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ABSTRACT

Sialic acid derivatives, analogs, and their conjugates are expected to be pharmaceutical candidates such as anti-influenza drugs and also useful probes for investigating the biological role of glycoconjugates. Derivatives of 3-fluorinated sialic acid (3-F-Sia) have been found to be excellent probes in investigating functions and mechanisms of a series of proteins. Here, we describe the syntheses of 3-F-Sia derivatives, which are useful in making biologically important conjugate probes. A practical method for the construction of 3-fluorinated sialosides based on the stereoselective formation of the corresponding anomeric O-trimethylsilyl ether and their nucleophilic attack by an alkyl halide, an allyl halide in particular, was developed. In addition, details of the synthesis of cytidine monophosphate (CMP)-3-F-Sia bearing a fluorescent tag, which has been proven to show dual functions as a substrate of CMP-sialic acid transporter (CST) and an inhibitor of sialyltransferase (STase), are described.

1. Introduction

Sialic acid, a member of the carbohydrate family, is often found in glycoproteins and glycolipids, some of which are known to be involved in important biological functions such as tumor metastasis, immune response, infection, and brain function. In fact, the analogs and derivatives of sialic acid have been shown to be potent inhibitors of influenza virus sialidase, and they are commercially available.[1,2] Moreover, sialic acid derivatives exhibiting immunoregulatory activity have been reported.[3] Given the important functions of a glycan-bearing sialic acid, its derivatives and analogs are expected to become valuable tools for investigating the biological roles of glycoconjugates.

3-Fluorinated sialic acid (3-F-Sia) is one of the simplest analogs,[4] whose glycoside is known to be resistant to both acidic hydrolysis and sialidase-catalyzed hydrolysis.[5] It is expected that introducing a fluorine atom at a particular position of α- and β-glycosides may stabilize the glycosidic linkage owing to the destabilization of the oxocarbenium intermediate formed during the hydrolysis reaction. For instance, the *p*-nitrophenyl α-glycoside of 3-F-Sia was reported to be an inhibitor of sialidase.[5] Furthermore, it was reported that an alkyl α-glycoside of 3-F-Sia bearing distearoylphosphatidylethanolamine inhibited influenza sialidase and hemagglutinin.[6]

The corresponding cytidine monophosphate (CMP)-sialic acid analog was found to be an inhibitor of sialyltransferase (STase).[7–9] These facts suggest that 3-F-Sia derivatives are promising modulators of important biological events in which sialic-acid-related enzymes are involved. In this respect, several groups have recently reported interesting results using 3-F-Sia derivatives.[10–12] CMP-sialic acid is synthesized in the nucleus unlike other sugar nucleotides, and it is transported through the nuclear pore to the cytoplasm and then into the Golgi apparatus via the CMP-sialic acid transporter (CST); however, the mechanisms of these events are not understood.[13] We expect that a chemical probe based on the structure of CMP-sialic acid would be a valuable tool for live-cell imaging owing to the advantage of its specific ability to be transported into Golgi vesicles. In this respect, a fluorescently tagged CMP-sialic acid derivative has been used previously to study the synthesis of sialylated glycosphingolipids.[14] The presence of a fluorine atom at the C-3 position of sialic acid was assumed to be tolerated by the CST because it mainly recognizes the nucleoside part of CMP-sialic acid.[15] A fluorescently labeled CMP-3″-F-Sia derivative (**1**) is, therefore, effective in visualizing Golgi vesicles, by virtue of selective transportation by the CST while inhibiting sialylation (Fig. 1). On the basis of these considerations, we reported

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the synthesis of a fluorescently tagged CMP-sialic acid analog **1** in which the C-3 position is fluorinated.[16] 4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) was selected as a fluorophore because it is uncharged, thereby minimizing the risk of interactions with amino acid side chains within the CST channel.

In this study, we describe the details of stereoselective syntheses of allyl glycosides of α- and β-3-F-Sia analogs. Stereoselective trimethylsilylation of an intermediate, a 2-hydroxy compound, is of central importance in this study. The 2-hydroxy compound is also used for the synthesis of a CMP-sialic acid analog bearing a fluorescent reporter functionality.

2. Results and discussion

We planned to synthesize compound **1**, which consisted of a CMP-β-3′′-F-Sia moiety, a fluorescent tag, and a linker. For the synthesis of **1**, a suitably protected 3-F-Sia was needed, in which the hydroxyl group at C-2 could act as the site of phosphorylation and the amino group at C-5 could be used to attach the fluorophore via a linker.

2.1. Preparation of 3-fluorinated sialic acid

A scaffold, 3-F-Sia, has been synthesized from a 2,3-ene compound using the electrophilic reagent Selectfluor™.[7] We found that the reaction was applicable to various substrates regardless of the presence of protecting groups. It was also found that the incorporation of the azide functionality instead of the acetamido group was tolerated. The reaction of benzyl-protected compound **2**[17] proceeded more smoothly than that of the corresponding tetraacetate to give **3** (69%) and **4** (24%) (Fig. 2). The stereoselectivity of fluorination at the C-3 position was nearly identical with that observed for the acetyl-protected counterpart.[3] The $^3J_{H\text{-}3,H\text{-}4}$ values observed for **3** (2.1 Hz) and **4** (9.0 Hz) supported the stereochemistry at the C-3 positions of individual compounds. Subsequent hydrogenolysis of the benzyl groups in compound **3** gave **5** (quant). On the other hand, **6**,[18] which does not contain any protecting groups on the hydroxyl groups, underwent fluorination under similar conditions to directly afford **5** in good yield (73%) with slightly improved selectivity, accompanied by its C-3 epimer **7** (18%). The acetamido group of **5** was removed using methanesulfonic acid in MeOH at 60 °C, and the liberated amine was subjected to diazo transfer reaction,[19,20] followed by acetylation to give **8** (58%). Selective removal of the anomeric acetate was found to be slow possibly due to the electron-withdrawing nature of the adjacent fluorine atom. This problem was overcome by hydrolyzing the methyl ester first to increase the electron density at the anomeric position. Thus, treatment of **8** with lithium iodide in pyridine[21] liberated carboxylic acid. Following this, the intermediate was first treated with hydrazine acetate and then with trimethylsilyldiazomethane to give **9** in good yield. Compound **9** having an azide functionality at the C-5 position is a useful precursor for various transformations; it should be emphasized that compound **9** was also obtained directly by the reaction of the 2,3-ene compound **10**[22] with Selectfluor, accompanied by its C-3 epimer **11**. In this manner, multi-step deprotection of anomeric acetate was no longer required.

2.2. Stereoselective synthesis of 3-fluorinated sialosides

Using benzyl-protected compound **3**, we investigated its application in the synthesis of allyl glycosides, which can easily be transformed into various conjugates. 3-Fluorinated sialosides have been shown to be resistant to hydrolysis, as mentioned in the introduction.[5] This suggests that the linkage between the anomeric position and the 'leaving group' of 3-F-Sia is stable, which was demonstrated in the study of the inhibitory activity of CMP-3-F-Sia.[7–9] This would be a serious problem in glycosylation using alcohols as the nucleophile despite the potential usefulness of the conjugates of 3-F-Sia, and this problem prompted us to find some other methods to synthesize conjugates of 3-F-Sia. We attempted to use the anomeric O-trimethylsilyl (TMS) ether intermediates. If the α- and β-O-TMS ethers are synthesized stereospecifically, the corresponding glycosides may be obtained by O-alkylation at the anomeric oxygen. Thus, the reaction of **3** and a bulky diethylaminotrimethylsilane (Et_2NTMS) was investigated and was found to preferentially give the α-O-TMS ether **12**α, whereas the reaction carried out in the presence of K_2CO_3 afforded the β-O-TMS ether **12**β (Scheme 1). Although more detailed investigations are required for a valid discussion, below, we consider a possible reason for the dramatic change in the outcome of α- and β-O-TMS ether formation. It has been reported that, in general, O-alkylation of anomeric glycosyl alkoxides of aldoses preferentially affords equatorial glycosides.[23] An explanation for this selectivity involves a rapid equilibrium between the axial and equatorial alkoxides with the enhanced nucleophilicity of the equatorial alkoxide based on the kinetic anomeric effect or the β-effect.[23–25] This effect was utilized for the synthesis of 2-deoxy-β-glycosides.[26] However, the applicability of this approach to sialic acid derivatives has not been clarified. In the case of sialic acid derivatives, it is necessary to consider the presence of the carboxyl group, often protected as a methyl ester, at a position opposite to the anomeric alkoxide. In addition, the effect of the fluorine atom at the adjacent C-3 position, in this particular case, cannot be ignored. In fact, the alkoxide of **3** was not suitable for the formation of the equatorial O-TMS derivative **12**α. We considered that K_2CO_3 might easily access the anomeric hydroxyl group, thus generating alkoxides with an axial preference. We believe that this axial orientation of the alkoxide antiperiplanar to the C-3 axial fluorine atom may be favored because of dipole moment geometry. In the absence of K_2CO_3, Et_2NTMS acts as a base for the deprotonation of the anomeric hydroxyl group. Simultaneously, the TMS group migrates from Et_2NTMS to the anomeric oxygen. The reagent Et_2NTMS might have better access to the

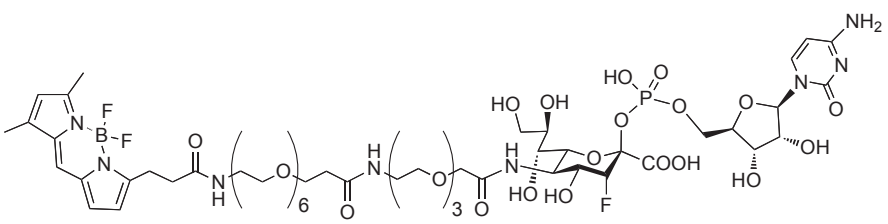

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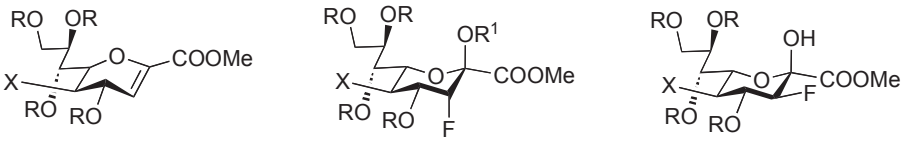
Fig. 1. Structure of compound **1**.



