The 2-Naphthylmethyl (NAP) Group in Carbohydrate Synthesis: First Total Synthesis of the GlyCAM-1 Oligosaccharide Structures

Jie Xia, James L. Alderfer, Conrad. F. Piskorz, and Khushi L. Matta*[a]

Abstract: Total syntheses of the GlyCAM-1 (glycosylation-dependent cell adhesion molecule-1) oligosaccharide structures: {α-NeuAc-(2→3)-β-Gal-(1→4)-[α-Fuc-(1→3)]-β-(6-*O*-SO_3Na)-GlcNAc-(1→6)}-[α-NeuAc-(2→3)-β-Gal-(1→3)]-α-GalNAc-OMe (**1**) and {α-NeuAc-(2→3)-β-Gal-(1→4)-[α-Fuc-(1→3)]-β-GlcNAc-(1→6)}-[α-NeuAc-(2→3)-β-Gal-(1→3)]-α-GalNAc-OMe (**2**) through a novel sialyl Lewis^x tetrasaccharide donor are described. Employing sequential glycosylation strategy, the starting trisaccharide was regio- and stereoselectively constructed through coupling of a disaccharide imidate with the monosaccharide acceptor phenyl-6-*O*-naphthylmethyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside with TMSOTf as a catalyst without affecting the SPh group. The novel sialyl Lewis^x tetrasaccharide donor **3** was then obtained by α-L-fucosylation of trisaccharide acceptor with the 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucoside donor. The structure of the novel sialyl Lewis^x tetrasaccharide was established by a combination of 2D DQF-COSY and 2D ROESY experiments. Target oligosaccharides **1** and **2** were eventually constructed through heptasaccharide which was obtained by regioselective assembly of advanced sialyl Lewis^x tetrasaccharide donor **3** and a sialylated trisaccharide acceptor in a predictable and controlled manner. Finally, target heptasaccharides **1** and **2** were fully characterized by 2D DQF-COSY, 2D ROESY, HSQC, HMBC experiments and FAB mass spectroscopy.

Keywords: glycosylations · oligosaccharides · protecting groups · total synthesis

Introduction

Glycoproteins and glycolipids are major components of the outer surface of eukaryotic cells and play a vital role in many fundamental biological processes such as, viral, bacterial, and parasitic infections, immune defense, and inflammation.[1] There is tremendous interest in structural studies of the sulfated oligosaccharide chains of O-linked mucin glycoproteins, such as, CF respiratory mucin,[2] colonic tumor associated glycoproteins,[3] and the natural ligands for selectins.[4] Therefore, the chemical synthesis of well defined oligosaccharides still receives much attention.[5] A sulfate group has been reported to be located at the C-6′ position of Gal or C-6 position of GlcNAc in the sialyl Lewis^X moiety O-linked to the C-6 position of GalNAc (Figure 1).

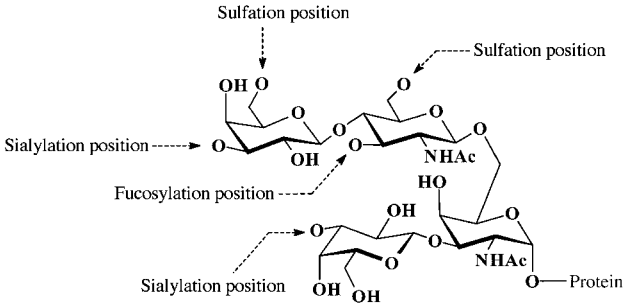

Figure 1. Core structure of GLYCAM-1.

Synthesis of this type of functional oligosaccharide structures requires a special protecting group which should have several features, including i) highly selective removal in the presence of O-benzyl groups, ii) stable in a variety of strong Lewis acid and bases or even in strong acids and bases, iii) and an electron-donor group instead an electron-withdrawing group. These requirements could be provided by introduction of the 2-naphthylmethyl (NAP) group because it is stable in variety of acid and base conditions and can be removed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) with high selectivity in the presence of benzyl groups.[6]

Classic strategies for oligosaccharide assembly are involved in the manipulation of the protecting groups between each glycosylation step. Such a manipulation is a consequence of increased linearity and inefficiency of oligosaccharide assembly. In order to increase assembly efficiency of complex

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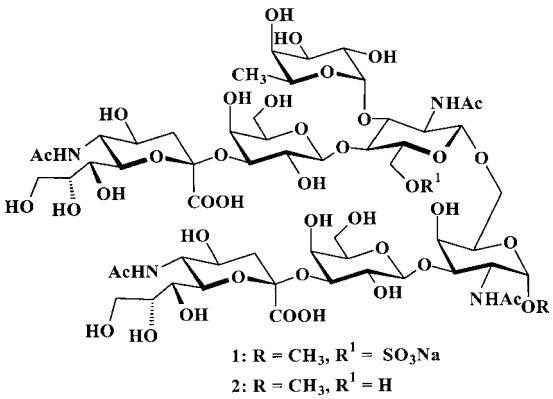
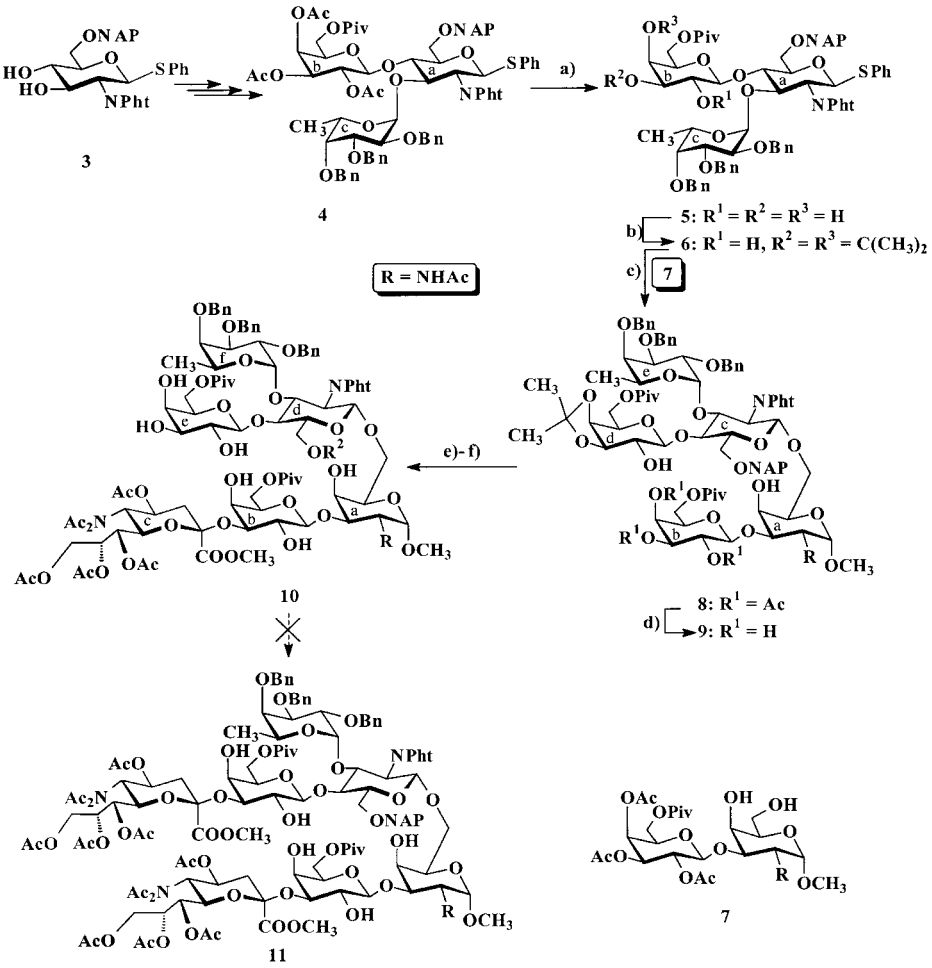
oligosaccharides by avoiding various unnecessary manipulations of each glycosylation step, several strategies of glycosylation have been developed for synthesis of such complex oligosaccharides. First, utilization of highly regio- and stereoselective glycosylation of partially or unprotected acceptors[7] based on differences in reactivity of the hydroxyl groups followed by analysis of structures using modern 2D NMR techniques.[8] Second, use of one-pot sequential glycosylation.[9] Third, employing two-directional glycosylation which exploits both the differences in the reactivities of an anomeric leaving group and the subtle control of nucleophilicities of sugar hydroxyl groups.[10] The major purpose of these strategies is to overcome the traditional, tedious multi-step protection/deprotection schemes and provide an easier route for the synthesis of complex, biologically active oligosaccharide molecules. Herein we utilize these approaches combined with the recently introduced 2-naphthylmethyl (NAP) group to efficiently perform the first total syntheses of highly complex oligosaccharides **1** and **2**, representative of the carbohydrate structures in GlyCAM-1[4, 11] (Scheme 1).



Scheme 1. Target structure of sialylated and sulfated oligosaccharides.



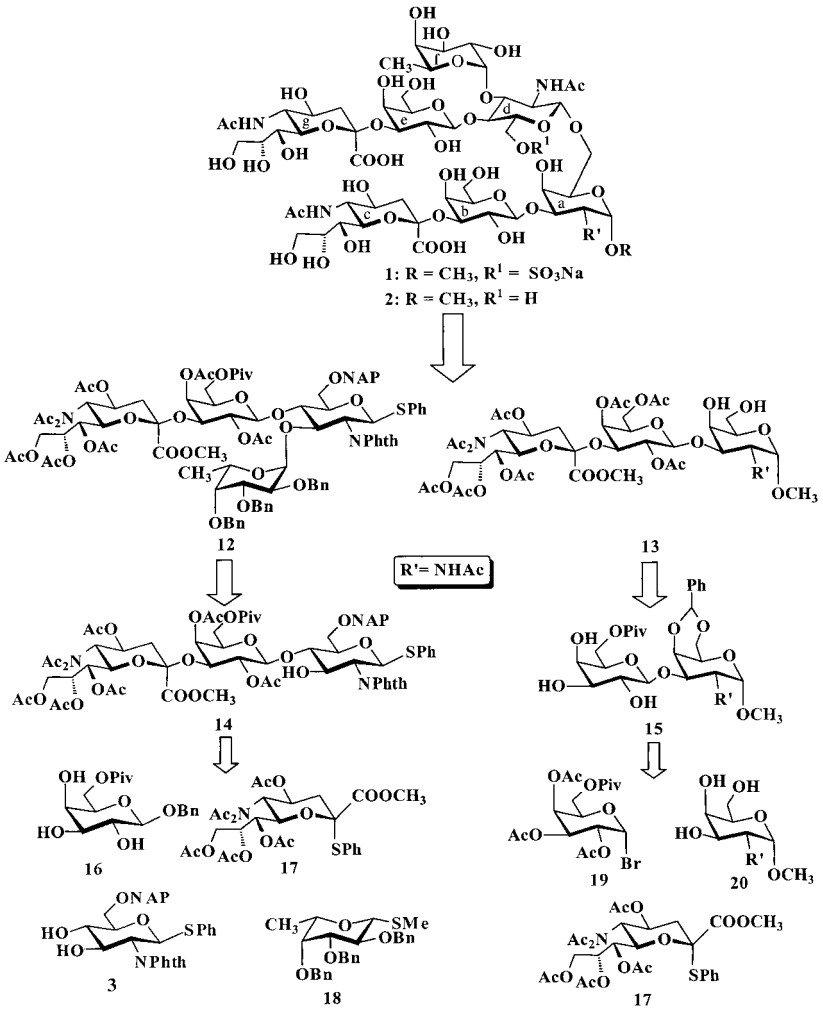
Scheme 2. The first pathway attempted to disialylated heptasaccharide **11**.

Results and Discussion

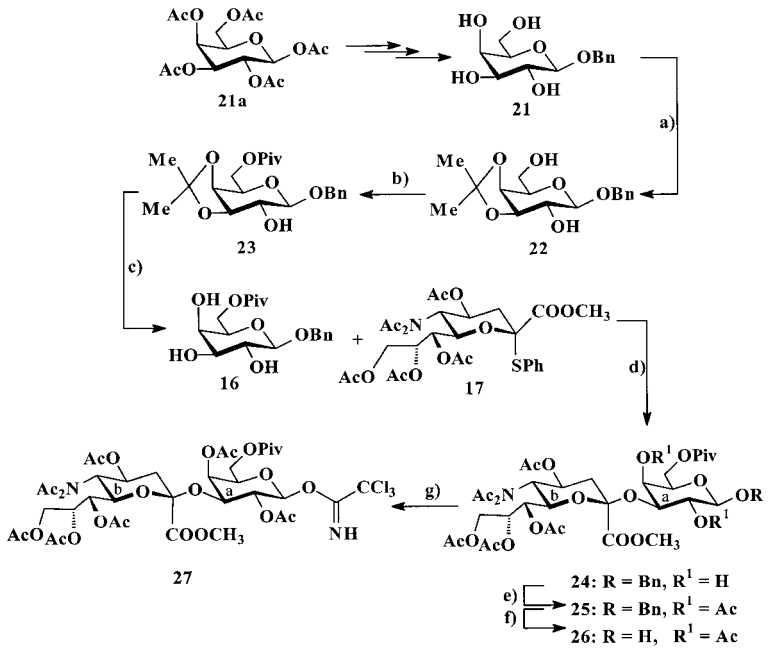
The GlyCAM-1 carbohydrate structures **1** and **2** are challenging synthetic targets because they require incorporating two α-(2 → 3)-sialic acid residues, recognized as one of the most difficult problems in synthetic carbohydrate chemistry. Sequential sialylation of the bulky acceptors **9** and **10** was attempted, but produced unsatisfactory amounts of heptasaccharide **11** due to a very poor yield for the sialylation of acceptor **10** (Scheme 2). The disappointing result led to a revised synthetic route which proved successful in later manipulations.

The retrosynthetic analyses of two heptasaccharide derivatives **1** and **2** are outlined in Scheme 3. This scheme relies on an approach which involves glycosylation at the 6-position of trisaccharide acceptor **13** with a new sialyl Lewis^x donor **12**. In turn, this donor **12** can be constructed by a sequential glycosylation route, starting from monosaccharide building blocks **3**, **16**, **17**, and **18**. The use of three different leaving groups (imidate, SMe, and SPh) which exhibit different reactivities in different coupling reactions facilitate the direct glycosylation by monosaccharide acceptor **3** without requiring additional steps for activation of its reactive anomeric center.[12] The synthetic route commences with synthesis of the tetrasaccharide **12**. Construction of novel intermediate **12** is performed through highly regio- and stereoselective glycosylation steps outlined in Schemes 4 and 5.

Starting from known **21**, compound **22** is obtained in high yield (89%) in a one-pot, two-step procedure. Selective protection of the primary hydroxyl group of **22** is accomplished by treatment with pivaloyl chloride in dry pyridine at 0



Scheme 3. Retrosynthetic analyses of the target oligosaccharides **1** and **2**.



Scheme 4. a) $(CH_3)C(OCH_3)_2$, CSA, RT, 12 h, then, $Et_3N/CH_3OH/H_2O$, reflux, 48 h, 89%; b) Piv-Cl/pyridine, 0 to 25 °C, 24 h, 78%; c) 60% HOAc, 60 to 65 °C, 1.5 h, 90%; d) NIS/TfOH, CH_3CN/CH_2Cl_2 1:1, 3 Å MS, −65 to 45 °C, 4 h, 66%; e) Ac_2O/pyridine 1:1, DMAP, RT, 12 h, 81%; f) Pd/C (10%), H_2, RT, 6 h, 84%; g) CCl_3CN, DBU, CH_2Cl_2, 0 °C, 2 h, 96%.

to 25 °C, giving compound **23** in good yield (78%). Monosaccharide acceptor **16** is obtained in excellent yield (90%) by treatment of its precursor **23** with 60% HOAc at 60 to 65 °C for 1.5 h.

