O-Glycoside Synthesis with Glycosyl Iodides under Neutral Conditions in 1 M $LiClO_4$ in CH_2Cl_2

Uschi Schmid and Herbert Waldmann*

Institut für Organische Chemie der Universität Karlsruhe,
Richard-Willstätter-Allee 2, D-76128 Karlsruhe, Germany
Fax: (internat.) + 49(0)721/608-4825
E-mail: waldmann@ochhades.chemie.uni-karlsruhe.de

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Glycosyl phosphates, imidates, trifluoroacetates, chlorides, and bromides are converted into the respective glycosyl iodides by treatment with LiI or NaI in 1 M solutions of $LiClO_4$ in CH_2Cl_2. Under these neutral conditions the reactive glycosyl iodides are activated, and react with different glycosyl acceptors to give *O*-glycosides in moderate yields, with the α-anomers predominating. The glycosylation reactions most probably proceed by the initial formation of β-configured glycosyl iodides from the α-configured precursors, and subsequent attack of the glycosyl acceptor on the equatorial iodide from the axial direction.

Glycoconjugates play important roles in numerous biological processes, e.g. they mediate cell adhesion processes, are involved in the regulation of intercellular communication, and may form the characteristic functional parts of cell surface antigens and determinants of the human blood group system.[1] Due to the importance of these roles the synthesis of tailor-made glycosides,[2] which might serve to study and influence biological phenomena, is of widespread and increasing interest, in particular from the point of view of medicinal chemistry.[3]

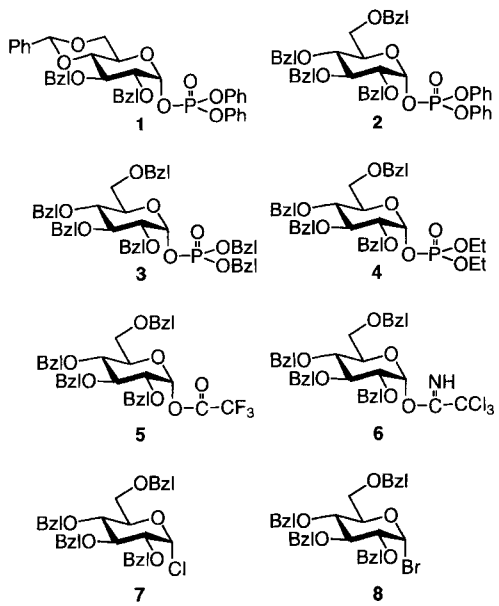
Numerous polyfunctional glycoconjugates contain many reactive functional groups as well as acid- and base-labile structures. Therefore the development of methods by which glycosidic bonds can be formed under the mildest, preferably neutral, conditions, and without the use of additional promoters, such as alkylating and oxidizing agents or heavy-metal salts, is highly desirable and of particular interest.[2] Addressing this problem we have recently reported[4][5] that these criteria are met by using concd. solutions of $LiClO_4$ in organic solvents as the reaction media.[6] For example, in these solvent systems glycosyl chlorides, bromides, fluorides, trichloroacetimidates and phosphates are activated under neutral conditions, and participate as glycosyl donors in reactions with different glycosyl acceptors.

We now report the full experimental details for the generation, in situ and under these mild conditions, of glycosyl iodides from other glycosyl donors. These activated carbohydrate derivatives are then activated and react smoothly with different glycosyl acceptors to give *O*-glycosides.[5] The use of glycosyl iodides instead of glycosyl bromides and chlorides is highly desirable since these carbohydrate derivatives display a significantly higher reactivity. However, since glycosyl iodides are too unstable to be handled and stored with the required reliability,[7] and often have, with a few exceptions, to be prepared under drastic conditions,[8][9] they could not be used advantageously in glycoside synthesis.

Results and Discussion

The in situ generation of glycosyl iodides and their subsequent use in glycosylation reactions was studied by means of the differently activated glucose derivatives **1**–**8** (Scheme 1; for the preparation of **1**–**6** see Experimental Section) and the glycosyl acceptors **9**–**16** (Scheme 2).

