9.9 Hz, H-4), 3.91−3.84 (1H, m, H-5), 3.74 (1H, dd, $J_{5,6a}$ = 4.2 Hz, $J_{6a,6b}$ = 10.8 Hz, H-6a), 3.73 (3H, s, $-OCH_3$), 3.63 (1H, dd, $J_{5,6b}$ = 1.5 Hz, H-6b), 2.55 (1H, d, $J_{2,OH}$ = 2.4 Hz, 2-OH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 154.9, 150.0, 138.3, 138.2, 137.8, 128.4−127.0, 117.7, 114.5, 98.2, 79.9, 75.0, 74.1, 73.2, 72.0, 71.5, 68.8, 68.2, 55.4. MALDI-MS: $[M + Na]^+$ calcd 579.24, found 579.32. Anal. Calcd for $C_{34}H_{36}O_7$: C, 73.36, H, 6.52. Found: C, 73.25; H, 6.55.

Methyl 3-*O*-Allyl-α-D-mannopyranoside (10). Methyl α-mannopyranoside (3.118 g, 16.1 mmol) and Bu_2SnO (4.402 g, 17.7 mmol) were refluxed in MeOH (80 mL) for 2 h. The obtained solution was evaporated under vacuum. To the residue suspended in toluene (100 mL) were sequentially added allyl bromide (14.0 mL, 165 mmol) and TBAI (5.94 g, 16.1 mmol). The mixture was kept under stirring at 65−70 °C for 20 h and concentrated. Silica gel flash chromatography of the residue (eluent ethyl acetate/petroleum ether from 7:3 to 8:2) yielded **10** slightly contaminated with tetrabutylammonium salts (estimated yield 65−70% on the basis of NMR integrations). The product thus obtained was directly submitted to the subsequent step. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.05−5.85 (1H, m, $-CH{=}CH_2$), 5.29 (1H, dq, *J* = 1.4 and 18.8 Hz, $-CH{=}CH_{cis}H_{trans}$), 5.17 (1H, bd, *J* = 10.4 Hz, $-CH{=}CH_{cis}H_{trans}$), 4.73 (1H, bs, H-1), 4.25−3.70 (6H), 3.65−3.40 (2H), 3.31 (3H, s, $-OCH_3$).

Methyl 3-*O*-Allyl-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (11). To a solution of compound **10** (estimated mass ca. 2.5 g, ca. 11 mmol) in dry DMF (13 mL) were sequentially added at 0 °C benzyl bromide (6.4 mL, 54 mmol) and sodium hydride (60% in oil, 1.75 g, 73 mmol). The mixture was allowed to warm to room temperature, and after 3 h MeOH (ca. 1 mL) was added. The mixture was diluted with DCM and the organic phase washed with water. The aqueous phase was re-extracted with DCM and the collected organic phases were 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/ethyl acetate 85:15) to yield **11** as an oil (5.465 g, 53% over two steps). $[\alpha]^{25}_D$ +29.4° (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.05−5.85 (1H, m, $-CH_2CH{=}CH_2$), 5.34 (1H, dq, *J* = 1.6 and 17.4 Hz, $-CH{=}CH_{cis}H_{trans}$), 5.17 (1H, dq, *J* = 10.2 Hz, $-CH{=}CH_{cis}H_{trans}$), 4.78 (1H, bs, H-1), 4.93−4.50 (6H, 3 × AB, benzyl CH_2), 4.15−4.05 (2H, m, $-OCH_2CH{=}CH_2$), 4.00−3.85 (2H), 3.85−3.70 (4H), 3.34 (3H, s, $-OCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.5, 138.4 (×2), 134.9, 128.2−127.5, 116.5, 99.0, 79.8, 75.0, 74.8, 74.5, 73.3, 72.5, 71.6, 71.0, 69.3, 54.7. MALDI-MS: $[M + Na]^+$ calcd 527.24, found 527.30. Anal. Calcd for $C_{31}H_{36}O_6$: C, 73.79, H, 7.19. Found: C, 73.65; H, 7.23.

