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PAPER

Synthesis of fluorinated Thomsen–Friedenreich antigens: direct deoxyfluorination of αGalNAc-threonine *tert*-butyl esters†

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Selectively 6-fluorinated analogs of the tumor-associated T_N antigen Fmoc-Thr(α-*O*-GalNAc)-O*t*Bu can be efficiently prepared using DAST-mediated de(hydr)oxyfluorination reactions of preformed and orthogonally protected glycosyl amino esters without affecting the labile protecting groups and *O*-glycosidic linkages. The resulting mono- and difluorinated T_N analogs are interesting building blocks for non-hydrolyzable mucin-type antigen mimetics, as illustrated by the unprecedented synthesis of two different multiply fluorinated Thomsen–Friedenreich derivatives. The reported deoxyfluoro antigen analogs represent important functional probes for carbohydrate-binding proteins and glycosyl-processing enzymes.

Introduction

Glycosylation is the predominant co- and post-translational modification in higher organisms. Because glycans are responsible for modulating the activity of proteins involved in fundamental biological processes,[1] synthetic oligosaccharides and glycoconjugates have acquired an increasing importance in the field of drug discovery in recent years. Good examples are mucin-type glycopeptide antigens characterized by the presence of *N*-acetyl-α-D-galactosamine (α-D-GalNAc) linked to the hydroxyl group of Ser/Thr (T_N antigen), which represent attractive tumor targets for immunotherapy.[2] For instance, the Thomsen–Friedenreich (TF) antigen is expressed in about 90% of human carcinomas[3] and plays a significant role in metastasis of breast and prostate cancer.[4] Synthetic carbohydrate-based vaccines comprising this antigen and its immediate precursor T_N antigen have been developed to elicit highly specific immune responses in mice.[5] Thr-*O*-linked T_N glycosides were also discovered on the envelope glycoprotein gp120 of HIV[6] and are commonly present in antifreeze glycopeptides.[7]

A major drawback of carbohydrate-based drug candidates stems from their low metabolic stabilities that erode the bioavailabilities of the compounds. With regard to carbohydrate-based vaccines, enzymatic degradation and loss of essential saccharidic recognition elements significantly affect the specificity of the elicited antibody response. As a consequence, there is considerable interest in utilizing non-hydrolyzable glycoconjugate mimics,[8] *e.g.*, deoxyfluoro sugars, *C*-glycosides, and *S*-glycosides for vaccine design.

Recently, the first syntheses of MUC1 glycopeptide analogs with Thomsen–Friedenreich (TF) antigen determinants containing one or two fluorine substituents in their glycan components were described.[9] Moreover, by conjugation of such a tumor-associated carbohydrate analog to tetanus toxoid (TTox), a novel synthetic cancer vaccine 6,6′F-TF-Thr-MUC1-TTox was obtained, which elicited a strong and specific immune response in mice.[10] With the aim of making related glycopeptides more easily available for biological evaluations, improved syntheses of TF and T_N analogs with F-substituents at strategic positions of both pyranose rings, the GalNAc (C-6) and Gal moiety (C-2′), are presented herein.

Results and discussion

Following a known strategy for the synthesis of the natural T_N-threonine conjugate,[11] the corresponding 6-fluoro analog **5** was previously synthesized by a stereoselective Koenigs–Knorr-type glycosylation[12] of Fmoc-Thr-O*t*Bu[13] (**4**) with α-3,4-di-*O*-acetyl-2-azido-2,6-dideoxy-6-fluorogalactosyl bromide (**3**).[9] The latter is accessible by azidonitration[14] of 3,4-di-*O*-acetyl-6-fluorogalactal **1** and anomeric exchange of the nitrate group in **2** for a bromide. The low yields of these two steps, which in case of the azidonitration reaction are not uncommon,[15] and the reduced activity of the donor α-$Ac_2$6F2N_3GalBr (**3**) in the subsequent glycosylation reaction with **4** markedly impaired formation of the T_N analog **5**. Hence, starting from galactal **1**, compound **5** was only accessible in an unsatisfying low yield of 14% over four steps (Scheme 1).[9]

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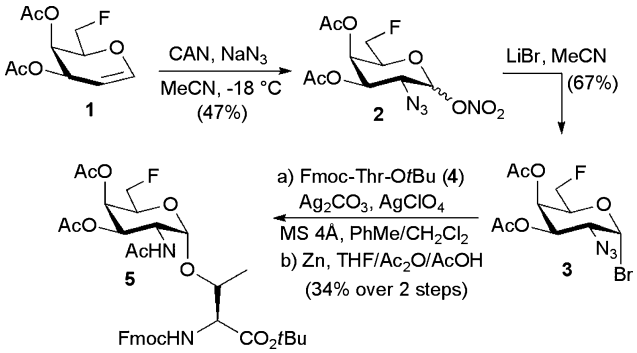


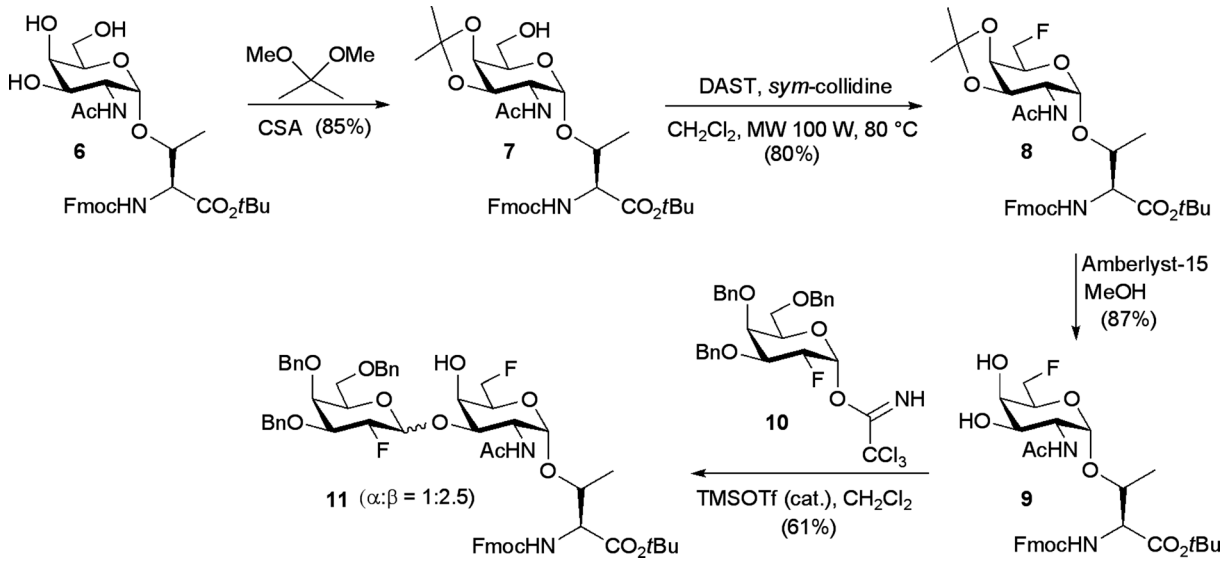
Scheme 1 Reported stepwise assembly of 6-fluoro T_N antigen **5** using 6F-Gal building blocks.[9]