The next reaction is regio- and stereoselective sialylation of acceptor **16**. This type of α-sialylation has been considered to be one of the most difficult types of O-glycosylation to be performed selectively. The difficulty results from the unique structural features of sialic acid: i) it exists solely as 2α-glycoside which is less favored in a stereoelectronic sense than the corresponding 2β-glycoside, and ii) the C-2 carbon, to which sugar residues must be attached in glycosylation reactions, is quaternary and carries an electron-withdrawing carboxylate group. Moreover, the lack of a participating functionality at C-3 complicates the control of the stereoselectivity of glycosylation. Therefore, there are a number of approaches which have been investigated in order to address this problem.[13] The new sialic donor **17**, which was prepared according to protocol reported by Boons and coworker,[14c] is a synthetic sialyl donor with defined configuration (determined by X-ray analysis). Because the C-3 position lacks participating functionality, it is important to use a defined configuration of donor **17** to avoid the complication of control of the stereoselectivity[15] of glycosylation. Additionally, sialyl donor **17** affords several advantages: i) it is relative inexpensive to prepare, ii) it is quite reactive during glycosylation, iii) a β-configuration of compound **17** is easily obtained by crystallization from anhydrous diethyl ether after column chromatography, and iv) the glycal is dramatically reduced by the trivial addition of the N-acetyl group.[14c, 20] It is reasonable that this donor is

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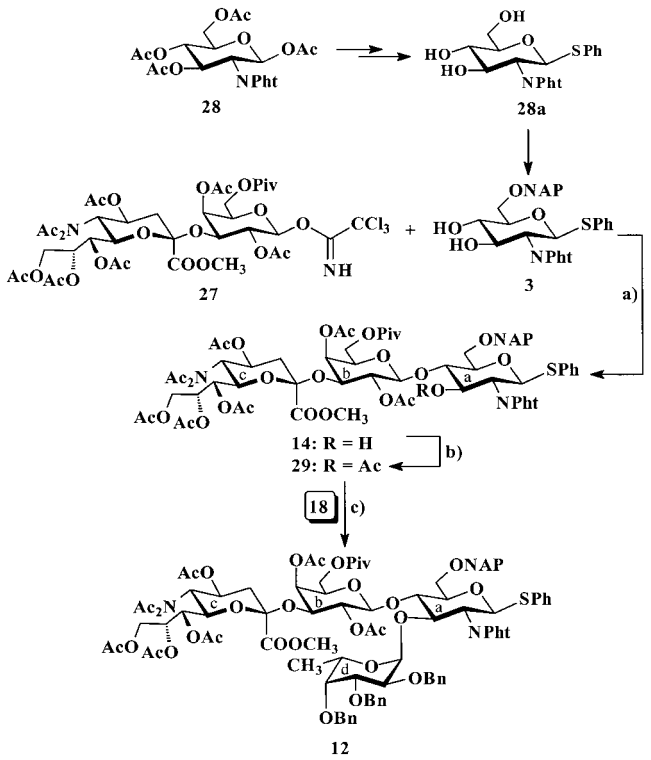


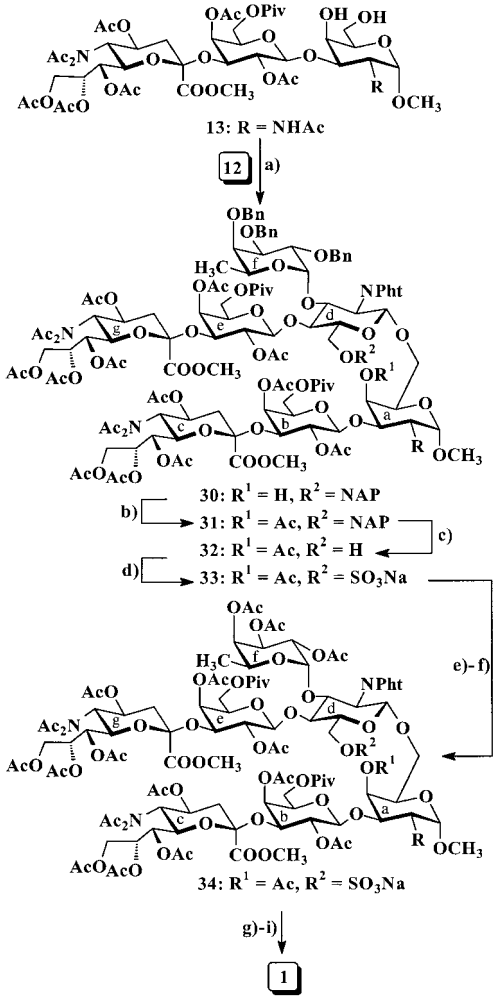
Scheme 5. a) TMSOTf, CH_2Cl_2, 4 Å MS, −40 to −45 °C, N_2, 1.5 h, 87 %; b) Ac_2O/pyridine 1:1, DMAP, RT, 12 h, 88 %; c) **18**, $CuBr_2/nBu_4NBr$, $ClCH_2CH_2Cl$/DMF 5:1, 65 h, 92 %.

thechoice. Total regio- and stereoselective sialylation of HO-3 of the galactose residue in acceptor **16** with donor **17** was accomplished because of the higher nucleophilicity of HO-3 compared with HO-2 and HO-4 of the same galactose residue, and employment of a defined configuration of sialyl donor **17**. The acetylation of **24** with Ac_2O/pyridine 1:1 was performed at room temperature in the presence of a catalytic amount of DMAP, providing the disaccharide **25** (see Experimental Section, Figure 2).

The (2→3)-linkage of **25** is deduced from a weak NOE cross peak between H-3 of the galactose residue and H-3a of the sialic acid residue,[16] and further confirmed by observation of a cross peak between H^a-3 and C^b-2 in HMBC spectrum. The α-configuration of the glycoside of **25** is assigned according to literature methods,[17] and further confirmed by observation of a strong cross peak between H^b-3a and C^b-1 in HMBC spectrum of **25** because the α-sialoside has a larger heteronuclear coupling constant[17b] ($^3J_{C\text{-}1,H\text{-}3a}$) than the β-sialoside.

The disaccharide imidate **27** is obtained by the standard procedure from **26** in good yield in two steps (Scheme 4). As illustrated in Scheme 5, the donor **27** and acceptor **3** are designed to take advantage of the differences in the reactivity of their leaving groups. Successful regioselective glycosylation of the 4-hydroxyl group of diol **3** with the disaccharide imidate **27** is achieved by the Schmidt glycosylation procedure,[18] using TMSOTf as a catalyst without affecting the SPh group of **3**; this in turn affords the trisaccharide **14** in excellent yield (87 %). A strong NOE cross peak between H^b-1 and H^a-4 of trisaccharide **14** is indicative of a (1→4) linkage of the glycoside. β-Configuration of the glycoside is confirmed by the presentation of a larger coupling constant of $^3J_{1b,2b}$ = 7.9 Hz. The trisaccharide acceptor **14** was fucosylated with methyl 2,3,4-tri-*O*-benzyl-thio-β-L-fucoside (**18**) catalyzed by $CuBr_2/nBu_4NBr$[19] to afford the desired sialyl Lewis^x donor **12** in almost quantitative yield (92 %). The structure of tetrasaccharide **12** is established by a combination of 2D DQF-COSY and 2D ROESY experiments. α-Fucopyranoside of tetrasaccharide **12** is indicated by a small coupling constant of $^3J_{1,2}$ = 3.1 Hz), which is characteristic feature for 1,2-*cis* fucopyranoside (see Experimental Section, Figures 3–4).

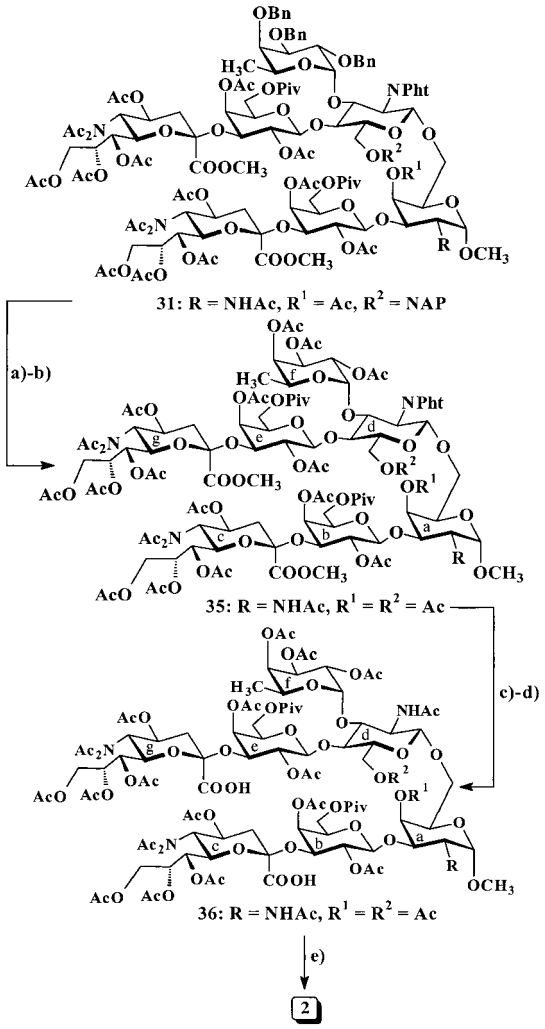
Target oligosaccharide **1** is constructed as outlined in Scheme 6. Due to the much higher reactivity of the primary hydroxyl group in acceptor **13**, glycosylation of HO-6 of **13**[20] with donor **12** is performed[21] with total regioselectivity under controlled reaction conditions, resulting in the formation of one glycosylation product. Thus, heptasaccharide **30** was obtained in good yield (67 %). The β-(1→6)-linkage of oligosaccharide **30** is confirmed through observation of NOEs



Scheme 6. a) NIS/TfOH, −65 to −60 °C, 1.5 h, 67 %; b) Ac_2O/pyridine 1:1, RT, 12 h, 80 %; c) DDQ, CH_2Cl_2/CH_3OH 4:1:H_2O:trace, 16 h, 73 %; d) SO_3/pyridine, pyridine, 0 to 5 °C, 9 h, 78 %; e) Pd/C 10 %, H_2, RT, 6 h; f) Ac_2O/pyridine 1:1, RT, DMAP, RT, 12 h, 85 % for e)–f); g) LiI, pyridine, 120 to 125 °C, 8–10 h; h) CH_3OH/NH_2-$NH_2 \cdot H_2O$ 5:1, 80 to 85 °C, 4–5 h, then, Ac_2O/pyridine 1:1, RT, 12 h; i) 1M, CH_3ONa/CH_3OH, H_2O/CH_3OH, RT, 12 h, 25 %.

cross peaks between H-6a, H-6b of *N*-acetylgalactosamine residue and H-1 of *N*-phthalimido protected glucosamine residue of oligosaccharide **30**. Therefore, oligosaccharide **30** is regio- and stereoselectively constructed in a predictable and controlled manner. Compound **31** is treated with Ac_2O/pyridine 1:1 and catalytic amounts of DMAP to give acetylated **31** in good yield (80%). Removal of the 2-naphthylmethyl (NAP) protecting group from **31** is affected by treatment with DDQ. Noteworthy the removal of the NAP protecting group from **31** warrants carefully controlled conditions because of acidic liability of tribenzyl fucose residue, which was reported by Kunz and co-workers.[22] A larger excess of DDQ and longer reaction time will lead to the loss of tribenzyl fucose residue. Conversion of **32** into **33** is obtained by treatment of **32** in pyridine with $SO_3 \cdot$pyridine. Compound **33** is subsequently converted into **34** in two steps: a) removal of the methyl group from the carboxyl group with lithium iodide in refluxing pyridine under N_2 atmosphere and b) removal of the *N*-phthalimido group with methanol/NH_2-$NH_2 \cdot H_2O$ 5:1, followed by Ac_2O/pyridine 1:1 treatment in the presence of catalytic amounts of DMAP. Finally, O-deacetylation of compound **34** with 1M sodium methoxide in methanol/water solution at room temperature give **1**. The structure and purity of **1** (see Figure 5) are established by two dimensional $^1H-^1H$ homonuclear correlations (DQF-COSY and ROESY), $^{13}C-^1H$ heteronuclear correlations (HSQC, HMBC) experiments and FAB mass spectroscopy.

The final route to target oligosaccharide **2** is outlined in Scheme 7. Compound **31** was treated with Pd/C (10%) in a mixture of dichloromethane/methanol 1.5:1 under hydrogen atmosphere, which results in the removal of the benzyl and 2-naphthylmethyl (NAP) protecting groups. Compound was then acetylated with Ac_2O/pyridine 1:1 in the presence of catalytic amounts of DMAP at room temperature for overnight to give compound **35** in 94% yield in two steps. A similar procedure was used for deprotection of **35**, to obtain target oligosaccharide **2** (as described for **1**). Thus, removal of the methyl group, removal of the *N*-phthalimido group, acetylation, and O-de-acetylation produced target oligosaccharide **2** in 33% yield in three steps. The structure and purity of **2** was established by two dimensional $^1H-^1H$ homonuclear correlation (DQF-COSY and ROESY), ^{13}C NMR and FAB mass spectroscopy.



Scheme 7. a) Pd/C (10%), H_2, RT, 6 h; b) Ac_2O/pyridine 1:1, RT, 12 h, 94% in two steps; c) LiI, pyridine, 120 to 125 °C, 8–10 h; d) NH_2-$NH_2 \cdot H_2O$/MeOH 1:5, 80 to 85 °C, 4–5 h; then Ac_2O/pyridine 1:1, DMAP, RT, 12 h; e) 1M CH_3ONa/CH_3OH, H_2O/CH_3OH, RT, 12 h, 33%.

Conclusion

In summary, we describe a concise and efficient pathway for total synthesis of the GlyCAM-1 oligosaccharides **1**–**2** through a novel sialyl Lewis^x donor **12** which was efficiently constructed in only nine steps from monosaccharide building block **3** and sialyl donors **12**, **27**, and **29**. These sialyl donors will be very useful for synthesis of oligosaccharides[23] containing α-Neu5Ac-(2→3)-β-Gal-(1→4)-GlcNAc fragment. Our strategy is based on the newly introduced 2-naphthylmethyl (NAP) group which can be easily removed by our methodology.

Experimental Section

General procedures: TLC was conducted on glass plates, precoated with 0.25 mm layer of silica gel 60 F-254 (Analtech GHLF uniplates); the components were located either by exposure to UV light or by spraying with a solution of 10% H_2SO_4, 0.2% *p*-anisaldehyde in ethanol solution. Solutions were concentrated under reduced pressure. The silica gel used for column chromatography was Baker Analyzed (60–200 mesh). Optical rotations were measured at 25 °C with Perkin–Elmer 241 polarimeter. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^1H NMR spectra were recorded at 303 K with either a Bruker AM-400 (400 MHz) or AMX-600 (600 MHz) spectrometer. The values of δ (ppm) are given relative to the signal ($\delta = 0$) for internal Me_4Si for solutions in $CDCl_3$, CD_2Cl_2, CD_3OD. ^{13}C NMR spectra were recorded at 303 K with a Bruker AM-400 (100.6 MHz) spectrometer using the signals for $CDCl_3$ ($\delta = 77.0$), CD_2Cl_2 ($\delta = 54.15$), CD_3OD ($\delta = 49.15$), [D_6]acetone ($\delta = 206.0$ or 29.8) as references. First-order chemical shifts and coupling constants (J/ Hz) were obtained from one-dimensional spectra and assignments of protons resonance were based on 2D DQF $^1H-^1H$ COSY, 2D ROESY. Two-dimensional double-quantum filtered phase sensitive $^1H-^1H$ correlated spectra (DQF $^1H-^1H$ COSY), rotating-frame nuclear overhauser enhancement spectroscopy (ROESY) (mixing time $\tau_m = 400$ ms) were recorded at 303 K using a Bruker AM-400 (400 MHz) spectrometer and a Bruker AMX-600 (600 MHz) spectrometer. Heteronuclear single quantum correlation

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(HSQC)[24] and heteronuclear multiple bond correlation (HMBC)[25] experiments were obtained on the AMX-600 spectrometer. All samples submitted for elemental analyses were dried under vacuum over P_2O_5 at room temperature. Elemental analyses were carried out by Robertson Laboratory, Madison, New Jersey. *p*-Toluenesulfonic acid monohydrate (*p*-TsOH · H_2O) was treated by co-evaporated with dry acetonitrile for three times at 80 °C. Methylene chloride, acetonitrile, methanol, benzene, DMF were kept dry over 4 Å MS, pyridine was redistilled over potassium hydroxide; nitromethane was freshly distilled over P_2O_5.