3-*O*-Allyl-2,4,6-tri-*O*-benzyl-D-mannopyranose (12). A solution of **11** (446 mg, 0.88 mmol) in 7:1 AcOH/1 M H_2SO_4 (5.4 mL) was heated at 110 °C for 70 min. The mixture was then diluted with DCM, and the organic phase was washed with water. The aqueous phase was re-extracted with DCM. Collected organic phases were washed with aqueous sodium carbonate and concentrated. The residue was purified by silica gel flash chromatography (eluent petroleum ether/ethyl acetate from 3:1 to 7:3) to yield **12** as a yellow oil (434 mg, α/β ca. 7:1, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.05−5.85 (1H, m, $-CH{=}CH_2$), 5.34 (1H, bd, *J* = 17.4 Hz, $CH_2CH{=}CH_{cis}H_{trans}$), 5.25 (1H, bs, H-1), 5.19 (1H, bd, *J* = 10.2 Hz, $CH{=}CH_{cis}H_{trans}$), 4.91−4.48 (6H, 3 × AB, benzyl CH_2), 4.15−4.00 (3H), 3.95−3.60 (5H), 3.24 (bs, 1-OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.3 (×2), 137.8, 134.8, 128.2−127.5, 116.4, 92.4, 79.3, 75.0, 74.9, 73.0, 72.4, 71.2, 70.9, 70.8, 69.5. MALDI-MS: $[M + Na]^+$ calcd 513.23, found 513.18. Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45, H, 6.99. Found: C, 73.28; H, 7.04.

Trichloroacetimidoyl 3-*O*-Allyl-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (4). To a solution of **12** (488 mg, 0.99 mmol) in DCM (5 mL) were sequentially added at 0 °C trichloroacetonitrile (400 μL, 4 mmol) and sodium hydride (60% in oil, 10 mg, 0.25 mmol). The mixture was allowed to warm to room temperature and concentrated after 40 min. The residue was chromatographed on neutral alumina (Brockman grade 2, eluent petroleum ether/ethyl acetate 9:1 with two drops of pyridine for every 100 mL of eluent) to yield **4** as an oil (560 mg, yield 89%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.69 (1H, s, −NH), 7.53−7.20 (aromatic protons), 6.52 (1H, s, H-1), 6.04−5.91 (1H, m, $-OCH_2-CH{=}CH_2$), 5.37 (1H, dd, *J* = 1.2 and 17.4 Hz, $CH{=}CH_{cis}H_{trans}$), 5.24 (1H, dd, *J* = 10.5 Hz, $-OCH_2-CH{=}C\ H_{cis}H_{trans}$), 4.99−4.57 (6H, 3 × AB, 3 × benzyl CH_2), 4.23 (1H, t, *J* = 9.6 Hz, H-4), 4.19−4.07 (3H, m, H-5 and $-OC\ H_2CH{=}CH_2$), 4.06 (1H, dd, $J_{1,2}$ = 1.8 Hz, $J_{2,3}$ = 2.7 Hz, H-2), 3.97 (1H, dd, H-3), 3.91 (1H, dd, $J_{5,6a}$ = 4.5 Hz, $J_{6a,6b}$ = 11.4 Hz, H-6a), 3.81 (1H, bd, H-6b). ^{13} C NMR ($CDCl_3$, 75 MHz): δ 160.0, 138.0 (×2), 137.6, 134.4, 128.1−127.1, 116.8, 95.9, 90.7, 78.7, 74.9, 74.5, 73.7, 73.0 (×2), 72.3, 70.8, 68.4. Anal. Calcd for $C_{32}H_{34}Cl_3NO_6$: C, 60.53, H, 5.40. Found: C, 60.41; H, 5.46.

2,4,6-Tri-*O*-benzyl-D-mannopyranose (13). To a solution of **12** (307 mg, 0.63 mmol) in methanol (2 mL) was added at room temperature palladium chloride (15 mg, 0.085 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/ ethyl acetate from 7:3 to 6:4) to provide diol **13** as an oil (α:β ca. 9:1, 205 mg, yield 72%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.5−7.10 (aromatic protons), 5.31 (1H, s, H-1), 4.89−4.51 (6H, 3 × AB, 3 × benzyl CH_2), 4.10−4.00 (2H, m, H-3, H-5), 3.84−3.64 (3H, m, H-2, H-6a, H-6b), 3.60 (1H, t, $J_{3,4} = J_{4,5}$ = 9.6 Hz, H-4), 2.92 (1-OH). ^{13} C NMR ($CDCl_3$, 75 MHz) 138.5, 137.9 (×2), 128.4−127.6, 91.5, 79.0, 78.6, 74.8, 73.4, 72.9, 71.5, 70.6, 69.7. Anal. Calcd for $C_{27}H_{30}O_6$: C, 71.98, H, 6.71. Found: C, 71.85; H, 6.77.