Fortunately though, this yield was considerably improved by direct dehydroxyfluorination of a suitably protected glycosyl amino acid ester – a reaction that has hitherto not been performed. Treatment of the T_N antigen derivative **6**[9b] with 2,2-dimethoxypropane under acidic conditions[16] afforded the corresponding 3,4-*O*-isopropylidene acetal **7** which was subjected to a nucleophilic fluorination reaction with commercially available *N*,*N*-diethylaminosulfur trifluoride DAST[17] (Scheme 2). Under microwave irradiation (100 W, 80 °C) and in the presence of *sym*-collidine as a HF scavenger, the reaction proceeded smoothly to provide the 6-fluoro-T_N derivative **8** in 80% yield after column chromatography. It is particularly noteworthy to state that neither the *O*-glycosidic linkage to threonine, nor the labile *tert*-butyl ester, which are both prone to facile elimination, were affected under these conditions. Selective acidolysis of the isopropylidene acetal in the presence of the *tert*-butyl ester finally provided Fmoc-Thr(α-6FGalNAc)-O*t*Bu (**9**),[9b] which after liberation of the carboxy group would be applicable to the synthesis of structurally modified mucin-type antigens and antifreeze glycopeptides. Moreover, compound **9** represents a key building block for the assembly of further fluoro analogs of tumor-associated TF antigens, as illustrated below.

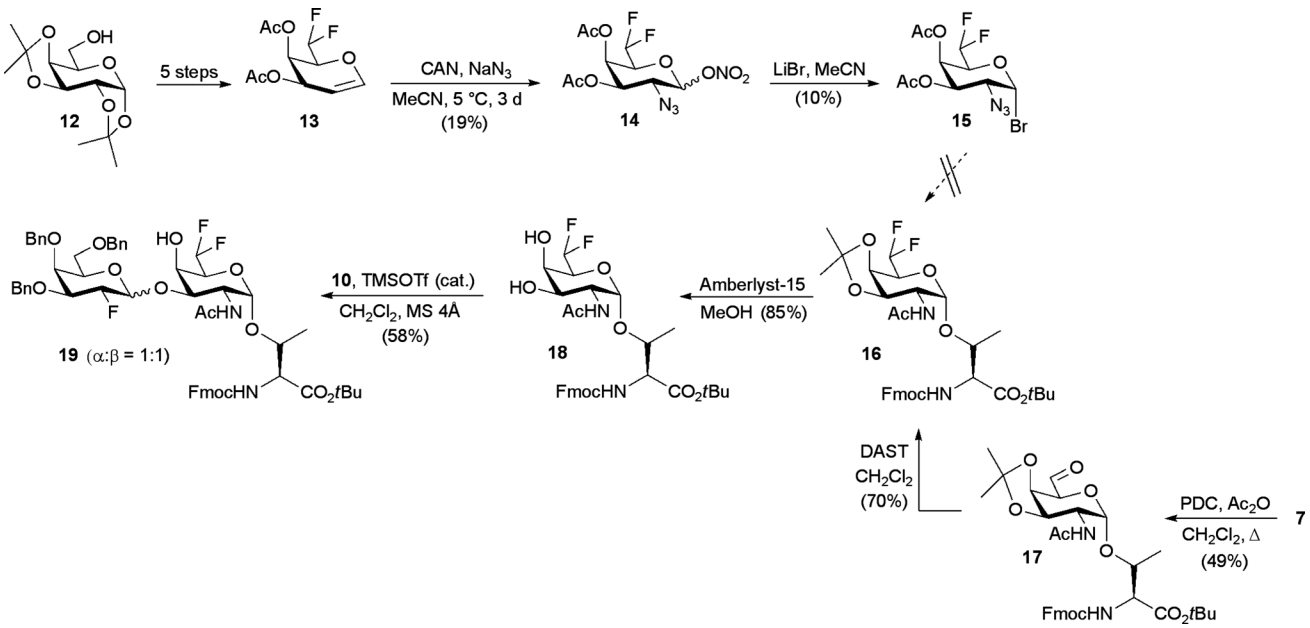
Hence, a novel 2′,6-difluoro-TF antigen analog **11** was prepared using the TMSOTf-promoted glycosylation of α-3,4,6-tri-*O*-benzyl-2-deoxy-2-fluorogalactosyl trichloroacetimidate (**10**)[9b] with 6-fluoro-T_N analog **9**. Interestingly, although the reaction occurred exclusively at 3-OH to provide the desired TF derivative **11** in 61% yield, only a moderate β-anomeric selectivity of 1 : 3 (α/β) was obtained. This markedly deviates from the previously observed[9b] high stereoselectivity of 1 : 10 (α/β) for the related glycosylation of non-fluorinated Fmoc-Thr(α-4,6-*O*-Bzn-GalNAc)-O*t*Bu[18] with $Bn_3$2FGal-TCI **10** (data not shown). Examples of such 2-deoxy-2-fluoroglycosylations are rare,[9,19] due to the lack of neighboring group participation and a strongly suppressed anomeric reactivity of the respective glycosyl donors. The stereochemistry of a given 2-fluorogalactosylation is not only dependent on the protecting groups of the galactosyl donor, but is also influenced by the nature of the accepting glycan part. Apparently, the differences in the electronic properties of the fluorinated acceptor **9** with regard to its non-fluorinated congener Fmoc-Thr(α-4,6-*O*-Bzn-GalNAc)-O*t*Bu caused the observed decrease in the β-selectivity of the glycosylation. Fortunately though, the anomeric products can be separated by column chromatography to provide TF analog β-**11** in quantities applicable to solid-phase glycopeptide synthesis and/or protein conjugation.