Scheme 1



As a first step the most advantageous precursor to glycosyl iodides was sought. To this end, the glucose derivatives

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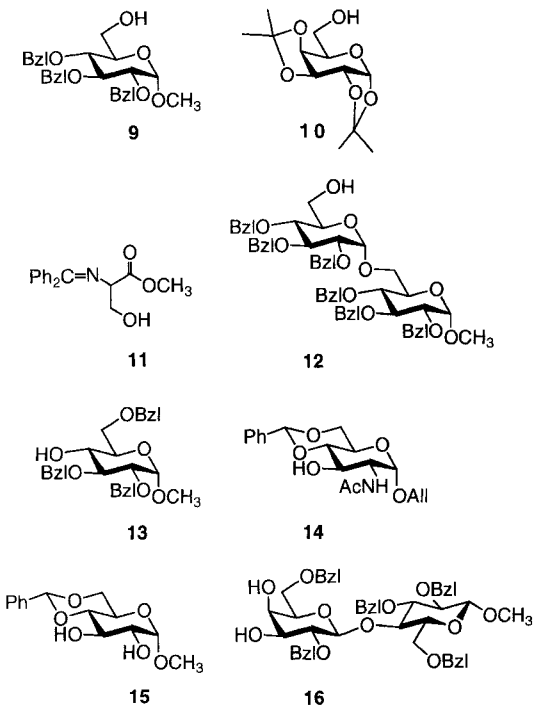
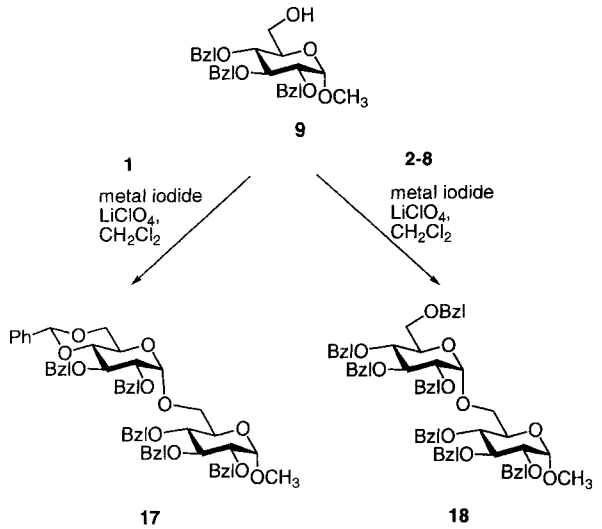
Scheme 2



1–**8** were treated with the glycosyl acceptor **9,** in 1 M solutions of $LiClO_4$ in various solvents (with LiI, NaI or I_2 as the iodide source), to give the glycosides **17** (obtained from **1**) and **18** (obtained from **2**–**8**) (Scheme 3, Table 1).

Scheme 3



The results given in Table 1 demonstrate that the glycosyl phosphates **1**–**4**, the trifluoroacetate **5** and the imidate **6** are all activated under these reaction conditions to give the glycosides **17** and **18,** in yields of 40–63%, with the α-anomers predominating (Table 1, entries 1–4, 6, 8, 10, and 12). In addition the glycosyl chloride **7,** and the respective bromide **8,** undergo the glycosylation reaction, albeit with lower yield.[10]

Table 1. Results of the glycosylations of the glycosyl acceptor **9** with the glycosyl donors **1**–**6** (Scheme 1) in 1 M $LiClO_4/CH_2Cl_2$ mixtures in the presence of an iodide source (Scheme 3)

Entry	Glycosyl donor	Disaccharide	Iodide source (equiv.)	Yield (%)	Anomeric ratio (α:β)
1	**1**	**17**	LiI (1.0)	44	15:1
2	**1**	**17**	NaI (1.0)	40	7:1
3	**1**	**17**	I_2 (2.0)	20	4:1
4	**2**	**18**	LiI (1.0)	63	3:1
5	**2**	**18**	–	57	2:1
6	**3**	**18**	LiI (1.7)	51	5:1
7	**3**	**18**	–	37	1.5:1
8	**4**	**18**	LiI (1.5)	45	5:1
9	**4**	**18**	–	8	1.5:1
10	**5**	**18**	LiI (1.0)	54	3:1
11	**5**	**18**	–	14	1:1
12	**6**	**18**	LiI (1.6)	63	2:1
13	**6**	**18**	–	79	1:1

The highest yield was recorded for the imidate **6,** whereas the phosphates **2**–**4** and the unstable trifluoroacetate displayed comparable results. However, for the phosphates **1**–**4** a significantly higher α-selectivity was observed. Therefore subsequent studies (vide infra), addressing the use of different glycosyl acceptors, were performed with these glycosyl donors.

