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Carbohydrate Research 325 (2000) 132–142

CARBOHYDRATE RESEARCH

An efficient access to protected disialylated glycohexaosyl threonine present on the leukosialin of activated T-lymphocytes

Latika Singh [a], Yuko Nakahara [a], Yukishige Ito [a], Yoshiaki Nakahara [a,b,*]

[a] *The Institute of Physical and Chemical Research (RIKEN), Hirosawa 2-1, Wako-shi, Saitama 351-0198, Japan*
[b] *Department of Industrial Chemistry, CREST, Japan Science and Technology Corporation (JST), Tokai University, Kitakaname 1117, Hiratsuka-shi, Kanagawa 259-1292, Japan*

Received 9 September 1999; accepted 18 November 1999

Abstract

The total synthesis of the threonine-linked core 2 class disialylated hexasaccharide in a completely protected form was accomplished for the first time. The L-threonine conjugate, *N*-(9-fluorenylmethoxycarbonyl)-*O*-{(5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonic acid)-(2→3)-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2-acetamido-2-deoxy-3,6-di-*O*-benzyl-β-D-glucopyranosyl-(1→6)-[(5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonic acid)-(2→3)-2,6-di-*O*-benzyl-β-D-galacto-pyranosyl-(1→3)]-2-acetamido-2-deoxy-α-D-galactopyranosyl-(1d→4c:1f→4e)-dilactone}-L-threonine allyl ester was synthesized via stereocontrolled glycosylations employing readily accessible monosaccharidic blocks; *t*-butyl-diphenylsilyl-2-azido-2-deoxy-3,6-di-*O*-benzyl-β-D-glucopyranose, *N*-(9-fluorenylmethoxycarbonyl)-*O*-(2-azido-6-*O*-*t*-butyldimethylsilyl-2-deoxy-α-D-galactopyranosyl)-L-threonine allyl ester, **8**, **9** and *N*-(9-fluorenylmethoxy-carbonyl)-*O*-(2-azido-4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-deoxy-α-D-galactopyranosyl)-L-threonine allyl ester. For the introduction of the amino acid, the azide group was used to temporarily mask the amino group of GalNAc so as to obtain an α-glycosidic linkage without participation from the C-2 substituent. The threonine was attached to the sugar unit at the monosaccharide stage to avoid loss of oligosaccharide at a later stage. The Fmoc and allyl ester protected amino acid at the reducing end facilitates efficient glycopeptide synthesis on solid-phase support.

Keywords: Core class 2; Sialic acid; Leukosialin; O-Linked glycoprotein

1. Introduction

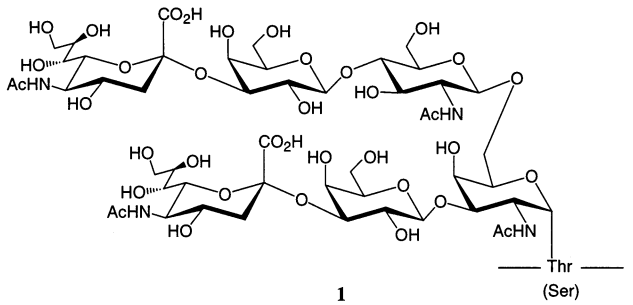
Cell-surface glycoproteins and glycolipids play an essential role in maintaining the function as well as the structure of cells. The carbohydrate structures on glycoproteins and glycolipids undergo marked alterations during development and differentiation, and are also cell-type and lineage specific [1]. The aberrant expression of carbohydrate structures is often associated with various pathological conditions and immunodeficiency [1,2].

Carbohydrate ligands on the surface of blood cells have been the subject of extensive studies. Leukosialin is a major sialoglycoprotein found on the surface of T-lymphocytes, granulocytes and monocytes [3]. Normal resting T-lymphocytes express on leukosialin the disialotetrasaccharides α-D-NeuAc-(2→3)-β-D-Gal-(1→3)-[α-D-NeuAc-

* Corresponding author. Tel./fax: +81-463-502075.
E-mail address: yonak@keyaki.cc.u-tokai.ac.jp (Y. Nakahara)

0008-6215/00/$ - see front matter
PII: S0008-6215(99)00313-4

(2→6)]-α-D-GalNAc-L-Ser/Thr. Activation of human T-lymphocytes by anti-CD3 antibodies and interleukin-2 results in an almost exclusive expression of the title core 2 disialylated hexasaccharide α-D-NeuAc-(2→3)-β-D-Gal-(1→4)-β-D-GlcNAc-(1→6) [α-D-NeuAc-(2→3)-β-D-Gal-(1→3)]-α-D-GalNAc-L-Ser/Thr (**1**) [4]. Overexpression of core 2 O-glycans on T-lymphocyte cell-surface glycoproteins has been associated with certain pathological phenomena including immunodeficient syndromes [5] such as the Wiskott–Aldrich syndrome [6], leukemia [7], AIDS [8], and malignant transformation [9]. In these diseases the core 2 O-glycans are highly expressed on resting T cells, whereas they are not expressed in normal, healthy individuals.



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Heterogeneity and low abundance of glycopeptides preclude the isolation and characterization of homogeneous glycans; therefore, synthesis of well-defined glycopeptide fragments remains the method of choice for structure–activity relationship studies. In the framework of our project designed to elucidate the nature of the functional importance of oligosaccharide structures on cell-surface glycoproteins, the protected L-threonine conjugate **2** of the title disialylated core 2 hexasaccharide was constructed as a building block for glycopeptide synthesis. There have been earlier reports on the syntheses of the asialo core 2 structures [10]; however, the sialylated analog has not been reported so far. We present here for the first time the total synthesis of the completely sialylated core 2 hexasaccharide.

