Carbohydrate Research 344 (2009) 1428–1433

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Comparative solution and solid-phase glycosylations toward a disaccharide library

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ARTICLE INFO

Article history:
Received 25 February 2009
Received in revised form 1 April 2009
Accepted 1 April 2009
Available online 10 April 2009

Dedicated to Professor Johannis P. Kamerling on the occasion of his 65th birthday

Keywords:
Oligosaccharide synthesis
Disaccharide library
Solid-phase chemistry

ABSTRACT

A comparative study on solution-phase and solid-phase oligosaccharide synthesis was performed. A 16-member library containing all regioisomers of Glc–Glc, Glc–Gal, Gal–Glc, and Gal–Gal disaccharides was synthesized both in solution and on solid phase. The various reaction conditions for different approaches and corresponding yields are analyzed and discussed.

1. Introduction

The advantages and disadvantages of solid-phase chemistry compared to solution-phase chemistry are generally well discussed and described.[1] Both strategies are commonly used to synthesize biomolecules. The chemical preparation of oligo- and polypeptides as well as oligo- and polynucleotides nowadays is almost exclusively performed on solid phase, thanks to the commercial availability of building blocks and solid supports. The different approaches to prepare these oligomers are generalized and have become routine procedures.[2] The third group of biomolecules that exists in oligo- or polymeric form is the carbohydrates on which organic chemists have worked for over a hundred years.[3] Great advances have been made for the preparation of carbohydrate oligomers in solution phase, but it still remains a challenging and time-consuming procedure. Due to the chemical nature of carbohydrates with multiple possible linkage points giving rise to different regioisomers, the synthesis of oligomers is complicated far beyond that encountered in the preparation of oligopeptides or oligonucleotides. The lack of commercially available protected and/or activated building blocks for oligosaccharide synthesis makes the situation even more complicated. Besides, until now no universal strategy has been found that gives general control over the stereochemical outcome of the newly formed stereocenter. We do believe that we are still a long way from finding a general approach that would solve the problems of oligosaccharide chemistry, and to this end numerous fundamental studies need to be performed until a generalized approach is reached. This process started more than 10 years ago with the first preparation of an oligosaccharide library in solution phase.[4–6] With the help of a solid support, the first libraries were published soon after,[7–9] and the effort to create different libraries is still ongoing.[10–13] In this paper a comparative study of a disaccharide library preparation will be discussed. A glucose–galactose disaccharide library has been prepared containing all regioisomers, but only 1,2-*trans* stereoisomers. The synthesis was performed both in solution phase and on solid support. For the solid-phase study, the donors were coupled to the resin to form an ester linkage via its 2-hydroxyl position, thus excluding formation of 1,2-cis stereoisomers. Donors for solution phase have a similar participating group in position 2 for the same reason.

2. Results and discussion

The two most common monosaccharide residues in nature are D-glucose and D-galactose, and consequently, these units have been used by organic chemists most frequently. In this study a set of disaccharides built from glucose and/or galactose have been prepared. To avoid stereochemical problems, only β-D-glycosides were prepared. For solution-phase chemistry the known glucose and

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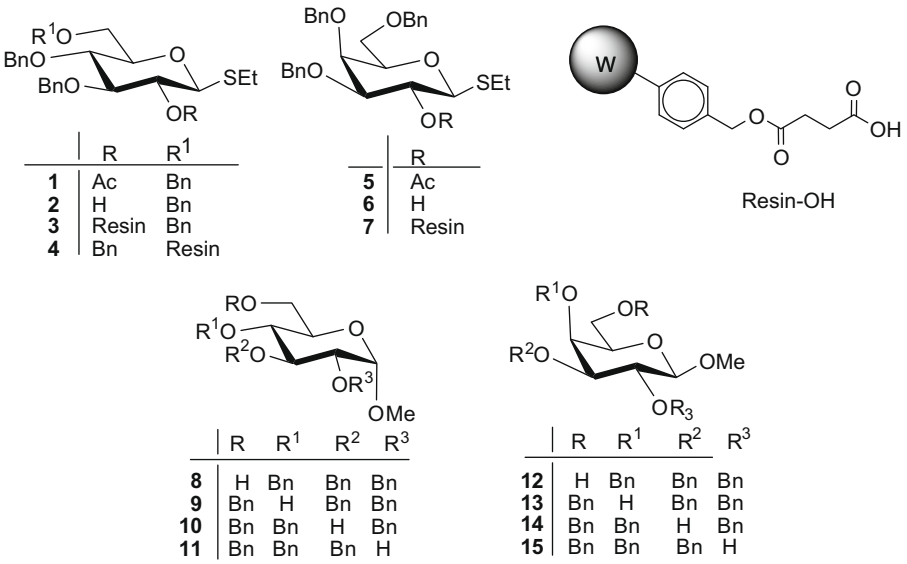
doi:10.1016/j.carres.2009.04.001



