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FERRIER GLYCOSYLATION REACTION CATALYZED BY $Bi(OTf)_3$-MONTMORILLONITE K-10: EFFICIENT SYNTHESIS OF 3,4-UNSATURATED SIALIC ACID DERIVATIVES: SYNTHESIS AND BIOLOGICAL EVALUATION AS INHIBITORS OF HUMAN PARAINFLUENZA VIRUS TYPE 1

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Abstract – The reaction of the 4,5-oxazoline derivative of sialic acid with various alcohols was effectively promoted by a catalytic amount of montmorillonite K-10 clay-supported $Bi(OTf)_3$ to produce a variety of 3,4-unsaturated sialic acids via the Ferrier glycosylation reaction in moderate yields. The deprotection of the isopropylidene group and hydrolysis of the ester group of **7a-g** gave **4a-f**, whose inhibitory activities against hPIV-1 sialidase were studied.

INTRODUCTION

N-Acetylneuraminic acid (Neu5Ac, **1**) and its various analogs are critical components of cell surface glycoconjugates involved in cellular recognition processes.[1] A variety of compounds have been reported to inhibit the action of influenza virus sialidase and, of these, the most interesting and the most extensively studied are 2-deoxy-2,3-didehydro-*N*-acetylneuraminic acid (Neu5Ac2en, **2**) and the corresponding analogs.[2] Among them, 2,3-didehydro-2,4-dideoxy-4-guanidinyl-*N*-acetylneuraminic acid (Zanamivir, **3**)[3] in Figure 1 has been approved for human use as a specific sialidase inhibitor for anti-influenza drugs.

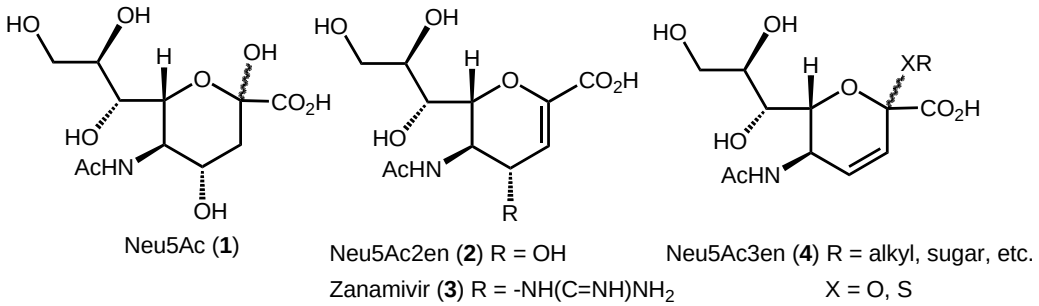


Figure 1. The structures of sialidase inhibitors

Human parainfluenza virus type 1 (hPIV-1) is a serious pathogen causing upper and lower respiratory disease in infants and young children;[4] however, there are no known effective inhibitors of hPIV-1 infection. Lewis acid-catalyzed allylic rearrangement of acyloxy glycals is a well-known Ferrier glycosylation reaction[5] and is widely employed to obtain 2,3-unsaturated glycosides, which are versatile chiral intermediates in the synthesis of several biologically active natural products.[6] Owing to its great significance in the area of carbohydrate chemistry, there has been growing interest in the development of the Ferrier glycosylation reaction by using a variety of catalysts. Despite their usefulness, strong Lewis acid catalysts, such as $BF_3 \cdot OEt_2$[7] and $SnCl_4$,[8] are generally employed to obtain 2,3-unsaturated glycosides. Other reagents, such as the clay catalyst montmorillonite K-10,[9] bismuth (III) trifluoromethanesulfonate (bismuth triflate) [$Bi(OTf)_3$],[10] $Bi(OTf)_3$-SiO_2,[10] DDQ,[11] *N*-iodosuccinimide,[12] $AuCl_3$,[13] and $Fe(OTf)_3$[14] and lanthanide triflates such as $Yb(OTf)_3$[15] and $Sc(OTf)_3$[16] are known to bring about the Ferrier glycosylation reaction under mild conditions. Bismuth triflate was also found to be a mild and effective promoter of glycosylation.[17] Recently, glycal derivatives as glycosyl donors have been utilized in *p*-allylpalladium strategies for the stereoselective synthesis of *O*-glycosides.[18]

