Solid-Phase Synthesis of a Branched Hexasaccharide Related to Lacto-*N*-Hexaose

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Dedicated to Professor Pierre Sinaÿ on the occasion of his 62nd birthday

Keywords: Carbohydrates / Oligosaccharides / Milk / Lactose / Trichloroacetimidates / Ring-closing metathesis / Solid-phase synthesis

Lactose donor **2** has been designed for the solid-phase synthesis of branched milk oligosaccharides and its synthesis from lactose is presented. This compound has been employed, together with the known DMM-protected lactose donor **3**, in the solid-phase synthesis of the branched hexasaccharide **1** related to lacto-*N*-hexaose. An isolated yield of 13% over six steps (71% per step) was obtained from linker-loaded resin **4**. This synthesis constitutes a successful application of the ring-closing metathesis-based linker strategy for the solid-phase synthesis of oligosaccharides.

Introduction

The solid-phase synthesis of oligosaccharides has become an area of intense activity during the last decade.[1] However, despite remarkable contributions from various groups, especially concerning work carried out using polystyrene-derived supports,[2] no general synthetic strategy has yet emerged and the solid-phase synthesis of complex oligosaccharides remains a challenging task. The well-known *O*-glycosyl trichloroacetimidate donors have already proven useful for solution-phase oligosaccharide synthesis[3] and have found wide application on various solid supports.[4−6] In an effort to develop their use for the solid-phase synthesis of human milk oligosaccharides on polystyrene-based supports, we describe herein the preparation of lactosyl donor **2** and its use in the solid-phase synthesis of the protected lacto-*N*-hexaose derivative **1** (Scheme 1). The block approach for the synthesis of both linear[4d] and branched[2b] oligosaccharides on solid supports has been reported previously. It seemed to us that this synthetic approach would be of particular utility in the field of milk oligosaccharides. Therefore, we have designed and prepared suitably protected lactosamine and lactose donors that could be of interest for solid-phase synthesis. The recently introduced dimethylmaleoyl (DMM) protected lactosamine donor **3**[7] (Scheme 1) has proved to represent a very valuable building block in the solution-phase synthesis of lactosamine-containing milk oligosaccharides[8] and therefore we decided to evaluate the utility of this compound in solid-phase procedures.

As far as the lactose part was concerned, an *O*-lactosyl trichloroacetimidate donor had to be designed that would allow linkage to both the 3b and 6b *O*-positions. Moreover, we decided to use a sequential synthetic strategy involving orthogonal protection of these two positions that would allow their selective deprotection and glycosylation (3b-*O* and 6b-*O* bear orthogonal protective groups, as shown in the structure of lactosyl donor **2**). If successful, this approach could be of great interest for the synthesis of more complex, asymmetrically branched target molecules in a combinatorial manner.

Besides the type of glycosyl donor, another key feature of any solid-phase oligosaccharide synthesis is the linker system. A further aim of the present study was to extend the use of our ring-closing metathesis (RCM) based linker.[9] Indeed, we recently reported on the use of linker **4** (Scheme 2) which, under the action of the Grubbs' catalyst **5**,[10−12] permits the release of the previously bound oligosaccharides as their 1-*O*-allyl derivatives. This linker system was found to possess both the stability and the cleavage efficiency required for our purposes.

Results and Discussion

Synthesis of Lactose Donor 2

Starting from lactose (Scheme 3), the di-*O*-allylated derivative **6** was prepared in four steps using a known procedure based on a dibutyltin oxide assisted regioselective allylation.[13] Introduction of the benzylidene moiety was best achieved using benzaldehyde dimethyl acetal in the presence of *p*-toluenesulfonic acid (*p*TsOH) as catalyst in DMF at 20 °C. In this way, the 4b,6b-*O*-benzylidene derivative **7** was obtained in 60% yield. Subsequent perbenzylation under standard conditions furnished **8** in 69% yield. At this point, a regioselective opening of the benzylidene ring using Li-