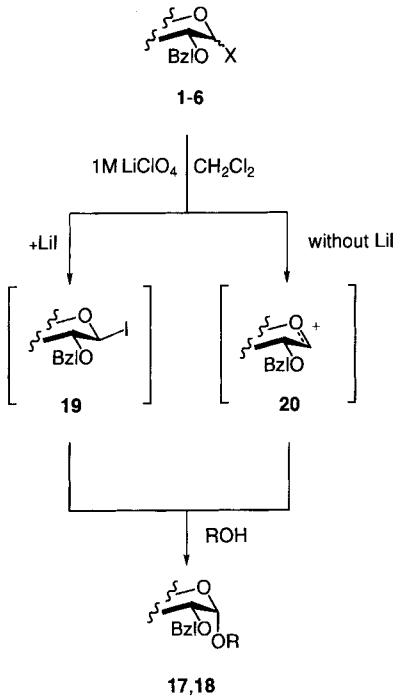
The fact that the outcome of the glycosylation reactions is markedly influenced by the presence of iodide is apparent from the observation that, in the absence of any iodide source, the yields (except for **6**, entry 13) and the stereoselectivity are lower (Table 1, entries 5, 7, 9, 11, and 13). The use of LiI or NaI results in comparable yields of the products, but in the presence of LiI the stereoselectivity of the glycoside formation is higher (entries 1 and 2). I_2 itself can also be employed as an iodide source, however, in this case, the yield is significantly lower (entry 3). The most efficient solvent is CH_2Cl_2; in ether the yields are substantially lower and CH_3CN often gives a lower stereoselectivity. Furthermore the best results were obtained in 1 M solutions of $LiClO_4$; if the perchlorate concentration is lowered, the stereoselectivity also decreases (data not shown). The nature of the alcohol present in the phosphate leaving group also influences the result of the glycoslylation reaction. Thus, the obviously more reactive diphenyl phosphate **2** gives the glycoside **18** with higher yield, although somewhat lower stereoselectivity, than the dibenzyl phosphate **3** and the diethyl phosphate **4** (Table 1, compare entries 4, 6, and 8).

In order to rationalize the experimental data detailed above we assume that the glycosylation reactions proceed by initial attack of the iodide on the α-configured glycosyl donors **1**–**6** to give rise to the reactive β-iodides **19** (Scheme 4), which then are activated in the $LiClO_4$ solution and attacked by the glycosyl acceptors from the axial direction to give predominantly the α-glycosides **17** and **18**. In the absence of LiI, oxonium ions (**20**) may be the decisive intermediates which can be attacked from both the axial and the equatorial direction, resulting in a lower ratio of anomers. These glycosyl cations can also be formed directly from the

glycosyl donors **1**–**6** in the presence of iodide. Therefore the yields and anomer ratios given in Table 1 for the different glycosyl donors vary.

This assumption is supported by the fact that, from the reaction mixture formed in the glycosylation of **9** with the glycosyl phosphate **1**, the associated unstable α-glycosyl iodide **21** could be isolated and characterized by ^{1}H- and ^{13}C-NMR spectroscopy (Scheme 5; see the Experimental Section). In addition, treatment of the glycosyl phosphate **2** with LiI in CD_2Cl_2 in the absence of a glycosyl acceptor, and a subsequent spectroscopic NMR investigation of the reaction mixture revealed that the β-glycosyl iodide **22** ($J_{1/2}$ = 8.3 Hz) was rapidly formed from **2**. **22** could, however, only be detected for a few minutes. Under these conditions it was converted into the α-iodide **23** which remained stable for ca. 24 h.