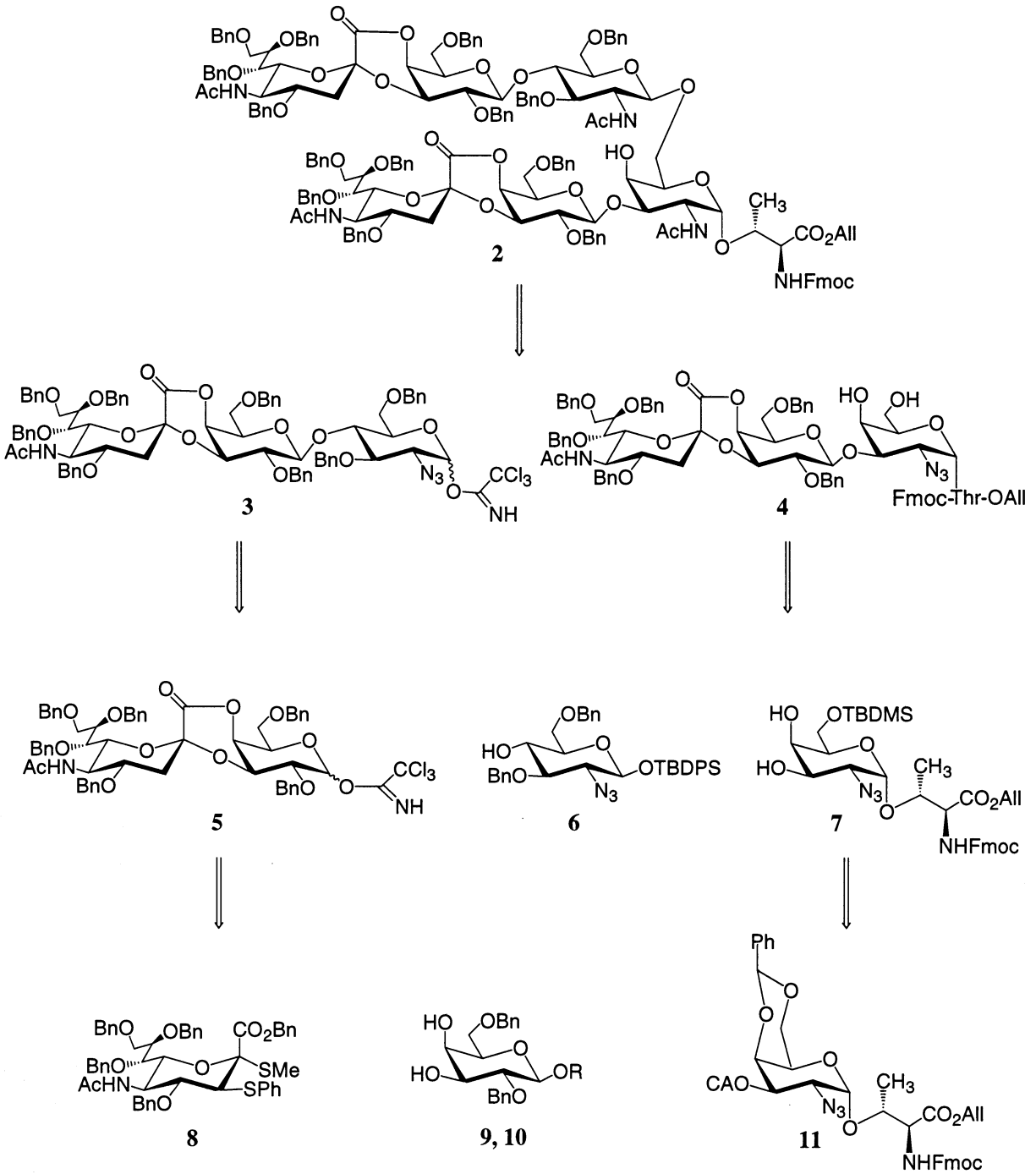
2. Results and discussion

The synthesis of the hexasaccharide **2** was designed to combine the two trisaccharides **3** and **4** to afford the hexasaccharide backbone [11]. As the α-D-NeuAc-(2→3)-D-Gal linkage appears in both the key intermediates **3** and **4**, we decided to construct this sequence first via the building blocks **8**, **9** and **10**. The disaccharide thus built was converted to its trichloroacetimidate **5**, which served as a common donor for the construction of **3** as well as **4** via coupling to the acceptors **6** and **7**, respectively. The azide groups, which are compatible with the sialic acid functionality, were used to mask the amino groups of GlcNAc **6** and GalNAc **7** (Scheme 1).

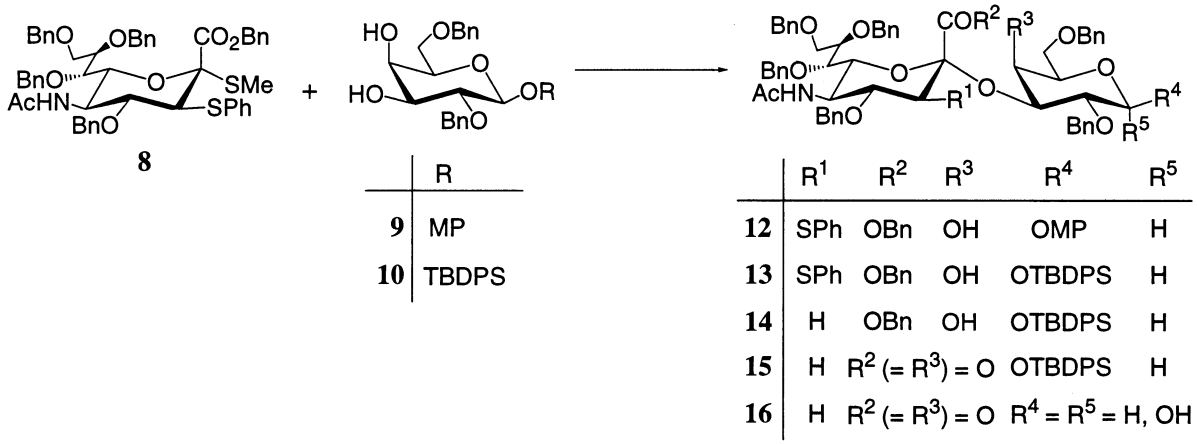
The synthesis of the hexasaccharide **2** commenced with the sialylation of the two galactopyranosyl acceptors **9** and **10** with the donor **8**. The neighboring group assisted sialylation of **9** and **10** with the donor **8** proceeded stereoselectively under well-established conditions [12] to afford the desired α-(2→3) sialylated disaccharides **12** and **13** in high yields. The D-galactopyranosyl derivative **9** having a 4-methoxyphenyl group at the anomeric position was prepared as earlier reported [13]. Glycosylation of **9** with the donor **8** to the disaccharide **12** and its subsequent conversion to the trichloroacetimidate **5** was accomplished according to the reported protocol [14]. Loss of material during oxidative cleavage of the anomeric 4-methoxyphenyl group (77% yield) from the disaccharide **12** led us to choose the galactopyranose acceptor **10** having the *tert*-butyldiphenylsilyl ether at the anomeric position, which can be efficiently removed by the fluoride anion. The β-D-galactopyranosyl derivative **10** was prepared from **9** by a series of standard functional group manipulations (1, Ac_2O–pyridine, 0 °C–room temperature, 10 h, 97%; 2, ceric ammonium nitrate, CH_3CN–H_2O, 0 °C, 10 min, 77%; 3, TBDPSCl, imidazole, 45 °C, 12 h, 94%; 4, NaOMe, MeOH–toluene, 99%). The NIS–TfOH-promoted sialylation of the acceptor **10** with the sialyl donor **8** afforded the disaccharide **13** in 77% yield. Triphenyltin hydride (5 equivalents)-promoted desulfurization of **13** led exclusively to the lactone **15** in 80% yield, thereby excluding the need for an additional step of conversion of the ester **14** to lactone **15**. Use of larger amounts of the promoter led to a mixture of the desulfurized ester **14** and

lactone **15**, which could be separated by chromatography but required an additional lactonization reaction with DBU for conversion of the benzyl ester **14** to the corresponding lactone **15**. Near-quantitative removal of the anomeric silyl ether was achieved with tetrabutylammonium fluoride in the presence of acetic acid in THF to afford the hemiacetal **16**. Subsequent conversion to the trichloroacetimidate **5** was accomplished as before (Scheme 2).

Glycosylation of the D-glucosamine acceptor **6** with the imidate **5** was then followed up. The acceptor **6** was prepared in a manner



Scheme 1. TBDPS, *t*-butyldiphenylsilyl; Fmoc, 9-fluorenylmethoxycarbonyl; All, allyl; R, MP(4-methoxyphenyl) or TBDPS (*t*-butyldiphenylsilyl); TBDMS, *t*-butyldimethylsilyl; CA, chloroacetyl.