Scheme 1. Donors and acceptors utilized for syntheses.

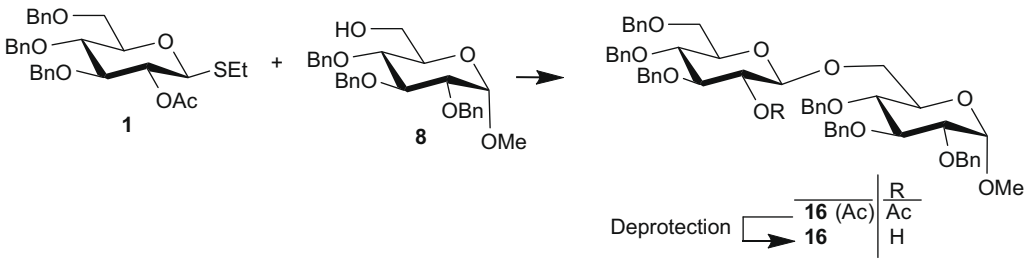
galactose donors (**1**[14] and **5**,[15] respectively) were selected, and their precursors (**2**[16] and **6**[15]) were used to attach the monosaccharides to the solid support obtaining resin-bound donors (**3** and **7**). Wang resin was modified with succinic anhydride as a linker, and an ester linkage was created afterwards between the carbohydrate and the solid support. A resin-bound donor **4** was also prepared from its precursor (**4**-OH)[17] in order to have a non-participating group at position 2. A complete set of glucose (**8**,[18] **9**,[19] **10**[20], and **11**[21]) and galactose (**12**,[22] **13**,[23] **14**[24], and **15**[25]) acceptors with a single free hydroxy function were used for both solution and solid-phase synthesis (Scheme 1).

Both in solution and on solid phase, the coupling reactions were performed in a 1:1 mixture of DCM and acetonitrile as solvent. This mixture is sufficient both to dissolve the catalyst and to swell the resin. Activation of the donor was achieved with the well-known combination of NIS and AgOTf.[26]

In solution phase the coupling reactions were performed at −15 °C, and the reaction time was generally around 30 min (Scheme 2). Since an excess of donor was used for the reaction, donor decomposition was always present in the mixture as can be seen in the HPLC chromatogram (Fig. 1, compound **30**). The peak at 4.2 min is due to donor decomposition, whereas the desired product is eluted at 7.7 min. Aqueous workup of the crude reaction mixtures was followed by column chromatography and removal of the 2′-acetate groups. The final products were purified again by column chromatography to afford the pure disaccharides.

For the solid-phase reactions commercially available Wang resin was modified by esterification with succinic anhydride in DCM, thus obtaining the linker-bound resin.[27] To couple the donor to the resin, the second carboxylic acid function of the succinic acid linker was activated with DCC to enable ester formation with the 2-OH function of the monosaccharide units. The efficiency of the loading was determined by gravimetry after cleaving the donor from the resin. Both resin-bound donors (**3** and **7**) showed relatively high (0.65 mmol/g) loadings. The coupling reactions were performed at room temperature with a reaction time of around 20 hours. After extensive washing of the resin, the crude resin-bound products were cleaved and purified by column chromatography in order to remove unreacted or decomposed donor (Scheme 3). Only a few side products were observed in the HPLC profile of the crude cleaved mixture of compound **18** (Fig. 2). Although by UV detection next to the product (retention time: 8.81 min) a strong signal of a side product (retention time: 3.16 min) was visible, evaporative light-scattering (ELS) detection showed a very clean composition of the mixture regarding nonvolatile (carbohydrate) type substances. Using resin-bound donors (**3** and **7**) there was no sign in the NMR spectra for the formation of α anomers as expected, due to neighboring group participation of the linker moiety. The use of resin-bound donor **4** resulted in the formation of a 2:1 mixture of anomers in favour of the β product (see 1D and 2D NMR in Supplementary data). Steric hindrance or another effect caused by the resin in position 6 seems to outweigh the expected formation of the α anomer as a main product, which is the case in having a non-participating group in position 2 in the solution-phase reactions. This donor was not used for further experiments.