While 6F-T_N antigen can be prepared from its azido-precursor **3**, albeit in low yields, the corresponding 6,6-difluoro analog **16** is not readily accessible *via* this route (Scheme 3). The low reactivity of both 2-azido-6,6-difluorogalactosyl nitrate **14** and 2-azido-6,6-difluorogalactosyl bromide **15** towards the exchange of the anomeric leaving groups (0.4% yield of **15** based on 1,2:3,4-di-*O*-isopropylidene galactose **12**[20]) impairs the formation of the 6,6-difluoro glycosyl amino acid **16** and renders its synthesis extremely inefficient.

Again, the preparation of **16** was therefore envisaged by direct deoxyfluorination reaction of a suitably protected T_N derivative. Towards this end, T_N antigen **6** was selectively converted into the 3,4-*O*-isopropylidene derivative **7**, and subsequent oxidation to the glycosyl aldehyde **17** was sought. However, initial treatment



Scheme 2 Synthesis of fluorinated T_N analog **9** and TF antigen analog **11**.



Scheme 3 Synthesis of bisfluorinated T_N analog **18** and TF antigen analog **19**.

of 3,4-*O*-isopropylidene acetal **7** with 1.5 equiv. of Dess–Martin periodinane[21] (DMP) did not result in any conversion of the starting material, and increasing the amount of DMP (up to 5 equiv.) eventually led to complete decomposition of **7**. A similar result was obtained under Swern conditions,[22] whereas smooth conversion to aldehyde **17** took place upon refluxing **7** with pyridinium dichromate (PDC) in the presence of Ac_2O.[23] However, **17** was found to decompose rapidly in solution, and hence, only a relatively low yield of 49% of the desired product was isolated after column chromatography. Fortunately though, the subsequent DAST-mediated conversion of **17** into bisfluorinated T_N antigen analog **16** proceeded smoothly to provide the desired product in 70% yield. The latter was then used for the preparation of a TF antigen analog **19** carrying a third fluorine substituent at position C-2 of the Gal moiety.

Therefore, compound **16** was selectively deprotected (**18**, 85%) and treated with $Bn_3$2FGal-TCI **10** in the presence of TMSOTf.[21] Although this galactosylation proceeded smoothly again, its stereoselectivity was completely lost, indicating the strong steering influence of the fluorine substituents at the accepting glycoside. Nevertheless, the anomeric mixture of **19** can be separated by column chromatography to provide sufficient quantities of β-**19** for subsequent synthetic transformations.

Conclusions

In summary, an improved protocol for the preparation of orthogonally protected 6-fluorinated α-GalNAc-threonine conjugates was developed based on DAST-mediated deoxyfluorination reactions of preformed glycosyl amino acid building blocks. In these reactions neither the isopropylidene and *tert*-butyl ester protecting groups, nor the labile *O*-glycosidic bonds were affected. The resulting fluorinated T_N antigen analogs **9** and **18** are of importance as glycomimetics with regard to tumor-associated mucin-type antigens and antifreeze glycopeptides. 6-Fluoro T_N analogs can be used as synthetic precursors for the preparation of more complex carbohydrate antigen mimetics, *e.g.* multiply fluorinated TF derivatives **11** and **19** which are also of interest as probes for carbohydrate binding proteins and glycosyl-processing enzymes. Finally, selectively fluorinated α-D-GalNAc-Thr/Ser conjugates represent novel tools for carbohydrate-based vaccines against cancer and HIV with increased biological half-lives. Further studies in these directions are currently pursued.

Experimental

General remarks

Solvents for moisture-sensitive reactions (toluene, MeCN, CH_2Cl_2) were distilled and dried according to standard procedures. Glycosylations were performed in flame-dried glassware under inert argon atmosphere. Reagents were purchased in the highest available commercial quality and used as supplied except where noted. Reactions were monitored by TLC with pre-coated silica gel 60 F_{254} aluminium plates (Merck KGaA, Darmstadt) using UV light as the visualizing agent and by dipping the plate into a 1 : 1 mixture of 1 M H_2SO_4 in EtOH and a 3% 3-methoxyphenol solution in EtOH followed by heating. Flash column chromatography was performed with silica gel (0.035–0.070 mm, 60 Å) from Acros. RP-HPLC analyses were performed on a JASCO-HPLC system with PerfectSil C18(2) (250 × 4.6 mm, 5 μm), Phenomenex Luna C18(2) (250 × 4.6 mm, 5 μm), and Phenomenex Jupiter C18(2) (250 × 4.6 mm, 5 μm) columns at flow rates of 1 mL min^{-1}. Preparative RP-HPLC separations were carried out on a JASCO-HPLC System with PerfectSil C18(2) (250 × 30 mm, 10 μm), Phenomenex Luna C18(2) (250 × 30 mm, 10 μm), and Phenomenex Jupiter C18(2) (250 × 30 mm, 10 μm) columns at flow rates of 20 mL min^{-1} or 10 mL min^{-1}. Mixtures of H_2O–MeCN and H_2O–MeOH were used as solvents.

^{1}H, ^{13}C, ^{19}F, and 2D NMR spectra were recorded on a Bruker AC-300 or a Bruker AM-400 spectrometer. The chemical shifts are reported in ppm relative to the signal of the deuterated solvent. Multiplicities are given as: s (singlet), br s (broad singlet), d (doublet), t (triplet), and m (multiplet). Assignment of proton and carbon signals was achieved by additional COSY, HMQC, and HMBC experiments when noted. The signals of the galactose saccharide portions were marked by primes (′), and those of the amino acid residues were assigned by greek letters. ESI- and HR-ESI-mass spectra were recorded on Micromass LCT and Q TOF Ultima 3 spectrometers, and FD-mass spectra on a Finnigan MAT-95 spectrometer. Optical rotations were measured at 546 nm and 578 nm with a Perkin–Elmer polarimeter 241.

