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Syntheses of fluorine-containing mucin core 2/core 6 structures using novel fluorinated glucosaminyl donors

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ABSTRACT

Syntheses of fluorinated mucin core 6 disaccharides and core 2 trisaccharides modified at the C-3 or C-4 position of the pertinent glucosamine residue required for mechanistic study of glycosyltransferases and sulfotransferases involved in the biosynthesis of *O*-glycans are reported. Novel fluorinated glucosaminyl donors were synthesized from 2-naphthylmethyl β-D-*N*-acetylglucosamine (β-*O*-NAP-GlcNAc) via double inversion of the C-3 or C-4 configuration. A one-step β-alkylation of GlcNAc was reported for the first time to afford β-*O*-NAP-GlcNAc in high yield, which constitutes the cornerstone of the synthetic strategy based on NAP-glycosides in oligosaccharides synthesis.

1. Introduction

Glycosyltransferases, sulfotransferases, and sialyltransferases are widely implicated in regulating the construction of oligosaccharides, polysaccharides, and glycoconjugates in various cells and tissues.[1] Any undesirable alteration in their basic structure results in various fundamental changes in their roles in specific cell signaling and recognition events of biological processes,[2] such as chronic inflammation, cancer metastasis, cartilage formation, and hormone regulation. Thus, it became imperative to study the mechanistic pathway of these enzyme families in order to understand their role in various biological processes. Modifications to the basic enzyme acceptor structures by introduction of fluoro groups can result in highly specific acceptors or inhibitors for these individual enzymes. Consequently, this might help in exploring their catalytic mechanism and in development of therapeutics for curing the medical complications that occur due to their malfunction. In this context, several laboratories are engaged in the synthesis of fluoro substituted saccharides and their application as probes to investigate various enzymes involved in carbohydrate metabolism has been reported.[3] It is now unambiguously accepted that fluorinated carbohydrates play an important role in investigating carbohydrates–enzyme and carbohydrate–selectin interactions. For instance, an efficient route for the synthesis of UDP-5-F-GlcNAc has been reported via epoxide fluoridolysis by Hartman and Coward.[4] UDP-5-F-GlcNAc was found to behave as a β-Gal-T acceptor but competed with UDP-GlcNAc for binding to *N*-acetyl glucosaminylphosphotransferase. Feng et al.[5] reported the chemo-enzymatic synthesis of UDP-4-F-GlcNAc and UDP-4-F-GalNAc, which would serve as potential candidates for novel anticancer drugs when acting as glycosyltransferase inhibitors. Blood group A and B glycosyltransferases were shown to act on C-6 fluoro substituted Gal whereas a C-3 fluoro substituent on Gal created competitive inhibitors for both enzymes.[3j] Berkin et al.[6] accomplished the synthesis of 4-F-GlcNAc and 4-F-GalNAc, which were evaluated as inhibitors of hepatic glycosaminoglycan biosynthesis. 3-Fluoro and 4-fluoro analogs of D-glucose were found to be higher affinity substrates than D-glucose for aldolase reductase while 2-fluoro and 4-fluoro analogs of D-glucitol were inactive substrates for sorbitol dehydrogenase.[3h] Esko et al. reported a series of synthetic acetylated analogs of disaccharide peracetylated GlcNAcβ1-3Galβ-*O*-naphthalenemethanol containing –H, –F, $-N_3$, $-NH_2$, or $-OCH_3$ instead of the hydroxyl groups at C-3′ and C-4′ positions of the terminal *N*-acetylglucosamine residue. These compounds were found to reduce the formation of the glycan sialyl Lewis X in tumor cells. In addition, the reduction of sLe^x by the 4′-deoxy analog also results in diminished experimental tumor metastasis by Lewis lung carcinoma in vivo.[7]

Interest in the synthesis of fluorine modified acceptors is also augmented due to the application of the fully acetylated derivatives of various fluoro sugars as specific decoys/primers for glycosyltransferases. Endogenous carboxyesterases present in the cells remove the acetyl groups from these acetylated fluoro sugars. The resulting deacetyalted derivatives can act as acceptors for the

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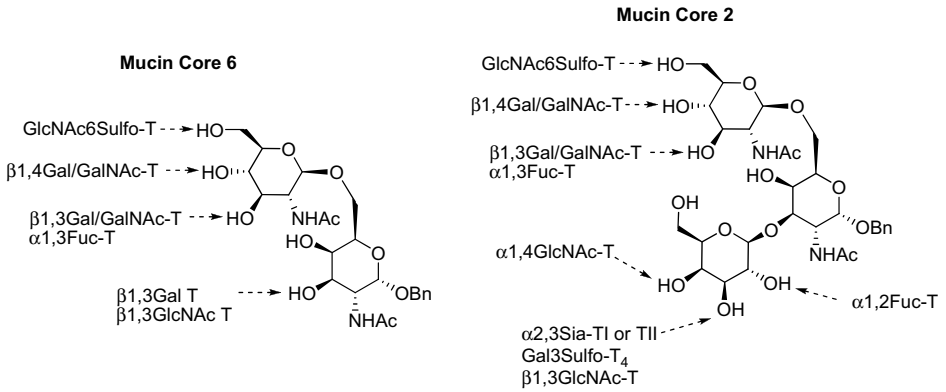


Figure 1. Glycosyltransferases and sulfotransferases acting on the mucin core 6 disaccharide and core 2 trisaccharide.

enzymes involved in the biosynthetic pathways of glycans. The anti-tumor activities of acetylated hexosamines were studied by Sharma et al.[8] and Thomas et al.[9] Matta et al. demonstrated the in vivo inhibition of ovarian tumor cell surface glycoprotein synthesis by peracetylated 3-F-GlcNAc and 4-F-GlcNAc.[10] Dimitroff et al.[3f,11] and Zollner et al.[12] introduced a new strategy to impede the selectin ligand production using peracetylated 4-F-GlcNAc as a glycosylation inhibitor. 4-F-GlcNAc was directly incorporated into native cutaneous lymphocyte associated antigen (CLA) expressed on human T cells, indicating direct inhibition of poly-*N*-acetyllactosamine elongation and selectin-binding determinants on PSGL-1 *O*-glycans. These observations establish a potential treatment approach for targeting pathologic lymphocyte trafficking to skin and indicate that 4-F-GlcNAc may be a promising agent for treatment of dermal tropism associated with malignancies and inflammatory disorder.

In addition to the exhaustive research carried out by other groups on fluoro analogs of carbohydrates for understanding the enzyme machinery, over the years our laboratory has been involved in the synthesis and examination of various fluoro acceptors for their specificity for these enzymes.[9,10,13] In this regard, we first reported the synthesis of UDP-6-F-GlcNAc and UDP-4-F-GalNAc used for the biological studies of GalNAc/GlcNAc transferases and phosphatetransferases.[13g] In this direction, the first synthesis of fluorinated mucin core 6 structure (GlcNAcβ1, 6GalNAcα-OR) using oxazoline as a 4-F-GlcNAc glycosyl donor was also reported.[9] Recently, we described the first effective syntheses and biochemical evaluation of fluorinated core 2-branched oligosaccharide analogs modified at the C-3 or C-4 position of the pertinent galactose.[13a,b] In continuation of our search for a better fluoro acceptor for various enzymes involved in biosynthesis of *O*-glycans, we report herein a straightforward syntheses of fluorinated mucin core 6 disaccharides and core 2 trisaccharides [GlcNAc-beta-1,6-(Gal-beta-1,3)-GalNAc-alpha-OR] modified at the C-3 or C-4 position of the glucosamine residue using a novel fluorinated glucosaminyl donor. These compounds would be used for the investigation of glycosyltransferases and sulfotransferases to determine the influence of enzyme activities resulting from structural modifications (Fig. 1).[14]

2. Results and discussion

2.1. Retrosynthetic analysis of fluorinated mucin core 2 and core 6 oligosaccharides

Figure 2 outlines the retrosynthetic analysis of fluorinated mucin core 2 and core 6 structures. Retrosynthetic scission of indicated bond in mucin core 6 disaccharides **1**, **2** and core 2 trisaccharides **3**, **4** provides fluorinated glucosaminyl donors **13**, **18** and glycosyl acceptors **19**, **24** as potential precursors. It was projected that C-3 or C-4 fluorinated glucosamine **13** and **18**, equipped with anomeric trichloroacetimidate function, could serve as the glycosyl donor in a Schmidt coupling reaction[15] with the primary hydroxyl group of the diol acceptor **19** and **24**. Based on the previous reports,[16] it was expected that the above coupling reaction should progress smoothly with the formation of the desired crucial β-glycosidic bond guided by the C-2 carbamate (*N*-Troc in **13** or *N*-Phth in **18**) functionality.

2.2. Retrosynthetic analysis of fluorinated glucosaminyl donors 13 and 18

The retrosynthetic analysis of key synthetic intermediates **13** and **18** is outlined in Figure 3. The 3-fluoro and 4-fluoro glucosaminyl donors could be synthesized from the same starting material, namely β-*O*-(2-naphthylmethyl)-GlcNAc **6** via double inversion of the C-3 or C-4 configuration. Use of NAP (2-naphthylmethyl) group as anomeric protection proved to be highly suitable for our purpose owing to its stability under a wide range of reaction conditions required for hydroxyl differentiation, amino protection and fluorination. Also, its chemoselective removal under DDQ oxidative conditions as required in the later part of our synthetic strategy is an added advantage.[17] The choice of a temporary protecting group for nitrogen is crucial to both fluorination and β-glycosylation. During the course of the synthesis of 4-deoxy-4-fluoro donor **13**, it was expected that the fluorination would advance smoothly in the presence of C-2 *N*-acetyl group,[5,6] whereas in the case of 3-deoxy-

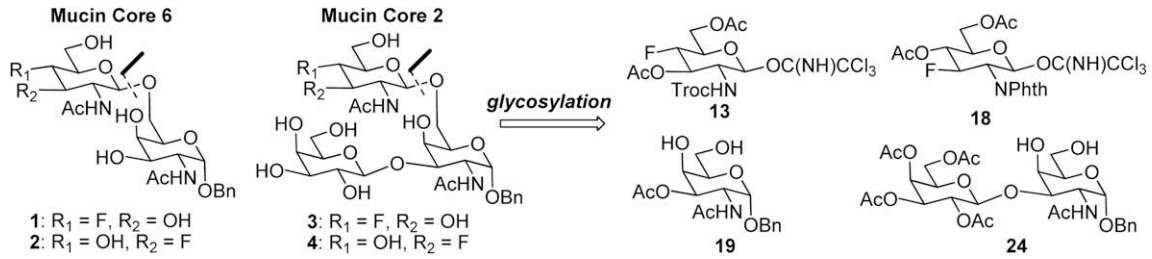


Figure 2. Retrosynthetic analysis of fluorinated mucin core 2 and core 6 structures.

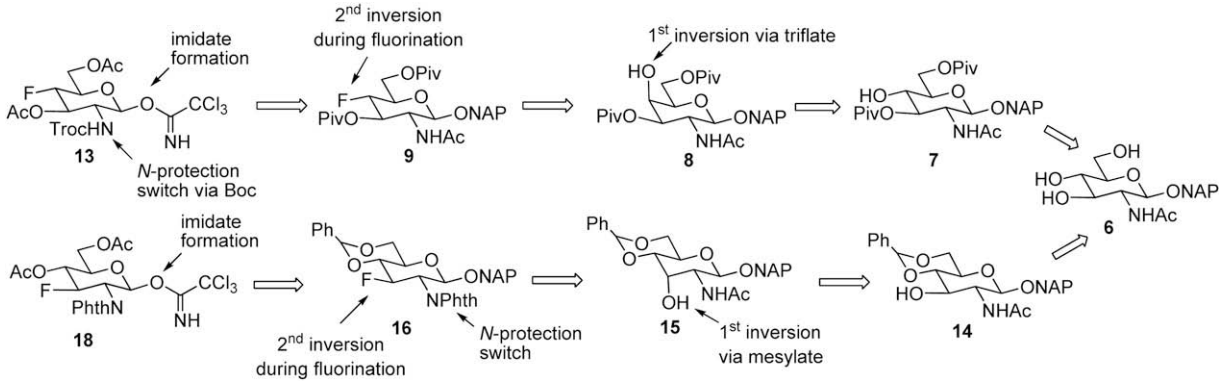
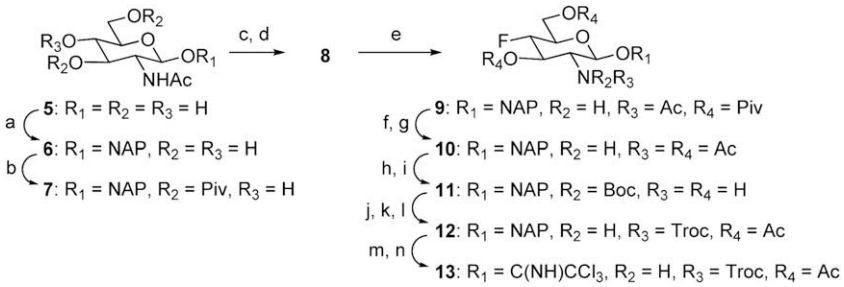


Figure 3. Retrosynthetic analysis of key synthetic intermediates **13** and **18**.