In order to design new hPIV-1 sialidase inhibitors, 3,4-unsaturated sialic acid derivatives are promising candidates as transition-state analogs for the enzyme reaction.[19] Compound **4a** (XR = OMe in Figure 1) was found to be a weak inhibitor against sialidase from influenza virus.[20] In keeping with our interest in the development of new inhibitors against hPIV-1 sialidase,[21-23] we reported our preliminary results[24] on the interesting use of $Bi(OTf)_3$-montmorillonite K-10 as an efficient catalyst for the synthesis of 3,4-unsaturated sialic acid derivative **4** via the Ferrier glycosylation reaction starting from sialic acid 4,5-oxazoline derivative **5**. To the best of our knowledge, this is the first report on $Bi(OTf)_3$-montmorillonite K-10-mediated Ferrier glycosylation reaction of sialic acid derivatives (Figure 2). We describe herein the synthesis of 3,4-unsaturated sialic acid derivatives promoted by $Bi(OTf)_3$-montmorillonite K-10 and their evaluation of their inhibitory activities against hPIV-1 sialidase.

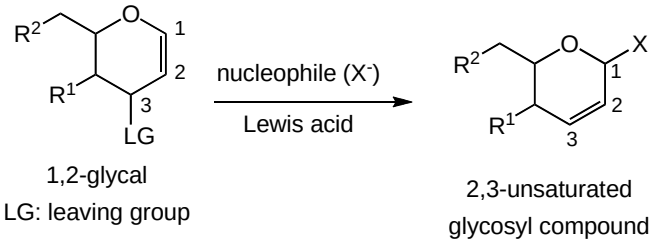
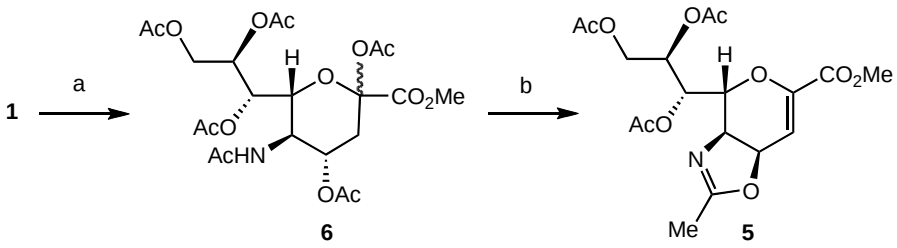


Figure 2. Ferrier glycosylation reaction

RESULTS AND DISCUSSION

Neu5Ac **1** was transformed with inversion of the configuration at C-4 into the oxazoline derivative **5**[25] by the treatment with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in 76% yield in three steps (Chart 1).



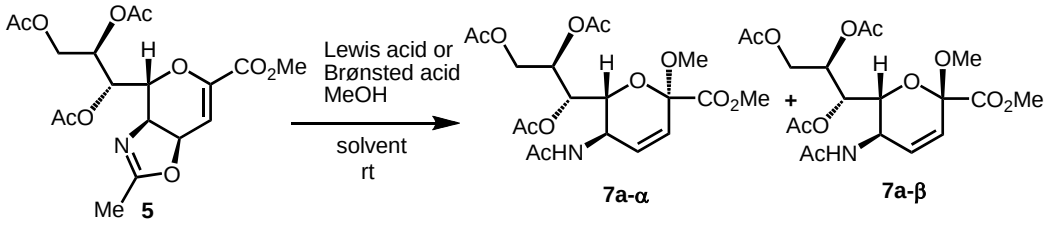
Reaction conditions: (a) (i) MeOH, IR120 (H^+), rt, 15 h, quant.; (ii) Ac_2O, pyridine, rt, 15 h, 98%; (b) TMSOTf, MeCN, 50 °C, 2 h, 78%.