2: X = NHAc, R = Bn
6: X = NHAc, R = H
10: X = N_3, R = Ac

3: X = NHAc, R = Bn, R^1 = H
5: X = NHAc, R = H, R^1 = H
8: X = N_3, R = R^1 = Ac
9: X = N_3, R = Ac, R^1 = H

4: X = NHAc, R = Bn
7: X = NHAc, R = H
11: X = N_3, R = Ac

Fig. 2. Structures of compound **2**–**11**.

equatorial OH than the axial OH because of two 1,3-diaxial interactions.

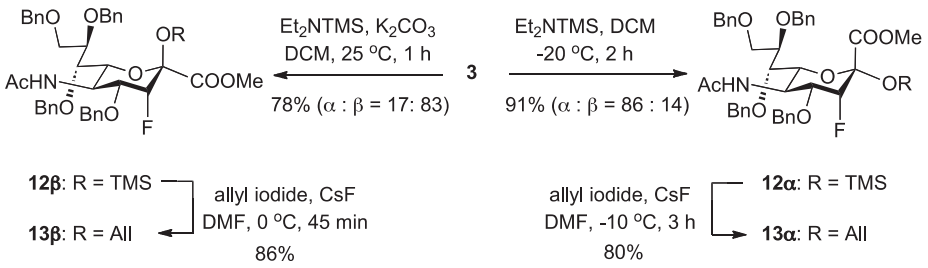
When 2-silyloxy-3-fluoro compounds **12**α and **12**β were treated with allyl iodide in the presence of cesium fluoride, they were successfully converted into the corresponding glycosides **13**α and **13**β, respectively, with retention of anomeric stereochemistry. The stereochemistry of 3-F-Sia can be estimated by the three-bond coupling of C-1—C-2—C-3—F-3 (axial) in ^{13}C NMR where the β-glycoside shows a small coupling constant ($J_{C1,F} \approx 0$).[4] In this study, it was shown that the above-mentioned three-bond coupling could be applied to **14**α ($J_{C1,F}$=3.7 Hz) and **14**β ($J_{C1,F}$=0 Hz) after removing all protecting groups (Fig. 3). It might also be possible to estimate the anomeric configuration of the type of compounds using the chemical shifts of H-4 and H-6 from the analogy that signals of hexose in α-glycosides shift downfield (ca. 0.3 ppm), caused by the axially oriented oxygen atom.[27] This was clearly observed for **14**α (δ 3.76, H-4 and 3.66 ppm, H-6) and **14**β (δ 4.06, H-4 and 3.92 ppm, H-6); thus, the concept was applied to assign other compounds. Although we did not attempt to synthesize other types of glycosides, we thought that the incorporation of allyl glycosides at the anomeric position was reasonable because they are useful in obtaining a variety of conjugates by routine transformations.[28–32] This two-step construction is considered to be practical for the synthesis of conjugates of 3-F-Sia.

2.3. Synthesis of fluorescently tagged CMP-3″-fluoro sialic acid

To expand the scope of the stereospecific synthesis of sialic acid derivatives and the utility of 3-F-Sia, we used compound **9**, which bears a 2-axial hydroxyl group, in the synthesis of a useful probe molecule **1**, which has been shown to be a substrate of the CST and an inhibitor of STase.[16] (Scheme 2) The amino compound **15**, obtained from the reduction of the azido group of **9** using Lindlar catalyst, was coupled with a bifunctional linker **16** using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM)[33] as a coupling reagent to give **17**. It was observed that the reactivity of the amino group was probably reduced because of the electronic effect of the fluorine atom at C-3. The conversion of **17** to a protected CMP-sialic acid derivative **19** was achieved according to an established procedure.[34] It was considered that the axial hydroxyl group in **17** could be directly used in phosphite formation with stereoretention under mild acidic conditions, as it has been reported that similar compounds could be obtained.[7] Thus, **17** was treated with 2-cyanoethyl 2′,3′-O,N^4-triacetylcytidine-5′-yl N,N-diisopropyl phosphoramidite **18** to give a phosphite, which was subsequently oxidized to a phosphate **19** using *t*-BuOOH. The lack of a detectable three-bond coupling constant (F-3″—C-3″—C-2″—C-1″) after the removal of the ester protecting groups indicated that the anomeric configuration of **20** was a β-configuration. In contrast, the *trans*-oriented isomer, which has an α-configuration, exhibits a coupling constant of 5—10 Hz.[4,35] Compound **21**, obtained by the reduction of **20** using Lindlar catalyst, was subjected to a coupling reaction using the succinimidyl ester of BODIPY C-3-tagged hexaethylene glycolyl propionic acid **22**, prepared from commercially available Fmoc-dPEG$_6$™-acid, to give **1** in excellent yield. It should be noted that the azido group of **20** would be highly versatile for further functionalization.

3. Conclusions

A method for the stereoselective synthesis of allyl α- and β-glycosides of 3-fluorinated sialic acid based on the stereoselective formation of the corresponding O-trimethylsilyl ethers and their nucleophilic substitution by allyl halide was developed. Utilizing a 2-hydroxy intermediate, we also synthesized a fluorescently tagged CMP-3″-fluorinated sialic acid derivative, which has been reported in a previous study to be useful in live imaging of cultured cells.[16] We believe that the chemical transformations including the stereospecific synthesis of allyl α- and β-glycosides described herein contribute to biological investigations.



Scheme 1. Stereoselective formation of α- and β-glycoside of 3-F-Sia.

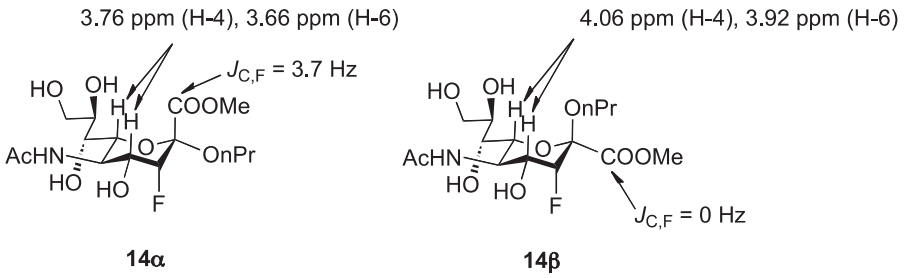


Fig. 3. Structures of compound **14**α and **14**β.