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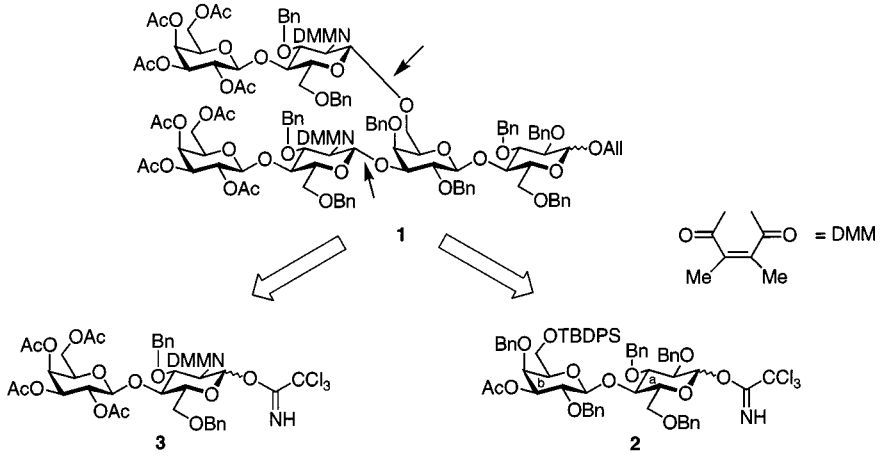
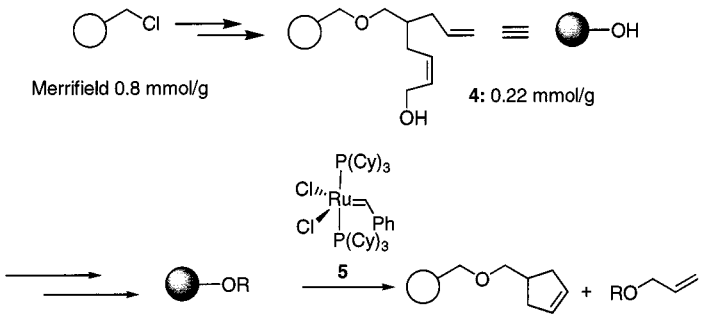
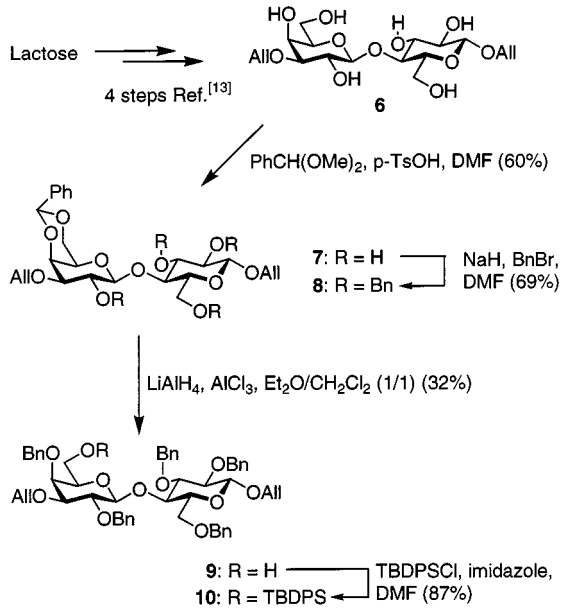


Scheme 1. Building blocks for the synthesis of branched lacto-*N*-hexaose derivative **1**



Scheme 2. Ring closing metathesis based linker system



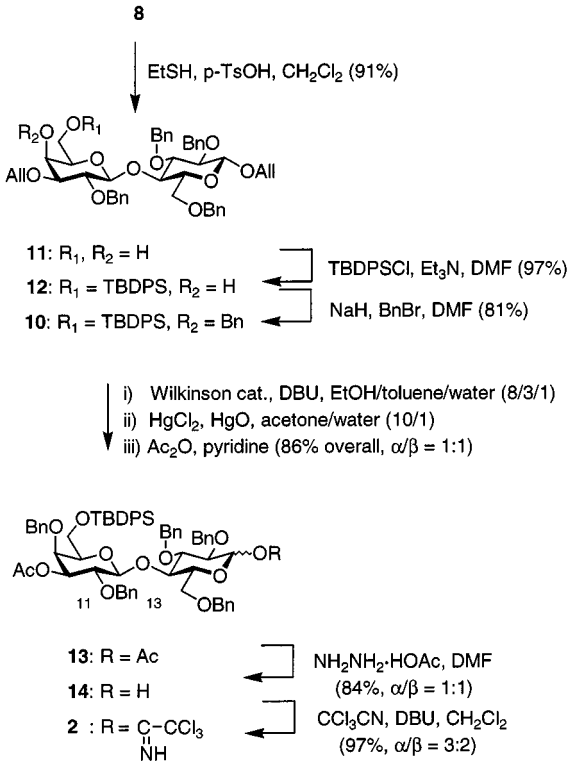
Scheme 3. Synthesis of lactose derivative **10**

$AlH_4/AlCl_3$ [14] was attempted, but the desired 4b-*O*-benzyl derivative **9** was isolated in just 32% yield.