Chart 1. Synthesis of oxazoline derivative 5

We first investigated the Ferrier glycosylation reaction to construct methyl ketoside of 3,4-unsaturated sialic acid derivatives **7a**. Thus, different reaction conditions, including promoters and solvents, were examined. These results are summarized in Table 1. The reaction between **5** and MeOH as a glycosyl acceptor using IR120 (H^+) as Brønsted acid at room temperature gave the 3,4-unsaturated glycoside **7a** in 31% yield as an anomeric mixture with the β-anomer as the major product (α/β = 6:94) (Table 1; entry 1). The α/β ratio of **7a**[26] was determined by ^{1}H-NMR analysis. Using Lewis acids, TMSOTf, $Hf(OTf)_4$, $Zn(OTf)_2$, $Yb(OTf)_3$, $Sc(OTf)_3$, and $InCl_3$ as promoters in MeCN, the reaction gave **7a** in 56%, 42%, 45%, 45%, 51%, and 69% yield, respectively, as almost a β-anomer (Table 1; entries 2-7). A relatively large amount of α-glycosides **7a** was obtained in MeCN in the presence of 0.8 equivalent of $BF_3{\cdot}OEt_2$ in 51% yield with an α/β ratio of 41:59, as expected from the more significant solvent participation of MeCN than of CH_2Cl_2 (entries 8 and 9). The solvent effect of CPME[27] was examined. When the reaction of **5** with MeOH was carried out using 0.8 equivalent of $BF_3{\cdot}OEt_2$ in CPME at room temperature, however, no increment of α-selectivity was observed (α/β ratio of 17:83, entry 10). When

both the 0.2 equivalent of $Bi(OTf)_3$ and 30% w/w montmorillonite K-10 were used as activators, the reactions gave **7a** in 50% and 63% yield, respectively (entries 11 and 12). Interestingly, the reaction of **5** with MeOH in the presence of 40% w/w $Bi(OTf)_3$-montmorillonite K-10 loading of 20% w/w $Bi(OTf)_3$ in MeCN showed remarkable improvement in the glycosylation yield (95%, α/β ratio of 7:93) (entry 13). This synergistic enhancement by the addition of montmorillonite K-10 to $Bi(OTf)_3$ was tentatively understood by the formation of a montmorillonite K-10-ROH complex, which might activate **5** under the influence of $Bi(OTf)_3$. This result shows that it is important to use the combination of $Bi(OTf)_3$ and montmorillonite K-10 for higher yields in the Ferrier glycosylation reaction. The solvent effects were tested; however, the yields of **7a** in CH_2Cl_2 and Et_2O decreased to 73% and 47% yield, respectively (entries 14 and 15).

Table 1. Ferrier glycosylation reaction of 4,5-oxazoline derivative of sialic acid **5**