Phenyl (6-*O*-pivaloyl-2,3,4-tri-*O*-acetyl-*β*-D-galactopyranosyl)-(1 → 4)-(2,3,4-tri-*O*-benzyl-*α*-L-fucopyranosyl)-2-deoxy-6-*O*-naphthylmethyl-2-phthalimido-1-thio-*β*-D-glucopyranoside (4):[26] ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.93 – 7.87 (m, 4H; ArH), 7.70 – 7.60 (m, 3H; ArH), 7.56 – 7.44 (m, 4H; ArH), 7.40 – 7.36 (m, 3H; ArH), 7.28 – 7.16 (m, 14H; ArH), 6.98 – 6.92 (m, 3H; ArH), 5.48 (d, J = 7.8 Hz, 1H; H^a-1), 5.21 (d, J = 2.8 Hz, 1H; H^c-4), 5.05 (dd, 1H; H^b-2), 4.95 (d, J_{gem} = 11.6 Hz, 1H; OCHAr, ABq), 4.87 (dd, J = 3.6, 10.4 Hz, 1H; H^b-3), 4.82 – 4.80 (m, $J_{1,2}$ = 3.3 Hz, 2H; OCHAr, H^c-1), 4.79 (d, $J_{1,2}$ = 7.6 Hz, 1H; H^b-1), 4.74 – 4.70 (m, 2H; H^a-3, OCHAr, ABq), 4.68 – 4.60 (m, 2H; H^c-5, J_{gem} = 11.8 Hz, OCHAr, ABq), 4.36 (t, J = 10.4 Hz, 1H; H^a-2), 4.26 (dd, 4H; 2OCH_2Ar), 4.18 (t, J = 9.2 Hz, 1H; H^a-4), 4.07 (dd, 1H; H^b-6b), 4.00 – 3.84 (m, 4H; H^b-6a, H^a-6b, H^a-6a, H^c-3), 3.80 (dd, 1H; H^c-2), 3.76 – 3.60 (m, 3H; H^c-4, H^a-5, H^b-5), 1.94 (s, 3H; Ac), 1.92 (s, 6H; 2Ac), 1.20 (d, J = 6.4 Hz, 3H; CH^c_3), 1.16 (s, 9H; *t*Bu); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 170.09 (C=O), 169.94 (C=O), 168.89 (C=O), 138.84, 138.35, 135.49, 134.42, 133.43, 133.25, 132.65, 131.89, 129.04, 128.70, 128.38, 128.34, 128.27, 128.19, 128.15, 128.09, 128.03, 127.99, 127.61, 127.42, 127.34, 127.17, 126.80, 126.49, 126.21, 126.01, 123.84, 99.77, 97.85, 84.53, 79.95, 79.77, 75.29, 74.75, 74.40, 73.88, 73.83, 73.19, 72.52, 71.20, 70.60, 69.20, 68.05, 66.90, 66.74, 60.30, 55.76, 20.80 (3Ac), 20.67 (Ac), 16.89 (CH_3); elemental analysis calcd (%) for $C_{75}H_{79}O_{19}NS \cdot H_2O$: C 66.80, H 5.90, N 1.04, S 2.38; found C 66.33, H 6.02, N 0.70, S 2.24.

Phenyl (6-*O*-pivaloyl-*β*-D-galactopyranosyl)-(1 → 4)-(2,3,4-tri-*O*-benzyl-*α*-L-fucopyranosyl)-2-deoxy-6-*O*-naphthylmethyl-2-phthalimido-1-thio-*β*-D-glucopyranoside (5): To a cold (−10 to −5 °C) solution of compound **4** (2.28 g, 1.71 mmol) in a mixture of dichloromethane/methanol (40 mL, 1:1) was added dropwise 1M sodium methanoxide/methanol solution until the pH of the solution was adjusted to 10 and stirred at the same temperature for 45 min. The reaction mixture was neutralized with acetic acid and concentrated. The crude product was applied to a column of silica gel and eluted with dichloromethane/methanol 20:1 to give pure compound **5** (1.65 g, 80%) as an amorphous solid. $[\alpha]_D^{25}$ = + 10.2 (c = 0.54 in chloroform); ^{1}H NMR (CD_3OD, 400 MHz): δ = 7.89 – 7.84 (m, 6H; ArH), 7.56 – 7.54 (m, 1H; ArH), 7.50 – 7.46 (m, 2H; ArH), 7.39 – 7.37 (m, 2H; ArH), 7.19 – 7.10 (m, 18H; ArH), 6.93 – 6.92 (m, 2H; ArH), 5.50 (d, $J_{1,2}$ = 10.8 Hz, 1H; H^a-1), 4.87 (d, J_{gem} = 11.6 Hz, 1H; OCHAr), 4.77 (d, J = 6.8 Hz, 1H), 4.75 – 4.72 (m, 2H), 4.68 – 4.62 (m, 2H), 4.53 (d, J_{gem} = 11.2, 1H; OCHAr), 4.49 – 4.44 (m, 2H), 4.34 (t, J = 10.8 Hz, 1H), 4.26 – 4.10 (m, 7H), 3.98 – 3.93 (m, 2H), 3.79 – 3.74 (m, 2H), 3.65 – 3.60 (m, 2H), 3.53 – 3.49 (t, J = 8.4 Hz, 1H), 3.45 – 3.43 (m, 1H), 3.28 – 3.25 (m, 1H), 1.16 (s, 9H; *t*Bu), 1.13 (d, J = 6.4 Hz, 3H; CH_3); ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 170.50 (C=O), 135.88, 133.64, 130.14, 129.39, 129.22, 129.19, 129.13, 128.89, 128.81, 128.55, 128.50, 128.33, 128.26, 127.67, 127.33, 127.10, 103.63, 99.85, 85.84, 81.22, 80.66, 79.80, 76.56, 76.38, 76.24, 76.01, 75.06, 74.53, 73.97, 73.79, 73.40, 72.58, 69.80, 69.70, 68.48, 64.71, 57.10, 27.99 (CH_3), 17.11 (CH_3); elemental analysis calcd (%) for $C_{69}H_{73}O_{16}NS$: C 68.81, H 6.11, N 1.16; found C 68.25, H 6.21, N 1.11.

Phenyl (6-*O*-pivaloyl-3,4-di-*O*-isopropylidene-*β*-D-galactopyranosyl)-(1 → 4)-(2,3,4-tri-*O*-benzyl-*α*-L-fucopyranosyl)-2-deoxy-6-*O*-naphthylmethyl-2-phthalimido-1-thio-*β*-D-glucopyranoside (6): A solution of compound **5** (1.16 g, 0.97 mmol), 2,2-dimethoxylpropane (18 mL), and camphor sulfonic acid (CSA, 73 mg) was stirred for 1 h at room temperature. The reaction mixture was neutralized with triethylamine and concentrated. The crude product was applied to a short column of silica gel eluted with dichloromethane/acetone 30:1 to give pure compound **6** (1.02 g, 85%) as an amorphous solid. ^{1}H NMR (CD_3OD, 600 MHz): δ = 7.90 – 7.87 (m, 4H; ArH), 7.68 – 7.60 (m, 3H; ArH), 7.57 – 7.40 (m, 5H; ArH), 7.26 – 7.15 (m, 17H; ArH), 7.02 – 7.00 (m, 2H; ArH), 5.57 (d, $J_{1,2}$ = 10.0 Hz, 1H; H^a-1), 4.93 (d, J_{gem} = 11.6 Hz, 1H; OCH_APh, ABq), 4.78 (d, J_{gem} = 11.0 Hz, 1H; $OCH_A'Ph$, ABq), 4.73 – 4.64 (m, 3H; H^c-1; OCH_BPh, H^a-3), 4.62 (dd, 2H; $OCH_2C_{10}H_7$, ABq), 4.57 (d, J_{gem} = 12.3 Hz, 1H; $OCH_B'Ph$, ABq), 4.46 (t, 1H; H^a-2), 4.41 (d, $J_{1,2}$ = 7.8 Hz, 1H; H^b-1), 4.38 – 4.19 (m, 5H; H^c-5, H^b-6b, H^b-6a, H^a-4, H^c-2), 4.05 (dd, 1H; H^a-6b), 3.98 (dd, 1H; H^a-6a), 3.91 (d, 1H; OCH_B''-Ph, ABq), 3.83 (dd, 1H; H^c-3), 3.80 – 3.70 (m, 5H; H^b-4, H^a-5, H^b-5, H^b-3), 3.47 (d, 1H; H^c-4), 3.33 – 3.31 (m, 1H; H^b-2), 1.35 (s, 3H; CH_3), 1.24 – 1.20 (m, 12H; *t*Bu, CH_3), 1.04 (d, J = 6.7 Hz, 3H; CH^c_3); ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 170.30 (C=O), 140.24, 135.99, 134.23, 130.44, 129.88, 129.70, 129.68, 129.55, 129.51, 129.28, 129.22, 129.11, 129.09, 128.94, 128.81, 128.76, 128.70, 128.61, 128.43, 127.81, 127.59, 125.06, 125.00, 124.96, 108.35, 102.62, 100.91, 85.85, 81.18, 80.97, 79.66, 76.44, 76.38, 76.17, 75.04, 74.86, 74.56, 74.34, 74.08, 72.43, 69.95, 68.98, 64.85, 58.35, 39.77, 29.16, 28.55, 27.06, 16.83 (CH_3); elemental analysis calcd (%) for $C_{72}H_{77}O_{16}NS$: C 69.49, H 6.24, N 1.13, S 2.58; found C 68.75, H 6.35, N 1.13, S 2.61.

Methyl (6-*O*-pivaloyl-2,3,4-tri-*O*-acetyl-*β*-D-galactopyranosyl)-(1 → 3)-[(6-*O*-pivaloyl-3,4-*O*-isopropylidene-*β*-D-galactopyranosyl)-(1 → 4)-[(2,3,4-tri-*O*-benzyl-*α*-L-fucopyranosyl)-(1 → 3)]-2-deoxy-6-*O*-naphthylmethyl-2-phthalimido-*β*-D-glucopyranosyl)-(1 → 6)]-2-acetamido-2-deoxy-*α*-D-galactopyranoside (8): A solution of compound **6** (1.03 g, 0.82 mmol), compound **7**[7] (500 mg, 0.82 mmol), and *N*-iodosuccinimide (NIS, 554 mg, 2.46 mmol) in dry dichloromethane (8 mL) containing 4 Å MS (9 g) was stirred for 2 h at −70 to −65 °C under N_2 atmosphere. Trifluoromethanesulfonic acid (70 μL) in dry dichloromethane (0.5 mL) was added dropwise at −65 to −60 °C and stirred at that temperature for 1 h. The reaction mixture was neutralized with sat. $NaHCO_3$ aqueous solution. The solids were filtered off and the organic layer was washed with sat. $NaHCO_3$ aqueous solution, 10% $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated to a crude residue, which was applied to a column of silica gel and eluted with dichloromethane/acetone 30:1 to give pure compound **8** (450 mg, 32%) as an amorphous solid. ^{1}H NMR (CD_3OD, 600 MHz): δ = 7.88 – 7.84 (m, 4H; ArH), 7.53 – 7.48 (m, 6H; ArH), 7.28 – 7.13 (m, 16H; ArH), 5.34 – 5.32 (m, 2H; ArH), 5.16 – 5.14 (m, 2H), 4.97 – 4.95 (m, 2H), 4.75 (d, J_{gem} = 12.6 Hz, 1H; OCHPh), 4.77 (d, J = 2.8 Hz, 1H), 4.67 – 4.64 (m, 2H), 4.50 – 4.44 (m, 2H), 4.40 – 4.00 (m, 12H), 4.00 – 3.80 (m, 6H), 3.70 – 3.50 (m, 10H), 3.35 (t, 1H), 2.87 (s, 3H; OCH_3), 2.17, 2.04, 1.96, 1.92 (4s, 4 × 3H; 4Ac), 1.34, 1.28 (2s, 2 × 3H; 2CH_3), 1.21, 1.16 (2s, 2 × 9H; 2*t*Bu), 1.02 (d, J = 6.4 Hz, 3H; CH^c_3); ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 178.40 (C=O), 178.20 (C=O), 174.26 (C=O), 170.29 (C=O), 169.75 (C=O), 169.58 (C=O), 139.10, 138.92, 138.50, 134.05, 133.17, 128.50, 128.34, 128.17, 127.92, 127.87, 127.43, 127.33, 127.19, 126.51, 126.46, 126.25, 110.02, 101.85, 100.00, 99.25, 99.15, 98.40, 79.42, 78.99, 78.14, 77.88, 75.58, 75.17, 74.93, 74.87, 74.83, 73.92, 73.74, 73.07, 72.80, 72.64, 70.97, 70.90, 70.76, 68.95, 68.83, 68.76, 67.15, 66.86, 61.20, 56.28, 54.39, 47.87, 27.38 (3CH_3), 27.21 (3CH_3), 23.57 (NAc), 20.87 (Ac), 20.82 (Ac), 20.74 (Ac), 16.90 (CH_3); elemental analysis calcd (%) for $C_{92}H_{111}O_{31}N_2$: C 63.47, H 6.43, N 1.61; found C 63.44, H 6.55, N 1.85.

Benzyl *β*-D-galactopyranoside (21): ^{1}H NMR (CD_3OD, 400 MHz): δ = 7.60 – 7.40 (m, 2H; ArH), 7.40 – 7.20 (m, 3H; ArH), 4.85 (d, J_{gem} = 12.4 Hz, 1H; OCH_APh, ABq), 4.65 (d, J_{gem} = 12.6 Hz, 1H; OCH_BPh, ABq), 4.32 (d, $J_{1,2}$ = 7.8 Hz, 1H; H-1), 3.88 (d, J = 2.8 Hz, 1H; H-4), 3.85 – 3.70 (m, 2H; H-2, H-3), 3.60 (t, 1H; H-5), 3.55 – 3.40 (m, 2H; H-6a, H-6b); ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 144.40, 134.42, 134.38, 133.81, 109.14 (C-1), 81.96, 80.23, 79.79, 76.90, 75.56, 67.77.