3-fluoro donor **18**, the reaction of 4,6-benzylidene protected *N*-acetyl allosamine or its corresponding 3-*O*-mesyl derivative with DAST and TBAF in acetonitrile would yield only the eliminated product.[18] On the basis of much precedence, the fluorination at C-3 would proceed successfully only when the NH_2 functional group was protected with a phthaloyl moiety.[19] Therefore, *N*-Phth protection was employed in the synthesis of 3-deoxy-3-fluoro donor **18**. Furthermore, the *N*-Phth protecting group in 3-fluoro donor **18** plays dual roles in both assisting fluorination and guiding stereochemistry of glycosylation.[19] Thus, during the course of the 'N-protection Switch,' the direct hydrolysis of *N*-acetyl allosamine **15** in refluxing sodium hydroxide solution would yield the free amine ready to be protected with the phthaloyl group. But, in the case of the 4-fluoro donor **13**, the *N*-Troc protecting group would control the stereochemical outcome of glycosylation (β-selective) through anchimeric assistance.[16a-d] Noteworthy, the *N*-Troc group is sensitive to basic conditions and potentially causes problems if carried through a multi-step sequence such as hydroxyl inversion and fluorination. Moreover, the C–F bond is unstable under strong basic conditions. Consequently, the transformation of N-protection from NHAc to NHTroc functionality should be carried out until the tail-end of the synthesis of **13**. Thus, an indirect route could be followed where N-deprotection of *N*-acetyl group via Boc derivative of NAP-glucosamine **9** under acid conditions would proceed efficiently.

2.3. Preparation of *N*-Troc-protected 4-deoxy-4-fluoro glucosaminyl imidate donor 13

Scheme 1 depicts the synthesis of 4-deoxy-4-fluoro imidate donor **13**. The 4-Fluoro analogue of 2-acetamido-2,4-dideoxy-D-glucose (**13**) was synthesized by double inversion of the configuration at C-4 of the corresponding 3,6-di-*O*-pivaloyl glucosamine **7** prepared from NAP-glucoside **6** in a one-step fashion. Thus, a one-step β-selective glycosylation of *N*-acetylglucosamine (**5**) was carried out using NAPBr and NaH in the presence of LiBr in DMF to afford β-*O*-NAP-GlcNAc (**6**) in good yield. The compound obtained was with high-purity (NMR) and does not require any uneconomical chromatographic purification. The special insoluble nature of NAP-glucoside **6**, either in water or dichloromethane, reduced the purification procedures to a simple and fast precipitation in an aqueous solution, followed by the removal of excess NAPBr via rinsing with dichloromethane (see Experimental section for detail). This one-step glycoside synthesis compares well with the standard peracetylation, selective anomeric deprotection, O-alkylation at C-1 and deacetylation steps, and the classical four-step Koenigs–Knorr synthesis[20] or its 'oxazoline' variant.[21] Therefore, the above β-alkylation constitutes the cornerstone of our novel strategy for oligosaccharide synthesis based on NAP-glycoside. Next, compound **6** was treated with pivaloyl chloride in a mixture of pyridine and dichloromethane (2:1) at 0 °C to afford **7** in a high yield of 91%. Exposure of the resulting compound **7** with trifluoromethanesulfonic anhydride (Tf_2O) in pyridine–/dichloromethane (1:10) afforded the 4-*O*-triflyl derivative, which was isolated and immediately treated with sodium nitrite in DMF to produce the inversion product **8** in 79% yield. Treatment of β-NAP-galactosamine **8** with diethylaminosulfur trifluride (DAST) in CH_2Cl_2 provided 4-fluorine analog **9** in 81% yield.[5,6,22] Noteworthy, the inversion of the configuration of equatorial 4-OH of inexpensive glucosaminide **7** leads to the expensive galactosamine derivative **8**, which is finally converted (the axial 4-OH of **8**) back to the cheap glucosamine derivative **9**. This synthetic sequence maneuver appeared particularly attractive owing to its economic value. Removal of the pivaloyl group required much stronger basic conditions and a longer time than the conventional deacetylation. Therefore, compound **9** was treated with 5% NaOMe (1 M) in MeOH at 45 °C for 20 h. This was followed by exposure of the resultant product to acetic anhydride and pyridine to afford per-acetate **10**. The cleavage of acetamido is difficult and usually proceeds in harsh

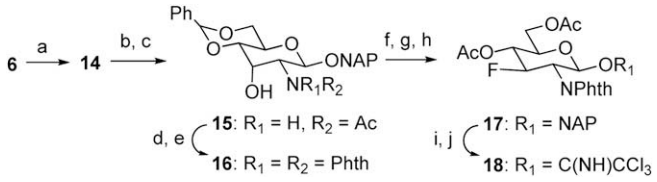


Scheme 1. (a) NaH, NAPBr, LiBr, DMF, rt, 89%; (b) PivCl, py/CH_2Cl_2 (2:1), 0 °C, 91%; (c) Tf_2O, Py/CH_2Cl_2 (1:10), 0 °C; (d) $NaNO_2$, DMF, rt, 79% over two steps; (e) DAST, CH_2Cl_2, rt, 81%; (f) NaOMe, MeOH, 45 °C; (g) Ac_2O, py, rt, 93% over two steps; (h) Boc_2O, DMAP, THF, 60 °C; (i) NaOMe, MeOH, rt, 94% over two steps; (j) 2 M HCl (aq), CH_2Cl_2, rt; (k) Troc-Cl, $NaHCO_3$ (satd aq)/ Et_2O; (l) Ac_2O, py, DMAP, rt, 91% over three steps; (m) DDQ, MeOH/CH_2Cl_2 (1:4), rt; (n) DBU, CCl_3CN, CH_2Cl_2, 0 °C to −5 °C, 93% over two steps.

conditions, such as refluxing in 1 M NaOH aqueous solution overnight.[17a] In order to avoid the extreme conditions that may destroy the frangible C–F bond, acetamide **10** can first be converted to an *N*-Boc derivative by an exchange process that relies on the reduced electrophilicity of the carbamate as well as its increased steric bulk. Based on this rationality, *tert*-butoxycarbonyl (Boc) protected carbamate **11** was prepared from **10**. Thus, treatment of **10** with *tert*-butoxycarbonyl anhydride (Boc_2O) in the presence of DMAP in THF at 60 °C followed by careful removal of both the *N*-acetyl group and *O*-acetyl moieties of the resulting compound under Zemplén conditions (cat. 1 M NaOMe solution in MeOH)[23] afforded the desired carbamate **11** in a 94% yield. Removal of the Boc group from the nitrogen of **11** in 2 M aq HCl in methanol afforded free amine. It is of some interest that the acid-mediated cleavage of the *N*-Boc-protected group is fully compatible with the NAP moiety in compound **11**. The anomeric NAP group showed its remarkable stability compared to the other ether protecting group, e.g., the *p*-methoxybenzyl (PMB) group, which was partially cleaved under similar acid conditions.[24] Treatment of the resultant free amine with trichloroethoxycarbonyl chloride (Troc-Cl) in a solution of sodium bicarbonate (satd aq)/ether (1:1), followed by O-acetylation, furnished the desired *N*-Troc derivative **12** in 91% yield over three steps. Removal of the anomeric NAP group in the presence of DDQ in dichloromethane/methanol (4:1),[17] followed by activation of the resultant hemiacetal with trichloroacetonitrile in the presence of DBU as a base, afforded the *N*-Troc-protected 4-fluoro glucosamine imidate **13** in high yield (93% over two steps).[15]

2.4. Preparation of *N*-Phth-protected 3-deoxy-3-fluoro glucosaminyl imidate 18

The 3-fluoro glucosaminyl donor **18** was also synthesized following the same strategy as used for NAP-glycoside **6** (Scheme 2). The difference lay in the C-2 participating group, introduced to afford synthesis (of respective donor), which is *N*-Phth in case of glycosyl donor **18** and *N*-Ac in case of 4-F-GlcNAc donor **13**. Treatment of **6** with dimethoxyl benzyl acetal in the presence of a catalytic amount of *p*-TsOH afforded 3-hydroxyl free 4,6-*O*-benzylidene



Scheme 2. (a) $PhC(OMe)_2$, *p*-TsOH, MeCN, rt, 94%; (b) MsCl, py; (c) NaOAc/H_2O/methoxyethanol, refluxed at 130 °C, 93% over two steps; (d) 30% KOH in 1,4-dioxane/methoxyethanol (5:3 v/v), refluxed at 120 °C; (e) phthalic anhydride, $NaHCO_3$, 84% over two steps; (f) DAST, CH_2Cl_2, rt; (g) 60% AcOH in H_2O, 60–65 °C; (h) Ac_2O, py, rt, 93% over three steps; (i) DDQ, CH_3OH/CH_2Cl_2 (1:4), rt; (j) Cl_3CCN, CH_2Cl_2, DBU, 0 °C to −5 °C, 92% over two steps.

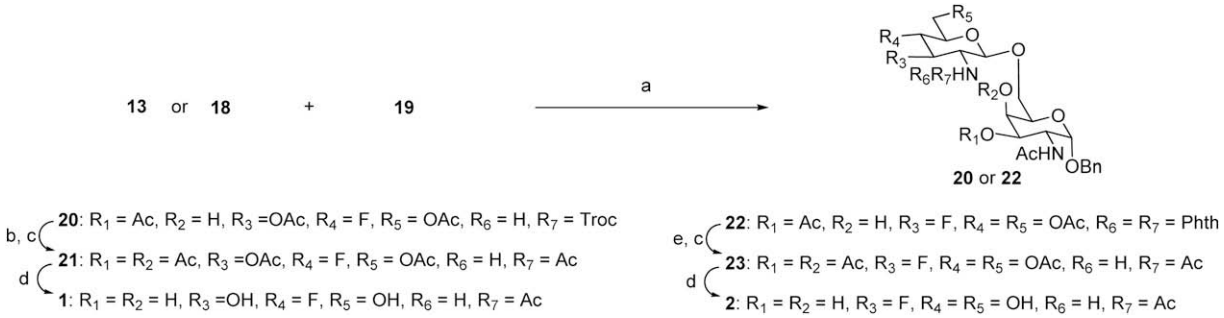
β-*O*-NAP-GlcNAc **14**. Inversion of hydroxyl group at position 3 of glucosamine **14** was anticipated to be accomplished via a two-step sequence. Thus, treatment of **14** with MsCl in pyridine, followed by the direct elimination of the resultant sulfonate with sodium acetate in refluxing $MeOCH_2CH_2OH/H_2O$ mixture afforded the desired NAP-allosaminide **15**. The natural unavailable allosamine derivative **15** was obtained by the inversion of the configuration of axial 3-OH of the readily available and inexpensive glucosamine precursor **14**. This synthetic sequence, similar to that of 4-F-GlcNAc donor **13**, also appeared attractive owing to its economic value. As a desired requisite in our synthesis, conversion of acetamido in **15** to *N*-Phth was effected successfully in two steps. Hydrolysis of acetamido group of **15** was carried out by refluxing with 30% KOH in 1,4-dioxane and $MeOCH_2CH_2OH$. Treatment of the resultant free amine with phthalic anhydride in the presence of $NaHCO_3$ yielded the desired *N*-Phth-protected product **16** in high yield. Fluorination of **16** was carried out using DAST,[22] which resulted in the inversion of configuration at C-3. This was followed by acetolysis of the bezylidene ring and then acetylation, providing the 3-fluorinated *N*-phth-protected NAP-glucoside **17** in an overall yield of 93% over three steps. Removal of NAP using DDQ,[17] followed by activation of the anomeric center as imidate using trichloroacetonitrile and DBU[15] yielded the 3-F-GlcNAc donor **18** in high yield (92% over two steps).