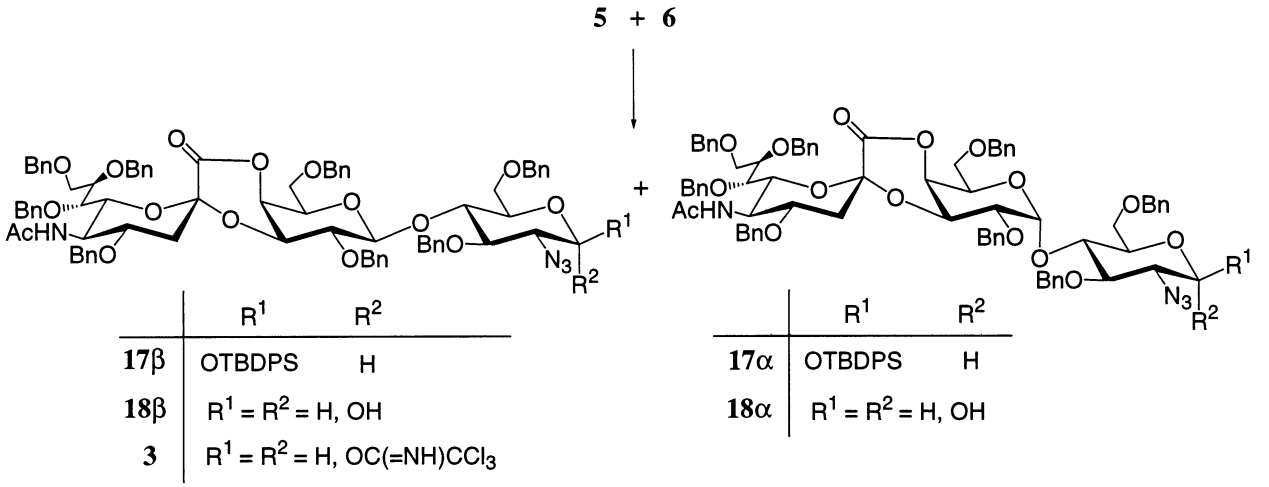


Scheme 2.

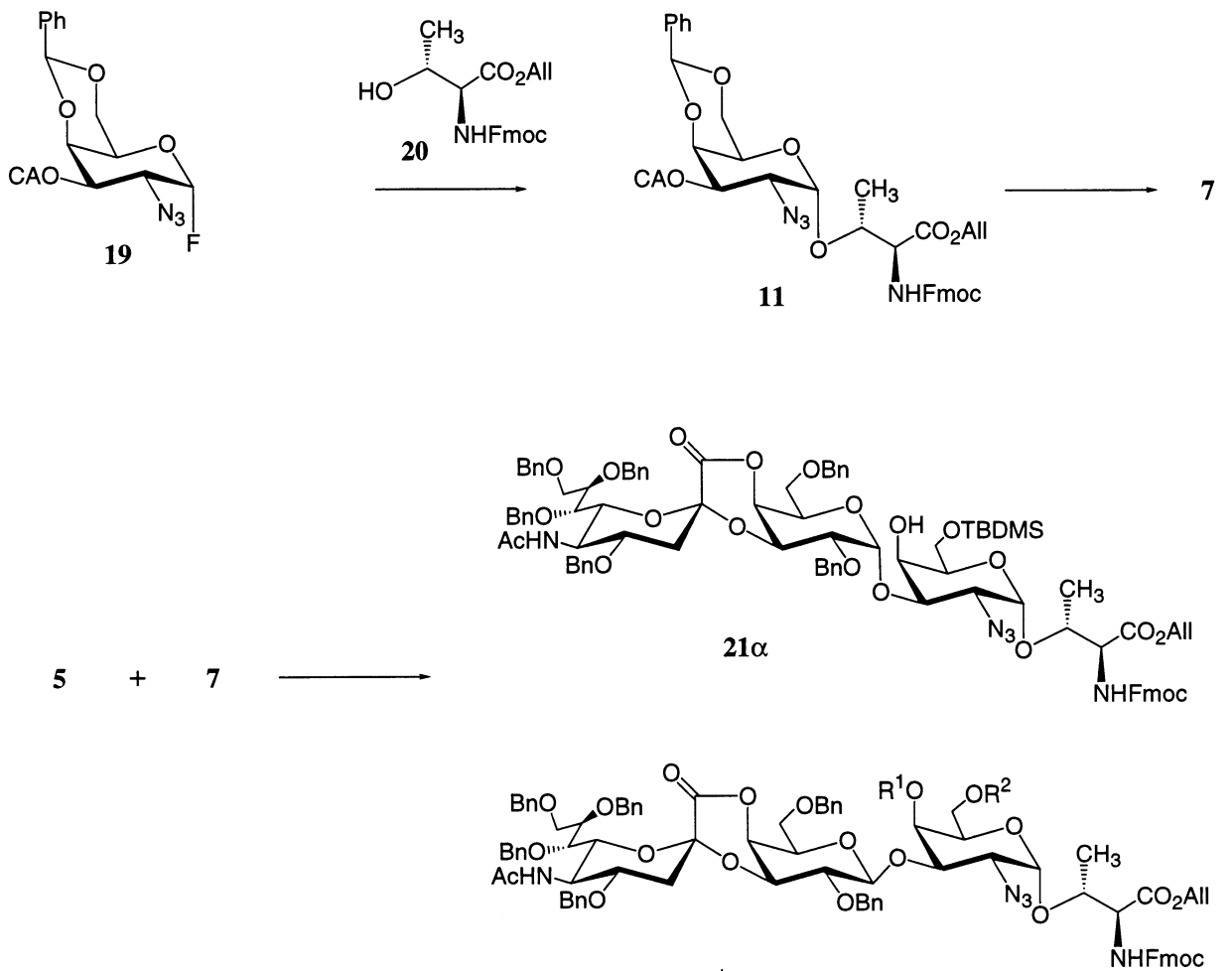
similar to the one used to prepare the analogous *tert*-butyldimethylsilyl ether [15] with a slight modification. In this case sodium cyanoborohydride-mediated reductive ring opening of the 4,6-*O*-benzylidene precursor afforded **6** regioselectively in 97% yield. The Me_3SiOTf-catalyzed reaction of the α-trichloroacetimidate **5** with **6** afforded the trisaccharides **17** (β:α = 2:1) in 75% yield as an inseparable mixture. The anomeric ratio of **17** was ascertained on the basis of the H-4b (β-Gal) signals in the ^1H NMR spectrum. The borontrifluoride diethyletherate-mediated reaction of **5** with **6** furnished **17** as a mixture (β:α = 6:1) in 29% yield. A major part of the trichloroacetimidate was converted to its corresponding α and β fluorides. Glycosylation of **6** with this fluoride donor resulted in low yields of the trisaccharide **17**. Separation of the trisaccharides **17** could be achieved after cleavage of the anomeric silyl ether to afford **18**β. This hemiacetal was then converted to its trichloroacetimidate **3** as a 1:1 anomeric mixture, which was used as such for the next glycosylation (Scheme 3).

We next focused our attention on the construction of the second trisaccharide **4**. The acceptor **7** was synthesized in a manner similar to that used for the analogous serine derivative [14]. The known glycosyl fluoride **19** [12b] and Fmoc threonine allyl ester **20** [16] were coupled in the presence of Cp_2ZrCl_2–$AgClO_4$ [17] to give α-glycoside **11** (76%). The D-galactosamine-derived acceptor **7** was prepared in three steps (1, hydrolysis of chloroacetate; 2, debenzylidenation; 3, regioselective silylation) from **11**. Glycosylation of the α imidate **5** with 2 equivalents of **7** promoted by $BF_3{\cdot}OEt_2$ (0.8 equivalents) in 2:1 toluene–$CHCl_3$ at −15 °C gave the β-glycoside **21**β (54%) and the α-glycoside **21**α (11%). The use of Me_3SiOTf as an alternative promoter for the above reaction led to an in situ cleavage of the *tert*-butyldimethylsilyl ether at the 6 position of the GalNAc acceptor **7**, followed by an additional glycosylation at this position to yield a pentasaccharide. The formation of the pentasaccharide was confirmed by FABMS. Compound **21**β was desilylated (80% aqueous CF_3CO_2H, 0 °C, 90%) to afford **4**, which was used as such as acceptor for the final glycosylation reaction (Scheme 4).