Benzyl 3,4-*O*-isopropylidene-*β*-D-galactopyranoside (22): (±)-CSA (210 mg) was added to a solution of benzyl *β*-D-galactopyranoside (**21**) (8.52 g, 31.8 mmol) in 2,2-dimethoxypropane (269 mL) and the solution was stirred overnight at room temperature. The reaction mixture was treated with triethylamine (0.92 mL) and concentrated to a residue, which was then dissolved in a mixture of methanol/water 10:1 (270 mL) and refluxed for 48 h. The reaction mixture was concentrated to a residue, which was applied to a column of silica gel eluted with hexane/ethyl acetate 1:1 to give a pure compound **22** (8.7 g, 89%) as an amorphous solid. R_f = 0.49 (CH_2Cl_2/MeOH 30:1); ^{1}H NMR ([D$_6$]acetone, 400 MHz): δ = 6.85 – 6.60 (m, 5H; ArH), 4.31 (d, J_{gem} = 11.8 Hz, 1H; OCH_APh, ABq), 4.04 (d, J_{gem} = 11.8 Hz, 1H; OCH_BPh, ABq), 3.76 (d, J = 3.7 Hz, 1H; H-4), 3.71 (d, $J_{1,2}$ = 8.2 Hz, 1H; H-1), 3.64 (dd, 1H; H-2), 3.46 (dd, 1H; H-3), 3.32 – 3.12 (m, 2H; H-6a, H-6b), 2.92 – 2.88 (m, 1H; H-5), 0.83, 0.68 (2s, 2 × 3H; 2CH_3); ^{13}C NMR ([D$_6$]acetone, 100.6 MHz): δ = 139.10, 128.96, 128.64, 128.21, 109.88 (ketal carbon), 102.83 (C-1), 80.65, 80.60, 74.85, 74.66, 74.16, 62.40, 28.47 (CH_3), 26.11 (CH_3); elemental analysis calcd (%) for $C_{16}H_{22}O_6$: C 61.93, H 7.15; found C 61.95, H 6.93.

Benzyl 3,4-*O*-isopropylidene-6-*O*-pivaloyl-*β*-D-galactopyranoside (23): Pivaloyl chloride (2.6 mL, 20.69 mmol) was added dropwise to a cold (ice bath) solution of compound **22** (6.10 g, 19.81 mmol) in dry pyridine (65 mL)

was added dropwise and reaction mixture was stirred at 0 to 25 °C for 12 h. The reaction mixture was concentrated to a crude residue, which was applied to a column of silica gel eluted with hexane/ethyl acetate 4:1 to give a pure compound **23** (6.02 g, 77 %) as an amorphous solid. $R_f = 0.71$ (hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.40 - 7.20$ (m, 5H; ArH), 4.92 (d, $J_{gem} = 11.6$ Hz, 1H; OCH_APh, ABq), 4.60 (d, $J_{gem} = 11.6$ Hz, 1H; OCH_BPh, ABq), 4.38 (dd, 1H; H-2), 4.24 (d, $J_{1,2} = 8.4$ Hz, 1H; H-1), 4.12 (dd, 1H), 4.06 (dd, 1H), 3.99 (ddd, 1H), 3.63 (ddd, 1H), 1.57 (s, 3H; CH_3), 1.33 (s, 3H; CH_3), 1.24 (s, 9H; *t*Bu); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 178.85$ (C=O), 136.86, 128.77, 128.53, 128.37, 110.62 (ketal carbon), 100.94 (C-1), 78.96, 73.80, 73.61, 71.32, 70.70, 63.38, 39.00, 28.27 (CH_3), 27.37 (3CH_3), 26.46 (CH_3); elemental analysis calcd (%) for $C_{21}H_{30}O_7$: C 63.94, H 7.67; found C 64.08, H 7.56.

Benzyl 6-*O*-pivaloyl-*β*-D-galactopyranoside (16): Compound **23** (7.0 g, 7.86 mmol) was dissolved in 60 % aqueous acetic acid and stirred at 60 to 65 °C for 1.5 h. The solution was then concentrated under reduced pressure. The crude residue was applied to a short column of silica gel and eluted with hexane/ethyl acetate 1:1 to give a pure compound **16** (5.64 g, 90 %) as an amorphous solid. $R_f = 0.13$ (hexane/EtOAc 1:1); ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 7.41 - 7.39$ (m, 2H; ArH), 7.34 – 7.26 (m, 3H; ArH), 4.87 (d, $J_{gem} = 11.9$ Hz, 1H; OCH_APh, ABq), 4.65 (d, $J_{gem} = 11.5$ Hz, 1H; OCH_BPh, ABq), 4.34 (dd, 1H; H-6b), 4.31 (d, $J_{1,2} = 7.3$ Hz, 1H; H-1), 4.22 (dd, $J = 4.8$, 10.7 Hz, 1H; H-6a), 3.81 (d, $J = 3.1$ Hz, 1H; H-4), 3.72 (dd, 1H), 3.59 (dd, 1H), 3.48 (dd, 1H), 1.22 (s, 9H; *t*Bu); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta =$ 184.90 (C=O), 144.10, 129.43, 129.33, 128.87, 103.89 (C-1), 74.91, 74.17, 72.56, 71.84, 70.43, 64.92, 32.69, 27.70 (CH_3); elemental analysis calcd (%) for $C_{18}H_{26}O_7$: C 61.00, H 7.41; found C 60.99, H 7.41.

Benzyl [methyl (*N*-acetyl-5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-*α*-D-*galacto*-non-*α*-ulopyranosy)onate]-(2 → 3)-6-*O*-pivaloyl-2,4-di-*O*-acetyl-*β*-D-galactopyranoside (25): A solution of compound **17** (4.65 g, 7.44 mmol), compound **16** (2.38 g, 6.76 mmol) and *N*-iodosuccinimide (NIS, 5.0 g, 22.2 mmol) in dry dichloromethane/acetonitrile 1:1 (132 mL) containing 3 Å MS (15 g) was stirred at −65 to −60 °C for 2 h under N_2 atmosphere. Trifluoromethanesulfonic acid (TfOH) (645 μL) in dry acetonitrile (2 mL) was added dropwise and stirred at −65 to −40 °C for 2 h. Additional portion of compound **17** (2.0 g) was added again and the stirring was continued at the same temperature for total 4 h. The mixture was neutralized with sodium bicarbonate solution. The solids were filtered off and the organic layer was washed with saturated sodium bicarbonate solution, 10 % $Na_2S_2O_3$, water, dried (Na_2SO_4) and concentrated to a crude residue. The residue was then applied to column of silica gel and eluted with dichloromethane/methanol 50:1 to give a pure compound **24** (66 %) as an amorphous solid. The compound **24** (2.5 g, 2.88 mmol) was then treated with Ac_2O/pyridine 1:1 in the presence of catalytic amounts of DMAP overnight at room temperature. The mixture was concentrated to a crude residue, which was passed through a column of silica gel and eluted with dichloromethane/methanol 30:1 to give a pure compound **25** (2.22 g, 81 %) as an amorphous solid. $R_f = 0.67$ (CH_2Cl_2/CH_3OH 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.40 - 7.20$ (m, 5H; ArH), 5.60 – 5.52 (m, 1H; H^b-4), 5.46 – 5.45 (m, 1H; H^b-8), 5.17 (dd, $J = 8.7$, 8.5 Hz, 1H; H^b-7), 5.11 – 5.06 (m, 2H; H^a-2, H^a-4), 4.93 – 4.90 (d, $J_{gem} = 12.2$ Hz, 1H; OCH_APh, ABq), 4.73 (d, $J_{1,2} = 7.8$ Hz, 1H; H^a-1), 4.67 – 4.62 (m, 2H; H^a-3, OCH_BPh), 4.59 (dd, $J =$ 10.5, 10.6 Hz, 1H; H^b-6), 4.32 – 4.24 (m, 2H; H^b-5, H^b-9b), 4.19 (dd, 1H; H^a-6b), 4.04 – 3.97 (m, 2H; H^a-6a, H^b-9a), 3.92 – 3.84 (m, 4H; H^a-5, $COOCH_3$), 2.67 (dd, $J = 5.5$, 12.7 Hz, 1H; H^b-3e), 2.35, 2.29 (2s, 2 × 3H; 2NAc), 2.17, 2.15, 2.09, 2.04, 1.99, 1.94 (6s, 6 × 3H; 6Ac), 1.61 (t, $J = 12.4$ Hz, 1H; H^b-3a), 1.21 (s, 9H; *t*Bu); ^{13}C NMR ($CDCl_3$, 100.6 MHz) $\delta = 177.79$ (C=O), 174.23 (C=O), 173.74 (C=O), 170.64 (C=O), 170.60 (C=O), 170.34 (C=O), 168.80 (C=O), 168.10 (C=O), 137.63, 128.44, 127.80, 127.71, 100.63 (C^a-1), 96.84 (C^b-2), 71.84, 71.26, 70.51, 70.33, 69.58, 67.91, 67.53, 67.24 (2C), 62.32, 61.00, 56.20, 53.10, 38.60, 28.22, 27.24, 26.83, 21.56 (Ac), 21.16 (Ac), 21.08 (Ac), 20.86 (Ac); elemental analysis calcd (%) for $C_{44}H_{59}O_{22}N$: C 55.40, H 6.23, N 1.47; found C 55.40, H 6.20, N 1.32.

[Methyl (*N*-acetyl-5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*glycero*-*α*-D-*galacto*-2-nonulopyranosyl)onate]-(2 → 3)-6-*O*-pivaloyl-2,4-di-*O*-acetyl-*β*-D-galactopyranosyl trichloroacetimidate (27): A solution of compound **25** (1.59 g, 1.67 mmol), Pd/C (10 %) (1.59 g) in a mixture of dichloromethane/methanol 4:1 (20 mL) was stirred for 24 h under H_2 atmosphere at room temperature. The solids were filtered off and the solution was concentrated to a residue, which was applied to a short column of silica gel eluted with dichloromethane/methanol 40:1 to give a pure compound **26** (1.29 g). To a cold (ice bath) solution of compound **26** (447 mg, 0.52 mmol) and trichloroacetonitrile (600 μL) in dry dichloromethane (8 mL) was added dropwise DBU (16 μL) and stirred for 2 h at the same temperature. The mixture was concentrated to a crude residue. The crude residue was passed through a short column of silica gel and eluted with hexane/ethyl acetate 1:1 to give a pure compound **27** (500 mg, 96 %) as amorphous solid. $R_f = 0.26$ (hexane/ethyl acetate 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.64$ (s, 1H; $NHCCCl_3$), 5.90 (d, $J_{1,2} = 7.8$ Hz, 1H; H^a-1, *β*-form), 5.60 – 5.40 (m, 2H; H^b-4, H^b-8), 5.25 (dd, 1H; H^a-2), 5.15 – 5.00 (m, 2H; H^b-7, H^a-4), 4.75 (dd, 1H; H^a-3), 4.55 (dd, 1H; H^b-6), 4.35 – 4.20 (m, 2H; H^b-5, H^b-9b), 4.20 – 4.00 (m, 3H; H^a-6b, H^a-5, H^a-6a), 3.95 (dd, 1H; H^b-9a), 3.88 (s, 3H; $COOCH_3$), 2.65 (dd, $J = 4.4$, 12.6 Hz, 1H; H^b-3e), 2.33, 2.25 (s, 3H; Ac), 2.15 (s, 6H; 2Ac), 2.08 (s, 3H; Ac), 2.00 (s, 6H; 2Ac), 1.95 (s, 3H; Ac), 1.81 (t, $J_{gem} = 12.4$ Hz, 1H; H^b-3a), 1.15 (s, 9H; *t*Bu); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 174.24$ (C=O), 173.82 (C=O), 170.76 (C=O), 170.34 (C=O), 170.13 (C=O), 170.02 (C=O), 169.57 (C=O), 169.10 (C=O), 161.32 (C=O), 96.95 (C^b-2), 96.42 (C^a-1), 71.66, 71.52, 69.72, 69.31, 68.00,

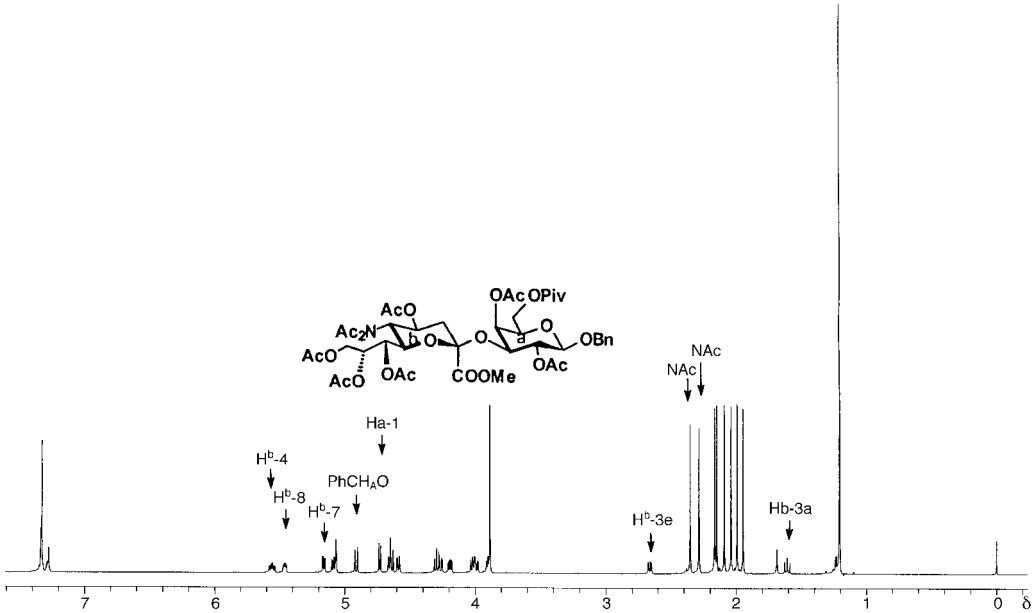

Figure 2. 600 MHz ^{1}H NMR spectrum of disaccharide **25** in $CDCl_3$ at 303.0 K.

0947-6539/01/0702-0362 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 2

67.33, 67.28, 62.62, 60.65, 56.19, 53.21, 38.62, 28.30, 27.26 (3 CH_3), 26.92, 21.67 (Ac), 21.12 (Ac), 21.08 (Ac), 20.93 (Ac); elemental analysis calcd (%) for $C_{39}H_{53}O_{22}N_2Cl_3$: C 46.46, H 5.30; found C 45.59, H 5.01.