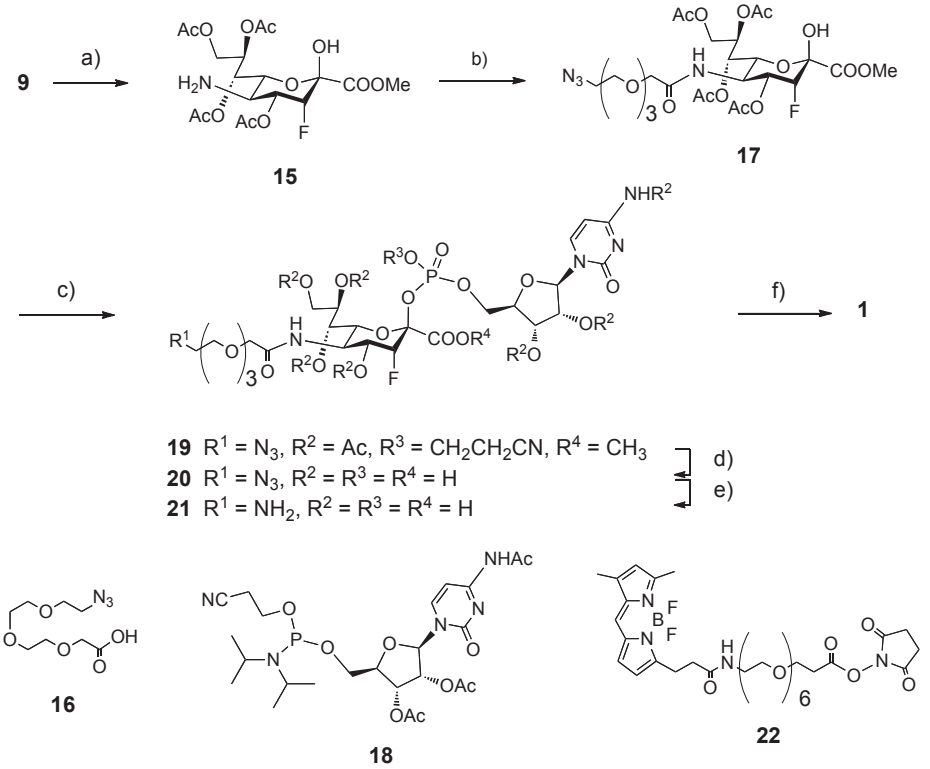
4. Experimental section

4.1. General methods for synthesis

Thin-layer chromatography (TLC) was performed on Merck Art. 5715, Kieselgel 60 F_{254}/0.25 mm thickness plates. Visualization was accomplished with UV light and 1% $Ce(SO_4)_2$—1.5% $(NH_4)_6MoO_{24}\cdot 4H_2O$—10% H_2SO_4 solution or 0.5% ninhydrin *n*-BuOH solution followed by heating. Preparative TLC was performed on Merck Art. 5745, Kieselgel 60 F_{254}/0.50-mm-thick plates. Silica gel column chromatography was conducted on Wakogel C-300 (Wako Pure Chemical Industries, Ltd.). Gel permeation chromatography was performed using Sephadex LH-20 or G-25 (Pharmacia Fine Chemicals). Optical rotation were measured in a 1.0 dm tube with a Horiba SPEA-200 polarimeter. Melting points were measured with Yanaco MP-S3 micro melting point apparatus. ^{1}H NMR (500 MHz) spectra were recorded with an AVANCE 500 spectrometer (Bruker Biospin Inc.) in deuterated solvent using Me_4Si (0.00 ppm) or the solvent peak (HDO: 4.79 ppm or CD_3OD: 3.31 ppm) as the internal standard. ^{13}C NMR (125 MHz) spectra were recorded with the same spectrometer using Me_4Si (0.00 ppm) or the solvent peak ($CDCl_3$; 77.0 ppm or CD_3OD; 49.0 ppm) as the internal standard. High resolution mass spectra (HRMS) were obtained on a LCMS—IT—TOF coupled with ESI interface (ion-trap TOF mass spectrometer with reflectron) (Shimadzu Corp.) or a tandem mass spectrometer (Synapt G2; Waters Corp.) using sodium trifluoroacetate as an external standard for instrument adjustment. {2-[2-(2-Azido-ethoxy)-ethoxy]-ethoxy}-acetic acid was purchased from Tokyo Chemical Industry Co. Ltd. Fmoc-dPEG$_6$™ acid was purchased from Quanta BioDesign, Ltd. BODIPY-FL SE™ was purchased from Molecular Probes Inc.

4.2. Methyl 5-acetamido-4,7,8,9-tetra-O-benzyl-5-deoxy-3-fluoro-D-erythro-L-manno-2-nonulopyranosonate (3) and methyl 5-acetamido-4,7,8,9-tetra-O-benzyl-5-deoxy-3-fluoro-D-erythro-L-gluco-2-nonulopyranosonate (**4**)

The mixture of compound **2**[17] (1.02 g, 1.5 mmol), Selectfluor™ (2.17 g, 6.1 mmol) and H_2O (4.5 mL) in DMF (13.5 mL) was stirred for 1.5 h at 60 °C. After cooling, the mixture was diluted with EtOAc,



Scheme 2. Synthesis of compound **1**. Reagent and conditions: a) H_2, Lindlar catalyst, 1,4-dioxane, quant; b) **16**, DMT-MM, THF, 55%; c) 1: **18**, 1*H*-tetrazole, MeCN, −20 °C; 2: *t*-BuOOH in decane, MeCN, 99%; d) DBU, THF then NaOMe, MeOH, H_2O, 50%; e) H_2, Lindlar catalyst, H_2O, quant; f) **22**, MeOH, H_2O, quant.

washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was applied on silica-gel column chromatography (3:2, *n*-hexane–EtOAc) to afford compound **3** (739 mg, 69%) and compound **4** (260 mg, 24%), respectively. Compound **3**; $[\alpha]_D^{25}$ −9.2° (*c* 1.44, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.37–7.21 (m, 20H, Ph), 4.88 (dd, 1H, $J_{3,4}$ 2.1 Hz, $J_{3,F}$ 50.0 Hz, H-3), 4.73 (d, 1H, *J* 11.8 Hz, benzyl), 4.64 (d, 1H, *J* 11.8 Hz, benzyl), 4.64 (s, 2H, benzyl), 4.59 (s, 2H, benzyl), 4.55 (d, 1H, *J* 11.8 Hz, benzyl), 4.51 (d, 1H, *J* 10.9 Hz, H-6), 4.43 (d, 1H, *J* 11.8 Hz, benzyl), 4.40 (ddd, 1H, $J_{4,5}$ 10.7 Hz, $J_{4,F}$ 28.9 Hz, H-4), 4.00 (dd, 1H, $J_{8,9a}$ 2.2 Hz, $J_{9a,9b}$ 10.8 Hz, H-9a), 3.93 (ddd, 1H, $J_{7,8}$ 6.6 Hz, $J_{8,9b}$ 4.5 Hz, H-8), 3.85–3.79 (m, 2H, H-5,7), 3.77 (s, 3H, OCH_3), 3.72 (dd, 1H, H-9b), 2.04 (s, 3H, NHAc); ^{13}C NMR ($CDCl_3$): δ 171.29, 170.55, 168.47, 138.61, 138.30, 138.08, 137.87, 129.38, 128.53, 128.46, 128.44, 128.24, 127.99, 127.97, 127.90, 127.76, 94.23 (d, *J* 24.7 Hz, C-2), 86.07 (d, *J* 184.1 Hz, C-3), 78.47 (C-8), 73.76 (C-7), 73.47 (d, *J* 17.5 Hz, C-4), 73.46, 72.70, 72.37, 71.69, 70.09 (C-6), 69.48 (C-9), 53.26 (OCH_3), 48.66 (C-5), 23.60 ($COCH_3$); ESIMS *m*/*z* calcd for $[C_{40}H_{44}FNO_9+Na]^+$; 724.2892, found 724.2898. Compound **4**; $[\alpha]_D^{25}$ −17.7° (*c* 0.69, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.38–7.27 (m, 20H, Ph), 4.89 (dd, 1H, $J_{3,4}$ 9.0 Hz, $J_{3,F}$ 49.7 Hz, H-3), 4.86 (d, 1H, *J* 11.8 Hz, benzyl), 4.77 (d, 1H, $J_{5,NH}$ 9.5 Hz, N*H*), 4.67 (d, 1H, *J* 10.6 Hz, benzyl), 4.65 (d, 1H, *J* 11.3, Hz, benzyl), 4.58 (d, 1H, *J* 12.0 Hz, benzyl), 4.55 (d, 2H, *J* 11.4 Hz, benzyl), 4.44 (d, 2H, *J* 11.0 Hz, benzyl), 4.32 (d, 1H, $J_{5,6}$ 10.9 Hz, H-6), 4.18 (q, 1H, $J_{4,5}$ 10.1 Hz, H-5), 3.96 (dt, 1H, $J_{4,F}$ 11.9 Hz, H-4), 3.85 (s, 3H, OCH_3), 3.78–3.69 (m, 3H, H-7,8,9a), 3.64 (dd, 1H, $J_{8,9b}$ 3.0 Hz, $J_{9a,9b}$ 10.6 Hz, H-9b), 2.05 (s, 3H, NHAc). ^{13}C NMR ($CDCl_3$): δ 169.92, 168.76, 138.11, 138.05, 138.03, 137.91, 129.04, 128.86, 128.58, 128.51, 128.44, 128.38, 128.35, 128.33, 128.29, 128.23, 128.17, 128.11, 128.02, 127.92, 127.82, 127.79, 127.74, 93.52 (d, *J* 21.3 Hz, C-2), 91.37 (d, *J* 191.94, C-3), 76.71, 74.38, 74.32, 74.19, 74.16, 73.44, 72.34, 70.15, 67.77, 54.04, 50.30 (d, *J* 7.5 Hz, C-5), 23.74; ESIMS *m*/*z* calcd for $[C_{40}H_{44}FNO_9+Na]^+$; 724.2892, found 724.2905.

4.3. Methyl 5-acetamido-5-deoxy-3-fluoro-D-erythro-L-manno-2-nonulopyranosonate (5) and methyl 5-acetamido-5-acetamido-5-deoxy-3-fluoro-D-erythro-L-gluco-2-nonulopyranosonate (**7**)

The mixture of compound **6** (5.5 mg, 18×10^{-6} mol), Selectfluor™ (9.6 mg, 27×10^{-6} mol) and H_2O (0.2 mL) was stirred for 4 h at 40 °C. After removal of the solvent, the residue was applied on silica-gel column chromatography (5:1, 3:1, DCM–MeOH) to afford compound **5**[4] (4.5 mg, 74%) and compound **7**[4] (1.1 mg, 18%), respectively. Compound **5** from **3**; To a MeOH (100 mL) solution of compound **3** (3.98 g, 5.67 mmol) was added $Pd(OH)_2$ (20% on carbon, ca. 50 mg) and aq HCl (1 M, 1 mL). The mixture was stirred for 5 h at room temperature under hydrogen atmosphere. After filtration, the filtrate was concentrated and the product was purified by silica gel column chromatography (65:25:4, $CHCl_3$–MeOH–H_2O) to afford compound **5** (1.94 g, quant).