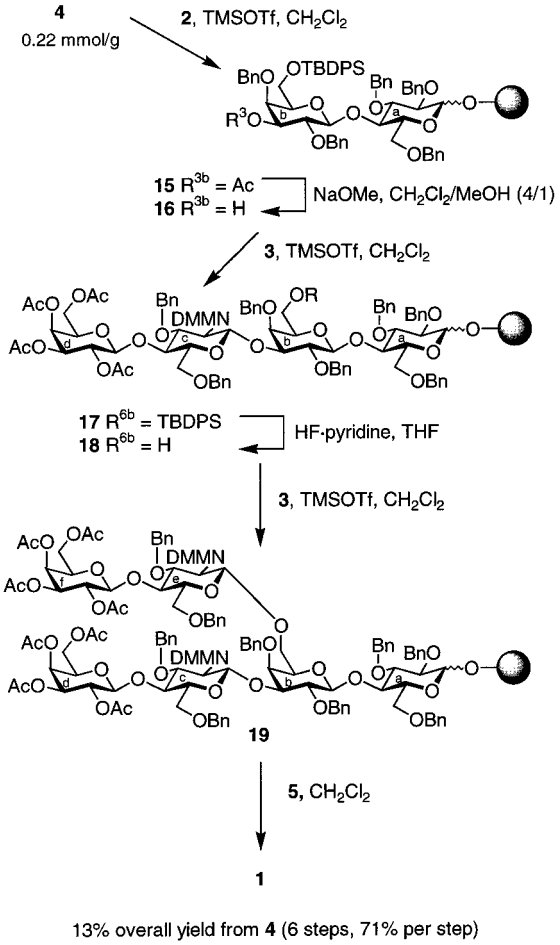
These conditions were found to lead to a product of further debenzylation along with that of benzylidene ring-opening. Subsequent silylation with *tert*-butyldiphenylsilyl chloride (TBDPSCl) and imidazole in DMF afforded the fully protected derivative **10**. We then turned to an alternative synthetic procedure (Scheme 4). The benzylidene group was completely removed using *p*TsOH and ethanethiol[15] in dichloromethane, giving **11** in high yield (91%). The primary alcohol was then silylated using TBDPSCl and triethylamine in DMF with complete regioselectivity, thereby affording **12** in practically quantitative yield (97%). Subsequent benzylation afforded **10** in 81% yield. Although slightly longer, this synthetic pathway appeared to be more efficient than the former one. The two allyl groups were subsequently removed using a two-step sequence. An isomerization step was first performed using Wilkinson's catalyst and 1,8-diaza[5.4.0]bicycloundec-7-ene (DBU), and then hydrolysis of the enol ethers was achieved using a catalyst system of mercury(II) chloride/mercury(II) oxide[16] in the presence of water. After acetylation, the derivative **13** was isolated in 86% yield. Selective deacetylation of the anomeric hydroxyl was achieved by treatment with hydrazinium acetate in DMF[17] to afford **14** in 84% yield (α/β ratio 1:1). Finally, lactosyl donor **2** was obtained in 97% yield using trichloroacetonitrile and DBU as catalyst.

Solid-Phase Synthesis of Hexasaccharide 1

With derivative **2** in hand, the sequential synthesis of hexasaccharide **1** was initiated. Linker-loaded resin **4** (0.22 mmol/g, determined by N elemental analysis of the 3,5-dinitrobenzoyl derivative) was obtained in two steps



Scheme 4. Synthesis of lactosyl donor **2**



Scheme 5. Synthesis of polymer-linked lacto-*N*-hexaose derivative **19** and liberation of **1** from the polymer support

from Merrifield resin as described previously.[9] The first glycosylation step was achieved using 3 equiv. of **2** and TMSOTf (0.3 equiv.) as catalyst in dichloromethane at room temperature (Scheme 5). This procedure was performed twice to ensure complete glycosylation. In the next step, removal of the *O*-acetyl protecting group using excess sodium methoxide in CH_2Cl_2/MeOH (4:1) at room temperature afforded resin **16**.

As in the subsequent steps, this reaction was monitored by TLC and MALDI-TOF analysis of the crude cleavage product from a small resin sample (4−5 mg). With bound acceptor **16** in hand, the next glycosylation step was performed using **3**[7] as the glycosyl donor. The reaction conditions used were similar to those employed for the first glycosylation step. At this stage, TLC/MALDI-TOF analysis of a cleaved sample of **17** showed that the expected tetrasaccharide was the major compound, but that trace amounts of tetrasaccharide having lost the TBDPS moiety were also present. Therefore, trace amounts of the compound corresponding to the target hexasaccharide and to unchanged disaccharide derived from acceptor resin **16** were also detected. This showed the TBDPS group to be suitably stable during the first two steps. Desilylation was subsequently achieved using an excess of HFpyridine in THF[2b] at room temperature to afford resin **18**. This reaction was complete, as shown by TLC/MALDI-TOF analysis of a sample cleaved from a small amount of resin. The final glycosylation step was then performed using **3**[7] as described above to give resin **19**. The subsequent cleavage was performed twice using 12 mol-% of **5** in dichloromethane at room temperature to yield, after purification, the hexasaccharide **1** in 13% overall yield (α/β ratio 1:1) based on **4**. The structural assignment of **1** was corroborated by its ^1H and ^{13}C NMR data.

Conclusion

The synthesis of the versatile lactosyl donor **2** from lactose has been achieved. Using the lactose building block **2** and the known DMM-protected lactosamine building block **3**, our recently introduced RCM linker strategy has been successfully applied to the solid-phase synthesis of the branched hexasaccharide **1** related to lacto-*N*-hexaose. Compound **1** was isolated in an encouraging overall yield (13% over 6 steps; 71% per step). Work aimed at optimizing the protecting group arrangement and the solid-phase glycosylation efficiency is currently underway in our laboratory with a view to facilitating the efficient synthesis of even more complex target molecules on solid supports.

