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Synthesis of phosphites and phosphates of neuraminic acid and their glycosyl donor properties – convenient synthesis of GM_3

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The importance and requirements for catalytic activation of sialyl donors are discussed, leading to the acid sensitive phosphite and phosphate moiety, respectively, as leaving group and nitriles as solvent. Therefore, from readily available *N*-acetylneuraminic acid, derivative **1** with phosphochloridites **2a–f** and Huenigs' base sialyl phosphites **3a–f** were prepared and isolated in high yields. Oxidation of **3a, c** with *tert*-butyl-hydroperoxide afforded the corresponding phosphates **4a, c**. As expected, phosphites **3** could be activated in acetonitrile by catalytic amounts of TMSOTf; thus, from **3a–e** as donors and lactose derivatives **8A, B** as acceptors the ganglioside building blocks **9A** and **9B**, respectively, were obtained in good yields. The best results were obtained with diethyl phosphite derivative **3a** as sialyl donor, which exceeded by far the reults obtained with the corresponding phosphate derivative **4a**. Trisaccharide **9B** was transformed into known **9A** and into the fully *O*-acetylated GM_3-trisaccharide **10.**

Keywords: Glycoside synthesis, nitrile effect, sialyl donors, sialyl phosphites and phosphates

Introduction

In chemical ganglioside synthesis, sialylation has been carried out by various methodologies [1–4]. Halogenoses of *O*, *N*-acylated neuraminic acid esters as donors (**L** = Hal in Scheme 1) activated by silver or mercury salts as promoters **P** gave, particularly with secondary hydroxy groups as acceptors, only modest yields of the desired α products [1–11]. Therefore, neighbouring group assistance with the help of auxiliary groups in the 3β position of the neuraminic acid molecule was employed [12–23]; however, the introduction and removal of the auxiliary groups, necessitating additional steps, limit the efficiency of this approach. Recently, thioglycosides of neuraminic acid derivatives have been proposed as sialyl group donors (**L** = SR in Scheme 1) [24–33]. The requirement of at least equimolar amounts of thiophilic reagents (*N*-iodosuccinimide (NIS) [32–34], DMTST [32, 33], methylsulfenyl bromide [35, 37], silver triflate [5–9, 35–37]) as promoters constitutes a disadvantage in this approach. The nitrile effect in *O*-glycosylation reactions [38–41], favouring under kinetically controlled conditions the equatorial glycoside (the α-glycoside of neuraminic acid), led with thio group activated neuraminic acid derivates to improved α-selectivities [27–34]. It was also found that the yields are dependent on the steric accessibility of the accepting hydroxy groups; for instance, the reactivity at the 3-*O* position of a galactose moiety increases from 3-*O* unprotected to 3,4-*O* unprotected and to 2,3,4-*O* unprotected derivatives [27, 37]. However, the performance of the reaction and the yields remained generally unsatisfactory, as exhibited in our investigations with a typical 3′,4′-*O* unprotected lactose acceptor [42, 43]. Therefore, improvements in the sialylation step in terms of yield of α-product and in ease of performance of the reaction are required [42, 43] after which the use of sialyl phosphites as sialyl donors has been described [44].

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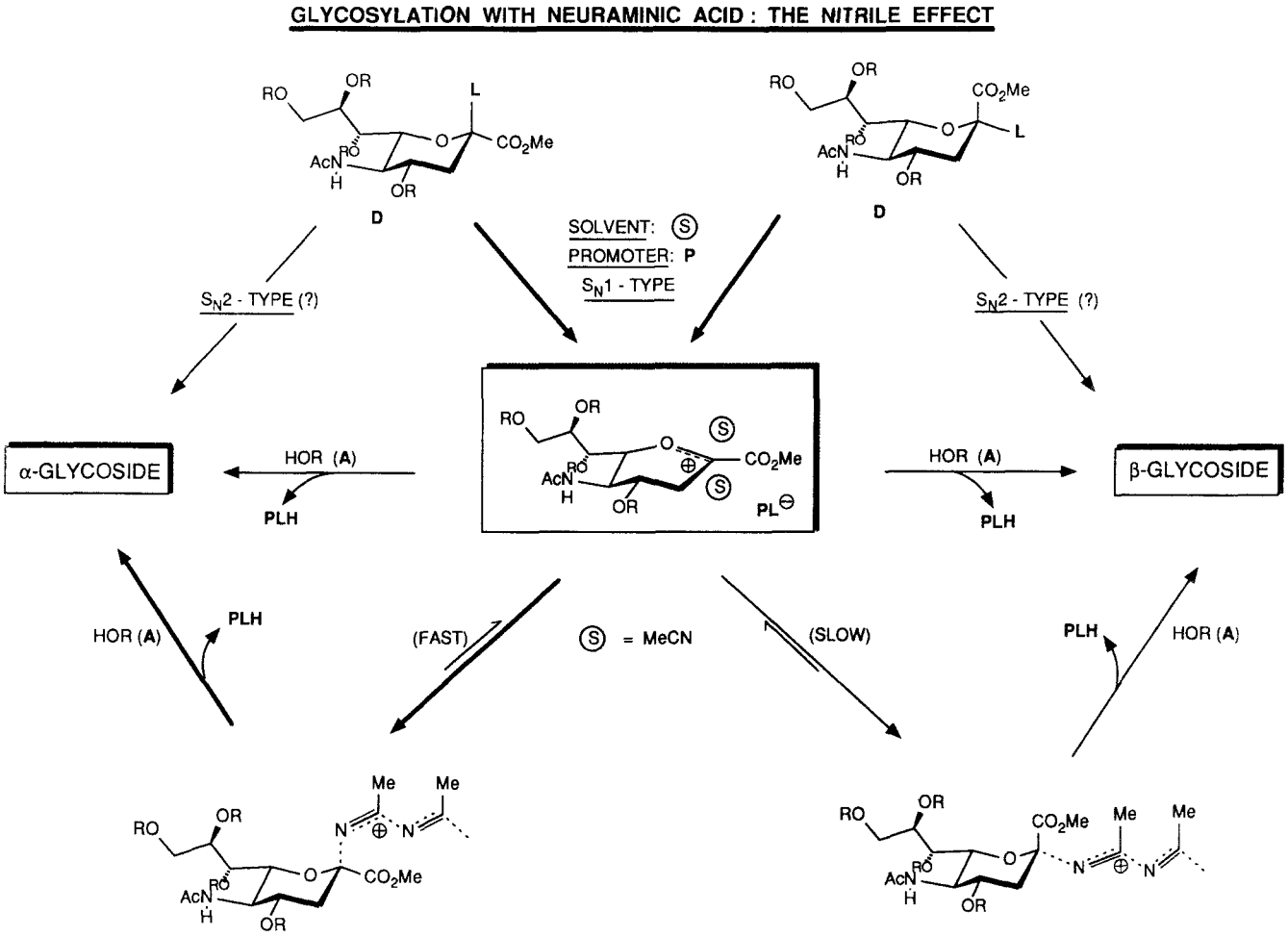
Sialyl donors requiring catalytic amounts of a promoter

The results obtained thus far rather preclude S_N2 type sialylation of *O*-nucleophiles due to steric hindrance at the anomeric centre of sialyl donors and also due to low nucleophilicity of oxygen acceptors (Scheme 1) [34, 42, 43]. Obviously, under S_N1 type conditions the promoter **P** generates from the sialyl donors, independent of their anomeric configuration, a (solvent separated) ion pair which in nitriles as solvent does not lead directly to the products [38–41]. It is intercepted under kinetically controlled conditions from the β-face by the solvent, leading to β-nitrilium–nitrile

