Reactivity-based one-pot total synthesis of fucose GM₁ oligosaccharide: A sialylated antigenic epitope of small-cell lung cancer

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The total synthesis of the sialic acid-containing antigenic epitope fucose GM₁ (Fuc-GM₁) by an improved reactivity-based one-pot synthetic strategy is reported. Based on a thioglycoside reactivity database, three saccharide building blocks, 3, 4, and 5, were designed and prepared to incorporate a descending order of reactivity toward thiophilic activation. Using the reactivity-based one-pot synthetic method, the fully protected Fuc-GM₁ glycoside 2 was furnished in a facile manner, which was globally deprotected to give the Fuc-GM₁ glycoside 1. In addition, using the promoter system 1-(benzensulfinyl)piperidine/trifluoromethanesulfonic anhydride, the product yield was improved and the reaction time was reduced in comparison with the N-iodosuccinimide/trifluoromethanesulfonic acid- and dimethyl (thiomethyl) sulfonium trifluromethanesulfonate-promoted systems.

Fuc-GM₁ ganglioside was first isolated from bovine thyroid tissue in 1979 (1). It is comprised of a hexasaccharide carbohydrate moiety and a ceramide-reducing end component. Within this carbohydrate framework is a tetrasaccharide (sugars a, b, d, and e) bearing a branched sialic acid residue (c) and a terminal fucose (f) (Fig. 1). It is found specifically in the tumor tissue of small-cell lung cancer (SCLC). SCLC accounts for 20% of lung cancer, which remains one of the leading causes of death in the United States (2). Unlike other cancer antigens, Fuc-GM₁ has a more restricted distribution in normal tissue, suggesting that this carbohydrate antigen may be a good target for active immunization. Development of an anti-(Fuc-GM₁) vaccine and mAb could potentially be of importance for diagnosis and immunotherapy of these tumors (3, 4). However, one of the barriers preventing effective production of an anticancer vaccine is the limited supply of chemically pure Fuc-GM₁ oligosaccharide. Despite the development of various oligosaccharide synthetic methods (5–8), the first synthesis of Fuc-GM₁ glycoside was reported by Allen and Danishefsky (9) two decades after its initial discovery. This elegant strategy incorporated the sulfonamide glycosidation method (10) in conjunction with a [3 + 3] convergent glycosidation, ultimately leading to the target glycoside. It required protecting group and anomeric leaving group manipulations and encountered a problem with stereoselective formation of the β(1,4) glycosidic bond between a bulky trisaccharide donor and the poor nucleophilic trisaccharide acceptor.

We envisioned that the incorporation of our programmable reactivity-based one-pot strategy (8) in the synthesis of the Fuc-GM₁ could simplify this complicated synthetic operation. In brief, the reactivity-based one-pot strategy is based on a developed competitive HPLC assay to assess quantitatively the reactivity of different thioglycosides, the so-called relative reactivity value (RRV). Such information is then used to guide the reactivity-based one-pot synthesis of an oligosaccharide without protecting group manipulation and intermediate isolation (8). Along with this development, we also report the use of a different thiophilic promoter to improve the efficiency of the reactivity-based one-pot methodology.

Materials and Methods

General. All chemicals were purchased and used without further purification. Dichloromethane (CH₂Cl₂) was distilled over calcium hydride. Propionitrile (EtCN) was treated with activated molecular sieves (MS) (AW-300) overnight before use. MS used in glycosylation were crushed and flame-activated before use. Reactions were monitored with analytical TLC on silica gel 60 F254 plates and visualized under UV (254 nm) and/or by staining with acidic ceric ammonium molybdate. Flash column chromatography was performed on silica gel (35–75 μm) or iatro beads. ¹H-NMR spectra were recorded on a Bruker DRX-500 (500 MHz) or DRX-600 (600 MHz) spectrometer at 20°C. Chemical shift (in ppm) was determined relative to either CDCl₃ (δ = 77.00 ppm). Peracylated lactosyl acetate 11 is commercially available and monosaccharide building blocks 3 (8), 6 (8), 9 (11), 14 (12), and 15 (8) are known compounds. Experimental details for the synthesis of the key thioglycoside building blocks, 4, 5, and 10, the protected Fuc-GM₁ 2 and the unprotected Fuc-GM₁ 1 are described. The synthesis of the remaining reaction intermediates 7, 8, 12, 13, and 16 and all of the characterization data for 1, 2, 4, 5, 7, 8, 10, 12, 13, and 16 together with their NMR spectra are reported separately in the Supporting Text and Figs. 4–23, which are published as supporting information on the PNAS web site, www.pnas.org.

Abbreviations: RRV, relative reactivity value; Fuc-GM₁, fucose GM₁; EtCN, propionitrile; MS, molecular sieves; NIS, N-iodosuccinimide; TfOH, trifluoromethanesulfonic acid; DMTST, dimethyl (thiomethyl) sulfonium trifluoromethanesulfonate; BSP, benzensulfinylpiperidine; Tf₂O, trifluoromethanesulfonic anhydride; sat. aq., saturated aqueous.

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CHEMISTRY
Disaccharide Building Block (4). Disaccharide precursor 10 (0.27 g, 0.27 mmol) was dissolved in dry pyridine (3 ml), and 1 M hydrazine hydrate (NH₂NH₂·H₂O) in pyr/AcOH mixture (vol/vol = 3:2) (0.81 ml, 0.81 mmol) was added. The reaction mixture was stirred at room temperature for 4 h and then penta-2,4-dione (1 ml) was added. The solvent was removed under reduced pressure, and the residue was dissolved in CH₂Cl₂, washed with H₂O and brine, dried (Na₂SO₄), concentrated, and purified by flash column chromatography purification (hexane/EtOAc, 2:1) to provide the desired disaccharide 4 (0.218 mg, 81%) as a white glassy residue.

Trisaccharide Building Block (5). Sialyl donor 14 (1.4 g, 1.9 mmol), lactoside acceptor 13 (2.8 g, 2.6 mmol), and MS (3 g) were stirred in dry CH₂Cl₂ (3 ml) at room temperature for 4 h and then penta-2,4-dione (0.218 mg, 81%) as a white glassy solid.