Sixteen different disaccharides were prepared separately by both methods, and all compounds were characterized by 1D-, and 2D NMR spectroscopy and MALDI-TOFMS (Chart 1; for ^{1}H and ^{13}C data see Tables 1 and 2). The yields of the reactions in solution and on solid phase were comparable, but were slightly favoured by solid-phase chemistry (see Table 3 for comparison of



Scheme 2. Solution-phase glycosylation.

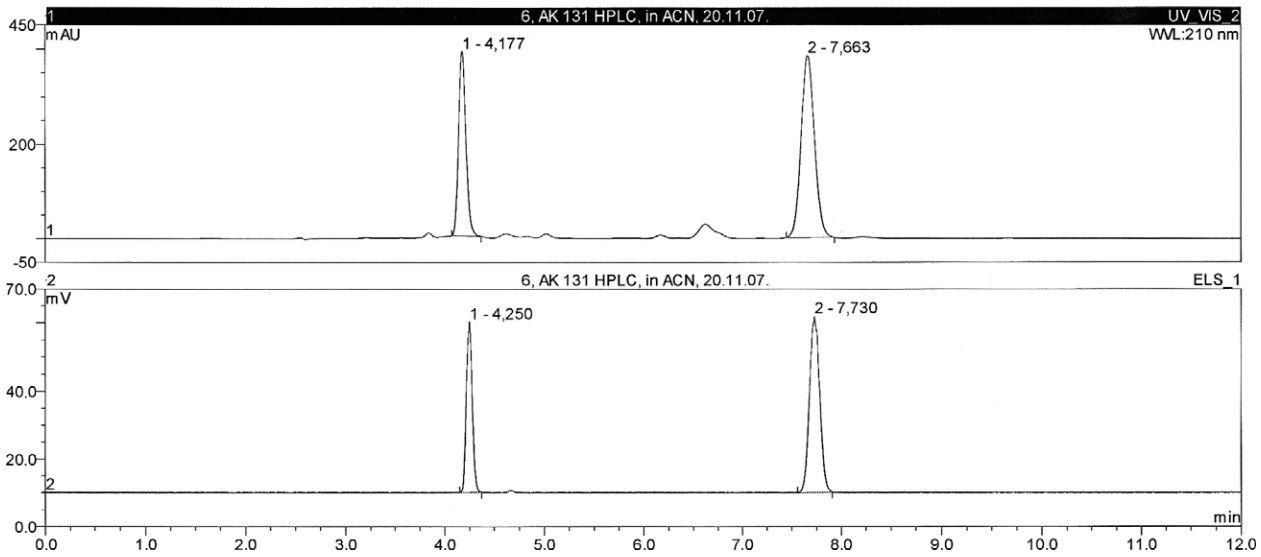
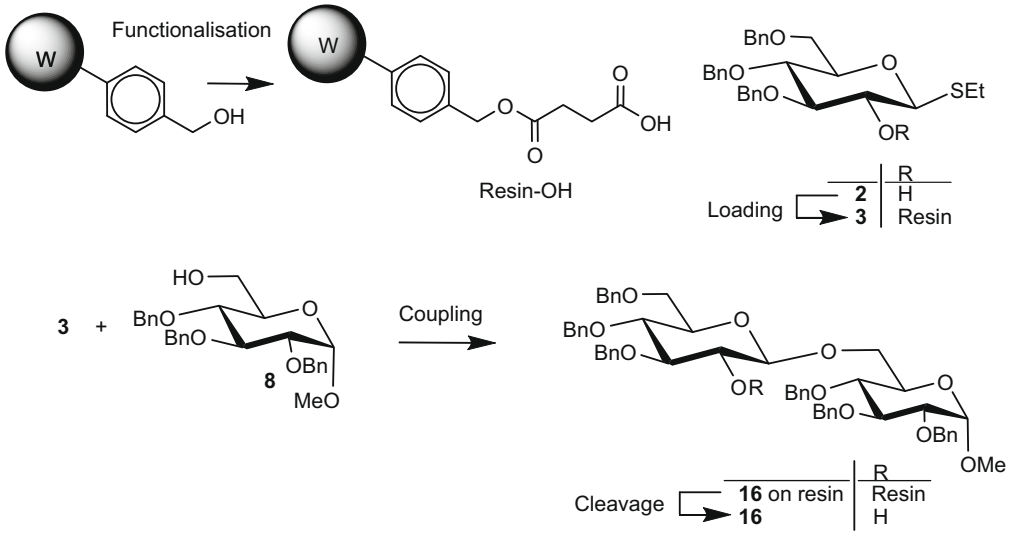