***N*-(9*H*-Fluoren-9-yl)-methoxycarbonyl-*O*-(2-acetamido-2-deoxy-3,4-isopropylidene-α-D-galactopyranosyl)-L-threonine-*tert*-butyl ester (7).** A solution of 509 mg (0.85 mmol) T_N antigen **6** in 20 mL 2,2-dimethoxypropane was stirred with 38 mg (0.16 mmol) (–)-10-camphersulfonic acid at room temperature for 3 d. The reaction was quenched with 0.13 mL triethylamine and the mixture was evaporated to dryness. The residue was dissolved in 22 mL of a mixture of methanol–water (10 : 1) and stirred at 65 °C for 3 h. The solvents were removed *in vacuo* and the residue was co-evaporated with toluene. Flash chromatography on silica gel (^{c}Hex–EtOAc, 1 : 4) provided **7** as a colorless amorphous solid (463 mg, 0.72 mmol, 85%); R_f 0.55 (EtOAc); analytical RP-HPLC (PerfectSil, H_2O–MeCN, 50 : 50 → 20 : 80, 30 min → 0 : 100, 10 min): t_R = 8.3 min; $[\alpha]_D^{23}$ = 53.4 (c = 1, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, COSY): δ = 7.78 (d, 2H, J = 7.3, 4-H-, 5-H-Fmoc), 7.61 (d, 2H, J = 6.1, 1-H-, 8-H-Fmoc), 7.44–7.37 (m, 2H, 3-H-, 6-H-Fmoc), 7.36–7.28 (m, 2H, 2-H-, 7-H-Fmoc), 6.03 (d, 1H, J = 9.7, NHAc), 5.43 (d, 1H, J = 9.4, NH-urethane), 4.80 (d, 1H, J = 3.1, 1-H), 4.48 (d, 2H, J = 6.6, CH_2-Fmoc), 4.33–4.20 (m, 3H, 2-H, CH-Fmoc, T$^\alpha$), 4.19–4.15 (m, 1H, 4-H), 4.15–4.08 (m, 2H, T$^\beta$, 5-H), 4.05 (dd, 1H, J = 4.9/9.2, 3-H), 3.97 (dd, 1H, J = 6.4/11.7, 6a/b-H), 3.84 (dd, 1H, J = 4.0/11.7, 6a/b-H), 2.03 (s, 3H, CH_3-NHAc), 1.60 (s, 3H, CH_3-acetal), 1.46 (s, 9H, *t*Bu), 1.34 (s, 3H, CH_3-acetal), 1.29 (d, 3H, J = 6.4, T$^\gamma$); ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT, HMQC), δ = 170.2, 170.1, 156.3 (C═O), 143.7, 143.6 (C1a-, C8a-Fmoc), 141.3 (C4a-, C5a-Fmoc), 127.8 (C3-, C6-Fmoc), 127.1 (C2-, C7-Fmoc), 125.0, 124.9 (C1-, C8-Fmoc), 120.0, 120.0 (C4-, C5-Fmoc), 110.1 (C_q-acetal), 100.0 (C1), 83.2 (C_q-*t*Bu), 76.7 (T$^\beta$), 74.9 (C3), 68.1 (C5), 73.4 (C4), 67.0 (CH_2-Fmoc), 62.8 (C6), 58.8 (T$^\alpha$), 50.1 (C2), 47.2 (CH-Fmoc), 28.1 (CH_3-*t*Bu), 27.8, 26.7 (CH_3-acetal), 23.4 (CH_3-NHAc), 18.7 (T$^\gamma$); ESI-MS (positive): 663.32 [M+Na]$^+$, 679.31 [M+K]$^+$, 1303.65 [2M + Na]$^+$; HR-MS (ESI-TOF): m/z: found: 663.2899 [M+Na]$^+$, $C_{34}H_{44}N_2NaO_{10}$ calcd.: 663.2894.

***N*-(9*H*-Fluoren-9-yl)-methoxycarbonyl-*O*-(2-acetamido-2,6-dideoxy-6-fluoro-3,4-isopropylidene-α-D-galactopyranosyl)-L-threonine-*tert*-butyl ester (8).** To a solution of protected T_N antigen **7** (881 mg, 1.38 mmol) in anhyd. CH_2Cl_2 (7 mL) were added 2,4,6-collidine (0.47 mL, 0.51 mmol) and DAST (0.24 mL, 1.82 mmol), and the reaction mixture was irradiated in a CEM *Discover*^{TM} microwave reactor for 1 h (80 °C, 100 W). The reaction was quenched by addition of MeOH (1.5 mL) and the solution was washed three times with aq. HCl (1 N) and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (^{c}Hex–EtOAc, 1 : 1) afforded **8** as a colorless amorphous solid (670 mg, 1.11 mmol, 80%); R_f 0.56 (^{c}Hex–EtOAc, 1 : 2); RP-HPLC (PerfectSil, H_2O–MeCN, 50 : 50 → 20 : 80, 30 min → 0 : 100, 10 min): t_R = 14.8 min, 17.3 min (conformer); $[\alpha]_D^{23}$ = 67.9 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY), δ = 7.78 (d, 2H, J = 7.4, 4-H-, 5-H-Fmoc), 7.61 (d, 2H, J = 7.3, 1-H-, 8-H-Fmoc), 7.41 (t, 2H, J = 7.3, 3-H-, 6-H-Fmoc), 7.36–7.28 (m, 2H, 2-H-, 7-H-Fmoc), 6.02 (d, 1H, J = 9.2, NHAc), 5.65 (d, 1H, J = 8.5, NH-urethane), 4.80–4.69 (m, 2H, 1-H, 6a/b-H), 4.62–4.56 (m, 1H, 6a/b-H), 4.55–4.46 (m, 2H, CH_2-Fmoc), 4.33–4.17 (m, 4H, 2-H, 5-H, CH-Fmoc, T$^\alpha$), 4.17–4.02 (m, 3H, 3-H, 4-H, T$^\beta$), 2.03 (s, 3H, CH_3-NHAc), 1.59 (s, 3H, CH_3-acetal), 1.46 (s, 9H, *t*Bu), 1.34–1.25 (m, 6H, CH_3-acetal {1.33}, T$^\gamma$); ^{13}C-NMR (100.6 MHz, $CDCl_3$, DEPT, HMQC), δ = 170.2, 170.1, 156.3 (C═O), 143.7, 143.6 (C1a-, C8a-Fmoc), 141.3 (C4a-, C5a-Fmoc), 127.8 (C3-, C6-Fmoc), 127.1 (C2-, C7-Fmoc), 125.0, 124.9 (C1-, C8-Fmoc), 120.0, 120.0 (C4-, C5-Fmoc), 110.2 (C_q-acetal), 100.1 (C1), 82.7 (d, J = 169.8, C6), 83.2 (C_q-*t*Bu), 77.0 (T$^\beta$), 74.8 (C3), 72.0 (d, J = 7.6, C4), 67.1 (d, J = 21.4, C5), 67.0 (CH_2-Fmoc), 58.9 (T$^\alpha$), 49.9 (C2), 47.2 (CH-Fmoc), 28.1 (CH_3-*t*Bu), 27.7, 26.6 (CH_3-acetal), 23.3 (CH_3-NHAc), 18.7 (T$^\gamma$); ^{19}F NMR (376.5 MHz, $CDCl_3$), δ = –227.7 (td, J = 15.3/47.0); ESI-MS (positive), m/z: 643.36 [M+H]$^+$, 665.34 [M+Na]$^+$, 681.32 [M+K]$^+$; HR-MS (ESI-TOF), m/z: found: 665.2829 ([M+Na]$^+$, $C_{34}H_{43}FN_2NaO_9$ calcd.: 665.2850).

