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Syntheses of 2-deoxy-2,3-didehydro-*N*-acetylneuraminic acid analogues modified by *N*-sulfonylamidino groups at the C-4 position and biological evaluation as inhibitors of human parainfluenza virus type 1

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ABSTRACT

Eleven novel sialidase inhibitors **9** and **10** with an *N*-sulfonylamidino group at the C-4 position of Neu 5Ac2en **1** against human parainfluenza virus type 1 (hPIV-1) were synthesized using copper-catalyzed three-component coupling reactions, and their inhibitory activities against hPIV-1 sialidase were studied.

1. Introduction

Human parainfluenza virus type 1 (hPIV-1), which belongs to the genus *Respirovirus*, family *Paramyxoviridae*, is a serious human pathogen causing upper and lower respiratory disease and is known to be a cause of croup in infants and young children.[1] At this time, there are no effective vaccines or specific therapies to control parainfluenza virus infections.[2] Parainfluenza virus has two spike glycoproteins, the hemagglutinin-neuraminidase (HN) glycoprotein and the fusion (F) glycoprotein, embedded in the envelope. HN proteins recognize sialic acid-containing glycolipids and glycoproteins of target cells and this recognition allows the virus to bind to target cells. Furthermore, HN protein also acts as a sialidase, removing sialic acid from virus particles and preventing the self-aggregation of virus and promoting the efficient spread of virus. Thus, the multifunctional roles of HN proteins in the viral life cycle make them an attractive target for the development of chemotherapeutics to treat hPIV infection. Among the diverse array of compounds related to the sialic acid family,[3] 5-acetamido-2,6-anhydro-3,5-dideoxy-D-*galacto*-D-*glycero*-non-2-enonic acid (Neu5Ac2en, **1**) is known as an inhibitor of sialidases from both bacterial and viral sources, occupying an important position in modern chemistry.[4] A variety of Neu5Ac2en analogs have been synthesized as competitive sialidase inhibitors. In sialic acids, C-4 position seems to play an important role in enzyme-substrate interactions. By molecular modeling techniques, von Itzstein and co-workers reported the design and biological evaluation of 4-deoxy-4-guanidino-Neu5Ac2en analogs (**2**) (zanamivir).[5] Neu5Ac2en derivatives with structural modifications at the C-4 position are particular candidates for the design of potent inhibitors as anti-paramyxovirus agents. In 2004, by the design of hPIV inhibitors using the X-ray structure of Newcastle disease virus (NDV), Portner and co-workers reported that com pounds BCX 2798 (**3**) and BCX 2855 (**4**) modified on C-4 and 5 positions of **1**, whose designs were based on the crystal structure of the HN of NDV, are specific and potent inhibitors of hPIVs.[6] We also demonstrated that 4-*O*-amidinomethyl- **5**,[7a,7b] 4-*O*-thiocarba moylmethyl- **6**,[7a,b,d] 4-*O*-ethyl- **7**,[7c] and 4-*O*-(2-thienyl-2-propynyl)Neu5Ac2en derivatives **8**[7e] have potential inhibitory activities against the sialidase from hPIV-1.

Multicomponent reactions (MCRs), offering a straightforward route to generate complexity and diversity in a single operation,

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have become important tools in modern preparative synthetic chemistry.[8] In particular, click chemistry is of great relevance in carbohydrate chemistry, where it is finding wide-ranging use in the preparation of drug-like molecules. Amidines are prominent structural pharmacophores in numerous bioactive natural products.[9]

Recently, to the design of new sialidase inhibitors, C-4 and C-7 triazole analogs[10a] of zanamivir and triazole-modified zanamivir analogs[10b] were preparing using click chemistry (Fig. 1). The introduction of a sulfonyl group into a wide range of heterocyclic compounds results in significant changes in the bioactivity of the compounds.[11] To the best of our knowledge, there is no report on the synthesis of Neu5Ac2en analogs with *N*-sulfonylamidino group **9** and **10** at the C-4 position of **1** using copper-catalyzed three-component coupling of sulfonyl azide, alkyne, and amine.

As part of a program aimed at identifying new inhibitors against the hPIV-1 sialidase, we report herein the synthesis of a novel compound **9** with an *N*-sulfonylamidino group at the C-4 position of **1** using the three-component coupling reaction as the key reaction. For further insight into the interaction of the sialidase with a substituent at C-4 of Neu5Ac2en derivatives, the synthesis of the *N*-sulfonylamidino derivatives **10** modified at C-4 using 4-amino Neu5Ac derivative **13** is also described (Scheme 1).

2. Results and discussion

2.1. Synthesis of 9

4-*O*-(2-Propynyl) Neu5Ac2en derivative **11**,[7d] a key intermediate for synthesizing target compounds **9**, contains an alkyne group, which was prepared from Neu5Ac in six steps (Scheme 2). Initially, methyl ester of Neu5Ac, derived from Neu5Ac, was converted to **15** in quantitative yield in two steps. Reaction of compound **15** with $PPh_3{\cdot}HBr$[12] in CH_3CN at 60 °C gave **16** in a 90% yield. Zemplen O-deacetylation of **16** with 0.1 M sodium methoxide in MeOH followed using subsequent protection by 2,2-dimethoxypropane and Amberlite 120 (H^+) in DMF afforded 8,9-*O*-isopropylidene compound **18** in 85% yield in two steps. Selective 4-*O*-alkylation of **18** with propargyl bromide using sodium hydride as a base in DMF at 0 °C successfully gave **11** in 56% yield.

MCRs[8b] were performed using the combination of 4-*O*-2-propynyl-Neu5Ac2en derivative **11**, amines (3.0 equiv), CuI (4 mol %), and Et_3N (3.0 equiv) in CH_2Cl_2 as shown in Table 1. Under the optimized conditions, many groups of three components were smoothly coupled to afford the corresponding *N*-sulfonylamidines (**12a–e**) in yields ranging from 60% to quantitative yield. When aniline was used as a nucleophile, the coupling reaction led to the recovery of **11** (Table 1, entry 2). In sharp contrast to the result of entry 3, when triethylamine was added as a base, the corresponding product **12b** was obtained in 60% yield (entry 3). When diethylamine, di-*iso*-propylamine, and *iso*-propylamine were used as a base under the same conditions, the products **12a,c–e** were successfully obtained in 85%, 80%, quant., and 64% yields, respectively (entries 1, 4, 5, and 6).

For the synthesis of **12f** with a primary amino group on the *N*-sulfonylamidino substituent, the coupling reaction of **11** with ammonium chloride by the combination of CuI (4 mol %) and azide gave **12f** in 54% yield (Scheme 3).

The removal of the isopropylidene group of **12a–e**, but not **12f**, with 80% acetic acid at 80 °C for 1 h gave the tetraols, whose methyl ester group was hydrolyzed with 0.1 M NaOH–MeOH (1:1) to give the *N*-sulfonylamidino compounds **9a–e** in 95% to quantitative yield (Table 2), after purification by chromatography on silica gel and then desalting, followed by lyophilization from a H_2O suspension.

2.2. Synthesis of 10

For comparing the inhibitory activity against the hPIV-1 sialidase between **9** and **10**, the synthesis of C-4 amino analog **13** as the key intermediate was accessed from **15** (Scheme 4). Reaction of **15** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in ethyl acetate at 50 °C gave the oxazoline **16**, which was treated with trimethylsilyl azide ($TMSN_3$) in *t*-BuOH in 80% yield in two steps. Hydrogenolysis with a Lindlar catalyst in EtOH gave the amino compound **13**[13] in a quantitative yield.

The synthesis of **10a–f** was based on MCRs in a manner similar to the preparation of **9**. The results are summarized in Table 3. When THF was used as solvent, the corresponding products **14a** were obtained in a low yield (Table 3, entry 1). In the case of using $CHCl_3$ as a solvent, compound **14a** was successfully obtained in 82% yield (entry 2). When TMS-acetylene was used as an alkyne under the same conditions, the desilylated product **14f** was obtained in 69% yield (entry 7).

Deprotection of the isopropylidene group of **14a–f** with 80% acetic acid at 80 °C for 1 h, followed by hydrolysis with 0.1 M NaOH/MeOH (1:1), gave the target compounds **10a–f** in yields ranging from 72% to quantitative yield (Table 4).