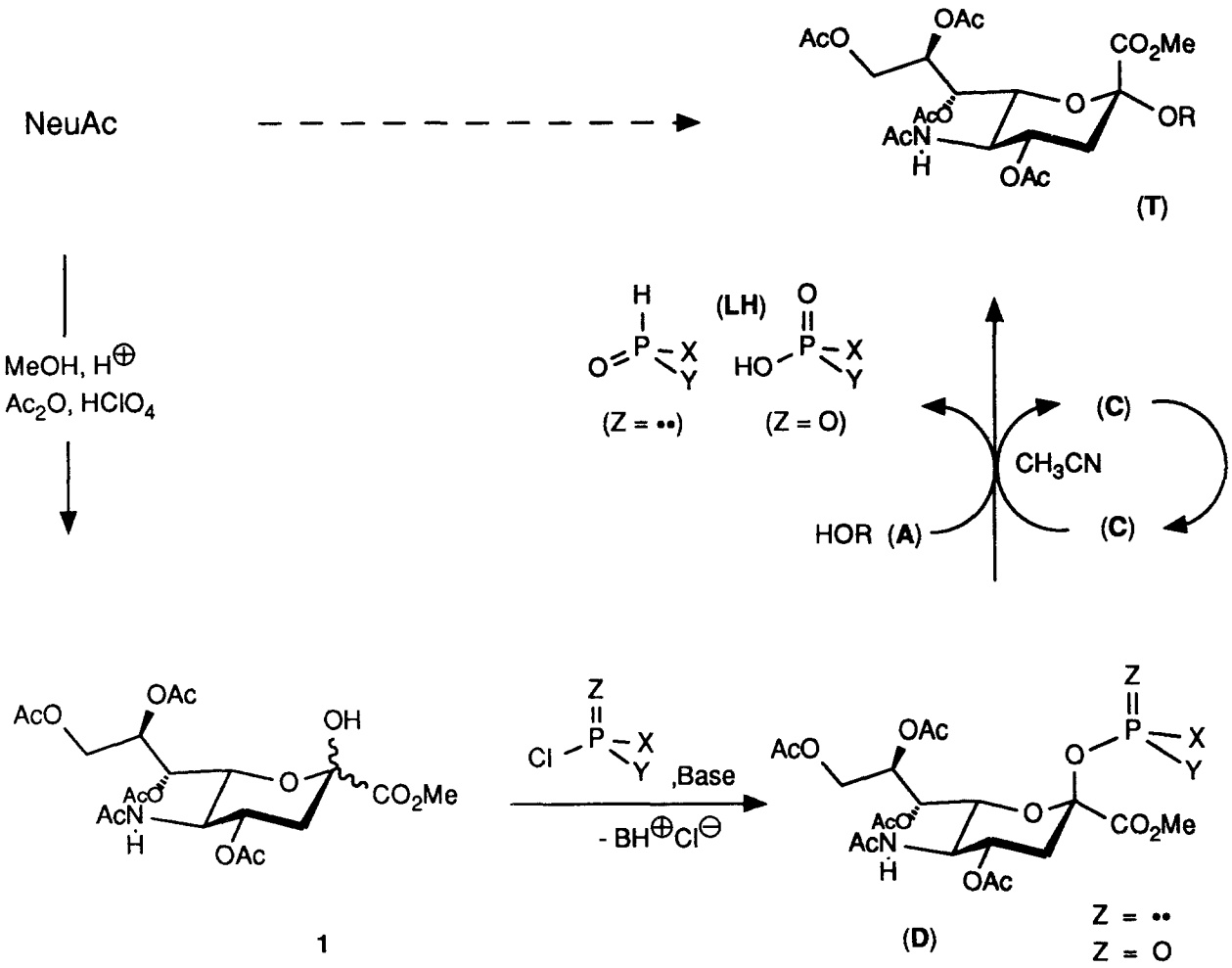


Scheme 1

conjugates (Scheme 1). Their reaction with the acceptor, prior to slow transformation into α-nitrilium–nitrile species, either directly or via intramolecular acceptor transposition [38–41], leads to the desired α product. If these assumptions are correct, for the generation of the decisive (solvent separated) ion pair in nitriles just a simple acid sensitive leaving group is required; it can be removed from the anomeric centre by catalytic amounts of a promoter (for instance, by TfOH, TMSOTf, etc.) if the leaving group **L**, due to appropriate choice, does not consume the catalyst. Consideration of various leaving groups **L** led to phosphite and phosphate moieties and their derivatives [41–43]; they can be attached readily to the anomeric hydroxy group as demonstrated for simple sugars [41, 45, 46; Y. Watanabe, personal communication] (reactions with glycosyl phosphates as glycosyl donors have been previously reported [38–40, 47–49]). Thus, a readily available neuraminic acid derivative, for instance **1** [50] (Scheme 2), will be transformed into a sialyl donor (**D**) which with alcohols as acceptors (**A**) and in nitriles as solvent will provide target molecules (**T**). The catalyst (**C**), due to the basicity of the leaving group of the sialyl donor (**D**), will preferentially attack **D**; however, the cleavage product thus generated from the leaving group (=**LH**) because of its low basicity will release the catalyst (**C**) with the help of the proton available from the acceptor hydroxy group (the translocation of protons or alternatively trimethylsilyl groups is open to discussion). Obviously, the phosphite:phosphonate system (Z = ··) seems to be especially suitable because basicity and strong leaving group character in the phosphite species (=**D**) are combined with relatively low acidity and basicity in the released phosphonate species (=**LH**). The same does not hold for the phosphate:phosphate system (Z = O) [41].

Results and discussion

Reaction of readily available methyl 4,7,8,9-tetra-*O*-acetyl-*N*-acetylneuraminate (**1**) [50] with diethyl phosphochloridite (**2a**) in acetonitrile as solvent afforded in the presence of Huenigs' base phosphite derivative **3a**, which was isolated in practically quantitative yield after flash chromatography (Scheme 3; Table 1). Based on the ^{1}H-NMR data obtained for H-3, H-4, and H-7 (see Table 3 in the Materials and methods section) the β configuration can be assigned to this

