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Reconsidering glycosylations at high temperature: precise microwave heating

Kim Larsen,[a] Kasper Worm-Leonhard,[a] Peter Olsen,[a] Andreas Hoel[b] and Knud J. Jensen*[a]

[a] *Department of Natural Sciences, Section for Bioorganic Chemistry, Royal Veterinary and Agricultural University, DK-1871, Frederiksberg, Denmark. E-mail: kjj@kvl.dk; Fax: +45 3528 2398; Tel: +45 3528 2430*

[b] *Biotage AB, SE-75318, Uppsala, Sweden*

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Current methods for glycosylation of complex alcohols, *e.g.* with glycosyl trichloroacetimidates, generally occur in the presence of a strong Lewis acid 'promoter', and at sub-ambient temperatures. However, the older literature reports high-temperature glycosylations, especially of phenols. We have described an efficient method for glycosylation of alcohols under neutral conditions, using as anomeric leaving group methyl 3,5-dinitrosalicylate (DISAL). Only a very few reports have described the use of microwaves to promote glycosylations, mainly of simple alcohols. Here we describe fast, high-temperature glycosylations using precise microwave heating in the synthesis of oligosaccharides, with both DISAL and widely used trichloroacetimidate glycosyl donors in the absence of strong Lewis acids. Also, we have applied microwave heating as a general protocol for evaluating new, potential glycosyl donors.

Introduction

Glycoconjugates play crucial roles in the development, growth, and proper function of an organism.[1] There are numerous biologically important poly- and oligosaccharides, *e.g.*, in glycans of *O*- and *N*-glycopeptides and -proteins, tumor-associated antigens, lipochitin nodulation factors, and amino glycoside antibiotics such as streptomycin. Synthesis of oligosaccharides of these glycoconjugates provides important tools for glycobiology.

Most glycosylation protocols rely on Lewis acid 'promoters' for activation of an anomeric leaving group, and glycosylations of aliphatic alcohols have generally been performed at below ambient temperature.[2] However, aryl glycosides can often be prepared in the absence of a Lewis acid promoter, *e.g.*, by generation of a phenoxide nucleophile or by nucleophilic aromatic substitution.[3] Also, classical work by Helferich and others described high-temperature glycosylations, especially of phenols.[4] Novel methods for glycosylation of aliphatic alcohols in the absence of strong Lewis acids, *i.e.* under mild conditions, hold great promise.[3] We have described a new, efficient method for glycosylation under strictly neutral or mildly basic conditions, or in the presence of lithium salts.[5] In this glycosylation technique, the anomeric leaving group on benzyl- or benzoyl-protected donors is methyl 3,5-dinitrosalicylate (DISAL) or its *para* regioisomer. The potential of DISAL glycosyl donors was demonstrated in their successful application to solution-phase[5a,d] and solid-phase[5b] oligosaccharide synthesis, glycosylation of natural product analogs (phenazines), as well as intramolecular glycosylation *via* a novel 1,9-glycosyl shift.[5c] DISAL glycosyl donors are prepared by a convenient and robust nucleophilic aromatic substitution protocol. These glycosylations are operationally simple and can be carried out in standard plastic vials. However, to further optimize this procedure we needed to shorten reaction times and improve yields.

Microwave heating can dramatically increase reaction rates in organic chemistry.[6] Modern microwave instruments allow precise control of temperature and pressure in sealed reaction tubes. However, changing the reaction temperature may alter the distribution between the main reaction and side-reactions, hence, while precise microwave heating can promote many reactions, not all reactions will benefit.[7] This technique has not been employed widely in glycosylations, with few exceptions.[8] Fraser-Reid and co-workers reported microwave-promoted glycosylation at 100 °C with *n*-pentenyl orthoesters in the presence of the strong Lewis acid *N*-iodosuccinimide (2.2 equiv).[8f] We hypothesized that glycosylations under mild conditions, *i.e.* in the absence of Lewis acid, could benefit from promotion by elevated temperatures. We were encouraged by preliminary results in which glycosylation of a secondary hydroxyl with a DISAL donor had proceeded with high β-selectivity by brief microwave heating to 130 °C.[5f]

Anomeric trichloroacetimidates are widely used glycosyl donors. They are conventionally activated by strong Lewis acids such as trimethylsilyl trifluoromethanesulfonate[9] or boron trifluoride etherate.[10] However, these promotors require special attention regarding temperature and moisture. Efficient glycosylations with trichloroacetimidates in the absence of strong Lewis acids would be desirable. Waldmann,[11] Lubineau[12] and co-workers have observed that glycosylation with trichloroacetimidates could be promoted by lithium salts at ambient temperature, albeit requring long reaction times. Our guiding question was whether precise microwave heating can be used *in general* to promote and accelerate α-selective glycosylations with DISAL donors and with well-established glycosyl trichloroacetimidates.