The conversion of 5-cuprated triazole intermediate **A** into the presumed ketenimine species **B** together with the loss of nitrogen

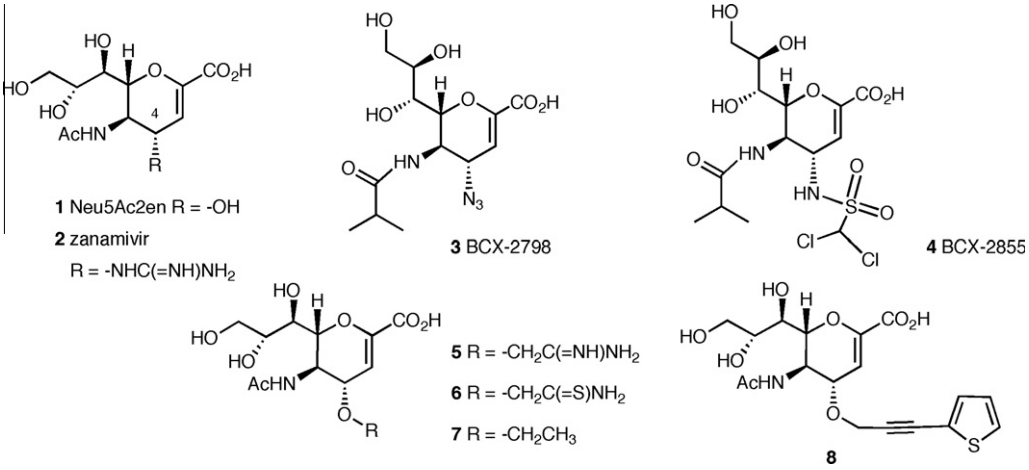
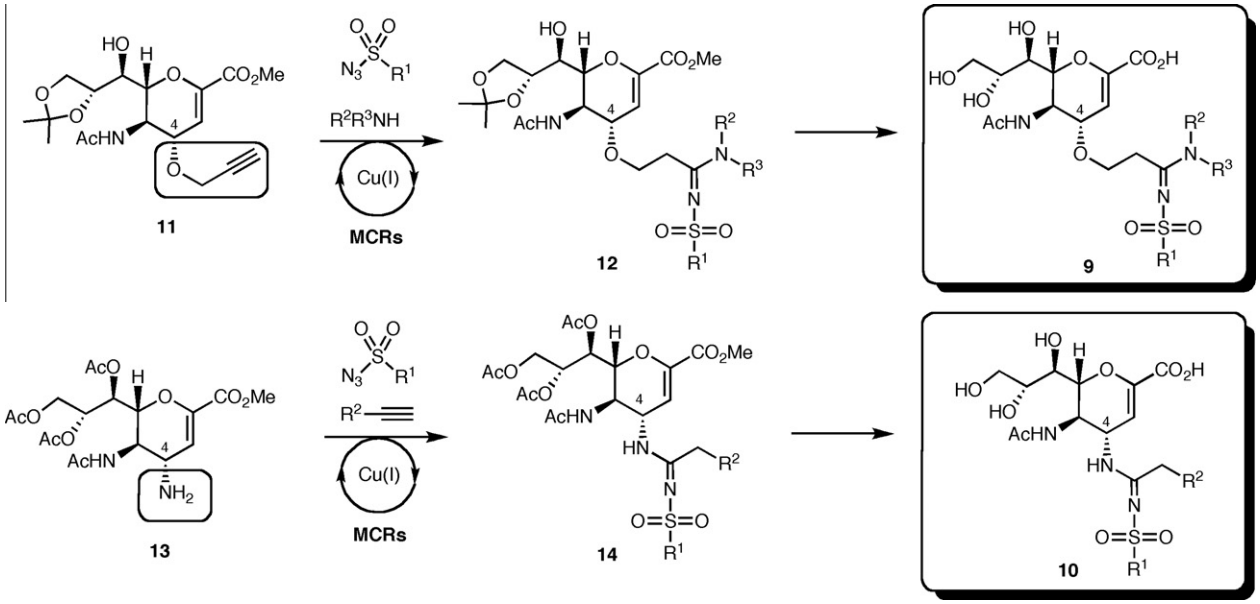
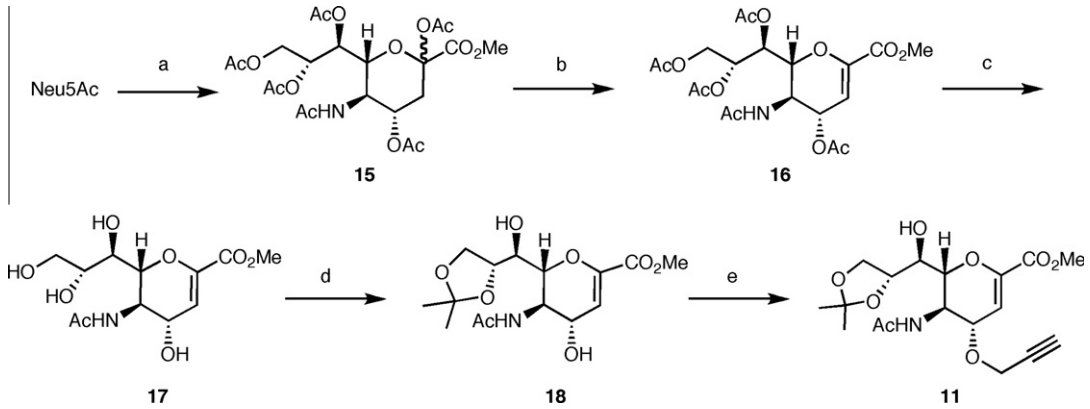


Figure 1. The structure of sialidase inhibitors.



Scheme 1. Synthesis of *N*-sulfonylamidino analogs **9** and **10** using MCRs.



Scheme 2. Reagents and conditions: (a) (i) MeOH, IR120 (H^+), (ii) Ac_20, pyridine, quant., in two steps; (b) PPh_3·HBr, CH_3CN, 60 °C, 4 h, 90%; (c) NaOMe, MeOH, quant.; (d) 2,2-dimethoxypropane, PTSA, DMF, 85%; (e) propargyl bromide, 15-crown-5 ether, NaH, DMF, 0 °C, 15 min, 56%.

gas results, upon reaction with amines, in the formation of amidines **C** (Scheme 5).[8,14]

3. Biological evaluation

The behavior of compounds **9** and **10** toward hPIV-1 sialidase was tested by a fluorometric assay using 4-methylumbelliferyl glycoside of *N*-acetyl-α-neuraminic acid by our previously reported method.[7b] As can be seen in Tables 5 and 6, among synthesized compounds **9** and **10**, compounds **9b** and **10d** showed efficient inhibitory activities (IC_{50} = 0.8 mM and 1.5 mM, respectively) against hPIV-1 sialidase. However, the degree of inhibition of **9b** was weaker than that of **1** (IC_{50} = 0.3 mM). It was found that inhibition of **9a,b** with a methyl residue on the *N*-sulfonyl substituent was stronger rather than that of **9c–e** of the 4-MeC_6H_4 residue with large hydrophobic groups.

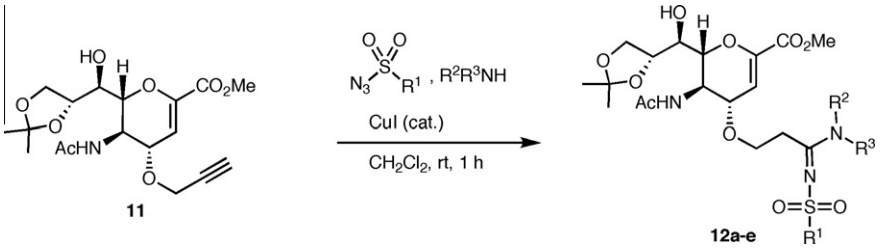
4. Conclusion

In conclusion, 2,3-didehydro sialic acids with a *N*-sulfonylamidino group at the 4-*O*-position were synthesized by copper-catalyzed multicomponent reaction. Compound **9b** (IC_{50} = 0.8 mM) was most potent among a series of compounds against hPIV-1 sialidase. However, the degrees of inhibition of both **9b** and **10d** were weaker than that of **1**. Compounds **9c–e** with relatively large hydrophobic groups showed decreased inhibitions of sialidase compared with **9a**,**b**. These results suggest that inferior activities of **9** and **10** compared **1** might be a result of steric or charge impediments/repulsion. The knowledge gained from our synthetic studies of the analogs of **1** as inhibitors of hPIV-1, for which there is as yet no crystal structure, will provide very important information for the development of anti-human parainfluenza virus drugs.

5. Experimental

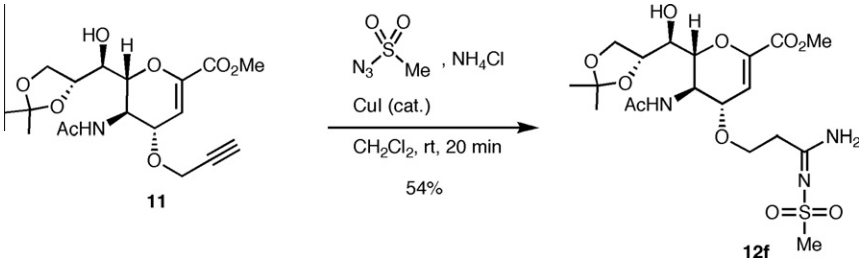
All melting points are uncorrected. Optical rotations were measured with a JASCO P-1030s (Japan) digital polarimeter. IR spectra were recorded on a SHIMADZU IRPrestige-21 (Japan) spectrometer. ^1H NMR spectra were recorded with a JEOL ECA-500 (500 MHz) (Japan) instrument. ^{13}C NMR spectra were recorded with a JEOL ECA-500 (126 MHz) (Japan) instrument. Chemical shifts are expressed in ppm relative to Me_4Si (d = 0) in $CDCl_3$ and in D_2O referenced

Table 1
Synthesis of **12a–e** by Cu(I)-catalyzed three-component coupling



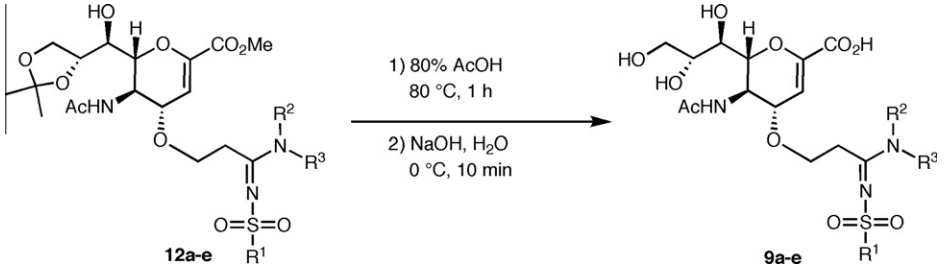
Entry	Azide (R^1)	Amine (R^2R^3NH)	Product	Yield (%)
1	Me	Et_2NH	12a	85
2	Me	$PhNH_2$	12b	No conversion[a]
3	Me	$PhNH_2$	12b	60[b]
4	4-MeC_6H_4	Et_2NH	12c	80
5	4-MeC_6H_4	*i*-Pr_2NH	12d	Quant.
6	4-MeC_6H_4	*i*-$PrNH_2$	12e	64

[a] 79% starting material **11** was recovered.
[b] Et_3N (1.2 equiv) was added.