4.4. Methyl 2,4,7,8,9-Penta-O-acetyl-5-azido-5-deoxy-3-fluoro-β-D-erythro-L-manno-2-nonulopyranosonate (**8**)

The mixture of compound **5** (0.86 g, 2.54 mmol) and MsOH (1 mL) in MeOH (25 mL) was stirred for 60 h at 60 °C. After cooling to room temperature, the solution was adjusted to pH 5–6 with AcONa and concentrated in vacuo. To the residue was added MeOH (17.8 mL), H_2O (8.7 mL), K_2CO_3 (0.45 g, 3.30 mmol), $CuSO_4\cdot5H_2O$ (6.9 mg, 0.25 mmol) and TfN_3 (0.4 M solution in DCM, 13.6 mL, 5.59 mmol) at room temperature. After being stirred for 18 h, the solution was concentrated in vacuo. The residue was purified with silica gel column chromatography (65:25:4, $CHCl_3$–MeOH–H_2O) to afford a corresponding 5-azido derivative (ca. 0.82 g, 99%). To the pyridine (25 mL) solution of 5-azido derivative (ca. 0.82 g) was added Ac_2O (1.1 mL) and 4-di(methylamino)pyridine (ca. 30 mg). After being stirred for 12 h at room temperature, the mixture was concentrated with additional MeOH. The residue was poured into satd $NaHCO_3$ and diluted extracted with $CHCl_3$ for three times. The organic layer was washed with H_2O, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified with silica gel column chromatography (2:1, *n*-hexane–EtOAc) to afford compound **8** (0.77 g, 58%). $[\alpha]_D^{26}$ −42.1° (*c* 0.63, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.51 (dd, 1H, $J_{6,7}$ 1.2 Hz, $J_{7,8}$ 6.7 Hz, H-7), 6.26–5.23 (m, 1H, H-8), 5.21 (ddd, 1H, $J_{3,4}$ 2.5 Hz, $J_{4,5}$ 9.5 Hz, $J_{4,F}$ 27.3 Hz, H-4), 4.97 (dd, 1H, $J_{3,F}$ 48.9 Hz, H-3), 4.47 (dd, 1H, $J_{8,9a}$ 2.3 Hz, $J_{9a,9b}$ 12.6 Hz, H-9a), 4.23 (dd, 1H, $J_{8,9b}$ 5.5 Hz, H-9b), 3.83 (s, 3H, OCH_3), 3.73–3.66 (m, 2H, H-5,6), 2.21, 2.21, 2.16, 2.06, 2.05 (each s, 15H, OAc). ^{13}C NMR ($CDCl_3$): δ 170.63, 170.11, 169.71, 166.98, 164.72, 94.85 (d, $J_{2,F}$ 28.5 Hz, C-2), 86.33 (d, $J_{3,F}$ 184.5 Hz, C-3), 71.57, 71.14 (d, $J_{4,F}$ 16.9 Hz, C-4), 70.11, 68.15, 61.87, 55.68, 53.52, 20.83, 20.76, 20.72, 20.67, 20.53. HRMS (ESI) *m*/*z* calcd for $[C_{20}H_{26}FN_3O_{13}+Na]^+$; 558.1342, found 558.1333.

4.5. Methyl 4,7,8,9-tetra-O-acetyl-2,6-anhydro-5-azido-2,3,5-trydeoxy-D-glycero-D-galacto-2-enoate (**10**)

The mixture of methyl (methyl 4,7,8,9-tetra-O-acetyl-5-azido-3,5-dideoxy-2-thio-D-*glycero*-D-*galacto*-non-2-ulopyranosid) onate[22] (0.50 g, 0.99 mmol), BSP (0.41 g, 1.98 mmol), TTBP (0.98 g, 3.96 mmol) and MS3A (ca. 1.5 g) in DCM (7 mL) was stirred for 1 h at room temperature. After cooling to −60 °C, to the solution was added Tf_2O (0.37 mL, 2.18 mmol) in DCM (3 mL). After being stirred for 1 h, the solution was poured into std. $NaHCO_3$ and the product was extracted with $CHCl_3$ for three times. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified with silica gel column chromatography (3:1, 3:2, *n*-hexaneEtOAc) to afford compound **10** (0.44 g, quant). $[\alpha]_D^{26}$ +47.6° (*c* 1.16, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.92 (br s, 1H, H-3), 5.56 (d, 1H, $J_{7,8}$ 6.4 Hz, H-7), 5.52 (br d, $J_{4,5}$ 9.0 Hz, 1H, H-4), 5.32 (br t, 1H, $J_{8,9b}$ 5.8 Hz, H-8), 4.51 (br d, 1H, $J_{9a,9b}$ 12.5 Hz, H-9a), 4.16 (dd, 1H, H-9b), 4.03 (d, 1H, $J_{5,6}$ 10.5 Hz, H-6), 3.75 (s, 3H, OCH_3), 3.63 (t, 1H, H-5), 2.14, 2.10, 2.04, 2.03 (each s, 12H, OAc). ^{13}C NMR ($CDCl_3$): δ 170.61, 170.09, 169.71, 169.51, 161.28, 144.87, 107.27 (C-3), 75.23 (C-6), 70.28 (C-4), 69.80 (C-8), 67.94 (C-7), 61.74 (C-9), 57.11 (C-5), 52.59, 20.85, 20.82, 20.72, 20.60. HRMS (ESI) *m*/*z* calcd for $[C_{18}H_{23}N_3O_{11}+Na]^+$; 480.1225, found 480.1237.

4.6. Methyl 4,7,8,9-tetra-O-acetyl-5-azido-5-deoxy-3-fluoro-D-erythro-L-manno-2-nonulopyranosonate (9) and methyl 4,7,8,9-tetra-O-acetyl-5-azido-5-deoxy-3-fluoro-D-erythro-L-gluco-2-nonulopyranosonate (**11**)

Compound **9** and **11** were obtained from **10** in the same manner as describe for **3** and **4** (quant, based on recovered 10% of **10**, compound **9**:**11**=7:3). The ratio was changed to 1:1 by use of H_2O in place of $MeNO_2$–H_2O (3:1) as a solvent (quant). Compound **9**; $[\alpha]_D^{26}$ +13.2° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.52 (dd, 1H, $J_{6,7}$ 1.2 Hz, $J_{7,8}$ 7.2 Hz, H-7), 5.38 (ddd, 1H, $J_{8,9a}$ 2.0 Hz, $J_{8,9b}$ 5.7 Hz, H-8), 5.27 (ddd, 1H, $J_{3,4}$ 2.3 Hz, $J_{4,5}$ 10.1 Hz, $J_{4,F}$ 27.6 Hz, H-4), 4.97 (dd, 1H, $J_{3,F}$ 49.8 Hz, H-3), 4.72 (br s, 1H, O*H*), 4.57 (dd, 1H, $J_{9a,9b}$ 12.6 Hz, H-9a), 4.19 (dd, 1H, H-9b), 3.87 (s, 3H, OCH_3), 3.85 (d, 1H, $J_{5,6}$ 10.4 Hz, H-6), 3.64 (t, 1H, H-5), 2.20, 2.19, 2.11, 2.07 (each s, 12H, OAc). ^{13}C NMR ($CDCl_3$): δ 171.09, 170.59, 170.06, 169.78, 167.27, 94.04 (d, $J_{2,F}$ 25.3 Hz, C-2), 86.30 (d, $J_{3,F}$ 184.5 Hz, C-3), 71.78 (d, $J_{4,F}$ 17.1 Hz, C-4), 70.09, 69.59, 68.25, 62.57, 56.18, 53.48, 20.97, 20.84, 20.78, 20.75, 20.68. HRMS (ESI) *m*/*z* calcd for $[C_{18}H_{24}FN_3O_{12}+Na]^+$; 516.1236, found 516.1227. Compound **11**; $[\alpha]_D^{26}$ −32.0° (*c* 1.13, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.54 (dt, 1H, $J_{3,4}$ 6.2 Hz, $J_{4,5}$ 10.2 Hz, H-4), 5.44 (d, 1H, $J_{7,8}$ 8.5 Hz, H-7), 5.25 (ddd, 1H, $J_{8,9a}$ 2.1 Hz, $J_{8,9b}$ 5.0 Hz, H-8), 4.75 (dd, 1H, $J_{3,F}$ 46.0 Hz, H-3), 4.25 (dd, 1H, $J_{9a,9b}$ 12.6 Hz, H-9a), 4.13 (dd, 1H, H-9b), 3.91 (d, 1H, $J_{5,6}$ 10.2 Hz, H-6), 3.90 (s, 3H, OCH_3), 3.334 (t, 1H,