Figure 1. HPLC profile of a solution phase glycosylation (exemplary compound **30**).



Scheme 3. Solid-phase glycosylation.

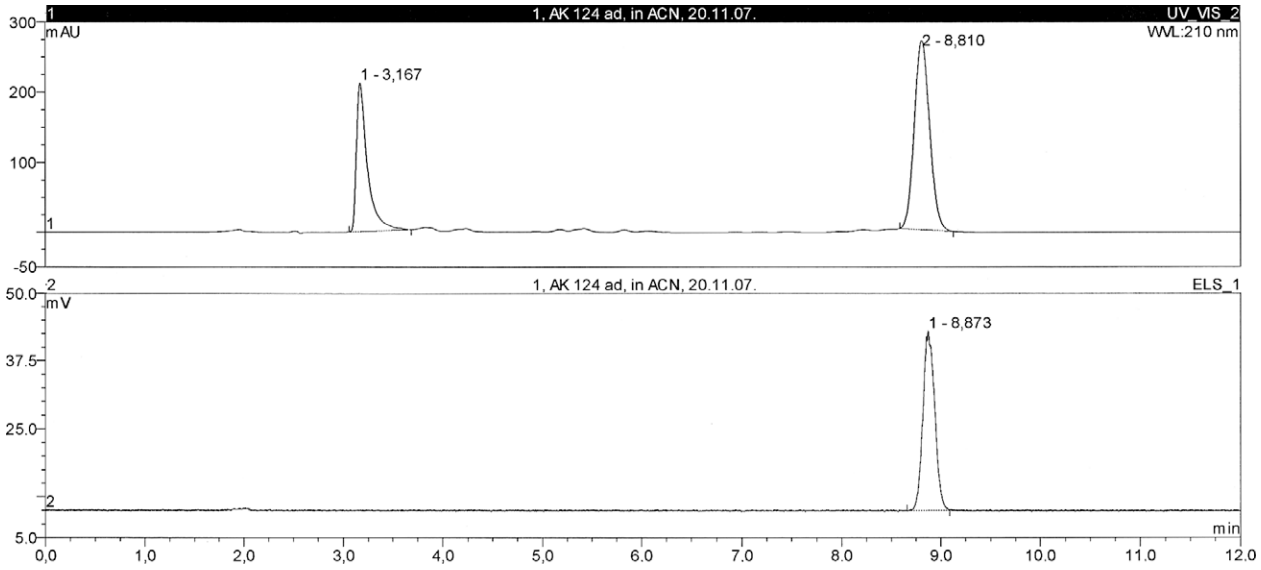


Figure 2. HPLC profile of a solid-phase glycosylation (exemplary compound **18**).

the two methods). The average yield in solution phase was 72% for two steps (coupling and deprotection) while on solid phase an average 78% was obtained. This could well be due to the additional chromatographic steps required for the solution-phase sequence. The significantly longer reaction time and higher temperature necessary for the solid-phase reactions did not lead to increased degradation of the products. Reducing the amount of activators (NIS/AgOTf) resulted in the appearance of intermediate orthoesters in both approaches. During the synthesis some unexpected technical problems turned up in the solid-phase process (e.g., solubility problems and decreased reactivities). The amount of NaOMe seemed to be crucial for the cleavage step and resulted in the formation of disaccharides having methyl succinate in position 2 (compounds **18** and **24**; see NMR, MS, and HPLC in Supplementary data). Treating these compounds with NaOMe in MeOH afforded the desired disaccharides.