Scheme 3. Synthesis of **12f**.

Table 2
Deprotection of **12a–e**

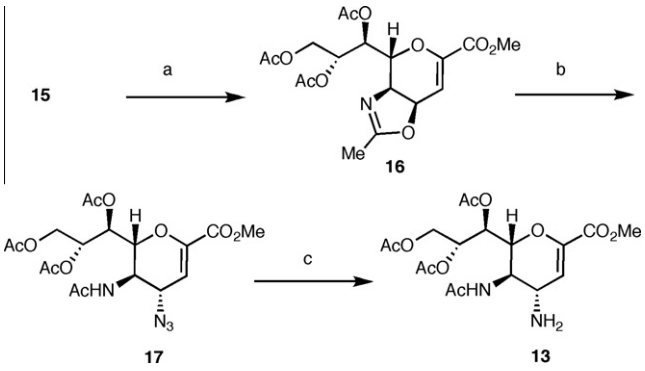


Entry	R^1	NR^2R^3	Product	Yield (%)
1	Me	NEt_2	9a	Quant.
2	Me	NHPh	9b	Quant.
3	4-MeC_6H_4	NEt_2	9c	Quant.
4	4-MeC_6H_4	N*i*-Pr_2	9d	95
5	4-MeC_6H_4	NH*i*-Pr	9e	Quant.

to HOD (4.85 ppm) as internal standards. Fast-atom-bombardment (FAB) mass spectra were obtained with a JEOL JMS-700 (Japan) mass spectrometer in the positive-ion mode using an NBA and thioglycerol matrix. High-resolution mass spectra (HR-MS) were recorded on a JEOL JMS-700 (Japan) instrument under FAB conditions. Column chromatography was performed on Silica Gel 60 (70–230 mesh, Merck). All reactions were monitored using TLC (Silica Gel 60 F_{254}, E. Merck, Germany) by charring after spraying 5% H_2SO_4 in MeOH and then heating.

5.1. Methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-4-*O*-[3-(diethylamino)-3-(methylsulfonylimino)propoxy]-8,9-*O*-isopropylidene-D-*glycero*-D-*galacto*-non-2-enonate (12a)

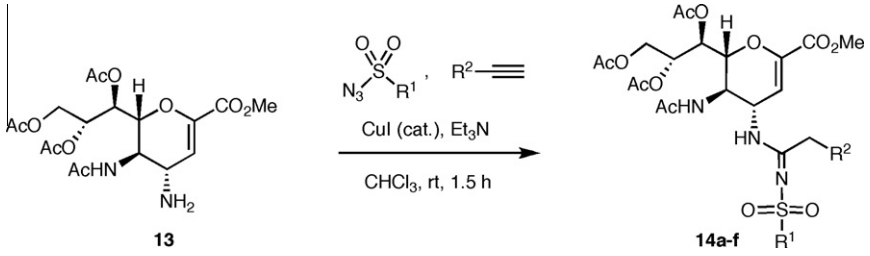
To a solution of compound **11** (43 mg, 0.11 mmol), CuI(I) (6 mg, 0.032 mmol), and methanesulfonyl azide (15.7 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was added diethylamine (9.5 mg, 0.13 mmol) and the resulting mixture was stirred under argon at room temperature for 1 h. For workup, saturated aqueous NH_4Cl (2 mL) was added



Scheme 4. Reagents and conditions: (a) TMSOTf, AcOEt, 50 °C, 3 h; (b) $TMSN_3$, *t*-BuOH, reflux, 9 h, 80% in two steps; (c) Lindlar catalyst, H_2, EtOH, rt, 9 h, quant.

and the mixture was stirred at ambient temperature for 1 h. The mixture was extracted with CH_2Cl_2, and the extracts was combined, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by chromatography over silica gel with chloroform/methanol (20:1). Yield of **12a**: 51 mg (85%) as an amorphous material. IR (neat) cm^{-1}: 3304, 3296, 1735, 1653, 1551, 1371, 1254, 1119. ^1H NMR ($CDCl_3$) δ: 6.91 (1H, d, J = 6.9 Hz), 5.97 (1H, d, J = 2.3 Hz), 5.08 (1H, d, J = 4.0 Hz), 4.67 (1H, s), 4.37 (1H, dt, J = 9.7, 4.0 Hz), 4.25 (1H, dd, J = 9.2, 2.3 Hz), 4.17–4.08 (3H, m), 4.09 (1H, m), 4.04–3.96 (1H, m), 3.89 (1H, d, J = 10.9 Hz), 3.77 (3H, s), 3.70 (1H, dd, J = 10.6, 3.7 Hz), 3.61 (1H, dd, J = 10.9 Hz), 3.57–3.48 (1H, m), 3.46 (1H, dd, J = 8.6, 6.9 Hz), 3.40 (3H, s), 3.28 (1H, d, J = 7.4 Hz), 3.28–3.24 (1H, m), 3.09 (1H, dt, J = 15.3, 7.2 Hz), 3.03 (3H, s), 2.13 (3H, s), 1.40 (3H, s), 1.36 (3H, s), 1.22 (3H, t, J = 7.2 Hz), 1.15 (3H, t, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 173.9, 164.4, 162.5, 145.1, 142.1, 141.1, 129.2, 125.6, 109.1, 107.9, 77.9, 75.7, 74.1, 69.5, 67.2, 67.1, 52.3, 49.2, 44.3, 44.1,

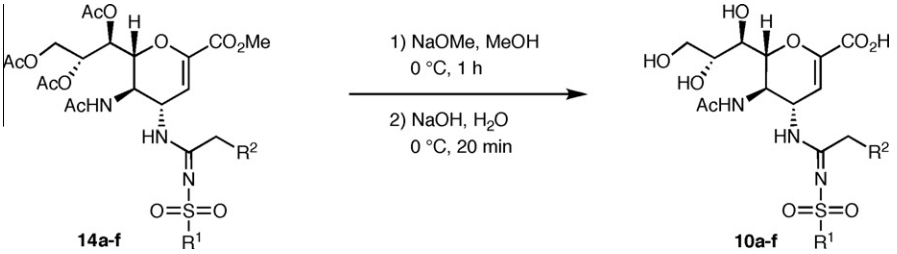
Table 3
Synthesis of **14a–f** by Cu(I)-catalyzed three-component coupling



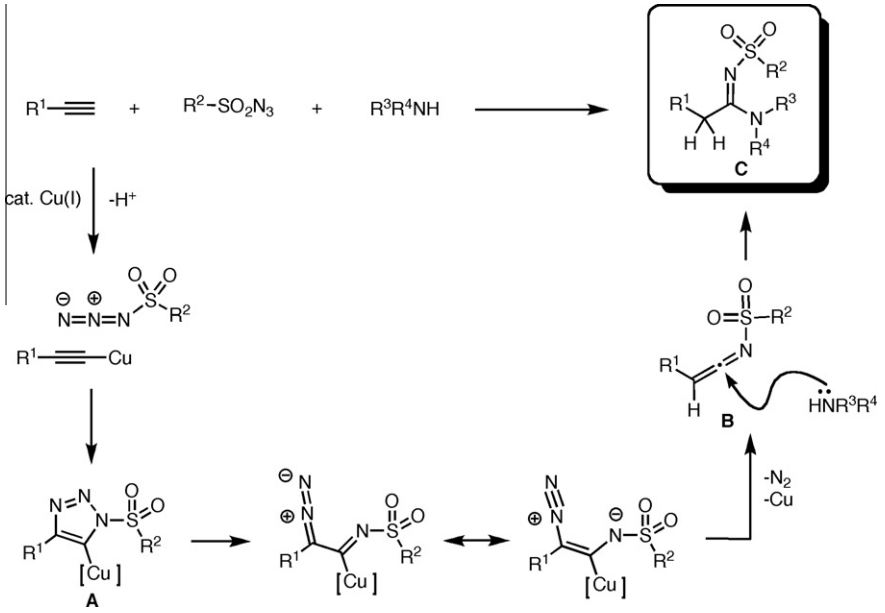
Entry	Azide (R^1)	Alkyne (R^2)	Product	Yield (%)
1	Me	1-Cyclohexenyl	14a	30[a]
2	Me	1-Cyclohexenyl	14a	82
3	Me	Ph	14b	64
4	Me	4-FC_6H_4	14c	69
5	Me	4-MeC_6H_4	14d	66
6	Me	2-Thienyl	**14e**	71
7	Me	TMS	14f	69[b]

[a] Run for 3 h with THF as a solvent.
[b] Desilylated product.