Thus, we studied the synthesis of oligosaccharides in the absence of added Lewis acids with microwave heating, aiming to determine general conditions for microwave-promoted glycosylations. We investigated glycosylations with DISAL and trichloroacetimidate donors, as well as reactions with glycosyl donors carrying a modified DISAL leaving group. Microwave heating was performed in closed (septum) vessels in a Biotage Initiator instrument. Reaction times were generally 5–40 min and the temperature in the 100–150 °C range. Reaction times *without* microwave heating had been up to 31 h.

Results and discussion

First, can glycosylations with a DISAL donor be accelerated by precise microwave heating? To answer this question we repeated previous experiments but now under microwave conditions (Scheme 1, Table 1). First, the reaction time for (solvolytic) glycosylation of methanol with DISAL donor **1** was reduced from 6 h at 30 °C[5a] to 5 min at 100 °C (Table 1, entry 1). Importantly, the reaction proceeded with inversion, as before. Similarly, glycosylation of cyclohexanol (5 equiv) in NMP also

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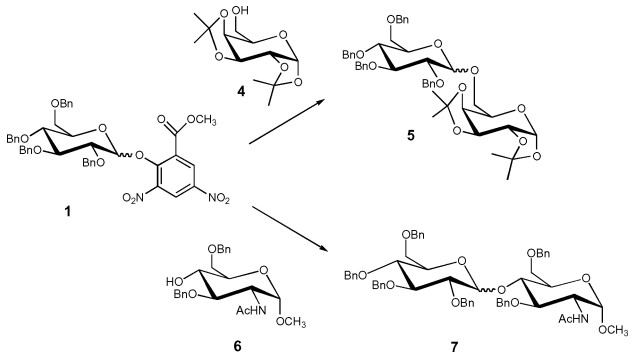
Table 1 Glycosylations with DISAL donor **1** (α/β 4.7 : 1)

Entry	Acceptor	Additive, solvent	Microwave	Product, yield (α/β ratio)
1	MeOH	MeOH	100 °C, 5 min	**2**, 91% (1 : 4.4)
2	Cyclohexanol	NMP	100 °C, 5 min	**3**, 71% (2.1 : 1)
3	**4**	NMP	130 °C, 40 min	**5**, 60% (1.9 : 1)
4	**4**	$LiClO_4$, $(CH_2Cl)_2$	100 °C, 30 min	**5**, 97% (2 : 1)
5	**6**	$LiClO_4$, $(CH_2Cl)_2$	100 °C, 40 min	**7**, 72% (4 : 1)



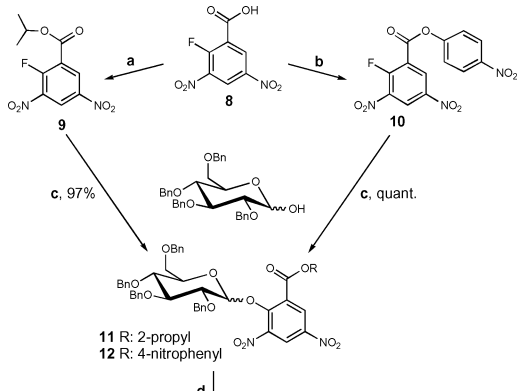
Scheme 1 Microwave promoted α-selective 1,6- and 1,4-glycosylation with DISAL donor **1**. Conditions and results in Table 1.

proceeded in 5 min at 100 °C (entry 2) (previously 2 h at 40 °C in NMP).[5a] It was gratifying to see that microwave heating at 130 °C accelerated the glycosylation of monosaccharide **4** to give disaccharide **5** in 60% yield (entry 3). Performing the same reaction in $(CH_2Cl)_2$ with $LiClO_4$ improved the yield to an impresive 97% (entry 4). The 4-OH in GlcNAc derivatives is considered one of the most challenging hydroxyls to glycosylate.[13] It was very rewarding to see that the 4-OH in GlcNAc derivative **6**[5b] was glycosylated in a high yield of 72% (α/β 4 : 1) (entry 5).