Phenyl [methyl (*N*-acetyl-5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*glycero*-α-D-*galacto*-2-nonulopyranosyl)onate]-(2 → 3)-(6-*O*-pivaloyl-2,4-di-*O*-acetyl-β-D-galacto-pyranosyl)-(1 → 4)-2-deoxy-6-*O*-naphthylmethyl-2-phthalimido-1-thio-β-D-glucopyranoside (14): A solution of compound **27** (683 mg, 0.68 mmol), and compound **3** (351 mg, 0.65 mmol) in dry dichloromethane (10–15 mL) containg 4 Å MS (12 g) was stirred for 2 h at −45 to −40 °C under N_2 atmosphere. TMSOTf (37 μL) in dry dichloromethane (0.5 mL) was added dropwise and stirred for 1.5 h at the same temperature. The reaction mixture was then neutralized with $NaHCO_3$. The solids were filtered off and the organic layer was washed with sat. $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated. The crude residue was passed through a short column of silica gel and eluted with dichloromethane/methanol 40:1 to give a pure compound **14** (420 mg, 87%) as an amorphous solid. $R_f = 0.45$ (CH_2Cl_2/MeOH 40:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.89–7.72 (m, 7H; ArH), 7.49–7.43 (m, 4H; ArH), 7.17–7.12 (m, 5H; ArH), 5.65 (d, $J_{1,2}$ = 10.4 Hz, 1H; H^a-1), 5.54–5.49 (m, 2H; H^c-4, H^c-8), 5.12 (dd, J = 2.0, 8.8 Hz, 1H; H^c-7), 5.05–4.98 (m, 2H; H^b-2, H^b-4), 4.81–4.78 (m, 3H; H^b-1, $J_{1,2}$ = 7.9 Hz, $OCH_2C_{10}H_7$), 4.70 (dd, J = 2.8, 9.9 Hz, 1H; H^b-3), 4.57 (dd, J = 2.0, 10.3 Hz, 1H; H^c-6), 4.47 (ddd, 1H; H^a-3), 4.32–4.21 (m, 3H; H^c-5, H^a-2, H^c-9b), 4.05–3.86 (m, 9H; H^b-6b, H^b-5, H^b-6a, H^a-6b, H^a-6a, H^c-9a, $COOCH_3$), 3.82 (dd, 1H; H^a-5), 3.66 (t, 1H; H^a-4), 2.63 (dd, J = 5.5, 12.2 Hz, 1H; H^c-3e), 2.34, 2.28, 2.16, 2.13, 2.05, 1.97, 1.94, 1.93 (8s, 8 × 3H; 8Ac), 1.58 (t, J_{gem} = 12.2 Hz, 1H; H^c-3a), 1.12 (s, 9H; *t*Bu); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 178.00 (C=O), 174.19 (C=O), 173.79 (C=O), 170.66 (C=O), 170.11 (C=O), 170.01 (C=O), 169.74 (C=O), 168.07 (C=O), 136.25, 134.23, 133.54, 129.03, 128.24, 128.13, 128.03, 127.90, 126.34, 126.16, 125.99, 125.87, 123.78, 123.48, 101.83 (C^b-1), 96.95 (C^c-2), 83.47 (C^a-1), 82.58, 78.80, 73.92, 71.57, 71.38, 71.34, 70.32, 69.75, 69.23, 67.91, 67.55, 67.36, 67.21, 62.52, 62.12, 56.10, 55.24, 53.30, 38.61, 28.29 (Ac), 27.01 (CH_3), 26.94 (Ac), 21.62 (Ac), 21.16 (Ac), 21.03 (Ac), 20.95 (Ac), 20.93 (Ac), 20.79 (Ac); elemental analysis calcd (%) for $C_{68}H_{78}O_{27}N_2S \cdot H_2O$: C 58.11, H 5.73, N 1.99, S 2.28; found C 57.79, H 5.60, N 1.94, S 2.26.

Trisaccharide 29: Compound **14** (25 mg, 2.88 mmol) was treated with Ac_2O/pyridine 1:1 (3 mL) in the presence of DMAP (2 mg) and stirred overnight at room temperature. The mixture was concentrated to a crude residue, which was passed through a short column of silica gel and eluted with dichloromethane/*n*-C_3H_7OH 30:1 to give a pure compound **29** in quantitative yield as an amorphous solid. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.90–7.80 (m, 6H; ArH), 7.74–7.70 (m, 3H; ArH), 7.56–7.42 (m, 4H; ArH), 7.22–7.12 (m, 3H; ArH), 5.82–5.78 (t, J = 9.1 Hz, 1H; H^a-3), 5.75 (d, $J_{1,2}$ = 10.8 Hz, 1H; H^a-1), 5.60–5.50 (m, 2H; H^c-4, H^c-8), 5.13 (dd, J = 2.0, 9.3 Hz, 1H; H^c-7), 4.98 (d, J = 2.5 Hz, 1H; H^b-4), 4.93 (dd, 1H; H^b-2), 4.87–4.82 (d, $J_{1,2}$ = 7.4 Hz, 1H; H^b-1), 4.78 (dd, 2H; $OCH_2C_{10}H_7$), 4.63 (dd, J = 3.4, 9.8 Hz, 1H; H^b-3), 4.55 (dd, J = 2.1, 10.3 Hz, 1H; H^c-6), 4.32–4.22 (m, 3H; H^c-5, H^c-9b, H^a-2), 4.16–4.02 (m, 2H; H^b-6b, H^a-4), 3.99–3.78 (m, 9H; H^c-9a, H^a-6b, H^a-6a, $COOCH_3$, H^b-6a, H^b-5, H^a-5), 2.64 (dd, J = 5.3, 10.0 Hz, 1H; H^c-3e), 2.34, 2.27 (2s, 2 × 3H; 2Ac), 2.17 (s, 6H; 2Ac), 2.01, 2.00, 1.99, 1.96, 1.84 (5s, 5 × 3H; 5Ac), 1.56 (t, J = 13.0 Hz, 1H; H^c-3a), 1.16 (s, 9H; *t*Bu); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 178.05 (C=O), 174.29 (C=O), 173.60 (C=O), 170.67 (C=O), 170.60 (C=O), 170.11 (C=O), 170.01 (C=O), 169.84 (C=O), 168.09 (C=O), 136.35, 134.21, 133.40, 129.03, 128.34, 128.13, 128.05, 127.93, 126.35, 126.18, 125.99, 123.88, 123.79, 123.58, 101.85, 96.96, 84.47, 82.58, 78.85, 73.93, 71.50, 71.38, 71.36, 70.33, 69.78, 69.33, 67.80, 67.55, 67.38, 67.23, 62.53, 62.42, 56.11, 55.25, 53.31, 38.81, 28.30 (Ac), 27.05 (Ac), 26.96 (Ac), 21.63 (Ac), 21.18 (Ac), 21.03 (Ac), 20.96 (Ac), 20.94 (Ac), 20.80 (Ac); elemental analysis calcd (%) for $C_{70}H_{80}O_{28}N_2S$: C 58.82, H 5.64, N 1.96, S 2.24; found C 58.55, H 5.50, N 1.96, S 2.24.

Tetrasaccharide 12: A solution of compound **14** (831 mg, 0.60 mmol), methyl 2,3,4,-tri-*O*-benzyl-1-thio-β-L-fucoside **18** (1.11g, 5.6 mmol), and *n*-tetrabutylamonium bromide (774 mg, 2.4 mmol) in dry 1,2-dichloroethane/DMF 5:1 (12 mL) containing 4 Å MS (8 g) were stirred for 2 h at room temperature under N_2 atmosphere. $CuBr_2$ (534 mg, 2.4 mmol) was added and the stirring was continued at the same temperature for 48 h. Additional portion of donor **18** (560 mg) and $CuBr_2$ (267 mg) was added and stirred at room temperature for 65 h total. The solids were filtered off and the organic layer was washed with sat. $NaHCO_3$ solution, water, dried (Na_2SO_4) and concentrated. The crude residue was passed through a column of silica gel and eluted with hexane/ethyl acetate 1:1 to give a pure compound **12** (1.0 g, 92%) as an amorphous solid. $R_f = 0.48$ (hexane/ethyl acetate 1:1); ^{1}H NMR ([D_7]DMF, 600 MHz): δ = 7.84–7.60 (m, 8H; ArH), 7.52–7.36 (m, 6H; ArH), 7.12–7.00 (m, 17H; ArH), 5.57–5.50 (m, 3H; H^c-8, H^c-4, H^a-1, $J_{1,2}$ = 10.9 Hz), 5.19 (dd, J = 2.3, 9.5 Hz, 1H; H^c-7), 5.00 (d, J = 3.8 Hz, 1H; H^b-4), 4.97 (d, $J_{1,2}$ = 9.1 Hz, 1H; H^b-1), 4.91 (dd, 1H; H^b-2), 4.87–4.85 (m, 2H; OCHAr, H^d-1), 4.82–4.65 (m, 5H; OCHAr, H^a-3, OCHAr, H^b-3, H^d-5), 4.62 (dd, 2H; OCH_2Ar, ABq), 4.59–4.47 (m, 3H; H^c-9b, OCHAr, H^a-2), 4.41 (d, J_{gem} = 12.1 Hz, 1H; OCHAr, ABq), 4.33–4.17 (m, 4H; H^c-9a, OCHAr, H^c-6, H^a-4), 4.09 (dd, 1H; H^c-5), 4.04–3.95 (m, 4H; H^a-6b, H^b-6b, H^b-5, H^a-6a), 3.92–3.78 (m, 6H; H^d-3, H^b-6a, $COOCH_3$, H^d-2), 3.80 (dd, 1H; H^d-2), 3.70 (dd, 1H; H^a-5), 3.62 (d, J = 2.8 Hz, 1H; H^d-4), 2.60 (dd, J = 4.9, 12.3 Hz, 1H; H^c-3e), 2.35, 2.28, 2.22, 2.10, 1.98, 1.97, 1.96, 1.79 (8s, 8 × 3H; 8Ac), 1.58 (t, J = 11.0 Hz, 1H; H^c-3a), 1.25 (d, J = 6.7 Hz, 3H; CH^d_3), 1.10 (s, 9H; *t*Bu); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 177.31 (C=O), 174.24 (C=O), 173.81 (C=O), 170.74 (C=O), 170.38 (C=O), 170.13 (C=O), 169.86 (C=O), 169.27 (C=O), 167.99 (C=O), 139.17, 138.88, 138.56, 136.17, 134.31, 133.47, 133.03, 132.51, 128.94, 128.31, 128.25, 128.23, 128.10, 128.04, 127.83, 127.81, 127.51, 127.29, 127.18, 127.03, 126.12, 125.94, 125.81, 125.67, 123.82, 99.79, 97.54, 96.79 (C^c-2), 84.07 (C^a-1), 80.02, 79.89, 77.69, 74.88, 74.79, 74.41, 73.60, 73.05, 73.03, 72.50, 71.90, 70.74, 70.35, 69.49, 68.47, 67.37, 67.30 (2C), 67.00, 66.65, 62.14, 60.12, 56.05, 55.60, 53.05, 38.65 [$C(CH_3)_3$], 38.55 [$(CH_2)^e$], 28.29 (Ac), 27.13 (CH_3), 26.94 (Ac), 21.52 (Ac), 21.22 (Ac), 21.07 (Ac), 20.88 (Ac), 20.75 (Ac), 16.92 (CH^d_3); elemental analysis calcd (%) for $C_{95}H_{106}O_{31}N_2S$: C 63.25, H 5.92, N 1.55, S 1.78; found C 63.17, H 6.40, N 1.40, S 1.70.

Heptsaccharide 30: A solution of compound **12** (420 mg, 0.23 mmol), compound **13** (240 mg, 0.22 mmol), and NIS (156 mg, 0.69 mmol) in dry dichloromethane (10 mL) containing 4 Å MS (10–12 g) was stirred for 2 h at −80 to −75 °C under N_2 atmosphere. TfOH (35 μL) in dry dichloromethane (0.5 mL) was added dropwise at −65 to −60 °C and stirred at the same temperature for 2 h. The reaction mixture was neutralized with sat. $NaHCO_3$ aqueous solution. The solids were filtered off and the organic layer was washed with sat. $NaHCO_3$ aqueous solution, 10% $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated. The crude residue was applied to a column of silica gel and eluted with dichloromethane/methanol 40:1 to give a pure compound **30** (420 mg, 67%) as an amorphous solid. $R_f = 0.48$ (CH_2Cl_2/MeOH 25:1); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.88–7.80 (m, 4H; ArH), 7.66–7.40 (m, 7H; ArH), 7.24–7.00 (m, 15H; ArH), 6.04 (d, J = 8.6 Hz, 1H; NHAc), 5.61–5.54 (m, 4H; H^c-4, H^g-4, H^c-8, H^g-8), 5.18 (dd, J = 1.7, 9.1 Hz, 1H; H^g-7), 5.12–5.08 (m, 2H; H^d-1, H^c-7), 5.08–4.89 (m, 6H; H^e-1, H^e-4, H^b-4, H^b-2, H^e-2, OCH_AAr), 4.86 (d, $J_{1,2}$ = 3.1 Hz, 1H; H^f-1), 4.82–4.75 (m, 3H; $OCH_A'Ar$, H^d-3, OCH_BAr), 4.71–4.54 (m, 9H; H^e-3, H^f-5, $OCH_A''Ar$, $OCH_B''Ar$, H^b-1, H^g-6, $OCH_B'Ar$, H^c-6, H^b-3), 4.45–4.36 (m, 2H; $OCH_A'''Ar$, H^d-2), 4.34–4.19 (m, 8H; H^a-2, H^g-5, H^d-4, H^c-5, $OCH_B'''Ar$, H^a-1, H^g-9b, H^c-9b), 4.10–3.80 (m, 21H; H^c-9a, H^d-6b, H^d-6a, $COOCH_3$, $COOCH_3$, H^a-3, H^f-3, H^a-4, H^g-9a, H^b-6a, H^e-6a, H^b-5, H^e-5, H^f-2), 3.70–3.58 (m, 3H; H^d-5, H^a-5, H^f-4), 2.81 (s, 3H; OCH_3), 2.63–2.59 (m, 2H; H^g-3e, H^c-3e), 2.35, 2.34 (2s, 2 × 3H; 2Ac), 2.28 (s, 6H; 2Ac), 2.24, 2.21, 2.16, 2.06, 2.05, 2.04, 2.03, 2.02, 2.01, 1.97 (10s, 10 × 3H; 10Ac), 1.94 (s, 6H; 2Ac), 1.93, 1.90, 1.78 (3s, 3 × 3H; 3Ac), 1.63–1.57 (m, 2H; H^c-3a, H^g-3a), 1.24 (d, J = 5.8 Hz, 3H; CH^f_3), 1.13, 1.09 (2s, 2 × 9H; 2*t*Bu); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 177.64 (C=O), 177.26 (C=O), 174.23 (C=O), 174.09 (C=O), 173.76 (C=O), 171.43 (C=O), 171.15 (C=O), 170.62 (C=O), 170.23 (C=O), 170.18 (C=O), 170.11(C=O), 170.05 (C=O), 169.87 (C=O), 169.85 (C=O), 169.74 (C=O), 169.71 (C=O), 169.23 (C=O), 167.93 (C=O), 139.23, 138.90, 138.36, 136.23, 133.45, 132.96, 128.26, 128.21, 128.19, 128.03, 127.97, 127.90, 127.77, 127.43, 127.19, 127.11, 126.99, 125.99, 125.72, 125.66, 125.58, 102.57, 99.56, 99.00, 98.09, 97.18, 96.75, 96.61, 79.86, 78.54, 77.65, 75.58, 74.62, 74.32, 72.97, 72.66, 72.47, 72.12, 71.88, 71.44, 70.79, 70.73, 70.60, 70.26, 69.43, 69.34, 69.28, 69.17, 68.60, 68.40, 67.40, 67.34, 67.28 (2C), 67.22, 67.04, 66.99, 66.91, 66.49, 63.10, 62.15, 60.76, 60.12, 56.61, 56.06, 55.80, 54.32, 53.12, 52.98, 48.17, 38.65, 38.63, 38.53, 38.30, 28.25 (2Ac), 27.15 (3 CH_3), 27.06 (3 CH_3), 26.94 (Ac), 26.89 (Ac), 23.26 (Ac), 21.56 (Ac), 21.40 (Ac), 21.20 (Ac), 21.14 (Ac), 21.07 (Ac), 20.86 (Ac), 20.84 (Ac), 20.81 (Ac), 20.72 (Ac), 16.91 (CH_3); elemental analysis calcd (%) for $C_{135}H_{168}O_{58}N_4$: C 58.43, H 6.10, N 2.02; found C 58.47, H 6.18, N 1.97.