Disaccharide Building Block Precursor (10). Galactosaminyl acceptor 8 (0.3 g, 0.55 mmol), galactosaminyl donor 9 (0.47 g, 0.72 mmol), and MS (0.75 g) were suspended in dry CH₂Cl₂ (3 ml) for 2 h under Ar. The mixture was then cooled to −45°C and 0.5 M trimethylsilyl trifluoromethanesulfonate in EtCN (380 μl, 0.19 mmol) was added. The reaction mixture was stirred at −30°C overnight, and then quenched with triethylamine. The reaction mixture was then filtered and concentrated under reduced pressure. The residue was diluted with CH₂Cl₂ and washed with saturated aqueous (sat. aq.) NaHCO₃, H₂O, and brine and dried (Na₂SO₄). The resulting crude mixture was purified by flash column chromatography (gradient eluent hexane/EtOAc; 1:1 → 1:1.5) to yield 5 (1.6 g, 53%) as a colorless glassy residue.

Disaccharide Building Block Precursor (10). Galactosaminyl acceptor 8 (0.3 g, 0.55 mmol), galactosaminyl donor 9 (0.47 g, 0.72 mmol), and MS (0.75 g) were suspended in dry CH₂Cl₂ (3 ml) for 2 h under Ar. The mixture was then cooled to −45°C and 0.5 M trimethylsilyl trifluoromethanesulfonate in EtCN (380 μl, 0.19 mmol) was added. The reaction mixture was stirred at −30°C overnight and then quenched with sat. aq. NaHCO₃ and solid Na₂S₂O₃. The reaction mixture was then cooled to −30°C, followed by the addition of the trisaccharide acceptor 5 (0.092 g, 0.17 mmol), disaccharide building block 4 (0.16 g, 0.16 mmol), and MS (0.75 g) were stirred in dry CH₂Cl₂ (2 ml) at room temperature for 1 h under Ar. The reaction mixture was cooled to −70°C, followed by the addition of Tf₂O (16 μl, 0.086 mmol), and the temperature was decreased gradually from −70°C to −10°C within 1 h. After the donor 3 was consumed, the reaction mixture was cooled to −70°C, followed by the addition of the trisaccharide acceptor 5 (0.34 g, 0.22 mmol). Subsequently, the second portion of Tf₂O (0.217 mg, 0.088 mmol) was added. The reaction temperature was increased gradually from −70°C to 0°C in 1 h and the mixture was stirred at 0°C for an additional 4 h. The reaction was quenched with triethylamine.

**Fig. 2.** Retrosynthetic analysis of the Fuc-GM₁ glycoside.
and the mixture was stirred under H2 (1 atm) at room temperature for 18 h. The reaction mixture was filtered and concentrated. The residue was purified by flash column chromatography (toluene/EtOAc, 1:2, followed by toluene/acetone, 4:1). The protected Fuc-GM1 2 (0.21 g, 47%) was obtained as a white glassy solid.

Deprotected Fuc-GM1 (1). Protected Fuc-GM1 2 (80 mg, 29 μmol) was dissolved in acetic anhydride/CH2Cl2 mixture (vol/vol = 1:1, 2 ml). To the solution was added freshly activated Zn dust (1 g, washed with 1 M HCl, H2O, MeOH, and Et2O, then dried under vacuum for 10 min). After 5 h, the reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was diluted with CH2Cl2 and subsequently washed with sat. aq. NaHCO3 and brine, dried (Na2SO4), and concentrated. The residue was purified by flash column chromatography (toluene/acetone, 3:1). The resulting N-acetamido product was dissolved in MeOH/CH2Cl2 (vol/vol = 1:1, 2 ml), and sodium methoxide (NaOMe) (25% wt in MeOH, 50 μl) was added. The mixture was stirred for 10 h at room temperature and neutralized with Amberlite IR-50 resin. After removal of the resin by filtration, the solution was concentrated to give the deacetylated residue, which was dissolved in MeOH with 10% (wt/H2O) and concentrated under reduced pressure. The residue was purified by flash column chromatography (toluene/acetone, 4:1). The protected Fuc-GM1 2 (0.21 g, 47%) was obtained as a white glassy solid.

Results and Discussion

Design of Sugar Building Blocks. Successful application of reactivity-based one-pot synthesis relies on a careful selection of protecting groups and design of building blocks. The Fuc-GM1 hexasaccharide was retrosynthetically disconnected into three saccharide building blocks: fucosyl building block 3, disaccharide building block 4, and sialylated trisaccharide building block 5 (Fig. 2). Implementation of reactivity-based one-pot oligosaccharide synthesis requires a descending order of reactivity for these three building blocks. Based on the reactivity database (13), the perbenzylated fucosyl thioglycoside 3 with a RRV of 7.2 × 104 was selected as the first donor. The reducing end component is the sialylated trisaccharide building block 5, which is prepared from a lactoside acceptor 13 and sialic acid donor 14. Because 5 is an O-glycoside, a zero RRV can be assumed. The design of the disaccharide building block 4 demanded special concern. Because 4 is used as an acceptor and donor, the presence of a C2-free hydroxyl group on the galactosyl unit as well as a thiotoluene functionality at the anomeric center of the galactosaminyl unit is required. In theory, its RRRV should fall between 7.2 × 104 and 0. This criterion could be easily addressed by using appropriate protecting groups.

For an efficient reactivity-based one-pot synthesis, not only is the reactivity value of the thioglycoside building block important, careful selection of the glycosylation promoter is also imperative. Although much success has been observed in our previous one-pot syntheses (14–16), some difficulties occur when either a very reactive donor and/or a poor nucleophilic acceptor is used in glycosylations promoted by NIS/TFOH, mainly because of the competitive formation of an undesired succinimide byproduct (8, 17). To address this problem, a combination of NIS/TFOH and DMTST was used initially to establish the one-pot synthetic route for the target glycoside. Subsequent efforts were focused on the application of a recently developed thioglycoside promoter system, the BSP/Tf2O, to our one-pot synthesis to improve the efficiency of the process (18).