2.5. Preparation of fluorinated mucin core 6 disaccacharides 1 and 2

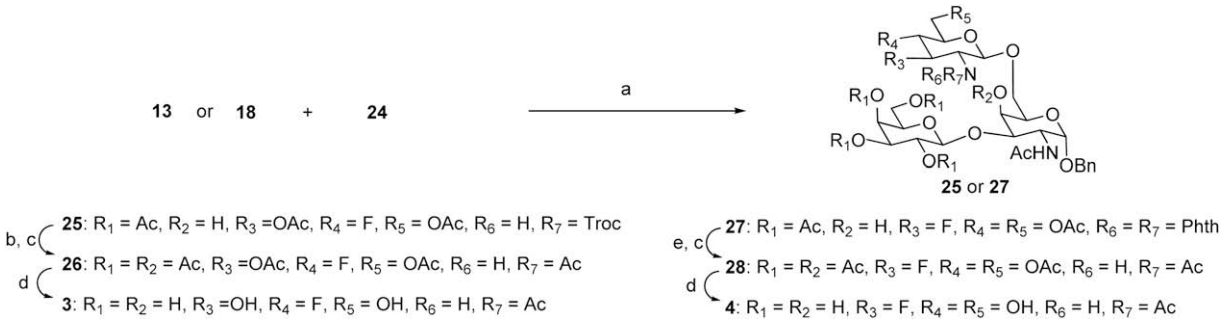
With the required starting material in hand, we turned our attention to the synthesis of fluorinated mucin core 6 disaccacharides **1** and **2** (Scheme 3). Coupling of 4-fluoro *N*-Troc glycosaminyl donor **13** with the known 4,6-diol galactosamine **19**[13a] mediated by TMSOTf[16] afforded the disacchride **20** in 85% yield. Conversion of the Troc carbamate into acetamido moiety was carried out with Cd dust in DMF/HOAc (2:1),[25] followed by treatment with acetic anhydride in pyridine to afford per-acetate **21**. Subsequent deacetylation under Zemplén conditions[23] proceeded smoothly, giving the target disaccharide **1**, which was precipitated as a white solid in MeOH. Similarly, glycosylation of diol **19** with 3-fluoro *N*-phth glycosaminyl donor **18** under TMSOTf-mediated conditions[16] afforded the required disaccharide **22**, which was further completely deprotected to provide the target mucin core 6 disaccharide **2** in good yield.

2.6. Preparation of fluorinated mucin core 2 trisaccharides 3 and 4

The synthesis of fluorinated mucin core 2 trisaccacharides **3** and **4** is outlined in Scheme 4. Coupling between **13** and **24**[13a] in the presence of TMSOTf afforded the trisaccharide **25** in 95% yield. This compound was converted into per-acetate **26** following same



Scheme 3. (a) TMSOTf , 4 Å MS, CH_2Cl_2, N_2, −65 to −70 °C, 85% for both **20** and **22**; (b) Cd, DMF/HOAc, N_2, rt; (c) Ac_2O, py, rt, 93% over two steps of b and c, 93% over two steps of e and c; (d) 5% NaOMe (1 M) in MeOH, 45 °C, 95% for **1** and 87% for **2**; (e) $NH_2NH_2 \cdot H_2O$/MeOH (1:5), 90 °C.

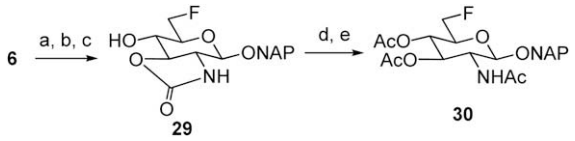


Scheme 4. (a) TMSOTf, 4 Å MS, CH_2Cl_2, −65 to −70 °C, 95% for **25** and 82% for **27**; (b) Cd, DMF/HOAc, N_2, rt; (c) Ac_2O, py, rt, 93% over two steps of b and c, 89% over two steps of e and c; (d) 5% NaOMe (1 M) in MeOH, 45 °C, 89% for both **3** and **4**; (e) $NH_2NH_2{\cdot}H_2O$/MeOH (1:5), 90 °C.

strategy as used for the synthesis of **21**. Thus, the reaction with Cd dust in DMF/HOAc (2:1),[25] followed by treatment with acetic anhydride in pyridine, provided the per-acetate **26** in good yield. Subsequent deacetylation gave the target trisaccharide **3**, which was precipitated as a white solid in methanol. Correspondingly, the glycosylation of disaccharide **19** with donor **18** gave the desired trisaccharide **27** in 82% yield. Trisaccharide **27** on complete deprotection provided the target mucin core 2 trisaccharide **4** in good yield.

2.7. Preparation of peracetylated 6-fluro GlcNAc 30 via oxazolidinone intermediate

In order to compare the C–F coupling constants with 3-F and 4-F-GlcNAc, 6-fluoro derivative **30** was readily prepared from the same starting material **6** via an oxazolidinone intermediate **29** (Scheme 5). Hydrolysis of starting material **6** in refluxing sodium hydroxide solution, followed by treatment of the resultant free amine with *p*-nitro-phenoxycarbonyl chloride (NPCC),[26] afforded oxazolidinone **29** in a high yield of 93%. Selective fluorination of the primary hydroxyl group followed by hydrolytic ring opening under mild conditions and acetylation readily afforded the target monosaccharide **30** in 91% yield over two steps. It is worth mentioning here that the application of oxazolidinone-protected 2-amino-2-deoxy-D-glucose derivatives as a glycosyl donor in the formation of α-linked glycosides has attracted wide attention.[26,27] Crich et al.[28] reported that it also affords a very convenient glycosyl acceptor, conferring high reactivity on the 4-hydroxy group in glycosylation. The NAP-glycoside could concentrate the bifunctional properties of oxazolidinone into a versatile intermediate **29**. Consequently, compound **29** would first serve as an active acceptor and then be converted to an imidate donor capable of introducing 1,2-*cis* glycoside after selective removal of the anomeric NAP group with DDQ. Further exploration of the versatile chemistry and reaction pathway of oxazolidinone-protected NAP-glycosamine is in progress and will be reported in due course.



Scheme 5. (a) NaOH aq (1 M), reflux, 110 °C, 92%; (b) NPCC, aq $NaHCO_3$, CH_3CN/H_2O, 0 °C, 93%; (c) DAST, CH_2Cl_2, rt, 93%; (d) NaOH, H_2O/THF, rt; (e) Ac_2O, DMAP, py, rt, 91% over two steps.

2.8. ^{13}C NMR of fluorinated GlcNAc derivatives

Carbon–fluorine coupling is especially useful for determining the fluorine position.[29] Replacement of a hydroxyl group by fluorine causes a downfield shift of the fluorine-bearing carbon signal by about 20 ppm. A fluorine atom shields the carbon atom adjacent to the fluorinated one. The signals of these carbon atoms are usually shifted upfield by 5 ppm. The $^1J_{C,F}$ values increase with the electronegativity of the geminal substituent. The $^1J_{C,F}$ of C-6 is observed as about 175 Hz and that of C-4 or C-3 is about 185 or 190 Hz. The $^2J_{C,F}$ of monodeoxy monofluoro sugars has a constant value of 18.5±0.5 Hz when the coupled fluorine atom is *gauche* to the oxygen substituent of the coupled carbon atom. Most of the observed $^2J_{C,F}$ values are in good agreement with this value. Usually, the typical value observed for $^3J_{C,F}$ is 6.0±1.0 Hz when the fluorine atom is *gauche* with respect to both the carbon atoms concerned and the ring oxygen atom. However, a carbon atom concerned having two oxygen atoms and a hydrogen atom as its substituent, when trans to the fluorine atom, would result in the magnitude of $^3J_{C,F}$ as 11.7 Hz.

The ^{13}C NMR spectrum of compound **17** gives evidence for the presence of fluorine at C-3 (Table 1). The $J_{C,F}$ values of 17.1 and 17.8 Hz are attributed to the two-bond carbon–fluorine coupling to C-2 and C-4, respectively. The coupling constants of 8.2 and 9.7 Hz are attributed to three-bond carbon–fluorine coupling to C-5 and C-1, respectively. The downfield shift of the ^{13}C NMR signal of C-3 to δ 88.5 and its $^1J_{C,F}$ coupling of 188.1 Hz is the unambiguous evidence that C-3 is fluorinated in the case of **17**. Furthermore, fluorine coupling at the anomeric carbon atom is a distinctive indication that C-3 is fluorinated, which is unique in the series of fluorinated glucosaminyl derivatives.

Table 1
^{13}C-Chemical shifts (ppm) and carbon–fluorine coupling constants (Hz)

Compound	C-1	C-2	C-3	C-4	C-5	C-6
17	97.1	55.0	*88.5*	69.1	71.1	61.8
3-F-GlcNAc	$^3J_{F\text{-}3,C\text{-}1}$ 9.7	$^2J_{F\text{-}3,C\text{-}2}$ 17.1	$^1J_{F\text{-}3,C\text{-}3}$ 188.1	$^2J_{F\text{-}3,C\text{-}4}$ 17.8	$^3J_{F\text{-}3,C\text{-}5}$ 8.2	
10	99.5	53.4	72.1	*87.3*	71.6	62.6
4-F-GlcNAc		$^3J_{F\text{-}4,C\text{-}2}$ 6.9	$^2J_{F\text{-}4,C\text{-}3}$ 18.8	$^1J_{F\text{-}4,C\text{-}4}$ 186.9	$^2J_{F\text{-}4,C\text{-}5}$ 23.6	
30	98.7	54.1	71.8	67.8	72.3	*81.1*
6-F-GlcNAc				$^3J_{F\text{-}6,C\text{-}4}$ 7.3	$^2J_{F\text{-}6,C\text{-}5}$ 18.2	$^1J_{F\text{-}6,C\text{-}6}$ 174.9

The ^{13}C NMR spectrum of compound **10** provides support for the existence of fluorine at C-4 (Table 1). The $J_{C,F}$ values of 18.8 and 23.6 Hz are attributed to the two-bond carbon–fluorine coupling to C-3 and C-5, respectively. The coupling constants of 6.9 Hz are attributed to three-bond carbon–fluorine coupling to C-2. The downfield shift of the ^{13}C NMR signal of C-4 to δ 87.3 and its $^1J_{C,F}$ coupling value of 186.9 Hz is clear-cut evidence that C-4 is fluorinated in **10**. The absence of fluorine coupling at the anomeric carbon atom is further evidence that C-3 is not fluorinated in the case of **10**. The coupling pattern of C–F was transferred from

monosaccharide to disaccharide and more complex oligosaccharide through glycosylation, which is important for structural characterization of the fluorinated carbohydrate.

The ^{13}C NMR spectrum of compound **30** gives evidence for the presence of fluorine at C-6 (Table 1). The $J_{C,F}$ values of 18.2 Hz is due to the two-bond carbon–fluorine coupling to C-5. The coupling constant of 7.3 Hz is owed to the three-bond carbon–fluorine coupling to C-4. Furthermore, the downfield shift of the ^{13}C NMR signal of C-6 to δ 81.1 and its coupling with the fluorine atom ($J_{C,F}$ 174.9 Hz) confirms the location of the fluorine atom.

3. Conclusions

In summary, an efficient access to fluorinated mucin core 6 disaccharides (**1** and **2**) and core 2 trisaccharides (**3** and **4**) tailored at the C-3 or C-4 position of the crucial glucosamine residue required for mechanistic study of enzymes involved in the biosynthesis of *O*-glycans has been developed. During the course of our synthesis, a novel one-step β-alkylation of GlcNAc is reported for the first time to afford β-*O*-NAP-GlcNAc in high yield, which epitomizes the foundation of a synthetic strategy based on NAP-glycosides in oligosaccharides synthesis. The novel fluorinated glucosaminyl donors **13** and **18** were obtained in high yields from a common intermediate, namely β-*O*-NAP-GlcNAc via double inversion of the C-3 or C-4 configuration. Further elaboration on this synthetic sequence and biological evaluation of various target fluorinated oligosaccharides is ongoing, and the results will be reported in due course.

