Syntheses of Anomerically Phosphodiester-Linked Oligomers of the Repeating Units of the *Haemophilus influenzae* Types c and f Capsular Polysaccharides

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Spacer-equipped dimers and trimers of the repeating units of the capsular polysaccharide of *Haemophilus influenzae* type c, −4)-3-*O*-Ac-*β*-D-Glc*p*NAc-(1→3)-α-D-Gal*p*-(1-OPO_3^-−, and type f, −3)-*β*-D-Gal*p*NAc-(1→4)-3-*O*-Ac-α-D-Gal*p*NAc-(1-OPO_3^-−, have been synthesized for use in immunological studies. H-Phosphonate chemistry was used for the formation of the interglycosidic phosphate diester linkages. Two types of building blocks, a spacer glycoside disaccharide starting monomer (**15** and **22**) and an anomeric monoester α-H-phosphonate disaccharide elongating monomer (**12** and **27**), were built up for each serotype structure from properly protected monosaccharide precursors using mainly thioglycosides as glycosyl donors. Stereospecificity in the formation of the α-linked monoester H-phosphonate was possible in type c through crystallization of the pure α-anomer of the precursor hemiacetal from an α/*β*-mixture, whereas in type f, the hemiacetal was isolated directly as exclusively the α-anomer. Subsequent phosphonylation using triimidazolylphosphine was performed without anomerization. Formation of the anomeric phosphate diester linkages was performed using pivaloyl chloride as coupling reagent followed by I_2/H_2O oxidation of the formed diester H-phosphonates. Original experiments afforded no diester product at all, but optimization of the oxidation conditions (lowering the temperature and dilution with pyridine prior to I_2 addition) gave the dimers in good yields (71% and 81%) and, subsequently, after removal of a temporary silyl protecting group in the dimers, the trimers in fair yields (36% and 37%), accompanied by hydrolysis of the dimer phosphate linkage. One-step deprotection through catalytic hydrogenolysis efficiently afforded the target dimer (**30** and **36**) and trimer structures (**32** and **39**). The synthetic scheme allows for further elongation to give higher oligomers.

Introduction

Haemophilus influenzae is a Gram-negative bacterium causing, among others, meningitis, pneumoniae, and otitis. The bacteria are divided into six serotypes, a−f, all corresponding to a specific capsular polysaccharide (CPS) structure.[1] Noncapsulated bacteria are referred to as nontypable *H. influenzae* (NTHi). There are already commercial glycoconjugate vaccines based on processed native CPS coupled to a carrier protein against type b,[2] which is the serogroup causing the most severe *H. influenzae* infections. In a program directed toward a more complete understanding of the immunological properties of the carbohydrate surface antigens of *H. influenzae*, well-defined synthetic structures from all the CPS serotypes and also the lipopolysaccharide (LPS) were a prerequisite. We have earlier reported the synthesis of structures from serotypes a,[3] b,[4] d,[5] and e,[6] as well as LPS structures.[7] In this paper, the syntheses of oligomer structures corresponding to the type c and type f CPSs are described.

Of the six different CPSs, four, types a, b, c, and f, are built up by repeating oligosaccharide units bridged by phosphate diester linkages.[1] In types c and f, one of these phosphate diester bonds is anomeric (Figure 1).[8−11] The synthesis of anomeric phosphodiesters is severely complicated, as compared to that of nonanomeric ones, by the requirement of stereospecificity in the linkage combined with the inherent instability of the formed diesters. The instability is due to the ability of the glycosyl ring to form a stabilized anomeric carbocation through the expulsion of an anomeric leaving group, e.g., a monoester phosphate, and is recognized by the fact that anomeric phosphotriesters are used as effective glycosyl donors.[12,13] The ease of formation of an anomerically pure phosphodiester as well as the stability of it varies greatly depending on the substrate. However, the yields are invariantly much lower than those obtained in nucleotide

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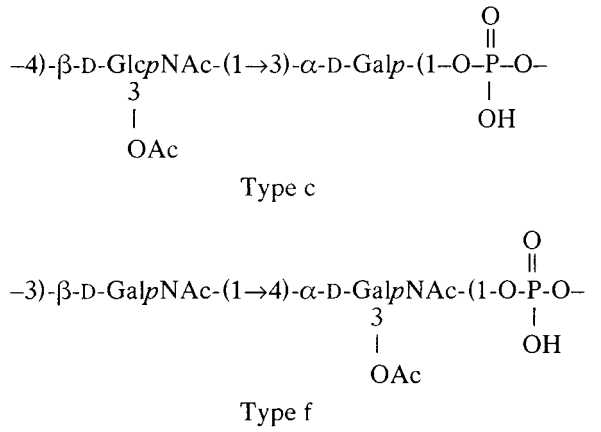


Figure 1. Structures of the repeating units of the capsular polysaccharides of *H. influenzae* types c[8,9] and f.[10,11]

synthesis, and only few examples of successful synthesis of anomerically linked oligomers of oligosaccharides have been reported.[14−18]

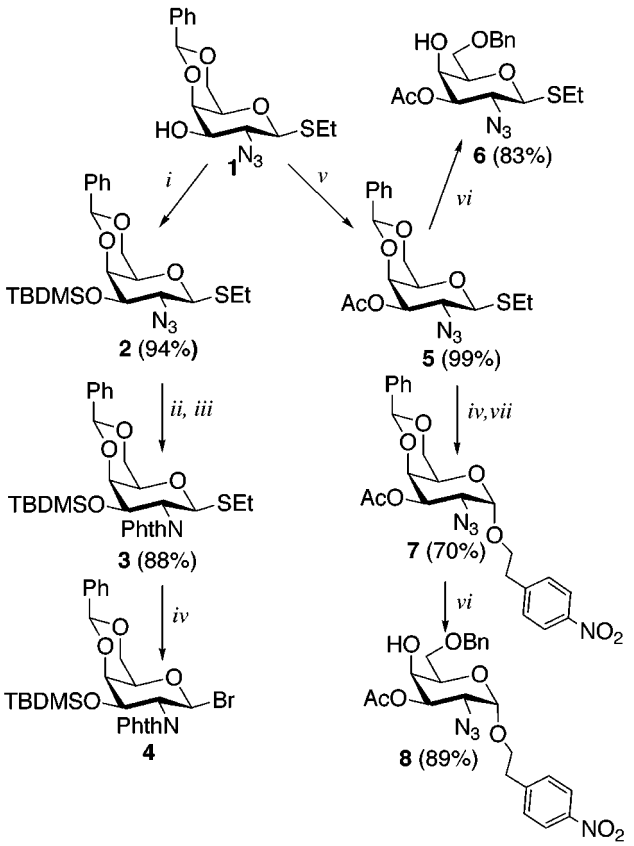
The repeating units of the CPS of *H. influenzae* types c (Hic) and f (Hif) contain added complexity in the form of aminosugars and acetyl substituents, the latter excluding the use of most ester-protecting groups and too basic reaction conditions. Also, the diester formation to give Hic structures was found to be unexpectedly problematic, because initial attempts to form a disaccharide phosphodiester using published conditions failed completely,[19] indicating a severe instability of the desired products.

In this article, the syntheses of a dimer and a trimer of the repeating unit of types c and f are presented. The phosphodiesters are formed using the H-phosphonate method,[20] and all structures are synthesized as spacer glycosides to facilitate the coupling to proteins and formation of immunogenic glycoconjugates.

Results and Discussion

Because of the instability of the anomeric phosphodiester linkage, it was decided to introduce the spacer as a stable *O*-glycoside, and accordingly, two disaccharide precursors were designed and constructed for each serotype, a spacer disaccharide starting monomer acceptor (**15** and **22**) and an anomeric monoester hydrogen phosphonate disaccharide elongating monomer (**12** and **27**) containing a temporary protecting group to allow continued elongations. As a spacer, a *p*-aminophenylethyl group was originally chosen, the phenyl group allowing easy UV detection and also the possibility of radioactive labeling by ^{135}I. However, hydrogenolysis to deprotect the synthesized type f structures also reduced the aromatic system in the spacer. Consequently, a nonaromatic spacer, 2-aminoethanol, was chosen for the type c structures, which increased the yield in the deprotection step considerably.

Scheme 1. Synthesis of Type f Monosaccharide Intermediates[a]



[a] Key: (i) TBDMS−Cl, imidazole, DMF; (ii) Ph_3P, CH_2Cl_2; (iii) phthalic anhydride, *n*-Bu_4NCN, toluene, reflux; (iv) Br_2, CH_2Cl_2; (v) Ac_2O, pyridine; (vi) $NaCNBH_3$, HCl/Et_2O, THF; (vii) *p*$NO_2PhCH_2CH_2OH$, Et_4NBr, DMF, CH_2Cl_2.

The synthesis of the starting and the elongating monomer of type f is summarized in Schemes 1 and 2. Because the repeating unit of *H. influenzae* type f is built up by two GalNAc residues, all of the necessary monosaccharide intermediates could be synthesized from a single precursor, ethyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-*β*-D-galactopyranoside (**1**) (Scheme 1), obtained via azidonitration of galactal.[21] Initially, attempts were made to use an even more convergent strategy, among others, utilizing the azido group as the sole amino group equivalent. However, glycosylations between the α-trichloroacetimidate analogue of the azido donor **2** and acceptor **6** gave exclusively the α-linked disaccharide, despite earlier results showing S_N2-type reactions and inverted anomeric configuration with this type of donor.[22] This result incited the introduction of a participating, *β*-directing N-protecting group in the donor, and consequently, donors **3** and **4** were synthesized. Also, the use of a common thiodisaccharide for the formation of both the starting and the elongating monomer was planned, but once more, stereoselectivity problems were encountered, this time in the introduction of the spacer moiety. Thus, coupling between donor **9** and the spacer, 2-(*p*-nitrophenyl)ethanol, using dimethyl(methylthio)sulfonium tri-

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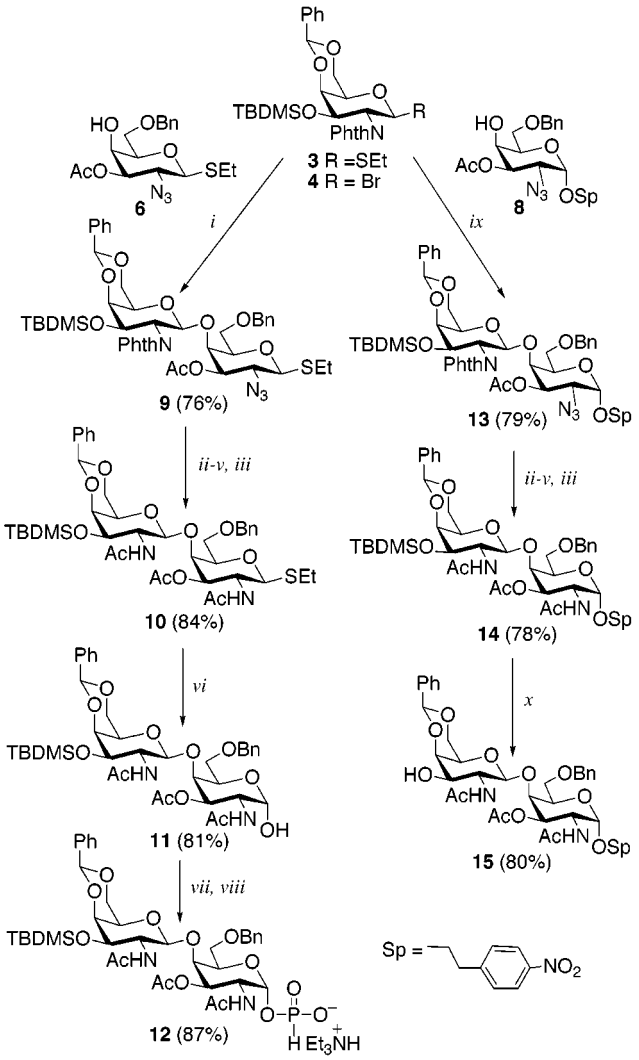
Scheme 2. Synthesis of Type f Starting and Elongating Disaccharide Monomers[a]



[a] Key: (i) AgOTf, DTBMP, CH_2Cl_2, −50 °C; (ii) $H_2NCH_2CH_2NH_2$, toluene/EtOH, reflux; (iii) Ac_2O, pyridine; (iv) Ph_3P, CH_2Cl_2; (v) H_2O, THF, reflux; (vi) NIS, H_2O, acetone; (vii) PCl_3, imidazole, Et_3N, MeCN; (viii) Et_3NHHCO_3, H_2O; (ix) DMTST, DTBMP, CH_2Cl_2; (x) $Et_3N(HF)_3$, THF.

flate[23] (DMTST) as promoter in diethyl ether gave mainly the β-glycoside (α/β 2:5). The use of the corresponding bromo sugar donor and halide-assisted conditions[24] did not yield any product at all. Therefore, it was decided to introduce the spacer at the monosaccharide level, where the halide-assisted glycosylation was found to work well (see below).