Syntheses of Building Blocks. With the synthetic plan in hand, we started the reactivity-based one-pot synthesis of Fuc-GM1 by preparing the three saccharide building blocks 3, 4, and 5.
Perbenzylated fucosyl thioglycoside 3 was prepared by a literature procedure (8). The disaccharide building block 4 can be accessed by glycosylation between a galactosyl donor and a galactosaminyl acceptor. 2-O-Levulinoyl-3,4,6-tri-O-benzyl-1-β-thio-D-galactoside 9 with a RRV of 4,000 was used as the galactosyl donor. The galactosaminyl acceptor should possess a C3-hydroxyl handle, a RRV smaller than 4,000, and a C2-participating group to dictate the Cβ-selective glycosidic bond formation. To address these requirements, we took the advantage of our knowledge on the properties of various protecting groups to design the galactosaminyl thioglycoside 8. The synthetic route for the galactosaminyl precursor 8 is shown (Scheme 1). Compound 6 was deacetylated by using Zemplén conditions (19), followed by benzylidene formation between the C4/C6 hydroxyls. The remaining C3 hydroxyl was converted to a levulinoyl (Lev) ester, giving the fully protected thioglycoside 7. Subsequent removal of the benzylidene protecting group was followed by reacetylation of the C4/C6 hydroxyls and selective Lev deprotection (20), yielding the galactosaminyl acceptor 8. The RRV of 8 was determined to be 3,269 by using the reference method described (8). Because thioglycoside donor 9 is more reactive than 8, a reactivity-based glycosylation was performed in the presence of NIS/TfOH to give the disaccharide precursor 10. Finally, removal of the Lev protecting group afforded the desired disaccharide building block 4 and its RRV was determined to be 2,839.

Sialylated trisaccharide building block 5 was assembled from sialyl phosphite 14 (12) and lactoside acceptor 13. Synthesis of 13 began with the commercially available peracetyl β-lactoside acetate 11 (Scheme 2). 11 was converted to a lactosyl bromide by using 33% hydrogen bromide in acetic acid, followed by reaction with benzyl N-(2-hydroxyethyl)-carbamate in the presence of silver carbonate (Ag2CO3) to provide an inseparable mixture of the desired β-lactoside and an orthoester byproduct. The acetyl protecting groups of the product mixture were removed and the C3/C4 hydroxyls were protected regioselectively with an isopropylidene acetal in the presence of p-toluene sulfonic acid. At this stage, the desired β-lactoside 12 could be isolated after chromatographic separation. Subsequent perbenzylization of 12 with benzyl bromide (BnBr) and sodium hydride (NaH) was followed by the deprotection of the C3/C4 isopropylidene acetal, giving the target acceptor 13. Regioselective glycosylation of 13 with 14 was promoted by trimethylsilyl trifluoromethanesulfonate in EtCN at ~30°C to afford the desired α-(2,3)-sialylated product 5 in 53% isolated yield with only a trace amount of β-isomer (21).

Implementation of Reactivity-Based One-Pot Synthesis of Fuc-GM1 Glycoside. With the desired carbohydrate building blocks, 3, 4, and 5, and their RRV determined, the stage was set for the synthesis of Fuc-GM1 glycoside.

Scheme 3. Reagents and conditions for NIS/Tf2O- and DMTST-promoted one-pot reaction: route a (i) NIS, TfOH, CH2Cl2, 70°C, 36%; (ii) DMTST, 0°C, 36%. Reagents and conditions for BSP/Tf2O-promoted one-pot reaction: route b (i) BSP, Tf2O, CH2Cl2, 70°C to −10°C, 47%; (ii) BSP, Tf2O, CH2Cl2, 70 to 0°C, 47%. Reagents and conditions for global deprotection: route c (i) Zn dust, acetic anhydride/CH2Cl2, 4-(dimethylamino)pyridine; (ii) NaOMe, CH2Cl2/MeOH; (iii) NaOH, THF/MeOH/H2O; (iv) Pd-black, MeOH with 10% (vol/vol) formic acid, H2 (1 atm), 44% over four steps.
reactivity-based one-pot synthesis of the Fuc-GM$_1$ glycoside (Scheme 3, route a). Perbenzylated fucosyl building block 3 (RRV = 7.2 × 10$^4$) was coupled with the less reactive disaccharide building block 4 (RRV = 2,839) in the presence of NIS/TIOH (22). After 2 h at −70°C, trisaccharide acceptor 5 was added, followed by the addition of DMTST (23). The second glycosylation required higher reaction temperatures (0°C) and a longer reaction time (1 day). The slow reaction rate was partially attributed to the glycosylation between two large sugar fragments and this had previously been observed during the synthesis of an N-acetyllactosamine octamer (16). In addition, the C$_4$-axial hydroxyl is a weak nucleophile, which further lowered the reaction rate. Nevertheless, the fully protected Fuc-GM$_1$ 2 was obtained in 36% isolated yield directly from the building blocks without protecting group manipulation and reaction intermediate isolation. This finding corresponds to an average yield of 60% per glycosylation step.

As access to the one-pot synthesis of the Fuc-GM$_1$ glycoside was accomplished, we turned our attention to improving the efficiency of the established one-pot synthetic protocol. Drawbacks of the present NIS/TIOH and DMTST system were the slow reaction rate (1 day) and moderate yield (36%). To solve this problem, we sought a better promoter. Such a promoter should enable the activation of either a reactive or nonreactive thioglycoside donor without the formation of undesired competitive byproducts. BSP/Tf$_2$O, a recently developed thiophilic reagent by Crich and Smith (18), is compatible to our reactivity-based one-pot glycosylation protocol and acts by *in situ* conversion of thioglycosides to glycosyl trifluoromethanesulfonates, which then couple with the nucleophilic acceptors efficiently.

To investigate the compatibility of BSP/Tf$_2$O with the present one-pot protocol, we first carried out a reactivity-based glycosylation reaction with a model system (Fig. 3), which incorporated a very active donor and a poor acceptor. This combination was known to be problematic, using the NIS/TIOH promoter system as succinamide byproducts are observed. Thioglycoside acceptor 15 (8) with a RRV of 9.4 was glycosylated with fucosyl donor 3 (RRV = 7.2 × 10$^4$) in the presence of BSP/Tf$_2$O. Despite the hindered acceptor site of 15, disaccharide product 16 was obtained in 95% isolated yield. Rather interestingly we have also determined that using a substoichiometric amount of BSP/Tf$_2$O provides efficient disaccharide formation. One possible rationalization may be that the reaction pathway produces sulfonium byproducts, which can further promote glycosylations, as shown in Fig. 3. This possibility is supported by the fact that slightly more than half an equivalent of BSP/Tf$_2$O provided a 95% yield of disaccharide product 16. Although no direct evidence for these sulfonium byproducts has been observed, detailed mechanistic studies should shed some light into the reaction pathway. It is also important to note that the reaction also proceeds efficiently with one equivalent of BSP/Tf$_2$O (90%), but the reaction must be quenched at low temperatures (−60°C) with triethylamine for optimal yields. Being encouraged by these results, we further investigated the application of the BSP/Tf$_2$O promoter system to the one-pot synthesis of the Fuc-GM$_1$ (Scheme 3, route b). For the BSP/Tf$_2$O promoted one-pot operation, the first stage glycosylation between fucosyl donor 3 and disaccharide acceptor 4 was completed in 1 h. For the second stage glycosylation between two trisaccharide fragments, the expected longer reaction time (3 h) was needed. The isolated yield of this BSP/Tf$_2$O promoted one-pot reaction was 47%, corresponding to an average of 67% per glycosylation step.