Experimental Section

General Remarks: Solvents were purified and dried according to standard procedures. All reactions were performed under argon in

dry solvents unless otherwise stated. − TLC was performed on plastic-backed silica gel 60 F_{254} plates. Detection was achieved by treatment with a solution of ammonium molybdate (20 g) and cerium(IV) sulfate (0.4 g) in 10% H_2SO_4 (400 mL), or with 15% H_2SO_4 and heating at 150 °C. − Flash chromatography was carried out on silica gel (Baker, 30−60 μm). Crude reaction products were adsorbed onto silica gel (Baker, 60−200 μm). Petroleum ether was used in the boiling range 35−70 °C; toluene, $CHCl_3$, MeOH, and EtOAc were distilled prior to use. − Optical rotations were determined at 21 °C with a Perkin−Elmer 241/MC polarimeter (1 dm cell). − NMR spectra were recorded on Bruker AC 250 and 600 DRX instruments using tetramethylsilane as internal standard. − Mass spectra were recorded on a MALDI-kompakt (Kratos) instrument in the positive mode using 2,5-dihydroxybenzoic acid in dioxane as matrix. − Microanalyses were performed in the Microanalytical Unit at the Fachbereich für Chemie, Universität Konstanz.

Allyl *O*-(3-*O*-Allyl-4,6-*O*-benzylidene-β-D-galactopyranosyl)-(1→4)-β-D-glucopyranoside (7): A mixture of **6** (760 mg, 1.8 mmol), benzaldehyde dimethyl acetal (1.35 mL, 9 mmol), and *p*TsOH (70 mg, 0.36 mmol) in dry DMF (20 mL) was stirred at room temp. for 16 h. After neutralization with triethylamine, the solvents were evaporated, and the residue was dried in vacuo. The crude product thus obtained was purified by flash chromatography ($CHCl_3$/MeOH, 92:8) to yield **7** (556 mg, 60%) as an amorphous white mass. − TLC (chloroform/methanol, 90:10): R_f = 0.45. − $[\alpha]_D$ = +4.0 (*c* = 0.5, chloroform). − ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.41 (m, 1 H, 5a-H), 3.43 (m, 1 H, 2a-H), 3.44 (m, 1 H, 3b-H), 3.52 (m, 1 H, 5b-H), 3.67 (m, 2 H, 3a-H, 4a-H), 3.85 (dd, ^2J = 12.3 Hz, $^3J_{5,6}$ = 4.1 Hz, 1 H, 6a-H), 3.97 (m, 1 H, 6′a-H), 3.99 (dd, $^3J_{1,2}$ = $^3J_{2,3}$ = 9.1 Hz, 1 H, 2b-H), 4.05 (dd, ^2J = 12.9 Hz, $^3J_{5,6}$ = 1.8 Hz, 1 H, 6b-H), 4.11 (m, 1 H, 1a-C*H*HCH=CH_2), 4.12 (m, 1 H, 3b-C*H*HCH=CH_2), 4.22 (m, 1 H, 3b-CH*H*CH=CH_2), 4.23 (d, $^3J_{4,3}$ = 3.2 Hz, 1 H, 4b-H), 4.27 (dd, ^2J = 12.9 Hz, $^3J_{5,6}$ = 1 Hz, 1 H, 6′b-H), 4.34 (m, 1 H, 1a-CH*H*CH=CH_2), 4.37 (d, $^3J_{1,2}$ = 7.9 Hz, 1 H, 1a-H), 4.50 (d, $^3J_{1,2}$ = 7.9 Hz, 1 H, 1b-H), 5.20 (m, 2 H, $CH_2CH=CH_2$), 5.30 (m, 2 H, $CH_2CH=CH_2$), 5.50 (s, 1 H, PhC*H*), 5.92 (m, 2 H, 2 × $CH_2CH=CH_2$), 7.05−7.40 (m, 5 H, Ph). − ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 62.0 (C-6a), 67.1 (C-5b), 69.0 (2b-C), 69.1 (C-6b), 72.5 (C-4b), 73.6 (C-2a), 74.7 (C-3a, C-5a), 79.0 (C-3b), 80.1 (C-4a), 101.3 (Ph*C*H), 101.6 (C-1a), 103.7 (C-1b). − MALDI-MS; *m*/*z*: 533.7 [M + Na^+]. − $C_{25}H_{34}O_{11}$ (510.5): calcd. C 58.82, H 6.71; found C 58.55, H 6.37.

Allyl *O*-(3-*O*-Allyl-2-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (8): To a mixture of **7** (685 mg, 1.34 mmol) and benzyl bromide (1.3 mL, 10.7 mmol) in DMF (20 mL) at 0 °C was added dry NaH (193 mg, 8.1 mmol). The reaction mixture was allowed to warm to room temperature and then stirred for 22 h. The reaction was then quenched by the careful addition of saturated aqueous NH_4Cl and the resulting mixture was extracted with diethyl ether (3 × 25 mL). The combined organic phases were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (toluene/ethyl acetate, 90:10) to yield **8** as a colorless oil (808 mg, 69%). − TLC (toluene/EtOAc, 90:10): R_f = 0.27. − $[\alpha]_D$ = +4.4 (*c* = 0.9, chloroform). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.00 (s, 1 H), 3.30−4.95 (m, 25 H), 5.10−5.40 (m, 4 H, 2 × $CH_2CH=CH_2$), 5.48 (s, 1 H, PhC*H*), 5.85−6.05 (m, 2 H, 2 × $CH_2CH=CH_2$), 7.10−7.60 (m, 25 H, 5 × Ph). − MALDI-MS; *m*/*z*: 894.4 [M + Na^+]. − $C_{53}H_{58}O_{11}$ (871.0): calcd. C 73.08, H 6.71; found C 72.77, H 6.63.