Table 4
Deprotection of **14a–f**

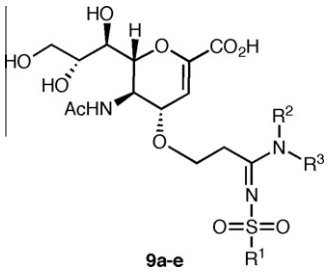


Entry	R^1	R^2	Product	Yield (%)
1	Me	Ph	10a	97
2	Me	4-FC_6H_4	10b	87
3	Me	4-MeC_6H_4	10c	83
4	Me	1-Cyclohexenyl	10d	Quant.
5	Me	2-Thienyl	10e	87
6	Me	H	10f	72



Scheme 5. Proposed route to *N*-sulfonylamidino compounds by using the three-component reaction.

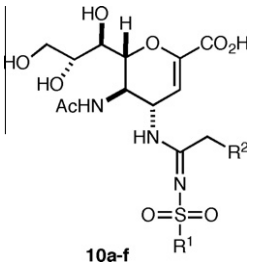
Table 5
Inhibitory activities of **9a**–**e** against hPIV-1 sialidase



9a-e

Entry	R^1	NR^2R^3	Product	IC_{50} (mM)
1	Me	NEt_2	**9a**	1.5
2	Me	NHPh	**9b**	0.8
3	4-MeC_6H_4	NEt_2	**9c**	9.1
4	4-MeC_6H_4	N*i*-Pr_2	**9d**	4.8
5	4-MeC_6H_4	NH*i*-Pr	**9e**	7.7

Table 6
Inhibitory activities of **10a**–**f** against hPIV-1 sialidase



10a-f

Entry	R^1	R^2	Product	IC_{50} (mM)
1	Me	Ph	10a	2.1
2	Me	4-FC_6H_4	10b	1.6
3	Me	4-*n*-PrC_6H_4	10c	1.6
4	Me	1-Cyclohexenyl	10d	1.5
5	Me	2-Thienyl	10e	2.0
6	Me	H	10f	16.0

31.2, 27.0, 25.3, 23.0, 21.4, 14.1, 12.1. MS (FAB) *m/z*: 550 $(M+H)^+$. HR-MS (FAB) calcd for $C_{23}H_{40}O_{10}N_3S$ $(M+H)^+$: 550.2434; found: 550.2383.

5.2. Methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-8,9-*O*-isopropylidene-4-*O*-[3-(phenylamino)-3-(methylsulfonylimino)propoxy]-D-*glycero*-D-*galacto*-non-2-enonate (12b)

The reaction was carried out using **11** (78 mg, 0.20 mmol), CuI(I) (3 mg, 0.020 mmol), methanesulfonyl azide (30.3 mg, 0.25 mmol), aniline (22.3 mg, 0.24 mmol) in THF (1 mL), and triethylamine (25.3 mg, 0.25 mmol) in a manner similar to the preparation of **12a**, to give **12b** (68 mg, 60%) as a yellow amorphous material. ^{1}H NMR (CD_3OD) δ: 7.36 (2H, d, J = 8.0 Hz), 7.11 (2H, t, J = 7.8 Hz), 6.93 (1H, t, J = 7.4 Hz), 5.85 (1H, d, J = 2.3 Hz), 4.40 (1H, br), 4.09–4.02 (2H, m), 3.91–3.84 (3H, m), 3.84–3.72 (3H, m), 3.51 (3H, s), 3.33–3.28 (1H, m), 2.91 (2H, t, J = 6.3 Hz), 2.80 (3H, s), 1.59 (3H, s), 1.11 (3H, s), 1.07 (3H, s). MS (FAB) *m/z*: 570 $(M+H)^+$. HR-MS (FAB) calcd for $C_{25}H_{36}O_{10}N_3S$ $(M+H)^+$: 570.2121; found: 570.2093.

5.3. Methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-8,9-*O*-isopropylidene-4-*O*-[3-(diethylamino)-3-(4-methylbenzene sulfonylimino)propoxy]-D-*glycero*-D-*galacto*-non-2-enonate (12c)

The reaction was carried out using **11** (70 mg, 0.18 mmol), CuI(I) (3 mg, 0.016 mmol), *p*-toluenesulfonyl azide (43.3 mg, 0.22 mmol), and diethylamine (16.1 mg, 0.22 mmol) in CH_2Cl_2 (1 mL) in a manner similar to the preparation of **12a**, to give **12c** (90 mg, 80%) as an amorphous material. IR (neat) cm^{-1}: 3307, 1734, 1653, 1549, 1260, 1139. ^{1}H NMR ($CDCl_3$) δ: 7.79 (2H, d, J = 8.6 Hz), 7.29 (2H, d, J = 9.7 Hz), 6.89 (d, 1H, J = 6.9 Hz), 6.00 (1H, d, J = 2.3 Hz), 5.02, 5.08 (1H, d, J = 4.0 Hz), 4.41–4.35 (1H, m), 4.33 (1H, dd, J = 8.9, 2.0 Hz), 4.18 (3H, tt, J = 14.9, 5.2 Hz), 4.11 (1H, q, J = 4.6 Hz), 4.03 (1H, dd, J = 16.6, 9.7 Hz), 3.91 (1H, d, J = 11.5 Hz), 3.78 (3H, s), 3.52–3.45 (2H, m), 3.44–3.32 (2H, m), 3.21–3.12 (3H, m), 2.42 (3H, s), 2.10 (3H, s), 1.40 (3H, s), 1.36 (3H, s), 1.22 (3H, t, J = 7.2 Hz), 1.08 (3H, t, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 173.9, 164.4, 162.5, 145.1, 142.1, 141.1, 129.2, 125.6, 109.1, 107.9, 77.9, 75.7, 74.1, 69.5, 67.2, 67.1, 52.3, 49.2, 44.3, 44.1, 31.2, 27.0, 25.3, 23.0, 21.4, 14.1, 12.1. MS

(FAB) *m/z*: 626 $(M+H)^+$. HR-MS (FAB) calcd for $C_{29}H_{44}O_{10}N_3S$ $(M+H)^+$: 626.2747; found: 626.2787.

5.4. Methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-8,9-*O*-isopropylidene-4-*O*-[3-(diisopropylamino)-3-(4-methylbenzenesulfonylimino)propoxy]-D-*glycero*-D-*galacto*-non-2-enonate (12d)

The reaction was carried out using **11** (63 mg, 0.16 mmol), CuI(I) (5 mg, 0.026 mmol), *p*-toluenesulfonyl azide (40 mg, 0.21 mmol), and *i*-Pr_2NH (20.2 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) in a manner similar to the preparation of **12a**, to give **12d** (109 mg, quant.) as an amorphous material. IR (neat) cm^{-1}: 3304, 1732, 1651, 1541, 1371, 1255, 1136, 1065. ^1H NMR ($CDCl_3$) δ: 7.78 (d, 2H, *J* = 8.6 Hz), 7.28 (2H, d, *J* = 7.4 Hz), 7.03 (1H, d, *J* = 6.9 Hz), 6.02 (1H, d, *J* = 1.7 Hz), 5.03 (1H, s), 4.40 (1H, dd, *J* = 9.7, 1.7 Hz), 4.35 (2H, dd, *J* = 13.5, 5.4 Hz), 4.24–4.13 (3H, m), 4.14–4.01 (3H, m), 3.91 (1H, d, *J* = 10.0 Hz), 3.77 (3H, s), 3.50 (1H, dd, *J* = 7.4, 4.0 Hz), 3.40–3.31 (1H, m), 3.31–3.21 (1H, m), 2.42 (3H, 3), 2.07 (3H, s), 1.40 (3H, s), 1.36 (3H, s), 1.33–1.15 (12H, m). ^{13}C NMR ($CDCl_3$) δ: 173.9, 162.4, 162.2, 145.1, 142.0, 141.0, 129.2, 125.6, 109.1, 108.9, 108.1, 107.1, 77.9, 77.4, 77.2, 75.4, 75.2, 74.3, 74.1, 72.6, 70.0, 69.4, 67.1, 67.0, 55.8, 52.4, 52.2, 49.0, 48.4, 48.2, 33.1, 26.9, 26.9, 25.3, 25.2, 23.1, 22.9, 21.4, 20.4, 19.9, 19.8. MS (FAB) *m/z*: 654 $(M+H)^+$. HR-MS (FAB) calcd for $C_{31}H_{48}O_{10}N_3S$ $(M+H)^+$: 654.3060; found: 654.3001.