Heptasaccharide 31: Compound **30** (310 mg, 0.11 mmol) was treated overnight at room temperature with Ac_2O/pyridine 1:1 (10 mL) in the presence of catalytic amounts of DMAP (5 mg). The reaction mixture was concentrated to a crude residue, which was passed through a short column of silica gel and eluted with dichloromethane/methanol 30:1 to give a pure

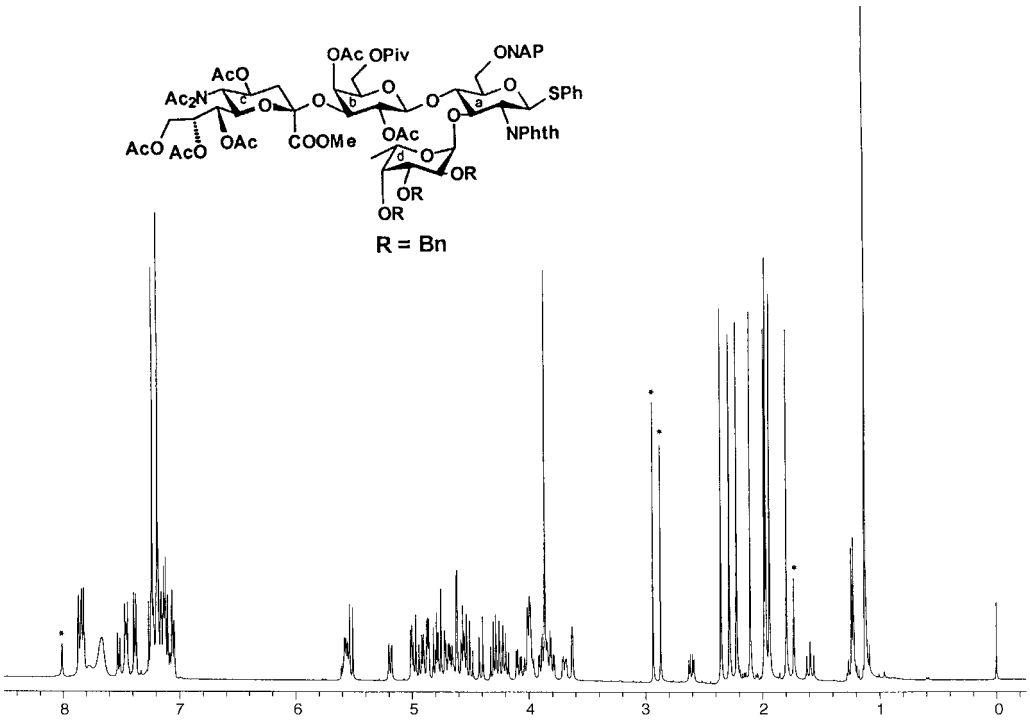

Figure 3. 400 MHz ^{1}H NMR spectrum of compound **12** at 303.0 K ([D_7]DMF and H_2O).

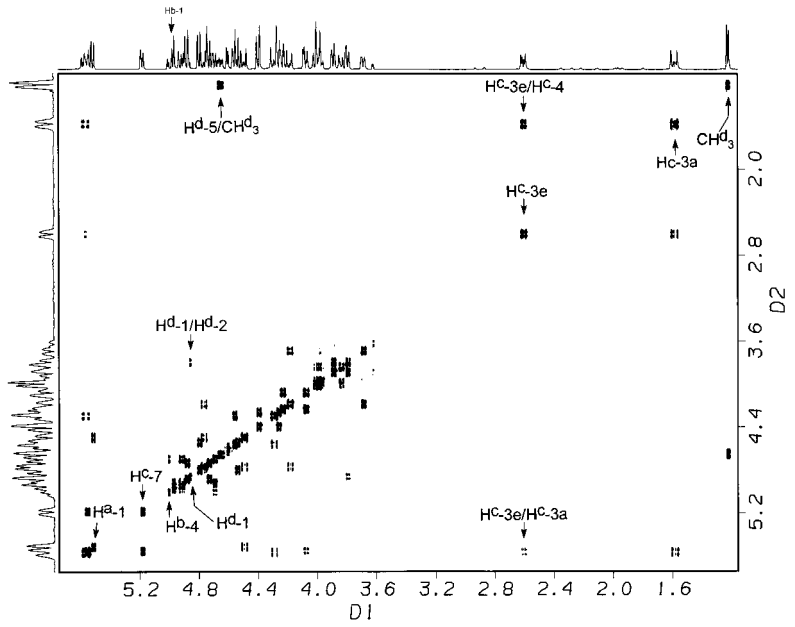

Figure 4. 600 MHz 2D DQF-COSY spectrum of tetrasaccharide **12** at 303.0 K.

compound **31** (248 mg, 80 %) as an amorphous solid. $R_f = 0.49$ (CH_2Cl_2/MeOH 30:1); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.86–7.80 (m, 5H; ArH), 7.68–7.60 (m, 3H; ArH), 7.48–7.40 (m, 4H; ArH), 7.30–7.00 (m, 14H), 5.96 (d, $J = 8.8$ Hz, 1H; NHAc), 5.60–5.47 (m, 4H; H^c-4, H^g-4, H^c-8, H^g-8), 5.24 (d, $J = 3.2$ Hz, 1H; H^a-4), 5.18 (dd, $J = 5.6$, $J_{7,8} = 8.9$ Hz, 1H; H^c-7), 5.12 (dd, $J = 2.8$, $J_{7,8} = 8.9$ Hz, 1H; H^g-7), 5.07 (d, $J_{1,2} = 7.4$ Hz, 1H; H^d-1), 5.03–4.98 (m, 2H; H^e-1, H^e-4), 4.96 (d, $J = 3.3$ Hz, 1H; H^b-4), 4.94–4.84 (m, 4H; H^e-2, OCH_AAr, H^b-2, H^f-1), 4.81–4.75 (m, 2H; $OCH_A'Ar$, OCH_BAr), 4.74–4.46 (m, 10H; H^d-3, H^e-3, H^f-5, $OCH_A''Ar$, $OCH_B''Ar$, H^b-1, H^c-6, H^g-6, $OCH_B'Ar$, H^b-3), 4.42–4.06 (m, 10H; $OCH_A'''Ar$, H^d-2, H^c-5, H^g-5, H^a-2, H^a-1, H^d-4, $OCH_B'''Ar$, H^c-9b, H^g-9b), 4.05–3.72 (m, 21H; H^g-9a, H^b-6b, H^d-6b, H^d-6a, H^e-6b, H^e-6a, H^b-6a, H^a-6b, H^f-3, H^c-9a, $COOCH_3$, $COOCH_3$, H^e-5, H^b-5, H^f-2, H^a-5, H^a-3), 3.62–3.56 (m, 2H; H^f-4, H^d-5), 3.25 (t, 1H; H^a-6a), 2.82 (s, 3H; OCH_3), 2.64–2.57 (m, 2H; H^c-3e, H^g-3e), 2.35 (s, 3H; Ac), 2.34 (s, 3H; Ac), 2.28, 2.24, 2.19, 2.14, 2.06 (5s, 3 × 3H; 3Ac), 2.03 (s, 6H; 2Ac), 2.02 (s, 6H; 2Ac), 2.01, 1.96, 1.94 (3s, 3 × 3H; 3Ac), 1.93 (s, 6H; 2Ac), 1.83 (s, 3H; Ac), 1.62–1.52 (m, 2H; H^c-3a, H^g-3a), 1.24 (d, $J = 6.9$ Hz, 3H; CH^f_3), 1.11, 1.10 (2s, 2 × 9H; 2*t*Bu); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 177.35$ (C=O), 174.29 (C=O), 174.19 (C=O), 174.04 (C=O), 171.24 (C=O), 171.03 (C=O), 170.60 (C=O), 170.48 (C=O), 170.37 (C=O), 170.23 (C=O), 170.10 (C=O), 170.04 (C=O), 169.94 (C=O), 169.92 (C=O), 169.23 (C=O), 168.06 (C=O), 139.37, 139.08, 138.56, 136.35, 134.15, 128.32, 128.24, 128.15, 128.10, 128.04, 127.88, 127.50, 127.22, 127.18, 127.12, 126.07, 125.98, 125.80, 125.73, 101.70, 99.71, 99.05, 98.25, 97.41, 96.95, 96.80, 79.96, 78.04, 75.98, 75.87, 75.05, 74.80, 74.49, 74.29, 73.27, 72.83, 72.65, 72.56, 72.05, 71.74, 70.96, 70.50, 70.33, 70.13, 69.73, 69.62, 69.42, 68.76, 68.55, 67.50 (3C), 67.30 (3C), 67.24 (3C), 66.66, 62.93, 62.34, 60.58, 60.35, 56.57, 56.29, 56.10, 54.65, 53.10, 53.03, 49.22, 38.73, 38.54, 28.26 (Ac), 27.21 (3CH_3), 27.18 (3CH_3), 26.87 (Ac), 23.38 (Ac), 21.56 (Ac), 21.43 (Ac), 21.25 (Ac), 21.23 (Ac), 21.14 (Ac), 21.10 (Ac), 21.02 (Ac), 20.89 (Ac), 20.86 (Ac), 20.77 (Ac), 16.98 (CH^f_3); elemental analysis calcd (%) for $C_{137}H_{170}O_{59}N_4$: C 58.42, H 6.08, N 1.99; found C 58.52, H 5.74, N 1.76.

Heptasaccharide 33: DDQ (22 mg, 0.098 mmol) was added to a solution of compound **31** (180 mg, 0.065 mmol) in a mixture of dichloromethane/methanol/water 4:1:trace (6 mL). The reaction mixture was stirred for 16 h at room temperature and concentrated. The crude residue was taken in dichloromethane and washed with sat. $NaHCO_3$ aqueous solution (3 × 50 mL), water, dried (Na_2SO_4), and concentrated to a crude residue, which was applied to short column of silica gel and eluted with dichloromethane/

0947-6539/01/0702-0364 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 2

methanol 30:1 to give a pure compound **32** (73%). To a cold (ice bath) solution of compound **32** (292 mg, 0.11 mmol) in dry pyridine (3–4 mL), was added SO_3·pyridine complex (27 mg, 0.17 mmol) and stirred at 0 to 25 °C for 4 h. An additional portion of SO_3·pyridine complex (50 mg) was added and stirred at the same temperature for a total of 9 h. The reaction mixture was quenched with methanol (50 μL) and concentrated to a crude residue, which was treated with Amberlite IR 120 (Na^+) cation exchange resin in methanol at room temperature for 4 h. The solid was filtered off and the organic layer was concentrated. The mixture was applied to a short column of silica gel and eluted with dichloromethane/methanol 20:1 to give a pure compound **33** (255 mg, 78%) as an amorphous solid. $R_f = 0.24$ (CH_2Cl_2/MeOH 20:1); ^{1}H NMR (CD_3OD, 600 MHz): $\delta = 7.86-7.80$ (m, 4H; ArH), 7.68–7.60 (m, 2H; ArH), 7.48–7.40 (m, 3H; ArH), 7.30–7.00 (m, 10H; ArH), 5.61–5.48 (m, 4H; H^c-4, H^g-4, H^c-8, H^g-8), 5.24 (d, J = 3.0 Hz, 1H; H^a-4), 5.18 (dd, J = 2.3, 8.9 Hz, 1H; H^c-7), 5.12 (dd, J = 2.8, 8.9 Hz, 1H; H^g-7), 5.08 (d, $J_{1,2}$ = 7.4 Hz, 1H; H^d-1), 5.03–4.98 (m, 2H; H^e-1, H^e-4), 4.96 (d, J = 3.3 Hz, 1H; H^b-4), 4.94–4.84 (m, 4H; H^e-2, OCH_AAr, H^b-2, H^f-1), 4.81–4.75 (m, 2H; $OCH_A'Ar$, OCH_BAr), 4.74–4.46 (m, 10H; H^d-3, H^e-3, H^f-5, $OCH_A''Ar$, $OCH_B''Ar$, H^b-1, H^c-6, H^g-6, $OCH_B'Ar$, H^b-3), 4.45–4.10 (m, 8H; H^d-2, H^c-5, H^g-5, H^a-2, H^a-1, H^d-4, H^c-9b, H^g-9b), 4.09–3.72 (m, 21H; H^g-9a, H^b-6b, H^d-6b, H^d-6a, H^e-6b, H^e-6a, H^b-6a, H^a-6b, H^f-3, H^c-9a, $COOCH_3$, $COOCH_3$, H^c-5, H^b-5, H^f-2, H^a-5, H^a-3), 3.62–3.56 (m, 2H; H^f-4, H^d-5), 3.25 (t, 1H; H^a-6a), 2.83 (s, 3H; OCH_3), 2.64–2.57 (m, 2H; H^c-3e, H^g-3e), 2.35, 2.34, 2.28, 2.25, 2.20, 2.15, 2.05 (7s, 7 × 3H; 7Ac), 2.04 (s, 6H; 2Ac), 2.02 (s, 6H; 2Ac), 2.01, 1.98, 1.95 (3s, 3 × 3H; 3Ac), 1.93 (s, 6H; 2Ac), 1.84 (s, 3H; Ac), 1.62–1.52 (m, 2H; H^c-3a, H^g-3a), 1.24 (d, J = 6.9 Hz, 3H; CH^f_3), 1.11, 1.10 (2s, 2 × 9H; 2*t*Bu); ^{13}C NMR (CD_3OD, 100.6 MHz): $\delta = 177.85$ (C=O), 174.29 (C=O), 174.19 (C=O), 174.05 (C=O), 172.24 (C=O), 171.03 (C=O), 170.61 (C=O), 170.48 (C=O), 170.37 (C=O), 170.25 (C=O), 170.10 (C=O), 170.08 (C=O), 169.93 (C=O), 169.90 (C=O), 169.23 (C=O), 168.06 (C=O), 139.32, 139.08, 134.15, 128.35, 128.24, 128.15, 128.11, 127.50, 127.22, 127.18, 127.12, 126.07, 125.95, 125.80, 125.73, 101.75, 99.73, 99.05, 98.35, 97.41, 96.95, 96.80, 79.96, 78.04, 75.98, 75.87, 75.05, 74.80, 74.49, 74.29, 73.27, 72.83, 72.65, 72.56, 72.05, 71.74, 70.96, 70.50, 70.33, 70.13, 69.73, 69.62, 69.42, 68.76, 68.55, 67.50 (3C), 67.30, 67.24, 66.67, 62.93, 62.34, 60.55, 60.35, 56.57, 56.39, 56.10, 54.65, 53.10, 53.03, 49.22, 38.73, 38.54, 28.26 (Ac), 27.21 (3CH_3), 27.18 (3CH_3), 26.87 (Ac), 23.38 (Ac), 21.56 (Ac), 21.43 (Ac), 21.25 (Ac), 21.23 (Ac), 21.14 (Ac), 21.11 (Ac), 21.02 (Ac), 20.89 (Ac), 20.76 (Ac), 20.75 (Ac), 16.98 (CH^f_3); elemental analysis calcd (%) for $C_{126}H_{161}O_{62}N_4SNa$: C 54.46, H 5.84, N 2.02; found C 54.40, H 6.15, N 1.98.