4. Experimental

4.1. General

TLC was conducted on glass plates precoated with a 0.25 mm layer of Silica Gel 60 F-254 (Analtech GHLF uniplates). The compounds were visualized either by exposure to UV light or by spraying with 5% H_2SO_4 and 0.2% *p*-anisaldehyde in a solution of ethanol and heating, or both. The solutions were concentrated under reduced pressure at <40 °C. The silica gel used for column chromatography was Baker Analyzed (60–200 mesh). ^1H NMR spectra were recorded at 30 °C with either a Bruker AM-400 (400 MHz) or an AMX-600 (600 MHz) spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal standard Me_4Si. ^{13}C NMR spectra were recorded at 303.0 K with a Bruker AM-400 (100.6 MHz) spectrometer using $CDCl_3$ (77.0 ppm) and CD_3OD (49.00 ppm) as references. All samples submitted for elemental analyses were dried for 48 h under vacuum over P_2O_5 at rt. Elemental analyses were performed at Robertson Laboratory, Madison, NJ. All solvents were purified using standard procedures.

4.2. 2-Naphthylmethyl 2-acetamido-2-deoxy-β-D-glucopyranoside (6)

N-acetylglucosamine **5** (2 g, 9.04 mmol) was completely dissolved in DMF (10 mL) containing LiBr (1.57 g, 18.08 mmol) after stirring for 1 h, following, which NaH (0.28 g, 11.66 mmol) and NAPBr (4 g, 18.08 mmol) were added successively in slots. The reaction mixture was then stirred at rt for 12 h, and, thereafter, was quenched with MeOH (5 mL) and DMF was evaporated under high vacuum. The resulting viscous liquid was slowly poured into a water/CH_2Cl_2 (1:1) mixture and stirred for 30 min. Compound **6** popped out of the water as a white solid, which was filtered, washed successively with water (100 mL), and dichloromethane (100 mL) to obtain pure **6** as a white solid (89%). The spectral data was consistence with the literature data.[30]

4.3. 2-Naphthylmethyl 2-acetamido-2-deoxy-3,6-di-*O*-pivaloyl-β-D-glucopyranoside (7)

To a solution of compound **6** (4 g, 8 mmol) in dichloromethane (30 mL) and pyridine (60 mL) was added pivaloyl chloride (4.2 ml, 24 mmol) and stirred for 3 h at 0 °C under an Argon atmosphere. After 3 h, methanol (5 ml) was added to quench the reaction and the mixture was diluted with dichloromethane (100 ml). The organic layer was separated and successively washed with 5% aq HCl, water, 5% aq $NaHCO_3$, dried over Na_2SO_4, and concentrated. The crude product was chromatographed on silica gel with hexanes/EtOAc (1:2) to furnish **7** as colorless crystals (3.95 g, 91%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.81–7.72 (m, 4H, ArH), 7.49–7.40 (m, 3H, ArH), 5.67 (br d, 1H, $J_{NH,2}$=8.8 Hz, N*H*), 4.97 (d, J_{gem}=12.6 Hz, Abq, 1H, PhC*H*$_A$O), 4.96 (t, $J_{3,2}$=$J_{3,4}$=9.1 Hz, 1H, H-3), 4.95 (dd, $J_{6a,5}$=3.5, J_{gem}=12.1 Hz, 2H, H-6), 4.75 (d, J_{gem}=12.6 Hz, Abq, 1H, PhC*H*$_B$O), 4.48 (d, $J_{1,2}$=8.3 Hz, 1H, H-1), 4.41 (s, 2H, H-2), 4.07 (t, 1H, $J_{4,3}$=$J_{4,5}$=9.0 Hz, H-4), 3.52 (t, $J_{3,4}$=9.0 Hz, 1H, H-3), 3.45 (br s, 1H, O*H*), 1.83 (s, 3H, NC*H*$_3$), 1.26 (s, 9H, *t*-Bu), 1.14 (s, 9H, *t*-Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.0 (N*C*=O), 167.2 and 167.4 (*C*=O), 134.9, 134.0, 128.2, 127.8, 127.7, 126.8, 126.3, 126.1, 125.8, 99.5 (C-1), 74.9 (C-5), 74.3 (C-3), 70.1 (O*C*H$_2$Ar), 69.4 (C-4), 63.2 (C-6), 53.8 (C-2), 27.2, 27.0, 23.5 (NCO*C*H$_3$); ESI-MS calcd for $C_{29}H_{39}O_8NNa$ (*m*/*z*) $[M+Na]^+$ 552.6, found 552.6. Anal. Calcd for $C_{29}H_{39}NO_8$: C, 65.77; H, 7.42; N, 2.64. Found: C, 65.71; H, 7.47; N, 2.60.

4.4. 2-Naphthylmethyl 2-acetamido-2-deoxy-3,6-di-*O*-pivaloyl-β-D-galactopyranoside (8)

To an ice-cold solution of **7** (4.48 g, 8.46 mmol) in CH_2Cl_2 (50 mL) and pyridine (7.0 mL), trifluoromethanesulfonic anhydride (4.76 g, 2 equiv) was added dropwise. The solution was stirred for 20 min at 0 °C, diluted with CH_2Cl_2 (200 mL), and washed successively with ice-cold aq solutions of $KHSO_4$ (10%), satd $NaHCO_3$, water, dried ($MgSO_4$), and concentrated under reduced pressure. The crude triflate was used without further purification. To a stirred solution of crude triflate in DMF (100 mL) was added $NaNO_2$ (1.75 g, 25.4 mmol), and after 40 h at rt, the mixture was concentrated and the residue was co-evaporated with toluene under reduced pressure to afford an oil that was subjected to flash chromatography on silica gel (2:1 EtOAc/hexanes). Compound **8** was isolated as tiny, white needles (3.53 g, 79%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.81–7.72 (m, 4H, ArH), 7.49–7.47 (m, 3H, ArH), 5.53 (d, $J_{NH,2}$=9.2 Hz, 1H, N*H*), 5.02 (dd, $J_{3,2}$=11.5 Hz, $J_{3,4}$=3.0 Hz, 1H, H-3), 4.73 (d, J_{gem}=12.6 Hz, 1H, OC*H*$_2$Ar), 4.70 (dq, 2H, J=11.2 Hz, H-6^a, H-6^b), 4.65 (d, $J_{1,2}$=8.6 Hz, 1H, H-1), 4.36 and 4.34 (dd, $J_{2,3}$=11.1 Hz, 2H, H-2, H-4), 4.30 (d, J_{gem}=12.6, 1H, OC*H*$_2$Ar), 3.93 (s, 1H, O*H*), 3.77 (dd, $J_{5,6}$=6.3 Hz, 1H, H-5), 1.87 (s, 3H, NC*H*$_3$), 1.47 (s, 9H, *t*-Bu), 1.18 (s, 9H, *t*-Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 178.3 (N*C*=O), 169.7 (*C*=O), 162.4 (*C*=O), 134.6, 133.3, 133.1, 128.2, 127.8, 127.7, 126.9, 126.3, 126.1, 125.8, 99.8 (C-1), 77.0, 76.7 (O*C*H$_2$Ar), 72.4 (C-3), 72.3 (C-5), 70.3 (O*C*H$_2$Ar), 67.0 (C-4), 62.6 (C-6), 50.8 (C-2), 27.2, 27.0, 23.3 (NCO*C*H$_3$); ESI-MS calcd for $C_{29}H_{39}O_8NNa$ (*m*/*z*) $[M+Na]^+$ 552.6, found 552.7. Anal. Calcd for $C_{29}H_{39}NO_8$: C, 65.77; H, 7.42; N, 2.65. Found: C, 65.74; H, 7.47; N, 2.67.

4.5. 2-Naphthylmethyl 2-acetamido-2,4-dideoxy-4-fluoro-3,6-di-*O*-pivaloyl-β-D-glucopyranoside (9)

To a solution of DAST (5.70 g, 35.3 mmol) in CH_2Cl_2 (20 mL) in a Teflon Erlenmeyer flask was added dropwise a solution of **8** (2.19 g, 4.16 mmol) in CH_2Cl_2 (40 mL) at −5 °C. The reaction mixture was allowed to warm to rt and stirred overnight, after which it was cooled to −5 °C and methanol (20 mL) was added dropwise to destroy the excess DAST. The solution was then concentrated under reduced pressure to afford a yellowish oil that was subjected to

flash chromatography on silica gel (2:3 hexanes/EtOAc) to obtain pure compound **9** as tiny, white needles (1.77 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.72 (m, 4H, ArH), 7.50–7.26 (m, 3H, ArH), 5.30 (br d, 1H, N*H*), 5.10 (dd, $J_{3,4}$=9.0, $J_{3,F}$=13.7 Hz, 1H, H-3), 5.04 (d, J_{gem}=12.6 Hz, 1H, OCH_2Ar), 4.76 (d, J_{gem}=12.6 Hz, 1H, OCH_2Ar), 4.56 (ddd, $J_{4,3}$=$J_{4,5}$=9.5 Hz, $J_{4,F}$=51.0 Hz, 1H, H-4), 4.51 (ddd, $J_{6,F}$=1.3, $J_{6,5}$=4.7, J_{gem}=12.1 Hz, 2H, H-6), 4.42 (ddd, $J_{2,1}$=$J_{2,3}$=$J_{2,NH}$=9.2 Hz, 1H, H-2), 4.27 (d, J=8.4 Hz, 1H, H-1), 3.72–3.70 (m, 1H, H-5), 1.87 (s, 3H, NCH_3), 1.47 (s, 9H, *t*-Bu), 1.18 (s, 9H, *t*-Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 178.0 (N*C*=O), 169.6 (*C*=O), 169.4 (*C*=O), 134.3, 133.2, 133.1, 128.3, 127.8, 127.7, 127.0, 126.3, 126.2, 125.7, 99.5 (C-1), 87.3 ($J_{4,F}$=187.3 Hz, C-4), 72.2 ($^2J_{3,F}$=17.8 Hz, C-3), 71.7 ($^2J_{5,F}$=21.5 Hz, C-5), 70.3 (OCH_2Ar), 62.6 (C-6), 53.5 ($^3J_{2,F}$=6.7 Hz, C-2), 27.2, 26.9, 23.2 (NCOCH_3); ESI-MS calcd for $C_{29}H_{38}O_7NFNa$ *m*/*z* [M+Na]$^+$ 554.6, found: 554.6. Anal. Calcd for $C_{29}H_{38}NO_7F$: C, 65.52; H, 7.21; N, 2.64; F, 3.57. Found: C, 65.61; H, 7.19; N, 2.67; F, 3.55.

4.6. 2-Naphthylmethyl 2-acetamido-2,4-dideoxy-4-fluoro-3,6-di-*O*-acetyl-β-D-glucopyranoside (10)

The compound **9** (14.87 g, 28 mmol) was treated with 1 M NaOMe/MeOH (1 mL) in MeOH (500 mL) for 8 h at 45 °C and concentrated. It was then applied to a short silica gel column and eluted with (CH_2Cl_2/MeOH, 7:1) to afford a pure compound, which was treated with acetic anhydride in pyridine/CH_2Cl_2 (1:1) for 4 h at rt, after which it was quenched with MeOH (10 mL) and concentrated. The residue was dissolved in CH_2Cl_2 (500 mL), washed with brine (600 mL), and dried (Na_2SO_4). The organic extract was filtered, concentrated in vacuum, and purified by flash chromatography (1:1, hexanes/EtOAc) to afford **10** (9.84 g, 93%) as an amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.73 (m, 4H, Ar*H*), 7.50–7.38 (m, 3H, Ar*H*), 5.53 (d, $J_{NH,2}$=9.5 Hz, 1H, N*H*), 5.22 (ddd, $J_{3,2}$=8.9, $J_{3,4}$=10.6, $J_{3,F}$=14.7 Hz, 1H, H-3), 5.03 (d, J=12.2 Hz, 1H, OCH_2Ar, ABq), 4.76 (d, J=12.8 Hz, 1H, OCH_2Ar, ABq), 4.73 (d, $J_{1,2}$=10.2 Hz, 1H, H-1), 4.60–4.56 (m, 2H, H-6^a, H-6^b), 4.48 (ddd-dt, $J_{4,3}$=$J_{4,5}$=9.5, $J_{4,F}$=51.0 Hz, 1H, H-4), 4.27 (ddd, $J_{2,NH}$=9.9, $J_{2,3}$=$J_{2,1}$=10.3 Hz, 1H, H-2), 4.12–4.10 (m, 1H, H-5), 2.12 and 2.04 (s, 6H, 2×OCH_3), 1.89 (s, 3H, NH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.5 (N*C*=O), 170.5 (*C*=O), 170.1 (*C*=O), 134.2, 133.1, 133.1, 128.3, 127.8, 127.7, 126.9, 126.3, 125.7, 99.5 (C-1), 87.3 ($^1J_{4,F}$=186.9 Hz, C-4), 72.1 ($^2J_{3,F}$=18.8 Hz, C-3), 71.6 ($^2J_{5,F}$=23.6 Hz, C-5), 70.8 (Ar*C*H), 62.6 (C-6), 53.4 ($^3J_{2,F}$=6.9 Hz, C-2), 23.2, 22.7, 20.6 (NCOCH_3); ESI-MS calcd for $C_{23}H_{26}O_7NFNa$ (*m*/*z*) [M+Na]$^+$ 470.5, found 470.4. Anal. Calcd for $C_{23}H_{26}O_7NF$: C, 61.74; H, 5.86; N, 3.13; F, 4.25. Found: C, 61.71; H, 5.90; N, 3.16; F, 4.28.