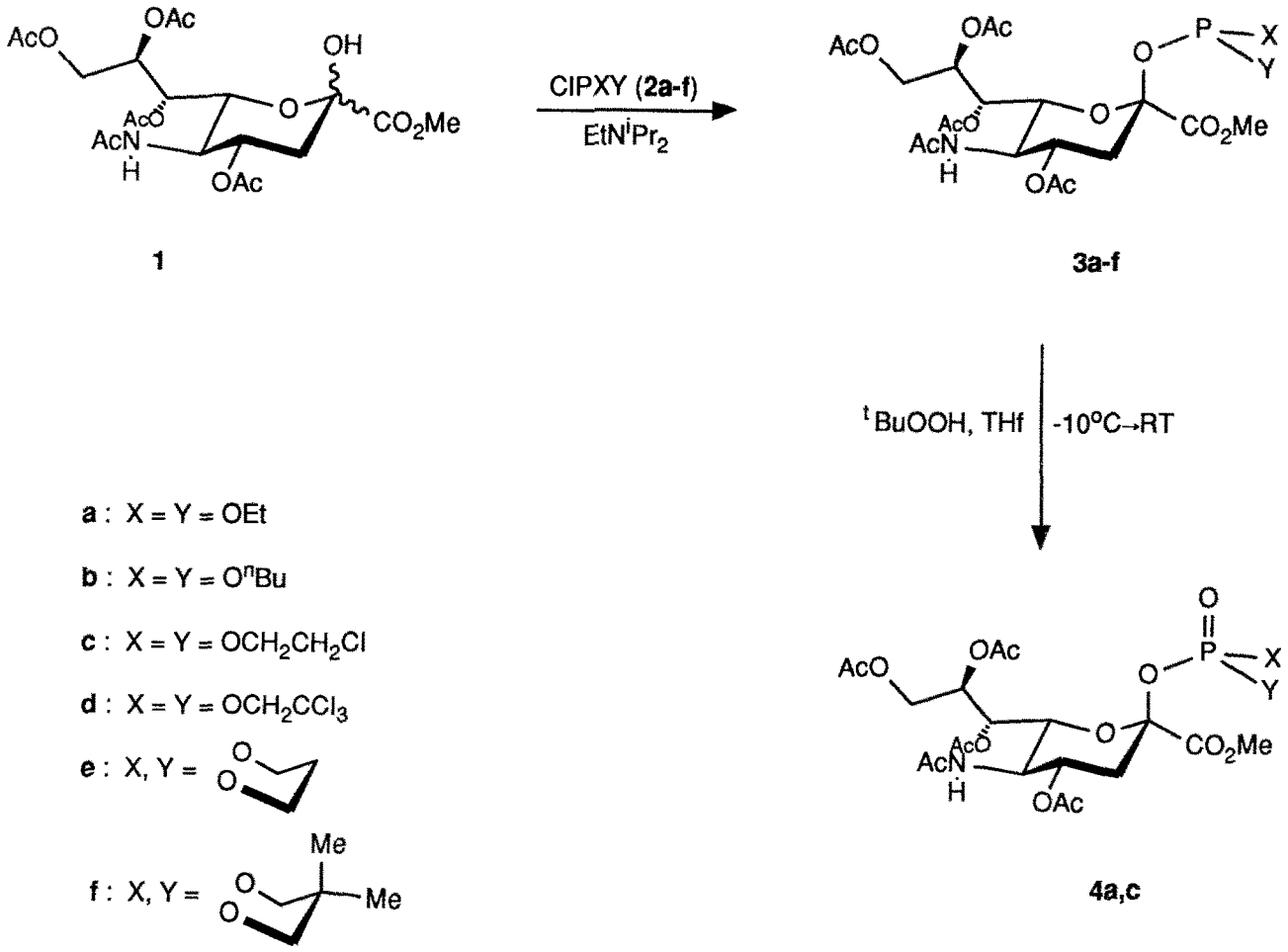


Scheme 2

compound [51]. Because of the ease of this synthesis, different phosphochloridites were employed to obtain eventually sialyl donors of varying reactivity. Thus, from phosphochloridite diesters **2b–f** under the same reaction conditions compounds **3b–f** were obtained in high yields (Table 1). Especially remarkable is the stability of bistrichloroethyl derivative **3d**, which can be purified by crystallization. Treatment of **3a, c** with *t*-butyl hydroperoxide in dry THF at $-10\,^{\circ}C$ and then gradually raising the temperature to $20\,^{\circ}C$ gave the corresponding phosphates **4a** and **4c**, respectively, again in high yields (Table 1).

Sialyl phosphite **3a** gave in methanol without catalyst addition directly the corresponding methyl glycoside [42, 43], thus hinting at the good glycosyl donor properties of sialyl phosphites. The investigation of these properties of phosphites **3a–e** and phosphate **4a** towards more demanding acceptors was performed with readily available 3′,4′-*O* unprotected lactose acceptor **8A** [52] and with 3′-*O* unprotected lactose acceptor **8B** [34] (Scheme 4); **8B** was synthesized from benzyl 3b-*O*-allyl-lactoside **5** [52] via 4b,6b-*O*-benzylidenation (→**6**), ensuing per-*O*-benzylation (→**7**), and then removal of the 3b-*O*-allyl protective group (Scheme 5). Acceptors **8A, B** are ideal starting materials for the synthesis of the *ganglio* series of glycosphingolipids, for instance gangliosides GM_1, GM_2 and GM_3, respectively.

As hoped, a solution of sialyl donor **3a** and acceptor **8A** in acetonitrile furnished at $-40\,^{\circ}C$ in the presence of catalytic amounts of TMSOTf (0.1 eq based on **3a**) the desired α-sialylated trisaccharide **9A** [53–56] in respectable yield (Scheme 5, Table 2), thus exhibiting the expected ease of performance and the overall efficiency of this methodology. Sialyl donors **3b–f**, having different leaving groups, did not lead to better results in **9A** formation. Particularly worth mentioning is the result of donor **3a** with acceptor **8B**, because full *O*-protection next to the accepting 3b-*O* position of galactose derivatives led generally to very low sialylation yields [26]. However, in this case a 38% yield of compound **9B** was obtained. For structural proof, compound **9B** was converted with $NaCNBH_3/HCl$ into trisaccharide **9A**. Hydrogenolytic *O*-debenzylation and then treatment with acetic anhydride in pyridine afforded the known [53–55] fully *O*-acylated GM_3-trisaccharide **10**, which was converted with the help of the azidosphingosine glycosylation procedure [57–60] essentially by using the published protocol [10, 11,



Scheme 3

Table 1. Synthesis of sialyl phosphites **3a–f** and sialyl phosphates **4a, c.**

Compound[a]	*Yield (%)*	R_F (*toluene:acetone*)
3a	97	0.37 (6:4)
3b	90	0.64 (1:1)
3c	87	0.59 (1:1)
3d[b]	76	0.65 (1:1)
3e	88	0.50 (1:1)
3f	81	0.56 (6:4)
4a	84	0.30 (6:4)
4c	76	0.48 (1:1)

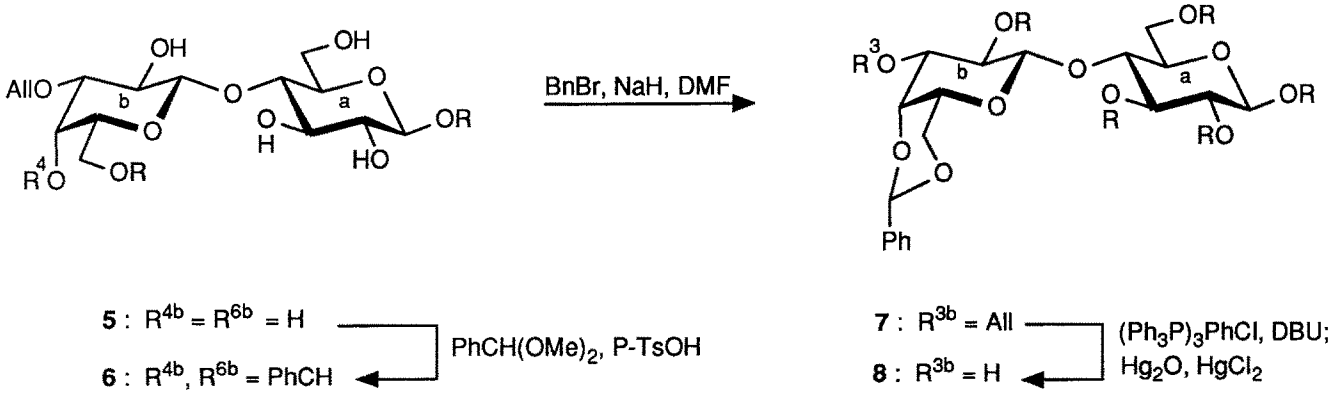
[a] For NMR data see Table 3.
[b] M.P. 110 °C.