3. Summary

A 16-member library containing all regioisomers of Glc–Glc, Glc–Gal, Gal–Glc, and Gal–Gal disaccharides has been synthesised in solution phase and on solid support. The isolated yields were compared, and no significant differences were found between the two processes, although some technical difficulties turned up during the solid-phase reactions. To avoid the formation of anomeric mixtures, participating groups were installed at position 2 of the donors giving rise to only β glycosides. In contrast, by having a non-participating group in the above-mentioned position, mix-

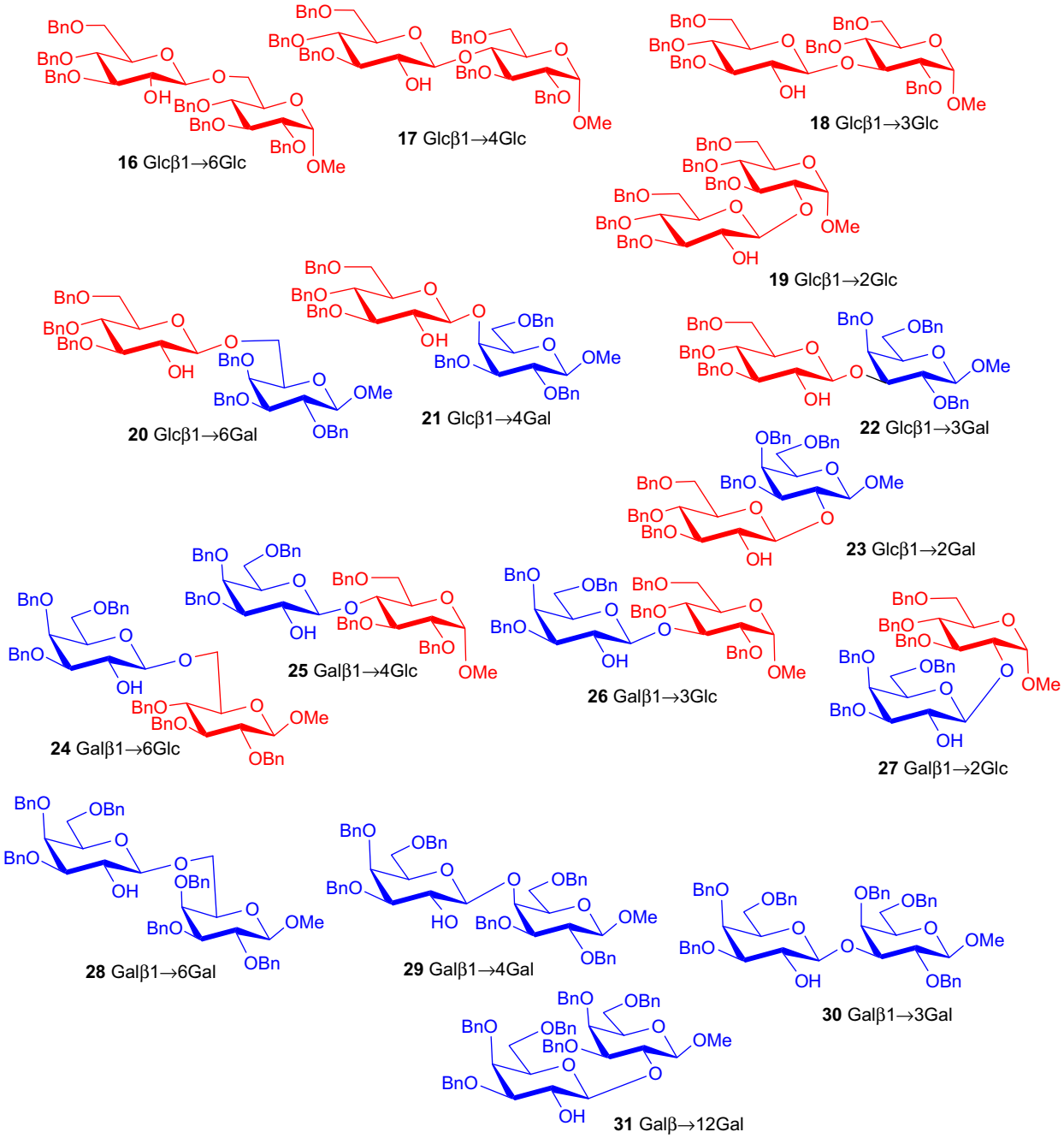


Chart 1. The disaccharide library.

