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Automated Solid-Phase Synthesis of Protected Oligosaccharides Containing β-Mannosidic Linkages

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Abstract: For automated oligosaccharide synthesis to impact glycobiology, synthetic access to most carbohydrates has to become efficient and routine. Methods to install "difficult" glycosidic linkages have to be established and incorporated into the overall synthetic concept. Described here is the first automated solid-phase synthesis of oligosaccharides containing the challenging β-mannosidic linkage. Carboxybenzyl mannoside building blocks proved effective β-mannosylation agents and resulted in excellent conversion and good to moderate selectivities. [(Triisopropylsilyl)oxy]-methyl ether (Tom), served as an orthogonal, minimally intrusive, and readily cleavable protecting group for the elongation of the C3 position of mannose. The desired oligosaccharide products were readily separated from by-products containing unwanted stereoisomers using reverse-phase HPLC. The methods described here expand the scope of carbohydrates currently accessible by automation as many oligosaccharides of biological interest contain β-mannosidic linkages.

Keywords: automation · carbohydrates · glycosides · oligosaccharide synthesis · solid-phase synthesis

Introduction

Well-defined oligosaccharides are indispensable tools for glycobiology. However, the synthesis of complex carbohydrates still presents a significant challenge.[1] Automated solid-phase oligosaccharide synthesis[2] has the potential to greatly accelerate the routine preparation of carbohydrates. Although a variety of oligosaccharides have been synthesized in an automated manner,[3–6] some glycosidic linkages have not been accessed yet using this solid-phase strategy. Methods for the stereoselective construction of all types of glycosidic linkages within the automation framework are crucial to developing a general method for the rapid synthesis of carbohydrates. β-Mannosidic linkages are frequently encountered in biologically important carbohydrate motifs such as *N*-glycans.

Tremendous progress concerning the solution-phase synthesis of β-mannosides has been made.[7] After many "indirect" methods such intramolecular aglycon delivery[8] and tethering[9] had been developed to overcome the challenges associated with β-mannoside formation, a more versatile, "direct" method was introduced by Crich and co-workers. This approach relies on the use of 4,6-*O*-benzylidene protected mannosyl sulfoxides or thiomannosides.[10] This modification of the sulfoxide method[11] utilizes a mannosyl building block (**A**, Scheme 1) that is pre-activated by trifluoromethanesulfonic anhydride (Tf_2O) to provide the α-mannosyl triflate **E**.[11] The incoming nucleophile displaces the anomeric triflate in an S_N2-like manner to provide the β-mannosidic product (β-**F**). Crich et al. observed that the α-mannosidic product was preferentially formed when the building block and nucleophile were mixed prior to activation, so pre-activation of the building block was found to be necessary for β-selectivity.

Subsequent to this breakthrough, modifications of this general approach with different types of anomeric leaving group have been introduced, including carboxybenzyl (CB) mannosides,[12] mannosyl pentenoates,[13] phosphites[14] and trichloroacetimidates.[15] In contrast to the Crich system, no adverse effect on the diastereoselectivity were seen when these building blocks were premixed prior to activation.

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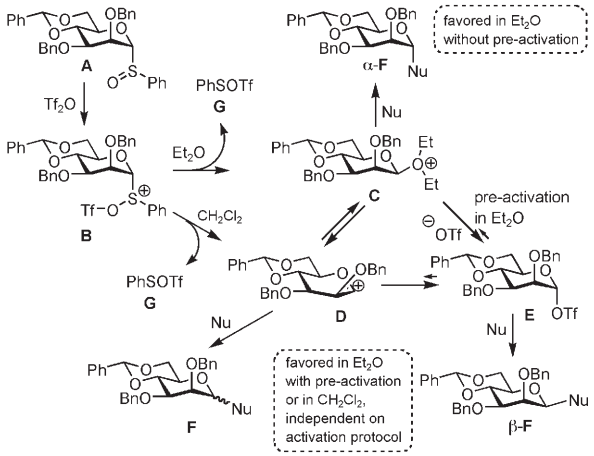


Scheme 1. Solvent effects in β-mannosylations following a "pre-activation" and "non pre-activation" protocol.

Two approaches to the solid-phase synthesis of β-mannosides have been reported thus far.[17] These methods make the construction of larger oligosaccharides on the solid support difficult because they either use the donor-bound approach or result in the cleavage of the β-mannoside from the resin during coupling. Here, we report the first automated solid-phase assembly of oligosaccharides containing the challenging β-mannosidic linkage via the advantageous acceptor bound approach.

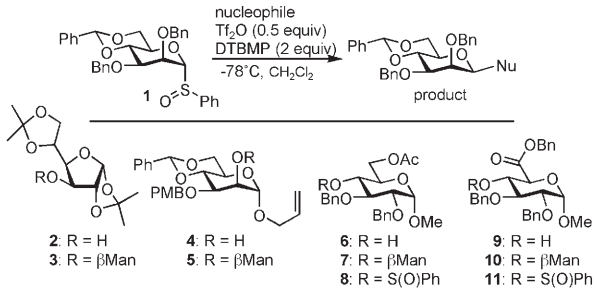
Results and Discussion

An ideal building block for automated β-mannosylation should be suitable for large-scale preparation, shelf-stable and allow for elongation to larger oligosaccharides. For ease of automation, no pre-activation of the building block should be necessary, its activation should be mild and should not generate electrophiles that are incompatible with our linker olefin.

The Crich method would be ideally suited for automation for a number of reasons. First, the method accommodates a broad range of nucleophiles, and 4,6-*O*-benzylidene mannosyl sulfoxides are readily available. Second, the activation conditions are very mild, even when used in large excess as it is often the case under the solid-phase paradigm. However, mannoside pre-activation at low temperature (typically −78 to −60 °C) presents a significant technical challenge in an automated setting. Furthermore, manipulation of the intermediate triflate is undesirable as it is both thermally and hydrolytically labile. Inspired by recent examples demonstrating the use of different types of 4,6-*O*-benzylidene mannosyl building blocks[12–15] without pre-activation, we reinvestigated the mannosyl sulfoxides in a "non pre-activation" protocol.

The pre-activation protocol was discovered in the Crich laboratory during experiments that employed diethyl ether as the solvent.[10] We reasoned that diethyl ether, a well-known participating solvent,[18] could play a decisive role in these condensations leading to the undesired formation of the α-product via β-etherate **C** (Scheme 1). Therefore, we changed the solvent to dichloromethane for our "non pre-activation" process. Indeed, when mannosyl sulfoxide **1** was dissolved in dichloromethane together with nucleophiles such as **2**, **4**, **6** and **9**, cooled to −78 °C and then treated with 0.5 equivalents of Tf_2O,[11,19a] the β-linked products were formed in moderate yield, but excellent diastereoselectivity (Table 1). However, several side products were observed.