53–55] into GM_3 (R. Brescello, unpublished results). Reaction of sialyl phosphate **4a** with acceptor **8A** under the reaction conditions described above required practically two equivalents of TMSOTf for donor activation. The results could by no means compete with those obtained for donor **3a**. In conclusion, sialyl phosphites, due to the ease of their syntheses and their convenient activation by catalytic amounts of TMSOTf, are important sialyl donors which give satisfactory yields even with less reactive acceptors as for instance **8A** and **8B** (as expected [27, 37], 2,3,4-*O* unprotected acceptors derived from galactose lead to higher yields [44].)

Materials and methods

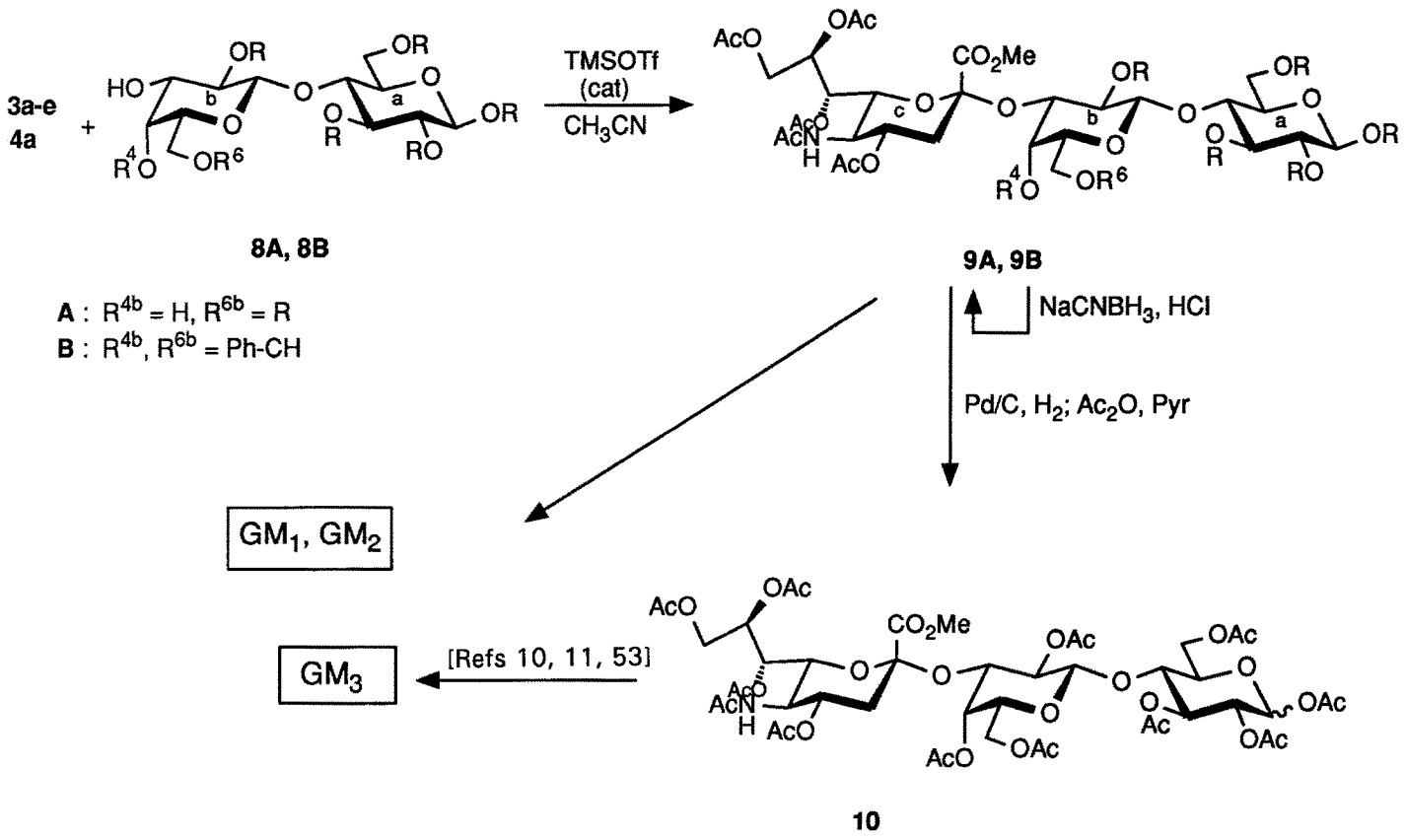
Solvents were purified and dried in the usual way; the boiling range of the petroleum ether used was 35–65 °C. ^{1}H-NMR spectra: Bruker WM 250 cryospec and Jeol JNM-GX 400, internal standard tetramethylsilane (TMS). Flash chromatography: J. T. Baker silica gel 60 (30–60 μm) at a pressure of 0.3 bar. Medium pressure chromatography: Merck silica gel LiChroprep Si 60 (15–25 μm) at a pressure

(R = Bn)



Scheme 4

(R = Bn)



Scheme 5

Table 2. Synthesis of trisaccharides **9A, B** from **3a–e**, **4a** and **8A, B** in CH_3CN at −40 °C.

Donor	*Acceptor*	*Ratio D(eq):A(eq)*	*Catalyst TMSOTf(eq)*	*Product*	*Yield (%)*
3a	**8A**	1:1.5	0.1	**9A**	55
3b	**8A**	1:1.5	0.1	**9A**	39
3c	**8A**	1:1	0.1	**9A**	32
3d	**8A**	1:1	0.2	**9A**	41
3e	**8A**	1:1	0.1	**9A**	23
3a	**8B**	1:1.1	0.1	**9B**	38
4a	**8A**	1:1	2.2	**9A**	21

of up to 10 bar. Thin-layer chromatography (TLC): Merck plastic plates silica gel 60 F_{254}, layer thickness 0.2 mm, detection by treatment with a solution of 15% H_2SO_4, followed by heating at 120 °C. Optical rotations: Perkin-Elmer polarimeter 241/MS, 1 dm cell.

General procedure for the synthesis of compounds **3a–f**

To a stirred solution of **1** (1 mmol) in dry CH_3CN (15 ml) was added EtN^iPr_2 (2.2 mmol) at room temperature; then the phosphochloride diester **2** (2 mmol) was injected under a nitrogen atmosphere at room temperature. Thereafter, the reaction mixture was evaporated *in vacuo* and the residue purified on a short silica gel column with the toluene:acetone mixtures given in Table 1. For yields, R_F values and NMR data of products **3a–f** see Tables 1 and 3. Compounds **3a–c, e, f** were used immediately in the glycosylation reactions. Compound **3d** is very stable; it can be crystallized from ethyl acetate:petroleum ether.

General procedure for the synthesis of compounds **4a, c**

A solution of phosphite **3a** or **3c** (1 mmol) in dry THF (12 ml) was cooled to −10 °C. After the addition of t-butyl hydroperoxide (1.5 ml) the mixture was allowed to warm up to room temperature. After 2 h the products **4a** and **4c**, respectively, were purified on silica gel with toluene:acetone (6.5:3.5) as eluent. For yields, R_F values and NMR data see Tables 1 and 3.