In terms of the reaction rate and product yield, the BSP/Tf$_2$O system was substantially better than the NIS/TIOH and DMTST combination in promoting the one-pot glycosylation.

With the development of an improved reactivity-based one-pot synthetic operation, we proceeded to the global deprotection of Fuc-GM$_1$. This process began with the removal of a Troc protecting group and reacetylation of the exposed amino functionality by reduction with zinc dust in acetic anhydride. The O-acetyl groups were removed, followed by alkaline hydrolysis of the methyl ester on the sialic acid residue. Unfortunately, the final hydrogenolysis of benzyl and Cbz protecting groups proved problematic by using either the Birch reduction conditions (24) or palladium-catalyzed hydrogenolysis in methanol. After a series of experiments, a successful deprotection was finally accomplished by catalytic transfer hydrogenation using palladium black in methanol with 10% formic acid under hydrogen (1 atm) at room temperature (25). Fully deprotected Fuc-GM$_1$ glycoside 1 was obtained in 44% yield from 2. The target glycoside 1 was characterized with standard NMR spectroscopic methods and high-resolution MS, which were in agreement with the literature reported data (9).

**Conclusion.** The total synthesis of a cancer related and antigenic carbohydrate epitope, the Fuc-GM$_1$ glycoside, was accomplished by an improved reactivity-based one-pot synthetic strategy. Through selection and careful design of various carbohydrate building blocks and application of the BSP/Tf$_2$O promoter system, an efficient reactivity-based one-pot synthetic protocol was successfully developed. Not only does the established one-pot protocol simplify the synthesis of the...
Fuc-GM₁ glycoside, application of the BSP/Tf₂O promoter system improves the efficiency of the synthesis by shortening the reaction time and increasing the glycosylation yield. The building blocks and their reactivity developed in this study should find use in the one-pot synthesis of other oligosaccharides. It is reasonable to assume that the incorporation of the BSP/Tf₂O promoter system in our reactivity-based one-pot strategy can apply to the synthesis of more challenging targets.

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Supporting information
Experimental details for the syntheses of reaction intermediates 7, 8, 12, 13, 15 and characterization data of compounds 1, 2, 4, 5, 7, 8, 10, 12, 13 and 15.

<table>
<thead>
<tr>
<th>Content</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR spectrum of deprotected Fucose GM1 glycoside 1</td>
<td>11</td>
</tr>
<tr>
<td>13C-Apt NMR spectrum of deprotected Fucose GM1 glycoside 1</td>
<td>12</td>
</tr>
<tr>
<td>1H NMR spectrum of protected Fucose GM1 glycoside 2</td>
<td>13</td>
</tr>
<tr>
<td>13C-Apt NMR spectrum of protected Fucose GM1 glycoside 2</td>
<td>14</td>
</tr>
<tr>
<td>1H NMR spectrum of disaccharide building block 4</td>
<td>15</td>
</tr>
<tr>
<td>13C-Apt NMR spectrum of disaccharide building block 4</td>
<td>16</td>
</tr>
<tr>
<td>1H NMR spectrum of trisaccharide building block 5</td>
<td>17</td>
</tr>
<tr>
<td>13C-Apt NMR spectrum of trisaccharide building block 5</td>
<td>18</td>
</tr>
<tr>
<td>1H NMR spectrum of 4,6-di-O-benzylidenyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonyl amino-3-O-levulinoyl-1-thio-β-D-galactopyranoside 7</td>
<td>19</td>
</tr>
<tr>
<td>13C-Apt NMR spectrum of 4,6-di-O-benzylidenyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-3-O-levulinoyl-1-thio-β-D-galactopyranoside 7</td>
<td>20</td>
</tr>
<tr>
<td>1H NMR spectrum of 4,6-di-O-benzylidenyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonyl amino-3-O-levulinoyl-1-thio-β-D-galactopyranoside 8</td>
<td>21</td>
</tr>
<tr>
<td>13C-Apt NMR spectrum of 4,6-di-O-benzylidenyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-3-O-levulinoyl-1-thio-β-D-galactopyranoside 8</td>
<td>22</td>
</tr>
<tr>
<td>1H NMR spectrum of disaccharide building block precursor 10</td>
<td>23</td>
</tr>
<tr>
<td>13C-Apt NMR spectrum of disaccharide building block precursor 10</td>
<td>24</td>
</tr>
<tr>
<td>1H NMR spectrum of 2-(benzyloxy carbonylamino)-ethyl 4-O-(3,4-di-O-isopropylidene -β-D-galactopyranosyl)-1-β-D-glucopyranoside 12</td>
<td>25</td>
</tr>
<tr>
<td>13C-Apt NMR spectrum of 2-(benzyloxy carbonylamino)-ethyl 4-O-(3,4-di-O-isopropylidene -β-D-galactopyranosyl)-1-β-D-glucopyranoside 12</td>
<td>26</td>
</tr>
<tr>
<td>1H NMR spectrum of lactoside acceptor 13</td>
<td>27</td>
</tr>
<tr>
<td>13C-Apt NMR spectrum of lactoside acceptor 13</td>
<td>28</td>
</tr>
<tr>
<td>1H NMR spectrum of p-methylphenyl 2,3,6-tri-O-benzoyl-4-O-(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)-1-thio-β-D-glucopyranoside 16</td>
<td>29</td>
</tr>
<tr>
<td>13C-Apt NMR spectrum of p-methylphenyl 2,3,6-tri-O-benzoyl-4-O-(2,3,4-tri-O-benzyl -α-L-fucopyranosyl)-1-thio-β-D-glucopyranoside 16</td>
<td>30</td>
</tr>
</tbody>
</table>
Experimental details for the syntheses of 7, 8, 12, 13, and 16 and the characterization data for 1, 2, 4, 5, 7, 8, 10, 12, 13, and 16.