4.7. 2-Naphthylmethyl 2-(*N*-*tert*-butyloxycarbonyl-acetamido)-2,4-dideoxy-4-fluoro-β-D-glucopyranoside (11)

To a stirred mixture of compound **10** (22.3 g, 50.06 mmol) and DMAP (0.61 g, 5.01 mmol) in THF (150 mL) was added Boc_2O (54.62 g, 250.3 mmol). Stirring was continued at 60 °C for 3 h, after which the reaction mixture was concentrated in vacuo and purified by flash chromatography (3:1, hexanes/EtOAc) to provide compound **11a**. ESI-MS: calcd for $C_{28}H_{39}O_6NFNa$ (*m*/*z*) [M+Na]$^+$ 570.5, found 570.5. The resultant Boc-protected compound **11a** was treated with methanol (100 mL) containing a catalytic amount of 1 M NaOMe solution and allowed to stir at rt for 1 h to afford deacetylated compound **11** (17.5 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) 7.83–7.82 (m, 4H, Ar*H*), 7.49–7.47 (m, 3H, Ar*H*), 5.10 (d, J_{gem}=12.1 Hz, 1H, OCH_2Ar), 4.80 (s, 1H, OCH_2Ar), 4.34 (d, $J_{1,2}$=8.3 Hz, 1H, H-1), 4.28 (ddd, $J_{4,F}$=50.8, $J_{4,3}$=$J_{4,5}$=8.7 Hz, 1H, H-4), 3.92–3.36 (m, 6H, H-6^a, H-6^b, H-5, H-3), 1.44 (s, 9H, Boc); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.5 (N*C*=O), 172.4 (*C*=O), 171.8 (*C*=O), 134.5, 132.9, 132.8, 127.8.1, 127.5, 127.3, 126.1, 125.8, 125.7, 125.3, 100.3 (C-1), 89.5 ($J_{C,F}$=187.2 Hz, C-4), 73.7 ($^2J_{5,F}$=23.8 Hz, C-5), 71.9 ($^2J_{3,F}$=19.1 Hz, C-3), 70.6 (Ar*C*H), 60.6 (C-6), 57.2 ($^3J_{2,F}$=5.8 Hz, C-2), 23.8, 22.7, 20.6 (NHCOCH_3); Anal. Calcd $C_{22}H_{33}O_3NF$: C, 69.81; H, 8.79; N, 3.70; F, 5.02. Found: C, 69.78; H, 8.76; N, 3.69; F, 5.04.

4.8. 2-(2,2,2-Trichloroethoxycarbonylamino)-2,4-dideoxy-4-fluoro-3,6-di-*O*-acetyl-β-D-glucopyranoside (12)

To a solution of compound **11** (6.12 g 16.2 mmol) in CH_2Cl_2 (50 mL) at rt, HCl (25 mL) was added and the solution was stirred for 24 h. The reaction mixture was then cooled in an ice bath, neutralized with 1 M NaOH, and concentrated to dryness under vacuum. Purification using a short column of silica gel (7:2:1, EtOAc/MeOH/H_2O) gave free amino alcohol as a white solid. Trichloroethoxycarbonyl chloride (2.23 mL, 16.2 mmol) was added dropwise at rt to a vigorously stirred solution of free amino alcohol in Et_2O (60 mL) and satd aq $NaHCO_3$ solution (60 mL). The reaction mixture was allowed to stir for 1.5 h. Et_2O was evaporated under vacuum, and a white solid was precipitated out from the solution, which was then filtered, washed with distilled water, and dried under vacuum to obtain an *N*HTroc-protected compound as a white solid. The resultant compound was treated with acetic anhydride (5 mL) and dry pyridine (10 mL) at rt in the presence of a catalytic amount of DMAP (5 mg) and stirred overnight. The reaction mixture was then concentrated, and the crude reside was purified by flash chromatography (2:1, hexanes/EtOAc) to afford **12** (8.55 g, 91%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.72 (m, 4H, ArH), 7.48–7.38 (m, 3H, ArH), 5.44 (d, $J_{NH,2}$=9.2 Hz, 1H, N*H*), 5.31 (ddd, $J_{3,2}$=9.0, $J_{3,4}$=10.8, $J_{3,F}$=14.2 Hz, 1H, H-3), 5.02 and 4.75 (d, 1H, J_{gem}=12.3 Hz, OCH_2Ar, ABq), 4.72 (s, 2H, OCH_2CCl$_3$), 4.70 (ddd, $J_{4,3}$=$J_{4,5}$=9.5, $J_{4,F}$=51.0 Hz, 1H, H-4), 4.57 (d, $J_{1,2}$=8.1 Hz, 1H, H-1), 4.45 (ddd, $J_{2,3}$=9.9, $J_{2,3}$=10.3, $J_{2,1}$=8.1 Hz, 1H, H-2), 4.24 (dd, $J_{6,5}$=4.5, $J_{6a,6b}$=12.1 Hz, 1H), 3.82 (m, 1H, H-5), 3.65 (br s, 1H), 2.10 and 2.01 (s, 6H, 2×CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.5 (N*C*=O), 170.6 (*C*=O), 170.1 (*C*=O), 154.3, 133.9, 133.1, 133.0, 128.2, 127.8, 127.6, 126.8, 126.2, 126.1, 125.6, 99.4 (C-1), 95.8 (OCH$_2$CCl_3), 87.0 ($J_{4,F}$=187.2 Hz, C-4), 74.5 (OCH_2CCl$_3$), 71.9 ($^2J_{3,F}$=19.1 Hz, C-3), 71.1 ($^2J_{5,F}$=23.8 Hz, C-5), 70.8 (OCHAr), 62.1 (C-6), 55.9 ($^3J_{C,F}$=5.8 Hz, C-2), 20.7 (OCH_3), 20.6 (OCH_3). ESI-MS calcd for $C_{24}H_{25}O_8NFCl_3Na$ (*m*/*z*) [M+Na]$^+$ 603.8. Found: 604.2. Anal. Calcd $C_{24}H_{25}O_8NFCl_3$: C, 49.63; H, 4.34; N, 2.41; F, 3.27; Cl, 18.31. Found: C, 49.61; H, 4.36; N, 2.40; F, 3.25; Cl, 18.33.

4.9. 2-(2,2,2-Trichloroethoxycarbonylamino)-2,4-dideoxy-4-fluoro-3,6-di-*O*-acetyl-glucopyranosyl trichloroacetimidate (13)

To a solution of compound **12** (371.2 mg, 0.64 mmol) in dichloromethane/methanol (10 mL, 4:1) was added DDQ (871 mg, 3.84 mmol) and stirred overnight. The reaction mixture was concentrated and taken up in dichloromethane (50 mL), washed with satd $NaHCO_3$ (3×50 mL), dried (Na_2SO_4), and concentrated. The residue thus obtained was chromatographed using hexane/EtOAc (2:1) as the eluent to provide alcohol as syrup. The resultant compound was treated with trichloroacetonitrile (1 mL) and DBU (20 μL) in dry dichloromethane (10 mL) at 0 to −5 °C for 2 h. The reaction mixture was then concentrated, and the crude reside was purified by flash chromatography (3:1, hexanes/EtOAc) to afford **13** (348.2 mg, 93%) as an amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H, OC(N*H*)CCl$_3$), 6.47 (d, $J_{1,2}$=3.1 Hz, 1H, H-1), 5.70 (d, $J_{NH,2}$=9.5 Hz, 1H, N*H*), 5.40 (ddd, $J_{3,2}$=9.0, $J_{3,4}$=10.8, $J_{3,F}$=14.2 Hz, 1H, H-3), 4.77 (s, 2H, OCH_2CCl$_3$), 4.47 (ddd, $J_{4,3}$=$J_{4,5}$=9.5, $J_{4,F}$=51.0 Hz, 1H, H-4), 4.29–4.31 (m, 2H, H-6^a, H-6^b), 4.25–4.23 (m, 1H, H-2), 3.90–3.92 (m, 1H, H-5), 2.06 (s, 3H, COCH_3), 2.03 (s, 3H, COCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.5 (N*C*=O), 170.3 (*C*=O), 170.1 (*C*=O), 94.1 (C-1), 95.8 (OCH$_2$CCl_3), 86.6 ($^1J_{C,F}$=187.2 Hz, C-4), 73.7 ($^2J_{3,F}$=18.4 Hz, C-3), 70.9 (OCH_2CCl$_3$), 69.5, 68.3, 67.6

($^2J_{5,F}$=23.2 Hz, C-5), 63.2 (C-6), 51.7 ($^3J_{2,F}$=6.8 Hz, C-2), 20.9 (O*C*H$_3$), 20.7 (O*C*H$_3$). ESI-MS calcd for $C_{15}H_{17}N_2O_8Cl_6FNa$ (*m*/*z*) $[M+Na]^+$ 608.0, found 607.0. Anal. Calcd for $C_{15}H_{17}N_2O_8Cl_6F$: C, 30.79; H, 2.93; N, 4.79; F, 3.25; Cl, 36.36. Found: C, 30.76; H, 2.96; N, 4.77; F, 3.27; Cl, 36.31.

4.10. 2-Naphthylmethyl 2-acetamido-2-deoxy-4,6-*O*-benzylidene-β-D-glucopyranoside (14)

Compound **6** (1.81 g, 3.72 mmol) was suspended in dry CH_3CN (19 mL) and treated with PhCH(OMe)$_2$ (2.64 mL, 17.5 mmol) and *p*-TsOH·H$_2$O (33.4 mg, 0.17 mmol) at rt for 2 h. After this time, the reaction mixture was diluted with CH_2Cl_2 (20 mL), neutralized with Et_3N, and evaporated to dryness. The residue was chromatographed using hexane/EtOAc (2:1) as the eluent to give **14** (1.56 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.65 (m, 4H, Ar*H*), 7.50–7.24 (m, 8H, Ar*H*), 5.10 (s, 1H, C*H*Ph), 4.80 (d, $J_{1,2}$=8.3 Hz, 1H, H-1), 4.50 (m, 1H, H-4), 4.44 (m, 1H, H-2), 4.20–4.17 (m, 2H, H-6, H-3), 3.80 (d, 1H, H-6′), 3.60 (m, 1H, H-5), 2.85–2.83 (s, 1H, 3-O*H*), 1.97 (s, 3H, NC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.2 (N*C*=O), 134.7, 134.4, 133.7, 130.2, 128.3, 127.7, 126.8, 126.3, 126.1, 125.8, 103.1 (*C*HPh), 99.5 (C-1), 73.1 (O*C*HAr), 70.9 (C-4), 70.1 (C-5), 65.7 (C-3), 63.2 (C-6), 51.8 (C-2), 23.5 (*C*H$_3$). Anal. Calcd for $C_{26}H_{27}NO_6$: C, 69.47; H, 6.05; N, 3.12. Found: C, 69.51; H, 6.09; N, 3.18.