***N*-(9*H*-Fluoren-9-yl)-methoxycarbonyl-*O*-(2-acetamido-2,6-dideoxy-6-fluoro-α-D-galactopyranosyl)-L-threonine-*tert*-butyl ester (9).** To a solution of 6F-T_N analog **8** (347 mg, 0.54 mmol) in 20 mL MeOH were added *Amberlyst-15* (30 mg). The mixture was stirred at room temperature for 14 h and then filtered. The solvents were removed *in vacuo* and the residue was co-evaporated with dichloromethane (3 × 10 mL) to yield **9** as a colorless amorphous solid (202 mg, 0.48 mmol, 89%); R_f 0.65 (CH_2Cl_2–EtOH, 5 : 0.4); RP-HPLC (Luna, H_2O–MeCN, 70 : 30, 5 min → 23 : 77, 25 min → 0 : 100, 30 min): t_R = 21.7 min; $[\alpha]_D^{23}$ = 26.5 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY), δ = 7.76 (d, 2H, J = 7.4, 4-H-, 5-H-Fmoc), 7.61 (d, 2H, J = 6.4, 1-H-, 8-H-Fmoc), 7.40 (t, 2H, J = 7.2, 3-H-, 6-H-Fmoc), 7.32 (t, 2H, J = 6.1, 2-H-, 7-H-Fmoc), 6.89 (d, 1H, J = 7.5, NHAc), 5.65 (d, 1H, J = 9.4 Hz, NH-urethane), 4.86 (d, 1H, J = 3.3, 1-H), 4.76–4.53 (m, 2H, 6a,b-H), 4.52–4.38 (m, 2H, CH_2-Fmoc), 4.30–4.22 (m, 3H, 2-H, CH-Fmoc, T$^\alpha$), 4.19–4.04 (m, 2H, T$^\beta$ {4.15}, 5-H {4.07}), 3.94 (m, 1H, 4-H), 3.82 (dd, 1H, J = 2.1/10.2, 3-H), 2.11 (s, 3H, CH_3-NHAc), 1.45 (s, 9H, *t*Bu), 1.31 (d, 3H, J = 6.3, T$^\gamma$); ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT, HMQC), δ = 174.0, 171.1, 156.4 (C═O), 143.7, 143.6 (C1a-, C8a-Fmoc), 141.3 (C4a-, C5a-Fmoc), 127.8, 127.7 (C3-, C6-Fmoc), 127.1 (C2-, C7-Fmoc), 125.0, 124.9 (C1-, C8-Fmoc), 120.0 (C4-, C5-Fmoc), 99.5 (C1), 83.3 (d, J = 169.0, C6), 83.4 (C_q-*t*Bu), 76.8 (T$^\beta$), 71.0 (C3), 69.5 (d, J = 20.2, C5), 68.1 (d, J = 7.1, C4), 67.1 (CH_2-Fmoc), 59.0 (T$^\alpha$), 50.9 (C2), 47.2 (CH-Fmoc), 28.0 (CH_3-*t*Bu), 22.8 (CH_3-NHAc), 18.7 (T$^\gamma$); ^{19}F NMR (376.5 MHz, $CDCl_3$), δ = –229.8 (bs); ESI-MS (positive), m/z: 625.28 [M+Na]$^+$, 641.26 [M+K]$^+$, 1227.57 [2M+Na]$^+$, 1243.55 [2M+K]$^+$; HR-MS (ESI-TOF), m/z: found: 625.2540 [M+Na]$^+$, $C_{31}H_{39}FN_2NaO_9$ calcd.: 625.2537.

***N*-(9*H*-Fluoren-9-yl)-methoxycarbonyl-*O*-(2-acetamido-2,6-dideoxy-6-fluoro-3-*O*-[2,3,4-tri-*O*-benzyl-2-deoxy-2-fluoro-β-D-galactopyranosyl]-α-D-galactopyranosyl)-L-threonine-*tert*-butyl ester (11).** A solution of glycosyl acceptor **9** (292 mg, 0.48 mmol)