Allyl *O*-(3-*O*-Allyl-2,4-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (9): To a refluxing suspension of **8** (435 mg, 0.5 mmol) and $LiAlH_4$ (80 mg, 2.1 mmol) in CH_2Cl_2/Et_2O (1:1, 10 mL), a solution of $AlCl_3$ (266 mg, 2 mmol) in Et_2O (5 mL) was added dropwise. The reaction mixture was then refluxed for a further 2 h. After dilution with EtOAc (50 mL), water (50 mL) was carefully added and the resulting mixture was vigorously stirred for 1 h at room temp. After separation of the layers, the aqueous phase was re-extracted with Et_2O (3 × 25 mL). The combined organic phases were washed with water (3 ×) and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (toluene/EtOAc, 70:30) to yield **9** (142 mg, 32%) as a colorless gum, along with 183 mg of a more polar compound resulting from monodebenzylation of **9**. − TLC (toluene/EtOAc, 70:30): R_f = 0.32. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.15−3.95 (m, 13 H), 4.05−4.25 (m, 3 H), 4.35−4.60 (m, 6 H), 4.70−5.05 (m, 7 H), 5.15−5.40 (m, 4 H, 2 × $CH_2CH=CH_2$), 5.85−6.05 (m, 2 H, 2 × $CH_2CH=CH_2$), 7.10−7.40 (m, 25 H, 5 × Ph).

Allyl *O*-(3-*O*-Allyl2-*O*-benzyl--β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (11): A mixture of **8** (874 mg, 1 mmol), EtSH (450 μL, 6 mmol), and *p*TsOH (40 mg, 0.21 mmol) in CH_2Cl_2 was stirred at room temp. for 16 h. The reaction was then quenched by the addition of an excess of Et_3N (200 μL). The solvents were removed in vacuo and the residue was purified by flash chromatography (toluene/EtOAc, 65:35) to give **11** (715 mg, 91%) as a white amorphous solid. − TLC (toluene/EtOAc, 75:25): R_f = 0.27. − $[\alpha]_D$ = +22.5 (*c* = 2, chloroform). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.19 (m, 1 H, 5b-H), 3.25 (dd, $^3J_{2,3}$ = 9.4 Hz, $^3J_{3,4}$ = 3.3 Hz, 1 H, 3b-H), 3.35−3.95 (m, 10 H), 4.10−4.20 (m, 3 H), 4.35−4.50 (m, 4 H), 4.50−5.00 (m, 7 H, 7 × PhC*H*H), 5.17−5.40 (m, 4 H, 2 × $CH_2CH=CH_2$), 5.85−6.05 (m, 2 H, 2 × $CH_2CH=CH_2$), 7.20−7.45 (m, 20 H, 4 × Ph). − MALDI-MS: *m*/*z* = 805.0 [M + Na^+]. − $C_{46}H_{54}O_{11}$ (782.9): calcd. C 70.57, H 6.95; found C 70.58, H 6.57.