(*N*-Phenyl)trifluoroacetimidoyl 2,4,6-Tri-*O*-benzyl-α,β-D-mannopyranoside (5). To a solution of diol **13** (399 mg, 0.89 mmol) in acetone (3 mL) were sequentially added at 0 °C Cs_2CO_3 (324 mg, 0.99 mmol) and (*N*-phenyl)trifluoroacetimidoyl chloride (220 μL, 1.8 mmol). The mixture was allowed to warm to room temperature and after 2 h concentrated under vacuum. The residue was purified by chromatography on neutral alumina (Brockman grade 2, eluent petroleum ether/ethyl acetate 9:1 with two drops of pyridine for every 100 mL of eluent) to yield **5** as a yellow oil (anomeric mixture α/β ca. 4:1, 492 mg, yield 89%). **Data for 5α.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50−6.81 (aromatic protons), 6.42 (1H, bs, H-1), 4.92−4.56 (6H, 3 × AB, 3 × benzyl CH_2), 4.08 (1H, m, H-3), 4.03−3.77 (5H), 2.75 (1H, d, $J_{3,OH}$ = 8.4 Hz, 3-OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.3, 138.0 (×2), 137.0, 129.0−127.7, 127.4, 124.3, 119.3, 94.5, 75.9, 75.5, 74.9, 73.8, 73.3, 72.7, 71.2, 68.5. Anal. Calcd for $C_{35}H_{34}F_3NO_6$: C, 67.62, H, 5.51. Found: C, 67.50; H, 5.59.

(*N*-Phenyl)trifluoroacetimidoyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyrano-

side (15α). Trichloroacetimidate **14** (26 mg, 0.038 mmol) and trifluoroacetimidate **5** (17 mg, 0.027 mmol) were coevaporated three times with toluene (3 × 0.5 mL) and dried under vacuum. After 4Å AW 300 MS were added, the mixture was dissolved with 4:1 toluene/Et_2O (1 mL) and cooled to −10 °C. After ca. 15 min of stirring, a solution of $Yb(OTf)_3$ in dioxane (20 mg/mL, 25 μL, 8.1 μmol) was added and after 30 min the reaction was quenched at the same temperature with pyridine. The mixture was filtered on a short plug of neutral alumina and concentrated. The residue was chromatographed on neutral alumina (Brockman grade 2, eluent petroleum ether/ethyl acetate 85:15 with two drops of pyridine for every 100 mL) to yield **15α** as an oil (18 mg, yield 58%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.60−6.75 (aromatic protons), 6.25 (1H, bs, H-1), 5.25 (1H, s, H-1′), 4.90−4.46 (14H, 7 × AB, 7 × benzyl CH_2), 4.15 (1H, dd, H-3), 3.94 (1H, d, $J_{2,3}$ = 3.3 Hz, H-2), 3.77 (1H, bd, H-2′), 4.20−3.60 (9H). ^{13} C NMR ($CDCl_3$, 75 MHz): δ 143.4, 138.7, 138.4, 138.2, 138.1, 138.0, 137.5, 129.3−119.4, 100.1, 94.7, 79.7, 75.8, 75.5, 74.9, 74.7, 74.5, 74.1, 73.39, 73.38, 72.7, 72.4, 72.2, 69.3, 68.6. MALDI-MS: $[M + Na]^+$ calcd 1166.46, found 1166.70. Anal. Calcd for $C_{69}H_{68}F_3NO_{11}$: C, 72.42, H, 5.99. Found: C, 72.40; H, 6.07.