4.11. 2-Naphthylmethyl 2-acetamido-2-deoxy-4,6-*O*-benzylidene-β-D-allopyranoside (15)[31]

To a stirred suspension of **14** (29.9 g, 66.8 mmol) in CH_2Cl_2 (200 mL) at rt was added pyridine (100 ml). After 10 min, MsCl (7.50 ml, 96.9 mmol) was added dropwise and stirred for 28 h. The reaction mixture was then diluted with CH_2Cl_2 (500 mL), and the organic layer was washed with H_2O (400 mL). The aqueous phase was extracted with CH_2Cl_2 (3×200 mL), and the combined organics were dried (Na_2SO_4) and evaporated to give a residue. The residue was suspended in 2-methoxyethanol/H_2O (550 ml, 10:1) and treated with NaOAc·3H$_2$O (28.0 g, 206 mmol) at 130 °C for 18 h, after which the reaction mixture was cooled to rt, and the solvents were evaporated. The residue obtained was dissolved in CH_2Cl_2 (1000 mL), then washed with brine (1×600 mL) and dried (Na_2SO_4). The organic extract was filtered, concentrated in vacuum, and purified by flash chromatography (1:1, hexanes/EtOAc) to afford **15** (27.8 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.65 (m, 8H, ArH), 7.50–7.24 (m, 8H, ArH), 5.87–5.86 (m, 1H), 5.59 (s, 1H), 4.44–4.41 (m, 1H), 4.39 (s, 1H), 4.24 (m, 1H), 4.18–4.16 (m, 1H), 3.83–3.79 (m, 1H), 3.75–3.73 (m, 1H), 1.97 (s, 3H, NC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.1, 134.6, 133.5, 130.1, 128.7, 127.5, 126.7, 126.4, 126.0, 125.4, 102.8, 98.4, 76.1, 70.7, 69.5, 63.9, 51.4, 23.7. Anal. Calcd for $C_{26}H_{27}NO_6$: C, 69.47; H, 6.05; N, 3.12. Found: C, 69.44; H, 6.02; N, 3.10.

4.12. 2-Naphthylmethyl 2-phthalimido-2-deoxy-4,6-*O*-benzylidene-β-D-allopyranoside (16)[28]

Compound **15** (13.3 g, 29.5 mmol) was added to a 30% KOH solution (80 mL) in 1,4-dioxane/methoxyethanol 80 mL (5:3 v/v) and refluxed at 120 °C for 18 h. The reaction mixture was cooled and neutralized with 2 N HCl until slightly basic to avoid amine hydrochloride formation. The solvents were removed under vacuum, and the residue obtained was dissolved in water and extracted with chloroform (4×100 mL). The combined extracts were then washed successively with water, brine, and dried over Na_2SO_4. The chloroform layer was then concentrated to give a yellowish-white solid, which on recrystallization from $CHCl_3$/hexanes afforded the free amine as a white solid. Reaction of the resultant free amine with phthalic anhydride in aq sodium bicarbonate gave the phthaloyl derivative **16** (13.3 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.84 (m, 5H, ArH), 7.81–7.55 (m, 6H, ArH), 7.50–7.30 (m, 5H, ArH), 5.84–5.82 (m, 1H), 5.01–4.98 (m, 1H), 4.78–4.74 (m, 1H), 4.43–4.40 (m, 1H), 4.21–4.13 (m, 2H), 3.82–3.76 (m, 2H), 2.83 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.6, 167.4, 137.3, 135.2, 133.7, 132.4, 132.3, 132.2, 132.1, 131.8, 128.8, 128.7, 128.0, 127.9, 127.6, 127.3, 127.0, 126.0, 125.1, 101.9, 97.1 (C-1), 86.8 (C-4), 76.2 (C-2), 70.9 (C-6), 68.4 (C-3), 57.9 (C-5). Anal. Calcd for $C_{32}H_{27}NO_7$: C, 71.49; H, 5.06; N, 2.61. Found: C, 71.52; H, 5.03; N, 2.59.

4.13. 2-Naphthylmethyl 2-phthalimido-2,4-dideoxy-3-fluoro-4,6-di-*O*-acetyl-β-D-glucopyranoside (17)

To a solution of DAST (5.70 g, 35.3 mmol) in CH_2Cl_2 (20 mL) in a Teflon Erlenmeyer flask was added dropwise a solution of **16** (2.23 g, 4.16 mmol) in CH_2Cl_2 (40 mL) at −5 °C. The reaction mixture was warmed to rt and stirred overnight, after which the reaction mixture was cooled to −5 °C and methanol (20 mL) was added dropwise to destroy the excess DAST. The solution was then concentrated under reduced pressure to afford a yellowish oil that was subjected to flash chromatography on silica gel (2:3, hexanes/EtOAc). The resultant compound was taken up in 60% aq acetic acid and stirred for 1.5 h at 60–65 °C. The solution was then concentrated under reduced pressure to obtain a crude residue, which on column chromatography (silica gel) with dichloromethane/methanol (60:1) afforded a pure compound as an amorphous solid. The resultant compound was treated with acetic anhydride in pyridine/CH_2Cl_2 (1:1) for 4 h at rt, then quenched with MeOH (1 mL). The reaction mixture was concentrated and taken in CH_2Cl_2 (50 mL), then washed with brine (60 mL), dried (Na_2SO_4), filtered, concentrated in vacuum, and purified by flash chromatography (1:1, hexanes/EtOAc) to afford **17** (1.52 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.75 (m, 6H, ArH), 7.60–7.40 (m, 5H, ArH), 5.08–4.93 (m, 2H), 4.78–4.71 (m, 1H), 4.57–4.33 (m, 2H), 4.31–4.23 (m, 1H), 4.15–4.05 (m, 1H), 3.51–3.39 (m, 1H), 2.05, 1.95 (s, 6H, 2×OC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.8, 169.3, 134.1, 134.0, 133.0, 132.8, 131.3, 128.2, 127.8, 127.6, 126.9, 126.2, 125.9, 125.5, 97.1 ($^3J_{1,F}$=9.7 Hz, C-1), 88.5 ($^1J_{3,F}$=188.1 Hz, C-3), 71.8 (Ar*C*H), 71.1 ($^3J_{5,F}$=8.2 Hz, C-5), 69.1 ($^2J_{3,F}$=17.8 Hz, C-4), 61.8 (C-6), 55.0 ($^2J_{2,F}$=17.1 Hz, C-2), 20.8, 20.7. Anal. Calcd for $C_{18}H_{18}NO_8F$: C, 54.69; H, 4.59; N, 3.54; F, 4.81. Found: C, 54.66; H, 4.53; N, 3.56; F, 4.83.

4.14. 2-Phthalimido-2,4-dideoxy-3-fluoro-4,6-di-*O*-acetyl-β-D-glucopyranosyl trichloroacetimidate (18)

Following a similar procedure to that for compound **13**, compound **18** (yield 92%) was prepared from compound **17**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.80 (m, 2H, ArH), 7.73–7.70 (m, 2H, ArH), 6.61–6.59 (m, 1H), 5.45–5.42 (m, 1H), 5.23–5.19 (m, 1H), 4.78–4.73 (m, 1H), 4.60–4.55 (m, 1H), 4.45–4.40 (m, 1H), 4.28–4.21 (m, 1H), 3.83–3.77 (m, 1H), 2.05, 2.01 (s, 6H, 2×OC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.3, 167.6, 132.3, 132.1, 127.7, 127.6, 86.9, 86.0 (C-3, *J*=188.0 Hz), 84.1 (C-1, *J*=9.7 Hz), 76.7 (C-4, *J*=17.8 Hz), 73.9, 65.8, 64.4, 21.0, 20.7. Anal. Calcd for $C_{20}H_{18}N_2O_8Cl_3F$: C, 44.51; H, 3.36; N, 5.19; Cl, 19.71; F, 3.52. Found: C, 44.53; H, 3.33; N, 5.17; Cl, 19.74; F, 3.55.

4.15. Benzyl *O*-[2-(2,2,2-trichloroethoxycarbonylamino)-2,4-dideoxy-4-fluoro-3,6-di-*O*-acetyl-β-D-glucopyranosyl]-(1-6)-2-acetamido-2-deoxy-3-*O*-acetyl-α-D-galactopyranoside (20)

A solution of compound **19** (178 mg, 0.367 mmol) and compound **13** (233.7 mg, 0.385 mmol) in dry dichloromethane (6 mL) containing 4 Å-MS (2.0 g) was stirred for 2 h at −65 to −70 °C under a N_2 atmosphere. After 2 h, TMSOTf (14 μL) in dry dichloromethane (0.5 mL) was added and stirred at the same temperature for 1 h

under a N_2 atmosphere. The reaction was then quenched with a satd sodium bicarbonate solution. The solids were filtered off and the organic layer was washed with satd sodium bicarbonate, dried with Na_2SO_4, and concentrated. The crude residue was passed through a short column of silica gel eluted with hexane/ethyl acetate (1.5:1) to afford disaccharide **20** (242.0 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.32 (m, 5H, ArH), 6.62 (d, J=9.4 Hz, 1H), 5.77 (d, J=9.8 Hz, 1H), 5.30–5.21 (m, 1H), 5.11 (dd, J=2.5, 8.6 Hz, 1H), 4.85 (d, J=3.4 Hz, 1H), 4.79–4.71 (m, 4H), 4.48–4.38 (m, 3H), 4.22 (dd, J=4.9, 12.1 Hz, 1H), 4.12–4.10 (m, 1H), 4.02–3.98 (m, 3H), 3.93–3.88 (m, 3H), 3.25 (m, 1H), 2.10, 2.06, 2.03 (s, 9H, 3×OCH_3), 1.93 (s, 3H, NCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.0, 170.8, 170.5, 170.1, 154.60, 136.9, 128.5, 128.4, 128.1, 101.8 (C-1_{GalNAc}), 97.0 (C-1_{GlcNAc}), 88.4 and 86.5 (C-4_{GlcNAc}, J=187.3 Hz), 74.1, 72.4 and 72.2 (C-3, J=18.3 Hz), 71.1, 70.9 and 70.7 (C-5_{GlcNAc}, J=23.4 Hz), 69.7, 69.6, 69.1, 67.4, 62.3, 55.7, 47.6, 23.1, 20.8, 20.6. Anal. Calcd for $C_{30}H_{38}O_{14}N_2Cl_3F$: C, 46.44; H, 4.94; N, 3.61; Cl, 13.71; F, 2.45. Found: C, 46.47; H, 4.93; N, 3.67; Cl, 13.74; F, 2.51.

4.16. Benzyl *O*-(2-acetamido-2,4-dideoxy-4-fluoro-3,6-di-*O*-acetyl -β-D-glucopyranosyl)-(1-6)-2-acetamido-2-deoxy-3-*O*-acetyl-α-D-galactopyranoside (21)

Cadmium dust (756 mg, 6.73 mmol) was added to a solution of **20** (263.8 mg, 0.34 mmol) in DMF/AcOH (1:1), and the reaction was stirred at rt under N_2. After 12 h, the reaction mixture was filtered through Celite®, rinsed with DMF (5 mL), and then azeotroped with toluene (5×20 mL). The residue was treated with acetic anhydride in pyridine/CH_2Cl_2 (1:1) for 4 h at rt, then quenched with MeOH (1 mL). The reaction mixture was concentrated under vacuum and the residue redissolved in CH_2Cl_2 (50 mL), washed with brine (60 mL), and dried (Na_2SO_4). The organic extract was filtered, concentrated in vacuum, and purified by flash chromatography (1:1, hexanes/EtOAc) to afford **21** (216.2 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.24 (m, 5H, ArH), 5.87 (d, J=8.9 Hz, 1H), 5.65 (d, J=9.6 Hz, 1H), 5.30–5.21 (m, 2H), 5.11 (dd, J=3.3, 11.3 Hz, 1H), 4.91 (d, J=3.6 Hz, 1H), 4.68 (d, J=11.8 Hz, 1H), 4.62 (d, J=8.3 Hz, 1H), 4.52 (ddd, J=3.7, 9.7, 11.3 Hz, 1H), 4.44–4.42 (m, 2H), 4.35 (m, 2H), 4.20 (dd, J=4.9, 12.2 Hz, 1H), 4.14 (m, 1H), 3.79–3.77 (m, 1H), 3.76 (m, 1H), 3.54–3.51 (m, 1H), 2.09 (s, 3H, OCH_3), 2.05 (s, 3H, OCH_3), 2.04 (s, 3H, OCH_3), 1.93 (s, 3H, OCH_3), 1.86 (6H, NCH_3 and OCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.8, 170.7, 170.6, 170.4, 170.3, 170.0, 136.9, 128.5, 128.2, 128.1, 100.6 (C-1_{GalNAc}), 96.9 (C-1_{GlcNAc}), 87.6 and 86.4 (C-4_{GlcNAc}, J=187.3 Hz), 72.2 and 72.1 (C-3, J=18.3 Hz), 71.3 and 71.2 (C-5_{GlcNAc}, J=23.4 Hz), 68.7, 67.9, 67.8, 67.5, 62.1, 54.3, 54.3, 47.6, 23.1, 20.7. Anal. Calcd for $C_{31}H_{41}O_{14}N_2F$: C, 54.38; H, 6.04; N, 4.09; F, 2.78. Found: C, 54.37; H, 5.97; N, 4.05; F, 2.81.