For Deprotected Fuc-GM<sub>1</sub> Glycoside (1). ¹H NMR (600 MHz, D<sub>2</sub>O) δ 5.07 (d, J = 3.5 Hz, 1H), 4.51 (d, J = 7.5 Hz, 1H), 4.44 (d, J = 6.6 Hz, 1H), 4.37–4.35 (m, 2H), 4.06–4.02 (m, 1H), 3.95 (dd, J = 10.1, 2.2 Hz, 1H), 3.92–3.90 (m, 3H), 3.81 (d, J = 11.4 Hz, 1H), 3.75–3.41 (m, 29H), 3.20–3.17 (m, 2H), 2.99 (s, 2H), 2.50 (dd, J = 13.2, 4.4 Hz, 1H), 1.85 (s, 6H), 1.73 (s, 1H), 1.03 (d, J = 6.6 Hz, 3H); ¹³C-Apt NMR (150 MHz, D<sub>2</sub>O) δ 174.56, 173.80, 173.54, 102.76, 102.14, 101.68, 101.58, 100.89, 98.70, 75.99, 75.39, 74.44, 74.34, 73.65, 72.57, 72.29, 71.83, 71.39, 69.52, 69.10, 68.69, 68.23, 67.99, 67.61, 66.89, 66.29, 62.39, 60.67, 60.45, 60.04, 59.54, 51.16, 51.07, 39.17, 36.86, 22.27, 21.60, 14.92; High Resolution Mass Spectrometry for C<sub>45</sub>H<sub>76</sub>N<sub>3</sub>O<sub>33</sub> (M − H)<sup>−</sup> calculated 1186.4366, found 1186.4619.

For Protected Fuc-GM<sub>1</sub> glycoside (2). ¹H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.52 (d, J = 7.4 Hz, 2H), 7.36–7.07 (m, 63H), 5.96 (d, J = 8.8 Hz, 1H), 5.52–5.47 (m, 2H), 5.09–5.26 (m, 6H), 4.96–4.92 (m, 2H), 4.84–4.72 (m, 6H), 4.68–4.38 (m, 19H), 4.33–4.29 (m, 3H), 4.22–4.15 (m, 4H), 4.10–3.94 (m, 11H), 3.89–3.86 (m, 2H), 3.81 (s, 3H), 3.76–3.73 (m, 2H), 3.67–3.62 (m, 5H), 3.56–3.44 (m, 10H), 3.35–3.26 (m, 2H), 2.34–2.30 (m, 1H), 2.15 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.92 (s, 3H), 1.90 (s, 3H), 1.88 (s, 3H), 1.03 (s, 3H); ¹³C-Apt NMR (150 MHz, CDCl<sub>3</sub>) δ 170.65, 170.36, 170.31, 169.81, 169.60, 169.27, 168.58, 156.42, 156.16, 154.10, 139.15, 138.91, 138.70, 138.61, 138.50, 138.29, 138.12, 137.83, 137.78, 136.61, 136.47, 129.56, 128.97, 128.43, 128.40, 128.33, 128.24, 128.20, 128.12, 128.08, 127.97, 127.90, 127.88, 127.81, 127.76, 127.68, 127.64, 127.61,
127.56, 127.52, 127.42, 127.28, 127.26, 127.23, 127.14, 127.07, 127.03, 126.86, 126.75, 126.67, 126.44, 103.50, 102.76, 101.69, 99.12, 97.49, 95.78, 83.46, 82.54, 81.66, 79.04, 78.92, 77.84, 76.46, 76.17, 76.10, 75.93, 75.87, 74.96, 74.87, 74.81, 74.71, 74.52, 74.22, 74.15, 73.97, 73.52, 73.39, 73.22, 73.12, 72.50, 72.45, 72.31, 71.92, 71.62, 70.72, 70.09, 69.09, 69.06, 68.34, 68.20, 68.18, 68.00, 67.87, 67.22, 67.16, 66.44, 62.48, 61.66, 54.91, 53.15, 51.36, 49.34, 47.03, 45.96, 35.59, 29.63, 23.15, 21.22, 20.90, 20.78, 20.58, 20.55, 20.45, 16.82; HRMS for C151H168Cl3N3O42Na (M + Na)+ calculated 2823.0060, found 2823.0114.

For Disaccharide Building Block (4).  

\[ \delta \]  

\[ \begin{align*} 
\text{1H NMR (500 MHz, CDCl}_3\text{)} & \delta 7.40--7.25 (m, 17H), 7.09 (d, J = 7.7 Hz, 2H), 5.77 (d, J = 6.6 Hz, 1H), 5.32 (d, J = 2.6 Hz, 1H), 4.92 (d, J = 11.4 Hz, 1H), 4.76--4.71 (m, 5H), 4.56 (d, J = 11.4 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 4.44 (d, J = 11.7 Hz, 1H), 4.38 (d, J = 8.1 Hz, 1H), 4.13--4.08 (m, 3H), 3.97--3.90 (m, 2H), 3.84--3.78 (m, 5H), 3.73 (t, J = 6.6 Hz, 1H), 3.65--3.58 (m, 4H), 3.38 (dd, J = 9.5, 2.6 Hz, 1H), 2.32 (s, 3H), 2.03 (s, 6H); 13C-Apt NMR (125 MHz, CDCl}_3\text{)} \delta 171.53, 170.39, 154.66, 138.45, 137.90, 137.84, 137.71, 132.46, 129.89, 129.51, 128.49, 128.46, 128.34, 128.23, 127.85, 127.82, 127.79, 127.68, 102.63, 95.60, 88.20, 81.14, 74.88, 74.57, 74.47, 73.85, 73.74, 73.48, 72.97, 72.60, 70.04, 69.41, 67.82, 62.24, 52.19, 21.08, 20.77, 20.73; HRMS for C47H52Cl3N3O13SNa (M + Na)+ calculated 998.2117, found 998.2106.

For Trisaccharide Building Block (5).  

\[ \delta \]  

\[ \begin{align*} 
\text{1H NMR (500 MHz, CDCl}_3\text{)} & \delta 7.45--7.13 (m, 35H), 5.52 (brs, 1H), 5.41 (brs, 1H), 5.34 (d, J = 9.9 Hz, 1H), 5.14 (d, J = 17.3 Hz, 2H), 5.00 (d, J = 10.7 Hz, 1H), 4.91--4.67 (m, 6H), 4.62--4.59 (m, 6H), 4.36--4.25 (m, 3H), 4.08--3.95 (m, 5H), 3.89--3.85 (m, 3H), 3.74 (s, 3H), 3.71--3.64 (m, 3H), 3.58--3.45 (m, 6H), 3.43--3.27 (m, 3H), 2.78 (brs, 1H), 2.52 (dd, J = 13.9, 4.0 Hz, 1H), 2.08 (s, 3H), 2.01
(s, 3H), 1.99 (s, 3H), 1.90 (s, 3H), 1.85 (s, 3H); $^{13}$C-Apt NMR (125 MHz, CDCl$_3$)