Benzyl O-(*3-O-Allyl-4,6-O-benzylidene-β-D-galactropyranosyl*)-(*1 → 4*)-*β-D-glucopyranoside* (**6**)

To a solution of **5** [52] (3.5 g, 7.41 mmol) in dry acetonitrile (100 ml) were added benzaldehyde dimethylacetal (3.4 g, 22.2 mmol) and *p*-toluenesulfonic acid (20 mg). The reaction mixture was neutralized with dry potassium carbonate after 45 min, filtered, and the solvent evaporated *in vacuo*. Recrystallization of the residue from methanol:petroleum ether gave **6** (3.78 g, 91%) as colourless crystals; m.p. 206 °C. TLC (toluene:acetone, 1:1 by vol) R_F 0.36. $[\alpha]_D^{20}$-8.7 (*c.* 1.0, $CHCl_3$). ^{1}H-NMR (250 MHz, C^2HCl_3): δ 2.54 (s, 1 H, OH), 2.80 (bs, 1 H, OH), 3.30–4.31 (m, 16 H, 2.2-H, 2 3-H, 2 4-H, 2 5-H, 4 6-H, 2 OH, CH_2—CH=CH_2), 4,42 (d, $J_{1,2}$ = 7.7 Hz, 1 H, 1-H), 4.50 (d, $J_{1,2}$ = 7.9 Hz, 1 H, 1-H), 4.62, 4.90 (2 d, J_{gem} = 11.7 Hz, 2 H, CH_2Ph), 5.18–5.35 (m, 2 H, CH_2—CH=CH_2), 5.50 (s, 1 H, CH_2Ph), 5.93 (m, 1 H, CH_2—CH=CH_2), 7.26–7.66 (m, 10 H, 2Ph).

$C_{29}H_{36}O_{11}$ (560.60). Calculated: C = 62.13, H = 6.47; found: C = 62.05, H = 6.54.

Benzyl 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* (**7**)

To a mixture of sodium hydride (812 mg, 33.8 mmol) and benzyl bromide in dry DMF (50 ml) was added dropwise a solution of **6** (3.65 g, 6.5 mmol) in dry DMF (25 ml) under cooling. After 12 h, methanol (3 ml) was added with caution to the reaction mixture which 30 min later was poured on ice water (100 ml). Extraction with diethyl ether (3 × 100 ml) and washing of the extract with saturated NaCl solution (3 × 50 ml) furnished an etheral solution from which the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography with petroleum ether:methyl acetate (5:2 by vol). Compound **7** (5.1 g, 85%) was obtained as colourless foam. TLC (petroleum ether:methyl acetate, 2:1 by vol) R_F 0.46. $[\alpha]_D^{20}$-5.0 (c. 1.0, $CHCl_3$). ^{1}H-NMR (250 MHz, C^2HCl_3): δ 3.03 (bs, 1 H, 5b-H), 3.31–4.25 (m, 13 H, 2 2-H, 2 3-H, 2 4-H, 1 5-H, 4 6-H, CH_2—CH=CH_2), 4.38, 4.57 (2 d, J_{gem} = 12.2 Hz, 2 H, CH_2Ph), 4.49 (d, $J_{1,2}$ = 7.9 Hz, 1 H, 1-H), 4.50 (d, $J_{1,2}$ = 7.6 Hz, 1 H, 1-H), 4.63–4.97 (7 d, 7 H, 7/2 CH_2Ph), 5.16–5.34 (m, 3 H, CH_2—CH=CH_2, 1/2 CH_2Ph), 5.50 (s, 1 H, CHPh), 5.92 (m, 1 H, CH_2—CH=CH_2), 7.15–7.52 (m, 30 H, 6 Ph).

$C_{57}H_{60}O_{11}$ (921.11). Calculated: C = 74.33, H = 6.57: found: C = 73.99, H = 6.59.

Table 3. NMR Data of compounds **3a–f**, **4a**, **c**.

3a. ^{1}H-NMR data (250 MHz, $C_6{}^2H_6$): δ 1.45, 1.28 (t, J = 7.1 Hz, 6 H, 2 CH_3), 1.67, 1.70, 1.74 (s, 9 H, 3 $COCH_3$), 1.89–1.97 (s, 7 H, 2 $COCH_3$, H-3a), 2.64 (dd, $J_{3e,3a}$ = 13.1 Hz, $J_{3e,4}$ = 4.9 Hz, 1 H, H-3e), 3.46 (s, 3 H, $COOCH_3$), 3.87–4.15 (m, 4 H, 2 CH_2), 4.51–4.60 (m, 3 H, H-5, H-6, H-9″), 5.09 (d, $J_{NH,5}$ = 9.9 Hz, 1 H, NH), 5.22 (dd, $J_{9',9''}$ = 12.3 Hz, $J_{8,9'}$ = 2.2 Hz, 1 H, H-9′), 5.43 (ddd, $J_{3e,4}$ = 4.9 Hz, $J_{3a,4}$ = 10.4 Hz, $J_{4,5}$ = 11.1 Hz, 1 H, H-4), 5.62 (ddd, $J_{8,9'}$ = 2.2 Hz, $J_{7,8}$ = 2.8 Hz, $J_{8,9''}$ = 7.9 Hz, 1 H, H-8), 5.76 (dd, $J_{7,8}$ = 2.8 Hz, 1 H, H-7).
^{1}H-NMR data (250 MHz, C^2HCl_3): δ 1.16–1.40 (m, 6 H, CH_3), 1.83 (s, 3 H, $NCOCH_3$), 1.97–2.98 (m, 13 H, H-3a, 4 $COCH_3$), 2.43 (dd, $J_{3a,3e}$ = 13.1 Hz, $J_{3e,4}$ = 4.9 Hz, 1 H, H-3e), 3.75 (s, 3 H, $COOCH_3$), 3.78–4.16 (m, 6 H, 2 CH_3, H-5, H-9″), 4.21 (dd, $J_{5,6}$ = 10.7 Hz, $J_{6,7}$ = 2.1 Hz, 1 H, H-6), 4.59 (dd, $J_{9',9''}$ = 12.3 Hz, $J_{8,9'}$ = 2.4 Hz, 1 H, H-9′), 5.09 (ddd, $J_{8,9''}$ = 7.3 Hz, 1 H, H-8), 5.22 (ddd, $J_{3e,4}$ = 4.9 Hz, 1 H, H-4), 5.37 (dd, $J_{7,8}$ = 2.4 Hz, 1 H, H-7), 5.53 (d, $J_{NH,5}$ = 9.8 Hz, 1 H, NH).
^{31}P-NMR (161.7 MHz, C^2HCl_3): δ 137.64 (β, 100%)

3b. ^{1}H-NMR data (250 MHz, C^2HCl_3): δ 0.81–0.92 (m, 6 H, 2 CH_3), 1.24–1.44 (m, 4 H, 2 CH_2), 1.45–1.70 (m, 4 H, 2 CH_2), 1.81 (s, 3 H, $NCOCH_3$), 1.94–2.05 (4 s, 13 H, H-3a, 4 $COCH_3$), 2.42 (dd, $J_{3a,3e}$ = 13.1 Hz, $J_{3e,4}$ = 4.9 Hz, 1 H, H-3e), 3.74 (s, 3 H, $COOCH_3$), 3.75–3.89 (m, 2 H, OCH_2), 3.96–4.16 (m, 4 H, H-5, H-9″, OCH_2), 4.19 (dd, $J_{5,6}$ = 10.6 Hz, $J_{6,7}$ = 2.0 Hz, 1 H, H-6), 4.57 (dd, $J_{9',9''}$ = 12.3 Hz, $J_{9',8}$ = 2.3 Hz, 1 H, H-9′), 5.07 (ddd, $J_{8,9''}$ = 7.3 Hz, 1 H, H-8), 5.19 (ddd, $J_{3e,4}$ = 4.9 Hz, 1 H, H-4), 5.35 (dd, $J_{7,8}$ = 2.4 Hz, 1 H, H-7), 5.62 (d, $J_{NH,5}$ = 9.8 Hz, 1 H, NH).