Allyl *O*-(3-*O*-Allyl-2-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (12): To a solution of **11** (714 mg, 0.91 mmol) and TBDPSCl (265 μL, 1 mmol) in DMF (5 mL) was added Et_3N (140 μL, 1.0 mmol) and the mixture was stirred at room temp. for 16 h. It was subsequently diluted with EtOAc (20 mL) and the organic phase was washed with water (3 ×) and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 85:15) to give **12** (905 mg, 97%) as a colorless oil. − TLC (petroleum ether/EtOAc, 85:15): R_f = 0.32. − $[\alpha]_D$ = −3.2 (*c* = 0.5, chloroform). − ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.97 (s, 9 H, *t*Bu), 3.15 (m, 1 H, 5b-H), 3.19 (dd, $^3J_{2,3}$ = 9.4 Hz, $^3J_{3,4}$ = 3.3 Hz, 1 H, 3b-H), 3.26 (m, 1 H, 5a-H), 3.34 (dd, $^3J_{1,2}$ = $^3J_{2,3}$ = 8.1 Hz, 1 H, 2a-H), 3.44 (m, 2 H, 2b-H, 3a-H), 3.60−3.65 (m, 2 H, 6b-H, 6a-H), 3.73 (dd, ^2J = 10.9 Hz, $^3J_{5,6}$ = 4.35 Hz, 1 H, 6′a-H), 3.78 (dd, ^2J = $^3J_{5,6}$ = 9.3 Hz, 1 H, 6′b-H), 3.86 (dd, $^3J_{2,3}$ = $^3J_{4,5}$ = 9.3 Hz, 1 H, 4a-H), 4.01 (m, 1 H, 4b-H), 4.02−4.15 (m, 3 H, 3 × C*H*HCH=CH_2), 4.30−4.35 (m, 4 H, 1a-H, 1b-H, 1 × C*H*HCH=CH_2, 1 × PhC*H*H), 4.45−4.85 (m, 7 H, 7 × PhC*H*H), 5.10−5.30 (m, 4 H, 4 × $CH_2CH=CH$*H*), 5.80−5.95 (m, 2 H, 2 × $CH_2CH=CH_2$), 6.95−7.65 (m, 30 H, 6 × Ph). − ^{13}C NMR (150.9 MHz, $CDCl_3$): δ (selected data) = 19.2 (*C*CH_3), 26.8 (C*C*H_3), 61.6 (C-6b), 65.7 (C-4b), 68.3 (C-6a), 73.8 (C-5b), 75.2 (C-5a), 76.4 (C-4a), 79.5 (C-2b), 81.2 (C-3b), 81.8 (C-2a), 82.8 (C-3a), 102.4−102.7 (C-1a, C-1b). − MALDI-MS; *m*/*z*: 1045.5 [M + Na^+]. − $C_{62}H_{72}O_{11}Si$ (1021.3): calcd. C 72.91, H 7.11; found C 72.97, H 7.10.

Allyl *O*-(3-*O*-Allyl-2,4-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (10):

From 9: To a mixture of **9** (200 mg, 0.23 mmol) and TBDPSCl (96 μL, 0.345 mmol) in DMF (10 mL) was added imidazole (31 mg, 0.45 mmol) and the reaction mixture was stirred for 16 h at room temp. It was subsequently diluted with diethyl ether and washed with water (3 ×) and brine. After drying over $MgSO_4$ and evaporation of the solvents in vacuo, the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 90:10) to yield **10** (222 mg, 87%) as a colorless oil.

From 12: To a mixture of **12** (5.24 g, 5.1 mmol) and benzyl bromide (1 mL, 8.4 mmol) in DMF (20 mL) at 0 °C was added dry NaH (200 mg, 8.3 mmol). The reaction mixture was allowed to warm to room temp. and stirred for a further 16 h. It was then diluted with EtOAc (100 mL) and the reaction was carefully quenched by the addition of saturated aqueous NH_4Cl (50 mL). The organic phase was then washed with brine (3 ×), dried over $MgSO_4$, and the solvents were evaporated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 90:10) to yield **10** (5.01 g, 88%) as a colorless oil. TLC (petroleum ether/EtOAc, 90:10): R_f = 0.22. − $[\alpha]_D$ = −7.1 (*c* = 1, chloroform). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.04 (s, 9 H, *t*Bu), 3.20−3.55 (m, 5 H), 3.60−3.95 (m, 6 H), 4.00−4.15 (m, 2 H), 4.23 (br. s, 2 H), 4.35−4.45 (m, 4 H), 4.50−5.10 (m, 9 H), 5.85−6.05 (m, 2 H, 2 × CH_2CH=CH_2), 6.90−7.60 (m, 35 H, 7 × Ph). − MALDI-MS; *m*/*z*: 1135.5 [M + Na^+]. − $C_{69}H_{78}O_{11}Si$ (1111.5).

Acetyl *O*-(3-*O*-Acetyl-2,4-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α/β-D-glucopyranoside (13): A mixture of **10** (656 mg, 0.59 mmol), Wilkinson's catalyst (55 mg, 59 μmol), and DBU (5 μL, 33 μmol) in EtOH/toluene/water (8:3:1, 24 mL) was refluxed for 20 h. The reaction mixture was then diluted with Et_2O (100 mL), the organic phase was washed with water and brine, and the solvents were removed in vacuo. The residue was redissolved in acetone/water (10:1, 30 mL), HgO (20 mg, 92 μmol) and $HgCl_2$ (800 mg, 2.95 mmol) were added, and the resulting mixture was stirred for 2 h at room temp. The solvents were then removed in vacuo and the residue was diluted with Et_2O (200 mL). The organic phase was then washed with water (1 ×), 10% aqueous KI solution (3 ×), further water (3 ×), and brine (1 ×). After drying over $MgSO_4$, the solvents were removed in vacuo and the residue was acetylated in Ac_2O/pyridine (1:1, 20 mL) and DMAP (20 mg, 16 μmol) for 16 h at room temp. The solvents were evaporated and the residue was dried by threefold coevaporation with toluene. The crude product was finally adsorbed onto silica gel (10 mL) in toluene and separated by flash chromatography (toluene/EtOAc, 92.5:7.5) to afford **13** (566 mg, 86%) as a white foam (α/β ratio 1:1). − TLC (petroleum ether/EtOAc, 9:1): R_f = 0.23. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.07 (s, 9 H, *t*Bu), 1.95, 1.97, 2.03, 2.16 (4 s, 6 H, 4 × CH_3CO), 3.25−4.05 (m, 17 H), 4.10 (br. s, 1 H, 4b-H), 4.30−4.45 (m, 2 H), 4.55−4.90 (m, 2 H), 4.99 (m, 1 H, 3b-H), 5.56 (d, $^3J_{1,2}$ = 7.8 Hz, 0.5 H, 1a$_\beta$-H), 6.38 (d, $^3J_{1,2}$ = 3.3 Hz, 0.5 H, 1a$_\alpha$-H), 6.90−7.65 (m, 35 H, 7 × Ph). − MALDI-MS; *m*/*z*: 1139.3 [M + Na^+]. − $C_{67}H_{74}O_{13}Si$ (1115.4): calcd. C 72.15, H 6.69; found C 71.72, H 6.40.