***p*-Methoxyphenyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (17).** Disaccharide donor **15α** (25 mg, 0.022 mmol) and acceptor **3** (9 mg, 0.017 mmol) were coevaporated three times with toluene (3 × 0.5 mL) and dried under vacuum. After 4Å AW 300 MS were added, the mixture was dissolved under argon with 4:1 toluene/Et_2O (0.7 mL), cooled to −60 °C, and stirred for 15 min. A solution of $Bi(OTf)_3$ in dioxane (20 mg/mL, 17 μL, 0.5 μmol) was then added, and after 20 min of stirring at −60 °C, the temperature was allowed to raise up to −20 °C over 60 min. Pyridine was added to quench the reaction and the mixture was filtered on a short plug of silica gel, concentrated, and purified by silica gel flash chromatography (eluent petroleum ether/ethyl acetate from 8:2 to 7:3) to yield **17** as an oil (22 mg, 84% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40−7.00 (benzyl protons), 6.98 and 6.72 (4H, 2 × d, J_{ortho} = 9.2 Hz, aromatic *p*-methoxyphenyl protons), 5.57 (1H, d, *J* = 1.6 Hz, H-1), 5.23 (1H, bs, anomeric proton), 5.22 (1H, d, *J* = 1.6 Hz, anomeric proton), 4.90−4.33 (20H, 10 × AB, 10 × benzyl CH_2), 4.26 (1H, t, H-2), 4.21 (1H, dd, *J* = 3.0 and 8.4 Hz), 4.13−4.06 (2H), 4.00−3.80 (7H), 3.73 (3H, s, $-OCH_3$), 3.77−3.62 (6H), 3.56 (1H, bd, *J* = 10.0 Hz). ^{13} C NMR ($CDCl_3$, 50 MHz) 154.8, 150.1, 138.8, 138.5−138.2, 128.2−127.0, 117.9, 114.5, 99.6, 99.5, 98.0, 80.0, 79.6, 75.5, 75.1, 75.0, 74.7, 74.2, 73.3, 73.2, 72.5, 72.3, 72.2, 72.1, 69.2, 68.9, and 55.6. MALDI-MS: $[M + Na]^+$ calculd 1533.67, found 1533.56. Anal. Calcd for $C_{95}H_{98}O_{17}$: C, 75.47, H, 6.53. Found: C, 75.28; H, 6.62.

***p*-Methoxyphenyl 3-*O*-Allyl-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (19).** Trichloroacetimidate **4** (123 mg, 0.194 mmol) and trifluoroacetimidate **5** (106 mg, 0.170 mmol) were coevaporated three times with anhydrous toluene (3 × 1 mL) and dried under vacuum for 1 h. The residue was dissolved under argon with 4:1 toluene/Et_2O (4.7 mL) in the presence of freshly activated 4Å AW300 MS. The mixture was then cooled to −10 °C and stirred for 15 min. A solution of $Yb(OTf)_3$ in dioxane (25 mg/mL, 125 μL, 0.005 mmol) was added at that temperature, and the mixture was stirred for 30 min and then cooled to −60 °C. Acceptor **3** (75 mg, 0.135 mmol) in 4:1 toluene/Et_2O (0.9 mL) and a solution of $Bi(OTf)_3$ in dioxane (16.6 mg/mL, 160 μL, 0.004 mmol) were subsequently added, and the temperature was allowed to warm up to 10 °C over 90 min. The reaction was quenched with some drops of pyridine and the mixture was filtered on a short plug of silica gel (eluent DCM/MeOH/acetonitrile 85:10:5), concentrated, and purified by silica gel flash chromatography (eluent petroleum ether/ethyl acetate from 9:1 to 8:2) to yield trisaccharide **19** as a yellow oil (118 mg, 60% overall yield). $[\alpha]^{25}_D$ +29.7° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50−7.10 (aromatic benzyl protons), 7.10 and 6.93 (4H, 2 × d, J_{ortho} = 9.2 Hz, aromatic *p*-methoxyphenyl protons), 5.80−5.95 (1H, m, $OCH_2-CH{=}CH_2$), 5.58 (1H, d, $J_{1,2}$ = 1.6 Hz, H-1), 5.26 (1H, dd, J_{trans} = 1.2 and 16.8 Hz, $-OCH_2-CH{=}CH_{cis}H_{trans}$), 5.24 (2H, bs, H-1′ and H-1″), 5.26 (1H, dd, J_{cis} = 10.4 Hz, $-OCH_2-CH{=}CH_{cis}H_{trans}$), 4.90−4.30 (18H, 9 × AB, 9 × benzyl CH_2), 4.27 (1H, t, H-2), 4.23 (1H, dd, *J* = 3.2 and 8.4 Hz), 4.15−4.10 (2H), 3.74 (3H, s, $-OCH_3$), 4.15−3.65 (16 H), 3.56 (1H, bd, *J* = 9.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) 154.9, 150.1, 138.6−138.2, 135.0, 128.3−127.0, 116.4, 118.0, 114.5, 99.5 (×2), 98.0 (C-1), 79.7, 79.6, 75.3, 75.2, 75.1, 74.8, 74.6, 73.2, 73.1, 71.0, 69.2, 68,8, 55.6. MALDI-MS $[M + Na]^+$ calcld 1483.65, found 1483.85. Anal. Calcd for $C_{91}H_{96}O_{17}$: C, 74.77, H, 6.62. Found: C, 74.60; H, 6.69.