4.17. Benzyl *O*-[2-acetamido-2,4-dideoxy-4-fluoro-β-D-glucopyranosyl]-(1-6)-2-acetamido-2-deoxy-α-D-galactopyranoside (1)

The compound **21** (191.5 mg, 0.28 mmol) was treated with 5% NaOMe (1 M) in MeOH (20 μL) in MeOH (10 mL) for 12 h at 45 °C and concentrated. It was then applied to a short silica gel column and eluted with (CH_2Cl_2/MeOH, 5:1) to give a pure disaccharide **1** (137.2 mg, 95%). ^{1}H NMR (400 MHz, $CDOD_3$) δ 7.34–7.26 (m, 5H, ArH), 4.94 (d, J=3.2 Hz, 1H), 4.76 (d, J=12.6 Hz, 1H, PhCH_AO, ABq), 4.50 (d, J=8.1 Hz, 1H), 4.48 (d, J=12.6 Hz, 1H, PhCH_AO, ABq), 4.08–3.95 (m, 3H), 3.92–3.80 (m, 5H), 3.78–3.58 (m, 4H), 2.09, 2.05 (s, 6H, 2×NCH_3); ^{13}C NMR (100.6 MHz, $CDOD_3$) δ 175.8, 174.7, 136.9, 128.5, 128.2, 104.6, 96.7, 87.7, 86.5, 83.4, 72.2, 72.1, 71.3 70.2, 62.3, 62.1, 56.3, 54.3, 23.3 (NCH_3), 23.1 (NCH_3). ESI-MS calcd for $C_{23}H_{33}O_{10}N_2FNa$ (m/z): 539.2, Found 539.5. Anal. Calcd for $C_{23}H_{33}O_{10}N_2F$: C, 53.48; H, 6.44; N, 5.42; F, 3.68. Found: C, 53.53; H, 6.43; N, 5.37; F, 3.63.

4.18. Benzyl *O*-[2-phthalimido-2,4-dideoxy-3-fluoro-4,6-di-*O*-acetyl-β-D-glucopyranosyl]-(1-6)-2-acetamido-2-deoxy- 3-*O*-acetyl-α-D-galactopyranoside (22)

Disaccharide **22** (yield 85%) was prepared from glycosyl donor **18** and acceptor **19** according to the procedure described for the preparation of compound **20**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.80 (m, 2H, ArH), 7.73–7.70 (m, 2H, ArH), 7.33–7.32 (m, 5H, ArH), 6.28–6.26 (m, 1H), 5.82–5.79 (m, 1H), 5.50–5.45 (m, 1H), 5.25–5.15 (m, 1H), 5.09–4.94 (m, 3H), 4.78–4.75 (m, 2H), 4.58–4.55 (m, 1H), 4.50–4.43 (m, 1H), 4.32–4.23 (m, 1H), 4.12–3.93 (m, 2H), 3.86–3.78 (m, 1H), 3.55–3.45 (m, 1H), 2.11, 2.07, 2.05 (s, 9H, 3×OCH_3), 2.01 (s, 3H, NCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.2, 170.9, 170.7, 164.4, 164.2, 136.6, 132.5, 129.4, 129.2, 128.5, 128.4, 128.1, 102.8, 97.4, 88.9, 86.7, 74.1, 73.5, 72.4, 72.2, 71.1, 70.9, 70.7, 69.6, 69.1, 67.3, 64.3, 63.5, 50.2, 48.6, 47.7, 23.1, 20.8, 20.6. Anal. Calcd for $C_{35}H_{39}O_{14}N_2F$: C, 57.53; H, 5.38; N, 3.83; F, 2.60. Found: C, 57.55; H, 5.43; N, 3.77; F, 2.63.

4.19. Benzyl *O*-[2-acetamido-2,4-dideoxy-3-fluoro-4,6-di-*O*-acetyl-β-D-glucopyranosyl]-(1-6)-2-acetamido-2-deoxy-3-*O*-acetyl-α-D-galactopyranoside (23)

A solution of compound **22** (40.8 mg, 0.056 mmol) in dry methanol (10 mL) was treated with NH_2–$NH_2 \cdot H_2O$ (2 mL) at 90 °C for 6 h. The reaction mixture was then concentrated and co-evaporated with dry toluene to complete dryness. The resulting compound was acetylated with anhydrous acetic anhydride and dry pyridine (1:1, 6 mL) in the presence of DMAP (5 mg) at rt. After completion of the reaction (overnight), the reaction mixture was concentrated and purified by flash chromatography (80:1, dichloromethane/methanol) to afford **23** (35.5 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.81 (m, 2H, ArH), 7.75–7.71 (m, 2H, ArH), 7.38–7.26 (m, 5H, ArH), 5.87–5.85 (m, 1H), 5.68–5.66 (m, 1H), 5.38–5.21 (m, 2H), 5.14–5.12 (m, 1H), 4.90–4.88 (s, 1H), 4.70–4.64 (m, 2H), 4.62 (d, J=8.3 Hz, 1H), 4.52 (ddd, J=3.7, 9.7, 11.3 Hz, 1H), 4.44–4.42 (m, 2H), 4.35 (m, 2H), 4.52–4.38 (m, 4H), 4.14 (m, 2H), 3.79–3.67 (m, 3H), 2.07, 2.05, 2.04, 1.97 (s, 12H, 4×OCH_3), 1.96, 1.87 (s, 6H, 2×NCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.9, 170.7, 170.6, 169.4, 169.0, 136.7, 128.4, 128.2, 128.1, 101.6, 100.9, 87.8, 86.6, 84.3, 72.4, 72.2, 71.3, 71.2, 68.8, 67.9, 54.5, 23.4, 20.8. Anal. Calcd for $C_{31}H_{41}O_{14}N_2F$: C, 54.38; H, 6.04; N, 4.09; F, 2.78. Found: C, 54.31; H, 5.99; N, 4.11; F, 2.73.

4.20. Benzyl *O*-[2-acetamido-2,4-dideoxy-3-fluoro-β-D-glucopyranosyl]-(1-6)-2-acetamido- 2-deoxy-α-D-galactopyranoside (2)

Disaccharide **2** (yield 87%) was prepared from **23** according to the procedure for preparation of compound **1**. ^{1}H NMR (400 MHz, $CDOD_3$) δ 7.36–7.23 (m, 5H, ArH), 4.97 (d, J=3.2 Hz, 1H), 4.76 (d, J=12.6 Hz, 1H, PhCH_AO, ABq), 4.50 (d, J=8.1 Hz, 1H), 4.48 (d, J=12.6 Hz, 1H, PhCH_AO, ABq), 4.67–4.62 (m, 1H), 4.48–4.46 (m, 1H), 4.28–3.80 (m, 10H), 3.78–3.64 (m, 2H), 3.54–3.40 (m, 2H), 2.08, 2.05 (s, 6H, 2×NCH_3); ^{13}C NMR (100.6 MHz, $CDOD_3$) δ 173.1, 172.4, 137.1, 128.6, 128.3, 128.2, 104.3, 97.2, 86.7, 84.5, 74.2, 73.7, 71.3 70.2, 65.7, 62.3, 62.1, 58.3, 57.9, 23.3, 23.1. ESI-MS calcd for $C_{23}H_{33}O_{10}N_2FNa$ (m/z) $[M+Na]^+$ 539.2, found 539.0. Anal. Calcd for $C_{23}H_{33}O_{10}N_2F$: C, 53.48; H, 6.44; N, 5.42; F, 3.68. Found: C, 53.53; H, 6.43; N, 5.37; F, 3.63.

4.21. Benzyl *O*-[2-(2,2,2-trichloroethoxycarbonylamino)-2,4-dideoxy-4-fluoro-3,6-di-*O*-acetyl-β-D-glucopyranosyl]-(1-6)-*O*-[2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1-3)]-2-acetamido-2-deoxy-α-D-galactopyranoside (25)

Trisaccharide **25** (yield 95%) was prepared from glycosyl donor **13** and disaccharide acceptor **24** according to the procedure for preparation of compound **20**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m,

5H, ArH), 6.81 (d, J=8.8 Hz, 1H), 5.72 (d, J=9.3 Hz, 1H), 5.33–5.31 (m, 2H), 5.13 (dd, J=8.1, 4.4 Hz, 1H), 4.95 (dd, J=3.1, 10.5 Hz, 1H), 4.71–4.55 (m, 5H), 4.50 (d, J=11.2 Hz, 1H), 4.30–4.21 (m, 1H), 4.07–4.01 (m, 4H), 3.87 (m, 3H), 3.70–3.66 (m, 1H), 3.51–3.46 (m, 1H), 2.13, 2.10, 2.05, 2.01, 2.00, 1.96 (s, 18H, 6×OCH_3), 1.94 (s, 3H, NCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.5, 170.3, 170.1, 170.0, 169.3, 154.6, 136.6, 128.8, 128.6, 128.3, 102.2 (C-1_{Gal}), 101.2 (C-1_{GlcNAc}), 96.4 (C-1_{GalNAc}), 87.9 and 86.1 (C-4_{GlcNAc}, J=186.8 Hz), 78.6, 73.9, 72.8, 72.7, 70.9, 70.8, 70.6, 69.7, 69.4, 68.9, 68.5, 66.8, 62.1, 61.3, 55.98 and 53.91(C-2_{GlcNAc}, $J_{C,F}$=8.0 Hz), 47.6, 23.2, 20.7, 20.6, 20.5, 20.4. ^{19}F NMR: −198.37, −198.42, −198.51, −198.55 (dd, 1F); ESI-MS calcd for $C_{42}H_{54}O_{22}N_2FCl_3Na$ (m/z) $[M+Na]^+$ 1087.3, found 1087.3. Anal. Calcd for $C_{42}H_{54}O_{22}N_2FCl_3$: C, 47.40; H, 5.11; N, 2.63; F, 1.79; Cl, 9.99. Found: C, 47.45; H, 5.07; N, 2.68; F, 1.83; Cl, 9.93.

4.22. Benzyl *O*-(2-acetamido-2,4-dideoxy-4-fluoro-3,6-di-*O*-acetyl-β-D-glucopyranosyl)-(1-6)-*O*-[2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1-3)]-2-acetamido-2-deoxy-4-*O*-acetyl-α-D-galactopyranoside (26)

Trisaccharide **26** (yield 93%) was prepared from compound **25** according to the procedure for preparation of compound **21**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.34 (m, 5H, ArH), 6.03–6.00 (m, 1H), 5.76–5.73 (m, 1H), 5.33–5.11 (m, 4H), 5.08–5.06 (m, 1H), 4.97–4.93 (m, 2H), 4.71–4.68 (m, 1H), 4.59–4.57 (m, 2H), 4.53–4.4.54 (m, 1H), 4.42–4.39 (m, 3H), 4.28–4.25 (m, 2H), 4.13–4.09 (m, 4H), 3.99–3.84 (m, 5H), 3.75–3.73 (m, 1H), 3.51–3.46 (m, 1H), 2.11, 2.10, 2.09, 2.08, 2.03, 2.00, 1.96 (s, 21H, 7×OCH_3), 1.95, 1.87 (s, 6H, 2×NCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.7, 170.5, 170.3, 170.2, 170.1, 170.1, 170.0, 136.9, 128.6, 128.5, 128.5,128.4, 128.3, 128.2, 101.0 (C-1_{Gal}), 100.4 (C-1_{GlcNAc}), 96.9 (C-1_{GalNAc}), 87.79 and 85.93 (C-4_{GlcNAc}, J=186.8 Hz), 72.9, 72.3, 72.1, 71.1, 71.2, 71.0, 70.8, 70.7, 69.6, 69.3, 68.7, 68.6, 66.7, 61.9, 61.1, 54.02 and 53.94 (C-2_{GlcNAc}, $J_{C,F}$=8.0 Hz), 48.8, 23.2, 23.1, 20.6, 20.6, 20.6, 20.5, 20.4. ^{19}F NMR: −198.37, −198.42, −198.51, −198.55 (dd, 1F); ESI-MS calcd for $C_{43}H_{57}O_{22}N_2FNa$ (m/z) $[M+Na]^+$ 995.9, found 995.8. Anal. Calcd for $C_{43}H_{57}O_{22}N_2F$: C, 53.09; H, 5.91; N, 2.88; F, 1.95. Found: C, 53.11; H, 5.94; N, 2.79; F, 1.91.