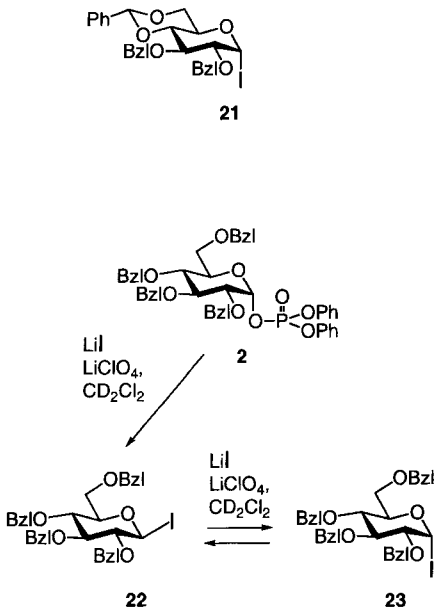
Scheme 4



In order to determine the scope of the $LiClO_4$ mediated glycosylation by intermediate formation of glycosyl iodides, the glycosyl phosphate **2** was treated with the glycosyl acceptors **10**–**16**, in 1 M solutions of $LiClO_4$ in CH_2Cl_2 in the presence of 1.5 equiv. of LiI, to give the glycosides **24**–**30** (Scheme 6). The results shown in Table 2 demonstrate that, in general, the glycosylations employing primary alcohols as glycosyl acceptors proceed with significantly higher yields than those with secondary hydroxy groups. Thus, the galactosyl disaccharide **24**, the serine glycoside **25** and the glucosyl trisaccharide **26** were formed in preparatively useful yields, and with the α-anomers predominating.

From the secondary alcohols **13**–**16** the glycosides are obtained in lower yields, but with appreciable α-selectivity. Obviously, under the reaction conditions iodide competes more efficiently with the less nucleophilic secondary hydroxy groups. Therefore the initially formed β-glycosyl

Scheme 5



Scheme 6

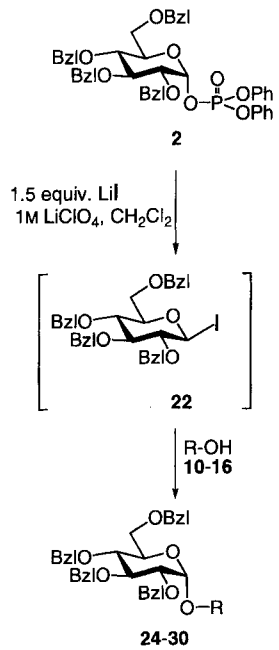


Table 2. Results of the glycosylations of the glycosyl acceptors **10**–**16** (Scheme 2) with the glycosyl donor **2** in 1 M $LiClO_4$/CH_2Cl_2 mixtures in the presence of 1.4 equiv. of LiI (Scheme 6)

Entry	Glycosyl donor	Glycoside	Yield (%)	Anomeric ratio (α:β)
1	**10**	**24**	45	3:1
2	**11**	**25**	46	only α
3	**12**	**26**	54	3:1
4	**13**	**27**	20	3:1
5	**14**	**28**	22	23:1
6	**15**	**29**	11	8:1
7	**16**	**30**	14	4:1

iodide is converted, in part, to the α-glycosyl iodide, which then reacts only slowly with the secondary glycosyl acceptors **13**–**16**. Both **15** and **16** incorporate two secondary alcohols. Remarkably, in both cases, only the 3-OH group was glycosylated. Thus, from **15** the disaccharide **29** was obtained, in which the 2-OH group of the benzylidene protected glucosyl residue is selectively unprotected. **16** was converted into the trisaccharide **30**, which has a free 4-OH in the central galactose.

In conclusion, we have demonstrated that carbohydrate derivatives with different leaving groups at the anomeric center can be activated by their in situ conversion into glycosyl iodides in 1 M solutions of $LiClO_4$ in CH_2Cl_2 in the presence of LiI. The seemingly (too) unstable glycosyl iodides can be advantageously employed as glycosyl donors in glycosylation reactions under neutral conditions, and without the addition of further promoters.