Silylation, with *tert*-butyldimethylsilyl chloride, of the 3-OH group in **1** to give **2** (94%) introduced a temporary protecting group to allow later elongation at this position (Scheme 1). The transformation of the azido group into a *N*-phthaloyl group, using a slightly modified version of the procedure published by Garcia et al.,[25] yielded thioglycoside donor **3** (88%) with a participating group to ascertain β-linkage formation in subsequent glycosylations. This donor can also effectively be turned into the corresponding bromo sugar donor **4** by treatment with bromine. Acetylation of **1** inserted the native acetyl substituent and gave **5** (99%), which was processed into two different 4-OH acceptors, **6** and **8**. Reductive opening of the benzylidene acetal[26] yielded the thioglycoside acceptor **6** (83%), whereas coupling with the spacer, 2-(4-nitrophenyl)ethanol, using halide-assisted conditions (→**7**, 70%), followed by benzylidene opening, gave the α-linked spacer glycoside acceptor **8** (89%). Attempts to use **6** as donor precursor instead of **5** in a halide-assisted glycosylation with the spacer were accompanied by acetyl migration, and a mixture of **8** and its 4-*O*-acetyl analogue (2:1) was obtained.

These monosaccharide intermediates were now utilized in the formation of the disaccharide monomers (Scheme 2). Silver triflate-promoted orthogonal glycosylation between the bromo sugar donor **4** and the thioglycoside acceptor **6** gave the β-linked disaccharide **9** (76%). The coupling between the two thioglycosides, **3** and **6**, was also tried. The azido group is more deactivating than the *N*-phthaloyl group,[27] and hence, **6** should act as the acceptor in such a glycosylation, but the reactivity difference was found to be too small to ensure an effective orthogonal coupling. At the best, 31% of **9** could be isolated using *N*-iodosuccinimide/trimethylsilyl triflate (NIS/TMSOTf)[28] as promoter at −50 °C. The glycosylation between the thioglycoside donor **3** and the spacer glycoside acceptor **8** with DMTST as promoter was straightforward, and disaccharide **13** was obtained in 79% yield. Because no more glycosylations were to be performed, the stereodirecting qualities of the azido (nonparticipating) and *N*-phthaloyl (participating) groups were not needed any more, and these were accordingly changed into the acetamido groups present in the target molecules. In a five-step sequence, **9** and **13** were converted to **10** (74%) and **14** (78%), respectively. Hydrolysis of the thioglycoside in **10** gave the hemiacetal **11** (81%). No stereoselectivity problems in the formation of the anomeric H-phosphonate elongating monomer were encountered, because **11** was isolated as the pure α-anomer, from which the α-monoester H-phosphonate **12** could easily be formed in 87% yield by treatment with triimidazolylphosphine followed by basic hydrolysis.[29] Removal of the *tert*-butyldimethylsilyl (TBDMS) group from **14** provided the starting monomer acceptor **15** (80%).

The syntheses of the starting and the elongating monomer of type c are summarized in Schemes 3 and 4. Originally also, the two type c monomers were planned to be synthesized from the same thioglycoside disaccharide, but the less efficient tin-promoted allylation of ethyl 1-thiogalactopyranosides[30] as compared to the corresponding trimethylsilylethyl (TMSE) *O*-glycoside,[31] in combination with problems of stereoselectivity in the introduction of the spacer at the disaccharide level, made

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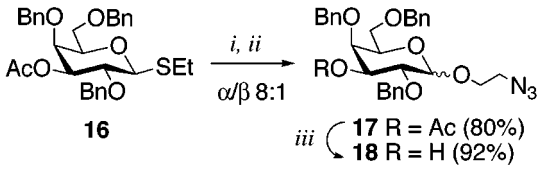
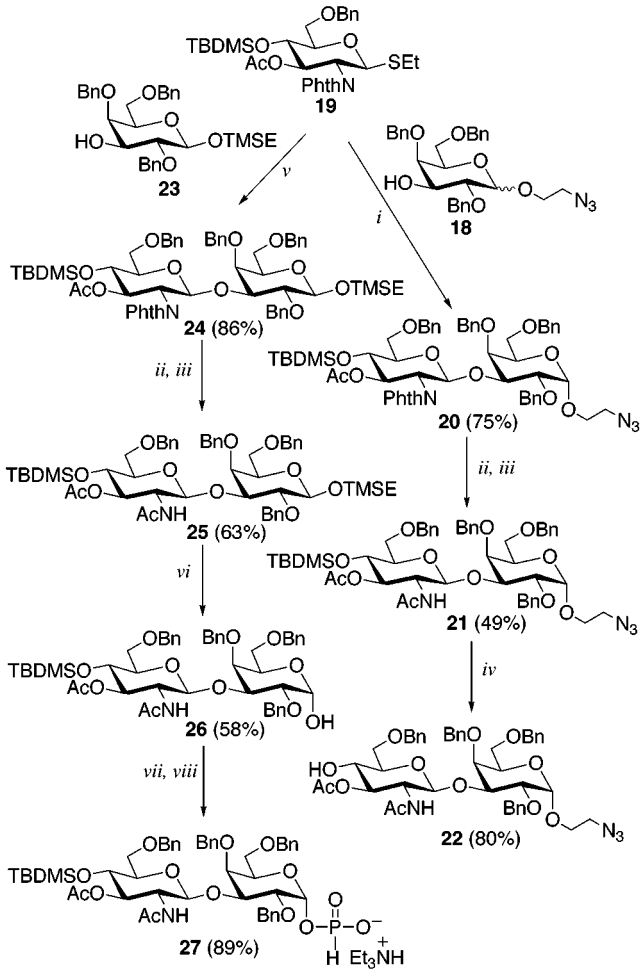
Scheme 3. Synthesis of a Type c Spacer Monosaccharide Acceptor[a]



[a] Key: (i) Br_2, CH_2Cl_2; (ii) $HOCH_2CH_2N_3$, Et_4NBr, DMF, CH_2Cl_2; (iii) NaOMe, MeOH/CH_2Cl_2.

Scheme 4. Synthesis of Type c Starting and Elongating Disaccharide Monomers[a]



[a] Key: (i) MeOTf, DTBMP, CH_2Cl_2; (ii) $H_2NCH_2CH_2NH_2$, toluene/EtOH, reflux; (iii) Ac_2O, pyridine; (iv) $Et_3N(HF)_3$, THF; (v) DMTST, DTBMP, CH_2Cl_2; (vi) TFA/CH_2Cl_2 2:1; (vii) PCl_3, imidazole, Et_3N, MeCN; (viii) Et_3NHHCO_3, H_2O.

the change to a less convergent synthesis of these two blocks necessary.[32]

Although it is a galactopyranose, which normally is quite α-selective in glycosylations because of the axial 4-substituent covering the *β*-side,[33] the chlorosugar of **16**[34] gave mainly the *β*-glycoside (α/*β* 1:2) in a silver triflate-promoted glycosylation with the spacer 2-azidoethanol. Application of halide-assisted glycosylation conditions[24] using the bromo sugar gave, as expected, much better α-selectivity, but still, the spacer glycoside **17** was obtained as an α/*β*-mixture (α/*β* 8:1), which could not be separated at this stage (Scheme 3). Deacetylation and methyl triflate-promoted glycosylation[35] with the thioglycoside donor **19** gave in good yield and with stereospecificity the *β*-(1→3)-linked disaccharide **20** (75%), isolated now as the pure α-galactoside (Scheme 4). Use of DMTST[23] as promoter in this coupling gave the elimination product of the donor as a main byproduct, but this formation could be suppressed to a large extent by the use of methyl triflate as promoter. Transformation of the phthalimido group into an acetamido group was accomplished using ethylenediamine, followed by acetylation to give **21** (49%). A major side reaction was base-promoted *O*-4→*O*-3 silyl migration[36,37] to give the 4′-*O*-acetyl-3′-*O*-TBDMS isomer of **21** as a byproduct in 30% yield, which explains the rather low yield of **21** in this transformation. However, the choice of suitable temporary protecting groups is rather limited, and the excellent properties shown by the TBDMS group later in the synthesis more than compensated for this loss of material at this early stage. Finally, removal of the silyl protecting group by treatment with $Et_3N(HF)_3$ yielded the starting monomer **22** (80%).

Coupling between the same donor as above, **19**, and the known TMSE glycoside acceptor **23**,[31] this time using DMTST-promotion (without elimination byproducts), gave disaccharide **24** (86%), which was transformed into the acetamido analogue **25** (63%), as discussed for derivative **21** above. Also here, silyl migration was a major side reaction (27%). The TMSE glycoside in **25** was hydrolyzed[38] to give the free hemiacetal and allow the introduction of the anomeric H-phosphonate. Fortunately, the pure α-anomer **26** (58%) could be crystallized out from the obtained α/*β*-mixture, which directly solved the steroselectivity problem because **26** could be phosphonylated[29] without epimerization to give the α-linked hydrogenphosphonate monoester **27** (89%).