***O*-(3-*O*-Acetyl-2,4-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α/β-D-glucopyranoside (14):** To a solution of **13** (3.9 g, 3.5 mmol) in DMF (20 mL) was added NH_2NH_3·OAc (546 mg, 5.9 mmol) and the reaction mixture was stirred for 8 h at room temp. Acetone (10 mL) was then added to quench the reaction. The resulting mixture was diluted with Et_2O (100 mL) and the organic phase washed with brine (3 ×), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (toluene/AcOEt, 85:15) of the residue yielded **14** (3.3 g, 84%) as a white foam (α/β ratio 1:1). − TLC (toluene/EtOAc, 85:15): R_f = 0.27. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.05 (s, 9 H, tBu), 1.95 (s, 3 H, CH_3CO), 3.01 (d, $^2J_{1,OH}$ = 2.2 Hz, 0.5 H, 1a-OH), 3.19 (d, $^2J_{1,OH}$ = 6.0 Hz, 0.5 H, 1a-OH), 3.24−3.94 (m, 10 H), 4.09 (m, 1 H), 4.30−4.38 (m, 2 H), 4.53−4.90 (m, 9.5 H), 4.98 (m, 1 H, 3b-H), 5.15 (m, 0.5 H, 1a-H), 6.85−7.65 (m, 35 H, 7 × Ph). − MALDI-MS; m/z: 1096.2 [M + Na^+]. − $C_{65}H_{72}O_{12}Si$ (1073.4): calcd. C 72.74, H 6.76; found C 72.47, H 6.68.

***O*-[(3-*O*-Acetyl-2,4-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α/β-D-glucopyranosyl] Trichloroacetimidate (2):** To a solution of **14** (2.4 g, 2.24 mmol) in CH_2Cl_2 (20 mL) was added CCl_3CN (5 mL, 5 mmol) and DBU (30 μL, 0.2 mmol) and the reaction mixture was stirred at room temp. for 2 h. The solvents were then removed in vacuo and the residue was purified by flash chromatography (petroleum ether/EtOAc/Et_3N, 86:13:1) to afford **2** (2.7 g, 97%) as a white foam (α:β, 3:2). − TLC (petroleum ether/EtOAc, 80:20): R_f = 0.48. − ^{1}H NMR (600 MHz, $CDCl_3$): δ (selected data) = 1.04 (s, 9 H, tBu), 1.94 (s, 1 H, CH_3CO_β), 1.95 (s, 2 H, CH_3CO_α), 3.33 (m, 1 H, 5b-H), 3.48 (m, 1 H, 5a$_\beta$-H, 6a$_\alpha$-H), 3.60−3.90 (m, 7 H, 2a-H, 2b-H, 3a-H, 5a$_\alpha$-H, 6a$_\beta$-H, 6′a-H, 6b-H, 6′b-H), 4.00−4.10 (m, 2 H, 4a-H, 4b-H), 4.25−5.00 (m, 12 H, 5 × $PhCH_2$, 1b-H, 3b-H), 5.74 (d, $^3J_{1,2}$ = 7.4 Hz, 0.33 H, 1a$_\beta$-H), 6.39 (d, $^3J_{1,2}$ = 3.25 Hz, 0.67 H, 1a$_\beta$-H). − ^{13}C NMR (150.9 MHz, $CDCl_3$): δ (selected data) = 19.1 (CCH_3), 20.97 (CH_3CO), 26.9 (CCH_3), 60.9 (C-6b), 67.3 (C-6b), 73.1 (C-5a$_\alpha$), 73.9 (C-5b), 74.4 (C-4b), 75.4 (C-3b), 75.5 (C-4a$_\alpha$), 75.7 (C-4a$_\beta$), 75.9 (C-5a$_\beta$), 77.7 (C-2b), 78.3 (C-2a$_\alpha$), 79.5 (C-3a$_\alpha$), 80.2 (C-2a$_\beta$), 82.7 (C-3a$_\beta$), 94.5 (C-1a$_\alpha$), 98.3 (C-1a$_\beta$), 102.4, 102.5 (C-1b). − $C_{67}H_{75}NO_{12}Si$ (1073.4): calcd. C 66.31, H 6.06, N 1.14; found C 65.95, H 5.96, N 0.77.