Table 1. β-Mannosylations using sulfoxide **1** in CH_2Cl_2 by a "non pre-activation" protocol.



Entry (α/β)	Nucleophile	Product(s)	Yield [%][a]	Selectivity
1	**2**	**3**	58	β
2	**4**	**5**	63	β
3	**6**	**7** (**8**)	50 (31)	1:13[b]
4	**9**	**10** (**11**)	50 (30)	β

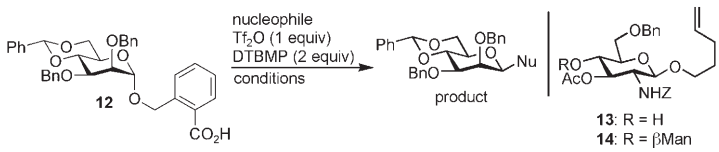
[a] Isolated product. [b] Based on LCMS analysis of the crude reaction mixture.

Importantly, acceptor-derived phenyl sulfinic ester **8** and **11** were formed in substantial amounts during couplings involving glucose **6** and glucuronic acid **9**. The generation of acceptor-derived side products is highly undesirable on resin as it directly reduces the overall yield. Furthermore, activation of phenyl sulfoxides generates the very electrophilic phenylsulfenyl triflate (PhSOTf, **G**, Scheme 1) that can react with the octenediol linker system commonly employed for solid-phase assembly. Thus, we abandoned the sulfoxides as possible β-mannosylating agents for automated solid-phase synthesis and shifted our attention to the investigation of carboxybenzyl glycosides.

The carboxybenzyl glycosides (e.g. **12**) were introduced as mannosylating agents[12,16] by the Kim laboratory and can be activated using Tf_2O in combination with a non-nucleophilic base such as di-*tert*-butylmethylpyridine (DTBMP) to access anomeric α-triflates **E** (Scheme 1), with phthalide as an inert by-product.

β-Mannosylations using carboxybenzyl glycoside **12** and the nucleophiles **4**, **6** and **13** were performed in solution to adjust the reaction parameters to suit an automated solid-phase protocol (Table 2). Increase of the reaction temperature from −60 to −30 °C and shortening the reaction time to 2 h did not influence the selectivity of the coupling (Table 2, entries 2 and 3). Changing the solvent from CH_2Cl_2 to tolu-

Table 2. β-Mannosylations using carboxybenzyl mannoside **12**.



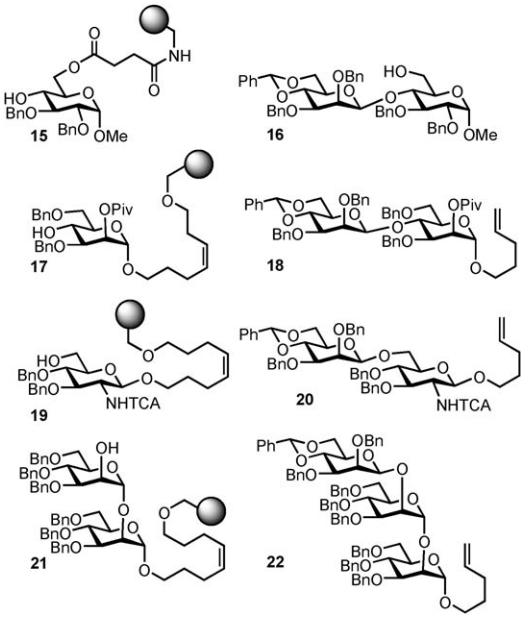
Entry	Conditions	Nucleophile	Product(s)	Yield [%][a]	Selectivity (α/β)
1	CH_2Cl_2, −60 °C to RT, overnight	**4**	**5**	81	β[b]
2	CH_2Cl_2, −60 °C to RT, overnight	**6**	**7**	85	1:10[c]
3	CH_2Cl_2, −30 °C (2 h)	**6**	**7**	–	1:10[c]
4	toluene, −30 °C (2 h)	**6**	**7**	–	1:11[c]
5	CH_2Cl_2, −60 °C to RT, overnight	**13**	**14**	82	1:4.5[c]

[a] Isolated product. [b] Based on NMR of isolated product. [c] Based on LCMS analysis of the crude reaction mixture.

ene, a mimic for the polystyrene resin environment during solid-phase assembly (Entry 4), did not affect the diastereoselectivity, but resulted in increased self-condensation of the carboxylic acid **12**.[16]

Encouraged by these glycosylations, we adopted the aforementioned conditions to the automated solid-phase synthesis of a series of di- and trisaccharides (Table 3). The reactions were conducted using two coupling cycles of five equivalents each of carboxyl mannoside and Tf_2O, and 15 equivalents of DTBMP, that were added to the cooled reaction chamber as a solution in CH_2Cl_2.[20] The carboxybenzyl building blocks **12** performed well on the automated synthesizer. After one coupling cycle, approximately 80% conversion was achieved. Repeating this coupling cycle led to near quantitative conversion, as judged by LCMS analysis of the crude reaction mixture after cleavage from the resin.

Table 3. Automated β-mannosylations using carboxybenzyl mannoside **12**.



Entry	Nucleophile	Cleaved product[a]	Yield [%]	Selectivity (α/β)[b]
1	**15**	**16**	77[c]	1:3.5
2	**15**	**16**	–	1:2.5[d]
3	**17**	**18**	–	1:3.5
4	**19**	**20**	47[c] (3 steps)	1:9
5	**21**	**22**	38[e] (6 steps)	1:3.7

[a] Products were cleaved from the resin by transesterification (NaOMe in CH_2Cl_2/MeOH) or cross-metathesis (the Grubbs 1st generation catalyst, $CH_2{=}CH_2$). [b] Based on LCMS analysis of the crude reaction mixture. [c] Based on α/β mixture. [d] Toluene was used as a solvent. [e] Based on pure β anomer.

Diastereomeric ratios were usually better than 3:1 in favor of the desired β-anomer when secondary nucleophiles were employed. Stereoselectivity as high as 9:1 in the case of the primary C6 position of glucosamine was observed (Table 3, entry 4). In contrast to solution phase syntheses, the stereoselectivity eroded when toluene was used as a solvent (Table 3, entry 2). The glycosylation selectivities of building block **12** are lower on solid-support than in solution, but since all mixtures could be separated by column chromatography or preparative HPLC, access to pure carbohydrates in good overall yields was possible. A representative coupling cycle for the automated β-mannosylation of compound **19** is summarized in Table 4.