With all of the starting and elongating monomers in hand, the formation of phosphodiester linkages was now attempted (Schemes 5 and 6). The H-phosphonate approach was chosen because earlier experiences showed this method to have advantages over the phopshoramidite method in the construction of anomeric phosphodiester linkages.[39] Early studies by Garegg and Helland indicated that it was not possible to form the Hic (1→4)-phosphodiester-linked disaccharide by using the normal approach with an anomeric H-phosphonate monoester as electrophile.[19] To try to solve this problem, a new methodology, in which a 4-*O*-linked nonanomeric H-phosphonate monoester was used as nucleophile in glycosylation-type couplings to glycosyl donors, was developed to give good yields of diester phosphates but as α/*β*-mixtures.[40] Initial experiments with disaccharide monomers gave exclusively the α-anomer, but these results were not reproducible. This prompted us to investigate the original reaction more thoroughly by ^{31}P NMR. It was then found that the phosphonate diester

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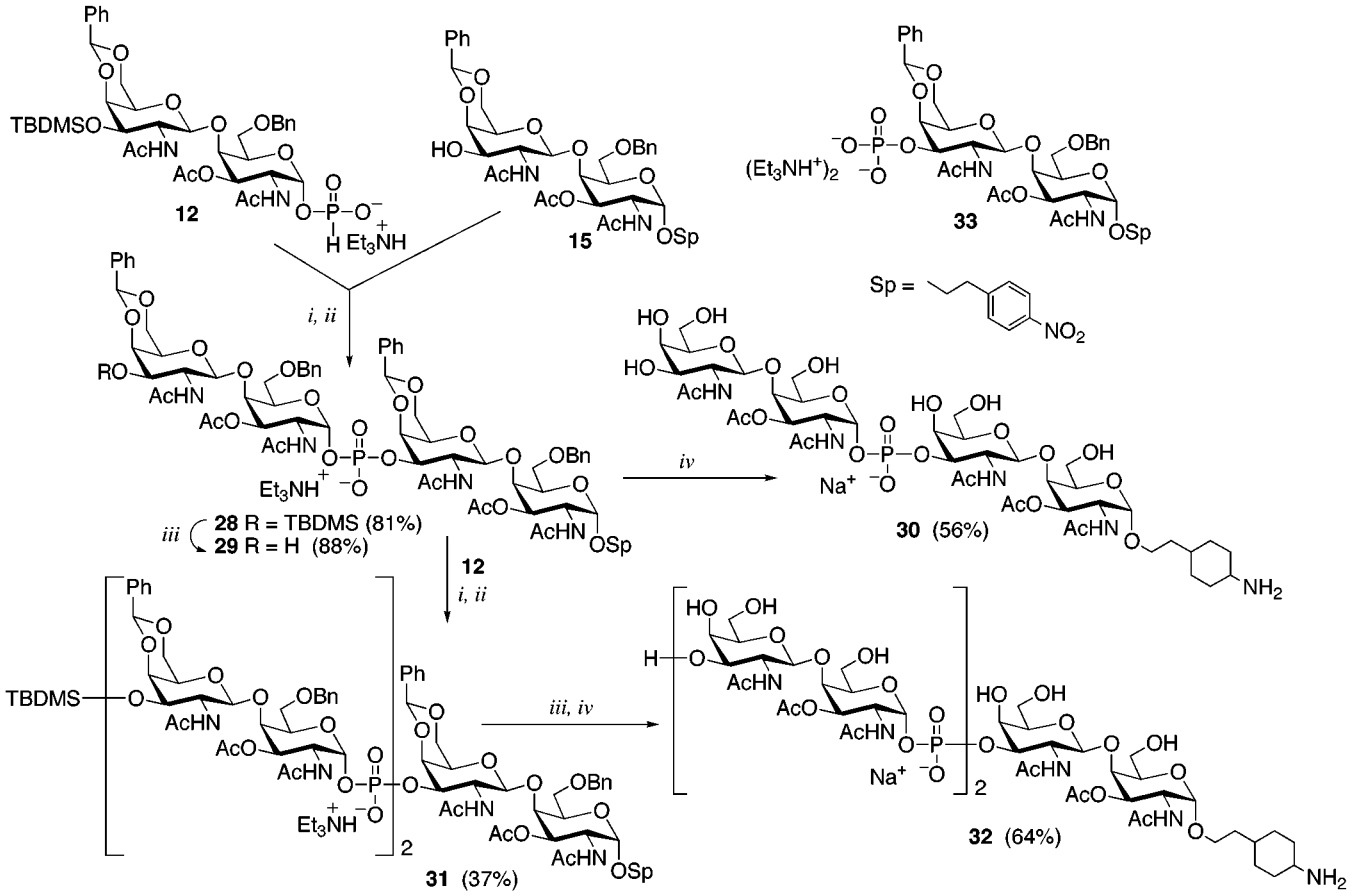
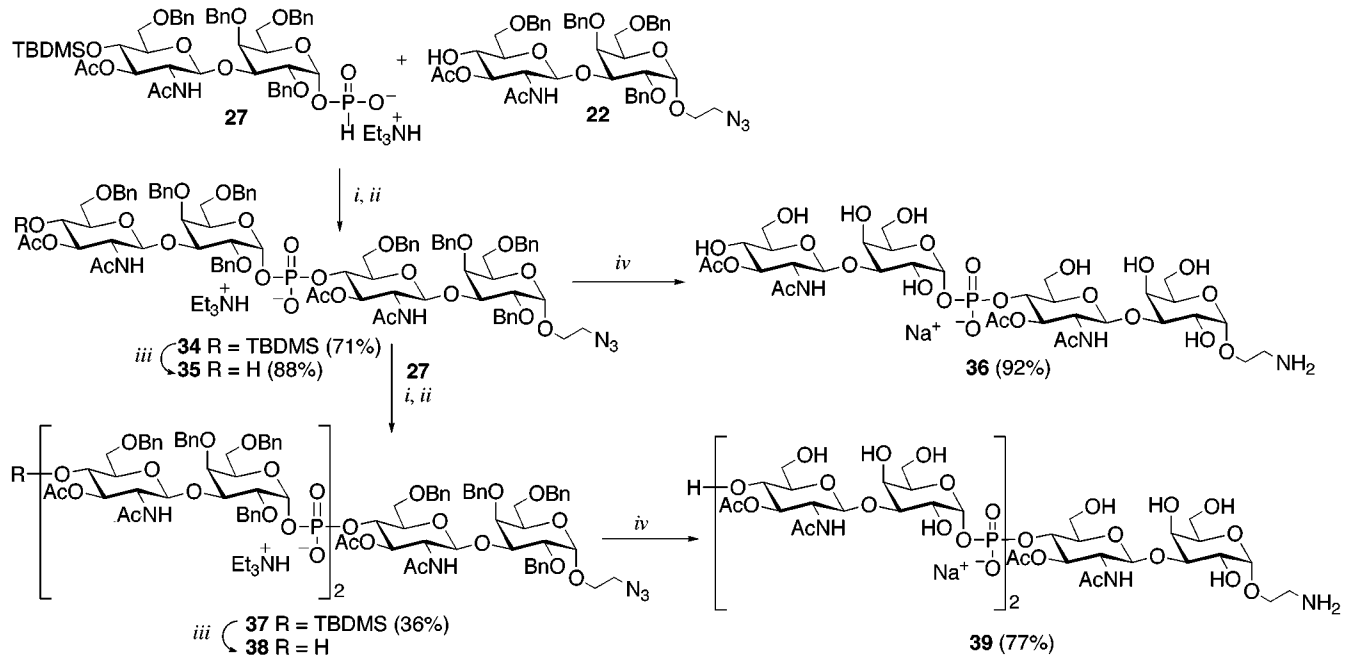
Scheme 5. Synthesis of a Dimer and a Trimer of the Repeating Unit of *H. influenzae* Type f CPS[a]



[a] Key: (i) Piv-Cl, pyridine; (ii) I_2, H_2O, −40 °C; (iii) $Et_3N(HF)_3$, THF; (iv) H_2, Pd/C, EtOH/HOAc/H_2O.

Scheme 6. Synthesis of a Dimer and a Trimer of the Repeating Unit of *H. influenzae* Type c CPS[a]



[a] Key: (i) Piv-Cl, pyridine; (ii) I_2, H_2O, −40 °C; (iii) $Et_3N(HF)_3$, THF; (iv) H_2, Pd/C, EtOH/HOAc/H_2O.

was formed almost quantitatively but that this intermediate was lost in the consecutive oxidation. Optimization of the oxidation step with monosaccharide monomers, mainly through lowering the temperature, then led to a working methodology for the construction of the desired phosphodiester. In the type f series, coupling of H-phosphonate **12** with acceptor **15**, employing pivaloyl chloride as coupling reagent, followed by I_2/H_2O oxidation yielded the phosphate diester **28** (81%) (Scheme 5). Removal of the TBDMS group without any cleavage of

the phosphate was achieved by treatment with $Et_3N(HF)_3$ to give the dimer acceptor **29** (88%).

As was found also for the continued formation of higher oligomers of the *H. influenzae* type c structure, the yield in the formation of the trimer was lowered quite drastically as compared to that of the dimer formation. In the first attempt, using the same conditions as for the formation of **28**, no trimer at all could be isolated; only a product, **33** (85%, Scheme 3), resulting from the cleavage of the phosphate diester bond in **29** was obtained. Once more, it was mainly the conditions during the oxidation that caused decomposition. Through dilution of the reaction mixture with pyridine before the iodine and water was added, less hydrolytic conditions were established, and the trimer **31** could be isolated in an acceptable yield of 37%, still accompanied by the formation of **33** (40%).

Finally, deprotection by catalytic hydrogenolysis of dimer **29** and desilylation and subsequent hydrogenolysis of trimer **31** were performed. These steps also reduce the nitro group to give an amino function, which is essential for the conjugation of the structures to a protein. Sometimes, hydrogenolysis of phosphate-containing derivatives is ineffective; however, with these compounds, the reaction proceeded most effectively, even reducing the aromatic ring system to give the target products as their cyclohexylamino derivatives, **30** (56%) and **32** (64%), respectively.

In the type c series, monomer H-phosphonate **27** was coupled to the starting monomer **22** to give the dimeric phosphodiester **34** in 71% yield (Scheme 6). Desilylation then gave the 4‴-OH intermediate **35** (88%), which now, as in the type f synthesis, could be either elongated or deprotected.

One-step deprotection by catalytic hydrogenolysis both removed all the benzyl-protecting groups and concomitantly reduced the spacer azido group to give **36** (92%). In the continued elongation of **35**, the same elongating monomer **27** and the optimized coupling conditions for the formation of the type f trimer were used. Although this appeared to be most promising initially on TLC, materials were lost, as discussed, during oxidation and workup. However, the trimer **37** could be isolated in a fair 36% yield.

Once more, the removal of the silyl-protecting group was high-yielding to give the 4⁗-OH derivative **38** with the possibility of further elongation. Catalytic hydrogenolysis then smoothly gave the deprotected amino-containing trimer **39** in 77% overall yield.

In conclusion, the syntheses of complex spacer glycosides of the dimers and trimers of the repeating units of the CPSs of *H. influenzae* type c and f have been accomplished in a stereospecific manner. The structures contain the natively found 3-*O*-acetyl substituents. In the formation of the anomeric interglycosidic phosphodiester linkages, care has to be taken because of the instability of the products, as was evident by initial failures. With the oxidation step performed at low temperatures and after dilution, the formation of the dimers could be obtained in 71% and 88% yields, respectively, and the subsequent elongation to the trimers could be performed in 36% and 37% yields. The synthetic scheme also allows for further elongation.

Experimental Section

General Methods. Melting points are uncorrected. Organic solutions were dried over $MgSO_4$ before concentration, which was performed under reduced pressure at less than 40 °C (bath temperature). NMR spectra were recorded at 25 °C and 300 or 400 MHz (^{1}H) and 75 or 100 MHz (^{13}C) in $CDCl_3$ with Me_4-Si as the internal standard ($\delta = 0$), unless otherwise stated. Mass spectra were recorded in the negative ion mode (ESI). TLC was performed on silica gel 60 F_{254} with detection by UV light and charring with 8% sulfuric acid. Silica gel (0.040−0.063 mm) was used for column chromatography.

Ethyl 2-Azido-4,6-*O*-benzylidene-2-deoxy-1-thio-*β*-D-galactopyranoside (1). A catalytic amount of 1 M NaOMe was added to a solution of ethyl 2-azido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-*β*-D-galactopyranoside[41] (2.56 g, 6.8 mmol) in MeOH/CH_2Cl_2 (7:3, 50 mL). After being stirred at room temperature for 1.5 h, the mixture was treated with Dowex 50 (H^+) resin, filtered, and concentrated. The residue was dissolved in MeCN (45 mL) after which α,α-dimethoxytoluene (2.0 mL, 14 mmol) and *p*-toluenesulfonic acid (44 mg) were added, and the resulting mixture was stirred at room temperature for 20 min. Neutralization with Et_3N, concentration, and purification on silica gel (toluene/EtOAc, 2:1) gave **1** as a solid (2.10 g, 6.2 mmol, 91%). $[\alpha]_D$ −45 (*c* 1.0, $CHCl_3$). mp 106−109 °C. ^{13}C NMR: δ 14.9, 23.9, 63.2, 69.0, 69.7, 73.1, 74.6, 83.3, 101.3, 126.2−137.1. ^{1}H NMR: δ 1.34 (t, 3H), 2.72−2.87 (m, 2H), 3.43 (d, 1H), 3.62−3.65 (m, 2H), 4.00 (dd, 1H), 4.19 (dd, 1H), 4.27 (d, 1H, $J = 9.6$ Hz), 4.32 (dd, 1H), 5.54 (s, 1H,), 7.37−7.51 (m, 5H). Anal. Calcd for $C_{15}H_{19}N_3O_4S$: C, 53.40; H, 5.68; N, 12.45. Found: C, 53.55; H, 5.70; N, 12.42.