$\delta$ 170.61, 170.47, 170.25, 169.92, 169.79, 168.23, 156.04, 138.90, 138.77, 138.46, 138.26, 138.22, 128.36, 128.19, 128.14, 128.13, 128.08, 128.04, 128.03, 127.99, 127.91, 127.72, 127.69, 127.47, 127.43, 127.34, 127.32, 127.30, 127.08, 103.48, 102.13, 98.32, 82.74, 81.69, 78.28, 76.18, 76.11, 75.25, 74.84, 74.78, 73.29, 73.15, 72.88, 72.57, 72.36, 69.04, 68.76, 68.28, 67.84, 67.76, 67.17, 67.10, 67.04, 62.17, 60.27, 52.88, 51.26, 48.93, 46.99, 45.88, 36.26, 22.96, 20.98, 20.69, 20.58, 20.40; HRMS for C$_{84}$H$_{96}$N$_2$O$_{25}$Na (M + Na)$^+$ calculated 1555.6194, found 1555.6247.

4,6-Di-0-Benzylidene-2-Deoxy-2-(2,2,2-Trichloroethoxycarbonylamino)-3-O-Levulinoyl-1-Thio-β-D-Galactopyranoside (7). To a solution of compound 6 (3.00 g, 5.11 mmol) in MeOH/CH$_2$Cl$_2$ (vol/vol = 1:1, 15 ml) was added NaOMe in MeOH (25% wt/vol, 0.2 mL) and the mixture was stirred at 0 °C for 2 h, followed by neutralization with Amberlite IR-50 resin (1.0 g) and filtration. Solvent was removed under reduced pressure to give the crude deacylated product, which was then dissolved in DMF/CH$_3$CN (vol/vol = 1:1, 20 ml), followed by the addition of benzaldehyde dimethyl acetal (1.5 equiv) and (±)-camphorsulfonic acid (CSA) (0.1 equiv). The mixture was stirred at room temperature for 8 h and then diluted with CH$_2$Cl$_2$ (200 ml), washed with saturated aqueous NaHCO$_3$ (20 ml x 3), and brine (10 ml), dried (MgSO$_4$) and concentrated under reduced pressure. The resulting crude benzylidene was dissolved in CH$_2$Cl$_2$ (20 ml), to which 1-ethyl-3-(3′-)dimethylaminopropyl)carbodiimide·HCl (EDC) (1.5 equiv), 3-(dimethylamino) pyridine (DMAP) (0.5 equiv) and levulinic acid (1.5 equiv) were added. The reaction mixture was stirred at room temperature for 16 h and diluted with CH$_2$Cl$_2$ (200 ml), washed with sat. aq. NaHCO$_3$ (20 ml x 3), dried (MgSO$_4$) and concentrated for flash column chromatography purification (CH$_2$Cl$_2$/EtOAc, 4:1) to give compound 7 (1.65 g, 50% over three steps) as a colorless syrup. $^1$H NMR (500 MHz,
4,6-Di-O-Benzylidene-2-Deoxy-2-(2,2,2-Trichloroethoxycarbonylamino)-3-O-Levulinoyl-1-Thio-β-D-Galactopyranoside (8). Compound 7 (1.65 g, 2.55 mmol) in 80% aqueous acetic acid (20 ml) was heated at 80 °C for 6 h and the solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (20 ml), to which pyridine (5 equiv), DMAP (0.05 equiv) and acetic anhydride (3 equiv) were added and the mixture was stirred at room temperature for 2 h. The reaction was quenched with addition of MeOH (10 ml) and the solvent was removed under reduced pressure. After coevaporation with toluene (10 ml x 3), the resulting residue was dissolved in pyridine (10 ml) and 1 M hydrazine hydrate (NH₂NH₂.xH₂O) in pyr/AcOH mixture (vol/vol = 3:2) (2 equiv) was added. The reaction was stirred at room temperature for 4 h and quenched with penta-2,4-dione (2 ml), and the solvent was removed under reduced pressure. The resulting residue was dissolved in CH₂Cl₂ (50 ml), washed with 1 M HCl (10 ml), H₂O (10 ml), and brine (10 ml), dried (Na₂SO₄), and concentrated for flash column chromatography purification (hexane/EtOAc, 2:1) to give compound 8 as a syrup (0.94 g, 70% over three steps). ¹H NMR (500 MHz, CDCl₃) δ 7.42 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 5.43 (d, J = 7.7 Hz, 1H), 5.32 (d, J = 3.3 Hz, 1H), 4.79–4.72 (m, 3H), 4.15 (d, J = 6.2 Hz, 2H), 4.08–3.98 (m, 1H), 3.86 (dd, J = 6.6, 6.2 Hz, 1H), 3.63 (q, J = 9.9 Hz, 1H), 3.14 (d, J = 4.4 Hz, 1H), 2.34 (s, 3H), 2.13 (s, 3H), 2.05 (s, 3H); ¹³C-Apt NMR (125
MHz, CDCl$_3$) $\delta$ 171.14, 170.57, 154.89, 138.41, 133.04, 129.65, 128.46, 95.71, 86.62, 74.70, 74.65, 71.41, 69.30, 62.30, 53.87, 21.13, 20.77, 20.71; HRMS for C$_{20}$H$_{24}$Cl$_3$NO$_8$SNa (M + Na)$^+$ calculated 566.0180, found 566.0177.