4.23. Benzyl *O*-[2-acetamido-2,4-dideoxy-4-fluoro-β-D-glucopyranosyl]-(1-6)-*O*-[β-D-galactopyranosyl-(1-3)]-2-acetamido-2-deoxy-α-D-galactopyranoside (3)

Trisaccharide **3** (yield 89%) was prepared from compound **26** according to the procedure described for the preparation of compound **1**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.56–7.53 (m, 5H, ArH), 5.05 (d, J=3.6 Hz, 1H), 4.69 (d, J=8.3 Hz, 1H), 4.59 (d, J=11.5 Hz, 1H, PhCH_AO, ABq), 4.53 (d, J=7.9 Hz, 1H), 4.40 (dd, J=3.8, 10.4 Hz, 1H), 4.25 (dd, J=2.4, 7.9 Hz, 1H), 4.13 (dd, J=2.6, 10.9 Hz, 1H), 4.02–3.78 (m, 10H), 3.73–3.70 (m, 1H), 3.68 (d, J=3.2 Hz, 1H), 3.59 (t, J=8.0 Hz, 1H), 3.41 (m, 1H), 2.06 (s, 6H, 2×NCH_3); ^{13}C NMR (100.6 MHz, $CDOD_3$, Ref δ=49.00) δ 129.7, 129.6, 129.3, 105.6 (C-1_{Gal}), 102.4 (C-1_{GlcNAc}), 97.2 (C-1_{GalNAc}), 77.9, 75.95, 74.3, 74.1, 73.5, 72.7, 71.6, 70.8, 70.5, 70.3, 69.8, 69.6, 68.2, 61.9, 61.0. ^{19}F NMR ($CDOD_3$) δ −198.37, −198.42, −198.51, −198.55 (dd, $J_{F\text{-}4,H\text{-}4}$ 50.3, $J_{F\text{-}4,H\text{-}3}$ 14.6 Hz). ESI-MS calcd for $C_{29}H_{43}O_{15}N_2FNa$ (m/z) $[M+Na]^+$ 701.7, found 701.7. Anal. Calcd for $C_{29}H_{43}O_{15}N_2F$: C, 51.32; H, 6.39; N, 4.13; F, 2.80. Found: C, 53.11; H, 5.94; N, 2.79; F, 1.91.

4.24. Benzyl *O*-[2-phthalimido-2,4-dideoxy-3-fluoro-4,6-di-*O*-acetyl-β-D-glucopyranosyl]-(1-6)-*O*-[2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1-3)]-2-acetamido-2-deoxy-α-D-galactopyranoside (27)

Following a similar procedure to that for compound **22**, trisaccharide **27** (yield 82%) was prepared from glycosyl donor **18** and disaccharide acceptor **24**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.80 (m, 2H, ArH), 7.76–7.70 (m, 2H, ArH), 7.39–7.24 (m, 5H, ArH), 6.78–6.74 (m, 1H), 5.82–5.80 (m, 1H), 5.66–5.63 (m, 1H), 5.50–5.45 (m, 1H), 5.30–5.19 (m, 1H), 5.02–4.90 (m, 5H), 4.78–4.72 (m, 1H), 4.60–4.57 (m, 1H), 4.45–4.40 (m, 1H), 4.31–4.18 (m, 8H), 3.83–3.79 (m, 1H), 3.52–3.47 (s, 1H), 2.12, 2.10, 2.09, 2.07, 2.02, 2.00 (s, 18H, 6×OCH_3), 1.96 (s, 3H, NCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.7, 170.4, 170.3, 170.2, 170.1, 170.0, 137.1, 128.6, 128.5, 128.4, 128.3, 128.2, 103.1, 98.5, 97.6, 89.7, 86.9, 73.5, 72.3, 72.1, 71.2, 71.1, 71.0, 70.8, 70.7, 69.6, 69.3, 68.7, 68.6, 66.7, 61.8, 61.2, 54.2, 47.8, 23.2, 23.1, 20.6, 20.5, 20.4. Anal. Calcd for $C_{47}H_{55}O_{22}N_2F$: C, 55.40; H, 5.44; N, 2.75; F, 1.86. Found: C, 55.44; H, 5.46; N, 2.79; F, 1.90.

4.25. Benzyl *O*-[2-acetamido-2,4-dideoxy-3-fluoro-4,6-*O*-benzylidene-β-D-glucopyranosyl]-(1-6)-*O*-[2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1-3)]-2-acetamido-2-deoxy-4-*O*-acetyl-α-D-galactopyranoside (28)

Following a similar procedure to that for compound **23**, trisaccharide **28** (yield 89%) was prepared from compound **27**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.24 (m, 5H, ArH), 5.91–5.85 (m, 1H), 5.66–5.63 (m, 1H), 5.38–5.35 (m, 2H), 5.09–5.04 (m, 2H), 4.97–4.94 (m, 1H), 4.71–4.60 (m, 2H), 4.58–4.37 (m, 6H), 4.20–4.16 (m, 2H), 3.98–3.74 (m, 4H), 3.51–3.41 (m, 1H), 2.11, 2.10, 2.09, 2.08, 2.03, 2.00, 1.96 (s, 21H, 7×OCH_3), 1.95, 1.87 (s, 6H, 2×NCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.7, 170.5, 170.3, 170.2, 170.1, 170.1, 170.0, 136.9, 128.6, 128.5, 128.5,128.4, 128.3, 128.2, 101.0 (C-1_{Gal}), 100.4 (C-1_{GlcNAc}), 96.9 (C-1_{GalNAc}), 87.79 and 85.93 (C-4_{GlcNAc}, J=186.8 Hz), 72.9, 72.3, 72.1, 71.1, 71.2, 71.0, 70.8, 70.7, 69.6, 69.3, 68.7, 68.7, 66.8, 61.9, 61.1, 54.02 and 53.94 (C-2_{GlcNAc}, $J_{C,F}$=8.0 Hz), 48.8, 23.2, 23.1, 20.6, 20.6, 20.5, 20.4, 20.4. ^{19}F NMR δ −198.37, −198.42, −198.51, −198.55 (dd, 1F); ESI-MS calcd for $C_{43}H_{57}O_{22}N_2FNa$ (m/z) $[M+Na]^+$ 995.9, found 995.8. Anal. Calcd for $C_{43}H_{57}O_{22}N_2F$: C, 53.09; H, 5.91; N, 2.88; F, 1.95. Found: C, 53.11; H, 5.94; N, 2.79; F, 1.91.

4.26. Benzyl *O*-[2-acetamido-2,4-dideoxy-3-fluoro-β-D-glucopyranosyl]-(1-6)-*O*-[β-D-galactopyranosyl-(1-3)]-2-acetamido-2-deoxy-α-D-galactopyranoside (4)

Following a similar procedure to that for compound **1**, trisaccharide **4** (yield 89%) was prepared from compound **28**. ^{1}H NMR (400 MHz, $CDOD_3$) δ 7.40–7.20 (m, 5H, ArH), 5.05–5.01 (m, 1H), 4.70–4.64 (m, 1H), 4.55–4.52 (m, 1H), 4.40–4.30 (m, 2H), 4.12–4.08 (s, 1H), 4.02–3.20 (m, 15H), 1.98, 1.94 (s, 6H, 2×NCH_3); ^{13}C NMR (100.6 MHz, $CDOD_3$) δ 176.8, 176.6, 138.5, 131.6, 130.5, 129.4, 129.2, 106.1, 102.3, 98.5, 91.2, 90.4, 76.2, 74.8, 71.8, 71.4, 71.2, 64.1, 63.8, 62.3, 61.1, 54.1, 23.5, 21.5. ESI-MS calcd for $C_{29}H_{43}O_{15}N_2FNa$ (m/z) $[M+Na]^+$ 701.7, found 702.1. Anal. Calcd for $C_{29}H_{43}O_{15}N_2F$: C, 51.32; H, 6.39; N, 4.13; F, 2.80. Found: C, 53.11; H, 5.94; N, 2.79; F, 1.91.

4.27. 2-Naphthylmethyl 2,4,6-trideoxy-4-*O*-acetyl-6-fluoro-β-D-glucopyranoside [2,3-*d*]-1,3-oxazolidin-2-one (29)

A solution of **6** (5 g, 13.85 mmol) in 1 M NaOH (500 ml) was refluxed at 110 °C for 15 h. The reaction mixture was then cooled to rt and neutralized with 2 M HCl. A white solid was precipitated from the solution. Filtration and desiccation under vacuum afforded the pure free amine (4.06 g, 92%). To an ice-cooled stirred solution of *p*-nitrophenoxycarbonyl chloride (19.50 g, 96.75 mmol) in acetonitrile (50 mL) was added over several minutes a stirred, ice bath-cooled mixture of the resultant free amine (18.84 g, 38.7 mmol, 1 equiv) and $NaHCO_3$ (16.25 g, 194 mmol) in 100 mL water. The mixture was vigorously stirred with ice bath cooling for 1 h after the addition of the final aliquot. After 1 h, the resulting aq mixture was extracted with ethyl acetate and the combined organic layers were washed with water, dried over Na_2SO_4, and concentrated in vacuo. Purification over a short column of silica gel with

ethyl acetate afforded oxazolidinone (9.20 g, 93%). To a solution of DAST (5.70 g, 35.3 mmol) in CH_2Cl_2 (20 mL) in a Teflon Erlenmeyer flask was added dropwise a solution of oxazolidinone (1.61 g, 4.16 mmol) in CH_2Cl_2 (40 mL) at −5 °C. The reaction mixture was allowed to warm to rt and stirred overnight. Thereafter, it was cooled to −5 °C and methanol (20 mL) was added dropwise to destroy the excess DAST and the solution was concentrated under reduced pressure to afford a yellowish oil that was subjected to flash chromatography on silica gel (2:3 hexanes/EtOAc) to afford **29** (1.50 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.76 (m, 4H, ArH), 7.54–7.41 (m, 3H, ArH), 5.25–5.10 (m, 1H), 5.10–5.00 (m, 2H), 4.85–4.78 (m, 2H), 4.20–4.10 (m, 1H), 4.05–3.96 (m, 1H), 3.80–3.65 (m, 1H), 3.50 (m, 1H); ^{13}C NMR (100.6 MHz, $CDOD_3$) δ 158.6, 135.2, 133.7, 131.8, 128.0, 127.6, 127.5, 127.3, 127.0, 126.0, 125, 99.1(C-1), 97.2 (C-3), 83.1 (C-6, J=174.8 Hz), 76.2 (C-2), 74.2 (C-5, J=18.1 Hz), 70.4 (C-4, J=7.2 Hz), 69.5; Anal. Calcd for $C_{20}H_{20}O_6NF$: C, 61.69; H, 5.18; N, 3.60; F, 4.88. Found: C, 61.73; H, 5.14; N, 3.67; F, 4.83.

4.28. 2-Naphthylmethyl 2-acetamido-2,4,6-trideoxy-3,4-di-*O*-acetyl-6-fluoro-β-D-glucopyranoside (30)

Sodium hydroxide (2 mL, 1 M) was added to a stirred solution of oxazolidinone **29** (1 g, 2.60 mmol) in THF (10 mL) at rt. The reaction mixture was stirred for 3 h, poured into H_2O (100 mL), and extracted with ethyl acetate (3×50 mL). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated in *vacuo*. The residue was crystallized from Et_2O to give free amine, which was treated with acetic anhydride (5 mL) and dry pyridine (10 mL) in the presence of a cat. amount of DMAP (5 mg) overnight at rt. After overnight stirring, the reaction mixture was concentrated and chromatographed on silica gel with hexanes/EtOAc (2:1) to give a pure compound **30** as a syrup (1.06 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.75 (m, 4H, ArH), 7.53–7.40 (m, 3H, ArH), 5.45–5.42 (m, 1H), 5.25–5.22 (m, 1H), 5.10–5.00 (m, 2H), 4.80–4.68 (m, 2H), 4.58–4.4 (m, 2H), 4.00–3.96 (m, 1H), 3.80–3.65 (m, 1H), 2.05 (s, 3H, Ac), 2.04 (s, 3H, OCH_3), 1.98 (s, 3H, OCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.8 (C=O), 135.5, 134.6, 128.6, 128.4, 128.0, 127.9, 127.2, 98.7, 81.1 (d, $^1J_{C-F}$=174.9 Hz), 72.3 (d, $^2J_{C-F}$=18.2 Hz), 71.8, 67.8 (d, $^3J_{C-F}$=7.3 Hz), 54.1, 21.5 (OCH_3), 19.5 (OCH_3). Anal. Calcd for $C_{23}H_{26}O_7NF$: C, 61.74; H, 5.86; N, 3.13; F, 4.25. Found: C, 61.71; H, 5.90; N, 3.16; F, 4.28.

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