Ethyl 4,6-*O*-Benzylidene-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-phthalimido-1-thio-*β*-D-galactopyranoside (3). Imidazole (1.17 g, 17 mmol) was added to a solution of **1** (2.91 g, 8.6 mmol) and *tert*-butyldimethylsilyl chloride (2.34 g, 16 mmol) in DMF (23 mL). The resulting mixture was stirred at 70 °C for 1.5 h and then taken up in toluene, washed with H_2O, $NaHCO_3$(aq), and H_2O, dried, filtered, and concentrated. Purification on silica gel using toluene/EtOAc (10:1) as eluent afforded 3.65 g (8.1 mmol, 94%) of **2** as a white solid. $[\alpha]_D$ −22 (*c* 1.1, $CHCl_3$).; mp 106−108 °C. ^{13}C NMR: δ −4.7, −4.6, 15.0, 18.0, 23.6, 25.7, 63.0, 69.1, 69.8, 74.3, 75.7, 83.3, 100.6, 125.9−137.6. Compound **2** (3.65 g, 8.1 mmol) and triphenylphosphine (2.54 g, 9.7 mmol) were dissolved in dry CH_2Cl_2 (30 mL) under N_2 and stirred for 20 h at room temperature, after which the reaction mixture was concentrated. Phthalic anhydride (1.80 g, 12 mmol) and *n*-tetrabutylammonium cyanide (217 mg, 0.81 mmol) were added to the residue dissolved in toluene (40 mL), and the mixture was refluxed for 44 h. An additional amount of *n*-tetrabutylammonium cyanide (217 mg, 0.81 mmol) was then added, and the mixture was concentrated and purified on silica gel (toluene/EtOAc, 10:1) to give **3** in 88% yield (3.97 g, 7.1 mmol). Crystallization from EtOH gave the title compound as a white solid. mp 156−158 °C. $[\alpha]_D$ +50 (*c* 0.85, $CHCl_3$). ^{13}C NMR: δ −5.0, −4.4, 14.8, 17.6, 22.8, 25.2, 52.4, 69.2, 69.5, 70.0, 76.1, 80.3, 122.7−137.7, 167.4, 168.5. ^{1}H NMR: δ 0.24 (s, 3H), 0.25 (s, 3H), 1.47 (t, 3H), 2.86−3.17 (m, 2H), 3.88 (d, 1H, $J = 1.1$ Hz), 4.30 (dd, 1H, $J = 1.9$, 12.4 Hz), 4.39 (d, 1H, $J = 1.9$ Hz), 4.63 (dd, 1H, $J = 1.7$, 12.4 Hz), 4.99 (m, 2H, $J = 6.6$ Hz), 5,56 (m, 1H), 5.79 (s, 1H), 7.60−8.11 (m, 9H). Anal. Calcd for $C_{29}H_{37}NO_6SSi$: C, 62.67; H, 6.71; N, 2.52. Found: C, 62.74; H, 6.80; N, 2.48.

2-(4-Nitrophenyl)ethyl 3-*O*-Acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside (7). Compound **1** (1.56 g, 4.6 mmol) was dissolved in pyridine (30 mL) and acetic anhydride (6 mL). After 2.5 h, the reaction mixture was coconcentrated with toluene and purified on silica gel (toluene/EtOAc, 5:1) to give 1.74 g (4.59 mmol, 99%) of **5**. $[\alpha]_D$ −0.95 (*c* 0.95, $CHCl_3$). ^{13}C NMR: δ 15.0, 20.9, 23.7, 59.5, 69.0, 69.5, 72.7, 73.9, 83.6, 100.8, 126.1−137.3, 170.1. To a solution of **5** (614 mg, 1.6 mmol) in dry CH_2Cl_2 (20 mL) under argon was added bromine (0.1 mL, 1.9 mmol). After 5 min, the solution was coconcentrated with toluene and dried in a vacuum. The residue was dissolved in dry CH_2Cl_2 (4 mL), and 2-(*p*-nitrophenyl)ethanol (812 mg, 4.9 mmol), 9 drops of DMF, and

(41) Paulsen, H.; Rauwald, W.; Weichert, U. *Liebigs Ann. Chem.* **1988**, 75.

4 Å molecular sieves were added. The mixture was cooled to 0 °C, and Et_4NBr (510 mg, 2.4 mmol) was added. Stirring under argon was continued at room temperature for 23 h. Then, the mixture was filtered through Celite, concentrated, and purified on a silica gel column (toluene/EtOAc, 9:1) to give 545 mg (1.1 mmol, 70%) of **7**. $[\alpha]_D$ +179 (*c* 0.90, $CHCl_3$). ^{13}C NMR: δ 20.9, 35.7, 57.0, 62.6, 68.1, 68.8, 69.1, 73.2, 98.3 ($J_{C,H}$ = 171 Hz), 100.5, 123.4−146.2, 170.2. ^1H NMR: δ 2.16 (s, 1H), 3.05 (dt, 2H), 3.39 (d, 1H, J = 1.1 Hz), 3.78−4.0 (m, 4H), 4.16 (dd, 1H, J = 1.7, 12.6 Hz), 4.36 (dd, J = 1.1, 3.6 Hz), 5.05 (d, 1H, J = 3.3 Hz), 5.25 (dd, 1H, J = 3.3, 11.3 Hz), 5.49 (s, 1H), 7.34−8.20 (m, 9H). Anal. Calcd for $C_{23}H_{24}N_4O_8$: C, 57.02; H, 4.99; N, 11.56. Found: C, 56.78; H, 4.93; N, 11.37.

Ethyl 4,6-*O*-Benzylidene-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-phthalimido-*β*-D-galactopyranosyl-(1→4)-3-*O*-acetyl-2-azido-6-*O*-benzyl-2-deoxy-1-thio-*β*-D-galactopyranoside (9). A solution of **5** (2.11 g, 5.6 mmol), $NaCNBH_3$ (3.54 g, 56 mmol), and 3 Å molecular sieves in THF (50 mL) was stirred under N_2 for 30 min. HCl in diethyl ether was added until the gas evolution ceased (7 mL). After 10 min, when TLC indicated complete conversion of the starting material into one single product, the reaction mixture was filtered through a layer of Celite, washed with THF, concentrated, and purified on silica gel (toluene/EtOAc, 4:1) to give a colorless oil. Another silica gel column (light petroleum/EtOAc, 2:1) was necessary in order to get pure **6** (1.75 g, 4.6 mmol, 83%). $[\alpha]_D$ −27 (*c* 0.93, $CHCl_3$). ^{13}C NMR: δ 15.1, 21.0, 24.6, 60.2, 67.6, 69.7, 73.7, 75.4, 76.4, 84.4, 127.6−137.1, 169.8. To a solution of **3** (1.20 g, 2.16 mmol) in dry CH_2Cl_2 (20 mL) under N_2 was added bromine (0.12 mL, 2.4 mmol). After 5 min, the solution was coconcentrated with toluene and dried in a vacuum. The residue (**4**) was dissolved together with **6** (633 mg, 1.66 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (409 mg, 2.0 mmol), and 4 Å molecular sieves in dry CH_2Cl_2 (30 mL) and stirred under N_2 at −50 °C for 40 min. Silver triflate (640 mg, 2.5 mmol) was then added in small portions during 5 min. After 15 min, Et_3N was added, and the reaction mixture was filtered through Celite, concentrated, and purified on a silica gel column (toluene/EtOAc, 8:1) to give **9** (1.10 g, 1.26 mmol) in 76% yield. $[\alpha]_D$ +31 (*c* 1.0, $CHCl_3$). ^{13}C NMR: δ −4.8, −4.5, 14.9, 17.7, 20.6, 22.4, 25.3, 54.2, 60.6, 66.3, 67.7, 68.2, 68.8, 72.2, 73.0, 75.2, 75.7, 77.1, 82.9, 98.3, 100.7, 122.5−138.1, 167.1, 168.8, 170.0. ^1H NMR: δ 0.19 (s, 3H), 0.22 (s, 3H), 0.86 (s, 9H), 1.44 (t, 3H), 2.30 (s, 3H), 2.64−2.93 (m, 2H), 3.32 (dd, 1H, J = 10.2, 10.2 Hz), 3.69 (s, 1H), 3.77 (m, 2H), 4.00 (dd, 1H), 4.18 (dd, 1H), 4.25 (d, 1H, J = 9.9 Hz), 4.27−4.35 (m, 3H), 4.76 (q, 2H), 4.79 (dd, 1H, J = 8.2, 11.0 Hz), 4.86 (dd, 1H, J = 2.5, 10.2 Hz), 5.07 (dd, 1H, J = 3.8, 11.0 Hz), 5.30 (d, 1H, J = 8.2 Hz), 5.73 (s, 1H), 7.41−8.09 (m, 14H). Anal. Calcd for $C_{44}H_{54}N_4O_{11}SSi$: C, 60.39; H, 6.22; N, 6.40. Found: C, 60.29; H, 6.33; N, 6.28.