and donor **10** (353 mg, 0.59 mmol) in anhyd. CH_2Cl_2 (20 mL) was stirred with activated, powdered molecular sieves (4 Å, 200 mg) for 1 h at room temperature under an argon atmosphere. The suspension was cooled to 0 °C, and TMSOTf (15 µL, 0.08 mmol) was added. After being stirred for 20 h, the reaction mixture was neutralized with solid $NaHCO_3$. The organic phase was concentrated *in vacuo* and purified by flash chromatography on silica gel (^{c}Hex–EtOAc, 2 : 1) to afford **11** as a colorless amorphous solid (303 mg, 0.29 mmol, 61%, α/β = 1 : 2.5); β-**11**: R_f 0.22, 0.29 (rotamer) (^{c}Hex–EtOAc, 1 : 1); RP-HPLC (Jupiter, H_2O–MeOH, 20 : 80 → 0 : 100, 30 min): t_R = 12.4 min, 13.4 min (rotamer); $[\alpha]_D^{23}$ = 31.5 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY), δ = 7.80–7.76 (m, 2H, 4-H-, 5-H-Fmoc), 7.64 (d, 2H, J = 7.4, 1-H-, 8-H-Fmoc), 7.40 (t, 2H, J = 7.6, 3-H-, 6-H-Fmoc), 7.38–7.25 (m, 17 H, 2-H-, 7-H-Fmoc, H_{ar}-Bn), 5.78 (d, 1H, J = 9.6, NHAc), 5.44 (d, 1H, J = 9.4, NH-Fmoc), 4.91 (d, 1H, J = 11.4, CH_2-Bn), 4.87 (d, 1H, J = 3.2, 1-H), 4.83–4.64 (m, 4H, CH_2-Bn {4.78, d, J = 12.2}, 2′-H, 6a/b-H, CH_2-Bn), 4.63–4.43 (m, 6H, 1′-H, CH_2-Fmoc {4.49, d, J = 6.7}, CH_2-Bn, 2-H, 6a/b-H), 4.43–4.40 (m, 2H, CH_2-Bn), 4.28 (t, 1H, J = 6.7, CH-Fmoc), 4.24–4.20 (m, 1H, T^α), 4.19–4.11 (m, 1H, T^β), 4.10–3.99 (m, 3H, 4-H, 5-H, 5′-H), 3.72–3.64 (m, 1H, 3-H), 3.54 (dd, 1H, J = 3.1/6.2, 3′-H), 3.88–3.85 (m, 1H, 4′-H), 3.60–3.52 (m, 2H, 3-H, 6a/b′-H), 3.50–3.45 (m, 1H, 6a/b′-H), 2.01 (s, 3H, CH_3-NHAc), 1.46 (s, 9H, *t*Bu), 1.30 (d, 3H, J = 6.5, T^γ); ^{13}C NMR (100.6 MHz, HMQC, $CDCl_3$), δ = 170.4, 170.1, 156.4 (C═O), 143.8, 143.7 (C1a-, C8a-Fmoc), 141.3 (C4a-, C5a-Fmoc), 137.9, 137.8, 137.5 (C_q-Bn), 128.5, 128.4, 128.3, 127.9, 127.8, 127.5, 127.1 (C_{ar}-Bn, C2-, C3-, C6-, C7-Fmoc), 125.0, 125.0 (C1-, C8-Fmoc), 120.0 (C4-, C5-Fmoc), 102.5 (d, J = 24.0, C1′), 100.4 (C1), 91.3 (d, J = 185.0, C2′), 83.2 (d, J = 167.6, C6), 83.1 (C_q-*t*Bu), 80.0 (C3), 79.7 (d, J = 13.7, C3′), 76.9 (T^β), 74.8 (CH_2-Bn), 74.0 (C4′), 73.6, 72.7 (CH_2-Bn), 69.2 (d, J = 20.9, C5), 68.7 (C6′), 68.3 (C5′), 68.0 (d, J = 7.0, C4), 67.0 (CH_2-Fmoc), 59.1 (T^α), 47.4 (C2), 47.2 (CH-Fmoc), 28.1 (CH_3-*t*Bu), 23.3 (CH_3-NHAc), 18.8 (T^γ); ^{19}F NMR (376.6 MHz, $CDCl_3$), δ = –228.9 (dt, J = 15.0/47.1, 6-F), –204.5 – –204.8 (m, 2′-F); MS-ESI (positive), m/z: 1059.46 $[M+Na]^+$; HR-MS (ESI-TOF), m/z: found: 1059.4435 $[M+Na]^+$, $C_{58}H_{66}F_2N_2NaO_{13}$ calcd.: 1059.4431.

***N*-(9*H*-Fluoren-9-yl)-methoxycarbonyl-*O*-(2-acetamido-2-deoxy-3,4-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranosyl)-L-threonine-*tert*-butyl ester (17).** To a suspension of pyridinium dichromate (420 mg, 1.12 mmol) and Ac_2O (0.32 ml, 3.37 mmol) in anhyd. CH_2Cl_2 (50 ml) was added protected T_N antigen **7** (715 mg, 1.12 mmol), dissolved in anhyd. CH_2Cl_2 (15 ml). The reaction mixture was refluxed for 3.5 h, neutralized with 3 drops of NEt_3, and concentrated *in vacuo*. Flash chromatography on silica gel (^{c}Hex–EtOAc–NEt_3, 1 : 2 : 0.001) afforded **17** as a colorless amorphous solid (351 mg, 0.55 mmol, 49%); R_f 0.20 (^{c}Hex–EtOAc, 1 : 2); RP-HPLC (Luna, H_2O–MeCN, 50 : 50, 10 min → 23 : 77, 15 min → 0 : 100, 35 min): t_R = 11.6 min; $[\alpha]_D^{23}$ = 62.1 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY), δ = 9.66 (s, 1H, 6-H), 7.78–7.71 (m, 2H, 4-H-, 5-H-Fmoc), 7.58 (d, 2H, J = 7.3, 1-H-, 8-H-Fmoc), 7.42–7.34 (m, 2H, 3-H-, 6-H-Fmoc), 7.33–7.25 (m, 2H, 2-H-, 7-H-Fmoc), 6.07 (d, 1H, J = 9.6, NHAc), 5.40 (d, 1H, J = 9.1, NH-urethane), 4.89 (d, 1H, J = 2.8, 1-H), 4.55–4.42 (m, 3H, 4-H, CH_2-Fmoc), 4.42–4.28 (m, 2H, 2-H, 5-H), 4.25–4.16 (m, 2H, CH-Fmoc, T^α), 4.15–4.03 (m, 2H, T^β, 3-H), 2.02 (s, 3H, CH_3-NHAc), 1.56 (s, 3H, CH_3-acetal), 1.45 (s, 9H, *t*Bu), 1.31 (s, 3H, CH_3-acetal), 1.20 (d, 3H, J = 6.9, T^γ); ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT, HMQC), δ = 198.0, 170.4, 170.3, 156.4 (C═O), 143.6 (C1a-, C8a-Fmoc), 141.4 (C4a-, C5a-Fmoc), 127.9 (C3-, C6-Fmoc), 127.1 (C2-, C7-Fmoc), 125.0, 124.9 (C1-, C8-Fmoc), 120.1 (C4-, C5-Fmoc), 110.6 (C_q-acetal), 100.1 (C1), 83.4 (C_q-*t*Bu), 76.9 (T^β), 74.6 (C3), 73.3 (C5), 72.5 (C4), 67.0 (CH_2-Fmoc), 58.7 (T^α), 49.8 (C2), 47.3 (CH-Fmoc), 28.1 (CH_3-*t*Bu), 27.7 (CH_3-acetal), 26.6 (CH_3-NHAc), 23.4 (CH_3-acetal), 18.6 (T^γ); FD-MS, m/z: 638.78 $[M+H]^+$; HR-MS (ESI-TOF), m/z: found: 661.2722 $[M+Na]^+$, $C_{34}H_{42}N_2NaO_{10}$ calcd.: 661.2737.