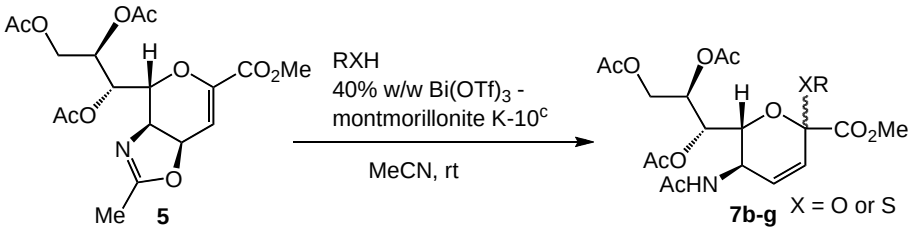
Entry	Brønsted or Lewis acid	Solvent	Time (h)	Yield (%)[a] (α/β ratio)[b]
1	IR120 (H^+)	-	20	31 (6 : 94)
2	TMSOTf (1.0 eq)	MeCN	4	56 (15 : 85)
3	$Hf(OTf)_4$ (1.0 eq)	MeCN	22	42 (21 : 79)
4	$Sc(OTf)_3$ (20% w/w)	MeCN	17	45 (17 : 83)
5	$Zn(OTf)_2$ (1.0 eq)	CH_2Cl_2	22	45 (19 : 81)
6	$Yb(OTf)_3$ (0.2 eq)	MeCN	17	51 (12 : 88)
7	$InCl_3$ (0.7 eq)	MeCN	14	69 (6 : 94)
8	$BF_3{\cdot}OEt_2$ (0.8 eq)	MeCN	39	51 (41 : 59)
9	$BF_3{\cdot}OEt_2$ (0.8 eq)	CH_2Cl_2	17	64 (16 : 84)
10	$BF_3{\cdot}OEt_2$ (0.8 eq)	CPME	12	60 (17 : 83)

11	$Bi(OTf)_3$ (0.2 eq)	MeCN	14	50 (23 : 77)
12	montmorillonite K-10 (30% w/w)	MeCN	40	63 (13 : 87)
13	$Bi(OTf)_3$ -montmorillonite K-10[c] (40% w/w)	MeCN	20	95 (7 : 93)
14	$Bi(OTf)_3$ -montmorillonite K-10[c] (40% w/w)	CH_2Cl_2	20	73 (8 : 92)
15	$Bi(OTf)_3$ -montmorillonite K-10[c] (40% w/w)	Et_2O	22	47 (9 : 91)

[a] Isolated yields after column chromatography.
[b] The anomeric ratio was determined on the basis of the integrated ratios of the hydrogens of methyl carboxylates of **7a** in the NMR spectra at 500 MHz.
[c] $Bi(OTf)_3$-montmorillonite K-10 loading of 20% w/w $Bi(OTf)_3$.

Next, the glycosyl donor of the propriety of **5** was evaluated by coupling with various alcohols. As summarized in Table 2, the reactions of **5** with ethyl, *n*-propyl, *i*-propyl, *n*-butyl, benzyl alcohols and 1-dodecanethiol were activated by 40% w/w $Bi(OTf)_3$ (20%) -montmorillonite K-10 in MeCN at room temperature to give **7b-g** in 77%, 44%, 32%, 50%, 41%, and 40% yield, respectively, as an anomeric mixture with the β-anomer as the major product.

Table 2. Ferrier glycosylation reaction of 4,5-oxazoline derivative of sialic acid **5**



Entry	RXH	Time (h)	Product	Yield (%)[a] (α/β ratio)[b]
1	EtOH	16	**7b**	77 (9 : 91)
2	*n*-PrOH	14	**7c**	44 (6 : 94)
3	*i*-PrOH	43	**7d**	32 (12 : 88)
4	*n*-BuOH	15	**7e**	50 (10 : 90)
5	*n*-BnOH	19	**7f**	41 (10 : 90)

6	$CH_3(CH_2)_{11}SH$	23	**7g**	40 (9 : 91)

[a] Isolated yields after column chromatography.

[b] The anomeric ratio was determined on the basis of the integrated ratios of the hydrogens of methyl carboxylates of **7b-g** in the ^1H NMR spectra at 500 MHz.

[c] $Bi(OTf)_3$-montmorillonite K-10 loading of 20% w/w $Bi(OTf)_3$.

The possible mechanism of the Ferrier glycosylation reaction involves the intermediacy of a cyclic allylic oxonium ion **X** with which the nucleophile undergoes α subsequent addition reaction (Chart 2). Molecular orbital calculations using the Spartan'04 Semi-Empirical Program PM3 of the cyclic allylic oxonium ion **X** in Chart 2 were carried out to study the origin of β orientation.