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Experimental Section

General: Melting points (uncorrected): Büchi 530 melting point apparatus. – ^1H and ^{13}C NMR: Bruker AC-250, Bruker AM-400 and Bruker DRX 500; internal standard tetramethylsilane (TMS). – MS: A.E.I. (Kratos), matrix = 3-nitrobenzyl alcohol. – Optical rotations: Perkin-Elmer polarimeter 241. – Elemental analyses: Elementar CHN-Rapid Analyzer. – TLC: Macherey-Nagel ALUGRAM® SIL G/UV254. – Flash chromatography: Silica gel (Baker, 40–60mm). – $LiClO_4$ was obtained from Acros as a > 99% pure solid. Prior to use it was dried extensively in vacuo at 150°C. – The glycosyl donors **2**,[11] **3**,[12] **4**,[11] **5**,[13] **6**,[12] **7**,[14] and **8**[12] and the glycosyl acceptors **9**,[15] **10**,[16] **11**,[17] **12**,[18] **13**,[19] **14**,[20] **15**,[21] and **16**[22] were prepared as described in the literature.

2,3-Di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranosyl Diphenyl Phosphate (**1**): 2.2 mmol *n*BuLi (1.6 M in hexane) was added to a solution of 865 mg (1.9 mmol) of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α,β-D-glucopyranose[23] in 25 ml of dry THF at −70°C. After 5 min, a solution of 2.6 mmol of diphenyl chlorophosphate in 4 ml of dry THF was also added. The mixture was stirred for 10 min and was then allowed to warm to room temp., quenched with a satd. solution of ammonium chloride, and extracted with dichloromethane (3 × 50 ml). The combined organic layers were dried with sodium sulfate and the solvent removed under reduced pressure to give a yellow powder. The crude product was purified by flash chromatography using *n*-hexane/ethyl acetate (4:1) as eluent. Yield 392 mg (30%) as a colorless solid, m.p. 90–91°C, R_f = 0.3 (*n*-hexane/ethyl acetate, 3:1). – $[\alpha]_{22}^{D}$ = 38.8 (*c* = 1.3, $CHCl_3$). – ^1H NMR (400 MHz, $CDCl_3$): δ = 3.55–3.64 (m, 3 H, 2-H, 4-H, 6-H), 3.80 (dd, $J_{5,6}$ = $J_{4,5}$ = 9.9 Hz, $J_{5,6'}$ = 4.8 Hz, 1 H, 5-H), 3.92–3.97 (m, 2 H, 3-H, 6'-H), 4.70–4.88 (m, 4 H, OCH_2Ph), 5.49 (s, 1 H, C*H*–Ph), 5.96 (d, $_{1,2}$ = 3.4 Hz, $J_{1,P}$ = 6.7 Hz, 1 H, 1-H), 7.11–7.46 (m, 25 H, Ph–*H*). – $C_{39}H_{37}O_9P$ (680.7): calcd. C 68.82, H 5.48; found C 68.50, H 5.45.

Characteristic NMR Data for the α-Glycosyl Iodide **21**: ^1H NMR (400 MHz, $CDCl_3$): δ = 2.87 (dd, $J_{1,2}$ = 4.2 Hz, $J_{2,3}$ = 8.8 Hz, 1 H, 2-H), 3.73–3.81 (m, 2 H, 4-H, 6-H_a), 3.92–3.40 (m, 2 H, 3-H, 5-H), 4.30 (dd, $J_{5,6b}$ = 4.8 Hz, $J_{6a,6b}$ = 10.2 Hz, 1 H, 6-H_b), 4.71–4.89 (m, 4 H, CH_2–Ph), 5.55 (s, 1 H, CH–Ph), 6.74 (d, $J_{1,2}$ = 4.2 Hz, 1 H, 1-H), 7.25–7.51 (m, 15 H, arom. H). – ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 67.8 (1 C, C-6), 69.6 (1 C, CH), 73.0, 75.5 (2 C, CH_2–Ph), 78.5, 78.9, 79.9 (3 C, CH), 80.2 (1 C, C-1), 101.4 (1 C, CH–Ph), 126.0–129.0 (15 C, C-arom.), 137.0, 137.2, 138.3 (3 C, C_{ipso}). – FAB-MS: 557 $[M - H]^+$.