5.5. Methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-8,9-*O*-isopropylidene-4-*O*-[3-(isopropylamino)-3-(4-methylbenzenesulfonylimino)propoxy]-D-*glycero*-D-*galacto*-non-2-enonate (12e)

The reaction was carried out using **11** (120 mg, 0.31 mmol), CuI(I) (10 mg, 0.053 mmol), *p*-toluenesulfonyl azide (75 mg, 0.38 mmol), and *i*-Pr_2NH (58.6 mg, 0.58 mmol) in CH_2Cl_2 (1 mL) in a manner similar to the preparation of **12a**, to give **12e** (123 mg, 64%) as an amorphous material. IR (neat) cm^{-1}: 3292, 1647, 1541, 1373, 1250, 1080. ^1H NMR ($CDCl_3$) δ: 7.81–7.76 (2H, m), 7.33–7.25 (2H, m), 6.99 (1H, d, *J* = 6.9 Hz), 6.11 (1H, d, *J* = 8.0 Hz), 6.01 (1H, d, *J* = 2.3 Hz), 5.09, 5.02 (1H, d, *J* = 4.0 Hz), 4.41–4.34 (1H, m), 4.32 (1H, dd, *J* = 9.2, 2.3 Hz), 4.19–3.99 (5H, m), 3.94 (1H, d, *J* = 11.5 Hz), 3.78 (3H, s), 3.51–3.55 (1H, m), 3.50–3.46 (1H, m), 3.29 (1H, td, *J* = 9.6, 5.0 Hz), 2.84–2.75 (1H, m), 2.43, 2.42 (3H, s), 2.18, 2.08 (3H, s), 1.42, 1.40 (3H, s), 1.37, 1.36 (3H, s), 1.28–1.24 (2H, m), 1.12 (4H, dd, *J* = 6.9, 4.0 Hz). MS (FAB) *m/z*: 612 $(M+H)^+$. HR-MS (FAB) calcd for $C_{28}H_{42}O_{10}N_3S$ $(M+H)^+$: 612.2591; found: 612.2620.

5.6. Methyl 5-acetamido-4-*O*-[3-amino-3-(methanesulfonylimino)propoxy]-8,9-*O*-isopropylidene-D-*glycero*-D-*galacto*-non-2-enonate (12f)

To a solution of compound **11** (70 mg, 0.18 mmol), CuI(I) (3 mg, 0.016 mmol), and ammonium chloride (12 mg, 0.22 mmol) in CH_2Cl_2 (4 mL) was added triethylamine (22.2 mg, 0.22 mmol) and methanesulfonyl azide (27.8 mg, 0.23 mmol) and the resulting mixture was stirred under argon at room temperature for 20 min. For workup, saturated aqueous NH_4Cl (1 mL) was added and the mixture was stirred at room temperature for 30 min. The mixture was extracted with CH_2Cl_2, and the extract was combined, dried over anhydrous $NaSO_4$, and concentrated. After the removal of the solvent, the residue was purified by chromatography over silica gel with AcOEt/methanol (20:1). Yield of **12f**: 48 mg (54%) as an amorphous material. $[\alpha]_D^{25}$ +46.4 (*c* 1.0, MeOH). ^1H NMR (CD_3OD) δ: 5.99 (1H, d, *J* = 2.3 Hz), 4.22 (1H, dd, *J* = 6.8, 4.0 Hz), 4.19 (1H, dd, *J* = 7.9, 5.1 Hz), 4.03 (1H, dd, *J* = 8.5, 6.2 Hz), 4.00 (2H, d, *J* = 5.7 Hz), 3.91 (1H, dd, *J* = 8.8, 5.4 Hz), 3.86–3.80 (1H, m), 3.69 (3H, s), 3.67 (1H, td, *J* = 6.2, 3.0 Hz), 3.48 (1H, d, *J* = 7.9 Hz), 2.86 (3H, s), 2.43 (2H, t, *J* = 6.0 Hz), 1.94 (3H, s), 1.26 (3H, s), 1.22 (3H, s). ^{13}C NMR (CD_3OD) δ: 174.6, 169.6, 163.9, 146.0, 110.3, 110.2, 79.5, 78.5, 76.1, 75.8, 70.8, 67.9, 66.3, 52.9, 41.6, 38.4, 27.2, 25.6, 22.8. MS (FAB) *m/z*: 494 $(M+H)^+$.

5.7. 5-Acetamido-2,6-anhydro-3,5-dideoxy-4-*O*-[3-(diethylamino)-3-(methylsulfonylimino)propoxy]-D-*glycero*-D-*galacto*-non-2-enonic acid (9a)

A solution of **12a** (30 mg, 0.55 mmol) in 80% AcOH (2 mL) was stirred at 80 °C for 30 min. The mixture was concentrated to dryness, the residue was dissolved in H_2O (1 mL) and a few drops of 1 M NaOH were added and then stirred at 0 °C for 10 min. The reaction solution was adjusted to pH 2 with Amberlite 120 (H^+), the solution was filtered to remove the resin, and the filtrate was concentrated. The residue was purified by silica gel column chromatography using $CHCl_3$/MeOH/H_2O (65:35:5) to give **9a** (29 mg, quant.) as an amorphous material. ^1H NMR (D_2O) δ: 5.93 (1H, d, *J* = 1.7 Hz), 4.20 (1H, dd, *J* = 8.5, 2.3 Hz), 4.10 (1H, d, *J* = 10.8 Hz), 4.02 (1H, dd, *J* = 10.8, 8.5 Hz), 3.87 (1H, dt, *J* = 11.9, 4.8 Hz), 3.70 (1H, dd, *J* = 12.2, 2.6 Hz), 3.77–3.70 (2H, m), 3.51–3.44 (2H, m), 3.44–3.36 (2H, m), 3.34–3.27 (2H, m), 2.97 (2H, t, *J* = 6.5 Hz), 2.92 (3H, s), 1.89 (3H, s), 1.05 (3H, t, *J* = 7.1 Hz), 0.99 (3H, t, 7.1 Hz). MS (FAB) *m/z*: 496 $(M+H)^+$. HR-MS (FAB) calcd for $C_{19}H_{34}O_{10}N_3S$ $(M+H)^+$: 496.1965; found: 496.1992.

5.8. 5-Acetamido-2,6-anhydro-3,5-dideoxy-4-*O*-[3-(phenylamino)-3-(methanesulfonylimino)propoxy]-D-*glycero*-D-*galacto*-non-2-enonic acid (9b)

The reaction was carried out using compound **12b** (30 mg, 0.055 mmol) in a manner similar to the preparation of **9a** to give **9b** (29 mg, quant.) as a yellow amorphous powder. $[\alpha]_D^{26}$ +21.8. (*c* 1.0, MeOH). IR (neat) cm^{-1}: 3296 (br), 1601, 1545, 1273, 1120, 791. ^1H NMR (CD_3OD) δ: 7.48 (2H, d, *J* = 8.0 Hz), 7.21 (2H, t, *J* = 8.0 Hz), 7.03 (1H, t, *J* = 7.2 Hz), 5.87 (1H, d, *J* = 2.3 Hz), 4.16 (1H, d, *J* = 6.3 Hz), 4.01 (2H, d, *J* = 6.3 Hz), 4.00–3.93 (1H, m), 3.85 (1H, dd, *J* = 13.5, 8.3 Hz), 3.74 (3H, ddd, *J* = 9.2, 5.7, 2.9 Hz), 3.67 (1H, dd, *J* = 11.5, 2.9 Hz), 3.49 (1H, dd, *J* = 10.9, 5.7 Hz), 3.39 (1H, d, *J* = 9.7 Hz), 3.09–2.98 (2H, m), 2.90 (3H, s), 1.67 (3H, s). MS (FAB) *m/z*: 516 $(M+H)^+$.

5.9. 5-Acetamido-2,6-anhydro-3,5-dideoxy-4-*O*-[3-(diethylamino)-3-(tosylimino)propoxy]-D-*glycero*-D-*galacto*-non-2-enonic acid (9c)

The reaction was carried out using compound **12c** (44 mg, 0.07 mmol) in a manner similar to the preparation of **9a** to give **9c** (40 mg, quant.) as an amorphous material. IR (neat) cm^{-1}: 3327, 1551, 1371, 1265, 1140, 1078, 675. ^1H NMR (D_2O) δ: 7.59 (2H, d, *J* = 8.6 Hz), 7.23 (2H, d, *J* = 8.0 Hz), 5.69 (2H, d, *J* = 2.3 Hz), 4.05 (1H, d, *J* = 10.9 Hz), 4.01 (1H, dd *J* = 9.2, 2.3 Hz), 3.91 (1H, d, *J* = 9.2 Hz), 3.89 (1H, d, 9.2 Hz), 3.73 (1H, ddd, *J* = 9.7, 5.7, 2.3 Hz), 3.69 (1H, dd, *J* = 11.7, 2.6 Hz), 3.56 (1H, dt, *J* = 12.2, 4.7 Hz), 3.47 (1H, dd, *J* = 11.5, 6.3 Hz), 3.51–3.40 (3H, m), 3.41–3.28 (3H, m), 2.91 (2H, tt, *J* = 20.0, 6.7 Hz), 2.22 (3H, s), 1.86 (3H, s), 1.02 (3H, t, *J* = 6.9 Hz), 0.97 (3H, t, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ: 173.9, 164.4, 162.5, 145.1, 142.1, 141.1, 129.2, 125.6, 109.1, 107.9, 77.9, 75.7, 74.1, 69.5, 67.2, 67.1, 52.3, 49.2, 44.3, 44.1, 31.2, 27.0, 25.3, 23.0, 21.4, 14.1, 12.1. MS (FAB) *m/z*: 572 $(M+H)^+$. HR-MS (FAB) calcd for $C_{25}H_{38}O_{10}N_3S$ $(M+H)^+$: 572.2278; found: 572.2267.