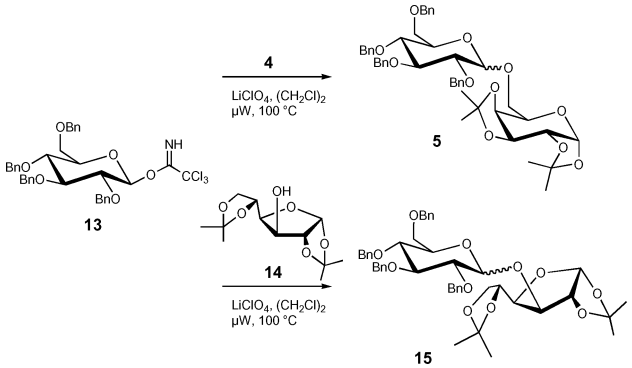
Next, can the reactivity of the DISAL donor be 'tuned' by substituting its methyl moiety for a sterically or electronically different group? To test this, the 2-propyl (**9**) and 2-(4-nitrophenyl) (**10**) ester analogs of DISAL were prepared and subjected to the above conditions for microwave glycosylation (Scheme 2). Thus, the aryl fluoride 2-fluoro-3,5-dinitrobenzoic acid (**8**) was converted to the 2-propyl ester **9** by treatment with oxalyl chloride (cat. DMF) followed by 2-propanol. The 2-propyl DISAL glycoside **11** was synthesized using the standard protocol for the preparation of DISAL glycosides. The nitrophenyl DISAL donor **12** was prepared in the same way.

Solvolytic glycosylation of MeOH with 2-propyl DISAL donor **11** proceeded in 5 min at 100 °C (Table 2, entry 1). Glycosylation of cyclohexanol (5 equiv) with conventional heating in NMP at 60 °C required 31 h (Table 2, entry 2). The same reaction but with microwave heating at 100 °C took only 5 min (Table 2, entry 3; somewhat lower yield but with improved α-selectivity). In these experiments the 2-propyl DISAL donor showed no real advantages compared to the original DISAL leaving group. Somewhat surprisingly, the nitrophenyl DISAL donor **12** proved less reactive (Table 2, entry 4). However, these microwave conditions provided a fast method for the evaluation of these modified DISAL glycosyl donors.

Finally, we wanted to study whether glycosylations with widely used trichloroacetimidates could be accelerated by microwave heating under very mild conditions. Thus, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl trichloroacetimidate **13**[14] was used to glycosylate cyclohexanol, the galactose derivative **4**, and the glucose derivative **14** (Scheme 3 and Table 3).



Scheme 2 Synthesis of DISAL donors **9** and **10** and subsequent glycosylations. *Reagents and conditions*: (a) i) oxalyl chloride, DMF, DCM, r.t.; ii) 2-propanol, 78%; (b) i) $SOCl_2$, THF, 80 °C; ii) 4-nitrophenol, THF, pyridine, 0 °C, 92%; (c) Li_2CO_3, DMAP, CH_2Cl_2, r.t., 20 min; (d) see Table 2.



Scheme 3 Microwave-promoted disaccharide synthesis using trichloroacetimidate donor **13** (Table 3).

Waldmann[11] reported that glycosylation of cyclohexanol with **13** in 1 M solutions of $LiClO_4$ in either Et_2O or DCM gave the cyclohexyl derivative **3** in 50–63% yield after 24 h. We now report that the same reaction in $(CH_2Cl)_2$ with 0.09 M $LiClO_4$ under microwave irradiation for 5 min at 100 °C increased the yield to 80% (Table 3, entry 1).

Table 2 Glycosylation with donors **11** and **12**

Entry	Donor (α/β ratio)	Conventional	Microwave	Product, yield (α/β ratio)
1	**11** (>49 : 1)	—	100 °C MeOH, 5 min	**2**, 73% (1 : 17)
2	**11** (>1 : 49)	60 °C, cyclohexanol, NMP, 31 h	—	**3**, 82% (1 : 1)
3	**11** (>1 : 49)	—	100 °C, cyclohexanol, NMP, 5 min	**3**, 64% (6.5 : 1)
4	**12** (>1 : 49)	—	150 °C, MeOH, 2 × 10 min	**2**, 54% (2 : 1)

Table 3 Microwave glycosylation with donor **13** in $(CH_2Cl)_2$ in the presence of $LiClO_4$