Triethylammonium 2-Acetamido-4,6-*O*-benzylidene-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-*β*-D-galactopyranosyl-(1→4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranosyl Hydrogenphosphonate (12). Compound **9** (740 mg, 0.85 mmol) was dissolved in EtOH/toluene (3:1, 15 mL). Addition of ethylenediamine (2.8 mL, 42 mmol) followed by reflux for 19 h gave the free amino compound. Concentration left a syrup which was subsequently treated with pyridine (15 mL) and acetic anhydride (5 mL) for 4 h at room temperature. Coconcentration with toluene followed by silica gel chromatography (toluene/EtOAc, 3:1) gave 588 mg (0.75 mmol, 88%) of the 2′-acetamido derivative as a white foam. $[\alpha]_D$ +16 (*c* 0.91, $CHCl_3$). ^{13}C NMR: δ −4.7, −4.6, 14.9, 18.0, 20.8, 23.6. 25.0, 25.5, 56.8, 61.6, 65.9, 67.6, 68.8, 68.9, 71.5, 73.0, 75.3, 76.0, 77.5, 83.8, 97.9, 100.4, 125.1−138.1, 170.1, 170.5. This compound (695 mg, 0.88 mmol) in CH_2Cl_2 (7 mL) was treated overnight with triphenylphosphine (278 mg, 1.1 mmol) to give the intermediate phosphazene. Concentration left a white foam which was dissolved in THF/water (5:1, 15 mL) and refluxed for 2 days. The reaction mixture was then diluted with $CHCl_3$ and water, the organic layer was separated off, and the aqueous layer was washed with additional $CHCl_3$. The combined organic phases were dried, filtered, and concentrated. The residue was treated with pyridine (20 mL) and acetic anhydride (6 mL) at room temperature for 1 day, coconcentrated with toluene, and purified on silica gel (gradient of $CHCl_3$/MeOH, 30:1−25:1) to give 597 mg (0.74 mmol, 84%) of **10**. $[\alpha]_D$ −15 (*c* 0.67, $CHCl_3$). ^{13}C NMR: δ −4.7, −4.6, 14.7, 18.0, 20.7, 23.1, 23.7, 24.1, 25.6, 49.1, 56.8, 65.7, 67.5, 68.9, 68.9, 71.9, 73.0, 74.0, 76.2, 77.5, 84.4, 98.0, 100.4, 125.9−138.1, 169.6, 171.1, 171.4. To a stirred solution of **10** (547 mg, 0.68 mmol) in acetone (12 mL) containing water (0.12 mL) was added *N*-iodosuccinimide (230 mg, 1.0 mmol). After 40 min, the reaction was diluted with CH_2Cl_2, washed twice with 1 M $Na_2S_2O_3$ and once with water, dried, filtered, and concentrated. Silica gel chromatography ($CHCl_3$/MeOH 16:1) gave **11** (425 mg, 0.56 mmol, 81%) as its pure α-anomer. $[\alpha]_D$ +32 (*c* 0.87, $CHCl_3$). ^{13}C NMR: δ −4.8, −4.6, 18.0, 20.7, 23.2, 23.7, 25.5, 48.0, 56.7, 65.7, 67.6, 69.0, 69.3, 69.6, 70.3, 72.8, 73.0, 76.2, 91.9 ($J_{C,H}$ = 171 Hz), 98.1, 100.4, 125.8−138.1, 169.9, 171.4. To a stirred solution of imidazole (163 mg, 2.4 mmol) in MeCN (4.5 mL) at 0 °C was added PCl_3 (64 μL, 0.74 mmol) and Et_3N (358 μL, 2.6 mmol). Stirring was continued at 0 °C for 15 min. Compound **11** (154 mg, 0.17 mmol) in MeCN (4.5 mL) was then added dropwise during 30 min. After that time, the reaction mixture was stirred at room temperature for 10 min, quenched with 1 mL of 1 M triethylammonium bicarbonate (TEAB), and after an additional 5 min, concentrated. From the residue was evaporated pyridine/Et_3N (4:1, 15 mL). The residue was then dissolved in $CHCl_3$ and washed four times with 0.5 M TEAB; the organic layer was dried by filtration through cotton, concentrated, and passed through a silica gel column ($CHCl_3$ containing 1% Et_3N, gradient of 0−9% MeOH) to give 158 mg (0.15 mmol, 87%) of **12**. $[\alpha]_D$ +35 (*c* 0.68, $CHCl_3$). ^{13}C NMR: δ −4.7, −4.6, 9.0, 18.0, 20.7, 23.2, 23.8, 25.6, 45.5, 47.9 ($^3J_{C,P}$ = 5.2), 56.8, 65.8, 67.6, 69.0, 69.2, 70.7, 70.8, 72.6, 72.8, 76.3, 93.5 ($^2J_{C,P}$ = 4.9), 98.2, 100.4, 125.9−138.3, 170.0, 171.2, 171.4. ^1H NMR: δ 0.05 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.21 (t, 9H), 1.91 (s, 3H), 2.05 (s, 3H), 2.13 (s, 3H), 3.23 (m, 1H), 3.44 (s, 1H), 3.56 (dd, 1H), 3.81 (dd, 1H), 3.95 (dd, 1H), 3.99 (d, 1H, J = 3.6 Hz), 4.10 (dd, 1H), 4.19 (d, 1H, J = 1.9 Hz), 4.28 (dd, 1H), 4.54 (dd, 2H), 4.73 (dt, 1H), 4.98 (dd, 1H, J = 3.6, 10.4 Hz), 5.19−5.23 (m, 2H, J = 8.2 Hz), 5.51 (s, 1H), 5.56 (dd, 1H, J = 3.3, 8.5 Hz), 6.12 (d, 1H), 6.50 (d, 1H), 6.96 (d, 1H, J = 629 Hz), 7.20−7.57 (m, 10H). ^{31}P NMR (CH_2Cl_2): δ 0.54. MS: calcd for $C_{44}H_{70}N_3O_{14}PSi$ [M − $Et_3NH]^-$, 821.3; found, 821.3.

2-(4-Nitrophenyl)ethyl 4,6-*O*-Benzylidene-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-phthalimido-*β*-D-galactopyranosyl-(1→4)-3-*O*-acetyl-2-azido-6-*O*-benzyl-2-deoxy-α-D-galactopyranoside (13). A solution of **7** (477 mg, 0.98 mmol), $NaCNBH_3$ (619 mg, 9.8 mmol), and 3 Å molecular sieves in THF (20 mL) was stirred under argon for 20 min. HCl in diethyl ether was added until the gas evolution ceased (3.5 mL). After 30 min, the reaction mixture was worked up as described for compound **6**. Two silica gel columns (toluene/EtOAc, 3:1) gave 89% (426 mg, 0.88 mmol) of **8**. $[\alpha]_D$ +141 (*c* 0.99, $CHCl_3$). ^{13}C NMR: δ 20.9, 35.7, 57.0, 68.0, 68.5, 68.5, 70.0, 70.5, 73.7, 98.1, 123.4−146.2, 169.8. A solution of **8** (376 mg, 0.77 mmol), **3** (687 mg, 1.2 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (159 mg, 0.77 mmol), and 4 Å molecular sieves in dry CH_2Cl_2 (20 mL) was stirred at room temperature under N_2 for 30 min. DMTST (600 mg, 2.3 mmol) was then added, and after 30 min, an additional amount of DMTST (100 mg, 0.39 mmol) and donor **3** (86 mg, 0.15 mmol) was added. After 1 h, the reaction was quenched with Et_3N, and the reaction mixture was filtered (Celite), concentrated, and purified on silica gel (toluene/EtOAc, 9:1) to give 79% (599 mg, 0.61 mmol) of **13**. $[\alpha]_D$ +86 (*c* 0.58, $CHCl_3$). mp 202−204 °C. ^{13}C NMR: δ −4.9, −4.5, 17.7, 20.5, 25.2, 35.6, 54.1, 58.2, 66.1, 67.4, 67.6, 68.8, 69.0, 69.6, 70.8, 73.0, 73.5, 75.6, 97.1, 98.4, 100.7, 122.4−146.4, 167.3, 168.7, 170.1. ^1H NMR: δ 0.22 (s, 3H), 0.25 (s, 3H), 0.89 (s, 9H), 2.29 (s, 3H), 3.18 (t, 2H), 3.45 (dd, 1H, J = 3.3, 11.0 Hz), 3.70 (s, 1H), 3.74−3.95 (m, 4H), 4.09 (m, 1H), 4.20 (dd, 1H), 4.27 (d, 1H, J = 3.0 Hz), 4.29 (d, 1H, J = 4.1 Hz), 4.33 (dd, 1H), 4.73 (dd,), 4.77 (dd, 1H, J = 8.2, 10.7 Hz), 5.01 (d, 1H, J = 3.8 Hz), 5.04 (dd, 1H, J = 3.8, 11.0 Hz), 5.26 (dd, 1H, J = 2.7, 11.3 Hz), 5.28 (d, 1H, J = 8.5 Hz), 5.75 (s, 1H), 7.47−8.33 (m, 18H). Anal. Calcd for

$C_{50}H_{57}N_5O_{14}Si$: C, 61.27; H, 5.86; N, 7.15. Found: C, 61.16; H, 5.97; N, 7.00.

2-(4-Nitrophenyl)ethyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-*β*-D-galactopyranosyl-(1→4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranoside (15). A solution of **13** (599 mg, 0.61 mmol) and ethylenediamine (2.0 mL, 30 mmol) in EtOH/toluene (3:2, 15 mL) was refluxed for 24 h and then coconcentrated with toluene. The residue was treated with pyridine (15 mL) and Ac_2O (5 mL) for 1 day. Coconcentration with toluene left a solid, which was purified on silica gel (toluene/EtOAc, 3:1) to give the 2′-NHAc derivative in 86% yield (467 mg, 0.52 mmol). $[\alpha]_D$ +78 (*c* 0.63, $CHCl_3$). ^{13}C NMR: δ −4.7, −4.6, 18.0, 20.8, 23.7, 25.5, 35.7, 56.8, 58.2, 65.9, 67.6, 67.7, 68.8, 69.2, 69.9, 70.4, 72.6, 73.0, 76.0, 97.6, 98.0, 100.5, 123.4−146.5, 170.1, 170.5. Triphenylphosphine (155 mg, 0.59 mmol) was added to this compound (437 mg, 0.49 mmol) dissolved in dry CH_2Cl_2 (3 mL). The mixture was stirred at room temperature for 20 h, concentrated, and dried in a vacuum to give a white foam, which was refluxed in a THF/water mixture (10:1, 9 mL) for 1 day and concentrated, and the residue was partitioned between $CHCl_3$ and water. The organic phase was dried, filtered, and concentrated. The residue was then stirred overnight in pyridine (9 mL) and acetic anhydride (3 mL), and then the solution was coconcentrated with toluene. Purification on silica gel ($CHCl_3$, gradient of 0−3% MeOH) gave **14**, slightly contaminated with triphenylphosphine oxide. ^{13}C NMR: δ −4.8, −4.6, 18.0, 20.7, 23.1, 23.6, 25.5, 35.5, 47.9, 56.8, 65.8, 67.1, 67.5, 68.9, 69.1, 70.0, 70.5, 72.4, 73.0, 76.2, 97.4, 98.0, 100.4, 123.3−146.3, 169.4, 171.2, 171.5. Compound **14** was dissolved in THF (4 mL) and treated with triethylamine tris(hydrogen fluoride) ($Et_3N(HF)_3$) (0.96 mL, 5.9 mmol) for 2 days at room temperature. The reaction mixture was then diluted with $CHCl_3$, washed with water, $NaHCO_3$(aq), and water, dried, filtered, concentrated, and purified on silica gel (two columns using a stepwise gradient of $CHCl_3$/MeOH, 30:1−2:1 and $CHCl_3$/MeOH, 15:1, respectively) which gave **15** (312 mg, 0.39 mmol, 80%). $[\alpha]_D$ +37 (*c* 0.62, $CHCl_3$). mp 116−119 °C. ^{13}C NMR: δ 20.7, 23.1, 23.4, 35.5, 47.9, 55.8, 66.2, 67.3, 68.6, 68.9, 69.8, 70.1, 71.1, 73.1, 74.8, 77.2, 97.4, 99.7, 100.9, 123.3−146.4, 169.3, 170.5, 172.8. ^1H NMR: δ 1.84 (s, 3H), 2.10 (s, 3H), 2.14 (s, 3H), 3.05 (dt, 2H), 3.40 (s, 1H), 3.57−3.80 (m, 5H), 3.95 (dd, 1H), 3.99−4.23 (m, 5H), 4.55 (s, 2H), 4.63 (dt, 1H), 4.80 (d, 1H, J' = 8.0 Hz), 4.81 (d, 1H, J = 4.4 Hz), 5.12 (dd, 1H, J = 2.5, 11.0 Hz), 5.39 (d, 1H), 5.55 (s, 1H), 6.23 (d, 1H), 7.25−8.20 (m, 14H). MS: calcd for $C_{40}H_{47}N_3O_{14}$ $[M + H]^+$, 794; found, 794.