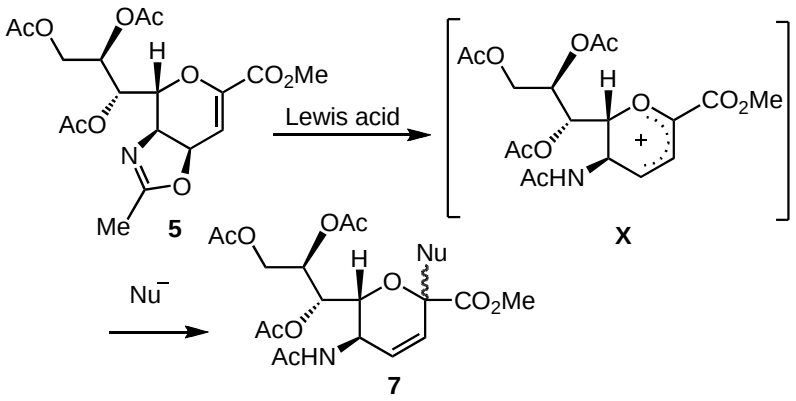


Chart 2. A possible mechanism for the formation of 7

The stereostructure of the lowest energy conformation of **X** is shown in Figure 3. The pyran ring has an almost planar conformation. This conformation led us to suppose that nucleophilic attack would occur from the β face of the donor moiety **X** to result in the predominant formation of β-glycoside, since the α face is hindered by the acetyl group at C-7 (Figure 3).

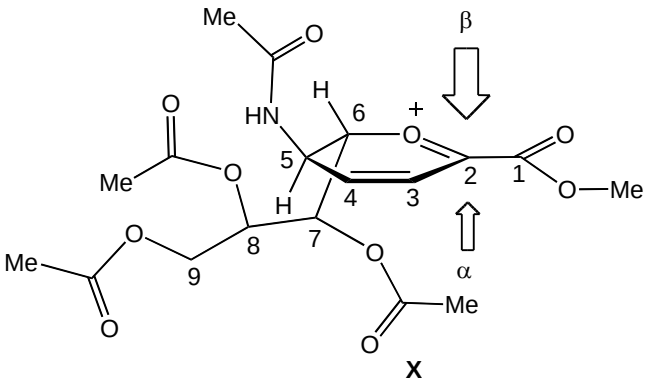
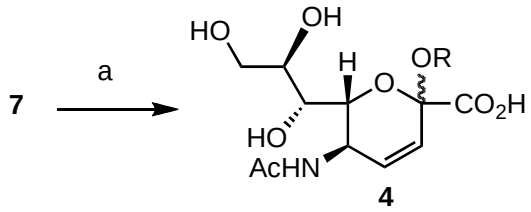


Figure 3. The stereostructure of the lowest energy conformation of X

De-*O*-acetylation of **4a** and subsequent saponification of the resulting methyl ester gave sialidase inhibitor **7a** in 92% yield in two steps (Table 3).

Table 3. Deprotection of **7** and its inhibitory activities against hPIV-1 sialidase



Reaction conditions: (a) (i) NaOMe, MeOH, rt, 15 h, 92%; (ii) 0.1 M KOH, MeOH, rt, 15 h, quant.

entry	compd	α : β	yield (%)	IC_{50} (mM)
1	**4a**	31 : 69	60	94
2	**4b**	11 : 89	52	12
3	**4c**	11 : 89	38	16
4	**4d**	67 : 33	32	3.0
5	**4e**	13 : 87	65	40
6	**4f**	60 : 40	28	2.9
7	**2**			0.2

BIOLOGICAL EVALUATIONS

The behavior of compounds **4a-f** toward hPIV-1 sialidase was tested by a fluorometric assay using 4-methylumbelliferyl *N*-acetyl-α-neuraminic acid as per our previously reported method.[22] As can be seen in Table 3, among synthesized compounds **4a-f**, compounds **4d** and **4f** showed the most inhibitory activity against hPIV-1 sialidase (IC_{50} = 2.9 mM and 3.0 mM, respectively) (Table 3, entries 4 and 6). However, the degree of inhibition of **4f** was much weaker than that of **1** (IC_{50} = 0.2 mM). It is suggested that the expression of inhibitory activity of sialic acid derivatives against hPIV-1 requires the structural feature of a 2,3-double bond of sialic acid.