5.10. 5-Acetamido-2,6-anhydro-3,5-dideoxy-4-*O*-[3-(diisopropylamino)-3-(tosylimino)propoxy]-D-*glycero*-D-*galacto*-non-2-enonic acid (9d)

The reaction was carried out using compound **12d** (48 mg, 0.078 mmol) in a manner similar to the preparation of **9a** to give

9d (442 mg, 95%) as an amorphous material. $[\alpha]_D^{25}$ +31.4 (*c* 1.0, MeOH). IR (neat) cm^{-1}: 3304, 1734, 1653, 1551, 1371, 1260, 1140. ^1H NMR (CD_3OD) δ: 7.75 (2H, d, *J* = 8.0 Hz), 7.33 (2H, d, *J* = 8.0 Hz), 6.04 (1H, s), 4.41 (1H, t, *J* = 6.6 Hz), 4.28 (1H, d, *J* = 8.0 Hz), 4.16–4.09 (2H, m), 4.05–3.98 (1H, m), 3.88 (1H, d, *J* = 3.4 Hz), 3.81 (1H, dd, *J* = 11.2, 2.6 Hz), 3.67–3.63 (2H, m), 3.54–3.59 (1H, m), 3.29–3.17 (1H, m), 2.41 (3H, s), 2.03 (3H, s), 1.28 (6H, t, *J* = 6.9 Hz), 1.20 (6H, t, *J* = 5.7 Hz). ^{13}C NMR (CD_3OD) δ: 174.8, 165.4, 143.8, 142.8, 130.4, 130.3, 127.0, 109.8, 78.2, 76.2, 71.0, 69.8, 67.8, 64.8, 33.7, 22.8, 21.4, 21.4, 20.6, 20.6, 20.4. MS (FAB) *m/z*: 750 $(M+H)^+$. HR-MS (FAB) calcd for $C_{39}H_{48}O_{10}N_3S$ $(M+H)^+$: 750.3060; found: 750.3021.

5.11. 5-Acetamido-2,6-anhydro-3,5-dideoxy-4-*O*-[3-(diisopropylamino)-3-(tosylimino)-propoxy]-D-*glycero*-D-*galacto*-non-2-enonic acid (9e)

The reaction was carried out using compound **12e** (102 mg, 0.17 mmol) in a manner similar to the preparation of **9a** to give **9e** (93 mg, quant.) as an amorphous material. IR (neat) cm^{-1}: 3292, 1647, 1545, 1256, 1138, 1088. ^1H NMR (CD_3OD) δ: 7.65 (2H, d, *J* = 8.0 Hz), 7.22 (2H, d, *J* = 8.0 Hz), 5.88 (1H, d, *J* = 2.3 Hz), 4.13 (1H, dd, *J* = 8.6, 2.3 Hz), 4.06 (1H, d, *J* = 11.5 Hz), 4.00 (1H, d, *J* = 8.6 Hz), 3.99–3.89 (1H, m), 3.83–3.73 (3H, m), 3.70 (1H, dd, *J* = 11.5, 2.9 Hz), 3.54 (1H, dd, *J* = 11.5, 5.7 Hz), 3.46 (1H, d, *J* = 9.2 Hz), 2.92–2.85 (1H, m), 2.81–2.73 (1H, m), 2.30 (3H, s), 1.92 (3H, s), 1.02 (3H, d, *J* = 2.9 Hz), 1.01 (3H, d, *J* = 2.9 Hz). MS (FAB) *m/z*: 558 $(M+H)^+$.

5.12. Methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-8,9-*O*-isopropylidene-4-[2-cyclohexenyl-*N*′-(methylsulfonyl)acetimidamido]-D-*glycero*-D-*galacto*-non-2-enonate (14a)

To a solution of compound **13** (100 mg, 0.23 mmol), CuI(I) (4 mg, 0.0212 mmol), methanesulfonyl azide (33.9 mg, 0.28 mmol), and 1-ethynylcyclohexene (30.8 mg, 0.29 mmol) in CH_2Cl_2 (2 mL) was added triethylamine (29.3 mg, 0.29 mmol) and the resulting mixture was stirred under argon at room temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2 (2 mL) and saturated aqueous NH_4Cl (2 mL) was added, then the mixture was stirred at room temperature for 30 min. The reaction solution was extracted with CH_2Cl_2, and the organic layer was dried over anhydrous $MgSO_4$, and concentrated. After the removal of the solvent, the residue was purified by chromatography over silica gel with *n*-hexane/AcOEt (1:8). Yield of **14a**: 51 mg (119 mg, 82%) as a pale yellow amorphous material. $[\alpha]_D^{26}$ +31.0 (*c* 1.0, MeOH). IR (neat) cm^{-1}: 2924, 1736, 1659, 1369, 1213, 1042. ^1H NMR ($CDCl_3$) δ: 6.12 (1H, d, *J* = 7.3 Hz), 5.97 (1H, d, *J* = 2.4 Hz), 5.65 (1H, d, *J* = 3.7 Hz), 5.63 (1H, s), 5.51 (1H, dd, *J* = 4.9, 1.2 Hz), 5.31 (1H, ddd, *J* = 7.3, 4.9, 2,4 Hz), 4.75 (1H, ddd, *J* = 10.4, 3.7, 2.4 Hz), 4.67 (1H, dd, *J* = 12.5, 2.7 Hz), 4.31 (2H, dd, *J* = 3.7, 2.4 Hz), 4.17 (1H, dd, *J* = 12.8, 6.7 Hz), 3.80 (3H, s), 3.52 (2H, s), 3.03 (3H, s), 2.10, 2.08, 2.06 (9H, 3s), 1.95 (3H, s), 1.53–1.68 (8H, m). ^{13}C NMR ($CDCl_3$) δ: 171.4, 170.7, 170.4, 169.9, 167.9, 161.7, 144.5, 130.4, 130.3, 108.7, 71.3, 67.7, 62.1, 52.6, 51.7, 45.6, 43.1, 41.6, 28.3, 25.3, 23.0, 22.4, 21.5, 21.0, 20.8, 20.7. MS (FAB) *m/z*: 630 $(M+H)^+$.

5.13. Methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-8,9-*O*-isopropylidene-4-[2-phenyl-*N*′-(methylsulfonyl)acetimidamido]-D-*glycero*-D-*galacto*-non-2-enonate (14b)

The reaction was carried out using **13** (172 mg, 0.40 mmol), CuI(I) (8 mg, 0.042 mmol), *p*-toluenesulfonyl azide (96 mg, 0.49 mmol), ethynylbenzene (50.0 mg, 0.49 mmol), and triethylamine (49.5 mg, 0.49 mmol) in $CHCl_3$ (5 mL) in a manner similar to the preparation of **14a**, to give **14b** (181 mg, 64%) as a pale yellow amorphous material. IR (neat) cm^{-1}: 3323, 1741, 1545, 1371, 1219, 1126. ^1H NMR ($CDCl_3$) δ: 7.41–7.32 (2H, m), 7.23 (2H, d, *J* = 6.7 Hz), 5.89 (1H, d, *J* = 2.4 Hz), 5.70 (1H, d, *J* = 7.3 Hz), 5.66 (1H, d, *J* = 9.7 Hz), 5.46 (1H, dd, *J* = 4.9, 2.4 Hz), 5.28 (1H, ddd, *J* = 6.7, 4.9, 2.4 Hz), 4.79 (1H, ddd, *J* = 7.7, 7.3, 2.4 Hz), 4.64 (1H, dd, *J* = 12.5, 2.7 Hz), 4.30 (1H, dd, *J* = 10.4, 1.8 Hz), 4.23, 4.21 (2H, 2*s*), 4.1–4.00 (2H, m), 3.78 (3H, s), 3.04 (3H, s), 2.06, 2.05, 2.05 (9H, 3s), 1.89 (3H, s). MS (FAB) *m/z*: 626 $(M+H)^+$. HR-MS (FAB) calcd for $C_{27}H_{36}O_{12}N_3$ $(M+H)^+$: 626.2020; found: 626.2051.