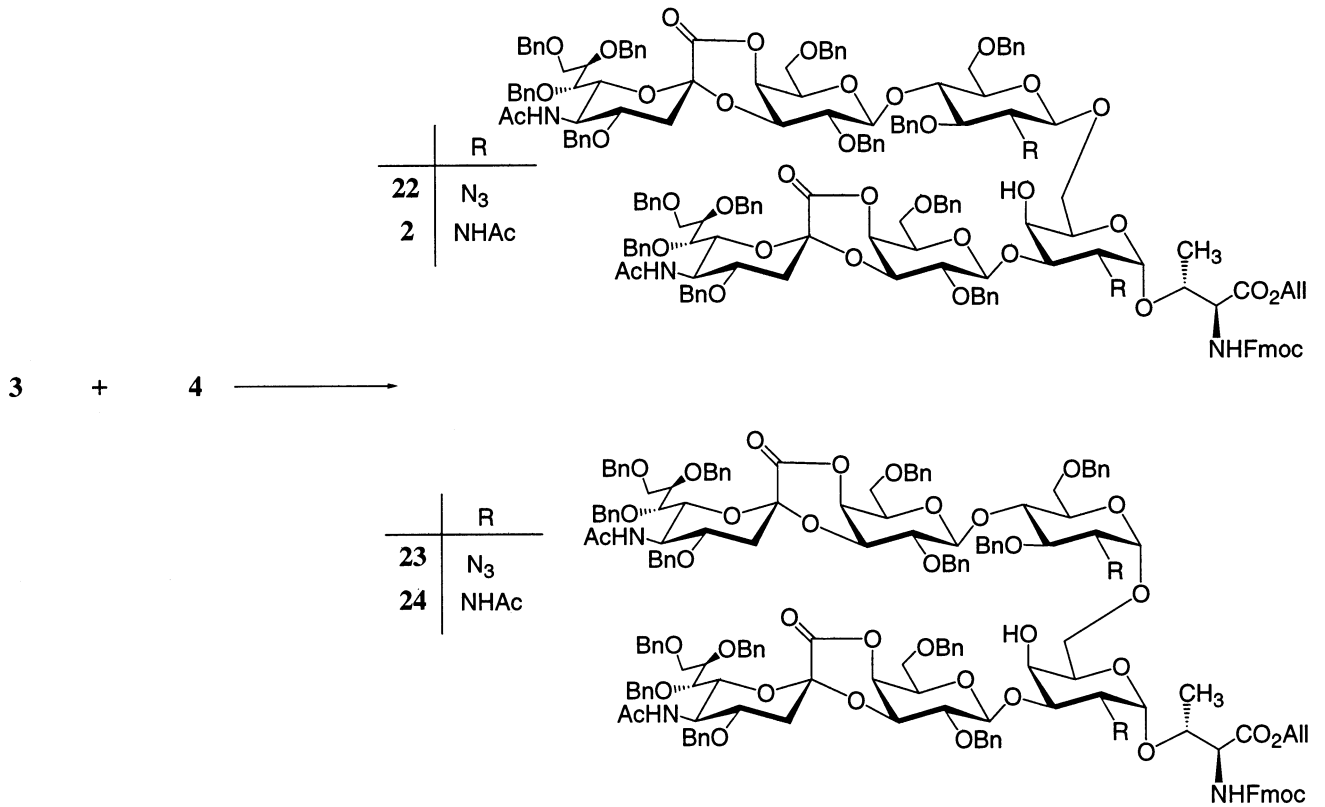
The hexasaccharidic backbone was constructed in a final glycosylation reaction of the two key trisaccharidic intermediates **3** and **4**. The Me_3SiOTf (0.5 equivalents)-promoted reaction in CH_2Cl_2 at −40 °C furnished a mixture of **22** and **23** (3:1) in 80% yield. To facilitate separation, the mixture of the two stereoisomers was treated with freshly distilled thioacetic acid in pyridine to reduce the azide into *N*-acetyl groups. Purification by column chromatography gave the target hexasaccharide **2** (68%) and **24** (22%) (Scheme 5). Use of thioacetic acid contaminated with traces of dithioacetic acid led to monothioacetylated byproduct [18] along with the expected products. The structural assignments were made



Scheme 3.



Scheme 4.



Scheme 5.

from ^{13}C NMR measurements, and their comparison with those of the disaccharide, *N*-(9-fluorenylmethoxycarbonyl)-*O*-[2-acetamido-4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-β-D-gluco-pyranosyl-(1→6)-2-acetamido-3-*O*-acetyl-2-deoxy-α-D-galactopyranosyl]-L-threonine allyl ester.

In conclusion, an efficient route to the synthesis of core class 2 hexasaccharide **2** in a fully protected form has been achieved for the first time.

3. Experimental

General.—Optical rotations were determined with a Jasco DIP-370 polarimeter for solutions in $CHCl_3$. Column chromatography was performed on Silica Gel 60 (E. Merck 70–230 mesh). Thin-layer chromatography (TLC) was performed on Silica Gel 60 F_{254} (E. Merck). ^1H and ^{13}C NMR spectra were recorded on a Jeol α 400, α 600 MHz or EX270 MHz spectrometer. Spectra were recorded in $CDCl_3$ using Me_4Si as an internal standard. Chemical shifts are expressed in ppm downfield. FAB mass spectra were measured on a Jeol JMS-HX-110 mass spectrometer. 3-Nitrobenzyl alcohol was used as the matrix. Molecular sieves were purchased from Nacarai Chemical Co. and activated at 180 °C under vacuum, immediately prior to use. Glycosylation reactions were performed under an atmosphere of Ar in anhydr solvents.**

tert-*Butyldiphenylsilyl-2,6-di*-O-*benzyl-β*-D-*galactopyranoside* (**10**).—To a soln of 3,4-di-*O*-acetyl-2,6-di-*O*-benzyl-D-galactopyranose (4.67 g, 10.51 mmol) and imidazole (1.57 g, 23.12 mmol) in dry DMF (40 mL) was added *tert*-butyldiphenylsilyl chloride (4.1 mL, 15.76 mmol), and the reaction mixture was allowed to stir for 12 h. The reaction was quenched with water, and the DMF was evaporated under high vacuum. The dark residual oil was extracted with EtOAc and washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was chromatographed on silica gel with 5:1 hexane–EtOAc to 2:1 hexane–EtOAc to yield 6.74 g (94%) of the silyl ether. To a soln of the silyl ether in MeOH–toluene (66–14 mL) was added 0.04 equiv of 0.2 N NaOMe in MeOH

and the reaction was allowed to stir for 12 h. The reaction was neutralized with Amberlyst 15 (H^+) resin, filtered, concentrated and chromatographed on silica gel with 1:1 hexane–EtOAc to obtain **10** (5.86 g, 93%). R_f 0.51 (1:1 hexane–EtOAc); $[\alpha]_D$ +21.7° (*c* 0.6); ^{1}H NMR (270 MHz): δ 7.09–7.23 (m, 20 H, Ar), 4.88 (d, 1 H, *J* 11.3 Hz, OC*H*$_2$Ph), 4.63 (d, 1 H, *J* 11.3 Hz, OC*H*$_2$Ph), 4.46 (d, 1 H, *J* 7.4 Hz, H-1), 4.25 (s, 1 H, OC*H*$_2$Ph), 4.24 (s, 1 H, OCH$_2$Ph), 3.70 (d, 1 H, *J* 2.9 Hz, H-4), 3.50 (m, 1 H, H-2), 3.44 (m, 1 H, H-6), 3.31 (m, 2 H, H-3, H-6′), 3.07 (m, 1 H, H-5), 1.02 (s, 9 H, *t*-Bu). ^{13}C NMR (67.5 MHz): δ 97.9 (C-1), 81.0 (C-2), 74.7 (O*C*H$_2$Ph), 73.4 (O*C*H$_2$Ph), 73.1 (C-3), 72.9 (C-5), 69.1 (C-4), 69.0 (C-6). Anal. Calcd for $C_{36}H_{42}O_6Si\cdot0.5\ H_2O$: C, 71.14; H, 7.13. Found: C, 71.51; H, 7.11.