The present findings should provide useful information for the development of anti-human parainfluenza virus compounds.

CONCLUSIONS

Our synthesis approach is the first example of the Ferrier glycosylation reaction for the construction of 3,4-unsaturated sialic acid derivatives. It is important to use the combination of $Bi(OTf)_3$ and

montmorillonite K-10 for higher yields in the Ferrier glycosylation reaction. We believe that this synthesis method provides a practical route to establish novel 3,4-unsaturated sialic acid analogs. The use of inexpensive and readily accessible $Bi(OTf)_3$ with high yields makes it a useful and attractive alternative to the more expensive lanthanide triflate or stoichiometric conventional Lewis acid-promoted *O*-glycosidation procedures. We are currently applying this methodology to the development of new hPIV-1 inhibitors.

EXPERIMENTAL

All melting points are uncorrected. Optical rotations were measured with a JASCO P-1030s (Japan) digital polarimeter. FT-IR spectra were recorded on a SHIMADZU IRPrestige-21 (Japan) spectrometer. ^{1}H 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 ($\delta = 0$) in $CDCl_3$ and in D_2O referenced to HOD (4.85 ppm) as internal standards. MS and high-resolution (HR)-FAB-MS data were obtained using a JEOL JMS-700 (Japan) spectrometer in the positive mode with an NBA matrix. MS and high-resolution ESI (HR-ESI) were measured on a JEOL JMS-T100LC (Japan) mass spectrometer. Column chromatography was performed on Silica Gel 60 (70-230 mesh, Merck). All reactions were monitored using TLC (Silica Gel $60F_{254}$, E. Merck, Germany) by charring after spraying 5% H_2SO_4 in MeOH and then heating.

5-Acetamido-2-methoxy-6-(1,2,3-triacetoxypropyl)-5,6-dihydro-2*H*-pyran-2-carboxylic acid methyl ester (7a): The oxazoline derivative **5** (50 mg, 0.12 mmol) was dissolved in a mixture of 1.0 mL of MeCN and 0.1 mL of MeOH under argon, and $Bi(OTf)_3$-montmorillonite K-10 (20 mg, 30% w/w) was added. The reaction mixture was allowed to stand at room temperature for 20 h. The reaction mixture was filtered over Celite, and several drops of NEt_3 were added. The solvent was then evaporated and the residue obtained purified by chromatography over silica gel with CH_2Cl_2/MeOH (10:1). Yield of **7a**: (51 mg) (95%); α-**7a**: ^{1}H-NMR ($CDCl_3$) δ: 1.99 (3H, s), 2.05, 2.12, 2.14 (each 3H, s), 3.34 (3H, s), 3.78 (3H, s), 4.24 (1H, dd, *J* = 12.4, 5.9 Hz), 4.26 (1H, ddd, *J* = 9.2, 9.8, 2.1 Hz), 4.48 (1H, dd, *J* = 2.4, 12.4 Hz), 4.52 (1H, m), 5.35 (1H, dd, *J* = 6.1, 2.1 Hz), 5.44 (1H, m), 5.59 (1H, d, *J* = 5.9 Hz), 5.78 (1H, dd, *J* = 10.1, 2.6 Hz), 6.07 (1H, dd, *J* = 1.9, 10.1 Hz). β-**7a**: ^{1}H-NMR ($CDCl_3$) δ: 1.99 (3H, s), 2.04, 2.10, 2.16 (each 3H, s), 3.29 (3H, s), 3.82 (3H, s), 4.05 (1H, dd, *J* = 10.2, 2.3 Hz), 4.24 (1H, dd, *J* = 12.5, 6.3 Hz) 4.63 (1H, dd, *J* = 2.3, 12.5 Hz), 4.64 (1H, d, *J* = 10.2 Hz), 5.35 (1H, m), 5.40 (1H, dd, *J* = 5.6, 2.3 Hz), 5.51 (1H, d, *J* = 9.6 Hz), 5.91 (2H, m). Positive ion MS (ESI) *m/z*: 468 $(M+Na)^+$. HR-MS (ESI) Calcd for $C_{19}H_{27}O_{11}NNa$ $(M+Na)^+$: 468.14818; Found: 468.14515.