5.14. Methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-8,9-*O*-isopropylidene-4-[2-(4-fluorophenyl)-*N*′-(methylsulfonyl)acetimidamido]-D-*glycero*-D-*galacto*-non-2-enonate (14c)

The reaction was carried out using **13** (100 mg, 0.23 mmol), CuI(I) (4 mg, 0.021 mmol), methanesulfonyl azide (33.9 mg, 0.28 mmol), 1-ethynyl-4-fluorobenzene (34 mg, 0.28 mmol), and triethylamine (29.3 mg, 0.29 mmol) in $CHCl_3$ (1 mL) in a manner similar to the preparation of **14a**, to give **14c** (102 mg, 69%) as a yellow amorphous material. $[\alpha]_D^{25}$ +25.9 (*c* 1.0, MeOH). IR (neat) cm^{-1}: 3283, 1724, 1545, 1261, 1119, 787. ^1H NMR ($CDCl_3$) δ: 7.23 (1H, d, *J* = 4.9 Hz), 7.21 (1H, d, *J* = 4.9 Hz), 7.08 (d, 1H, *J* = 8.5 Hz), 7.06 (1H, d, *J* = 8.5 Hz), 5.89 (1H, d, *J* = 2.4 Hz), 5.76 (1H, d, *J* = 7.3 Hz), 5.69 (1H, d, 9.7 Hz), 5.47 (1H, dd, *J* = 4.9, 2.4 Hz), 5.28 (1H, tt, *J* = 7.3, 3.5 Hz), 4.75 (1H, ddd, *J* = 7.3, 3.5 Hz), 4.65 (dd, 1H, *J* = 12.2, 2.4 Hz), 4.30 (1H, dd, *J* = 10.4, 1.8 Hz), 4.21–4.10 (4H, m), 3.78 (3H, s), 3.05 (3H, s), 2.07, 2.05, 2.05 (9H, 3s), 1.89 (3H, s). ^{13}C NMR ($CDCl_3$) δ: 171.7, 170.7, 170.5, 169.9, 167.4, 163.4, 161.6, 161.5, 144.6, 131.5, 131.5, 128.4, 128.4, 116.4, 116.24, 108.5, 71.4, 67.7, 62.04, 52.6, 52.6, 51.7, 45.8, 43.2, 38.6, 29.7, 22.9, 21.0, 20.6, 14.2. MS (FAB) *m/z*: 644 $(M+H)^+$.

5.15. Methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-8,9-*O*-isopropylidene-4-[2-*p*-tolyl-*N*′-(methylsulfonyl)acetimidamido]-D-*glycero*-D-*galacto*-non-2-enonate (14d)

The reaction was carried out using **13** (90 mg, 0.21 mmol), CuI(I) (4 mg, 0.021 mmol), methanesulfonyl azide (30.3 mg, 0.25 mmol), 4-ethynyltoluene (29.0 mg, 0.25 mmol), and triethylamine (25.3 mg, 0.25 mmol) in $CHCl_3$ (1 mL) in a manner similar to the preparation of **14a**, to give **14d** (88 mg, 66%) as a pale yellow amorphous material. IR (neat) cm^{-1}: 3337, 1744, 1541, 1371, 1219, 1128. ^1H NMR ($CDCl_3$) δ: 7.26 (1H, d, *J* = 7.3 Hz), 7.15 (1H, d, *J* = 7.9 Hz), 6.98–7.04 (2H, m), 5.87 (1H, d, *J* = 2.4 Hz), 5.59 (1H, d, *J* = 7.3 Hz), 5.46 (1H, dd, *J* = 4.9, 3.6 Hz), 5.45 (1H, s), 5.27 (1H, ddd, *J* = 6.7, 4.9, 2.4 Hz), 4.80 (1H, ddd, *J* = 10.4, 7.3, 2.4 Hz), 4.63 (1H, dd, *J* = 12.5, 2.7 Hz), 4.29 (1H, dd, *J* = 10.4, 1.8 Hz), 4.19 (2H, s), 4.16–4.00 (2H, m), 3.78 (3H, s), 3.05 (3H, s), 2.36 (3H, s), 2.07, 2.05, 2.05 (3H, 3s), 1.91 (3H, s). ^{13}C NMR ($CDCl_3$) δ: 171.3, 170.7, 170.3, 169.9, 167.9, 161.6, 144.6, 139.2, 132.2, 130.6, 129.3, 129.0, 126.7, 108.6, 71.2, 67.6, 62.1, 52.6, 51.5, 45.8, 43.1, 39.3, 22.9, 21.4, 21.4, 20.9, 20.8, 20.8, 20.6. MS (FAB) *m/z*: 640 $(M+H)^+$.

5.16. Methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-8,9-*O*-isopropylidene-4-[2-(thiophen-2-yl)-*N*′-(methylsulfonyl)acetimidamido]-D-*glycero*-D-*galacto*-non-2-enonate (14e)

The reaction was carried out using **13** (90 mg, 0.21 mmol), CuI(I) (4 mg, 0.021 mmol), methanesulfonyl azide (30.3 mg, 0.25 mmol), 2-ethynylthiophene (27 mg, 0.25 mmol), and triethylamine (25.3 mg, 0.25 mmol) in $CHCl_3$ (1 mL) in a manner similar to the preparation of **14a**, to give **14e** (95 mg, 71%) as a pale brown amorphous material. IR (neat) cm^{-1}: 3310, 1736, 1541, 1369, 1213, 1121, 1043, 854. ^1H NMR ($CDCl_3$) δ: 7.32 (1H, d, *J* = 5.5 Hz), 7.04 (1H, dd, *J* = 5.5, 3.0 Hz), 6.98 (1H, d, *J* = 3.0 Hz), 5.51 (1H, d, *J* = 10.4 Hz), 5.47 (1H, dd, *J* = 4.9, 2.4 Hz), 5.28 (1H, td, *J* = 6.1,

3.0 Hz), 4.77 (1H, ddd, *J* = 10.4, 7.3, 2.4 Hz), 4.64 (1H, dd, *J* = 12.2, 2.4 Hz), 4.45 (2H, s), 4.31 (1H, dd, *J* = 10.4 Hz, 1.8 Hz), 4.21–4.10 (4H, s), 3.79 (3H, s), 3.06 (3H, s), 2.07, 2.06, 2.05 (9H, 3s), 1.93 (3H, s). ^{13}C NMR ($CDCl_3$) δ: 171.4, 170.7, 170.4, 169.9, 166.5, 161.6, 144.6, 133.0, 129.3, 127.9, 126.9, 108.4, 71.2, 67.6, 62.0, 52.6, 51.7, 45.7, 43.2, 33.4, 23.0, 23.0, 20.9, 20.8, 20.6. MS (FAB) *m/z*: 632 $(M+H)^+$.

5.17. Methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-8,9-*O*-isopropylidene-4-[*N*′-(methylsulfonyl)acetimidamido]-D-*glycero*-D-*galacto*-non-2-enonate (14f)

The reaction was carried out using **13** (90 mg, 0.21 mmol), CuI(I) (4 mg, 0.021 mmol), methanesulfonyl azide (30.3 mg, 0.25 mmol), trimethylsilyl acetylene (24.6 mg, 0.25 mmol), and triethylamine (25.3 mg, 0.25 mmol) in $CHCl_3$ (1 mL) in a manner similar to the preparation of **14a**, to give trimethylsilyl compound (109 mg, 83%). For the preparation of **14f**, to a solution of trimethylsilyl compound (80 mg, 0.13 mmol) in THF (2 mL) was added TBAF (48 mg, 0.18 mmol) at room temperature, and the mixture was stirred for 30 min at the same temperature. The reaction mixture was extracted with AcOEt and the organic layer was washed with saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated to dryness. The residue was chromatographed by silica gel with AcOEt/MeOH (40:1) to give **14f** (64 mg, 69%) as a pale yellow amorphous material. ^{1}H NMR ($CDCl_3$) δ: 6.34 (1H, d, *J* = 6.7 Hz), 6.04 (1H, d, *J* = 9.7 Hz), 6.02 (1H, d, *J* = 2.4 Hz), 5.52 (1H, dd, *J* = 4.9, 2.4 Hz), 5.30 (1H, ddd, *J* = 6.7, 4.8, 2.4 Hz), 4.73 (1H, ddd, *J* = 9.7, 6.7, 2.4 Hz), 4.67 (1H, dd, *J* = 12.5, 2.7 Hz), 4.35 (1H, dd, *J* = 9.7, 2.4 Hz), 4.25 (1H, d, *J* = 9.7 Hz), 4.19 (1H, dd, *J* = 12.8, 7.3 Hz), 3.80 (3H, s), 3.02 (3H, s), 2.39 (3H, s), 2.10, 2.80, 2.07 (each 3H, s), 1.99 (3H, s). ^{13}C NMR ($CDCl_3$) δ: 172.3, 170.7, 170.5, 169.8, 166.5, 161.6, 144.3, 108.6, 71.2, 67.6, 62.0, 52.6, 51.6, 46.2, 42.8, 23.1, 20.9, 20.9, 20.8, 20.5. MS (FAB): *m/z* 550 $(M+H)^+$.