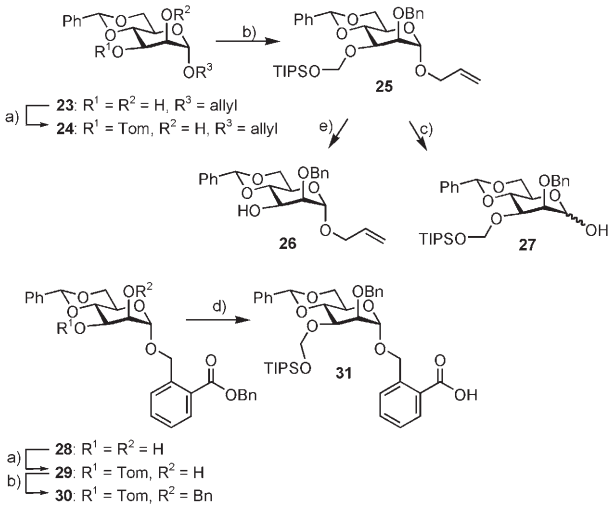
Table 4. Coupling cycle for glycosylation of compound **19**.

Step	Function	Reagents	*t* [min]
1	wash	THF	5
2	wash	CH_2Cl_2	10
3	glycosylation	5 equiv building block **12**, 5 equiv Tf_2O, 15 equiv DTBMP, CH_2Cl_2, −30 °C	120
4	wash	CH_2Cl_2, −30 °C	10
5	glycosylation	5 equiv building block **12**, 5 equiv Tf_2O, 15 equiv DTBMP, CH_2Cl_2, −30 °C	120
6	wash	CH_2Cl_2, −30 °C	5
7	wash	20% piperidine, DMF	2
8	wash	CH_2Cl_2	5
9	wash	alternating CH_2Cl_2 and methanol	18
10	wash	CH_2Cl_2	5
11	wash	THF	5

After conditions to install β-mannosides on solid support had been established, the synthesis of oligosaccharides by elongation at the C3 hydroxyl was explored.[21] The choice of protecting groups for the C3 position of β-mannosylation agents is limited. Acyl groups have been shown to efficiently participate in the condensation reaction of the benzylidene mannoside building blocks to provide the undesired α-linked saccharides,[22,10e] and allyl, *p*-methoxybenzyl or naphthylmethyl ethers require deprotection conditions that are

incompatible with the solid-phase format. Silyl ethers are attractive protecting groups as they are orthogonal to most other protecting groups employed during oligosaccharide assembly and are readily cleaved. However, silyl ethers are sterically demanding and can erode the selectivity of the β-mannosylation reactions.[23,24] To retain the attractive features of silyl ethers, but reduce the steric bulk, we employed the [(triisopropylsilyl)oxy]methyl (Tom) ether that is routinely used for RNA synthesis.[25]

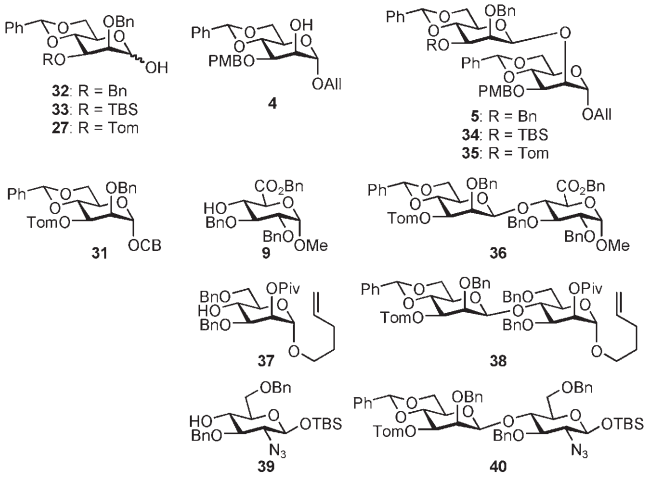
Various building blocks were prepared to evaluate the C3-*O*-Tom protecting group in solution phase glycosylations (Scheme 2). The regioselective alkylation of the 2,3-*O*-stannylidene of diol **23** with triisopropylsilyloxymethyl chloride (Tom-Cl) afforded Tom-protected mannose **24**. Benzylation, and subsequent allyl cleavage gave mannose **27**. Placement of the Tom group on carboxybenzyl mannoside **28** proceeded uneventfully[26] before benzylation of the C2-hydroxyl and generation of the carboxylic acid furnished mannosyl building block **31**.



Scheme 2. Synthesis of the C3-*O*-Tom protected mannosyl building blocks **27** and **31**. a) Bu_2SnCl_2, DIPEA, $ClCH_2CH_2Cl$, then Tom-Cl, **24**: 91%, **29**: 85%; b) BnBr, NaH, DMF, **25**: quant., **30**: 96%; c) $PdCl_2$, HOAc, H_2O, NaOAc, EtOAc, 74%; d) H_2, Pd/C, EtOAc, MeOH, 96%; e) TBAF, THF (94%) or TBAF, HOAc, THF (88%).

The 3-*O*-Tom-protected mannose building block performed well in the construction of β-mannosidic linkages in solution (Table 5). The Tom protecting group is compared to other C3 protecting groups. (Table 5, entries 1–3). The previously published 3-*O*-*tert*-butyldimethylsilyl ether building block **33** caused complete loss of selectivity when compared to the 3-*O*-benzyl ether in **32**.[23b] However, when the oxymethyl bridged silyl ether building block **31** was used, the desired β-linked product was formed with excellent selectivity (Table 5, entry 3). The 3-*O*-Tom protected carboxybenzyl mannoside **31** gave good results with other nucleophiles (Table 5, entries 4–6) using the "non-pre-activation" protocol. The condensation with glucosamine-derived nucleophile **39** (Table 5, entry 7) also proceeded in good selectivity and yield. Investigation of the fluoride mediated deprotection of the Tom-ketal on allyl mannoside **25** (Scheme 2) revealed that 1.5 equivalents of tetrabutylammonium fluoride in wet THF sufficed to cleave the Tom group within five minutes in solution. Cleavage under buffered conditions, in the presence of two equivalents acetic acid, required 3.5 h. The Tom protecting group thus proved a good alternative as C3 protecting group in β-mannosylations, giving excellent selectivities and deprotection conditions orthogonal to typical carbohydrate synthesis.

Table 5. Condensations of C3-*O*-Tom protected mannosides.