***N*-(9*H*-Fluoren-9-yl)-methoxycarbonyl-*O*-(2-acetamido-2,6-dideoxy-6,6-difluoro-3,4-isopropylidene-α-D-galactopyranosyl)-L-threonine *tert*-butyl ester (16).** A solution of **17** (340 mg, 0.53 mmol) in anhyd. CH_2Cl_2 (20 mL) was stirred for 3 h at room temperature with DAST (0.14 mL, 1.16 mmol). The reaction was quenched by addition of MeOH (2 mL) and the solvents were removed *in vacuo*. Flash chromatography on silica gel (^{c}Hex–EtOAc, 1 : 2) gave **16** (244 mg, 0.37 mmol, 70%) as a colorless amorphous solid; R_f 0.62 (^{c}Hex–EtOAc, 1 : 2); RP-HPLC (Luna, H_2O–MeCN, 50 : 50 → 20 : 80, 30 min → 0 : 100, 10 min): t_R = 22.1 min; $[\alpha]_D^{23}$ = 83.5 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY), δ = 7.76 (d, 2H, J = 7.4, 4-H-, 5-H-Fmoc), 7.59 (d, 2H, J = 7.3, 1-H-, 8-H-Fmoc), 7.43–7.36 (m, 2H, 3-H-, 6-H-Fmoc), 7.34–7.28 (m, 2H, 2-H-, 7-H-Fmoc), 6.10 (ddd, 1H, J = 6.7/11.2/54.3, 6-H), 5.97 (d, 1H, J = 9.7, NHAc), 5.29 (d, 1H, J = 7.6, NH-urethane), 4.78 (s, 1H, 1-H), 4.57–4.41 (m, 2H, CH_2-Fmoc), 4.35–4.26 (m, 1H, 2-H), 4.26–4.15 (m, 3H, 4-H, CH-Fmoc, T^α), 4.14–4.01 (m, 2H, 5-H, T^β), 4.02 (dd, 1H, J = 9.0/4.9, 3-H) 2.02 (s, 3H, CH_3-NHAc), 1.59 (s, 3H, CH_3-acetal), 1.44 (s, 9H, *t*Bu), 1.33 (s, 3H, CH_3-acetal), 1.26 (d, 3H, J = 6.4, T^γ); ^{13}C NMR (100.6 MHz, $CDCl_3$, HMQC), δ = 170.2, 170.0, 156.3 (C═O), 143.8, 143.6 (C1a-, C8a-Fmoc), 141.4 (C4a-, C5a-Fmoc), 127.8 (C3-, C6-Fmoc), 127.1 (C2-, C7-Fmoc), 125.0, 124.9 (C1-, C8-Fmoc), 120.1 (C4-, C5-Fmoc), 114.3 (dd, J = 238.3/245.5, C6) 110.5 (C_q-acetal), 100.2 (C1), 83.3 (C_q-*t*Bu), 77.5 (T^β), 74.6 (C3), 70.8 (d, J = 6.5, C4), 68.0 (dd, J = 22.7/31.6, C5), 66.9 (CH_2-Fmoc), 58.8 (T^α), 49.8 (C2), 47.3 (CH-Fmoc), 28.1 (CH_3-*t*Bu), 27.7 (CH_3-acetal), 26.6 (CH_3-NHAc), 23.4 (CH_3-acetal), 18.5 (T^γ); ^{19}F NMR (376.5 MHz, $CDCl_3$), δ = –130.7 (dd, J = 53.8/298.1, 6aF), –127.1 (ddd, J = 11.2/58.0/298.1, 6bF); ESI-MS (positive), m/z: 683.27 $[M+Na]^+$; HR-MS (ESI-TOF), m/z: found: 683.2767 $[M+Na]^+$, $C_{34}H_{42}F_2N_2NaO_9$ calcd.: 683.2756.

***N*-(9*H*-Fluoren-9-yl)-methoxycarbonyl-*O*-(2-acetamido-2,6-dideoxy-6,6-difluoro-α-D-galactopyranosyl)-L-threonine *tert*-butyl ester (18).** To a solution of 6,6F-T_N analog **16** (220 mg, 0.33 mmol) in 20 mL MeOH were added *Amberlyst-15* (30 mg). The mixture was stirred at room temperature for 14 h and then filtered. The solvents were removed *in vacuo* and the residue was co-evaporated with dichloromethane (3 × 10 mL) to yield **18** as a colorless amorphous solid (171 mg, 0.28 mmol, 85%); R_f 0.40 (EtOAc); RP-HPLC (Luna, H_2O–MeCN, 60 : 40 → 0 : 100, 60 min): t_R = 19.6 min; $[\alpha]_D^{23}$ = 31.7 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY), δ = 7.76 (d, 2H, J = 7.2, 4-H-, 5-H-Fmoc), 7.61 (d, 2H, J = 7.3, 1-H-, 8-H-Fmoc), 7.39 (t, 2H, J = 6.0, 3-H-, 6-H-Fmoc), 7.32 (t, 2H, J = 7.4, 2-H-, 7-H-Fmoc), 7.21–7.13 (m, 1H, NHAc), 6.01 (dt, 1H, J = 6.4/56.0, 6-H), 5.74 (d, 1H, J = 8.7, NH-urethane), 4.88 (d, 1H, J = 2.9, 1-H), 4.54–4.36 (m, 2H, CH_2-Fmoc), 4.36–4.28 (m, 1H, 2-H), 4.28–4.21 (m, 2H, CH-Fmoc, T^α),