H-5), 2.16, 2.15, 2.08, 2.04 (each s, 12H, OAc). ^{13}C NMR ($CDCl_3$): δ 170.77, 169.95, 169.80, 169.50, 167.19, 93.48 (d, $J_{2,F}$ 21.6 Hz, C-2), 87.36 (d, $J_{3,F}$ 197.6 Hz, C-3), 71.60 (d, $J_{4,F}$ 18.8 Hz, C-4), 68.76 (C-6), 68.61 (C-8), 67.52 (C-7), 61.99 (C-9), 59.85 (d, $J_{5,F}$ 6.3 Hz, C-5), 54.22, 20.85, 20.80, 20.72, 20.69. HRMS (ESI) *m*/*z* calcd for $[C_{18}H_{24}FN_3O_{12}+NH_4]^+$; 511.1682, found 511.1705. Compound **9** from **8**; To a pyridine (6.0 mL) solution of lithium iodide (0.78 g, 5.75 mmol) was added compound **8** (0.77 g, 1.44 mmol), and the mixture was stirred for 3 h at 110 °C. After cooling, the reaction was stopped with aq HCl (1 M) and the product was extracted with $CHCl_3$ for three times. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified with silica gel column chromatography (1:1–2:3, *n*-hexane–acetone) to afford 2-OAc-COOH derivative (0.44 g, 59%). To a DMF (5.6 mL) solution of 2-OAc-COOH derivative (0.44 g, 0.84 mmol) was added hydrazine acetate (0.11 g, 1.27 mmol). After being stirred for 8 h at room temperature, the mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was applied on gel-filtration column (LH-20, MeOH) to afford 2-OH-COOH derivative (0.37 g, 92%). To a benzene–CH_3OH (3:1, 7.2 mL) solution of 2-OH-COOH derivative (0.74 g, 1.54 mmol) was added (trimethylsilyl)diazomethane (2.0 M solution in n-hexane, 1.7 mL) at 0 °C. After being stirred for 30 min at room temperature, the reaction mixture was concentrated in vacuo. The residue was purified with silica gel column chromatography (2:1, 1:1, *n*-hexane–acetone) to afford compound **9** (0.68 g, 89%).

*4.7. Methyl 5-acetamido-4,7,8,9-tetra-O-benzyl-5-deoxy-3-fluoro-2-O-trimethylsilyl-α-D-erythro-L-manno-2-nonulopyranosonate (12α) and methyl 5-acetamido-4,7,8,9-tetra-O-benzyl-5-deoxy-3-fluoro-β-D-erythro-L-manno-2-nonulopyranosonate (**12**β)*

2-O-Silylation in the absence of K_2CO_3; To a DCM (1.0 mL) solution of compound **3** (55 mg, 0.08 mmol) was added $TMSNEt_2$ (0.15 mL, 0.8 mmol) at −20 °C, and the mixture was stirred for 1 h under nitrogen atmosphere. To the mixture was added $TMSNEt_2$ (0.15 mL, 0.8 mmol) again. After being stirred for 1 h, the mixture was poured into a cold aq HCl (0.01 M), and the products were extracted with DCM. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel chromatography (4:1, 1:1, *n*-hexane–EtOAc) to afford **12**α (47 mg, 78%) and a less polar **12**β (8 mg, 13%). 2-O-Silylation in the presence of K_2CO_3; To a DCM (2.0 mL) solution of compound **3** (28.7 mg, 0.04 mmol) was added K_2CO_3 (24.9 mg, 0.18 mmol) and $TMSNEt_2$ (39×10^{-6} L, 0.20 mmol) at 0 °C, and the mixture was stirred for 1.5 h under nitrogen atmosphere. To the mixture was added $TMSNEt_2$ (20×10^{-6} L, 0.10 mmol) again and stirred for 30 min. After filtration, the filtrate was poured into a water, and the products were extracted with DCM. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel chromatography (4:1, 1:1, *n*-hexane–EtOAc) to afford **12**α (4.2 mg, 13%) and **12**β (20.7 mg, 65%). Compound **12**α; $[\alpha]_D^{22}$ +7.0° (*c* 0.89, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.37–7.20 (m, 20H, Ph), 5.02 (dd, 1H, $J_{3,4}$ 1.5 Hz, $J_{3,F}$ 49.8 Hz, H-3), 4.72 (d, 1H, *J* 11.0 Hz, benzyl), 4.70 (d, 1H, *J* 11.1 Hz, benzyl), 4.67 (s, 2H, benzyl), 4.60 (d, 1H, *J* 11.4 Hz, benzyl), 4.56 (d, 1H, *J* 12.1 Hz, benzyl), 4.51 (d, 1H, *J* 11.5 Hz, benzyl), 4.51 (d, 1H, N*H*), 4.49 (d, 1H, *J* 11.7 Hz, benzyl), 4.07–3.94 (m, 4H, H-4,5,6,8), 3.79 (dd, 1H, $J_{8,9a}$ 2.2 Hz, $J_{9a,9b}$ 10.8 Hz, H-9a), 3.72 (d, 1H, $J_{7,8}$ 8.7 Hz, H-7), 3.67 (dd, 1H, $J_{8,9b}$ 3.4 Hz, H-9b), 3.58 (s, 3H, OCH_3), 1.77 (s, 3H, NHAc), 0.18 (s, 9H, $SiMe_3$); ^{13}C NMR ($CDCl_3$): δ 170.26, 168.47, 138.73, 138.59, 138.08, 137.72, 128.41, 128.33, 128.31, 128.27, 128.16, 128.14, 127.94, 127.92, 127.64, 127.62, 127.44, 127.40, 96.66 (d, *J* 17.3 Hz, C-2), 86.95 (d, *J* 187.5 Hz, C-3), 77.68 (C-8), 74.46 (C-7), 74.42 (d, *J* 18.9 Hz, C-4), 73.65, 73.30, 72.20, 71.08, 68.04 (C-9), 52.44 (OCH_3), 47.40 (C-5), 23.74 ($COCH_3$), 1.65 ($SiMe_3$). HRMS (ESI) *m*/*z* calcd for $[C_{43}H_{52}FNO_9Si+Na]^+$; 796.3288, found 796.3293. Compound **12**β; $[\alpha]_D^{26}$ −17.7° (*c* 1.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.40–7.21 (m, 20H, Ph), 4.86 (dd, 1H, $J_{3,4}$ 1.9 Hz, $J_{3,F}$ 49.4 Hz, H-3), 4.80 (d, 1H, *J* 11.9 Hz, benzyl), 4.74 (d, 1H, *J* 11.8 Hz, benzyl), 4.73 (ddd, 1H, $J_{4,5}$ 10.8 Hz, $J_{4,F}$ 28.6 Hz, H-4), 4.68 (d, 1H, *J* 11.8 Hz, benzyl), 4.66 (d, 1H, *J* 11.9 Hz, benzyl), 4.61 (d, 1H, *J* 11.6 Hz, benzyl), 4.58 (d, 1H, $J_{5,6}$ 9.7 Hz, H-6), 4.57 (s, 2H, benzyl), 4.49 (d, 1H, *J* 11.6 Hz, benzyl), 4.33 (d, 1H, $J_{5,NH}$ 7.0 Hz, N*H*), 4.18 (dd, 1H, $J_{8,9a}$ 1.9 Hz, $J_{9a,9b}$ 10.7 Hz, H-9a), 3.96 (ddd, 1H, $J_{7,8}$ 5.9 Hz, $J_{8,9b}$ 6.7 Hz, 8-H), 3.85–3.80 (m, 2H, H-7,9b), 3.76 (s, 3H, OCH_3), 3.47 (dt, 1H, H-5), 2.05 (s, 3H, NHAc), 0.08 (s, 9H, $SiMe_3$); ^{13}C NMR ($CDCl_3$): δ 170.68, 167.84, 138.79, 138.62, 138.32, 137.85, 129.75, 128.54, 128.38, 128.30, 128.23, 128.09, 128.01, 127.84, 127.73, 127.62, 127.44, 127.38, 95.49 (d, *J* 27.3 Hz, C-2), 88.06 (d, *J* 184.0 Hz, C-3), 81.03 (C-8), 74.14 (C-7), 73.36, 72.94, 72.11, 71.83, 71.70 (d, *J* 14.8 Hz, C-4), 71.64 (C-9), 70.37 (C-6), 52.78 (OCH_3), 49.70 (C-5), 23.50 ($COCH_3$), 0.58 ($SiMe_3$). HRMS (ESI) *m*/*z* calcd for $[C_{43}H_{52}FNO_9Si+Na]^+$; 796.3288, found 796.3285.