5-Acetamido-2-ethoxy-6-(1,2,3-triacetoxypropyl)-5,6-dihydro-2*H*-pyran-2-carboxylic acid methyl ester (7b): The reaction was carried out using **5** (50 mg, 0.12 mmol) and $Bi(OTf)_3$-montmorillonite K-10 (20 mg, 30% w/w) in a mixture of 1.0 mL of MeCN and 0.1 mL of EtOH in a manner similar to the preparation of **7a**, to give **7b** (20 mg, 77%). β-**7b**: ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, t, *J* = 7.1 Hz), 1.98 (3H, s), 2.04, 2.10, 2.16 (each 3H, s), 3.41 (1H, m), 3.64 (1H, m), 3.81 (3H, s), 4.07 (1H, dd, *J* = 10.3, 2.9 Hz), 4.24 (1H, dd, *J* = 12.3, 6.3 Hz), 4.65 (1H, dd, *J* = 2.7, 12.3 Hz), 4.68 (1H, m), 5.29 (1H, m), 5.39 (1H, dd, *J* = 2.9, 4,5 Hz), 5.51 (1H, d, *J* = 9.7 Hz), 5.89 (1H, d, *J* = 10.3 Hz), 5.94 (1H, dd, *J* = 2.0, 10.3 Hz). ^{13}C-NMR ($CDCl_3$) δ:15.3, 20.7, 20.8, 21.1, 23.3, 43.0, 52.8, 60.4, 62.3, 68.3, 70.6, 71.3, 96.1, 126.2, 133.3, 167.8, 169.8, 170.1, 170.5, 170.6. Positive ion MS (ESI) *m/z*: 482 $(M+Na)^+$. HR-MS (ESI) Calcd for $C_{20}H_{29}O_{11}NNa$ $(M+Na)^+$: 482.16383; Found: 482.16209.

5-Acetamido-2-propoxy-6-(1,2,3-triacetoxypropyl)-5,6-dihydro-2*H*-pyran-2-carboxylic acid methyl ester (7c): The reaction was carried out using **5** (50 mg, 0.12 mmol) and $Bi(OTf)_3$-montmorillonite K-10 (20 mg, 30% w/w) in a mixture of 1.0 mL of MeCN and 0.1 mL of *n*-PrOH in a manner similar to the preparation of **7a**, to give **7c** (43 mg, 77%). β-**7c**: ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, *J* = 7.5 Hz), 1.57 (2H, m), 1.96 (3H, s), 2.02, 2.08, 2.14 (each 3H, s), 3.27 (1H, m), 3.52 (1H, m), 3.79 (3H, s), 4.06 (1H, dd, *J* = 10.3, 2.3 Hz), 4.24 (1H, dd, *J* = 12.6, 7.4 Hz), 4.65 (1H, m), 4.69 (1H, dd, *J* = 2.1, 12.6 Hz), 5.25 (1H, m), 5.38 (1H, dd, *J* = 2.3, 5.8 Hz), 5.45 (1H, d, *J* = 9.7 Hz), 5.86 (1H, dd, *J* = 10.0, 2.6 Hz), 5.94 (1H, d, *J* = 10.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 10.4, 20.7, 20.8, 21.0, 23.0, 23.3, 42.9, 52.8, 62.4, 66.3, 68.5, 70.8, 71.8, 96.0, 126.2, 133.2, 167.7, 169.9, 170.2, 170.5, 170.6. Positive ion HR-FABMS (NBA) (*m/z*) Calcd for $C_{21}H_{32}NO_{11}$ $[M+H]^+$: 474.1975; Found 474.1960.