For Disaccharide Building Block Precursor (10). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.44 (d, $J = 8.1$ Hz, 2H), 7.20 (m, 15H), 7.07 (d, $J = 8.1$ Hz, 2H), 5.36 (d, $J = 3.3$ Hz, 1H), 5.32 (d, $J = 10.3$ Hz, 1H), 5.23 (d, $J = 10.3$, 8.1 Hz, 1H), 4.91 (d, $J = 12.1$ Hz, 1H), 4.87 (d, $J = 11.8$ Hz, 1H), 4.61 (d, $J = 12.5$ Hz, 1H), 4.54 (d, $J = 12.1$ Hz, 1H), 4.53 (d, $J = 11.8$ Hz, 1H), 4.48 (d, $J = 11.8$ Hz, 1H), 4.45 (d, $J = 12.5$ Hz, 1H), 4.43 (d, $J = 11.8$ Hz, 1H), 4.37 (d, $J = 7.7$ Hz, 1H), 4.31 (dd, $J = 10.3$, 3.3 Hz, 1H), 4.09 (dd, $J = 11.7$, 4.4 Hz, 1H), 4.02 (dd, $J = 11.7$, 7.7 Hz, 1H), 3.88 (d, $J = 2.2$ Hz, 1H), 3.80 (dd, $J = 7.7$, 4.4 Hz, 1H), 3.56–3.63 (m, 2H), 3.49 (dd, $J = 6.6$, 6.3 Hz, 1H), 3.42–3.45 (m, 1H), 3.38 (dd, $J = 10.3$, 2.6 Hz, 1H), 2.97 (ddd, $J = 17.6$, 11.0, 2.6 Hz, 1H), 2.86 (ddd, $J = 17.6$, 11.0, 2.6 Hz, 1H), 2.47 (ddd, $J = 17.3$, 5.5, 2.9 Hz, 1H), 2.32 (s, 3H), 2.24 (ddd, $J = 17.3$, 5.5, 2.9 Hz, 1H), 2.21 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H); $^{13}$C-Apt NMR (125 MHz, CDCl$_3$) $\delta$ 208.57, 171.35, 170.49, 170.09, 153.87, 138.51, 137.93, 137.85, 137.71, 133.01, 129.40, 129.07, 128.46, 128.44, 128.42, 128.40, 128.14, 127.79, 127.74, 127.71, 127.43, 102.40, 95.86, 84.89, 79.65, 75.94, 75.19, 74.25, 74.06, 73.53, 72.51, 71.80, 71.31, 69.67, 68.33, 63.12, 52.96, 37.53, 29.98, 27.48, 21.09, 20.75, 20.72; HRMS for C$_{52}$H$_{58}$Cl$_3$NO$_{15}$SNa (M + Na)$^+$ calculated 1096.2485, found 1096.2491.

2-(Benzyloxycarbonylamino)-Ethyl 4-O-(3,4-Di-O-Isopropylidene-β-D-Galactopyranosyl)-1-β-D-Glucopyranoside (12). To a stirred solution of peracetyl lactosyl acetate 11 (10.00 g, 14.74 mmol) in AcOH/acetic anhydride (vol/vol = 1:1, 20 ml) was added 33% HBr in AcOH (25 ml) and the mixture was stirred at room temperature for 2 h.
The solution was then poured into water (200 ml) and extracted with CH$_2$Cl$_2$ (200 ml x 3). The organic phase was washed with saturated aqueous NaHCO$_3$ (200 ml x 3), dried (Na$_2$SO$_4$), and concentrated under reduced pressure to give the crude lactosyl bromide as a white foamy residue, which was coevaporated with toluene (20 ml x 3). A mixture of HOCH$_2$CH$_2$NHCbz (2 equiv), Ag$_2$CO$_3$ (1.2 equiv), I$_2$ (0.05 equiv), and MS (12 g) in dry CH$_2$Cl$_2$ (40 ml) was stirred at room temperature for 2 h, to which the lactosyl bromide in dry CH$_2$Cl$_2$ (30 ml) was added and the mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous Na$_2$S$_2$O$_3$ (10 ml) and diluted with CH$_2$Cl$_2$ (300 ml). After removal of MS by filtration, the solvent was removed to give a syrup, which was coevaporated with toluene (10 ml x 3). This was dissolved in MeOH (30 ml), and NaOMe (25% wt/vol, 0.4 ml) was added. The solution was stirred at room temperature for 2 h and neutralized with amberlite IR 50 (2.5 g). Subsequent removal of resin by filtration and removal of solvent in vacuum gave a white solid. This white solid was suspended in acetone (30 ml), and 2,2 dimethoxypropane (1.5 equiv) and p-TsOH (0.1 equiv) were added. The reaction mixture was stirred at room temperature for 2 h and quenched with triethylamine (5 ml). The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH, 7:1) to give compound 12 as a colorless oily residue (2.88 g, 35% over four steps). $^1$H NMR (500 MHz, CD$_3$OD) $\delta$7.40–7.09 (m, 5H), 5.16 (s, 2H), 4.35 (d, $J$ = 8.1 Hz, 1H), 4.29 (d, $J$ = 8.1 Hz, 1H), 4.17 (dd, $J$ = 5.5, 2.2 Hz, 1H), 4.04 (dd, $J$ = 7.4, 5.5 Hz, 1H), 3.92–3.94 (m, 1H), 3.92–3.72 (m, 5H), 3.65–3.59 (m, 1H), 3.57–3.50 (m, 2H), 3.44 (dd, $J$ = 8.1, 7.3 Hz, 1H), 3.40–3.37 (m, 2H), 3.32–3.28 (m, 1H), 3.25 (dd, $J$ = 8.8, 8.0 Hz, 1H), 1.46 (s, 3H), 1.31 (s, 3H); $^{13}$C-Apt NMR (125 MHz, CD$_3$OD) $\delta$158.90, 138.28, 129.45, 128.97, 128.82, 111.07, 104.27, 104.12, 80.80, 76.33, 76.12, 75.30, 75.01, 74.78, 74.40, 70.00, 67.45, 62.38, 61.71, 41.95, 28.40, 26.49; HRMS for C$_{25}$H$_{37}$NO$_{13}$Na (M + Na)$^+$ calculated 582.2157, found 582.2156.
**Lactoside Acceptor (13).** To a stirred solution of compound 12 (2.88 g, 5.16 mmol) in N,N-dimethylformamide (30 ml) was added BnBr (7.5 equiv) and NaH (60% in mineral oil, 7.5 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and diluted with EtOAc (400 ml) and quenched with H2O (50 ml). The organic layer was washed with H2O (100 ml), saturated aqueous NaHCO3 (100 ml), and brine (100 ml), dried (Na2SO4) and concentrated to give a pale yellow oil. This was then dissolved in 80% aqueous acetic acid (20 ml) and heated at 80 °C for 2 h. The solution was concentrated for flash column chromatography purification (hexane/EtOAc, 2:1) to give 13 (4.37 g, 80% over two steps) as an colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.36–7.10 (m, 35H), 5.13 (d, J = 20.2 Hz, 2H), 4.98 (d, J = 11.0 Hz, 1H), 4.85–4.73 (m, 3H), 4.73–4.66 (m, 3H), 4.61–4.52 (m, 3H), 4.45–4.36 (m, 4H), 4.04–3.89 (m, 3H), 3.81–3.28 (m, 13H); ¹³C NMR (125 MHz, CDCl₃) δ 154.81, 139.01, 138.30, 138.07, 128.47, 128.38, 128.35, 128.34, 128.32, 128.31, 128.28, 128.02, 127.95, 127.82, 127.66, 127.58, 127.57, 127.54, 127.51, 127.50, 127.24, 127.17, 103.67, 102.51, 82.72, 81.75, 79.96, 76.35, 75.21, 74.96, 74.83, 73.45, 73.42, 73.13, 72.81, 68.72, 68.60, 68.09, 67.24, 51.40; HRMS for C₆₄H₆₉NO₁₃Na (M + Na)⁺ calculated 1082.4661, found 1082.4653.