*4.8. Methyl (Allyl 5-acetamido-4,7,8,9-tetra-O-benzyl-5-deoxy-3-fluoro-α-D-erythro-L-manno-2-nonulopyranosid)onate (**13**α)*

To the mixture of CsF (1.99 g, 13.1 mmol) and allyl iodide (5.06 g, 30.1 mmol) in DMF (23 mL) was added a DMF (69 mL) solution of compound **12**α (4.70 g, 6.1 mmol) at −10 °C under nitrogen atmosphere. The mixture was stirred for 3 h, diluted with EtOAc and poured into aq HCl (0.01 M). The organic layer, combined with subsequent extraction from aqueous layer, was washed (0.5 M aq $Na_2S_2O_4$), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (2:1, 1:1, *n*-hexane–EtOAc) to afford **13**α (3.60 g, 80%): $[\alpha]_D^{24}$ −24.1° (*c* 2.27, $CHCl_3$); ^{1}H NMR($CDCl_3$): δ 7.41–7.26 (m, 20H, Ph), 5.86–5.78 (m, 1H, $CH_2CH{=}CH_2$), 5.21 (br d, 1H, *J* 17.2 Hz, $CH_2CH{=}CH_2$), 5.12 (br d, 1H, *J* 10.4 Hz, $CH_2CH{=}CH_2$), 5.05 (dd, 1H, $J_{3,4}$ 1.6 Hz, $J_{3,F}$ 51.6 Hz, H-3), 4.74 (s, 2H, benzyl), 4.73 (d, 1H, *J* 11.6 Hz, benzyl), 4.61 (d, 1H, *J* 11.9 Hz, benzyl), 4.58 (d, 2H, *J* 11.2 Hz, benzyl), 4.56 (d, 1H, *J* 11.7 Hz, benzyl), 4.49 (d, 1H, *J* 12.0 Hz, benzyl), 4.38 (dd, 1H, $J_{5,6}$ 10.6 Hz, $J_{6,7}$ 1.5 Hz, H-6), 4.32–4.29 (m, 1H, $CH_2CH{=}CH_2$), 4.27 (ddd, 1H, $J_{4,5}$ 10.8 Hz, $J_{4,F}$ 28.3 Hz, H-4), 4.12 (d, 1H, $J_{5,NH}$ 7.1 Hz, N*H*), 4.06–4.02 (m, 2H, H-8, $CH_2CH{=}CH_2$), 3.95 (dd, 1H, $J_{8,9a}$ 2.3 Hz, $J_{9a,9b}$ 10.8 Hz, H-9a), 3.77 (dd, 1H, $J_{8,9b}$ 4.9 Hz, H-9b), 3.73 (dd, 1H, $J_{7,8}$ 6.2 Hz, H-7), 3.61 (s, 3H, OCH_3), 3.54 (dt, 1H, H-5), 2.05 (s, 3H, NHAc); ^{13}C NMR($CDCl_3$): δ 170.52, 166.57 (d, *J* 2.9, C-1), 138.78, 13 8.25, 138.19, 137.62, 133.62, 129.54, 128.48, 128.34, 128.29, 128.23, 128.11, 12 7.97, 127.90, 127.80, 127.77, 127.54, 127.39, 117.07, 97.54 (d, *J* 16.4, C-2), 87.24 (d, *J* 190.7, C-3), 78.89, 73.96, 73.36, 72.77, 72.54 (d, *J* 18.4, C-4), 72.21, 71.63, 71.59, 69.72, 65.79, 52.48, 48.74 (d, *J* 4.0, C-5), 23.47. HRMS (ESI) *m*/*z* calcd for $[C_{43}H_{48}FNO_9+Na]^+$; 764.3205, found 764.3198.

*4.9. Methyl (Allyl 5-acetamido-4,7,8,9-tetra-O-benzyl-5-deoxy-3-fluoro-β-D-erythro-L-manno-2-nonulopyranosid)onate (**13**β)*

Compound **13**β was obtained from **12**β in the same manner as describe for **13**α (86%): $[\alpha]_D^{26}$ −22.3° (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.39–7.26 (m, 20H, Ph), 5.72–5.64 (m, 1H, $CH_2CH{=}CH_2$), 5.13 (br d, 1H, *J* 17.2 Hz, $CH_2CH{=}CH_2$), 5.08 (br d, 1H, *J* 10.7 Hz, $CH_2CH{=}CH_2$), 5.05 (dd, 1H, $J_{3,4}$ 2.2 Hz, $J_{3,F}$ 49.4 Hz, H-3), 4.85 (d, 1H, *J* 12.0 Hz, benzyl), 4.75 (d, 1H, *J* 11.8 Hz, benzyl), 4.66 (d, 1H, *J* 11.8 Hz, benzyl), 4.65 (d, 1H, *J* 11.2 Hz, benzyl), 4.63 (d, 1H, *J* 11.5 Hz, benzyl), 4.63 (ddd, 1H, $J_{4,5}$ 10.8 Hz, $J_{4,F}$ 28.4 Hz, H-4), 4.58 (d, 1H, *J* 11.9 Hz, benzyl), 4.55 (d, 1H, *J* 11.9 Hz, benzyl), 4.45 (d, 1H, *J* 11.6 Hz, benzyl), 4.44 (br d, 1H, $J_{5,6}$ 10.1 Hz, H-6), 4.32 (br d, 1H, $J_{5,NH}$ 7.4 Hz, N*H*), 4.16 (dd, 1H, $J_{8,9a}$ 2.6 Hz, $J_{9a,9b}$ 10.8 Hz, H-9a), 4.04–3.98 (m, 2H, H-8, $CH_2CH{=}CH_2$), 3.84–3.71 (m, 3H, H-7,9b, $CH_2CH{=}CH_2$), 3.75 (s, 3H,

OMe), 3.57 (dt, 1H, H-5), 2.05 (s, 3H, NHAc); ^{13}C NMR($CDCl_3$): δ 170.53, 166.39, 138.67, 138.41, 138.26, 137.77, 132.48, 129.67, 128.51, 128.40, 128.31, 128.30, 128.05, 127.92, 127.85, 127.63, 127.53, 127.48, 127.46, 127.38, 117.15, 98.00 (d, *J* 27.3 Hz, C-2), 87.04 (d, *J* 181.1 Hz, C-3), 80.07, 73.49, 73.26, 72.70 (d, *J* 17.4 Hz, C-4), 72.13, 71.96, 71.86, 70.47, 70.44, 64.20, 52.76, 49.30, 23.47. HRMS (ESI) *m*/*z* calcd for $[C_{43}H_{48}FNO_9+Na]^+$; 764.3205, found 764.3215.

4.10. Methyl (n-propyl 5-acetamido-5-deoxy-3-fluoro-α-D-erythro-L-manno-2-nonulopyranosid)onate (**14**α)

To a MeOH (2.0 mL) solution of compound **13**α (9 mg, 0.01 mmol) was added $Pd(OH)_2$ (20% on carbon, ca. 5 mg) and aq HCl (1 M, 0.6 mL). The mixture was stirred for 20 h at room temperature under hydrogen atmosphere. After filtration, the filtrate was concentrated and the product was applied on gel-filtration column (LH-20, MeOH) to afford compound **14**α (6 mg, quant); ^{1}H NMR (CD_3OD): δ 4.97 (dd, 1H, $J_{3,4}$ 2.1 Hz, $J_{3,F}$ 50.9 Hz, H-3), 4.16 (t, 1H, $J_{4,5}$=$J_{5,6}$ 10.6 Hz, H-5), 3.87–3.76 (m, 3H, H-8,9a, CH_2CH$_2$CH$_3$), 3.85 (s, 3H, OCH_3), 3.76 (ddd, 1H, H-4), 3.65–3.62 (m, 2H, H-6,9b), 3.51 (dd, 1H, $J_{6,7}$ 1.4 Hz, $J_{7,8}$ 8.9 Hz, H-7), 3.43–3.41 (m, 1H, CH_2CH$_2$CH$_3$), 1.99 (s, 3H, NHAc), 1.56 (qt, 2H, *J* 6.8 Hz, CH$_2$CH_2CH$_3$), 0.90 (t, 3H, *J* 7.4 Hz, CH$_2$CH_2CH$_3$); ^{13}C NMR (CD_3OD): δ 173.74, 167.78 (d, *J* 3.7 Hz, C-1), 97.97 (d, *J* 16.5 Hz, C-2), 89.58 (d, *J* 188.5 Hz, C-3), 73.31, 70.76, 68.99, 68.80 (d, *J* 11.1 Hz, C-4), 66.10, 63.38, 52.05, 48.11, 48.05, 47.94, 47.88, 47.35, 47.09, 22.51, 21.30, 9.31.

4.11. Methyl (n-propyl 5-acetamido-5-deoxy-3-fluoro-β-D-erythro-L-manno-2-nonulopyranosid)onate (**14**β)

Compound **14**β was obtained from **13**β in the same manner as describe for **14**α (quant.); ^{1}H NMR (CD_3OD): δ 4.82 (dd, 1H, $J_{3,4}$ 2.4 Hz, $J_{3,F}$ 55.0 Hz, H-3), 4.20 (t, 1H, $J_{4,5}$=$J_{5,6}$ 10.5 Hz, H-5), 4.06 (ddd, 1H, $J_{4,F}$ 30.0 Hz, H-4), 3.92 (d, 1H, H-6), 3.86–3.78 (m, 3H, H-8,9a, CH_2CH$_2$CH$_3$), 3.83 (s, 3H, OCH_3), 3.66 (dd, 1H, $J_{8,9b}$ 4.9 Hz, $J_{9a,9b}$ 11.2 Hz, H-9b), 3.51 (d, 1H, $J_{7,8}$ 9.3 Hz, H-7), 3.11 (dt, 1H, *J* 6.3 Hz, *J* 8.6 Hz, CH_2CH$_2$CH$_3$), 1.99 (s, 3H, NHAc), 1.57 (qt, 2H, J 6.8 Hz, CH$_2$CH_2CH$_3$), 0.94 (t, 3H, *J* 7.4 Hz, CH$_2$CH_2CH$_3$); ^{13}C NMR (CD_3OD): δ 173.93, 167.18 (s, C-1), 97.83 (d, *J* 27.1 Hz, C-2), 89.41 (d, *J* 178.1 Hz, C-3), 70.41, 69.47, 68.01, 67.31 (d, *J* 18.4 Hz, C-4), 64.45, 63.27, 51.48, 47.61, 47.55, 47.44, 47.38, 46.76, 46.59, 21.37, 20.80, 8.92.