tert-*Butyldiphenylsilyl*-*5*-*acetamido*-*4,7,8,9*-*tetra*-O-*benzyl*-*3,5*-*dideoxy*-D-*glycero*-α-D-*galacto*-*2*-*nonulopyranosylonic acid*-*(2→3)*-*2,6*-*di*-O-*benzyl*-β-D-*galactopyranoside*-*(1b→4a)*-*lactone* (**15**).—A mixture of **8** (1 g, 1.1 mmol), **10** (1 g, 1.66 mmol) and 3 Å molecular sieves (1 g) and NIS (375 mg 1.67 mmol) in dry CH_3CN (12 mL) was allowed to stir for 1 h at −40 °C. To the cooled reaction mixture was added TfOH (19.6 μL, 222 μmol). After 1 h the reaction was quenched with aq $NaHCO_3$, filtered through Celite and concentrated in vacuo. The residue was extracted with EtOAc and washed successively with aq $Na_2S_2O_3$, 1 M Na_2CO_3 and brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography with 4:1 toluene–EtOAc to obtain 1.23 g (77%) of **13**. A mixture of **13** (115 mg, 80 μmol), Ph_3SnH (140 mg, 400 μmol, as its 1 M soln in benzene) and AIBN (3.6 mg, 22 μmol) in dry benzene (3 mL) were heated at 90 °C for 1 h. An additional 1.5 mg of AIBN was added after every 30 min for 3 h, and the reaction was allowed to stir at 90 °C for a total of 7 h. The reaction mixture was then cooled to ambient temperature, filtered through Celite, concentrated in vacuo, and chromatographed on silica gel with 9:1 toluene–EtOAc to 4:1 toluene–EtOAc to obtain 78 mg (80%) of **15**. R_f 0.53 (7:3 toluene–EtOAc); $[\alpha]_D$ +27.3° (*c* 0.1); ^{1}H NMR (270 MHz): δ 7.61–7.11 (m, 40 H, Ar), 5.01 (d, 1 H, *J* 3.4 Hz, H-4a), 4.25 (1 H, H-1a), 3.76 (dd, 1 H, *J* 9.4, *J* 4.1 Hz, H-3a), 3.30–3.38 (m, 1 H, H-2a), 3.30–3.38 (m, 1 H, H-6a), 3.14 (dd, 1 H, *J* 9.8, *J* 6.2 Hz, H-6a′), 2.80 (m, 1 H, H-5a), 2.20 (dd, 1 H, *J* 4.8, *J* 13.3 Hz, H-3b eq), 1.65 (m, 1 H, H-3b ax), 1.64 (s, 3 H, NHCOC*H*$_3$), 1.02 (s, 9 H, *t*-Bu). ^{13}C NMR (67.5 MHz): δ 170.0, 165.5 (O*C*=O, NH*C*=O), 97.1 (C-1a), 95.3 (C-2b). Anal. Calcd for $C_{75}H_{81}NO_{13}Si\cdot0.5\ H_2O$: C, 72.56; H, 6.66; N, 1.13. Found: C, 72.51; H, 6.60; N, 1.29.

5-*Acetamido*-*4,7,8,9*-*tetra*-O-*benzyl*-*3,5*-*dideoxy*-D-*glycero*-α-D-*galacto*-*2*-*nonulopyranosylonic acid*-*(2→3)*-*2,6*-*di*-O-*benzyl*-α *and* β-D-*galactopyranosyl trichloroacetimidate*-*(1b→4a)*-*lactone* (**5**).—A soln of **15** (846 mg, 694 μmol), AcOH (600 μL, 10.5 mmol) and TBAF (3.8 μL, 3.8 mmol, as its mol soln in THF) in dry THF (15 mL) was stirred for 12 h at room temperature (rt). The reaction mixture was then concentrated in vacuo, co-evaporated with toluene and chromatographed on silica gel with 4:1 toluene–EtOAc to give the hemiacetals **16** (685 mg, 99%). To a stirred mixture of **16** (117 mg, 117 μmol) and DBU (1.9 μL, 13.3 μmol) in dry CH_2Cl_2 (3 mL), was added CCl_3CN (118 μL, 1.17 mmol) at −10 °C. After stirring for 2 h, the mixture was chromatographed on silica gel 4:1 toluene–EtOAc to obtain **5** as two fractions of pure α-imidate and α:β (1:9) mixture (94 mg, 30 mg, respectively, 93%). The physical data of the product were identical to those previously reported [14].

tert-*Butyldiphenylsilyl*-*2*-*azido*-*2*-*deoxy*-*3,6*-*di*-O-*benzyl*-β-D-*glucopyranose* (**6**).—To an ice-cooled mixture of *tert*-butyldiphenylsilyl 2-azido-2-deoxy-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (3.3 g, 5.3 mmol), $NaBH_3CN$ (3.33 g, 53 mmol) and 4 Å molecular sieves in dry THF (100 mL) was slowly added a mol soln of HCl in dioxane until effervescence ceased. The reaction mixture was then filtered through Celite and concentrated in vacuo. The residual syrup was extracted with EtOAc and washed successively with aq $NaHCO_3$, water and brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography with 4:1 hexane–EtOAc to 2:1 hexane–EtOAc to obtain **6** (3.2 g, 97%). R_f 0.35 (4:1 hexane–EtOAc); $[\alpha]_D$ −12.8° (*c* 1.1); ^{1}H NMR (270 MHz): δ 7.72–

7.23 (m, 40 H, Ar), 4.87 (d, 1 H, *J* 11.2 Hz, OC*H*$_2$Ph), 4.74 (d, 1 H, *J* 11.2 Hz, OC*H*$_2$Ph), 4.43 (d, 1 H, *J* 11.8 Hz, OC*H*$_2$Ph), 4.37 (d, 1 H, *J* 7.6 Hz, H-1), 4.35 (d, 1 H, *J* 11.8 Hz, OC*H*$_2$Ph), 3.64 (ddd, 1 H, *J* 2.3, *J* 9.5, *J* 8.9 Hz, H-4), 3.52–3.40 (m, 3 H, H-2, H-6, H-6′), 3.14 (dd, 1 H, *J* 8.9, *J* 9.9 Hz, H-3), 2.99 (m, 1 H, H-5), 2.55 (d, 1 H, *J* 2.3 Hz, OH), 1.11 (s, 9 H, *t*-Bu). Anal. Calcd for $C_{36}H_{41}N_3O_5Si$: C, 69.31; H, 6.62; N, 6.74. Found: C, 69.29; H, 6.65; N, 6.76.