Table 1
^{1}H NMR data: chemical shift (δ) and coupling constants (Hz) for **16**–**31**

	1	2	3	4	5	6	1′	2′	3′	4′	5′	6′	OMe	2′-OH
16	4.83, ~3 Hz	3.46	3.75	3.46	3.62	3.97, 3.67	4.28, 7.88 Hz	3.29	3.46	3.40	3.68	3.67, 3.61	3.28	5.68, 5.68 Hz
17	4.79, 3.47 Hz	3.39	3.69	3.83	3.70	3.94, 3.74	4.36, 7.88 Hz	3.27	3.40	3.40	3.27	3.61, 3.48	3.29	5.58, 3.46 Hz
18	4.74, ~3 Hz	3.53	4.13	3.44	3.58	3.61	4.80, 7.63 Hz	3.35	3.42	3.45	3.35	3.63, 3.51	3.25	5.55, 4.06 Hz
19	4.84, 3.56 Hz	3.59	3.78	3.43	3.50	3.66, 3.59	4.57, ~8 Hz	3.34	3.48	3.43	3.43	3.51	3.23	5.72, 6.11 Hz
20	4.29, 7.57 Hz	3.48	3.60	4.09	3.71	3.88, 3.67	4.36, 7.56 Hz	3.26	3.46	3.41	3.47	3.62	3.41	5.41 br s
21	4.31, 7.12 Hz	3.69	3.66	4.19	3.70	3.71, 3.53	4.58, 7.63 Hz	3.27	3.42	3.41	3.39	3.61	3.43	5.03, 4.07 Hz
22	4.27, 7.63 Hz	3.44	3.77	3.90	3.64	3.67, 3.38	4.56, ~8 Hz	3.73	3.54	3.98	3.74	3.65, 3.56	3.40	5.34, 5.09 Hz
23	4.31, 7.25 Hz	3.81	3.76	3.98	3.72	3.54	4.70, 6.97 Hz	3.30	3.42	3.42	3.32	3.60, 3.54	3.34	5.34, 4.41 Hz
24	4.79, 3.46 Hz	3.44	3.73	3.61	3.64	3.55, 3.48	4.22, 7.63 Hz	3.54	3.44	3.91	3.60	3.91, 3,64	3.28	5.31, 5.34 Hz
25	4.76, 3.47 Hz	3.37	3.63	3.76	3.44	3.53, 3.33	4.29, 7.57 Hz	3.55	3.36	3.91	3.65	3.92, 3.72	3.28	5.33, 5.04 Hz
26	4.69, 3.46 Hz	3.47	4.09	3.37	3.55	3.62, 3.57	4.74, 7.57 Hz	3.68	3.48	3.97	3.59	3.43, 3.59	3.28	5.28, 4.10 Hz
27	4.75, 3.78 Hz	3.56	3.76	3.42	3.59	3.60, 3.57	4.45, 7.57 Hz	3.59	3.45	3.93	3.68	3.53	3.24	5.46, 5.36 Hz
28	4.36, 7.57 Hz	3.74	3.60	4.08	3.70	n.d.	4.38, 7.25 Hz	3.56	3.47	3.94	3.70	n.d.	3.41	5.22, 5.05 Hz
29	4.25, 7.89 Hz	3.43	3.64	4.17	3.66	3.67, 3.51	4.30, 7.63 Hz	3.59	3.47	3.89	3.69	3.67, 3.51	3.42	5.31, 5.34 Hz
30	4.30, 7.63 Hz	3.47	3.82	3.98	3.70	3.69, 3.50	4.60, 7.63 Hz	3.41	3.53	3.50	3.52	3.49, 3.45	3.40	5.56, 5.60 Hz
31	4.27, 6.68 Hz	3.76	3.73	3.95	3.68	3.52	4.65, 7.63 Hz	3.53	3.41	3.89	3.55	3.52	3.30	5.10, 4.70 Hz