4.12. Methyl 4,7,8,9-tetra-O-acetyl-5-amino-5-deoxy-3-fluoro-D-erythro-L-manno-2-nonulopyranosonate (**15**)

To a 1,4-dioxane (1.5 mL) solution of compound **9** (72 mg, 0.146 mmol) was added Lindlar catalyst (palladium on calcium carbonate, poisoned with lead ca. 10 mg). The mixture was stirred for 20 h at room temperature under hydrogen atmosphere. After filtration, the filtrate was concentrated to afford compound **15** (68 mg, quant); ^{1}H NMR ($CDCl_3$): δ 5.51–5.46 (m, 2H, H-7,8), 5.09 (ddd, 1H, $J_{3,4}$ 2.3 Hz, $J_{4,5}$ 10.6 Hz, $J_{4,F}$ 27.9 Hz, H-4), 4.92 (dd, 1H, $J_{3,F}$ 49.9 Hz, H-3), 4.56 (dd, 1H, $J_{8,9a}$ 1.6 Hz, $J_{9a,9b}$ 12.5 Hz, H-9a), 4.24 (dd, 1H, $J_{8,9b}$ 4.9 Hz, H-9b), 3.87 (s, 3H, OCH_3), 2.98 (t, 1H, H-5), 2.17, 2.17, 2.11, 2.06 (each s, 12H, OAc).

4.13. Methyl 4,7,8,9-tetra-O-acetyl-5-{2-[2-(2-Azido-ethoxy)-ethoxy]-ethoxy}acetamido-5-deoxy-3-fluoro-D-erythro-L-manno-2-nonulopyranosonate (**17**)

To a THF (1.5 mL) solution of compound **15** (68 mg, 0.145 mmol) was added compound **16** (68 mg, 0.291 mmol) and DMT-MM (81 mg, 0.291 mmol). After being stirred for 20 h at room temperature, the mixture was concentrated and applied on gel-filtration column (LH-20, MeOH) to afford compound **17** (54 mg, 55%): $[\alpha]_D^{26}$ +22.1° (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.20 (d, 1H, $J_{5,NH}$ 10.1 Hz, N*H*), 5.42 (dd, 1H, $J_{6,7}$ 2.0 Hz, $J_{7,8}$ 4.4 Hz, H-7), 5.34 (ddd, 1H, $J_{3,4}$ 2.2 Hz, $J_{4,5}$ 10.9 Hz, $J_{4,F}$ 27.4 Hz, H-4), 5.28 (ddd, 1H, $J_{8,9a}$ 2.3 Hz, $J_{8,9b}$ 8.0 Hz, H-8), 4.99 (dd, 1H, $J_{3,F}$ 49.7 Hz, H-3), 4.84 (dd, 1H, $J_{9a,9b}$ 12.4 Hz, H-9a), 4.50 (q, 1H, $J_{5,6}$ 10.3 Hz, H-5), 4.39 (br d, 1H, H-6), 4.11 (dd, 1H, H-9b), 3.91 {q, 2H, *J* 16.3 Hz, OCH_2C(=O)}, 3.86 (s, 3H, OCH_3), 3.76–3.65 (m, 10H, OCH_2), 3.51–3.42 (m, 2H, CH_2N_3), 2.16, 2.08, 2.06, 2.04 (each s, 12H, OAc). ^{13}C NMR ($CDCl_3$): δ 170.95, 170.63, 170.60, 170.53, 170.42, 170.37, 167.63, 94.30 (d, $J_{2,F}$ 25.1 Hz, C-2), 86.52 (d, $J_{3,F}$ 185.3 Hz, C-3), 71.70, 70.73, 70.45, 70.34, 69.96 (d, $J_{4,F}$ 17.3 Hz, C-4), 69.92, 69.67, 63.03, 53.53, 50.82, 44.03, 30.94, 20.97, 20.87, 20.84, 20.74. HRMS (ESI) *m*/*z* calcd for $[C_{26}H_{39}FN_4O_{16}+Na]^+$; 705.2237, found 705.2235.

4.14. Methyl (5-(2-(2-(2-azido-ethoxy)-ethoxy)ethoxy)-acetamido-4,7,8,9-tetra-O-acetyl-2-(N-acetyl-2′,3′-di-O-acetyl-cytidin-5′-O-cyamoethylphosphoryl)-3,5-dideoxy-3-fluoro-β-D-erythro-L-manno-2-nonulopyranos)onate (**19**)

To the mixture of compound **17** (33 mg, 48.3×10^{-6} mol) and 2-cyanoethyl 2′,3′-O,N^4-triacetylcytidin-5′-yl N,N-diisopropyl phosphoroamidite **18** (83 mg, 0.145 mmol) in MeCN (121×10^{-6} L) was added 1*H*-tetrazole (17 mg, 0.242 mmol) at −20 °C under nitrogen atmosphere. After being stirred for 1 h at 0 °C, the mixture was poured into satd $NaHCO_3$ and the product was extracted with EtOAc for three times. A combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. To the residue was added MeCN (0.5 mL) and *t*-BuOOH (ca. 5 M in decane, 97×10^{-6} L, 0.161 mmol) at room temperature. After being stirred for 20 min, the mixture was poured into satd $NaHCO_3$ and the product was extracted with EtOAc for three times. A combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was applied on gel-filtration column (LH-20, MeOH) to afford compound **19** (55 mg, 99%); ^{1}H NMR ($CDCl_3$): δ 9.16 (s, 1H, N*H*Ac), 7.82 {d, 1H, $J_{5'',NH}$ 9.9 Hz, C(=O)N*H*}, 7.68 (d, 1H, $J_{2,3}$ 7.6 Hz, H-2), 7.46 (d, 1H, H-3), 5.73 (dd, 1H, *J* 6.3 Hz, *J* 3.9 Hz, H-2′), 5.69–5.65 (m, 2H, H-1′,3′), 5.64 (br t, 1H, *J* 2.5 Hz, H-7″), 5.41 (ddd, 1H, $J_{3'',4''}$ 1.8 Hz, $J_{4'',5''}$ 11.1 Hz, $J_{4'',F}$ 27.2 Hz, H-4″), 5.28–5.26 (m, 1H, H-8″), 5.09 (dd, 1H, $J_{3'',F}$ 48.8 Hz, H-3″), 4.77–4.75 (m, 2H, H-6″,9″a), 4.67 (q, 1H, $J_{5'',6''}$ 10.5 Hz, H-5″), 4.55–4.45 (m, 2H, H-5′), 4.40–4.30 (m, 3H, H-4′,CH_2CH$_2$CN), 4.22 (dd, 1H, $J_{8'',9''b}$ 8.4 Hz, $J_{9''a,9''b}$ 12.2 Hz, H-9″b), 3.98 {d, 2H, *J* 3.6 Hz, CH_2C(=O)NH}, 3.92 (s, 3H, OCH_3), 3.70–3.60 (m, 10H, OCH_2), 3.39 (q, 2H, *J* 5.0 Hz, CH_2N_3), 2.79 (t, 2H, J 6.0 Hz, CH$_2$CH_2CN), 2.23, 2.17, 2.13, 2.12, 2.07, 1.99, 1.92 (each s, 21H, OAc).

4.15. 5-(2-(2-(2-Azido-ethoxy)-ethoxy)ethoxy)-acetamido-2-(cytidin-5′-O-phosphoryl)-3,5-dideoxy-3-fluoro-β-D-erythro-L-manno-2-nonulopyranosonic acid bis sodium salt (**20**)

The mixture of compound **19** (55 mg, 47.8×10^{-6} mol) and DBU (67 mg, 0.478 mmol) in THF (0.5 mL) was stirred for 10 min at room temperature. To the mixture was added NaOMe (24 mg, 0.478 mmol in MeOH 0.5 mL) and H_2O (0.5 mL). After being stirred for 20 h at room temperature, the mixture was applied on gel-filtration column (G-25, H_2O) to afford compound **20** (20.2 mg, 50%); $[\alpha]_D^{26}$ −2.3° (*c* 0.63, H_2O); ^{1}H NMR (D_2O): δ 7.95 (d, 1H, $J_{2,3}$ 7.6 Hz, H-2), 6.10 (d, 1H, H-3), 5.96 (d, 1H, $J_{1',2'}$ 4.4 Hz, H-1′), 4.89 (dd, 1H, $J_{3'',4''}$ 2.2 Hz, $J_{3'',F}$ 48.4 Hz, H-3″), 4.38 (t, 1H, $J_{4'',5''}$=$J_{5'',6''}$ 10.6 Hz, H-5″), 4.31–4.17 (m, 7H, H-2′,3′,4′,5′a,5′b,4″,6″), 4.13 {s, 2H, CH_2C(=O)NH}, 3.96 (ddd, 1H, $J_{7'',8''}$ 9.7 Hz, $J_{8'',9''a}$ 2.4 Hz, $J_{8'',9''b}$ 6.6 Hz, H-8″), 3.87 (dd, 1H, $J_{9''a,9''b}$ 11.9 Hz, H-9″a), 3.74–3.69 (m, 10H, OCH_2), 3.60 (dd, 1H, H-9″b), 3.47 (t, 2H, *J* 4.9 Hz, CH_2N_3), 3.42 (d, 1H, H-7″). ^{13}C NMR (D_2O): δ 173.15, 171.29, 166.12, 157.74, 141.53, 97.99 (dd, $^2J_{2'',F}$ 32.2 Hz, $^2J_{2'',P}$ 6.6 Hz, C-2″), 96.52 (C-3), 90.40 (dd,

$J_{3'',F}$ 176.2 Hz, $^{3}J_{3'',P}$ 13.7 Hz, C-3″), 88.95 (C-1′), 82.78 (d, $^{3}J_{4',P}$ 8.1 Hz, C-4′), 74.24 (C-2′), 71.42 (C-6″), 70.17, 69.63, 69.55, 69.47, 69.43, 69.26, 69.18, 68.70, 67.62 (d, $^{2}J_{4'',F}$ 17.5 Hz, C-4″), 65.07 (d, $^{2}J_{5',P}$ 5.4 Hz, C-5′), 62.83 (C-9″), 50.06 (CH_2N_3), 46.59 (C-5″). HRMS (ESI) *m*/*z* calcd for $[C_{26}H_{39}FN_7O_{19}P+Na]^+$; 872.1710, found 872.1702.