tert-*Butyldiphenylsilyl 5-acetamido-4,7,8,9-tetra*-O-*benzyl*-*3,5*-*dideoxy*-D-*glycero*-α-D-*galacto*-*2*-*nonulopyranosylonic acid*-(*2*→*3*)-*2,6*-*di*-O-*benzyl*-β- *and* -α-D-*galactopyranosyl*-(*1*→*4*)-*2*-*azido*-*2*-*deoxy*-*3,6*-*di*-O-*benzyl*-β-D-*glucopyranoside*-(*1b*→*4a*)-*lactone* (**17**).—To a mixture of **6** (46 mg, 73.7 μmol) and 4 Å molecular sieves (50 mg) in 1:1 CH_2Cl_2–hexane (1.2 mL) at −40 °C was added Me_3SiOTf (4.9 μL, 27.6 μmol). The mixture was allowed to stir for 15 min, and to it was added **5** (63 mg, 55.3 μmol). The reaction was quenched with $NaHCO_3$, diluted with EtOAc and filtered through Celite. The organic phase was washed successively with aq $NaHCO_3$ water and brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography with 4:1 toluene–EtOAc to afford **17** (66 mg, 75%, β:α = 2:1). R_f 0.38 (4:1 toluene–EtOAc); **17**β: ^{1}H NMR (400 MHz): δ 5.15 (d, 1 H, *J* 4.4 Hz, H-4b), 4.25–4.40 (m, H-1a, H-1b), 2.28 (dd, 1 H, *J* 5.1, *J* 13.4 Hz, H-3c eq), 1.75 (s, 3 H, NHCOC*H*$_3$), 1.1 (s, 9 H, *t*-Bu); ^{13}C NMR (100 MHz): 101.7 (C-1b), 96.7 (C-1a), 95.3 (C-2c), 23.7 (*C*H$_3$C=O), 37.7 (C-3c); **17**α ^{1}H NMR (400 MHz): δ 5.52 (d, 1 H, *J* 3.9 Hz, H-1b), 5.26 (d, 1 H, *J* 3.4 Hz, H-4b), 4.25–4.40 (d, H-1a), ^{13}C NMR (100 MHz): 96.8 (C-1a), 96.9 (C-1b), 95.3 (C-2c); FABMS $[M + Na]^+$ 1622.3.

5-*Acetamido*-*4,7,8,9*-*tetra*-O-*benzyl*-*3,5*-*dideoxy*-D-*glycero*-α-D-*galacto*-*2*-*nonulopyranosylonic acid*-(*2*→*3*)-*2,6*-*di*-O-*benzyl*-β-D-*galactopyranosyl*-(*1*→*4*)-*2*-*azido*-*2*-*deoxy*-*3,6*-*di*-O-*benzyl*-β-D-*glucopyranosyl trichloroacetimidate*-(*1c*→*4b*)-*lactone* (**3**).—A mixture of **17** (45 mg, 28 μmol), AcOH, (24 μL, 422 μmol) and 1 M TBAF soln in THF (155 μL, 155 μmol) in dry THF (5 mL) was stirred at rt for 12 h. The reaction mixture was diluted with EtOAc, concentrated in vacuo, extracted with EtOAc and washed successively with water and brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography with 10:1 $CHCl_3$–*tert*-butylmethyl ether to obtain **18** as an anomeric mixture. This mixture was purified by preparative TLC using $CHCl_3$–*tert*-butylmethyl ether to afford the hemiacetals as two fractions consisting of pure **18**β and **18**α (20 mg and 16 mg, respectively, 94%). To a soln of **18**β (14 mg, 10.3 μmol), CCl_3CN (10.3 μL, 103 μmol) in CH_2Cl_2 (1 mL) at −10 °C was added DBU (0.3 μL, 2.05 μmol as a soln in CH_2Cl_2). The reaction mixture was chromatographed on silica gel with 4:1 toluene–EtOAc to abtain **3** as an α:β 1:1 mixture (14.8 mg, 96%). R_f 0.54 (7:3 toluene–EtOAc); **3** ^{1}H NMR (400 MHz): δ 8.63 (s, 2 H, 2 C=NH), 6.27 (d, 1 H, *J* 3.4 Hz, H-1a α), 5.50 (d, 1 H, *J* 8.2 Hz, H-1a β), 5.08 (d, 2 H, *J* 3.9 Hz, H-4b α,β), 2.32–2.21 (m, 2 H, H-3c eq α,β), 1.69 (s, 3 H, NHCOC*H*$_3$), 1.68 (s, 3 H, NHCOC*H*$_3$), 1.69 (m, H-3c ax α,β).

N-*(9-Fluorenylmethoxycarbonyl)*-O-*(2-azido-4,6*-O-*benzylidene*-*3*-O-*chloroacetyl*-*2*-*deoxy*-α-D-*galactopyranosyl)*-L-*threonine allyl ester* (**11**).—A mixture of Cp_2ZrCl_2 (2.1 g, 7.2 mmol), $AgClO_4$ (1.48 g, 7.2 mmol), and dried, powdered 4 Å molecular sieves (5.5 g) in dry CH_2Cl_2 (53 mL) was stirred at rt for 30 min under Ar, then cooled in an ice–MeOH bath (−15 °C). A soln of **19** (1.33 g, 3.6 mmol) and **20** (1.60 g, 4.3 mmol) in dry CH_2Cl_2 (70 mL) was added, and the mixture was stirred between −15 °C and rt overnight. After the reaction was quenched with aq $NaHCO_3$, the mixture was diluted with EtOAc, and filtered through Celite. The filtrate was washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was chromatographed on silica gel with 93:7 toluene–EtOAc to afford crystalline **11** (1.70 g, 76%). Compound **11**: R_f 0.30 (9:1 toluene–EtOAc); mp 78–80 °C; $[\alpha]_D$ +161.2° (*c* 1.0); ^{1}H NMR (400 MHz): δ 7.8–7.3 (m, 13 H, Ar), 5.94 (m, 1 H, –C*H*=CH$_2$), 5.69 (d, 1 H, *J* 9.6 Hz, NH), 5.56 (s, 1 H, PhC*H*(O)$_2$), 5.36 (brd, 1 H, *J* 17.2 Hz, CH=C*H*$_2$), 5.28 (brd, 1 H, *J* 10.2 Hz, CH=C*H*$_2$), 5.12 (d, 1 H, *J* 3.6 Hz, H-1), 4.68 (brd, 2 H, *J* 5.6 Hz,

–CH_2CH=CH_2), 4.16 (s, 2 H, –CH_2Cl), 4.02 (dd, 1 H, *J* 3.6, *J* 11.2 Hz, H-2), 3.82 (brs, 1 H, H-4), 1.33 (d. 3 H, *J* 6.3 Hz, Thr–CH_3); Anal. Calcd for $C_{37}H_{37}ClN_4O_{10}$: C, 60.61; H, 5.09; N, 7.64; Cl, 4.84. Found: C, 61.18; H, 5.17; N, 7.26; Cl, 4.91.

N-*(9-Fluorenylmethoxycarbonyl)*-O-*(2-azido-6*-O-tert-*butyldimethylsilyl-2-deoxy*-α-D-*galactopyranosyl)*-L-*threonine allyl ester* (**7**).—A stirred mixture of **11** (860 mg, 1.17 mmol) and thiourea (500 mg, 6.45 mmol) in dry DMF (30 mL) was heated at 70 °C under Ar for 1 h. After cooling, the mixture was concentrated in vacuo. The residue was extracted with 1:1 ether–EtOAc, washed with water and brine, dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography with 4:1 toluene–EtOAc to give the de-chloroacetylated product as crystals (630 mg, 82%); R_f 0.46 (7:3 toluene–EtOAc); mp 73–74 °C; $[\alpha]_D$ + 125.0° (*c* 1.0).