***p*-Methoxyphenyl 2,4,6-Tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (20).** $PdCl_2$ (2 mg, 0.011 mmol) was added to a solution of trisaccharide **19** (110 mg, 0.075 mmol) in MeOH/DCM 9:1 (6 mL). After 3 h under stirring the mixture was concentrated under vacuum, resuspended with DCM/MeOH 95:5, filtered on a short plug of silica gel, concentrated, and purified by silica gel flash chromatography (eluent toluene/acetone 96:4) to yield **20** as an oil (98 mg, yield 92%). $[\alpha]^{25}_D$ +35.2° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50−7.10 (benzyl aromatic protons), 6.99 and 6.73 (4H, 2 × d, J_{ortho} = 9.2 Hz, *p*-methoxyphenyl protons), 5.60 (1H, d, *J* = 1.6 Hz, H-1), 5.27 (1H, bs, anomeric proton), 5.23 (1H, d, *J* = 1.6 Hz, anomeric proton), 4.85−4.30 (18 H, 9 × AB, 9 × benzyl CH_2), 4.28 (1H, t, H-2), 4.25 (1H, dd, *J* = 3.2 Hz, 9.6 Hz), 4.20−4.10 (2H), 3.74 (3H, s, $-OCH_3$), 4.05−3.60 (14 H, m), 3.52 (1H, bd, *J* = 11.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.9, 150.2, 138.7, 138.3, 138.2 (x6), 137.7, 128.5−126.9, 117.9, 114.5, 99.6, 98.5, 98.0, 79.6, 78.7, 77.5, 75.1 (×2), 74.9, 74.7, 74.5, 74.2, 73.3, 73.2, 73.1, 72.4, 72.3, 72.1, 72.0, 71.7, 71.6, 69.2, 68.7, 55.6 ($-OCH_3$). MALDI-MS $[M + Na]^+$ calcld 1443.62, found 1443.78. Anal. Calcd for $C_{88}H_{92}O_{17}$: C, 74.35, H, 6.52. Found: C, 74.18; H, 6.61.

***p*-Methoxyphenyl 3-*O*-Allyl-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (21).** Trichloroacetimidate **4** (44 mg, 0.069 mmol) and trifluoroacetimidate **5** (29 mg, 0.047 mmmol) were coevaporated three times with anhydrous toluene (3 × 1 mL) and dried under vacuum for 45 min. The residue was dissolved under argon with 4:1 toluene/Et_2O (1.5 mL) in the presence of freshly activated 4Å AW300 MS and the resulting mixture was cooled to −10 °C and stirred for 15 min. A solution of $Yb(OTf)_3$ in dioxane (22.5 mg/mL, 40 μL, 1.4 μmol) was added at that temperature, the mixture was stirred for 30 min and then cooled to − 60 °C. Acceptor **20** (44 mg, 0.031 mmol) in 4:1 toluene/Et_2O (0.4 mL), a solution of $Bi(OTf)_3$ in dioxane (16.6 mg/mL, 49 μL, 1.2 μmol) were subsequently added, and the temperature was allowed to raise up to room temperature over 2 h. The reaction was quenched with some drops of pyridine and the mixture was filtered on a short plug of silica gel (eluent DCM/MeOH/acetonitrile 85:10:5), concentrated, and purified by silica gel flash chromatography (eluent petroleum ether/ethyl acetate from 9:1 to 8:2) to yield pentasaccharide **21** as an oil (40 mg, yield 56%). $[\alpha]^{25}_D$ +25.3° (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40−7.00 (benzyl protons), 6.98 and 6.73 (4H, 2 × d, J_{ortho} = 9.2 Hz, aromatic *p*-methoxyphenyl protons), 6.00−5.90 (1H, m, $-OCH_2-CH{=}CH_2$), 5.60 (1H, bs, H-1), 5.28 (3H, bs, 3× anomeric protons), 5.25 (1H, bs, anomeric proton), 5.23 (1H, bd, J_{trans} = 17.6 Hz, $-CH{=}CH_{cis}H_{trans}$), 5.08 (1H, bd, *J* = 10.4 Hz, $-CH{=}CH_{cis}H_{trans}$), 4.75−4.25 (30H, 15 × AB, 15 × benzyl CH_2), 4.30−4.20 (3H), 4.15−4.10 (2H), 4.05−3.68 (16H), 3.74 (3H, s, $-OCH_3$), 3.65−3.60 (2H), 3.60−3.55 (3H), 3.55−3.45 (3H), 3.38 (1H, bd, *J* = 10.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 154.9, 150.2, 139.0, 138.7, 138.4 (×4), 138.3 (×4), 138.2 (×4), 138.1, 135.0, 128.5−126.8, 118.0, 116.4, 114.5, 99.9, 99.6, 99.4, 99.3, 98.0, 76.7, 76.6, 78.9, 78.4, 77.8, 77.3,