General Procedure for the Solid-Phase Glycosylation (Procedure A): Dry, acceptor-loaded resins were directly swollen in CH_2Cl_2 solutions (1−1.5 mL/100 mg resin) containing the appropriate donor (3 equiv.) under argon. After 15 min. under agitation, 0.3 equiv. of a freshly prepared 0.25 M TMSOTf solution in $CHCl_2$ was added and shaking was continued for 1 h at room temp. The resin was then filtered off, washed with THF (4 × 5 mL) and CH_2Cl_2 (4 × 5 mL), and dried under high vacuum. This procedure was repeated a second time prior to undertaking the next step.

General Procedure for Analytical Cleavage (Procedure B): Resin (4−5 mg) was swollen in degassed CH_2Cl_2 (500 μL) and the resulting suspension was shaken for 10 min. under argon. A few crystals of **5** were added and the resulting mixture was agitated for 4 h under an inert atmosphere. After this time, TLC analysis proved satisfactory. The resin and catalyst were filtered off by passage through a short pad of silica gel (2 × 0.6 cm) and the cleaved organic compounds were rinsed off with excess AcOEt. The combined filtrate and washings were concentrated in vacuo, and the residue was redissolved in dioxane and analyzed by TLC and MALDI-TOF.

Resin 15: Resin **4** was glycosylated with **2** according to Procedure A.

Resin 16: Resin **15** was swollen in dry CH_2Cl_2 (1.5 mL/100 mg) under argon and the resulting suspension was agitated for 10 min. A solution of NaOMe in MeOH (0.5 M, 5 equiv.) was then added and the reaction mixture was shaken for a further 2 h at room temp. The resin was then filtered off and washed until neutral with a

0.2 M solution of AcOH in THF. It was then washed with THF (4 × 5 mL) and CH_2Cl_2 (4 × 5 mL) and dried under high vacuum.

Resin 17: Resin **16** was glycosylated with **3** according to Procedure A.

Resin 18: Resin **17** was swollen in dry THF (1 mL/100 mg) under argon. After 10 min. of agitation, 100 μL of a 30% HFpyridine solution was added and the agitation was maintained for 20 h. The resin was then filtered off and washed with THF (1 × 5 mL), CH_2Cl_2 (1 × 5 mL), DMF (6 × 5 mL), and further alternate portions of THF and CH_2Cl_2 (2 × 5 mL of each), and dried under high vacuum.

Resin 19: Resin **18** was glycosylated with **3** according to Procedure A.

Allyl 3,6-Di-*O*-[(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-(3,6-di-*O*-benzyl-2-deoxy-2-dimethylmaleimido-β-D-glucopyranosyl)]-(1→3/6)-(2,4-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α,β-D-glucopyranoside (1): Resin **19** (30 μmol) was washed with dry CH_2Cl_2 (2 × 5 mL) and was then allowed to swell in CH_2Cl_2 (5 mL) under argon. The resulting suspension was degassed by passing a stream of argon through it for 20 min. Catalyst **5** (3 mg, 3.6 μmol, 12 mol-%) was then added and the resulting mixture was agitated for 4 h at room temp. The resin was then filtered off, washed with CH_2Cl_2 (5 × 5 mL), and dried under high vacuum. It was then submitted to the cleavage conditions once more. The crude product thus obtained was purified by two successive flash chromatographic separations (toluene/AcOEt, 65:35 and toluene/AcOEt, 70:30) to afford **1** (9.4 mg, 13% overall yield based on resin **4**) as an amorphous solid (α/β ratio 1:1). − TLC (toluene/EtOAc, 60:40): R_f = 0.57. − ^{1}H NMR (600 MHz, $CDCl_3$): δ (selected data) = 1.67 [br. s, 12 H, 4 × CH_3 (DMM)], 1.80−2.01 (several s, 24 H, 8 × CH_3CO), 3.21 (1 H, 6b-H), 3.78 (1 H, 2e-H), 3.81 (1 H, 6′b-H), 3.78 (1 H, 2e-H), 3.88 (1 H, 2c-H), 3.92 (0.5 H, 1a$_\beta$-H), 4.12 (0.5 H, 1b-H), 4.21 (0.5 H, 1b-H), 4.42 (1 H, 1f-H), 4.52 (1 H, 1d-H), 4.59 (0.5 H, 1a$_\alpha$-H), 4.77 (1 H, 1e-H), 5.10 (1 H, 1c-H), 5.85−5.95 (m, 1 H, $CH_2CH{=}CH_2$), 7.0−7.40 (m, 45 H, 9 × Ph). − ^{13}C NMR (150.9 MHz, $CDCl_3$): δ (selected data) = 96.2 (C-1a$_\alpha$), 98.5 (C-1e), 99.7 (C-1c), 100.4 (C-1f), 100.8 (C-1d), 102.8 (C-1b), 102.9 (C-1a$_\beta$), 102.9 (C-1b). − MALDI-MS; *m/z* 2417.0 [M + Na^+]. − $C_{130}H_{146}N_2O_{41}$ (2392.6).

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