A mixture of the crystals (130 mg, 198 μmol), 80% aq CF_3CO_2H (3 mL) and CH_2Cl_2 (1 mL) was stirred at 0 °C for 3 h, diluted with water and toluene, and concentrated in vacuo. The residue was extracted in EtOAc and washed successively with aq $NaHCO_3$, water and brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography with 10:1 $CHCl_3$–MeOH to afford the triol (109 mg), which was dissolved in DMF (1.75 mL) and stirred with *tert*-BuMe_2SiCl (65 μL, 249 μmol) and imidazole (29 mg, 422 μmol) for 4 h at 40 °C. The reaction was quenched with water and concentrated in vacuo. The residue was extracted in EtOAc and washed successively with water and brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography with 2:1 hexane–EtOAc to afford **7** (139 mg, 87%). R_f 0.48 (10:1 $CHCl_3$–MeOH); $[\alpha]_D$ + 56.1° (*c* 3.3); ^{1}H NMR (270 MHz): δ 7.76 (m, 2 H, Ar), 7.62 (m, 2 H, Ar), 7.40 (m, 2 H, Ar), 7.31 (m, 2 H, Ar), 5.92 (m, 1 H, –C*H*=CH_2), 5.70 (d, *J* 9.5 Hz, NH), 5.36 (brd, 1 H, *J* 17.1 Hz, –C=CH_2), 5.27 (brd, 1 H, *J* 10.2 Hz, –C=CH_2), 4.97. (d, 1 H, *J* 3.6 Hz, H-1), 4.70 (d, 2 H, *J* 5.9 Hz, CO_2CH_2), 3.52 (dd, *J* 3.6, *J* 10.2 Hz, H-2), 1.30 (d, 3 H, *J* 6.3 Hz, Thr–CH_3), 0.90 (s, 9 H, *t*-Bu), 0.10 (s, 6 H, 2 Me). Anal. Calcd for $C_{34}H_{46}N_4O_9Si{\cdot}0.5\ H_2O$: C, 59.03; H, 6.85; N, 8.10. Found: C, 58.89; H, 6.77; N, 7.99.

N-*(9-Fluorenylmethoxycarbonyl)*-O-*[(5-acetamido-4,7,8,9-tetra*-O-*benzyl-3,5-dideoxy*-D-*glycero*-α-D-*galacto-2-nonulopyranosylonic acid)*-*(2→3)*-*(2,6-di*-O-*benzyl*-β- *and* α-D-*galactopyranosyl)*-*(1→3)*-*2-azido-6*-O-tert-*butyldimethylsilyl-2-deoxy*-α-D-*galactopyranosyl-(1c→4b)-lactone]*-L-*threonine allyl ester* (**21**).—A mixture of **5** (50 mg, 44 μmol), **7** (36 mg, 53 μmol), and powdered AW 300 molecular sieves (550 mg) in 2:1 toluene–CH_2Cl_2 (2 mL) was stirred at rt for 1 h and then cooled to −15 °C. To the mixture was added 0.2 M $BF_3{\cdot}OEt_2$ (176 μL, 35.2 μmol). The reaction mixture was diluted with ether and filtered through Celite. The filtrate was washed successively with aq $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on silica gel with 4:1 toluene–EtOAc to afford **21**α (7.6 mg, 11%) and **21**β (40 mg, 54%) and **7** (16 mg, 43% recovery). **21**β: R_f 0.38 (4:1 toluene–EtOAc); $[\alpha]_D$ + 18.7° (*c* 2.1); ^{1}H NMR (400 MHz): δ 7.75 (d, 2 H, *J* 7.3 Hz, Ar), 7.61 (d, 2 H, *J* 7.3 Hz, Ar) 5.92 (m, 1 H, CH_2CH=CH_2), 5.68 (d, 1 H, *J* 9.8 Hz, NH), 5.35 (d, 1 H, *J* 16.8 Hz, C=CH_2), 5.25 (d, 1 H, *J* 10.6 Hz, –C=CH_2), 5.20 (d, 1 H, *J* 3.6 Hz, H-4b), 5.03 (d, 1 H, *J* 3.6 Hz, H-1a), 4.42 (m, H-1b), 2.19 (dd, 1 H, *J* 4.6, *J* 14.1 Hz, H-3c eq), 1.69 (s, 3 H, NHCOCH_3), 1.35 (d, 3 H, *J* 6.5 Hz, Thr–CH_3), 0.86 (s, 9 H, *t*-Bu).^{13}C NMR (100 MHz): δ 102.9 (C-1b, *J* 158.5 Hz,), 100.0 (C-1a, *J* 171.4 Hz), 95.4 (C-2c), 37.5 (C-3c), 23.6 (NHCO*C*H_3), 19.0 (*C*H_3–Thr). FABMS $[M + Na]^+$ 1681.3; **21**α: R_f 0.39 (4:1 toluene–EtOAc); ^{1}H NMR (400 MHz): δ 7.72 (d, 2 H, *J* 7.6 Hz, Ar), 7.58 (d, 2 H, *J* 7.5 Hz, Ar), 5.93 (m, 1 H, –CH=CH_2), 5.63 (d, 1 H, *J* 9.8 Hz, NH–Thr), 5.34 (m, 2 H, H-4b, –CH=CHH′), 5.22 (d, *J* 10.3 Hz, –CH=CHH′), 4.96 (d, 1 H, *J* 3.8 Hz, C-1a), 4.91 (d, 1 H, *J* 3.7 Hz, H-1b), 4.51 (m, H-3b), 4.02 (m, H-3a), 3.59 (dd, 1 H, *J* 3.8, *J* 9.6 Hz, H-2b), 3.42 (m, H-2a), 2.40 (dd, 1 H, *J* 5.1, *J* 13.2 Hz, H-3c eq), 1.87 (dd, 1 H, *J* 10.7, *J* 13.2 Hz, H-3c ax), 1.77 (s, 3 H, $NHCOCH_3$), 0.90 (s, 9 H, *t*-Bu), 0.07 (s, 6 H, 2 CH_3). ^{13}C NMR (100 MHz): δ 169.7, 169.6, 165.1 (O–*C*=O, NH*C*=O, *C*O_2 all not assigned), 99.8 (C-1a), 95.2 (C-1b), 95.1 (C-2c), 38.1 (C-2c), 25.9 (t-Bu), 23.8 (NHCO*C*H_3), 18.9 (*C*H_3–Thr).