Entry	Donor	Acceptor	Reaction time	Product, yield (α/β ratio)
1	**13**	Cyclohexanol	5 min	**3**, 80% (2 : 1)
2	**13**	**4**	25 min	**5**, 80% (1 : 1)
3	**13**	**14**	30 min	**15**, 72% (1.5 : 1)

The glycosylation of **4** with **13** under microwave conditions increased the yield from its previous value of 45–47% to 80%. In this case, the time for microwave irradiation was increased to 25 min to ensure complete conversion to the disaccharide **5** (Table 3, entry 2). Finally, the glycosylation of acceptor **14** proceeded in 72% yield after 30 min of microwave irradiation at 100 °C (entry 3). This compares favorably with the results obtained by Lubineau[11] using LiOTf (0.5 equiv), which gave 77% yield after 86 h. These glycosylations gave α/β ratios comparable to those obtained by Waldmann[11] and Lubineau.[12] During our microwave-promoted glycosylations, no hydrolysis or rearrangement of the trichloroacetimidate was detected.

Summary

In conclusion, microwave heating to 100–130 °C efficiently promoted *O*-glycosylations with DISAL donors in either NMP or $(CH_2Cl)_2$ with $LiClO_4$. Even the difficult 1,4-glycosylation of a GlcNAc derivative was achieved. Glycosylation with widely used trichloroacetimidates in the presence of $LiClO_4$ were also promoted by precise microwave heating. These glycosylations are operationally simple. The obtained α/β ratios were comparable to those previously obtained at 20–60 °C; glycosylation of sterically demanding alcohols with DISAL donors proceeded with α-selectivity. The key to this success appears to be the absence of strong Lewis acids. These conditions have also been applied in the screening of new, potential glycosyl donors. Evaluation of two new DISAL donor analogs under microwave conditions showed that they could *O*-glycosylate, but that they had no improved properties compared to the original DISAL donor. We have thus demonstrated that heating to temperatures hitherto not generally applied can be used to accelerate slow glycosylations in oligosaccharide synthesis. Here, we have focused on α-selective glycosylations; very recently we reported a β-selective glycosylation under comparable conditions.[5f] We believe that the simplicity and efficiency of these microwave-promoted glycosylations in the absence of strong Lewis acids should make these protocols widely applicable.

Experimental

Molecular sieves (4 Å) were activated under high vacuum at 150 °C for 24 h. CH_3NO_2 was purified by vacuum distillation to remove the water–CH_3NO_2 azeotrope, and stored in dark bottles over 4 Å molecular sieves. The water content (<20 ppm) was measured by Karl-Fischer titration. All other solvents were distilled and/or stored over 3 Å or 4 Å molecular sieves as appropriate. Analytical HPLC was performed on a Waters 600 system with a 996 diode array detector and a 717 Autosampler equipped with a 3.9 × 50 mm Nova-Pak C18 4 μm 60 Å column. The following solvents were used: 0.1% TFA–H_2O (A); 0.1% TFA–CH_3CN (B); H_2O (C); CH_3CN (D). Analytical HPLC was performed on microfiltered or centrifuged 0.1% solutions in MeCN (for more hydrophilic compounds, solubility was improved by addition of water). The following programs were used:

Program A: 0.00 min: 1.00 ml min^{-1}, 95.0% A, 5.0% B; 7.00 min: 1.00 ml min^{-1}, 5.0% A, 95.0% B; 8.50 min: 1.00 ml min^{-1}, 5.0% A, 95.0% B; 9.00 min: 1.00 ml min^{-1}, 95.0% A, 5.0% B; 15.00 min: 1.00 ml min^{-1}, 95.0% A, 5.0% B.

Program B: 0.00 min: 1.00 ml min^{-1}, 95.0% C, 5.0% D; 7.00 min: 1.00 ml min^{-1}, 5.0% C, 95.0% D; 8.50 min: 1.00 ml min^{-1}, 5.0% C, 95.0% D; 9.00 min: 1.00 ml min^{-1}, 95.0% C, 5.0% D; 15.00 min: 1.00 ml min^{-1}, 95.0% C, 5.0% D.

Characteristic absorption maxima were: Bn: 256–257 nm, DISAL-OH: 220 nm and 286 nm.

Preparative HPLC was performed on a Waters 600 system with Waters 996 diode array detector and three consecutive columns (40 × 100 mm prep. NOVA Pak HR C18 6 μm 60 Å units). Linear gradients of CH_3CN (D) and water (MilliQ) (C) were used.