77.2, 76.9, 76.8, 75.7, 75.2, 75.1, 75.0, 74.7, 74.5, 74.3, 73.3, 73.2, 73.1, 72.7, 72.6, 72.5, 72.3, 72.2, 72.0, 71.9, 71.0, 69.4, 69.3, 69.2, 69.0, 68.8, 55.6. MALDI-MS $[M + Na]^+$ calcld 2349.05, found 2348.93. Anal. Calcd for $C_{145}H_{152}O_{27}$: C, 74.85, H, 6.58. Found: C, 74.63; H, 6.66.

***p*-Methoxyphenyl α-D-Mannopyranosyl-(1→3)-α-D-mannopyranosyl-(1→3)-α-D-mannopyranosyl-(1→3)-α-D-mannopyranosyl-(1→2)-α-D-mannopyranoside (1).** $PdCl_2$ (2 mg, 0.011 mmol) was added to a solution of pentasaccharide **21** (37 mg, 0.014 mmol) in MeOH/DCM 9:1 (3 mL). After ca. 60 min under stirring the mixture was concentrated under vacuum, resuspended with DCM/MeOH 95:5, filtered on a short plug of silica gel, and concentrated. The residue was dissolved with several aliquots of MeOH/formic acid 9:1 (total volume 4 mL) and added under argon to palladium on charcoal (10%, 50 mg) previously wet with the same solution. The mixture was ultrasonicated for 2 h, then filtered on a plug of celite, and concentrated under vacuum. The residue was eluted with water and methanol on a short column of mixed-bed ion-exchange resin and concentrated to yield pentasaccharide **1** as a white amorphous solid (9 mg, 70% over two steps). $[\alpha]^{25}_D$ +43.3° (*c* 0.6, H_2O). ^1H NMR (D_2O, 400 MHz): δ 7.08 and 6.93 (4H, 2 × d, J_{ortho} = 10.2 Hz, *p*-methoxyphenyl protons), 5.71 (1H, d, $J_{1,2}$ = 1.6 Hz, H-1), 5.09 (2H, bs, 2 × anomeric protons), 5.07 (1H, d, $J_{1,2}$ = 1.2 Hz, anomeric proton), 5.01 (1H, d, $J_{1,2}$ = 1.8 Hz, anomeric proton), 4.21 (1H, dd, J = 1.8 and 3.0 Hz), 4.18−4.16 (2H), 4.13 (1H, dd, J = 1.8 and 3.4 Hz, H-2), 4.08 (1H, dd, J = 3.0 and 8.8 Hz), 4.03−4.01 (2H), 3.98 (1H, m), 3.96 (1H, m), 3.76 (3H, s, $-OCH_3$), 3.92−3.60 (21H). ^{13}C NMR (D_2O, 50 MHz) 155.9, 151.0, 120.1, 116.3, 103.6 (×2), 103.5, 103.4, 99.1, 80.3, 80.2, 79.3, 74.8, 74.7, 74.6, 71.6, 71.3, 70.9, 68.1, 68.0, 67.5, 67.4, 62.3, 61.9, 57.0. MALDI-MS: $[M + Na]^+$ calculd 957.31, found 957.45. Anal. Calcd for $C_{37}H_{58}O_{27}$: C, 47.54, H, 6.25. Found: C, 47.38; H, 6.30.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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