N - *(9 - Fluorenylmethoxycarbonyl)* - O - *[(5-acetamido-4,7,8,9-tetra*-O-*benzyl-3,5-dideoxy-*D-*glycero*-α-D-*galacto*-2-*nonulopyranosylonic acid)*-(2→3)-*(2,6-di*-O-*benzyl*-β-D-*galacto-pyranosyl)*-(1→3)-2-*azido*-2-*deoxy*-α-D-*galactopyranosyl-(1c→4b)-lactone]*-L-*threonine allyl ester* (**4**).—To a soln of **21**β (37 mg, 21 μmol) in CH_2Cl_2 at 0 °C was added 80% aq CF_3CO_2H (2 mL) and the soln was stirred for 3 h. It was then neutralized with solid $NaHCO_3$, diluted, and extracted with EtOAc. The organic phase was washed successively with water and brine, dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography on silica gel with 3:2 toluene–EtOAc to afford **4** (28.8 mg, 90%). R_f 0.35 (3:2 toluene–EtOAc); $[\alpha]_D$ +65.1° (*c* 0.7); ^{1}H NMR (400 MHz): δ 7.68 (d, 2 H, *J* 7.4 Hz, Ar), 7.54 (d, 2 H, *J* 7.2 Hz, Ar), 5.75 (m, 1 H, –C*H*=CH$_2$), 5.63 (d, 1 H, *J* 9.5 Hz, NH), 5.28 (d, 1 H, *J* 16.9 Hz, –C=C*H*$_2$), 5.18 (d, 1 H, *J* 10.1 Hz, =C*H*$_2$), 5.18 (d, 1 H, *J* 3.8 Hz, H-4b), 4.96 (d, 1 H, *J* 3.6 Hz, H-1a), 2.13 (dd, 1 H, *J* 4.8, *J* 13.5 Hz, H-3c eq.), 1.61 (m, H-3c ax), 1.60 (s, 3 H, NHCOC*H*$_3$). 1.24 (d, 3 H, *J* 6.2 Hz, Thr–C*H*$_3$); ^{13}C NMR (100 MHz): δ 170.5, 170.4, 165.4 (NH*C*O, O–*C*=O, *C*O$_2$All), 103.1 (C-1b), 100.0 (C-1a), 95.9 (C-2c), 23.9 (NHCO*C*H$_3$), 19.2 (*C*H$_3$–Thr). Anal. Calcd for $C_{87}H_{93}N_5O_{21}$: C, 67.64; H, 6.06; N, 4.53. Found: C, 67.23; H, 6.19; N, 4.32.

N - *(9 - Fluorenylmethoxycarbonyl)* - O - *{(5-acetamido-4,7,8,9-tetra*-O-*benzyl-3,5-dideoxy-*D-*glycero*-α-D-*galacto*-2-*nonulopyranosylonic acid)*-(2→3)-*(2,6-di*-O-*benzyl*-β-D-*galacto-pyranosyl)*-(1→4)-2-*acetamido*-2-*deoxy*-3,6-*di*-O-*benzyl*-β-D-*glucopyranosyl*-(1→6)-*[(5*-acetamido-4,7,8,9-tetra-O-*benzyl*-3,5-*dideoxy*-D-*glycero*-α-D-*galacto*-2-*nonulopyranosylonic acid)*-(2→3)-2,6-*di*-O-*benzyl*-β-D-*galactopyranosyl*-(1→3)*]*-2-*acetamido*-2-*deoxy*-α-D-*galactopyranosyl-(1d→4c:1f→4e)-dilactone}*-L-*threonine allyl ester* (**2**).—To a mixture of **3** (13 mg, 8.6 μmol), **4** (15.3 mg, 9.9 μmol) and 4 Å molecular sieves (60 mg) in CH_2Cl_2 (1.6 mL) at −40 °C was added Me_3SiOTf (0.08 μL, 4.6 μmol, as its soln in CH_2Cl_2). After 1 h the reaction was quenched with $NaHCO_3$, diluted with EtOAc and filtered through Celite. The organic phase was washed successively with water and brine, dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography on silica gel with 1:1 hexane–EtOAc to afford **22** and **23** as a mixture (20 mg, β:α = 3:1, 80%). Compounds **22** and **23** (9 mg, 3.1 μmol) were stirred with freshly distilled AcSH (152 μL) and pyridine (76 μL) for 12 h under a N_2 atmosphere. The reaction mixture was diluted and co-evaporated with toluene, and the residual yellow liquid was purified by column chromatography on silica gel over a gradient of 1:1, 1:2, 1:3 hexane–EtOAc to afford **2** (6.2 mg, 68%) and **24** (2.0 mg, 22%). **2** R_f 0.30 (1:3 hexane–EtOAc); $[\alpha]_D$ +27.5° (*c* 0.4); ^{1}H NMR (600 MHz): δ 7.74 (d, 2 H, *J* 7.3 Hz, Ar), 7.61 (m, 2 H, Ar) 5.85 (m, 1 H, C*H*=CH$_2$), 5.32 (d, 2 H, *J* 17.1 Hz, –C=C*H*$_2$), 5.27 (d, 2 H, *J* 10.2 Hz, =C*H*$_2$), 5.14 (d, 1 H *J* 3.4 Hz, H-4, Gal), 5.12 (d, *J* 3.4 Hz, H-4, Gal), 4.81 (m, 2 H, H-1, GlcNAc, H-1, GalNAc), 3.88–4.02 (m, H-4, NeuNAc, H-4, NeuNAc′ not assigned), 2.29 (m, 1 H, H-3eq, NeuNAc), 2.07 (m, 1 H, H-3eq, NeuNAc′) 1.84 (s, 3 H, NHCOC*H*$_3$), 1.82 (s, 3 H, NHCOC*H*$_3$), 1.75 (s, 3 H, NHCOC*H*$_3$), 1.70 (s, 3 H, NHCOC*H*$_3$), 1.77 (t, 1 H, *J* 10.7 H-3ax, NeuNAc), 1.62 (t, 1 H, *J* 10.7 H-3ax, NeuNAc′), 1.28 (3 H, Thr–C*H*$_3$). ^{13}C NMR (150 MHz): δ 103.4, 102.0 (C-1 Gal, C-1, Gal′ not assigned), 100.6 (C-1, GalNAc), 99.8 (C-1, GlcNAc), 95.3 (C-2, NeuAc, C-2, NeuAc′ not assigned), 23.4, 23.6, 23.7 (NHCO*C*H$_3$ × 4), 18.3 (Thr–*C*H$_3$). FABMS $[M+1]^+$ 2920.5, $[M+Na]^+$ 2942.9; **24** R_f 0.40 (1:3 hexane–EtOAc); $[\alpha]_D$ +33.9° (*c* 0.2); ^{1}H NMR (600 MHz): δ 7.77 (m, 2 H, Ar), 7.63 (m, 2 H, Ar) 5.72 (m, 1 H, C*H*=CH$_2$), 5.22 (m, 2 H, –CH=C*H*$_2$), 5.15 (d, *J* 3.4 Hz, H-4, Gal), 5.11 (d, *J* 2.9 Hz, H-4, Gal′), 4.75–4.81 (m, 2 H, H-1, GlcNAc, H-1, GalNAc not assigned), 3.97–4.78 (m, H-4, NeuNAc, H-4, NeuNAc′ not assigned), 2.30 (m, 1 H, H-3eq, NeuNAc), 2.05 (m, 1 H, H-3eq, NeuNAc′), 1.83 (s, 3 H, NHCOC*H*$_3$), 1.81 (s, 3 H, NHCOC*H*$_3$), 1.75 (s, 3 H, NHCOC*H*$_3$), 1.75 (m, H-3ax, NeuNAc), 1.69 (s, 3 H, NHCOC*H*$_3$), 1.58 (m, 1 H, H-3ax, NeuNAc), 1.27 (3 H, Thr–C*H*$_3$). ^{13}C NMR (150 MHz): δ 103.3, 102.2 (C-1 Gal, C-1 Gal′ not assigned), 100.6 (C-1, GlcNAc), 97.2 (C-1, GalNAc), 95.3 (C-2, NeuAc, C-2, NeuAc′ not assigned), 23.7, 23.5, 23.4, 23.0

($NHCOCH_3 \times 4$), 18.5 (Thr–CH_3). FABMS $[M + Na]^+$ 2942.9.

Acknowledgements

We are grateful to Dr J. Uzawa, Dr H. Koshino, and T. Chijimatsu for the NMR and Dr Y. Ohnishi for the FABMS measurements. We thank A. Takahashi for technical assistance.

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