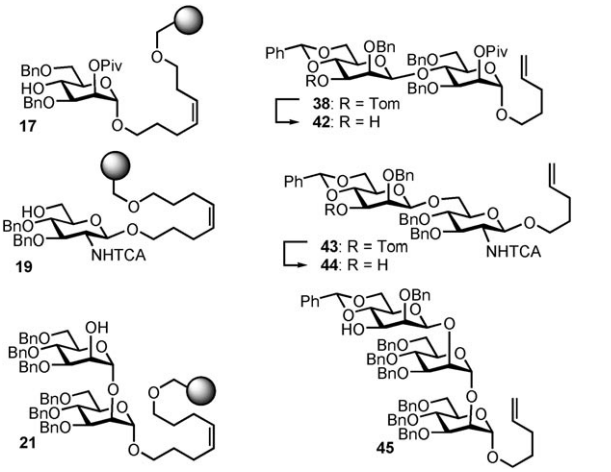


Entry	Building block[a]	Nucleophile	Product	Yield [%]	Selectivity (α/β)
1	**32**	**4**	**5**	81[b]	(β)
2	**33**	**4**	**34**	92[b]	2:3
3	**27**	**4**	**35**	90	(β)
4	**31**	**4**	**35**	81	(β)
5	**31**	**9**	**36**	73	1:15[c]
6	**31**	**37**	**38**	94	1:9[d]
7	**31**	**39**	**40**	85	1:7[c]

[a] Coupling conditions for dehydrative condensations: 1-OH mannosides (1.5 equiv) were pre-activated using Ph_2SO (3 equiv) and Tf_2O (1.5 equiv) in the presence of TTBP (5 equiv) at −40 °C to −25 °C over 1.5 h. The nucleophile was added and the mixture stirred overnight while warming to room temperature before the reaction was quenched by the addition of triethylamine. Condensation of the CB-mannosides were accomplished with the described "non pre-activation" protocol. [b] Taken from ref. [23b]. [c] Determined by LCMS analysis. [d] Determined by NMR analysis.

With this information in hand, CB-mannoside building block **31** was used for the automated synthesis of a series of β-mannosides (Table 6). We were gratified to find that the selectivities of couplings involving building block **31** generally increased compared to the 3-*O*-benzyl mannoside **12** counterpart. Coupling of **31** and nucleophile **17** gave product in 1:6.5 α/β selectivity (Table 6, entry 1) compared to 1:3.5 obtained with building block **12** (Table 3, entry 3). The selectivity for nucleophile **21** increased from 1:3.7 (Table 3, entry 5) to 1:6.5 (Table 6, entry 3). Tom-cleavage at the trisaccharide stage of the automated synthesis using five equivalents of TBAF in THF required 15 min and was repeated once.[27] Trisaccharide **45** was isolated in 41% yield over

Table 6. Automated solid-phase β-mannosylations using C3-*O*-Tom protected carboxybenzyl mannoside **31**.



Entry	Nucleophile	Cleaved product[a]	Yield [%]	Selectivity (α/β)
1	**17**	**42**	51[c] (4 steps)	(1:6.5)[f]
2	**19**	**44**	58[e] (3 steps)	(1:5)[f]
3	**21**	**45**	41[d] (7 steps)	(1:6.5)[b]

[a] Products were cleaved from the resin by cross-metathesis (the Grubbs 1st generation catalyst, CH_2=CH_2). [b] Based on LCMS analysis of the crude reaction mixture. [c] After TBAF-mediated deprotection of the Tom group. [d] Based on pure β anomer. [e] Based on α/β mixture. [f] Determined by LCMS analysis of the crude Tom-deprotected disaccharide.

seven steps. For couplings involving glucosamine nucleophile **19** the selectivity decreased from 1:9 to 1:5.

To demonstrate that multiple β-mannosidic linkages can be installed in the same molecule, trisaccharide **52** was assembled in solution (Scheme 3) and by automated solid-phase synthesis (Scheme 4). Using the automated synthesizer, octenediol-functionalized resin **46** was treated with mannosyl trichloroacetimidate **47** followed by sodium methoxide mediated acetate removal. Coupling of Tom-protected CB-mannoside building block **31** was followed by cleavage of the Tom group by subjecting the resin manually to TBAF (2×5 equiv, 15 min each) in THF. Final mannosylation using dibenzyl mannoside building block **12** by automation gave the immobilized trisaccharide. Cleavage of the oligosaccharide product from the resin by cross-metathesis was achieved using the Grubbs first generation pre-catalyst under an ethylene atmosphere. Trimannoside **52** was isolated in 50% yield (over six steps) as a mixture of anomers with the desired anomer as the major product (8:1:1.3 in favor of the desired product (Figure 1)). This result compares favorably to the solution-phase synthesis (**37**→**52**, 55% over three steps). Pure trisaccharide **52**, containing the two desired β-mannosidic linkages was isolated using preparative HPLC.

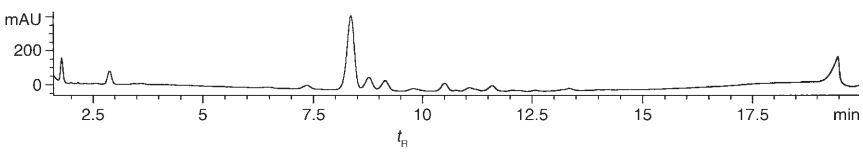
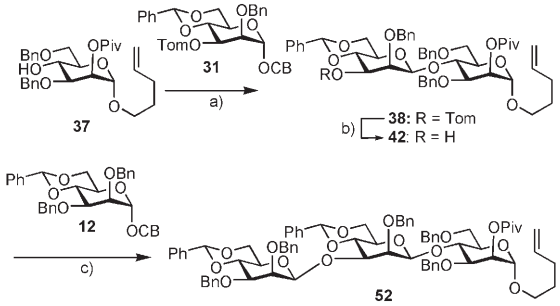
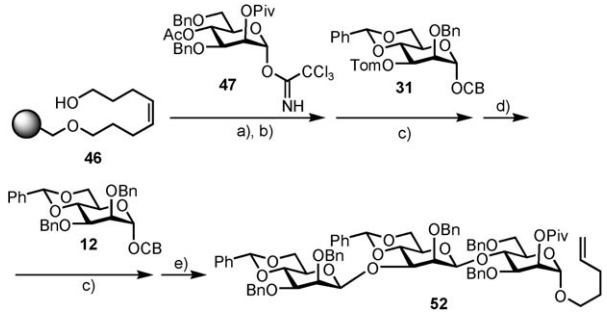


Figure 1. Crude HPLC trace. Product **52** (t_R = 8.4 min) and its anomers (t_R = 8.8 and 9.1 min).



Scheme 3. Synthesis of trimannoside **52** in solution. a) Tf_2O, DTBMP, CH_2Cl_2, −30 °C, 94% (α/β 1:9); b) TBAF, THF, 79%; c) Tf_2O, DTBMP, CH_2Cl_2, −30 °C, 74% (α/β 1:15).



Scheme 4. Synthesis of trimannoside **52** on solid support. a) **47** (4.5 equiv), TMSOTf (0.5 equiv), toluene, CH_2Cl_2, 15 min, repeated once; b) NaOMe (10 equiv), MeOH, CH_2Cl_2, 0 min, repeated once; c) building block (5 equiv), Tf_2O (5 equiv), DTBMP (15 equiv), CH_2Cl_2, −30 °C, 2 h, repeated once; d) TBAF (5 equiv), THF, 20 min, repeated once; e) the Grubbs 1st generation catalyst, ethylene atmosphere, CH_2Cl_2, overnight, 50% from resin **46** (of a mixture of anomers (8:1.3:1 in favor of the desired product **52**).