Heptasaccharide 34: A solution of compound **33** (195 mg, 71 μmol), Pd/C(10%) (195 mg) in dry dichloromethane/methanol 1.5:1 (10 mL) was stirred for 7.5 h at room temperature under H_2 atmosphere. The solid was filtered off and organic layer was concentrated. The crude residue was treated with Ac_2O/pyridine 1:1 (10 mL) in the presence of catalytic amounts of DMAP (5 mg) at room temperature overnight. The reaction mixture was concentrated and passed through a short column of silica gel and eluted with dichloromethane/methanol 20:1 to give a pure compound **34** (160 mg, 87%) as an amorphous solid. ^{1}H NMR (CD_3OD, 600 MHz): $\delta = 8.00-7.80$ (m, 4H; ArH), 5.62–5.52 (m, 2H; H^c-4, H^g-4), 5.51–5.45 (m, 1H; H^c-8), 5.43–5.39 (m, 1H; H^g-8), 5.28 (d, J = 2.7 Hz,1H; H^f-4), 5.24 (d, J = 3.0 Hz, 1H; H^a-4), 5.19 (dd, J = 7.8 Hz, 1H; H^c-7), 5.17–5.09 (m, 2H; H^g-7, H^f-5), 5.08–5.05 (m, 2H; $J_{1,2}$ = 9.2 Hz, H^d-1), 5.05–4.95 (m, 3H; H^f-3), 4.81 (d, $J_{1,2}$ = 4.5 Hz, 1H; H^f-1), 4.80–4.56 (m, 4H; H^f-2, H^c-6, H^g-9b, H^g-6), 4.45–4.00 (m, 9H; H^d-6b, H^g-5, H^d-6a, H^c-9b, H^g-6, H^c-5, H^a-1, H^d-2), 4.00–3.78 (m, 12H; H^a-6b, H^c-9a, H^a-3, H^a-3, H^e-6a, H^d-4, H^a-6b), 3.40–3.30 (m, 1H; H^a-6a), 3.00 (s, 3H; OCH_3), 2.62–2.55 (m, 2H; H^c-3e, H^g-3e), 2.35, 2.34, 2.36, 2.33, 2.30 (5s, 5 × 3H; 5NAc), 2.23, 2.20, 2.15, 2.10, 2.08 (5s, 5 × 3H; 5Ac), 2.05 (s, 9H; 3Ac), 2.03, 2.02, 1.99, 1.97, 1.95, 1.94, 1.87 (7s, 7 × 3H; 7Ac), 1.84 (t, J = 12.4 Hz, 1H; H^c-3a), 1.47 (t, J = 11.7 Hz, 1H; H^g-3a), 1.27, 1.19 (2s, 2 × 9H; 2*t*Bu), 1.15 (d, J = 7.2 Hz, 3H; CH^f_3); ^{13}C NMR (CD_3OD, 100.6 MHz): $\delta = 179.73$ (C=O), 179.32 (C=O), 176.79 (C=O), 176.50 (C=O), 176.33 (C=O), 176.09 (C=O), 173.16 (C=O), 172.89 (C=O), 172.81 (C=O), 172.78 (C=O), 172.64 (C=O), 172.39 (C=O), 172.35 (C=O), 172.18 (C=O), 172.14 (C=O), 172.03 (C=O), 171.85 (C=O), 171.75 (C=O), 171.71 (C=O), 171.66 (C=O), 169.63 (C=O), 169.54 (C=O), 136.05, 124.84, 102.83, 101.91, 100.61, 100.08, 99.72, 98.29, 96.72, 77.63, 75.80, 75.32, 73.26, 73.11, 73.00, 72.95, 71.88, 71.65, 71.63, 71.56, 71.42, 71.05, 70.74, 70.13, 69.89, 69.55, 69.13, 68.80, 68.53, 68.42, 68.31, 67.05, 65.81, 63.62, 63.47, 63.01, 61.84, 58.56, 58.04, 57.34, 55.80, 53.91, 53.85, 50.63, 39.83, 38.88, 28.45 (NAc), 28.35 (NAc), 28.09 (3CH_3), 27.82 (3CH_3), 27.12 (NAc), 26.53 (NAc), 23.30 (NAc), 21.98 (Ac), 21.94 (Ac), 21.81(Ac), 21.61 (Ac), 21.45 (Ac), 21.23 (Ac), 21.21 (Ac), 21.11 (Ac), 21.01 (Ac), 20.92 (Ac), 20.89 (Ac), 20.81 (Ac), 20.77 (Ac), 20.67 (Ac), 20.62 (Ac), 16.63 (CH^f_3), FABMS (positive ion mode): for $C_{111}H_{149}O_{65}N_4SNa$: 2633.7; found: 2656.8 $[M+Na]^+$.

Heptasaccharide 1: Lithium iodide (968 mg) was added to a solution of compound **34** (160 mg) in dry pyridine (8 mL). The reaction mixture was refluxed at 120 to 125 °C for 8.5 h under N_2 atmosphere. The dark yellow solution was then evaporated to dryness and co-evaporated with toluene to a corresponding carboxylic acid as dark yellow amorphous solid which was directly used for next reaction. A solution of the above in methanol (15 mL), was treated with NH_2-NH_2·H_2O solution (3 mL) for 4 h at 80 to 85 °C, the reaction mixture was concentrated and co-evaporated with toluene then acetylated with Ac_2O/pyridine 1:1 in the presence of catalytic amount of DMAP at room temperature overnight. The acetylated mixture was concentrated and passed through a short column of silica gel and eluted with dichloromethane/methanol to give a bright film. To a solution of this bright yellow film in methanol/water 1:1 (3 mL) was added a catalytic amount of 1M sodium methoxide solution (200 μL) and stirred at room temperature for 24 h. The mixture was then concentrated under reduced

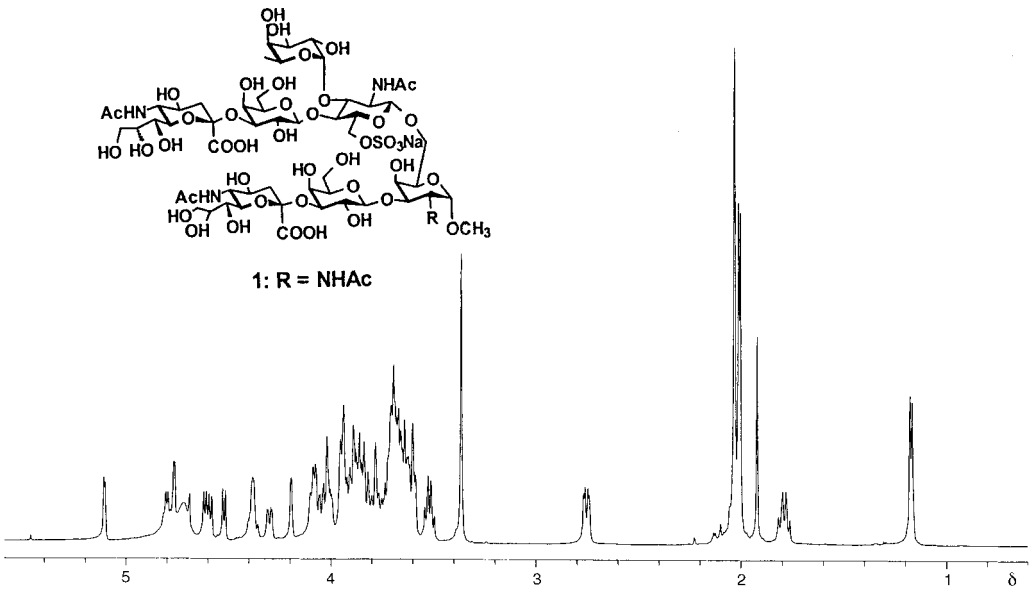

Figure 5. 600 MHz ^{1}H NMR spectrum of compound **1** (D_2O) at 303.0 K.

pressure. The crude mixture was then applied to a short column of silica gel and eluted with n-C_3H_7OH/HOAc/H_2O 1:1:1 to give a pure compound **1** (15 mg) in total 25% yield. $R_f = 0.24$ (n-C_3H_7OH/HOAc/H_2O 1:1:1); ^{1}H NMR (D_2O, 600 MHz): $\delta = 5.11$ (d, $J_{1,2} = 3.9$ Hz, 1H; H^f-1), 4.81–4.76 (m, 2H; H^f-5, H^a-1, $J_{1,2} = 3.3$ Hz), 4.62 (d, $J_{1,2} = 8.3$ Hz, 1H; H^e-1), 4.59 (d, $J_{1,2} = 9.0$ Hz, 1H; H^d-1), 4.52 (d, $J_{1,2} = 8.3$ Hz, 1H; H^b-1), 4.38–4.32 (dd, 2H; H^d-6b, H^d-6a, sulfated position), 4.30 (dd, $J = 3.2$, 10.0 Hz, 1H; H^a-2), 4.20 (d, $J = 2.3$ Hz, 1H; H^a-4), 4.10–3.96 (m, 4H; H^e-3, H^b-3, H^a-5, H^d-4, H^a-3), 3.95–3.56 (m, 32H; H^e-4, H^d-2, H^b-4, H^f-3, H^f-4, H^f-2), 3.56–3.49 (m, 2H; H^e-2, H^b-2), 3.36 (s, 3H; OCH_3), 2.77–2.72 (m, 2H; H^c-3e, H^g-3e), 2.05, 2.03, 2.00, 1.92 (4s, 4 × 3H; 4Ac), 1.83–1.75 (ddd, 2H; H^c-3a, H^g-3a), 1.17 (d, $J = 6.6$ Hz, 3H; CH^f_3); ^{13}C NMR (D_2O,150 MHz): (HSQC and HMBC) $\delta = 174.20$ (C=O), 174.10 (C=O), 173.55 (C=O), 172.70 (C=O), 172.48 (C=O), 172.30 (C=O), 103.29 (C^b-1), 100.47 (C^d-1), 100.05 (C^e-1), 98.67 (C^g-2), 98.53 (C^c-2), 97.38 (C^f-1), 96.99 (C^a-1), 75.85, 75.77, 74.92, 74.53, 74.20, 73.93, 73.34, 73.26, 71.49, 71.41, 71.36, 71.23, 70.48, 70.35, 69.90, 69.23, 67.99, 67.85, 67.78, 67.73, 67.36, 66.91, 66.68, 66.44, 66.07, 65.99, 65.25 (C^e-5), 64.48 (C^d-6), 61.09, 61.00, 60.00, 59.48, 54.42, 53.53, 50.33, 50.26, 47.11 (C^a-2), 38.30, 23.10, 23.00 22.38, 22.10, 16.30 (CH^e_3); FABMS (positive ion mode): m/z: calcd for $C_{57}H_{93}O_{44}N_4SNa$: 1592; found 1591 $[M-H]^+$.

Heptasaccharide 35: A solution of compound **31** (310 mg, 71 μmol), and Pd/C (10%) (310 mg) in dry dichloromethane/methanol 1.5:1 (10 mL) was stirred for 6 h at room temperature under H_2 atmosphere. The solid was filtered off and organic layer was concentrated to a crude residue, which was treated with Ac_2O/pyridine 1:1 (10 mL) in the presence of catalytic amounts of DMAP (5 mg) overnight at room temperature. The reaction mixture was concentrated. The residue was passed through a short column of silica gel and eluted with dichloromethane/methanol 20:1 to give a pure compound **35** (267 mg, 94%) as an amorphous solid. $R_f = 0.49$ (CH_2Cl_2/MeOH 30:1); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.84–7.66 (m, 4H; ArH), 6.00 (d, $J = 8.8$ Hz, 1H; NHAc), 5.62–5.48 (m, 4H; H^g-4, H^g-8, H^c-4, H^c-8), 5.27 (d, $J = 3.2$ Hz, 1H; H^f-4), 5.23 (dd, $J = 2.3$, 8.9 Hz, 1H; H^c-7), 5.14 (d, $J = 3.1$ Hz, 1H; H^a-4), 5.08 (dd, 1H; H^f-3), 5.05 (dd, $J = 2.8$, 9.3 Hz, 1H; H^g-7), 5.02–5.01 (m, 2H; H^f-5, H^e-4), 5.05 (d, $J_{1,2} = 7.6$ Hz, 1H; H^d-1), 4.93 (d, $J = 2.8$ Hz, 1H; H^b-4), 4.90–4.81 (m, 3H; H^f-1, H^e-2, H^b-2), 4.79 (dd, 1H; H^f-2), 4.74 (d, $J = 7.8$ Hz, 1H; H^e-1), 4.73 (t, 1H; H^d-3), 4.63 (dd, 1H; H^e-3), 4.60–4.55 (m, 3H; H^g-6, H^b-1, H^c-6), 4.51 (dd, 1H; H^b-3), 4.46–4.44 (m, 1H), 4.44–4.23 (m, 5H; H^c-5, H^g-5, H^g-9b, H^c-9b, H^a-2), 4.22 (d, $J = 2.9$ Hz, 1H; H^a-1), 4.19–4.10 (m, 4H; H^c-9a, H^d-6b, H^d-6a, H^d-2), 4.03 (t, 1H; H^d-4), 3.92–3.70 (m, 14H; H^e-6b, H^a-6b, H^b-5, $COOCH_3$, $COOCH_3$, H^e-5, H^g-9a, H^b-6b, H^e-6a, H^b-6a), 3.25 (t, 1H; H^a-6a), 2.82 (s, 3H; OCH_3), 2.64–2.58 (m, 2H; H^c-3e, H^g-3e), 2.38 (s, 3H; NAc), 2.34 (s, 3H; Ac), 2.30, 2.26, 2.24 (3s, 3 × 3H; 3NAc), 2.20, 2.16, 2.14 (3s, 3 × 3H; 3Ac), 2.09 (s, 6H; 2Ac), 2.07 (s, 9H; 3Ac), 2.04 (s, 6H; 2Ac), 2.02, 2.01, 1.99 (3s, 3 × 3H; 3Ac), 1.93 (s, 6H; 2Ac), 1.88 (s, 3H; Ac), 1.62–1.52 (m, 2H; H^c-3a, H^g-3a), 1.23 (d, $J = 6.9$ Hz, 3H; CH^f_3), 1.11, 1.10 (2s, 9H; 2tBu); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 177.48$ (C=O), 174.30 (C=O), 174.04 (C=O), 171.23 (C=O), 170.63 (C=O), 170.58 (C=O), 170.38 (C=O), 170.25 (C=O), 170.15 (C=O), 170.04 (C=O), 169.94 (C=O), 169.92 (C=O), 169.25 (C=O), 168.36 (C=O), 139.34, 139.08, 128.25, 128.24, 128.15, 128.10, 101.71, 99.78, 99.05, 98.26, 97.42, 96.96, 96.81, 79.91, 78.03, 75.91, 75.88, 75.06, 74.81, 74.50, 74.30, 73.27, 72.81, 72.66, 72.57, 72.05, 71.74, 70.95, 70.51, 70.32, 70.13, 69.73, 69.62, 69.43, 68.76, 68.56, 67.53, 67.31, 67.25, 66.67, 62.94, 62.35, 60.59, 60.36, 56.58, 56.30, 56.11, 54.66, 53.12, 53.04, 49.22, 38.74, 38.55, 28.27 (Ac), 27.22 (CH3), 27.19 (CH3), 26.88 (Ac), 23.39 (Ac), 21.54 (Ac), 21.44 (Ac), 21.26 (Ac), 21.25 (Ac), 21.15 (Ac), 21.11 (Ac), 21.03 (Ac), 20.89 (Ac), 20.87 (Ac), 20.78 (Ac), 16.90 (CH^f_3); elemental analysis calcd (%) for $C_{113}H_{152}O_{63}N_4$: C 52.27, H 5.95, N 2.18; found C 52.05, H 5.74, N 1.81.