2-Azidoethyl 3-*O*-Acetyl-2,4,6-tri-*O*-benzyl-D-galactopyranoside (17). To a solution of ethyl 2,4,6-tri-*O*-benzyl-1-thio-*β*-D-galactopyranoside[42] (3.39 g, 6.9 mmol) in pyridine (50 mL) was added acetic anhydride (10 mL). The mixture was stirred at room temperature overnight and then coconcentrated with toluene. The residue was purified by silica gel chromatography (toluene/EtOAc, 15:1) to give 91% (3.33 g, 6.2 mmol) of ethyl 3-*O*-acetyl-2,4,6-tri-*O*-benzyl-1-thio-D-galactopyranoside (**16**). $[\alpha]_D$ +30 (*c* 1.0, $CHCl_3$). ^{13}C NMR: δ 15.0, 20.8, 25.0, 68.2, 73.4, 74.6, 74.9, 75.4, 76.6, 76.6, 85.3, 127.6−138.2, 170.2. This compound (1.16 g, 2.2 mmol) was treated with bromine (122 μL, 2.4 mmol) in CH_2Cl_2 for 15 min, and then the mixture was concentrated. After being dried in a vacuum, the residue was dissolved in dry CH_2Cl_2 (6 mL), 2-azidoethanol (0.43 mL, 6.3 mmol), and DMF (12 drops), and 4 Å molecular sieves was added. After the mixture was cooled to 0 °C under argon, Et_4NBr (680 mg, 3.2 mmol) was added, and the solution was stirred at room temperature for 40 h, filtered through Celite, concentrated, and purified on silica gel (toluene/EtOAc, 10:1) to give **17** as an α/*β*-mixure (8:1) (1.07 g, 1.9 mmol, 88%). $[\alpha]_D$ +60 (*c* 1.0, $CHCl_3$). ^{13}C NMR: δ (α product) 20.9, 50.5, 66.7, 68.3, 68.8, 72.1, 72.9, 73.2, 73.8, 75.0, 75.4, 97.6, 127.4−138.0, 169.9. ^1H NMR: δ 1.95 (s, 3H), 3.41−3.59 (m, 5H), 3.76−3.81 (m, 1H, Hb spacer), 4.03 (dd, 1H, J = 3.7, 10.6 Hz), 4.06 (d, 1H, J = 2.93 Hz), 4.10 (t, 1H), 4.41−4.71 (m, 6H), 4.84 (d, 1H, J = 3.66 Hz), 5.27 (dd, 1H, J = 3.8, 10.6 Hz), 7.23−7.34 (m, 15H). Anal. Calcd for $C_{31}H_{35}N_3O_7$: C, 66.30; H, 6.28; N, 7.48. Found: C, 66.17; H, 6.41; N, 7.46.

Ethyl 3-*O*-Acetyl-6-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-phthalimido-1-thio-*β*-D-glucopyranoside (19). A mixture of ethyl 3-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-*β*-D-galactopyranoside[43] (4.49 g, 9.25 mmol), TBDMS−Cl (2.51 g, 16.6 mmol), and imidazole (1.26 g, 18.5 mmol) in DMF (25 mL) was heated at 70 °C for 24 h, diluted with toluene, washed with water, saturated $NaHCO_3$(aq), and water, dried, and concentrated. The residue was purified on silica gel (toluene/EtOAc 10:1) to furnish **19** (97%, 5.38 g, 8.97 mmol). $[\alpha]_D$ +14 (*c* 0.87, $CHCl_3$). mp 36 °C. ^{13}C NMR: δ −4.8, −4.4, 15.1, 17.9, 20.9, 24.1, 25.6, 54.3, 68.2, 69.6, 73.3, 75.1, 80.4, 80.6, 123.4−138.3, 167.6, 167.9, 170.2. ^1H NMR: δ 0.02 (s, 3H), 0.06 (s, 3H), 0.81 (s, 9H), 1.24 (t, 3H), 1.87 (s, 3H), 2.62−2.75 (m, 2H), 3.68−3.95 (m, 4H), 4.27 (dd, 1H, J = 10.6, 10.3 Hz), 4.63 (dd, 2H), 5.52 (d, 1H, J = 10.6 Hz), 5.62 (dd, 1H, J = 10.3, 8.4 Hz), 7.29−7.88 (9H). Anal. Calcd for $C_{31}H_{41}NO_7SSi$: C, 62.07; H, 6.89; N, 2.34. Found: C, 61.89; H, 7.03; N, 2.29.

2-Azidoethyl 3-*O*-Acetyl-6-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (20). Compound **17** (1.01 g, 1.8 mmol) was dissolved in CH_2Cl_2/MeOH (3:2, 25 mL), and a catalytic amount of 1 M NaOMe in MeOH was added. After being stirred at room temperature overnight, the reaction mixture was neutralized with Dowex 50 (H^+) resin, filtered, concentrated, and purified on silica gel (toluene/EtOAc, 8:1) which yielded **18** in 92% yield (860 mg, 1.66 mmol, α/*β* 12:1). $[\alpha]_D$ +32 (*c* 1.1, $CHCl_3$). ^{13}C NMR: δ 50.5, 66.7, 68.8, 69.4, 69.8, 72.7, 73.2, 74.9, 76.3, 77.1, 97.1, 127.4−138.1. To a stirred solution of **18** (807 mg, 1.6 mmol), donor **19** (1.29 g, 2.2 mmol), DTBMP (319 mg, 1.6 mmol), and 4 Å molecular sieves in dry CH_2Cl_2 (50 mL) under argon was added MeOTf (230 μL, 2.0 mmol). After the mixture was stirred at room temperature for 26 h, an additional amount of MeOTf (200 μL) was added, stirring was continued for another 18 h, and then the mixture was quenched with Et_3N (0.5 mL), filtered through Celite, concentrated, and passed through a silica gel column (light petroleum/EtOAc, 3:1) to give **20** (1.23 g, 1.2 mmol) in 75% yield. $[\alpha]_D$ −24 (*c* 1.0, $CHCl_3$). ^{13}C NMR: δ −4.8, −4.3, 17.9, 20.9, 25.6, 50.4, 55.8, 66.5, 68.5, 69.1, 69.3, 69.4, 72.8, 73.1, 73.2, 74.1, 74.9, 75.4, 77.4, 78.3, 97.7 ($J_{C,H}$ 169 Hz), 99.1 ($J_{C,H}$ 167 Hz), 122.8−138.6, 167.2, 167.4, 169.7. ^1H NMR: δ 0.02 (s, 3H), 0.06 (s, 3H), 0.81 (s, 9H), 1.86 (s, 3H), 3.22−3.34 (m, 2H,), 3.37−3.47 (m, 3H), 3.59−3.64 (m, 1H), 3.66−3.70 (m, 2H), 3.75 (d, 2H), 3.88 (d, 1H), 3.95 (dd, 1H), 3.98 (dd, 1H), 4.06 (d, 1H), 4.13 (dd, 1H, J = 2.9, 10.3 Hz), 4.19 (d, 1H), 4.28 (dd, 1H, J = 8.4, 10.6 Hz), 4.40 (d, 1H, J = 3.7 Hz), 4.40 (dd, 2H), 4.51 (d, 1H), 4.54 (dd, 2H), 4.98 (d, 1H), 5.67 (d, 1H, J = 8.4 Hz), 5.67 (dd, 1H, J = 8.4, 10.6 Hz), 6.98−7.76 (m, 24H). Anal. Calcd for $C_{58}H_{68}N_4O_{13}Si$: C, 65.89; H, 6.48; N, 5.30. Found: C, 65.70; H, 6.49; N, 5.15.

2-Azidoethyl 2-Acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-*β*-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (22). A solution of disaccharide **20** (1.18 g, 1.1 mmol) and ethylenediamine (3.7 mL, 56 mmol) in ethanol/toluene (3:1, 24 mL) was refluxed for 18 h and then coconcentrated with toluene. The residue was treated with pyridine (20 mL) and acetic anhydride (6 mL) overnight, then DMAP (50 mg) was added, and stirring was continued for 4 h. Coconcentration of the solvent with toluene and subsequent purification on silica gel (toluene/EtOAc, 3:1) left the desired product **21** (0.53 g, 0.55 mmol) in 49% yield together with the 4′-*O*-acetyl-3′-*O*-silyl compound (30%). $[\alpha]_D$ −16 (*c* 1.1, $CHCl_3$). ^{13}C NMR: δ −4.8, −4.3, 17.9, 21.2, 23.0, 25.6, 50.5, 54.4, 66.7, 68.5, 68.7, 69.2, 69.7, 72.7, 73.1, 73.2, 74.7, 75.8, 76.0, 77.1, 78.6, 97.5, 102.6, 126.9−138.5, 169.3, 170.9. Disaccharide **21** (0.51 g, 0.53 mmol) was dissolved in THF (6 mL), and $Et_3N(HF)_3$ (1.03 mL, 6.3 mmol) was added. The mixture was stirred under an argon atmosphere for 48 h. An additional amount of

(42) van Dorst, J. A. L. M.; van Heusden, C. J.; Tikkanen, J. M.; Kamerling, J. P.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1997**, *297*, 209.

(43) Buskas, T.; Konradsson, P. *J. Carbohydr. Chem.* **2000**, *19*, 25.

$Et_3N(HF)_3$ (1.03 mL, 6.3 mmol) was added, stirring was continued for another 24 h, and then the mixture was diluted with CH_2Cl_2, extracted with water, saturated $NaHCO_3$(aq), and water, dried, filtered, and concentrated. The residue was passed through a silica gel column using toluene/EtOAc 2:3 as eluent, which gave 362 mg (0.42 mmol, 80%) of the desilylated disaccharide **22** as a solid. $[\alpha]_D$ −21 (*c* 0.55, $CHCl_3$). mp 43−46 °C. ^{13}C NMR: δ 20.9, 23.0, 50.5, 53.9, 66.7, 69.2, 69.7, 70.2, 70.3, 72.7, 73.2, 73.5, 73.7, 74.6, 76.0, 76.8, 78.2, 97.5, 102.5, 127.1−138.4, 169.5, 171.4. ^{1}H NMR: δ 1.69 (s, 3H), 2.04 (s, 3H), 3.29 (d, 1H), 3.31 (m, 6H), 3.72−3.79 (m, 4H), 3.93−3.97 (m, 2H), 3.99 (dd, 1H), 4.11 (dd, 1H), 4.15 (ddd, 1H), 4.35−4.70 (7H), 4.71 (d, 1H), 4.72 (d, 1H, J = 3.7 Hz), 4.90 (dd, 1H), 4.94 (d, 1H), 5.49 (d, 1H, J = 9.5 Hz), 7.23−7.36 (20H). Anal. Calcd for $C_{46}H_{54}N_4O_{12}$: C, 64.62; H, 6.37; N, 6.55. Found: C, 64.50; H, 6.39; N, 6.45.

2-(Trimethylsilyl)ethyl 3-*O*-Acetyl-6-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-*β*-D-galactopyranoside (24). To a mixture of **19** (792 mg, 1.32 mmol), 2-(trimethylsilyl)ethyl 2,4,6-tri-*O*-benzyl-*β*-D-galactopyranoside[31] (**23**, 559 mg, 1.02 mmol), DTBMP (313 mg, 1.52 mmol), and 4 Å molecular sieves in dry CH_2Cl_2 (20 mL) was added DMTST (911 mg, 3.56 mmol). After the mixture was stirred at room temperature for 15 min under nitrogen, Et_3N was added, and the mixture was filtered (Celite), concentrated, and subjected to silica gel chromatography (toluene/EtOAc, 10:1) to give the disaccharide **24** (86%, 955 mg, 0.88 mmol) as a white powder. An aliqoute recrystallized from EtOH had a melting point of 150−151 °C. $[\alpha]_D$ −9.1 (*c* 1.05, $CHCl_3$). ^{13}C NMR: δ −4.8, −4.3, −1.6, 17.9, 18.3, 20.9, 25.6, 55.9, 67.3, 68.8, 69.1, 69.7, 73.3, 73.5, 73.8, 74.4, 74.8, 75.7, 76.3, 77.2, 78.5, 81.5, 98.9, 103.4, 123.1−139.1, 167.7, 167.8, 170.1. ^{1}H NMR: δ 0.00 (s, 9H), 0.11 (s, 3H), 0.15 (s, 3H), 0.90 (m, 11H), 1.95 (s, 3H), 3.47 (m, 1H), 3.61−3.83 (7H), 3.89 (dd, J = 9.89, 2.9 Hz), 3.96 (m, 1H), 4.03 (dd, 1H), 4.10 (d, 1H, J = 2.9 Hz), 4.28−4.37 (3H), 4.47−5.06 (7H), 5.71 (dd, 1H), 5.83 (dd, 1H, J = 8.1 Hz), 7.17−7.77 (24 H). Anal. Calcd for $C_{61}H_{77}NO_{13}Si_2$: C, 67.31; H, 7.13; N, 1.29. Found: C, 67.06; H, 7.21; N, 1.23.