Table 2
^{13}C NMR data: chemical shift (δ) for **16**–**31**

	1	2	3	4	5	6	1′	2′	3′	4′	5′	6′	OMe
16	97.71	80.36	82.06	n.d.	70.07	68.98	103.87	74.58	n.d.	78.29	70.10	69.33	55.30
17	97.54	79.64	80.58	77.41	70.41	69.24	103.27	75.29	78.40	85.51	75.29	69.94	55.49
18	96.63	79.76	77.71	76.24	69.79	68.63	102.59	74.63	77.27	84.70	74.63	69.17	54.69
19	99.92	81.44	81.61	78.30	74.80	69.87	105.26	74.75	85.58	78.32	78.32	69.86	55.58
20	104.59	75.08	82.11	74.31	73.26	68.22	103.68	74.80	85.64	78.21	79.43	69.78	57.12
21	103.74	78.84	80.86	73.80	72.55	69.78	102.52	74.53	84.37	77.14	74.09	68.84	56.08
22	103.52	78.56	82.10	76.23	72.49	68.88	104.92	71.13	81.91	74.10	72.64	68.88	56.19
23	102.65	76.64	83.62	74.47	73.32	69.33	103.47	75.01	85.59	78.34	75.01	69.70	56.09
24	97.03	79.79	81.52	77.40	73.09	68.70	103.88	70.69	82.24	74.37	70.16	67.97	55.08
25	96.91	82.28	73.03	76.18	79.56	68.37	102.94	70.70	79.40	74.06	69.77	68.40	54.64
26	97.14	82.62	77.95	76.31	70.09	69.43	103.19	71.47	80.20	74.67	73.28	69.01	55.03
27	99.77	81.18	81.67	78.56	71.21	69.23	105.66	71.21	82.66	75.03	73.62	70.29	55.37
28	104.38	82.87	82.04	74.17	73.41	69.68	104.38	71.24	79.53	74.85	73.41	69.68	57.10
29	104.87	82.78	81.81	73.97	73.40	69.70	103.54	71.59	82.78	75.12	73.70	69.70	56.94
30	103.51	78.38	82.27	76.72	72.61	69.12	104.51	74.54	84.68	77.75	74.01	68.61	56.25
31	102.69	75.76	83.12	74.56	73.38	69.49	103.98	73.58	82.82	75.05	71.90	69.49	56.16

tures of anomers were obtained. All in all, solid-phase preparations afforded cleaner reaction mixtures with less chromatographic purification necessary, but still more work must be done to establish solid-phase techniques as a daily routine in the field of carbohydrate chemistry.

4. Experimental

4.1. General

Commercially available starting materials were used without further purification. Wang resin was purchased from Novabiochem, Darmstadt, Germany. Solvents were dried according to standard methods. NMR spectra were recorded on a Bruker AMX-400 (100.62 MHz for ^{13}C) or DRX-500 (125.83 MHz for ^{13}C) spectrometer in DMSO-d_6 as solvent. All chemical shifts are quoted in ppm downfield from the characteristic signals of the solvents used (^{1}H: 2.50 ppm, ^{13}C: 39.43 ppm). Kieselgel 60 (E. Merck, Darmstadt, Germany) was used for column chromatography. MALDI-TOFMS measurements were carried out on a Bruker Biflex III mass spectrometer. 2,5-Dihydroxybenzoic acid was used as the matrix, and 100–200 laser shots were applied for each spectrum.

4.2. General protocols for solution-phase reactions

4.2.1. Coupling

Molecular sieves (4 Å, 100 mg) were added to a solution of donor (0.15 mmol) and acceptor (0.1 mmol) in anhyd DCM (3 mL), and the mixture was stirred for 1 h. Then NIS (0.3 mmol) and AgOTf (0.01 mmol) in CH_3CN (3 mL) were added to the mixture at −40 °C, and the mixture was stirred at −15 °C. When TLC showed the disappearance of the acceptor, pyridine (100 μL) was added, and the mixture was diluted with DCM (20 mL), washed with aq $Na_2S_2O_3$ (1 × 10 mL) and aq $NaHCO_3$ (1 × 10 mL), dried,