3c. ^{1}H-NMR data (250 MHz, $C_6{}^2H_6$): δ 1.65 (s, 3 H, $COCH_3$), 1.68 (s, 3 H, $COCH_3$), 1.74 (s, 3 H, $COCH_3$), 1.92–1.96 (2 s, 7 H, H-3a, 2 $COCH_3$), 2.52 (dd, $J_{3e,3a}$ = 13.1 Hz, $J_{3e,4}$ = 4.9 Hz, 1 H, H-3e), 3.28 (t, 2 H, J = 5.7 Hz, CH_2Cl), 3.40 (s, 3 H, $COOCH_3$), 3.46 (t, 2 H, J = 5.7 Hz, CH_2Cl), 3.95–4.03 (m, 2 H, OCH_2), 4.12–4.16 (m, 2 H, OCH_2), 4.45 (dd, $J_{9',9''}$ = 12.3 Hz, $J_{8,9''}$ = 7.5 Hz, 1 H, H-9″), 4.52–4.58 (m, 2 H, H-5, H-6), 5.07 (dd, $J_{9',9''}$ = 12.3 Hz, $J_{8,9'}$ = 2.3 Hz, 1 H, H-9′), 5.09–5.12 (m, 1 H, NH), 5.37–5.47 (m, 1 H, H-4), 5.59 (ddd, $J_{8,9'}$ = 2.3 Hz, $J_{8,9''}$ = 7.5 Hz, 1 H, H-8), 5.74–5.76 (m, 1 H, H-7).
^{1}H-NMR data (250 MHz, C^2HCl_3): δ 1.84 (s, 3 H, $NCOCH_3$), 1.97 (s, 6 H, 2 $COCH_3$), 2.02 (s, 3 H, $COCH_3$), 2.08 (s, 3 H, $COCH_3$), 2.40 (dd, $J_{3e,3a}$ = 13.07 Hz, $J_{3e,4}$ = 4.8 Hz, 1 H, H-3e), 3.62 (t, 2 H, J = 5.5 Hz, CH_2Cl), 3.69 (t, 2 H, J = 5.5 Hz, CH_2Cl), 3.78 (s, 3 H, $COOCH_3$), 4.21–4.03 (m, 6 H, H-5, H-9″, 2 OCH_2), 4.26 (dd, $J_{5,6}$ = 10.7 Hz, $J_{6,7}$ = 2.2 Hz, 1 H, H-6), 4.50 (dd, $J_{8,9'}$ = 2.4 Hz, $J_{9',9''}$ = 12.4 Hz, 1 H, H-9′), 5.09 (ddd, $J_{8,9'}$ = 2.4 Hz, 1 H, H-8), 5.23 (ddd, $J_{3e,4}$ = 4.8 Hz, 1 H, H-4), 5.35 (dd, $J_{6,7}$ = 2.2 Hz, 1 H, H-7), 5.51 (dd, $J_{NH,5}$ = 10.0 Hz, 1 H, NH).

3d. ^{1}H-NMR data (250 MHz, $C_6{}^2H_6$): δ 1.63 (s, 3 H, $COCH_3$), 1.66 (s, 3 H, $COCH_3$), 1.76 (s, 3 H, $COCH_3$), 1.94–2.04 (2 s, 7 H, H-3a, 2 $COCH_3$), 2.42 (dd, $J_{3a,3e}$ = 13.2 Hz, $J_{3e,4}$ = 4.8 Hz, 1 H, H-3e), 3.32 (s, 3 H, $COOCH_3$), 4.37 (dd, $J_{9',9''}$ = 12.4 Hz, $J_{8,9''}$ = 6.9 Hz, 1 H, H-9″), 4.48–4.58 (m, 3 H, H-5, OCH_2CCl_3), 4.67–4.75 (m, 2 H, OCH_2CCl_3), 4.85 (dd, $J_{6,7}$ = 6.2 Hz, $J_{5,6}$ = 11.6 Hz, 1 H, H-6), 4.93 (dd, $J_{8,9'}$ = 2.4 Hz, $J_{9',9''}$ = 12.4 Hz, 1 H, H-9′), 5.00 (d, $J_{NH,5}$ = 7.3 Hz, 1 H, NH), 5.39 (ddd, $J_{3e,4}$ = 4.8 Hz, 1 H, H-4), 5.57 (ddd, $J_{8,9'}$ = 2.4 Hz, 1 H, H-8), 5.73 (dd, $J_{7,8}$ = 1.6 Hz, 1 H, H-7).
^{31}P-NMR (161.7 MHz, C^2HCl_3): δ 135.74 (β, 100%)
^{1}H-NMR data (250 MHz, C^2HCl_3): δ 1.85 (s, 3 H, $COCH_3$), 1.97 (s, 3 H, $COCH_3$), 1.98 (s, 3 H, $COCH_3$), 2.04–2.18 (2 s, 7 H, H-3a, 2 $COCH_3$), 2.40 (dd, $J_{3a,3e}$ = 4.8 Hz, $J_{3e,4}$ = 13.2 Hz, 1 H, H-3e), 3.83 (s, 3 H, $COOCH_3$), 4.06 (dd, $J_{8,9''}$ = 6.2 Hz, $J_{9',9''}$ = 12.5 Hz, 1 H, H-9″), 4.12–4.26 (m, 2 H, H-5, H-6), 4.36–4.64 (m, 5 H, H-9′, 2 OCH_2CCl_3), 5.09 (ddd, $J_{7,8}$ = 2.5 Hz, $J_{8,9''}$ = 6.2 Hz, 1 H, H-8), 5.21 (ddd, $J_{3e,4}$ = 4.8 Hz, $J_{3a,4}$ = 11.4 Hz, 1 H, H-4), 5.32–5.38 (m, 2 H, NH, H-7).

3e. ^{1}H-NMR data (250 MHz, C^2HCl_3): δ 1.52–1.63 (m, 1 H, CH), 1.82 (s, 3 H, $NCOCH_3$), 1.95–2.09 (4 s, 13 H, H-3a, 4 $COCH_3$), 2.18–2.23 (m, 1 H, CH), 2.51 (dd, $J_{3a,3e}$ = 13.2 Hz, $J_{3e,4}$ = 4.8 Hz, 1 H, H-3e), 3.75 (s, 3 H, $COOCH_3$), 4.03–4.12 (m, 2 H, H-5, H-9″), 4.26 (dd, $J_{5,6}$ = 10.6 Hz, $J_{6,7}$ = 2.0 Hz, 1 H, H-6), 4.33–4.48 (m, 4 H, 2 OCH_2), 4.55 (dd, $J_{9',9''}$ = 12.3 Hz, $J_{9,8}$ = 2.4 Hz, 1 H, H-9′), 5.09 (m, 1 H, H-8), 5.32 (ddd, $J_{3e,4}$ = 4.9 Hz, 1 H, H-4), 5.37 (dd, $J_{7,8}$ = 2.3 Hz, 1 H, H-7), 5.92 (dd, $J_{NH,5}$ = 9.8 Hz, 1 H, NH).

3f. ^{1}H-NMR data (250 MHz, C^2HCl_3): δ 0.70 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.82 (s, 3 H, $NCOCH_3$), 1.92–2.07 (4 s, 13 H, H-3a, 4 $COCH_3$), 2.47 (dd, $J_{3a,3e}$ = 13.1 Hz, $J_{3e,4}$ = 4.9 Hz, 1 H, H-3e), 3.72 (s, 3 H, $COOCH_3$), 3.87–4.12 (m, 6 H, H-5, H-9″, $OCH_2CMe_2CH_2O$), 4.21 (dd, $J_{5,6}$ = 10.6 Hz, $J_{6,7}$ = 2.0 Hz, 1 H, H-6) 4.50 (dd, $J_{9',9''}$ = 12.3 Hz, $J_{8,9'}$ = 2.4 Hz, 1 H, H-9′), 5.08 (m, 1 H, H-8), 5.23 (ddd, $J_{3e,4}$ = 4.9 Hz, 1 H, H-4), 5.36 (dd, $J_{7,8}$ = 2.3 Hz, 1 H, H-7), 6.19 (d, $J_{NH,5}$ = 9.9 Hz, 1 H, NH).