Characteristic NMR Data for the β-Glycosyl Iodide **22** *and the α-Glycosyl Iodide* **23**: β-Glycosyl iodide **22**: ^1H NMR (500 MHz,CD_2Cl_2): δ = 5.73 (d, $J_{1,2}$ = 8.3 Hz, 1 H, 1-H). – α-Glycosyliodide **23**: ^1H NMR (500 MHz, CD_2Cl_2): δ = 2.83 (dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 8.9 Hz, 1 H, 2-H), 3.65 (d, $J_{6,6'}$ = 10.1 Hz, 6-H), 3.75–3.79 (m, 3 H, 4-H, 5-H, 6'-H), 3.88 (dd, , $J_{2,3}$ = $J_{3,4}$ = 8.9 Hz, 1 H, 3-H), 4.45–4.93 (m, 8 H, OCH_2Ph), 6.96 (d, $J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 7.14–7.39 (m, 20 H, Ph–*H*).

General Procedure for the Glycosylations: The glycosyl acceptor **9**–**16** (0.2 mmol) was added to a mixture of the glycosyl donor **1**–**6** (0.1 mmol), 3 mmol of $LiClO_4$ (dried before use for 1 d at 150°C/0.1 Torr), 0.25g of powdered molecular sieves 4 Å, 0.2 mmol of LiI and 3 ml of CH_2Cl_2. After stirring for 3 d at room temp. under argon, the reaction mixture was dild. with 25 ml of CH_2Cl_2, filtered and washed once with 10 ml of a concd. aqueous solution of sodium thiosulfate, and then with 10 ml of water. The organic layer was dried with Na_2SO_4 and concd. under reduced pressure. The residue was purified by flash chromatography by using *n*-hexane/ethyl acetate mixtures as eluent. According to this procedure the following compounds were prepared (for yields and anomeric ratios see Table 1 and Table 2).

Methyl (2,3-Di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**17**): Colorless oil, R_f = 0.13 (*n*-hexane/ethyl acetate, 4:1). – Major isomer (α): ^1H NMR (400 MHz, $CDCl_3$): δ = 3.35 (s, 3 H, OCH_3), 3.43–4.02 (m, 11 H, 2a-H–6a-H, 2b-H–6'b-H), 4.20 (dd, $J_{6,6'}$ = 10.1 Hz, $J_{5,6'}$ = 4.8 Hz, 1 H, 6'b-H), 4.43–4.98 (m, 12 H, 10 O*CH*Ph, 1a-H, 1b-H), 5.53 (s, 1 H, C*H*–Ph), 7.13–7.49 (m, 30 H, Ph–H). – Relevant signals for both isomers in the ^{13}C NMR (100.6 MHz, $CDCl_3$) (α): δ = 97.9 (1 C, C-1b), 98.1 (1 C, C-1a); (β): δ = 98.1 (1 C, C-1a), 104.3 (1 C, C-1b). – $C_{55}H_{58}O_{11}$ (895.1): calcd. C 73.81, H 6.53; found C 73.44, H 6.53.

Methyl (2,3,4,6-Tetra-O-benzyl-α/β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**18**): See ref.[24].

1,2:3,4-Di-O-isopropylidene-6-O-(2,3,4,6-tetra-O-benzyl-α/β-D-glucopyranosyl)-α-D-galactopyranose (**24**): See ref.[25].

N-(Diphenylmethylene)-^{3}O-(2,3,4,6-tetra-O-benzyl-α/β-D-glucopyranosyl)serine Methyl Ester (**25**): See ref.[26].

Methyl [(2,3,4,6-Tetra-O-benzyl-α/β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranosyl]-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**26**): Colorless oil, R_f = 0.45 (*n*-hexane/ethyl acetate, 3:1). – ^1H NMR (400 MHz, $CDCl_3$) (α and β): δ = 3.28 (s, 3 H, $OCH_{3,\beta}$), 3.32 (s, 3 H, $OCH_{3,\alpha}$), 3.38–4.17 (m, 36 H, 2a-H–6'b-H_α, 2b-H–6'b-H_α, 2c-H–6'c-H_α, 2a-H–6'a-H_β, 2b-H–6b'-$H_{\beta\alpha\alpha}$, 2c-H–6'c-H_β), 4.13 (d, $J_{1,2}$ = 7.7 Hz, 1 H, 1c-H_β), 4.39–5.02 (m, 45 H, 40 O*CH*–Ph, 1a-H_α, 1b-H_α, 1c-H_α, 1a-H_β, 1b-H_β), 7.09–7.33 (m, 100 H, Ph–*H*). – $C_{89}H_{94}O_{16}\cdot H_2O$ (1437.73): calcd. C 74.35, H 6.73; found C 74.16, H 6.69.