Conclusion

We report the development of synthetic protocols for the incorporation of β-mannosidic linkages by automated solid-phase synthesis using stable CB glycosides. The formation of the challenging β-mannosidic bond was achieved for the first time by automated solid-phase synthesis. The Tom ether group served as an efficient protecting group to mask the C3 position of mannose, allowing for stereoselective coupling and mild, orthogonal deprotection. The Tom group should prove valuable as a sterically minimally intrusive protecting group in oligosaccharide synthesis. The scope of oligosaccharide structures accessible by automated solid-phase synthesis using this β-mannosylation technique has been increased significantly. Currently, we are applying this methodology to prepare a series of *N*-linked oligosaccharides.

Experimental Section

All chemicals used were reagent grade and used as supplied. Tf_2O was purified by drying over P_2O_5 for 4 h, followed by distillation. All reactions were performed in oven-dried glassware under an inert argon atmosphere unless noted otherwise. Reagent grade dichloromethane (CH_2Cl_2), was passed through activated neutral alumina column prior to use. Triethylamine was distilled over CaH_2 and stored over KOH. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates (0.25 mm). Compounds were visualized by UV irradiation or dipping the plate in a cerium sulfate/ammonium molybdate solution. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka Kieselgel 60 (230–400 mesh). LCMS analysis was performed on an Agilent 1100 Series LC/MSD instrument on a Waters Symmetry C18 5 μm column (3.9×150 mm), using solvent systems A (20% isopropanol and 0.1% TFA in H_2O) and B (20% isopropanol and 0.1% TFA in acetonitrile), at a flow rate of 1 mL min^{-1}.^{1}H and ^{13}C and NMR spectra were recorded on a Varian Mercury 300 (300 and 75 MHz, respectively), spectrometer in $CDCl_3$ unless specified otherwise, with chemical shifts referenced to internal standards $CDCl_3$ (7.26 ppm ^{1}H, 77.0 ppm ^{13}C). High-resolution mass spectral (HRMS) analyses were performed by the MS-service at the Laboratory for Organic Chemistry at ETH Zurich. ESI-MS and MALDI-MS were run on an IonSpec Ultra instrument. The automated synthesis was performed on an ABI 431 A peptide synthesizer with a custom-made jacketed glass reaction vessel. IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer. Optical rotations were measured at room temperature using a Perkin Elmer 241 polarimeter. Recycling HPLC system (GPC: LC-9101 Japan Analytical Industry Co. Ltd., JAIGEL-2H and 2.5H, mobile phase: $CHCl_3$) was used for size exclusion chromatography. Preparative HPLC was performed using a Waters 1525 pump and Waters 2487 detector on a Waters Sunfire prep C_8 reversed-phase column (10×150 mm). The stereochemistry of β-mannosides was confirmed by the characteristic chemical shift of H5.[10c]

General procedure A: **Condensations by using *S*-phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-deoxy-1-thia-α-D-mannopyranoside sulfoxide (1)**: A mixture of **1** (1.25 equiv), acceptor (**2**, **4**, **6** or **9**; 1.0 equiv, ≈0.15 mmol, 0.04 M) and di-*tert*-butylmethylpyridine (DTBMP, 2.5 equiv) in CH_2Cl_2 was stirred over freshly activated powdered molecular sieves for 30 min and cooled to −78 °C. Trifluoromethanesulfonic anhydride (Tf_2O, 0.65 equiv) was added and the reaction mixture was allowed to very slowly warm to room temperature overnight. The reaction was quenched by the addition of triethylamine (≈5 equiv), filtered over Celite in a mixture of aqueous $Na_2S_2O_3$ (1 M) and saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with saturated aqueous NaCl, dried ($NaSO_4$) and concentrated. The crude product was purified by flash silica gel column chromatography (EtOAc in hexanes or toluene) to provide the title compound.

General procedure B: **Condensations by using carboxybenzyl donors**: A mixture of **12**[12] (1.25 equiv), acceptor (**4**, **6** or **13**; 1.0 equiv, ≈0.12 mmol, 0.04 M) and di-*tert*-butylmethylpyridine (DTBMP, 3.0 equiv) in CH_2Cl_2 was stirred over freshly activated powdered molecular sieves for 30 min and cooled to −60 °C. Trifluoromethanesulfonic anhydride (Tf_2O, 1.25 equiv) was added and the reaction mixture was allowed to very slowly warm to room temperature overnight. The reaction was quenched by the addition of triethylamine (≈5 equiv), filtered over Celite and concentrated. The crude product was purified by flash silica gel column chromatography (EtOAc in hexanes or toluene) to provide the title compound.

Allyl 4,6-*O*-benzylidene-3-*O*-(triisopropylsilyloxymethyl)-α-D-mannopyranoside (24): Allyl mannoside **23** (3.08 g, 10.0 mmol) in 1,2-dichloroethane (40 mL), was treated with dibutyltindichloride (3.04 g, 10.0 mmol) and *N*,*N*-diisopropylethylamine (6.3 mL, 36 mmol), until all starting material was dissolved, and the resulting solution was stirred for an additional 1.5 h, after which the mixture was brought to 80 °C. Triisopropylsilyloxymethylchloride[25] (2.9 g, 13 mmol) was added and the reaction mixture was stirred for 15 min, after which it was cooled to RT. The mixture was diluted with CH_2Cl_2 (150 mL) and washed with saturated aqueous $NaHCO_3$ (100 mL). The water layer was extracted three times with CH_2Cl_2, after which the organic layers were combined, filtered over Celite, dried ($MgSO_4$) and concentrated. The crude product was purified by flash silica gel column chromatography (cyclohexane/EtOAc 2:1) to give the pure title compound as a yellow oil (34.51 g, 9.1 mmol, 91%). R_f=0.60 (hexanes/EtOAc 2:1); $[\alpha]_D^{20}$=+74.1 (c=1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.59–7.34 (m, 5H), 5.98–5.84 (m, 1H), 5.57 (s, 1H), 5.36–5.19 (m, 2H), 5.17 (d, 1H, J=4.8 Hz), 5.05 (d, 1H, J=5.1 Hz), 4.94 (d, 1H, J=1.2 Hz), 4.29–3.81 (m, 8H), 2.97 (d, 1H, J=1.5 Hz), 1.15 ppm (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=138.3, 137.6, 133.5, 128.8, 128.3, 128.0, 127.8, 127.6, 126.1, 116.9, 101.6, 98.7, 90.1, 78.8, 78.2, 73.8, 73.3, 68.8, 67.9, 64.3, 17.9, 12.0 ppm; IR: $\tilde{\nu}$=2944, 1464, 1044 cm^{-1}; HR-MS: m/z: calcd for $C_{26}H_{42}O_7Si$+Na^+: 517.2598; found: 517.2583.

Allyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(triisopropylsilyloxymethyl)-α-D-mannopyranoside (25): Allyl mannoside **24** (3.42 g, 6.90 mmol) and benzyl bromide (1.07 mL, 8.97 mmol) were dissolved in DMF (30 mL) and cooled to 0 °C. Sodium hydride (317 mg, 7.94 mmol, 60% in mineral oil) was added in small portions. The mixture was allowed to reach room temperature and stirred for 1 h. Methanol (0.5 mL) was added to quench the reaction, after which the mixture was diluted with diethyl ether and washed with water. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash silica gel chromatography (0% to 10% EtOAc in hexanes) yielded **25** as a colorless oil (4.03 g, 6.90 mmol, 100%). R_f=0.65 (hexanes/EtOAc 3:1); $[\alpha]_D^{20}$=+54.3 (c=1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.59–7.34 (m, 10H), 5.98–5.84 (m, 1H), 5.66 (s, 1H), 5.35–5.17 (m, 4H), 4.98 (d, 1H, J=12.0 Hz), 4.91 (d, 1H, J=1.2 Hz), 4.78 (d, 1H, J=12.0 Hz), 4.41 (dd, 1H, J=3.3, 10.2 Hz), 4.32–4.24 (m, 2H), 4.21 (m, 1H), 3.92 (m, 4H), 1.15 ppm (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=138.6, 137.9, 133.8, 129.1, 128.6, 128.4, 128.1, 127.9, 126.4, 117.2, 101.9, 99.0, 90.4, 79.0, 78.5, 74.1, 73.6, 69.1, 68.2, 64.6, 18.2, 12.3 ppm; IR: $\tilde{\nu}$=2943, 1463, 1044 cm^{-1}; HR-MS: m/z: calcd for $C_{33}H_{48}O_7Si$+Na^+: 607.3067; found: 607.3049.

2-*O*-Benzyl-4,6-*O*-benzylidene-3-*O*-(triisopropylsilyloxymethyl)-α-D-mannopyranoside (27): Allyl mannoside **25** (507 mg, 0.969 mmol) was dissolved in EtOAc (6 mL). Aqueous acetic acid (90%, 20 mL) was added, followed by NaOAc (476 mg, 5.80 mmol) and $PdCl_2$ (258 mg, 1.46 mmol) and the mixture was stirred overnight. After filtration over Celite, the mixture was diluted with EtOAc and washed with water. The aqueous phase was extracted once with EtOAc and the combined organic layers were washed with saturated aqueous $NaHCO_3$ until they reached neutral pH. The aqueous phase was extracted three times with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (0→17.5% EtOAc in hexanes) gave the title compound as a colorless oil (389 mg, 0.714 mmol, 74%). R_f=0.45 (hexanes/EtOAc 3:1); major isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.53–7.30 (m, 10H), 5.61 (s, 1H), 5.12 (m, 3H), 4.89 (d, 1H, J=12.0 Hz), 4.69 (d, 1H, J=12.0 Hz), 4.35 (1H, m), 4.02–4.62 (m, 4H), 3.82–3.92 (m, 2H), 3.46 (brs, 1H), 1.10 ppm (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=138.3, 137.5, 128.7, 128.3, 128.2, 128.0, 127.8, 127.5, 126.12, 126.06, 101.6, 94.0, 90.1, 78.8, 78.3, 73.7, 72.9, 68.8, 64.1, 17.8, 11.9 ppm; IR: $\tilde{\nu}$=2944, 1464, 1095 cm^{-1}; HR-MS: m/z: calcd for $C_{30}H_{44}O_7Si$+Na^+: 567.2754; found: 567.2737.

4,6-Benzyloxycarbonylbenzyl-*O*-benzylidene-3-*O*-(triisopropylsilyloxymethyl)-α-D-mannopyranoside (29): Benzyloxycarbonylbenzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**28**)[12] (2.10 g, 4.27 mmol) in 1,2-dichloroethane (22 mL), was treated with dibutyltindichloride (1.43 g, 4.70 mmol) and DIPEA (2.97 mL, 17.1 mmol), until all starting material was dissolved, and the resulting solution was stirred for an additional 2 h. Triisopropylsilyloxymethylchloride[25] (1.05 mL, ≈4.7 mmol) was added and the reaction mixture was stirred overnight. The mixture was diluted with CH_2Cl_2 (150 mL) and washed with saturated aqueous $NaHCO_3$ (100 mL). The water layer was extracted three times with CH_2Cl_2, after which the organic layers were combined, washed with aqueous saturated NaCl, dried over $MgSO_4$ and concentrated. The crude product was purified by flash silica gel column chromatography (0→15% EtOAc in hexanes) to give the pure title compound as a colorless oil (2.27 g, 3.34 mmol, 79%).

R_f=0.45 (hexanes/EtOAc 3:1); $[\alpha]_D^{20}$=+70.9 (c=1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.07 (m, 1H), 7.68 (m, 1H), 7.59–7.36 (m, 12H), 5.61 (s, 1H), 5.37 (s, 2H), 5.25–5.21 (m, 2H), 5.13–5.08 (m, 2H), 5.01 (d, 1H, J=14.4 Hz), 4.31–4.23 (m, 3H), 4.13 (t, 1H, J=9.0 Hz), 3.98 (m, 1H), 3.88 (t, 1H, J=9.9 Hz), 2.99 (br s, 1H), 1.11 ppm (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.2, 139.6, 137.3, 135.6, 130.5, 128.7, 128.4, 128.1, 128.0, 127.9, 127.7, 127.2, 127.0, 126.0, 101.8, 99.8, 89.9, 77.8, 74.6, 70.9, 68.8, 67.4, 66.7, 63.7, 17.9, 11.9 ppm; IR: $\tilde{\nu}$=2934, 1713, 1256, 1046 cm^{-1}; HR-MS: m/z: calcd for $C_{30}H_{50}O_9SiNa^+$: 701.3116; found: 701.3102.

Benzyloxycarbonylbenzyl-2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(triisopropylsilyloxymethyl)-α-D-mannopyranoside (30): Mannopyranoside **29** (4.55 g, 6.70 mmol) and benzyl bromide (1.03 mL, 8.66 mmol) were dissolved in DMF (35 mL) and cooled to 0°C. Sodium hydride (308 mg, 7.70 mmol, 60% in mineral oil) was added in small portions. The mixture was allowed to reach room temperature and stirred for 1.25 h. Saturated aqueous NH_4Cl was added to quench the reaction, after which the mixture was diluted with diethyl ether and washed with water. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash silica gel chromatography (0→10% EtOAc in hexanes) yielded **30** (4.97 g, 96%). R_f=0.45 (hexanes/EtOAc 3:1); $[\alpha]_D^{20}$=+68.8 (c=1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.03 (d, 1H, J=8.1 Hz), 7.59–7.36 (m, 19), 5.59 (s, 1H), 5.31 (s, 2H), 5.16–5.09 (m, 3H), 5.87–4.95 (m, 3H), 4.72 (d, 1H, J=11.7 Hz), 4.38 (dd, 1H, J=3.3, 9.9 Hz), 4.22 (d, 2H), 4.00 (m, 1H), 3.88 (m, 2H), 1.13 ppm (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.7, 140.3, 138.5, 137.9, 136.0, 132.7, 130.9, 129.0, 128.9, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.3, 127.2, 126.4, 101.8, 99.5, 90.3, 79.0, 78.3, 73.9, 73.5, 69.0, 67.6, 66.9, 64.8, 18.1, 12.2 ppm; IR: $\tilde{\nu}$=2933, 1713, 1256, 1041 cm^{-1}; HR-MS: m/z: calcd for $C_{45}H_{56}O_9SiNa^+$ 791.3591; found: 791.3586.

Carbonylbenzyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(triisopropylsilyloxymethyl)-α-D-mannopyranoside (31): Mannopyranoside **30** (1.0 g, 1.30 mmol) and NH_4OAc (300 mg, 3.9 mmol) were dissolved in EtOAc/methanol 1:4 (50 mL). The mixture was degassed three times and then Pd/C (94 mg) was added. The suspension was degassed once more. H_2 was bubbled through the mixture for 1 min, after which the solution was stirred for 2 h under an H_2 atmosphere. The catalyst was filtered off and the solvents were evaporated in vacuo. The crude product was purified by flash silica gel column chromatography (30→80% EtOAc in hexanes, containing 1% AcOH) to provide the title compound as a white foam (869 mg, 1.28 mmol, 98%). R_f=0.50 (hexanes/EtOAc 1:1, 5% AcOH); $[\alpha]_D^{20}$=+66.1 (c=1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.6 (br s, 1H), 8.12 (d, 1H, J=7.5 Hz), 7.59–7.36 (m, 14), 5.61 (s, 1H), 5.22–5.13 (m, 3H), 5.02–4.89 (m, 3H), 4.74 (d, 1H, J=12.0 Hz), 4.43 (dd, 1H, J=3.0, 10.2 Hz), 4.27 (d, 2H), 4.05 (m, 1H), 3.91 (m, 2H), 1.12 ppm (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.7, 140.9, 138.5, 137.8, 133.5, 131.8, 129.0, 128.6, 128.3, 128.0, 127.9, 127.4, 127.3, 126.4, 101.8, 99.5, 90.3, 79.0, 78.4, 74.0, 73.4, 69.0, 67.7, 64.9, 18.1, 12.2 ppm; IR: $\tilde{\nu}$=2944, 1713, 1046 cm^{-1}; HR-MS: m/z: calcd for $C_{38}H_{50}O_9SiNa^+$: 701.3116; found: 701.3104.

***n*-Pentenyl 3,6-di-*O*-benzyl-4-*O*-[2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-triisopropyl-silyloxymethyl-β-D-mannopyranosyl]-2-*O*-pivaloyl-α-D-mannopyranoside (38)**: Using general procedure B, **38** was prepared on a 0.096 mmol (acceptor glycoside) scale in 94% yield (α/β 1:9). $[\alpha]_D^{20}$=−1.5 (c=0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.43–7.27 (m, 20H), 5.83 (m, 1H), 5.44 (s, 1H), 5.36 (m, 1H), 5.10–4.98 (m, 4H), 4.88–4.78 (m, 3H), 4.73–4.63 (m, 4H), 4.48 (d, 1H, J=11.7 Hz), 4.22 (t, 1H, J=9.6 Hz), 4.03–3.68 (m, 9H), 3.57 (t, 1H, J=9.9 Hz), 3.46 (m, 1H), 3.03 (m, 1H), 2.15 (m, 2H), 1.72 (m, 2H), 1.20 (s, 9H), 1.08 ppm (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.4, 138.7, 138.6, 138.2, 137.8, 137.5, 128.7, 128.2, 128.0, 127.4, 127.3, 127.1, 126.1, 115.0, 101.5, 101.3, 97.7, 89.5, 78.5, 78.4, 78.1, 75.6, 75.2, 73.3, 71.5, 71.1, 69.0, 68.9, 68.5, 67.3, 39.0, 30.4, 28.7, 27.2, 12.2, 12.1 ppm; IR: $\tilde{\nu}$=2943, 2871, 1730, 1456, 1093 cm^{-1}; HR-MS: m/z: calcd for $C_{60}H_{82}O_{13}Si$+Na^+ 1061.542; found: 1061.542.

***n*-Pentenyl 3,6-di-*O*-benzyl-4-*O*-[2-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl]-2-*O*-pivaloyl-α-D-mannopyranoside (42)**: Mannopyranoside **38** (85 mg, 0.085 mmol) was dissolved in THF (1 mL), after which TBAF (1 M in THF, 0.1 mL) was added. The mixture was stirred for 10 min after which the mixture was diluted with EtOAc and washed with water and a saturated aqueous solution of NaCl. The organic phase was dried over $MgSO_4$, and concentrated. Flash silica gel column chromatography (5→20% EtOAc in hexanes) gave the title compound (55 mg, 0.064 mmol, 79%). R_s=0.50 (hexanes/EtOAc 2:1); $[\alpha]_D^{20}$=−11.1 (c=0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.43–7.27 (m, 20H), 5.83 (m, 1H), 5.41 (s, 1H), 5.37 (m, 1H), 5.10–4.97 (m, 2H), 4.93 (d, 1H, J=11.7 Hz), 4.84 (d, 1H, J=2.1 Hz), 4.75 (d, 1H, J=12.0 Hz), 4.67 (s, 2H), 4.61–4.55 (m, 3H), 4.48 (d, 1H, J=12.07 Hz), 4.23 (t, 1H, J=9.6 Hz), 3.87–3.65 (m, 6H), 3.59–3.42 (m, 3H), 2.95 (m, 1H), 2.34 (br s, 1H), 2.14 (m, 2H), 1.73 (m, 2H), 1.22 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.3, 138.4, 138.04, 137.95, 137.7, 137.1, 128.9, 128.3, 128.1, 128.0, 127.8, 127.7, 127.4, 127.2, 126.8, 126.1, 115.0, 101.8, 101.3, 97.7, 79.1, 78.9, 75.6, 75.4, 74.9, 73.3, 71.3, 70.9, 70.8, 68.7, 68.6, 68.3, 67.3, 66.7, 39.0, 30.3, 28.6, 27.2 ppm; IR: $\tilde{\nu}$=3054, 1729, 1421, 695 cm^{-1}; HR-MS: m/z: calcd for $C_{50}H_{60}O_{12}$+Na^+: 875.3983; found: 875.3988.