Triethylammonium 2-Acetamido-3-*O*-acetyl-6-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-*β*-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranosyl Hydrogenphosphonate (27). Disaccharide **24** (740 mg, 0.68 mmol) was treated with ethylenediamine (2.0 mL) for 14 h as described above. In the acetylation step, DMAP (25 mg) was added after 7 h; stirring was then continued for another 20 h. Workup and purification on silica gel (toluene/EtOAc, 4:1) afforded **25** (63%, 431 mg, 0.43 mmol) and its regioisomer (27%). $[\alpha]_D$ −17 (*c* 1.0, $CHCl_3$). ^{13}C NMR: δ −4.8, −4.3, −1.5, 17.9, 18.4, 21.1, 22.7, 25.6, 54.3, 67.0, 68.7, 68.9, 69.0, 73.1, 73.3, 73.4, 74.1, 74.4, 75.8, 76.1, 76.3, 79.6, 80.8, 101.9, 103.1, 126.3−139.1, 169.4, 170.8. Compound **25** was dissolved in dry CH_2Cl_2 (2.2 mL) under argon and cooled to 0 °C. Anhydrous TFA (4.4 mL) was added. After 30 min, *n*-propyl acetate and toluene were added, and the mixture was concentrated. The residue was crystallized from diethyl ether/light petroleum to afford the α-hemiacetal **26** (58%, 220 mg, 0.24 mmol). $[\alpha]_D$ −23 (*c* 0.75, $CHCl_3$). ^{13}C NMR: δ −4.4, −3.9, 18.3, 21.6, 23.3, 26.0, 54.9, 69.1, 69.3, 69.3, 70.1, 73.0, 73.5, 75.0, 76.2, 76.3, 77.1, 78.1, 79.9, 91.8, 103.1, 126.9−139.2, 170.1, 171.2. Compound **26** (214 mg, 0.24 mmol) was phosphonylated as described for derivative **11** to give 89% (225 mg, 0.21 mmol) yield of **27**. $[\alpha]_D$ +6.3 (*c* 0.99, $CHCl_3$). ^{13}C NMR: δ −4.8, −4.3, 8.7, 17.9, 21.2, 22.8, 25.7, 45.3, 54.4, 68.4, 68.6, 69.3, 70.3, 71.6, 73.1, 74.9, 75.8 (J = 5.4 Hz), 76.0, 76.6, 77.2, 78.5, 92.7 ($J_{C,P}$ = 5.4 Hz), 102.5, 126.3−138.6, 169.6, 170.9. ^{1}H NMR: δ 0.06 (s, 3H), 0.11 (s, 3H), 0.84 (s, 9H), 1.16 (t, 9H), 1.52 (s, 3H), 2.02 (s, 3H), 2.85 (q, 6H), 3.41−3.71 (5H), 3.91 (dd, 1H), 3.97 (ddd, 1H), 4.07 (d, 1H), 4.14 (ddd, 1H), 4.24 (dd, 1H, J = 10.4, 3.0 Hz), 4.30 (t, 1H), 4.39−4.58 (6H), 4.68 (d, 1H, J = 8.5 Hz), 4.82 (dd, 1H), 4.84−5.00 (2H), 5.27 (d, 1H), 5.81 (dd, 1 H, J = 3.3, 8.8 Hz), 7.06 (d, 1H, J = 638 Hz), 7.20−7.39 (20 H). ^{31}P NMR (CH_2Cl_2): δ 0.56. MS: calcd for $C_{56}H_{81}N_2O_{14}PSi$ [M − Et_3NH]$^-$, 962.4; found, 962.4.

2-(4-Nitrophenyl)ethyl 2-Acetamido-4,6-*O*-benzylidene-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-*β*-D-galactopyranosyl-(1→4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranosyl Phosphate-(1→3)-2-acetamido-4,6-*O*-benzylidene-2-deoxy-*β*-D-galactopyranosyl-(1→4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranoside Triethylammonium Salt (28). H-Phosphonate **12** (161 mg, 0.17 mmol) and acceptor **15** (126 mg, 0.16 mmol) were dried by evaporation of pyridine (4 mL). The residue was then dissolved in pyridine (2.9 mL) under argon, and pivaloyl chloride (49 μL, 0.40 mmol) was added. After 15 min, the reaction mixture was cooled to −40 °C, and water (160 μL) and iodine (48 mg, 0.19 mmol) were added. When the mixture had attained 0 °C (1.5 h), it was diluted with $CHCl_3$ and washed twice with 1 M $Na_2S_2O_3$ and twice with water; the organic phase was filtered through Na_2SO_4 and concentrated. Purification on silica gel ($CHCl_3$/MeOH, 5:1 containing 1% Et_3N) gave 81% (222 mg, 0.13 mmol) yield of phosphodiester **28**. $[\alpha]_D$ +40 (*c* 0.41, $CHCl_3$). ^{13}C NMR: δ −4.7, −4.6, 9.0, 18.0, 20.7, 21.0, 23.1, 23.2, 23.4, 23.7, 25.5, 35.6, 45.2, 48.0, 48.1, 51.3, 56.8, 65.8, 65.8, 67.2, 67.6, 68.6, 69.0, 69.4, 69.6, 70.0, 70.2, 71.1, 71.3, 72.7, 72.7, 73.1, 73.9, 76.2, 94.8 ($J_{C,P}$ = 4.6 Hz), 97.3, 98.2, 100.4, 101.0, 101.9, 123.4−146.5, 169.1, 170.9, 171.0, 171.2, 171.4, 171.8. ^{1}H NMR (assorted signals): δ 0.05 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 1.06 (t, 9H), 1.80 (s, 3H), 1.89 (s, 3H), 2.01 (s, 3H), 2.10 (s, 3H), 2.11 (s, 3H), 2.13 (s, 3H), 3.01 (t, 2H), 4.82 (d, 1H, J = 3.6 Hz), 4.97 (dd, 1H), 5.06 (dd, 1H), 5.48 (s, 1H), 5.53 (s, 1H). ^{31}P NMR (CH_2Cl_2): δ −1.9. MS: calcd for $C_{84}H_{115}N_6O_{28}PSi$ [M − Et_3NH]$^-$, 1612.6; found, 1612.7.

2-(4-Aminocyclohexyl)ethyl 2-Acetamido-2-deoxy-*β*-D-galactopyranosyl-(1→4)-2-acetamido-3-*O*-acetyl-2-deoxy-α-D-galactopyranosyl Phosphate-(1→3)-2-acetamido-2-deoxy-*β*-D-galactopyranosyl-(1→4)-2-acetamido-3-*O*-acetyl-2-deoxy-α-D-galactopyranoside Sodium Salt (30). Phosphodiester **28** (222 mg, 0.13 mmol) was treated with $Et_3N(HF)_3$ (340 μL, 2.1 mmol) in THF (2.4 mL). After being stirred at room temperature for 41 h, the reaction mixture was partitioned between CH_2Cl_2 and TEAB; the organic phase was filtered through Na_2SO_4, concentrated, and purified on silica gel ($CHCl_3$/MeOH, 5:1 containing 1% Et_3N), which gave **29** in 88% yield (183 mg, 0.11 mmol). $[\alpha]_D$ +45 (*c* 0.67, $CHCl_3$). ^{13}C NMR: δ 8.2, 20.8, 21.0, 23.2, 23.3, 23.5, 35.6, 45.4, 48.1, 48.4, 51.3, 54.8, 65.7, 66.4, 67.1, 68.6, 69.3, 69.5, 69.9, 70.7, 71.1, 71.3, 71.5, 72.9, 73.0, 73.1, 73.5, 73.9, 74.9, 77.2, 94.4, 97.3, 100.5, 100.9, 102.0, 123.3−146.3, 168.8, 170.0, 170.4, 170.8, 171.3, 173.4. ^{31}P NMR (CH_2Cl_2): δ −2.0. Desilylated diester **29** (50 mg, 31 μmol) and palladium on activated carbon (10%, 50 mg) in EtOH/HOAc/water (2:1:1, 4 mL) were stirred under H_2 (110 psi) for 3 days. Additional Pd/C (25 mg) was added after 17 h. Filtration (Celite), concentration, lyophilization, and purification on a Biogel P2 column (water containing 1% *n*-butanol) gave **30** (20.0 mg, 17.5 μmol, 56%). $[\alpha]_D$ +122 (*c* 0.97, H_2O). ^{13}C NMR (D_2O): δ 21.2, 22.6, 22.8, 23.1, 23.3, 27.1, 27.3, 30.8, 30.9, 33.5, 35.9, 48.9, 49.1, 49.8, 51.2, 52.2, 53.5, 61.0, 61.3, 61.8, 61.8, 67.1, 67.8, 68.6, 70.8, 70.9, 71.3, 72.0, 74.1, 74.6, 75.1, 75.5, 95.1 ($J_{C,P}$ = 6.0 Hz), 97.7, 103.1, 173.8, 173.9, 174.4, 174.8, 175.3, 175.4. ^{1}H NMR (assorted signals, D_2O): δ 1.00−1.91 (12H), 1.97 (s, 3H), 2.00 (s, 3H), 2.08 (s, 3H), 2.10 (s, 3H), 2.15 (s, 3H), 2.15 (s, 3H), 5.19 (dd, 1H), 5.20 (dd, 1H), 5.50 (dd, 1H, J' = 3.7 Hz, J = 7.3 Hz). ^{31}P NMR (D_2O): δ −1.9. HRMS: calcd for $C_{44}H_{73}N_5O_{26}P$ [M − Na]$^-$, 1118.4281; found, 1118.4264.

2-(4-Nitrophenyl)ethyl 2-Acetamido-4,6-*O*-benzylidene-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-*β*-D-galactopyranosyl-(1→4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranosyl Phosphate-(1→3)-2-acetamido-4,6-*O*-benzylidene-2-deoxy-*β*-D-galactopyranosyl-(1→4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranosyl Phosphate-(1→3)-2-acetamido-4,6-*O*-benzylidene-2-deoxy-*β*-D-galactopyranosyl-(1→4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranoside Bistriethylammonium Salt (31). Compounds **12** (29 mg, 0.031 mmol) and **29** (50 mg, 0.031 mmol) were dried by evaporation of pyridine (3 × 1 mL). The residue was dissolved in the same

solvent (0.4 mL) under argon, and pivaloyl chloride (5.8 μL, 0.047 mmol) was added. After 15 min, the reaction mixture was cooled to −40 °C, and a solution of pyridine/water (19:1, 1.64 mL) and iodine (10 mg, 0.037 mmol) were added. After 20 min (−30 °C), the reaction was worked up as described for derivative **28**. Silica gel chromatography ($CHCl_3$/MeOH, 3:1 containing 1% Et_3N) afforded 37% yield of **31** (29 mg, 0.011 mmol). $[\alpha]_D$ +52 (*c* 1.0, $CHCl_3$). ^{13}C NMR: δ −4.7, −4,6, 8.7, 18.0, 20.7, 21.0, 21.1, 22.8, 23.3, 23.3, 23.5, 23.8, 25.5, 35.6, 45.5, 48.1, 48.4, 51.0, 56.7, 65.6, 65.9, 67.1, 67.6, 68.7, 69.0, 69.5, 69.8, 70.0, 70.3, 70.8, 71.0, 71.2, 71.4, 71.6, 72.4, 72.7, 73.1, 73.8, 74.0, 76.2, 77.1, 94.2, 94.7, 97.3, 98.2, 100.3, 101.0, 102.5, 102.6, 123.4−146.5, 168.9, 170.3, 170.5, 170.7, 171.0, 171.2, 171.3, 171.7. MS: calcd for $C_{122}H_{169}N_9O_{42}P_2Si$ [M − 2(Et_3NH)]$^{2-}$, 1158.9; found, 1159.2.