Heptasaccharide 2: Lithium iodide (200 mg) was added to a solution of compound **35** (89 mg) in dry pyridine (2 mL). The reaction mixture was refluxed at 120 to 125 °C for 8.5 h under N_2 atmosphere. The dark yellow solution was evaporated to dryness, co-evaporated with toluene to a corresponding carboxylic acid as dark yellow amorphous solid which was directly used for next reaction. A solution of the above in methanol (5 mL) was treated with NH_2-$NH_2 \cdot H_2O$ (1 mL) and stirred for 4 h at 80 to 85 °C. The reaction mixture was concentrated, co-evaporated with toluene then acetylated with Ac_2O/pyridine 1:1 in the presence of catalytic amount of DMAP at room temperature for overnight. The acetylated mixture was concentrated and passed through a short column of silica gel and eluted with dichloromethane/methanol 10:1 to give a bright film **36**. Compound **36** in methanol/water (1 mL) was treated with a catalytic amount of 1M sodium methoxide solution (50 μL) at room temperature for 24 h. The reaction mixture was then concentrated under reduced pressure to give a crude residue, which was applied to a short column of silica gel and eluted with n-C_3H_7OH/HOAc/H_2O 1:1:1 to give a pure compound **2** (4.5 mg) in total 33% yield. $R_f = 0.24$ (n-C_3H_7OH/HOAc/H_2O 1:1:1); ^{1}H NMR (D_2O, 600 MHz): $\delta = 5.10$ (d, $J_{1,2} = 3.2$ Hz, 1H; H^f-1), 4.82–4.77 (m, 2H; H^f-5, H^a-1, $J_{1,2} = 3.4$ Hz), 4.61 (d, $J_{1,2} = 8.6$ Hz, 1H; H^e-1), 4.59 (d, $J_{1,2} = 8.8$ Hz, 1H; H^d-1), 4.53 (d, $J_{1,2} = 8.4$ Hz, 1H; H^b-1), 4.30 (dd, $J = 3.2$, 10.0 Hz, 1H; H^a-2), 4.20 (d, $J = 2.8$ Hz, 1H; H^a-4), 4.11–3.96 (m, 4H; H^e-3, H^b-3, H^a-5, H^d-4, H^a-3), 3.95–3.56 (m, 34H; H^e-4, H^d-2, H^b-4, H^f-3, H^f-4, H^f-2), 3.55–3.48 (m, 2H; H^e-2, H^b-2), 3.35 (s, 3H; OCH_3), 2.78–2.72 (m, 2H; H^c-3e, H^g-3e), 2.04, 2.02, 2.00, 1.93 (4s, 4 × 3H; 4Ac), 1.85–1.74 (ddd, 2H; H^c-3a, H^g-3a), 1.17 (d, $J = 6.7$ Hz, 3H; CH^f_3); FABMS (positive ion mode): m/z: calcd for $C_{57}H_{94}O_{41}N_4$: 1490 $[M]^+$; found 1491 $[M+H]^+$.

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[1] a) A. Varki, *Glycobiology* **1993**, *3*, 97; b) Y. C. Lee, T. R. Lee, *Acc. Chem. Res.* **1995**, *28*, 321; c) R. A. Dwek, *Chem. Rev.* **1996**, *96*, 683; d) B. Ganem, *Acc. Chem. Res.* **1996**, *29*, 340; e) E. E. Shimanel, G. J. McGarvey, J. A. Jablonowski, C.-H. Wong, *Chem. Rev.* **1998**, *98*, 833; f) C.-H. Wong, *Acc. Chem. Res.* **1999**, *32*, 376.

[2] J.-M. Lo-Guidice, J.-M. Wieruszeski, J. Lemoine, A. Verbert, P. Roussel, G. Lamblin, *J. Biol. Chem.* **1994**, *269*, 18794;

[3] a) C. Capon, C. L. Laboisse, J-M. Wieruszeski, J-J. Maoret, C. Augeron, B. Fournet, *J. Biol. Chem.* **1992**, *267*, 19248; b) C. Capon, J-M. Wieruszeski, J. Lemoine, J. C. Byrd, H. Leffler, Y. S. Kim, *J. Biol. Chem.* **1997**, *272*, 31957;

[4] S. Hemmerich, H. Leffler, S. D. Rosen, *J. Biol. Chem.* **1995**, *270*, 12035.

[5] a) K. C. Nicolaou, N. J. Bockovich, D. R. Carcanague, *J. Am. Chem. Soc.* **1993**, *115*, 8843; b) S. Tsuboi, Y. Isogai, N. Hada, J. K. King, O. Hindsgaul, M. Fukuda, *J. Biol. Chem.* **1996**, *271*, 27213; c) R. K. Jain, R. Vig, R. Rampal, E. V. Chandrasekaran, K. L. Matta, *J. Am. Chem. Soc.* **1994**, *116*, 12123.

[6] a) A. K. Sarkar, K. S. Rostand, R. K. Jain, K. L. Matta, J. D. Esko, *J. Biol. Chem.* **1997**, *272*, 25608; b) M. J. Gaunt, J. Yu, J. B. Spencer, *J. Org. Chem.* **1998**, *63*, 4172; c) J. Xia, S. A. Abbas, R. D. Locke, C. F. Piskorz, J. L. Alderfer, K. L. Matta, *Tetrahedron Lett.* **2000**, *41*, 169.

[7] a) A. Marra, P. Sinaÿ, *Carbohydr. Res.* **1990**, *195*, 303; b) A. Hasegawa, H. Ohki, T. Nagahama, H. Ishida, M. Kiso, *Carbohydr. Res.* **1991**, *212*, 277; c) H. Kondo, Ichikawa, C.-H. Wong, *J. Am. Chem. Soc.* **1992**, *114*, 8748; d) M. Wilstermann, L. O. Konow, U. Nilsson, A. K. Ray, G. Magnusson, *J. Am. Chem. Soc.* **1995**, *117*, 4742; e) R. K. Jain, R. Vig, R. D. Locke, A. Mohammad, K. L. Matta, *Chem. Commun.* **1996**, 65; f) D. Sames, X.-T. Chen, S. J. Danishefsky, *Nature*, **1997**, *389*, 587; g) Z. Gan, S. Cao, Q. Wu, R. Roy, *J. Carbohydr. Chem.* **1999**, *18*, 755; h) J. B. Schwarz, S. D. Kuduk, X.-T. C. D. Sames, P. W. Glunz, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 2662; i) J. R. Allen, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 10875.

[8] a) M. Rance, O. W. Sorensen, G. Bodenhausen, G. Wagner, R. R. Ernst, K. Wüthrich, *Biochem. Biophys. Res. Commun.* **1983**, *117*, 479; b) A. A. Bothner-By, R. L. Stephens, J. Lee, C. D. Warren, R. W. Jeanloz, *J. Am. Chem. Soc.* **1984**, *106*, 811; c) W. Willker, D. Leibfritz, R. Kerssebaum, W. Bermel, *Magn. Reson. Chem.* **1993**, *31*, 287.

[9] a) S. Raghavan, D. Kane, *J. Am. Chem. Soc.* **1993**, *115*, 1580; b) H. Ada, T. Harada, T. Takahashi, *J. Am. Chem. Soc.* **1994**, *116*, 1580; c) H. K. Chenault, A. Castro, *Tetrahedron Lett.* **1994**, *35*, 9145; d) S. V. Ley; H. W. M. Priepke, *Angew. Chem.* **1994**, *106*, 2412; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2292; e) Z. Zhang, I. R. Ollmann, X.-S. Ye, R. Wischnat, T. Baasov, C.-H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 734; f) H. Yamada, T. Kato, T. Takahashi, *Tetrahedron Lett.* **1999**, *40*, 4581.

[10] a) T. Zu, G.-J. Boons, *Angew. Chem.* **1999**, *111*, 3704; *Angew. Chem. Int. Ed.* **1999**, *38*, 3495; b) T. Zu, G.-J. Boons, *Angew. Chem.* **1998**, *110*, 2000; *Angew. Chem. Int. Ed.* **1998**, *37*, 1898; c) T. Zu, G.-J. Boons,

  0947-6539/01/0702-0366 $ 17.50+.50/0

Tetrahedron Lett, **1998**, *39*, 2187; d) T. Zu, G.-J. Boons, *J. Chem. Soc. Perkin Trans. 1* **1998**, 857.

[11] a) Y. Imai, L. A. Lasky, S. D. Rosen, *Nature* **1993**, *361*, 555; b) S. D. Rosen, C. R. Bertozzi, *Curr. Biol*. **1996**, 6, 261; c) L. A. Marcaurelle, C. R. Bertozzi, *Chem. Eur. J.* **1999**, *5*, 1384.

[12] O. Kanie, Y. Ito, T. Ogawa, *J. Am. Chem. Soc*. **1994**, *116*, 12073.

[13] a) Y. Ito, T. Ogawa, *Tetrahedron* **1990**, *46*, 89; b) K. C. Nicolaou, C. W. Hummel, W. J. Bockovich, C.-H. Wong, *J. Chem. Soc. Chem. Commun.* **1991**, *870*; c) A. Kameyama, H. Ishida, M. Kiso, A. Hasegawa, *Carbohydr. Res.* **1991**, *209*, C1; d) A. Hasegawa, T. Nagahama, H. Ohki, K. Hotta, H. Ishida, M. Kiso, *J. Carbohydr. Chem*. **1991**, *10*, 493; e) S. J. Danishefsky, K. Koseki, D. A. Griffith, J. Gervay, J. M. Peterson, F. E. McDonald, T. Oriyawa, *J. Am. Chem. Soc*. **1992**, *114*, 8331; f) T. J. Martin, R. R. Schmidt, *Tetrahedron Lett*. **1992**, *33*, 6123; g) T. J. Martin, R. Brescello, A. Toepfer, R. R. Schmidt, *Glycoconjugate J.* **1993**, *10*, 16; h) A. Hasegawa, K. Fushimi, H. Ishida, M. Kiso, *J. Carbohydr. Chem*. **1993**, *12*, 1203; i) U. Spregard, G. Kretzschmar, E. Bartnik, C. Huls, H. Kunz, *Angew. Chem.* **1995**, *107*, 1104; *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 990; j) W. Stahl, U. Sprengard, G. Kretzschma, H. Kunz, *Angew. Chem*. **1994**, *106*, 2186; *Angew. Chem. Int. Edit*. **1994**, *33*, 2096; k) V. Martichonok, G. M. Whitesides, *J. Am. Chem. Soc.* **1996**, *118*, 8187; l) B. Liebe, H. Kunz, *Angew. Chem.* **1996**, *108*, 3367; *Angew. Chem. Int. Ed. Engl.* **1996**, *36*, 618; m) C. Unverzagt, *Tetrahedron Lett.* **1997**, *38*, 5627; n) M. Wilstermann, G. Magnusson, *J. Org. Chem.* **1997**, *62*, 7961; o) U. Ellervik, H. Grundberg, G. Magusson, *J. Org. Chem*. **1998**, *63*, 9323; p) K. Peilstocker, H. Kunz, *Synlett*. **2000**, 820; q) K. Peilstocker, H. Kunz, *Synlett*. **2000**, 823.

[14] a) S, Fujita, M, Numata, M. Sugimoto, K. Tomita, T. Ogawa, *Carbohydr. Res.* **1994**, *263*, 181; b) J. C. Castro-Palomino, R. R. Schmidt, *Tetrahedron Lett*. **1995**, 38, 6871; c) A. Demchenko, G. J. Boons, *Tetrahedron Lett*. **1998**, *39*, 3065; d) A. Demchenko, G. J. Boons, *Chem. Eur. J.* **1999**, *5*, 1278.

[15] a) M. Lengenmüller, Y. Ito, T. Ogawa, *Tetrahedron* **1998**, *54*, 1381; b) S. K. Bhattacharya, S. J. Danishefsky, *J. Org. Chem*. **2000**, *65*, 144.

[16] K. Scheffler, B. Ernst, A. Katopodis, J. L. Magnani, W.-T. Wang, R. Weisemann, T. Peters, *Angew. Chem.* **1995**, *107*, 2034; *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 1841.

[17] a) K. Okamoto, T. Kono, T. Goto, *Bull. Chem. Soc. Jpn*. **1987**, *60*, 637; b) H. Hori, T. Nakajima, Y. Nishida, H. Ohrui, *Tetrahedron Lett*. **1988**, *29*, 6317; c) T. Ercegovic, G. Magnusson, *J. Chem. Soc. Chem. Commun*. **1994**, 831; d) S. J. Danishefsky, J. Gervay, J. M. Peterson, F. E. McDonald, K. Koseki, D. A. Griffith, T. Oriyama, S. P. Marsden, *J. Am. Chem. Soc.* **1995**, *117*, 1940; e) T. Ehara, A. Kameyama, Y. Yamada, H. Ishida, M. Kiso, A. Hasegawa, *Carbohydr. Res.* **1996**, *281*, 237.

[18] a) R. R. Schmidt, J. Michel, *Angew. Chem.* **1980**, *92*, 763; *Angew. Chem. Int. Ed. Engl*. **1980**, *19*, 731; b) R. R. Schmidt, W. Kinzy, *Adv. Carbohydr. Chem. Biochem*. **1994**, *50*, 21; c) J. Redemann, A. Geyer, R. R. Schmidt, *Angew. Chem.* **1998**, *110*, 1309; *Angew. Chem. Int. Ed*. **1998**, *37*, 1241; d) C. Gege, J. Vogel, G. Bendas, U. Rothe, R. R. Schmidt, *Chem. Eur. J.* **2000**, *6*, 111.

[19] S. Sato, M. Mori, Y. Ito, T. Ogawa, *Carbohydr. Res.* **1986**, *197*, C6.

[20] J. Xia, J. L. Alderfer, C. F. Piskorz, K. L. Matta, *Chem. Eur. J.* **2000**, *6*, 3442.

[21] a) G. H. Veeneman, S. H. Van Leeuwen, J. H. van Boom, *Tetrahedron Lett*. **1990**, *31*, 1331; b) P. Konradsson, U. E. Udodong, B. Fraser-Reid, *Tetrahedron Lett.* **1990**, *31*, 4313.

[22] a) H. Kunz, C. Unverzagt, *Angew. Chem.* **1988**, *99*, 1763; *Angew. Chem. Int. Ed. Engl*. **1988**, *27*, 1697; b) A. Dan, M. Lergenmüller, M. Amano, Y. Nakahara, T. Ogawa, Y. Ito, *Chem. Eur. J.* **1998**, *4*, 2182; c) A. Cappa, E. Marcantoni, E. Torregiani, G. Bartoli, M. C. Bellucci, M. Bosco, L. Sambri, *J. Org. Chem.* **1999**, *64*, 5696.

[23] a) C. H. Hokke, A. A. Berwerff, G. W. R. Dedem, J. P. Kamerling, J. F. G. Vliegenthart, *Eur. J. Biochem*. **1995**, *228*, 981; b) A. Geyer, G. Hummel, H. Eisele, S. Reinhardt, R. R. Schmidt, *Chem. Eur. J.* **1996**, *2*, 981; c) J. J. M. van Rooijen, J. R. Kamerling, J. F. G. Vliegenthart, *Glycobiology* **1998**, *8*, 1065; d) D. K. Baseschlin, A. R. Chaperon, L. G. Green, M. G. Hahn, S. J. Ince, S. V. Ley, C.-H. Wong, *Chem. Eur. J.* **2000**, *6*, 172; e) V. Wittmann, A. K. Datta, K. M. Koeller, C.-H. Wong, *Chem. Eur. J.* **2000**, *6*, 162.

[24] a) G. Bodenhausen, D. Ruben, *Chem. Phys. Lett.* **1980**, *69*, 185; b) A. L. Davis, J. Keeler, E. D. Laue, D. Moskau, *J. Magn. Reson*. **1992**, *98*, 207.

[25] a) A. Bax, M. F. Summers, *J. Am. Chem. Soc*. **1986**, *108*, 2093; b) M. F. Summers, L. G. Marzilli, A. Bax, *J. Am. Chem. Soc*. **1986**, *108*, 4285.

[26] Chemical synthesis of sulfated oligosaccharides with β-Gal-(1$\rightarrow$4)-[α-Fuc-(1$\rightarrow$3)]-β-GlcNAc-(1$\rightarrow$6)-β-Gal-(1$\rightarrow$3)-α-GalNAc-OMe sequence: J. Xia, T. Srikrishnan, J. L. Alderfer, R. K. Jain, C. F. Piskorz, K. L. Matta, *Carbohydr. Res.* **2000**, *329*, 69.

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