Program A: 0.00 min: 0.00 ml min^{-1}, 95.0% C, 5.0% D; 1.00 min: 20.00 ml min^{-1}, 95.0% C, 5.0% D; 20.00 min: 20.00 ml min^{-1}, 50.0% C, 50.0% D; 60.00 min: 20.00 ml min^{-1}, 5.0% C, 95.0% D; 75.00 min: 20.00 ml min^{-1}, 0.0% C, 100.0% D; 81.00 min: 0.00 ml min^{-1}, 0.0% C, 100.0% D.

^1H, ^{13}C, gHSQC, HMBC and H,H-COSY NMR spectra were recorded on a Bruker Avance 300 spectrometer. The chemical shifts are referred to the residual solvent signal. Chemical shifts (δ) values are in ppm, coupling constants (J) are in Hz. Mass determination (high-resolution MS, HR-MS) was performed on a Micromass LCT instrument with an ESI probe. For TLC, Merck TLC aluminum sheets coated in silica gel 60 F_{254} were used. Compounds containing UV-absorbing groups were visualized under UV light (254 nm), and carbohydrates were developed with 2 M H_2SO_4 followed by charring with a heat gun. Vacuum liquid chromatography (VLC) was performed on columns of Merck 60H silica packed under vacuum. The crude product was dissolved in CH_2Cl_2, the equivalent amount of silica added, concentrated, placed on the column and finally covered with acid-rinsed sea sand. Chromatography was thereafter run with the appropriate eluents until the product was collected. Microwave experiments was carried out in a Biotage Initiator (Biotage, Sweden). The reaction times are specified as the ramp time, and the hold times at the final temperature. Temperatures are measured by IR, and pressure *via* the septum. The new compounds described in this paper are all fully characterized. All known compounds have been verified by NMR and ESI-MS.

Isopropyl 2-fluoro-3,5-dinitrobenzoate (9)

In a dry, round-bottomed flask, 2-fluoro-3,5-dinitrobenzoate (**8**) (305 mg; 1.3 mmol) was dissolved in dry DCM (9 mL). Dry DMF (30 μL) was added and oxalyl chloride (125 μL; 1.45 mmol) was added to the solution. Moderate gas evolution from the solution was seen after addition of oxalyl chloride. After 90 min dry 2-propanol (0.71 mL) was added, and after an additional 60 min the reaction mixture was concentrated under vacuum, yielding a yellowish-white powder. Recrystallization from toluene–hexane gave white crystals (284 mg; 78%), mp 92–93 °C. ^1H NMR (300 MHz, $CDCl_3$): 9.05 (s, 2H, $H_a + H_b$), 5.35 (m, 1H, $(CH_3)_2CH$), 1.46 (s, 3H, CH_3), 1.44 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 160.2, 157.7 (d, 1C, $J_{C-F} = 287$ Hz, C–F), 142.7, 138.7, 131.6, 125.6, 124.0, 71.5, 21.8, 21.8.

4-Nitrophenyl 2-fluoro-3,5-dinitrobenzoate (10)

To **8** (2.3 g; 10.0 mmol) in a dry round-bottomed flask was added thionyl chloride (40 mL) under Ar. The reaction mixture was refluxed for 2 h 45 min, followed by the removal of thionyl chloride under reduced pressure. The residue was further dried under high vacuum, resolubilized in dry THF (40 mL) and cooled to 0 °C. 4-Nitrophenol (1.4 g; 10.0 mmol) with dry pyridine (810 μL) in dry THF (10 mL) was added dropwise

under Ar over 5 min. After 15 min, the cold bath was removed and the reaction mixture was filtered over a layer of silica gel, which was subsequently washed with THF (3 × 20 mL). The organic fractions was pooled and concentrated to dryness under vacuum, and crystallized from toluene to yield slightly yellowish crystals (3.2 g; 92%), mp 146–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 9.25 (dd, 1H, $J_{H_b–F}$ = 5.3 Hz, $J_{H_a–H_b}$ = 2.8 Hz, H_b), 9.19 (dd, 1H, $J_{H_a–F}$ = 5.8 Hz, $J_{H_a–H_b}$ = 3.0 Hz, H_a), 8.9 (d, 2H, $J_{H_a'–H_b'}$ = 9.2 Hz, H_a'), 7.51 (d, 2H, $J_{H_a'–H_b'}$ = 9.0 Hz, H_b'). ^{13}C NMR (75 MHz, $CDCl_3$): 158.4, 158.3, 158.1 (d, 1C, $J_{C–F}$ = 289 Hz, C–F), 154.2, 146.2, 142.9, 132.0, 132.0, 126.2, 125.6, 125.6, 122.9, 122.9.