4.18–4.07 (m, 2H, T^{β} {4.15}, 4-H {4.11}), 3.93–3.75 (m, 2H, 3-H, 5-H) 2.15 (s, 3H, CH_3-NHAc), 1.45 (s, 9H, *t*Bu), 1.30 (d, 3H, J = 6.2, T^{γ}); ^{13}C NMR (100.6 MHz, $CDCl_3$, HMQC), δ = 174.5, 171.0, 156.5 (C═O), 143.7, 143.6 (C1a-, C8a-Fmoc), 141.3, 141.3 (C4a-, C5a-Fmoc), 127.8 (C3-, C6-Fmoc), 127.1 (C2-, C7-Fmoc), 125.1, 125.0 (C1-, C8-Fmoc), 120.0, 120.0 (C4-, C5-Fmoc), 114.3 (dd, J = 238.4/241.9, C6), 99.4 (C1), 83.4 (C_q-*t*Bu), 77.2 (T^{β}), 70.5–69.9 (m, C3, C5), 67.3–67.0 (m, CH_2-Fmoc, C5), 58.9 (T^{α}), 50.9 (C2), 47.2 (CH-Fmoc), 28.0 (CH_3-*t*Bu), 22.5 (CH_3-NHAc), 18.6 (T^{γ}); ^{19}F NMR (376.5 MHz, $CDCl_3$), δ = −130.8 (dd, J = 55.6/298.7, 6aF), −129.6 (ddd, J = 10.4/57.8/298.2, 6bF); ESI-MS (positive), m/z: 643.25 $[M+Na]^+$, 1263.53 $[2M+Na]^+$; HR-MS (ESI-TOF), m/z: found: 643.2464 $[M+Na]^+$, $C_{31}H_{38}F_2N_2NaO_9$ calcd.: 643.2443.

***N*-(9*H*-Fluoren-9-yl)-methoxycarbonyl-*O*-(2-acetamido-2,6-dideoxy-6,6-difluoro-3-*O*-[2,3,4-tri-*O*-benzyl-2-deoxy-2-fluoro-β-D-galactopyranosyl]-α-D-galactopyranosyl)-L-threonine-*tert*-butyl ester (19).** A solution of glycosyl acceptor **18** (146 mg, 0.24 mmol) and donor **10** (215 mg, 0.36 mmol) in anhyd. CH_2Cl_2 (20 mL) was stirred with activated, powdered molecular sieves (4 Å, 200 mg) for 1 h at room temperature under an argon atmosphere. The suspension was cooled to −20 °C, and TMSOTf (12 µL, 0.06 mmol) was added. After being stirred for 3 h at −20 °C, the reaction mixture was warmed to 0 °C, stirred for further 18 h, and filtered through a pad of celite. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (^{c}Hex–EtOAc, 2 : 1) to afford **19** as a colorless amorphous solid (147 mg, 0.14 mmol, 58%, α : β = 1 : 1); **β-19**: (74 mg, 0.07 mmol, 29%); R_f 0.35 (^{c}Hex–EtOAc, 1 : 1); RP-HPLC (PerfectSil, H_2O–MeCN, 25 : 75 → 10 : 90, 30 min → 0 : 100, 10 min): t_R = 11.5 min; $[\alpha]_D^{23}$ = 29.5 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 7.78–7.76 (m, 2H, 4-H-, 5-H-Fmoc), 7.63 (d, 2H, J = 7.3, 1-H-, 8-H-Fmoc), 7.40 (t, 2H, J = 7.4, 3-H-, 6-H-Fmoc), 7.37–7.25 (m, 17H, 2-H-, 7-H-Fmoc, H_{ar}-Bn), 6.15–5.82 (m, 2H, 6-H {6.00, dt, J = 6.3/57.7}, NHAc {5.83, d, J = 10.0}), 5.49 (d, 1H, J = 8.9, NH-Fmoc), 4.91–4.88 (m, 2H, 1-H, CH_2-Bn), 4.79–4.60 (m, 4H, 2′-H, 2-H, CH_2-Bn), 4.58–4.47 (m, 4H, 1′-H, CH_2-Fmoc, CH_2-Bn), 4.44 (d, 1H, J = 11.8, CH_2-Bn), 4.39 (d, 1H, J = 11.8, CH_2-Bn), 4.27–4.20 (m, 3H, 4-H, CH-Fmoc, T^{α}), 4.20–4.13 (m, 1H, T^{β}), 3.91–3.79 (m, 3H, 4′-H, 5-H, 5′-H), 3.72–3.67 (m, 1H, 3-H), 3.60–3.50 (m, 2H, 3′-H, 6a/b′-H), 3.49-3.43 (m, 1H, 6a/b′-H), 2.01 (s, 3H, CH_3-NHAc), 1.46 (s, 9H, CH_3-*t*Bu), 1.29 (d, 3H, J = 6.3, T^{γ}); ^{13}C NMR (100.6 MHz, HMQC, $CDCl_3$), δ = 170.5, 170.2, 156.4 (C═O), 143.8, 143.6 (C1a-, C8a-Fmoc), 141.3 (C4a-, C5a-Fmoc), 137.9, 137.8, 137.5 (C_q-Bn), 128.5, 128.3, 127.9, 127.8, 127.6, 127.1 (C_{ar}-Bn, C2-, C3-, C6-, C7-Fmoc), 125.0, 125.0 (C1-, C8-Fmoc), 120.0 (C4-, C5-Fmoc), 114.2 (dd, J = 243.6/238.6, C6), 102.6 (d, J = 23.9, C1′), 100.5 (C1), 91.3 (d, J = 185.5, C2′), 83.2 (C_q-*t*Bu), 79.9 (d, J = 16.1, C3′), 79.2 (C3), 77.2 (T^{β}), 74.8 (CH_2-Bn), 74.0 (C4′), 73.9 (C5′), 73.6, 72.7 (CH_2-Bn), 69.9 (dd, J = 29.7/22.7, C5), 68.6 (C6′), 67.6 (C4), 66.9 (CH_2-Fmoc), 59.1 (T^{α}), 47.3 (C2), 47.2 (CH-Fmoc), 28.1 (CH_3-*t*Bu), 23.2 (CH_3-NHAc), 18.7 (T^{γ}); ^{19}F NMR (376.6 MHz, $CDCl_3$), δ = −131.0 (dd, J = 54.5/296.8, 6aF), −129.7 (ddd, J = 10.2/57.7/297.1, 6bF), −205.1 ppm (dd, J = 12.6/51.5, 2′-F); MS-ESI (positive), m/z: 1077.38 $[M+Na]^+$, 1093.36 $[M+K]^+$, 2131.78 $[2M+Na]^+$; HRMS-ESI (positive), m/z: found: 1077.4337 $[M+Na]^+$, $C_{58}H_{65}F_3N_2NaO_{13}$ calcd.: 1077.4336.

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