4a. ^{1}H-NMR data (250 MHz, $C_6{}^2H_6$): δ 1.21 (t, 3 H, CH_3), 1.29 (t, 3 H, CH_3), 1.80 (s, 3 H, $COCH_3$), 1.84 (s, 3 H, $COCH_3$), 1.88 (s, 3 H, $COCH_3$), 2.00–2.05 (2 s, 7 H, H-3a, 2 $COCH_3$), 2.82 (dd, $J_{3a,3e}$ = 13.5 Hz, $J_{3e,4}$ = 4.9 Hz, 1 H, H-3e), 3.60 (s, 3 H, $COOCH_3$), 4.15–4.27 (m, 4 H, 2 OCH_2), 4.57–4.73 (m, 2 H, H-5, H-9″), 4.81 (dd, $J_{6,7}$ = 2.2 Hz, $J_{5,6}$ = 10.8 Hz, 1 H, H-6), 5.20 (dd, $J_{8,9'}$ = 2.1 Hz, $J_{9',9''}$ = 12.2 Hz, 1 H, H-9′), 5.51 (ddd, $J_{3e,4}$ = 4.9 Hz, 1 H, H-4), 5.81 (ddd, $J_{8,9'}$ = 2.1 Hz, $J_{8,9''}$ = 7.8 Hz, 1 H, H-8), 5.87 (m, 1 H, H-7), 6.06 (d, $J_{NH,5}$ = 10.0 Hz, 1 H, NH).
^{1}H-NMR data (250 MHz, C^2HCl_3): δ 1.19–1.28 (m, 6 H, 2 CH_3), 1.78 (s, 3 H, $NCOCH_3$), 1.91–2.03 (4 s, 13 H, H-3a, 4 $COCH_3$), 2.54 (dd, $J_{3a,3e}$ = 13.5 Hz, $J_{3e,4}$ = 4.9 Hz, 1 H, H-3_e), 3.73 (s, 3 H, $COOCH_3$), 4.00–4.19 (m, 6 H, H-5, H-9″, 2 OCH_2), 4.38 (dd, $J_{6,7}$ = 2.3 Hz, $J_{5,6}$ = 10.8 Hz, 1 H, H-6), 4.52 (dd, $J_{9',9''}$ = 12.3 Hz, $J_{8,9'}$ = 2.3 Hz, H-9′), 5.15–5.26 (m, 2 H, H-4, H-8), 5.37 (m, 1 H, H-7), 6.06 (d, $J_{NH,5}$ = 10.1 Hz, 1 H, NH).

(*table continues on next page*)

Table 3—*continued*

4c. ^{1}H-NMR data (250 MHz, $C_6{}^2H_6$): δ 1.69 (s, 3 H, $COCH_3$), 1.77 (s, 3 H, $COCH_3$), 1.78 (s, 3 H, $COCH_3$), 1.99 (s, 3 H, $COCH_3$), 2.00 (s, 3 H, $COCH_3$), 1.96–2.04 (m, 1 H, H-3a), 2.73 (dd, 1 H, $J_{3a,3e}$ = 13.5 Hz, $J_{3e,4}$ = 4.9 Hz, 1 H, H-3e), 3.34–3.48 (m, 4 H, 2 CH_2Cl), 3.51 (s, 3 H, $COOCH_3$), 4.18–4.32 (m, 4 H, 2 OCH_2), 4.47–4.68 (m, 2 H, H-5, H-9″), 4.71 (dd, $J_{6,7}$ = 2.2 Hz, $J_{5,6}$ = 10.8 Hz, 1 H, H-6), 5.07 (dd, $J_{9',9''}$ = 12.2 Hz, $J_{8,9'}$ = 2.1 Hz, 1 H, H-9′), 5.41 (ddd, $J_{3e,4}$ = 4.9 Hz, 1 H, H-4), 5.65 (d, $J_{NH,5}$ = 10.0 Hz, 1 H, NH), 5.73 (ddd, $J_{8,9'}$ = 2.1 Hz, $J_{8,9''}$ = 7.6 Hz, 1 H, H-8), 5.80 (m, 1 H, H-7).
^{1}H-NMR data (250 MHz, C^2HCl_3): δ 1.86 (s, 3 H, $NCOCH_3$), 1.97–2.12 (4 s, 13 H, H-3a, 4 $COCH_3$), 2.63 (dd, $J_{3a,3e}$ = 13.5 Hz, $J_{3e,4}$ = 4.9 Hz, 1 H, H-3a), 3.66–3.78 (m, 4 H, 2 CH_2Cl), 3.84 (s, 3 H, $COOCH_3$), 4.12–4.22 (m, 2 H, H-5, H-9″), 4.29–4.38 (m, 4 H, 2 OCH_2), 4.41 (dd, $J_{6,7}$ = 2.3 Hz, $J_{5,6}$ = 10.8 Hz, 1 H, H-6), 4.52 (dd, $J_{9',9''}$ = 12.3 Hz, $J_{8,9'}$ = 2.3 Hz, H-9′), 5.20–5.31 (m, 2 H, H-4, H-8), 5.39–5.42 (m, 1 H, H-7), 5.23 (d, $J_{NH,5}$ = 10.2 Hz, NH).

Benzyl O-(*2-*O*-Benzyl-4,6-*O*-benzylidene-β-*D*-galactopyranosyl*)-(*1* → *4*)-*2,3,6-tri*-O*-benzyl-β-*D*-galactopyranoside* (**8B**)

To a solution of **7** (4.72 g, 5.1 mmol) in ethanol:water (9:1 by vol, 100 ml) was added tris(triphenylphosphine)rhodium chloride (0.45 g, 0.5 mmol) and DBU (0.1 ml). The reaction mixture was refluxed for 2 h and then the solvents evaporated *in vacuo*. The residue was purified by chromatography on a short silica gel column with petroleum ether:methyl acetate (2:1 by vol). To the solution of the propenyl intermediate in acetone:water (9:1 by vol, 15 ml) was added dropwise a solution of $HgCl_2$ (1.5 g, 3.2 mmol) in acetone:water (9:1 by vol, 30 ml). After 3 h the reaction mixture was filtered over silica which was subsequently washed with $CHCl_3$ (150 ml). The filtrate was washed with KI solution (30%, 3 × 30 ml). The organic layer was concentrated and purified by flash chromatography (petroleum ether:methyl acetate, 3:2 by vol) R_F 0.48. $[\alpha]_D^{20}$-23.5 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (250 MHz, C^2HCl_3): δ 2.42 (bd, 1 H, 4b-OH), 3.09 (bs, 1 H, 5b-H), 3.28–4.28 (m, 11 H, 2 2-H, 2 3-H, 2 4-H, 1 5-H, 4 6-H), 4.38–4.82 (m, 9 H, 1a-H, 1b-H, 7/2 CH_2Ph), 4.95, 4.96, 5.17 (3 d, J_{gem} = 10.8 Hz, 12.0 Hz, 10.4 Hz, 3 H, 3/2 CH_2Ph), 5.52 (s, 1 H, CHPh), 7.17–7.52 (m, 30 H, 6 Ph).

Analytical data: $C_{54}H_{56}O_{11}$ (881.04). Calculated: C = 72.14, H = 6.50; found: C = 72.06, H = 6.54.