Methyl (2,3,4,6-tetra-O-benzyl-α/β-D-glucopyranosyl)-(1→4)-2,3,6-tri-O-benzyl-α-D-glucopyranoside (**27**): See ref.[27].

Allyl (2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl)-(1→3)-2-acetylamino-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside (**28**): Colorless oil, R_f = 0.59 (*n*-hexane/ethyl acetate, 1:1). – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.89 (s, 3 H, OCH_3), 3.22 (dd, $J_{3,4}$ = 9.9 Hz, $J_{4,5}$ = 9.0 Hz, 1 H, 4b-H), 3.40–3.46 (m, 2 H, 6b-H, 2b-H), 3.73–3.80 (m, 2 H, 6'b-H, 6a-H), 3.86–4.00 (m, 4 H, 3b-H, 4a-H, 5a-H, $OCH_2CH{=}CH_2$), 4.10–4.17 (m, 2 H, 5b-H, OCH_2CH=

CH_2), 4.22–4.30 (m, 3 H, 3a-H, 6'a-H, OCH_2-Ph), 4.41–4.60 (m, 5 H, 2a-H, 4 OC*H*–Ph), 4.72 (d, J_{gem} = 10.8 Hz, 1 H, OCH_2–Ph), 4.84 (d, J_{gem} = 11.4 Hz, 1 H, OCH_2–Ph), 4.88 (d, $J_{1,2}$ = 3.6 Hz, 1 H, 1a-H), 4.96 (d, J_{gem} = 10.8 Hz, 1 H, OCH_2–Ph), 5.19 (d, J_{cis} = 10.4 Hz, 1 H, $OCH_2CH{=}CH_2$), 5.28 (dd, J_{trans} = 17.2 Hz, ^4J = 1.2 Hz, 1 H, $OCH_2CH{=}CH_2$), 5.47 (d, $J_{1,2}$ = 3.4 Hz, 1 H, 1b-H), 5.74–5.83 (m, 1 H, $OCH_2CH{=}CH_2$), 6.23 (d, 1 H, Ph–*H*), 7.11–7.38 (m, 24 H, Ph–*H*). – $C_{52}H_{57}N_1O_{11}$ (872.0): 872.4 [M^+] (MS-FAB).

Methyl (2,3,4,6-Tetra-O-benzyl-α/β-D-glucopyranosyl)-(1→3)-4,6-O-benzylidene-α-D-glucopyranoside (**29**): See ref.[28].

Methyl [(2,3,4,6-tetra-O-benzyl-α/β-D-glucopyranosyl)-(1→3)-2,6-di-O-benzyl-β-D-galactopyranosyl)]-(1→4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside (**30**): Colorless oil, R_f = 0.52 (toluene/acetone, 10:1). – Major isomer (α): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.53 (s, 3 H, OCH_3), 3.24–4.02 (m, 18 H, 2a-H–6'a-H, 2b-H–6'b-H, 2c-H–6'c-H), 4.27 (d, $J_{1,2}$ = 7.6 Hz, 1 H, 1a-H), 4.30 (d, J_{gem} = 11.9 Hz, 1 H, OCH_2–Ph), 4.37–5.04 (m, 19 H, 17 OC*H*–Ph, 1b-H, 1c-H), 7.08–7.45 (m, 45 H, Ph–*H*). – Relevant signals of both isomers in the ^{13}C NMR (125.7 MHz, $CDCl_3$) (α): δ = 94.6 (1 C, C-1c), 102.5 (1 C, C-1b), 104.7 (1 C, C-1a); (β): δ = 102.4 (1 C, C-1b), 103.2 (1 C, C-1c), 104.8 (1 C, C-1a). – $C_{82}H_{88}O_{16}$ (1329.59): calcd. C 74.08, H 6.67; found C 74.16, H 6.69.

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