2-(4-Aminocyclohexyl)ethyl 2-Acetamido-2-deoxy-β-D-galactopyranosyl-(1→4)-2-acetamido-3-*O*-acetyl-2-deoxy-α-D-galactopyranosyl phosphate-(1→3)-2-acetamido-2-deoxy-β-D-galactopyranosyl-(1→4)-2-acetamido-3-*O*-acetyl-2-deoxy-α-D-galactopyranosyl Phosphate-(1→3)-2-acetamido-2-deoxy-β-D-galactopyranosyl-(1→4)-2-acetamido-3-*O*-acetyl-2-deoxy-α-D-galactopyranoside Disodium Salt (32). Compound **31** (28 mg, 0.011 mmol) was dissolved in THF (0.8 mL) and treated with $Et_3N(HF)_3$ (33 μL, 0.20 mmol) at room temperature for 2 days and then concentrated. The residue was hydrogenolyzed (110 psi) in EtOH/HOAc/water (4:1:2, 2 mL) containing Pd/C (10%, 30 mg). Additional catalyst was added after 7, 24, and 48 h (10 mg). After 3 days, the reaction mixture was worked up and purified as described for compound **30** to give **32** in 64% yield (12.0 mg, 7.1 μmol). $[\alpha]_D$ +82 (*c* 0.93, H_2O). ^{13}C NMR (assorted signals, D_2O): δ 21.3, 22.7, 22.9, 23.3, 23.4, 49.2, 52.3, 53.6, 95.2 (b), 97.7, 103.2, 173.8, 173.9, 174.9, 175.4. ^1H NMR (assorted signals, D_2O): δ 1.97 (s, 3H), 2.01 (s, 6H), 2.08 (s, 3H), 2.10 (s, 6H), 2.15 (s, 6H), 2.17 (s, 3H), 5.20 (m, 3H), 5.50 (2dd, 2H). ^{31}P NMR: δ −1.7 (D_2O). HRMS: calcd for $C_{62}H_{101}N_7O_{40}P_2$ [M + H − 2Na]$^-$, 1646.5638; found, 1646.5605.

2-Azidoethyl 2-Acetamido-3-*O*-acetyl-6-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranosyl Phosphate-(1→4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranoside Triethylammonium Salt (34). Compounds **22** (133 mg, 0.16 mmol) and **27** (100 mg, 0.094 mmol) were coupled as described for the formation of compound **28**. Silica gel chromatography ($CHCl_3$ containing 1% Et_3N, gradient of 2.5−9% MeOH) gave diester **34** (71%, 127 mg, 0.66 mmol). $[\alpha]_D$ −8.3 (*c* 0.96, $CHCl_3$). ^{13}C NMR: δ −4.8, −4.2, 8.5, 17.9, 21.2, 21.2, 22.8, 22.9, 25.6, 45.2, 50.5, 53.7, 54.2, 66.6, 69.1, 69.4, 69.6, 69.8, 70.1, 70.5, 71.0, 72.1, 72.6, 73.0, 73.1, 73.2, 74.4, 74.7, 75.7, 75.8, 76.0, 77.0, 77.5, 78.8, 80.1, 94.8 ($J_{C,P}$ = 6.1 Hz), 97.5, 102.7, 103.0, 126.8−138.7, 169.6, 169.7, 170.2, 171.0. ^1H NMR (assorted signals): δ 4.02 (d, 1H), 4.13 (dd, 1H), 4.77 (d, 1H, *J* = 3.7 Hz), 5.72 (dd, 1H, *J* = 2.9, 8.1 Hz). ^{31}P NMR ($CDCl_3$): δ −2.3. MS: calcd for $C_{102}H_{133}N_6O_{26}PSi$ [M − Et_3NH]$^-$, 1814.7; found, 1814.8.

2-Aminoethyl 2-Acetamido-3-*O*-acetyl-2-deoxy-β-D-glucopyranosyl-(1→3)-α-D-galactopyranosyl Phosphate-(1→4)-2-acetamido-3-*O*-acetyl-2-deoxy-β-D-glucopyranosyl-(1→3)-α-D-galactopyranoside Sodium Salt (36). Diester **34** (57 mg, 0.030 mmol) in THF (1.2 mL) was treated with $Et_3N(HF)_3$ (117 μL, 0.71 mmol) at room temperature for 4 days, diluted with CH_2Cl_2, washed with TEAB, filtered through Na_2SO_4, and concentrated. The residue was subjected to silica gel chromatography ($CHCl_3$/MeOH, 10:1 containing 1% Et_3N) to give **35** (88%, 47 mg, 0.026 mmol). $[\alpha]_D$ −5.4 (*c* 0.58, $CHCl_3$). ^{13}C NMR: δ 8.4, 20.8, 21.1, 22.8, 23.0, 45.1, 50.5, 53.3, 53.8, 66.6, 69.2, 69.7, 69.8, 70.2, 70.4, 70.4, 71.1, 72.1, 72.5, 73.0, 73.1, 73.5, 74.3, 74.5, 74.6, 74.7, 75.7, 76.2, 77.0, 77.1, 78.4, 80.0, 94.7, 97.4, 102.6, 103.3, 126.8−138.7, 169.6, 169.9, 170.9, 171.4. ^{31}P NMR (CH_2Cl_2): δ −3.0. Compound **35** (26 mg, 14 μmol) was hydrogenolyzed as described for derivative **29** to yield **36** (13.0 mg, 13 μmol, 92%). $[\alpha]_D$ +50 (*c* 0.90, H_2O). ^{13}C NMR (D_2O): δ 21.2, 21.7, 23.0, 23.0, 40.2, 55.0, 55.1, 61.1, 61.2, 61.9, 62.1, 64.7, 67.9, 68.4, 69.8, 71.8, 72.3, 72.5, 74.9, 75.8, 76.2, 76.3, 79.8, 79.9, 96.8 ($J_{C,P}$ = 6.6 Hz), 99.5, 102.6, 102.9, 174.0, 174.2, 175.3, 175.4. ^1H NMR (assorted signals, D_2O): δ 1.98 (s, 3H), 1.98 (s, 3H), 2.12 (s, 3H), 2.22 (s, 3H, CH_3CO), 3.27−3.31 (m, 2H), 3.55 (1H), 3.64 (1H), 4.28 (ddd, 1H), 4.87 (d, 1H, *J* = 8.8 Hz), 4.91 (d, 1H, *J* = 8.4 Hz), 5.06 (dd, 1H, *J* = 10.3, 10.3 Hz), 5.23 (dd, 1H, *J* = 10.3, 10.3 Hz), 5.49 (dd, 1H, *J* = 6.6 Hz). ^{31}P NMR (D_2O): δ −1.9. HRMS: calcd for $C_{34}H_{57}N_3O_{26}PNa$ [M − Na]$^-$, 954.2968; found, 954.3033.

2-Azidoethyl 2-Acetamido-3-*O*-acetyl-6-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranosyl Phosphate-(1→4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranosyl Phosphate-(1→4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranoside Bis-triethylammonium Salt (37). Phosphonate **27** (33 mg, 31 μmol) and diester **35** (56 mg, 31 μmol) were dried by evaporation of pyridine (3 × 1 mL) and then dissolved in the same solvent (0.4 mL) under an argon atmosphere, and pivaloyl chloride (5.8 μL, 47 μmol) was added. After 15 min, the mixture was cooled to −40 °C, and a solution of pyridine/water (19:1, 1.6 mL) was added, immediately followed by the addition of iodine (10 mg, 37 μmol). When the reaction had attained 5 °C (2 h), it was worked up as described for compound **28**. Silica gel chromatography ($CHCl_3$ containing 1% Et_3N, gradient of 0−9% MeOH) left the diphosphate **37** (36%, 32 mg, 11 μmol), slightly contaminated with starting phosphonate **27**. $[\alpha]_D$ −1.7 (*c* 0.69, $CHCl_3$). ^{13}C NMR: δ −4.8, −4.2, 8.4, 17.8, 21.2, 21.2, 22.7, 22.9, 23.0, 25.7, 45.1, 50.5, 53.5, 53.8, 54.5, 66.6, 69.2, 69.4, 69.6, 69.8, 70.4, 71.8, 72.1, 72.7, 72.9, 73.1, 73.1, 73.2, 73.6, 73.9, 74.3, 74.7, 74.8, 75.5, 75.7, 76.0, 77.1, 77.3, 78.8, 80.2, 80.5, 94.8 (b), 95.5 (b), 97.5, 102.7, 103.0, 103.4, 126.9−138.6, 169.9, 170.0, 170.3, 171.1. ^{31}P NMR ($CDCl_3$): δ −2.7. MS: calcd for $C_{152}H_{198}N_8O_{40}P_2Si$ [M − 2(Et_3NH)]$^{2-}$, 1330.5; found, 1330.7.

2-Aminoethyl 2-Acetamido-3-*O*-acetyl-2-deoxy-β-D-glucopyranosyl-(1→3)-α-D-galactopyranosyl Phosphate-(1→4)-2-acetamido-3-*O*-acetyl-2-deoxy-β-D-glucopyranosyl-(1→3)-α-D-galactopyranosyl Phosphate-(1→4)-2-acetamido-3-*O*-acetyl-2-deoxy-β-D-glucopyranosyl-(1→3)-α-D-galactopyranoside Disodium Salt (39). Diphosphate **37** (30 mg, 10 μmol) in THF (0.8 mL) was treated with $Et_3N(HF)_3$ (41 μL, 250 μmol) at room temperature for 5 days and then concentrated with a stream of nitrogen and dried in a vacuum overnight. The residue was dissolved in ethanol/acetic acid/water (2:1:1, 2 mL) and hydrogenolyzed over Pd/C (30 mg) at 110 psi for 2 days. Additional catalyst (15 mg) was added after 24 h. Workup and purification as described for compound **30** gave the deprotected trimeric structure **39** (12.0 mg, 8.1 μmol, 77%). $[\alpha]_D$ +38 (*c* 0.82, H_2O). ^{13}C NMR (D_2O): δ 21.0, 21.4, 22.8, 22.8, 54.8, 54.9, 55.0, 60.9, 61.0, 61.6, 61.7, 61.9, 64.4, 67.7, 68.2, 69.6, 71.6, 72.1, 72.2, 72.3, 74.7, 75.5, 76.0, 76.1, 79.7, 96.5, 99.2, 102.3, 102.6, 102.7, 173.8, 173.9, 175.1, 175.2. ^1H NMR (assorted signals, D_2O): δ 1.98 (s, 9H), 2.12 (s, 3H), 2.15 (s, 6H), 3.27−3.31 (m, 2H), 4.21 (d, 1H, *J* = 2.9 Hz), 4.23 (bd, 2H), 4.29 (ddd, 2H), 4.85−4.91 (3d, 3H, *J* = 8.4 Hz), 4.98 (d, 1H, *J* = 3.7 Hz), 5.05 (dd, 1H, *J* = 9.5, 10.3 Hz), 5.22 (dd, 2H, *J* = 9.5, 9.9 Hz), 5.49 (dd, 2H, *J* = 6.2 Hz). ^{31}P NMR (D_2O): δ −1.9. HRMS: calcd for $C_{50}H_{83}N_4O_{40}P_2$ [M + H − 2Na]$^-$, 1441.4059; found, 1441.4067.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **12**, **15, 22**, **27**, **28**, **30**, **31**, **32**, **34**, **36**, **37**, and **39**. This material is available free of charge via the Internet at http://pubs.acs.org.

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