Table 3
Comparative table for solution and solid phase methods

	Glycosylation conditions						Deprotection conditions	Average yield (over two steps, calculated for the acceptor) (%)	Best yield/ worst yield (%)
	Solvent	Donor/ acceptor ratio	Promoter	Temperature	Work-up	Reaction time			
Solution phase reactions	DCM/MeCN, 1:1	1.5:1	NIS (3 equiv)/ AgOTf (cat)	−40 to −15 °C	Aqueous extractions	30 min–1 h	NaOMe in DCM/ MeOH, 5:1	72	88 (**16**); 58 (**21**)
Solid phase reactions	DCM/MeCN, 1:1	0.65:1	NIS (2 equiv)/ AgOTf (cat)	−50 to +20 °C	Wash and drain	10 h	NaOMe in DCM/ MeOH, 5:2	78	90 (**16**); 55 (**25**)

filtered, and concentrated. Column chromatography (3:2 hexane–EtOAc) of the residue gave the fully protected disaccharide.

4.2.2. Deprotection

NaOMe was added (pH ~ 9) to a solution of fully protected disaccharide (0.08 mmol) in DCM (5 mL) and MeOH (2 mL). When TLC showed complete conversion, Amberlite IR-120 (H^+) was added to neutralize the mixture, then the resin was filtered off and the filtrate was concentrated. Column chromatography (3:2 hexane–EtOAc) of the residue gave the disaccharide.

4.3. General protocols for solid-phase reactions

4.3.1. Functionalization of the Wang resin

A mixture of succinic anhydride (10 equiv) and DMAP (100 mg) in DCM (5 mL) and pyridine (2 mL) was added to Wang resin (1 g, preswollen in DCM). The mixture was shaken for 10 h, then the resin was drained and washed sequentially with DCM (5 × 5 mL), DMF (5 × 5 mL), and DCM (5 × 5 mL).

4.3.2. Loading

Monosaccharide derivative (0.2 mmol), DCC (100 mg) and DMAP (50 mg) were added in DCM (5 mL) to the functionalized resin (1 g), and the mixture was shaken for 10 h. Then the resin was drained and washed sequentially with DCM (2 × 5 mL), DMF (3 × 5 mL), DCM (5 × 5 mL), and MeOH (2 × 5 mL). The resin was dried overnight under high vacuum.

4.3.3. Determination of loading

To the sample of resin (~50 mg, preswollen in DCM), NaOMe (10 mg) in DCM (2 mL) and MeOH (0.5 mL) was added, and the mixture was shaken for 1 h. The resin was drained and washed with DCM (5 × 3 mL). The combined filtrates were washed with water (2 × 3 mL), dried, filtered, and concentrated. Column chromatography of the residue gave the monosaccharide derivative.

The loading was calculated using the following equation, where x is the loading in mol/g, z is the mass of the sugar cleaved from the resin in mg, y is the mass of the loaded resin in mg, and M is the molecular weight of the sugar residue cleaved from the resin in g/mol.

$$x = \frac{z}{y * M}$$

Loadings obtained: 4 Glc 6-OH, 0.54 mmol/g, 3 Glc 2-OH, 0.65 mmol/g, 7 Gal 2-OH, 0.65 mmol/g.

4.3.4. Coupling

A mixture of the sugar-loaded resin (100 mg, 0.065 mmol), monosaccharide acceptor (0.1 mmol), and 4 Å molecular sieves (50 mg) was stirred in DCM (3 mL) for 2 h. A mixture of NIS (0.13 mmol) and AgOTf (0.01 mmol) in CH_3CN (3 mL) was added at −50 °C. The mixture was allowed to warm to rt and stir for 10 h. The reaction was stopped by adding pyridine (100 μL), then the resin was drained and washed sequentially with DCM (5 × 5 mL), DMF (5 × 5 mL), and DCM (5 × 5 mL).

4.3.5. Cleavage

NaOMe (50 mg) in DCM (5 mL) and MeOH (1 mL) was added to the resin and shaken for 30 min. The resin was drained and washed with DCM (5 × 5 mL). The combined organic phases were washed with water (2 × 10 mL), dried, filtered, and concentrated. Column chromatography (3:2 hexane–EtOAc) of the residue gave the disaccharide derivative.

Acknowledgments

Support of this work by the Deutsche Forschungsgemeinschaft (SFB 470, A5) and Glycom A/S is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.04.001.

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