Synthesis of DISAL and DISAL-derived donors 1, 11, and 12

The hemiacetal (0.75 mmol), Li_2CO_3 (110 mg) and DISAL or the DISAL derivative (0.9 mmol) were suspended in dry CH_2Cl_2 (15 mL). A solution of DMAP (28 mg) in dry CH_2Cl_2 (2 mL) was added dropwise over 20 min at RT. This changed the color of the mixture from colorless to yellow to orange. After a total reaction time of 30 min the crude reaction mixture was transferred to a packed VLC column. Elution was performed using CH_2Cl_2–Et_2O (95 : 5).

2,4-Dinitro-6-(methoxycarbonyl)phenyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranoside (1α/β)

The observed NMR data were identical with literature values.[5a,b,f]

2,4-Dinitro-6-(isopropoxycarbonyl)phenyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranoside (11)

Obtained as a slightly yellow foam (569 mg; 97%, α/β 3 : 1) after evaporation of solvents from column chromatography. ^{1}H NMR: (300 MHz, $CDCl_3$): 8.78 (d, 1H, H_a + H_b), 8.74 (d, 1H, H_a + H_b), 8.64 (d, 1H, H_a + H_b), 8.54 (d, 1H, H_a + H_b), 7.47–7.20 (m, 40H, H_{arom}), 5.63 (d, 1H, $J_{H1–H2}$ = 3.3 Hz, H-1α), 5.31 (m, 2H, $(CH_3)_2CH$, both anomers), 5.20 (d, 1H, $J_{H1–H2}$ = 7.2 Hz, H-1β), 5.04 (m, 3H, Ph–C*H*), 4.80 (d, 1H, Ph–C*H*), 4.70 (d, 1H, Ph–C*H*), 4.60 (d, 1H, Ph–C*H*), 4.59 (m, 2H, Ph–C*H*,), 4.50 (d, 1H, Ph–C*H*), 4.46 (d, 1H, Ph–C*H*), 4.39 (m, 2H, Ph–C*H*), 4.14 (1H, $J_{H2–H3}$ = 10.0 Hz, H-3α), 4.02 (ddd, 1H, $J_{H4–H5}$ = 10 Hz, $J_{H5–H6}$ = 2.2 Hz, H-5α), 3.79–3.71 (m, 5H, H-4α, H-3α, H-2β, H-6β), 3.68–3.57 (m, 3H, H-2α, H-6α, H-3β), 3.60 (dd, 1H, H-4β), 3.34 (ddd, 1H, H-5β), 1.43 (m, 12H, $(CH_3)_2CH$). ^{13}C NMR: (75 MHz, $CDCl_3$): for both anomers 162.7, 162.3, 153.8, 151.3, 144.7–122.4, 104.6, 103.4, 84.1, 82.1, 81.4, 80.9, 76.5, 75.8, 75.6, 75.1, 75.1, 75.0, 74.1, 73.9, 73.5, 71.2, 71.0, 68.7, 67.9, 53.4, 29.7, 21.8, 21.7, 21.6. ES-MS: *m/z* calcd. for $C_{44}H_{48}N_2O_{12}Na$ $[M + NH_4]^+$ 810.32; found 810.34.

2,4-Dinitro-6-(4-nitrophenoxycarbonyl)phenyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranoside (12)