**p-Methylphenyl 2,3,6-Tri-O-Benzoyl-4-O-(2,3,4-Tri-O-Benzyl-α-L-Fucopyranosyl)-1-Thio-β-D-Glucopyranoside (16).** A solution of compound 3 (51 mg, 0.10 mmol), compound 15 (51 mg, 0.09 mmol), BSP (0.59 equiv), and MS (0.6 g) in CH₂Cl₂ (2 ml) was stirred at room temperature for 45 min. The solution was cooled to −70 °C and Tf₂O (0.7 equiv) was added. The reaction mixture was heated from −70 °C to −0 °C while stirring over 2 h and quenched with triethylamine (100 µl). After removal of MS by filtration, the filtrate was concentrated directly for flash column chromatography purification (hexane/EtOAc, 3:1) to furnish 16 (82 mg, 95%) as a white glassy residue.
$^1$H NMR (600 MHz, CDCl$_3$) δ 7.99 (dd, $J = 8.3, 1.3$ Hz, 2H), 7.81 (dd, $J = 8.3, 1.3$ Hz, 2H), 7.76 (dd, $J = 8.3, 1.2$ Hz, 2H), 7.55 (t, $J = 7.4$ Hz, 1H), 7.42–7.11 (m, 25H), 6.77 (d, $J = 7.9$ Hz, 2H), 5.61 (t, $J = 9.2$ Hz, 1H), 5.16(t, $J = 9.7$ Hz, 1H), 4.98 (dd, $J = 11.8, 1.8$ Hz, 1H), 4.76–4.74 (m, 4H), 4.70 (d, $J = 11.8$ Hz, 1H), 4.64 (d, $J = 11.8$ Hz, 1H), 4.60 (d, $J = 11.4$ Hz, 1H), 4.56 (dd, $J = 12.2, 4.8$ Hz, 1H), 4.41 (d, $J = 11.8$ Hz, 1H), 3.88–3.85 (m, 2H), 3.83–3.79 (m, 2H), 3.62 (q, $J = 6.6$ Hz, 1H), 3.37 (s, 1H), 2.14 (s, 3H), 0.51 (d, $J = 6.6$ Hz, 3H); $^{13}$C-Apt NMR (150 MHz, CDCl$_3$) δ 165.96, 165.90, 165.09, 138.56, 138.33, 138.29, 137.99, 133.89, 133.09, 133.02, 132.98, 129.99, 129.81, 129.73, 129.70, 129.42, 129.37, 129.22, 128.37, 128.33, 128.24, 128.18, 128.07, 127.68, 127.49, 127.40, 100.48, 85.36, 79.14, 77.77, 76.19, 75.58, 75.51, 74.78, 74.29, 72.63, 70.77, 67.62, 62.99, 21.10, 15.90; HRMS for C$_{61}$H$_{58}$O$_{12}$Na (M + Na)$^+$ calculated 1037.3541, found 1037.3554.
Fig. 4. $^1$H NMR spectrum of deprotected Fuc GM$_1$ glycoside 1.
Figure 5. $^{13}$C Apt NMR spectrum of deprotected Fuc-GM$_1$ glycoside 1.
Figure 6. $^1$H NMR spectrum of protected Fuc-GM$_1$ glycoside 2.
Fig. 7. $^{13}$C-Apt NMR spectrum of protected Fuc-GM$_1$ glycoside 2.
Fig. 8. $^1$H NMR spectrum of disaccharide building block 4.
Fig. 9. $^{13}$C-Apt NMR spectrum of disaccharide building block 4.
Fig. 10. NMR spectrum of trisaccharide building block 5.
Fig. 11. $^{13}$C-Apt NMR spectrum of trisaccharide building block 5.
Fig. 12. $^1$H NMR spectrum of 4,6-di-O-benzylidenyl-2-deoxy-2-(2,2,2-trichloroethoxy carbonylamino)-3-O-levulinoyl-1-thio-β-D-galactopyranoside 7.
Fig. 13. $^{13}$C-Apt NMR spectrum of 4,6-di-O-benzylidenyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-3-O-levulinoyl-1-thio-β-D-galactopyranoside 7.
Fig. 14. $^1$H NMR spectrum of 4,6-di-$O$-benzylidenyl-2-deoxy-2-(2,2,2-trichloroethoxyl carbonylamino) -3-$O$-levulinoyl-1-thio-$\beta$-D-galactopyranoside 8.
Fig. 15. $^{13}$C -Apt NMR spectrum of 4,6-di-$O$-benzylidenyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-3-$O$-levulinoyl-1-thio-$\beta$-$D$-galactopyranoside 8.
Fig. 16. $^1$H NMR spectrum of disaccharide building block precursor 10.
Fig. 17. $^{13}$C-Apt NMR spectrum of disaccharide building block precursor 10.
Fig. 18. $^1$H NMR spectrum of 2-(benzyloxycarbonylamino)-ethyl 4-O-(3,4-di-O-isopropylidene-β-D-galactopyranosyl)-1-β-D-glucopyranoside 12.
Fig. 19. $^{13}$C-Apt NMR spectrum of 2-(benzyloxycarbonylamino)-ethyl 4-O-(3,4-di-O-isopropylidene-β-D-galactopyranosyl)-1-β-D-glucopyranoside 12.
Fig. 20. $^1$H NMR spectrum of lactoside acceptor 13.
Fig. 21. $^{13}\text{C}$-Apt NMR spectrum of lactoside acceptor 13.
Fig. 22. $^1$H NMR spectrum of $p$-methylphenyl 2,3,6-tri-$O$-benzoyl-4-$O$-(2,3,4-tri-$O$-benzyl-$\alpha$-L-fucopyranosyl)-1-thio-$\beta$-D-glucopyranoside 16.
Fig. 23. $^{13}$C-Apt NMR spectrum of $p$-methylphenyl 2,3,6-tri-$O$-benzoyl-4-$O$-(2,3,4-tri-$O$-benzyl-$\alpha$-$L$-fucopyranosyl)-1-thio-$\beta$-$D$-glucopyranoside 16.