5.18. 5-Acetamido-2,6-anhydro-3,5-dideoxy-4-[2-phenyl-*N*′-(methylsulfonyl)acetimidamido]-D-*glycero*-D-*galacto*-non-2-enonic acid (10a)

To a solution of **14a** (80 mg, 0.13 mmol) in MeOH (2 mL) was added two drops of 25% NaOMe at 0 °C, and the mixture was stirred for 1 h at the same temperature. The reaction mixture was evaporated to dryness, the residue was dissolved in H_2O (2 mL), and to the mixture was added two drops of 1 M NaOH at 0 °C and the mixture was stirred for 30 min at the same temperature. The reaction mixture was treated with Amberlite IRC-120 (H^+), the suspension was filtered, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel using $CHCl_3$/MeOH/H_2O (65:35:5, v/v/v) to give **10a** (61 mg, 97%) as an amorphous material. IR (neat) cm^{-1}: 3281, 1541, 1261, 1119, 731. ^{1}H NMR (CD_3OD) δ: 7.27–7.14 (3H, m), 7.11 (2H, t, *J* = 6.0 Hz), 5.74 (1H, dd, *J* = 6.3, 2.3 Hz), 5.00–4.93 (1H, m), 4.17 (1H, dd, *J* = 9.7, 5.7 Hz), 4.08 (2H, dd, *J* = 14.9, 6.3 Hz), 3.79 (1H, d, *J* = 5.7 Hz), 3.77–3.71 (1H, m), 3.49–3.42 (2H, m), 2.79, 2.77 (3H, s), 1.76, 1.75 (3H, s). MS (FAB) *m/z*: 486 $(M+H)^+$. HR-MS (FAB) calcd for $C_{20}H_{28}O_9N_3S$ $(M+H)^+$: 486.1546; found: 486.1540.

5.19. 5-Acetamido-2,6-anhydro-3,5-dideoxy-4-[2-(4-fluorophenyl)-*N*′-(methylsulfonyl)acetimidamido]-D-*glycero*-D-*galacto*-non-2-enonic acid (10b)

The reaction was carried out using **14b** (68 mg, 0.11 mmol) in a manner similar to the preparation of **10a**, to give **10b** (48 mg, 87%). $[\alpha]_D^{24}$ +33.2 (*c* 1.0, MeOH) as a pale yellow amorphous material. IR (neat) cm^{-1}: 3308, 1734, 1655, 1543, 1371, 1256, 1223, 1121, 1045. ^{1}H NMR (D_2O) δ: 7.11 (1H, d, *J* = 4.6 Hz), 7.10 (1H, d, *J* = 5.2 Hz), 6.94 (1H, d, *J* = 8.6 Hz), 6.92 (1H, d, *J* = 8.6 Hz), 5.58 (1H, d, *J* = 2.3 Hz), 4.94 (1H, dd, *J* = 10.3, 2.3 Hz), 4.14 (1H, d, *J* = 10.9 Hz), 4.09–4.01 (2H, m), 3.77–3.70 (3H, m), 3.68 (3H, dd, *J* = 12.0, 2.3 Hz), 3.45 (2H, d, *J* = 12.0, 2.3 Hz), 3.43 (2H, d, *J* = 10.3 Hz), 2.79 (3H, s), 1.73 (3H, s). ^{13}C NMR (CD_3OD) δ: 174.4, 168.7, 166.0, 164.4, 162.4, 147.5, 132.2, 132.1, 132.0, 116.3, 108.7, 78.1, 71.1, 69.8, 64.8, 50.8, 49.8, 43.4, 39.0, 22.8. MS (FAB) *m/z*: 526 $(M+Na)^+$.

5.20. 5-Acetamido-2,6-anhydro-3,5-dideoxy-4-[2-*p*-tolyl-*N*′-(methylsulfonyl)acetimidamido]-D-*glycero*-D-*galacto*-non-2-enonic acid (10c)

The reaction was carried out using **14c** (54 mg, 0.084 mmol) in a manner similar to the preparation of **10a**, to give **10c** (35 mg, 83%) as a pale yellow amorphous material. IR (neat) cm^{-1}: 3283, 1717, 1541, 1263, 1119. ^{1}H NMR (CD_3OD) δ: 7.26 (1H, d, *J* = 7.3 Hz), 7.15 (1H, d, *J* = 7.9 Hz), 7.04–6.98 (2H, m), 5.87 (1H, d, *J* = 2.4 Hz), 5.59 (1H, d, *J* = 7.3 Hz), 5.46 (1H, dd, *J* = 4.9, 3.0 Hz), 5.45 (3H, s), 5.27 (1H, ddd, *J* = 6.7, 4.9, 2.4 Hz), 4.80 (1H, ddd, *J* = 10.4, 1.8 Hz), 4.19 (2H, s), 4.16–4.09 (2H, m), 3.78 (3H, s), 3.05 (3H, s), 2.36 (3H, s), 2.07, 2.05, 2.05 (each 3H, s), 1.91 (3H,s). MS (FAB) *m/z*: 500 $(M+H)^+$. HR-MS (FAB) calcd for $C_{21}H_{30}O_9N_3S$ $(M+H)^+$: 500.1703; found: 500.1691.

5.21. 5-Acetamido-2,6-anhydro-3,5-dideoxy-4-[2-cyclohexenyl-*N*′-(methylsulfonyl)acetimidamido]-D-*glycero*-D-*galacto*-non-2-enonic acid (10d)

The reaction was carried out using **14c** (64 mg, 0.010 mmol) in a manner similar to the preparation of **10a**, to give **10d** (49 mg, quant.) as a pale yellow amorphous material. IR (neat) cm^{-1}: 3292, 1717, 1541, 1263, 1119. ^{1}H NMR (CD_3OD) δ: 5.66 (1H, d, *J* = 2.3 Hz), 5.46 (1H, s), 4.92 (1H, m), 4.11 (2H, t, *J* = 2.9 Hz), 3.76 (1H, ddd, *J* = 9.2, 5.2, 2.9 Hz), 3.68 (1H, dd, *J* = 11.5, 2.9 Hz), 3.52 (2H, dd, *J* = 10.9, 5.7 Hz), 3.45 (1H, d, *J* = 9.7 Hz), 3.43–3.38 (1H, m), 2.85 (3H, s), 1.90 (2H, s), 1.86 (3H, s), 1.81 (2H, s), 1.55–1.47 (2H, m), 1.47–1.40 (2H, m), 1.14 (2H, m). MS (FAB) *m/z*: 490 $(M+H)^+$. HR-MS (FAB) calcd for $C_{20}H_{32}O_9N_3S$ $(M+H)^+$: 490.1859; found: 490.1901.

5.22. 5-Acetamido-2,6-anhydro-3,5-dideoxy-4-[2-(thiophen-2-yl)-*N*′-(methylsulfonyl)acetimidamido]-D-*glycero*-D-*galacto*-non-2-enonic acid (10e)

The reaction was carried out using **14c** (39 mg, 0.062 mmol) in a manner similar to the preparation of **10a**, to give **10e** (26 mg, 87%) as a pale brown amorphous material. IR (neat) cm^{-1}: 3292, 1717, 1549, 1265, 1120. ^{1}H NMR (CD_3OD) δ: 7.18 (1H, dd, *J* = 5.2, 1.1 Hz), 6,92 (1H, d, *J* = 3.4 Hz), 6.83 (1H, dd, *J* = 5.2, 3.4 Hz), 5.69 (1H, d, *J* = 2.3 Hz), 4.90 (1H, dd, *J* = 9.7, 2.3 Hz), 4.31 (1H, d, *J* = 14.9 Hz), 4.13–4.07 (2H, m), 4.03, 4.00 (2H, 2s), 3.76 (1H, ddd, *J* = 9.7, 5.2, 2.9 Hz), 3.68 (1H, dd, *J* = 11.5, 2.9 Hz), 3.53 (1H, d, *J* = 5.2 Hz), 3.51 (1H, d, *J* = 5.2 Hz), 3.48–3.21 (1H, m), 2.75 (3H, s), 1.78 (3H, s). MS (FAB) *m/z*: 492 $(M+H)^+$. HR-MS (FAB) calcd for $C_{18}H_{26}N_3O_9S$ $(M+H)^+$: 492.1110; found: 492.1158.

5.23. 5-Acetamido-2,6-anhydro-3,5-dideoxy-4-[*N*′-(methylsulfonyl)acetimidamido]-D-*glycero*-D-*galacto*-non-2-enonic acid (10f)

The reaction was carried out using **14c** (45 mg, 0.08 mmol) in a manner similar to the preparation of **10a**, to give **10f** (24 mg, 72%) as a pale yellow amorphous material. IR (neat) cm^{-1}: 3283, 1541, 1251, 1115. ^{1}H NMR (CD_3OD) δ: 5.82 (1H, d, *J* = 2.3 Hz,), 5.02 (1H,

dd, J = 10.3, 2.3 Hz), 4.31 (1H, d, J = 10.9 Hz), 4.19 (1H, t, J = 10.3 Hz), 3.89 (1H, ddd, J = 9.2, 5.2, 2.9 Hz), 3.82 (1H, dd, J = 11.5, 2.9 Hz), 3.66 (1H, dd, J = 11.5, 5.7 Hz), 3.61 (1H, d, 9.7 Hz), 2.99 (3H, s), 2.34 (3H, s), 2.00 (3H, s). MS (FAB) *m/z*: 410 $(M+H)^+$. HR-MS (FAB) calcd for $C_{14}H_{24}N_3O_9S$ $(M+H)^+$: 410.1233; found: 410.1177.

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