General procedure for the glycosylation

A solution of the donor **3a–e** or **4a** (1 mmol) and the acceptor **8A** [52] or **8B**, respectively (1–1.5 mmol, see Table 2) in dry acetonitrile (4 ml) was cooled to −40 °C. Under a nitrogen atmosphere the catalyst TMSOTf (see Table 2) dissolved in dry acetonitrile (0.5 ml) is added. After 1 h the solution was neutralized with triethylamine and evaporated *in vacuo*. The residue was purified by flash chromatography with the toluene:acetone mixtures given below. For yields see Table 2.

Benzyl O-[*methyl-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*D*-*glycero*-α-*D*-galacto-2-nonulopyranosyl)onate*]-(*2* → *3*)-O-(*2,6-di-*O*-benzyl-β-*D*-galactopyranosyl*)-(*1* → *4*)-*2,3,6-tri*-O*-benzyl-β-*D*-glycopyranoside* (**9A**)

(a) *From* **3a–e** *or* **4a** *and* **8A**. See general glycosylation procedure.

(b) *From* **9B**. To the mixture of **9B** (54 mg, 39 μmol), sodium cyanoborohydride (99 mg, 1.58 mmol), and molecular sieves (4 Å, 50 mg) in dry THF (2 ml) was added a saturated solution of HCl in diethyl ether until the reaction mixture became acidic. After 18 h, solid sodium hydrogen carbonate, diethyl ether (50 ml), and then a saturated solution of sodium hydrogen carbonate (10 ml) were added. The mixture was filtered over glass wool, the organic layer was separated, and the solvent evaporated *in vacuo*. The residue was purified by flash chromatography with dichloromethane:methanol (75:2 by vol) to give **9A** (48 mg, 90%). TLC (dichloromethane:methanol, 15:1 by vol) R_F 0.63. $[\alpha]_D^{20}$-6.6 (*c* 1.0, $CHCl_3$), −4.8 (*c* 0.52, CHCl) [56]. ^{1}H-NMR (400 MHz, $C_6{}^2H_6$); δ 1.58, 1.61, 1.71, 1.89, 2.03 (5 s, 15 H, 5 CH_3CO), 2.14 (dd, *J* = 12.5 Hz, 1 H, 3c-H_a), 2.68 (dd, $J_{3,3}$ = 12.9 Hz, $J_{3,4}$ = 4.6 Hz, 1 H, 3c-H_e), 2.93 (bs, 1 H, 4b-OH), 3.33 (m, 1 H, 5a-H), 3.36 (s, 3 H, OMe), 3.57–3.72 (m, 3 H, 2a-H, 3a-H, 5b-H), 3.78–3.87 (m, 2 H, 6a-H_b, 2b-H), 3.94–4.01 (m, 2 H, 6a-H_a, 6c-H), 4.03 (d, $J_{5,NH}$ = 10.5 Hz, 1 H, NH), 4.12 (dd, 1 H, 4b-H), 4.22 (dd, 1 H, 9c-H), 4.29 (d, J_{gem} = 11.7 Hz, 1 H, 1/2 CH_2Ph), 4.32–4.46 (m, 4 H, 4a-H, 3b-H, 5c-H, 1/2 CH_2Ph), 4.48 (d, $J_{1,2}$ = 7.6 Hz, 1 H, 1a-H), 4.48–4.63 (3 d, 3 H, 3/2 CH_2Ph), 4.69 (dd, $J_{9,9}$ = 12.7 Hz, 1 H, 9c-H_a), 4.77–4.88 (m, 4 H, 4c-H, 3/2 CH_2Ph), 4.91 (d, $J_{1,2}$ = 7.8 Hz, 1 H, 1b-H), 4.92 (d, J_{gem} = 11.7 Hz, 1 H, 1/2 CH_2Ph), 4.95 (d, J_{gem} = 10.7 Hz, 1 H, 1/2 CH_2Ph), 5.02 (d, J_{gem} = 11.5 Hz, 1 H, 1/2 CH_2Ph), 5.29 (d, J_{gem} = 10.7 Hz, 1 H, 1/2 CH_2Ph), 5.44 (dd, $J_{6,7}$ = 2.2 Hz, $J_{7,8}$ = 7.6 Hz, 1 H, 7c-H), 5.79 (ddd, 1 H, 8c-H), 6.96–7.69 (m, 30 H, 6 Ph).

Analytical data: $C_{74}H_{85}NO_{23}$ (1356.50). Calculated: C = 65.52, H = 6.32, N = 1.03; found: C = 65.52, H = 6.41, N = 1.09.

Benzyl O-[*methyl-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*D*-*glycero*-α-*D*-galacto-2-nonulopyranosyl)onate*]-(*2 → 4*)-*2,3,6-tri-*O*-benzyl-β-D-glucopyranoside* (**9B**).

From **3a** and **8b** as described in the general procedure for the glycosylation. TLC (dichloromethane:methanol, 15:1 by vol) R_F 0.63 $[\alpha]_D^{20}$-12.5 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $C_6{}^2H_6$) δ 1.58, 1.61, 1.75, 1.91, 2.14 (5 s, 15 H, 5 CH_3CO), 2.16 (dd, J = 12.7 Hz, 1 H, 3c-H_a), 2.85 (dd, J = 12.7 Hz, $J_{3,4}$ = 4.4 Hz, 1 H, 3c-H_e), 3.30 (s, 3 H, OMe), 3.35 (m, 2 H), 3.69 (m, 2 H, 2a-H), 3.79–3.87 (m, 3 H), 3.95–4.05 (m, 3 H, 6a-H, 6c-H), 4.17–4.35 (m, 5 H, 9c-H_b), 4.41–4.49 (m, 3 H, 1a-H), 4.54 (d, J_{gem} = 10.5 Hz, 1 H, 1/2 CH_2Ph), 4.57 (d, J_{gem} = 12.0 Hz, 1 H, 1/2 CH_2Ph), 4.59–4.68 (m, 4 H), 4.73–4.92 (m, 7 H, 4c-H, 6/2 CH_2Ph), 4.96, 5.01 (2 d, J_{gem} = 11.2 Hz, 2 H, 2/2 CH_2Ph), 5.48 (dd, $J_{6,7}$ = 2.4 Hz, $J_{7,8}$ = 8.5 Hz, 1 H, 7c-H), 5.52 (d, J_{gem} = 11.2 Hz, 1 H, 1/2 CH_2Ph), 5.64 (s, 1 H, CHPh), 5.87 (ddd, 1 H, 8c-H), 7.06–7.80 (m, 30 H, 6 Ph).

Analytical data: $C_{74}H_{83}NO_{23} \cdot 3/4H_2O$ (1367.99). Calculated: C = 64.97, H = 6.23, N = 1.02; found: C = 64.97, H = 6.14, N = 1.00.

O-[*Methyl-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-*α*-D-galacto-2-nonulopyranosyl)onate*]-(*2 → 3*)-O-(*2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl*)-(*1 → 4*)-*2,3,6-tri-*O*-acetyl-α,β-D-glucopyranosyl-acetate* (**10**).

A solution of **9A** (1.0 g, 0.74 mmol) in methanol (90 ml) and acetic acid (6 ml) was hydrogenated in the presence of palladium on carbon. Then the reaction mixture was filtered and the solvent evaporated *in vacuo*. The residual O unprotected trisaccharide was treated with acetic anhydride (10 ml) in pyridine (20 ml). After 8 h the reaction mixture was concentrated *in vacuo* and the residue purified by flash chromatography with toluene:acetone (2:1 by vol) to give **10** (650 mg, 80%). Compound **10** had physical data (R_F, ^{1}H-NMR) which accorded with published values [10, 11, 53–55].

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