4.16. 5-(2-(2-(2-Aminoethoxy)-ethoxy)ethoxy)-acetamido-2-(cytidin-5′-O-phosphoryl)-3,5-dideoxy-3-fluoro-β-D-erythro-L-manno-2-nonulopyranosonic acid bis sodium salt (**21**)

To a H_2O (1.0 mL) solution of compound **20** (1.6 mg, 1.88×10^{-6} mol) was added Lindlar catalyst (ca. 3 mg). The mixture was stirred for 20 h at room temperature under hydrogen atmosphere. After filtration, the filtrate was concentrated to afford compound **21** (1.6 mg, quant); ^{1}H NMR (D_2O): δ 7.93 (d, 1H, $J_{2,3}$ 7.6 Hz, H-2), 6.09 (d, 1H, H-3), 5.81 (d, 1H, $J_{1',2'}$ 4.3 Hz, H-1′), 4.89 (br d, 1H, $J_{3'',F}$ 48.7 Hz, H-3″), 4.38 (t, 1H, $J_{4'',5''}$=$J_{5'',6''}$ 10.7 Hz, H-5″), 4.30–4.12 {m, 9H, H-2′,3′,4′,5′a,5′b,4″,6″, CH_2C(=O)NH}, 3.96 (ddd, 1H, $J_{7'',8''}$ 9.5 Hz, $J_{8'',9''a}$ 2.6 Hz, $J_{8'',9''b}$ 6.6 Hz, H-8″), 3.86 (dd, 1H, $J_{9''a,9''b}$ 11.9 Hz, H-9″a), 3.74–3.69 (m, 10H, OCH_2), 3.61 (dd, 1H, H-9″b), 3.43 (d, 1H, H-7″), 3.11 (t, 2H, *J* 4.7 Hz, CH_2NH_2).

4.17. Succinimidyl 3-{15-[2-(4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene-3-propionyl)-aminoethoxy]-pentaethyleneglycoloxy}-propionate (**22**)

To a DCM (2.2 mL) solution of Fmoc-dPEG$_6$™-Acid (127 mg, 0.221 mmol) was added piperidine (0.262 mL, 2.65 mmol), and the mixture was stirred for 20 h at room temperature. After concentration, the residue was applied on gel-filtration column (LH-20, MeOH) to afford corresponding amine (78 mg, quant); ^{1}H NMR (CD_3OD); δ 3.79 (t, 2H, *J* 5.1 Hz), 3.73–3.61 (m, 24H), 3.14 (t, 2H, *J* 5.0 Hz), 2.43 (t, 2H, *J* 6.2 Hz). To a suspension of amine (4.4 mg, 12.5×10^{-6} mol) in DCM (0.2 mL) was added pyridine (ca. 10 mg) and BODIPY-FL SE™ (5.1 mg, 13.0×10^{-6} mol) in DCM (0.8 mL), successively. After being stirred for 20 h at room temperature, the mixture was poured into 1 M aq HCl and the product was extracted with DCM for three times. The organic layer was washed with H_2O, dried over $MgSO_4$ and concentrated in vacuo. The residue was applied on PTLC (1:1, EtOAc–MeOH) to afford BODIPY labeled acid (7.6 mg, 97%); ^{1}H NMR (CD_3OD): δ 7.45 (s, 1H), 7.02 (d, 1H, *J* 4.0 Hz), 6.34 (d, 1H, *J* 4.0 Hz), 6.22 (s, 1H), 3.71 (t, 2H, *J* 6.4 Hz), 3.63–3.59 (m, 12H), 3.54 (t, 2H, *J* 5.4 Hz), 3.38 (t, 2H, *J* 5.4 Hz), 3.23 (t, 2H, *J* 7.7 Hz), 2.63 (t, 2H, *J* 7.7 Hz), 2.1 (s, 3H), 2.51 (t, 2H, *J* 6.4 Hz), 2.29 (s, 3H). To a DCM (1.2 mL) solution of BODIPY labeled acid (7.6 mg, 12.1×10^{-6} mol) was added N-hydroxysuccinimide (5.1 mg, 43.5×10^{-6} mol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide monohydrochloride (8.4 mg, 43.5×10^{-6} mol), successively. After being stirred for 20 h at room temperature, the mixture was poured into aq HCl (1 M) and the product was extracted with DCM for three times. The organic layer was washed with H_2O, dried over $MgSO_4$ and concentrated in vacuo. The residue was containing compound **22** as 90% purity (9.7 mg, quant); ^{1}H NMR ($CDCl_3$): δ 7.45 (s, 1H), 7.02 (d, 1H, *J* 4.0 Hz), 6.34 (d, 1H, *J* 4.0 Hz), 6.22 (s, 1H), 3.81 (t, 2H, *J* 6.1 Hz), 3.62–3.58 (m, 12H), 3.53 (t, 2H, *J* 5.4 Hz), 3.37 (t, 2H, *J* 5.4 Hz), 3.22 (t, 2H, *J* 7.7 Hz), 2.89 (t, 2H, *J* 6.1 Hz), 2.82 (s, 4H), 2.63 (t, 2H, *J* 7.6 Hz), 2.51 (t, 2H, *J* 6.4 Hz), 2.29 (s, 3H).

4.18. 5-(2-(2-(2-BODIPY-dPEG$_6$-amidoethoxy)-ethoxy)ethoxy)-acetamido-2-(cytidin-5′-O-phosphoryl)-3,5-dideoxy-3-fluoro-β-D-erythro-L-manno-2-nonulopyranosonic acid bis sodium salt (**1**)

To a MeOH–H_2O (1:1, 0.2 mL) solution of compound **20** (1.6 mg, 1.88×10^{-6} mol) and compound **22** (1.6 mg, 2.21×10^{-6} mol) was stirred for 20 h at room temperature. The mixture was applied on gel-filtration column (LH-20, 1:1, MeOH–H_2O) to afford compound **1** (2.7 mg, quant); ^{1}H NMR (D_2O): δ 7.90 (d, 1H, $J_{2,3}$ 7.6 Hz, H-2), 7.50, 6.31 (each s, 2H, BODIPY), 7.07, 6.37 (each d, 2H, *J* 3.9 Hz, BODIPY), 6.05 (d, 1H, H-3), 5.93 (d, 1H, $J_{1',2'}$ 4.4 Hz, H-1′), 4.89 (dd, 1H, $J_{3'',4''}$ 2.2 Hz, $J_{3'',F}$ 48.4 Hz, H-3″), 4.37 (t, 1H, $J_{4'',5''}$=$J_{5'',6''}$ 10.6 Hz, H-5″), 4.31–4.05 {m, 9H, H-2′,3′,4′,5′a,5′b,4″,6″, CH_2C(=O)NH}, 3.96 (ddd, 1H, $J_{7'',8''}$ 9.6 Hz, $J_{8'',9''a}$ 2.2 Hz, $J_{8'',9''b}$ 7.0 Hz, H-8″), 3.87 (dd, 1H, $J_{9''a,9''b}$ 11.9 Hz, H-9″a), 3.74–3.50 (m, 35H, H-9″b, OCH_2), 3.42 (d, 1H, H-7″), 3.34 (t, 2H, *J* 5.9 Hz, CH_2NH), 3.18 (t, 2H, *J* 6.9 Hz, BODIPY-CH_2CH_2), 2.67 (t, 2H, *J* 7.2 Hz, BODIPY-CH_2CH_2), 2.50, 2.26 (each s, 6H, BODIPY), 2.47 {t, 2H, *J* 6.2 Hz, CH_2CH_2C(=O)NH}. ^{13}C NMR (D_2O): δ 90.4 (d, $J_{3'',F}$ 201.2 Hz, C-3″), 82.8 (C-4′), 74.1 (C-2′), 71.3 (C-6″), 67.5 (C-4″), 65.1 (C-5′), 62.8 (C-9″), 46.7 (C-5″). HRMS: $[C_{55}H_{83}BF_3N_8Na_2O_{27}P+3Na]^{3+}$ calcd for 500.4874, found 500.4864, $[C_{55}H_{83}BF_3N_8O_{27}P\text{-}2H]^{2-}$ calcd for 693.2581, found 693.2556.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.carres.2014.12.010. These data include MOL files and InChiKeys of the most important compounds described in this article.

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