***n*-Pentenyl 3,6-di-*O*-benzyl-4-*O*-[2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-β-D-mannopyranosyl]-2-*O*-pivaloyl-α-D-mannopyranoside (52)**: Using general procedure B, **52** was prepared on a 0.053 mmol (acceptor glycoside) scale. LCMS analysis (85% B in A: 2 min; linear gradient to 95% B in A in 30 min) of the reaction mixture revealed the α/β ratio to be 12:1; β-**52**: t_R=4.83 min; α-**52**; t_R=5.85 min. Flash silica gel column chromatography (0→25% EtOAc in hexanes) gave the title compound (50 mg, 0.039 mmol, 74%). R_f=0.60 (hexanes/EtOAc 2:1); $[\alpha]_D^{20}$=−44.0 (c=1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.50–7.10 (m, 35H), 5.81 (m, 1H), 5.51 (s, 1H), 5.49 (s, 1H), 5.37 (dd, 1H, J=1.8, 3.0 Hz), 4.97–5.07 (m, 2H), 4.88 (d, 1H, J=11.7 Hz), 4.80–4.84 (m, 2H), 4.74 (s, 1H), 4.70 (s, 1H), 4.54–4.67 (m, 7H), 4.48 (d, 1H, J=12.0 Hz), 4.25 (t, 1H, J=9.6 Hz), 3.95–4.18 (m, 5H), 3.61–3.90 (m, 9H), 3.46 (m, 1H), 3.27 (dd, 1H, J=3.0, 9.6 Hz), 3.10 (m, 2H), 2.13 (m, 2H), 1.70 (m, 2H), 1.20 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.4, 138.5, 138.4, 138.2, 138.12, 138.07, 137.7, 137.4, 137.3, 128.8, 128.7, 128.26, 128.21, 128.1, 128.0, 127.9, 127.64, 127.56, 127.4, 127.34, 127.27, 127.2, 126.1, 125.9, 115.0, 101.6, 101.2, 101.1, 97.8, 97.7, 78.4, 77.2, 75.6, 75.0, 74.7, 74.6, 74.5, 74.2, 73.4, 72.0, 71.2, 71.1, 69.2, 68.5, 68.4, 67.7, 67.39, 67.33, 39.0, 30.3, 28.7, 27.2 ppm; IR: $\tilde{\nu}$=2672, 1730, 1453, 1091 cm^{-1}; HR-MS: m/z: calcd for $C_{77}H_{87}O_{17}$+Na^+: 1305.576; found: 1305.576.

General procedure for the automated solid-phase synthesis of β-mannoside-containing oligosaccharides

Automated module A: The resin is washed with CH_2Cl_2 for 15 s followed by hexanes for 10 s; repeated six times.

Automated module B: The resin is washed six times with CH_2Cl_2 for 15 s each.

Automated module C: The building block (5 equiv, 0.125 mmol) and DTBMP (15 equiv, 0.375 mmol) in CH_2Cl_2 (2.5 mL) is delivered to the reaction vessel containing the resin. The mixture is allowed to cool for 3 min (with vortex for 30 s followed by standing for 30 s). Tf_2O (5 equiv, 0.125 mmol, in 0.5 mL CH_2Cl_2) is added to the reaction vessel with vortex. The reaction mixture is then left for 120 min (with vortex for 30 s followed by standing for 30 s). After that time, the solution is drained and the resin is washed once with CH_2Cl_2.

Automated module D: The resin is washed six times with THF for 15 s each.

Automated module E: The resin is washed six times with MeOH/CH_2Cl_2 1:9 for 15 s each.

Automated module F: The resin is washed is treated with TBAF (5 equiv, 0.125 mmol) in 1.6 mL THF for 15 min (with vortex for 30 s followed by standing for 30 s). After that time, the solution is drained and the resin is washed once with THF; repeated once.

Automated module G: The resin is treated with 1.5 mL 20% piperidine/DMF for 35 s, then washed once with CH_2Cl_2.

Automated module H: The resin is washed with CH_2Cl_2 for 15 sec followed by MeOH for 15 s; repeated six times.

Automated module I: The resin is washed six times with acetic acid (0.2 M in THF) for 15 s each.

Automated module J: The resin is washed six times with DMF for 15 s each.

Automated module K: The resin is submitted to piperidine (20% v/v in DMF, 2 mL) for 5 min (with vortex for 30 s, followed by standing for 30 s). After that time, the solution is drained and the resin is submitted to the same conditions twice.

***n*-Pentenyl 3,6-di-*O*-benzyl-4-*O*-[2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-β-D-mannopyranosyl]-2-*O*-pivaloyl-α-D-mannopyranoside (52)**: Resin **46** (0.22 mmol g^{-1}, 113 mg, 0.025 mmol) was loaded in the reaction vessel of the synthesizer. Modules D, A, B were performed. The resin was glycosylated twice with building block **47** (4.5 equiv, 0.112 mmol) in toluene (2 mL) and TMSOTf (0.5 equiv, 0.012 mmol in 0.5 mL CH_2Cl_2) for 15 min with one module B in between. Modules B, D, B, were performed. The acetate protecting group was removed by treating the resin twice with NaOMe (10 equiv, 0.25 mmol) in MeOH (0.4 mL) and CH_2Cl_2 (3.5 mL) for 30 min. Modules E, D, I, D, A, B, D, A and B were executed. The reaction vessel was cooled to −30 °C. Module C was then performed twice with building block **31** with two modules B in between. The resin was subjected to module B and G. The reaction vessel was warmed to room temperature, and modules B, H, and B were performed. The resin was then treated twice manually with TBAF (5 equiv, 0.125 mmol) in THF (1.5 mL) for 20 min each, before washing with THF and CH_2Cl_2 several times. The resin was charged in the synthesizer reaction vessel. Module D, A, and B were performed. The reaction vessel was then cooled to −30 °C. Module C was performed twice with building block **12** with two modules B in between. The resin was subjected to module B and G. The reaction vessel was warmed to room temperature, and modules B, H, and B were performed. The resin was charged in a 10 mL round-bottom flask and swelled with CH_2Cl_2 (2 mL) under an atmosphere of argon. The Grubbs 1st generation catalyst (2 mg) was added and the flask was put under ethylene atmosphere and stirred overnight. The resin was washed eight times with CH_2Cl_2. The resulting solution was filtered through a pipette column with 3 cm silica, eluting with ethyl acetate. The eluted solution was concentrated under vacuum. The crude residue was purified by column chromatography to afford the title compound **52** (16 mg, 12.5 mmol, 50% yield from resin **46**) as a mixture of anomers. Anomerically pure **52** was obtained by preparative HPLC. The spectroscopic data of this compound was in perfect agreements with the compound prepared in solution.

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[27] The use of TBAF on the ABI peptide synthesizer might have resulted in a selenoid valve failure, so we refrained from performing further Tom deprotection by automation. This technical difficulty will be overcome by the next generation of synthesizer developed in our laboratory.

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