Obtained as a white foam (200 mg; quant.; α/β 2 : 1) after evaporation of solvents from column chromatography. ^{1}H NMR: (300 MHz, $CDCl_3$): 8.98 (d, 1H, $J_{H_a–H_b}$ = 3.0 Hz, H_b), 8.87 (d, 1H, $J_{H_a–H_b}$ = 2.6 Hz, H_a), 8.18 (d, 2H, $J_{H_a'–H_b'}$ = 9.6 Hz, H_a'), 8.09 (d, 2H, $J_{H_a'–H_b'}$ = 9.2 Hz, H_b'), 7.35–6.79 (m, 40H, H_{arom}), 6.52 (d, 1H, $J_{H1–H2}$ = 3.6 Hz, H-1α), 5.73 (d, 1H, $J_{H1–H2}$ = 7.7 Hz, H-1β), 4.85–4.44 (m, 16H, PhC*H*), 3.82–3.48 (m, 12H, H-2, H-3, H-4, H-5, $H\text{-}6_{ab}$, from both anomers). ^{13}C NMR: (75 MHz, $CDCl_3$): 161.8–159.0, 150.7, 150.1, 144.3–137.2, 131.1–124.8, 116.1, 115.7, 95.2, 93.6, 84.7, 81.3, 80.7, 78.6, 76.4, 75.7, 75.5, 75.3, 75.0, 74.8, 73.8, 73.6, 73.6, 73.5, 68.0, 67.8. ESI-MS: *m/z* calcd. for $C_{47}H_{45}N_3O_{14}Na$ $[M + NH_4]^+$ 889.29; found 889.30.

Optimization of glycosylation conditions (Table 1 + 2)

Conventional heating: The glycosyl donor (0.027 to 0.05 mmol) was dissolved in dry methanol or dry NMP (1 mL) in a microcentrifuge tube (Plasticbrand), crushed 3 Å molecular sieves were added, and for the glycosylation of cyclohexanol (5 equiv.), NMP was added. The mixture was stirred at 60 °C, during which time the progress of the reaction was monitored by HPLC and TLC (30% EtOAc in hexane). Evaporation of the solvent was followed by purification by either VLC chromatography (hexane–EtOAc 18 : 1 → 1 : 1) or preparative HPLC to give the products indicated in Table 2.

Microwave heating: The glycosyl donor (typically 0.05 mmol) were dissolved in either dry methanol or NMP (500 μL), and in the case of NMP, cyclohexanol (0.25 mmol) was added followed by mixing. The reaction mixture was subjected to microwave radiation for 5 min at 100 or 150 °C (see Tables 1 and 2), a sample (12 μL) was diluted in acetonitrile (0.7 mL) and analyzed by analytical HPLC. From a series of test reactions, the product was purified by preparative HPLC and characterized by NMR and ES-MS.

Methyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranoside (2α/β)

The observed NMR data were identical with literature values.[15]

Cyclohexyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranoside (3α/β)

The observed NMR data were identical with literature values.[16]

General procedure for the microwave-assisted glycosylation reactions (Table 1–3)

The glycosyl donor (0.075 mmol, 1.5 equiv), the glycosyl acceptor (0.05 mmol, 1 equiv), activators and additives (if required – see Tables 2 and 3), crushed 3 Å molecular sieves, and a magnetic stirrer bar were placed in a 5 mL microwave reaction vial and fitted with a septum, which was then pierced with a needle. The closed vial was then evacuated under high vacuum; Ar was let in followed by re-evacuation. This cycle was repeated twice and the mixture left to dry for 1–2 h. Ar was let in, the needle was removed, dry solvent (500 μL) was added under argon and the reaction mixture was subjected to microwave radiation for 5 min at 100 °C (unless stated othervise). The reaction mixture was transferred to a 15 mL Falcon plastic tube, centrifuged for 3 min at 4000 rpm and the supernatant was transferred to a new 15 mL Falcon plastic tube and concentrated to dryness under a stream of air. The residue was loaded onto a preparative HPLC column with 2 mL of CH_3CN and purified, followed by evaporation of appropriate fractions.

1,2;3,4-Di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosyl)-α-D-galactopyranoside (5α/β)

The observed NMR data were identical with literature values.[17]

Methyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosyl)-α-D-glucopyranoside (7α/β)

The observed NMR data were identical with literature values.[5b]

O-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopranosyl)trichloroacetimidate (13)

A solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (1 g; 1.8 mmol) and trichloroacetonitrile (16 mL) in dry CH_2Cl_2 (65 mL) was stirred vigorously with anhydrous K_2CO_3 (6.5 g) over night at room temperature under Ar atmosphere. The mixture was diluted with dry Et_2O (30 mL) and filtered through a layer of sand and silica gel. The silica gel layer was washed several times with Et_2O and the combined filtrates were evaporated to give the trichloroacetimidate in a chromatographically pure form as a colorless syrup (quantitative) as the β anomer. The observed NMR data were identical with literature values.[18]

1,2;5,6-Di-*O*-isopropylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosyl)-α-D-glucofuranoside (15α/β)

The observed NMR data were identical with literature values.[17]

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References and notes

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