5-Acetamido-2-isopropoxy-6-(1,2,3-triacetoxypropyl)-5,6-dihydro-2*H*-pyran-2-carboxylic acid methyl ester (7d): The reaction was carried out using **5** (50 mg, 0.12 mmol) and $Bi(OTf)_3$-montmorillonite K-10 (20 mg, 30% w/w) in a mixture of 1.0 mL of MeCN and 0.1 mL of *i*-PrOH in a manner similar to the preparation of **7a**, to give **7d** (19 mg, 32%). β-**7d**: ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, d, *J* = 5.7 Hz), 1.23 (3H, d, *J* = 6.3 Hz), 1.97 (3H, s), 2.04, 2.05, 2.09 (each 3H, s), 3.80 (3H, s), 4.11-4.16 (2H, m), 4.27 (1H, dd, *J* = 12.6, 8.0 Hz), 4.72 (1H, m), 4.83 (1H, dd, *J* = 12.6, 2.0 Hz), 5.28 (1H, m), 5.41 (1H, dd, *J* = 3.0, 5.0 Hz), 5.45 (1H, d, *J* = 9.7 Hz), 5.84 (1H, d, *J* = 10.0 Hz), 6.04 (1H, dd, *J* = 2.3, 10.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 20.7, 21.1, 22.7, 23.3, 24.6, 42.9, 52.7, 62.7, 67.8, 69.4, 71.2, 72.5, 94.5, 126.7, 132.3, 168.0, 169.8, 170.1, 170.6, 170.9. Positive ion MS (ESI) *m/z*: 496 $(M+Na)^+$. HR-MS (ESI) Calcd for $C_{21}H_{31}O_{11}NNa$ $(M+Na)^+$: 496.17948; Found: 496.18086.

5-Acetamido-2-butoxy-6-(1,2,3-triacetoxypropyl)-5,6-dihydro-2*H*-pyran-2-carboxylic acid methyl

ester (7e): The reaction was carried out using **5** (50 mg, 0.12 mmol) and $Bi(OTf)_3$-montmorillonite K-10 (20 mg, 30% w/w) in a mixture of 1.0 mL of MeCN and 0.1 mL of *n*-BuOH in a manner similar to the preparation of **7a**, to give **7e** (30 mg, 50%). β-**7e**: ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, *J* = 7.4 Hz), 1.36 (2H, dt, *J* = 15.5, 7.4 Hz), 1.54 (2H, m), 1.97 (3H, s), 2.03, 2.09, 2.15 (each 3H, s), 3.31 (1H, m), 3.56 (2H, m), 3.80 (3H, s), 4.07 (1H, dd, *J* = 10.3, 2.3 Hz), 4.25 (1H, dd, *J* = 12.3, 7.5 Hz), 4.67 (1H, m), 4.69 (1H, dd, *J* =2.5, 12.3 Hz), 5.26 (1H, m), 5.39 (1H, dd, *J* = 2.3, 2.3 Hz), 5.49 (1H, d, *J* = 9.7 Hz), 5.87 (1H, d, *J* = 10.0 Hz), 5.94 (1H, dd, *J* = 2.3, 10.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 13.8, 19.2, 20.71, 20.74, 21.0, 23.3, 31.8, 42.9, 52.7, 62.4, 64.6, 68.5, 70.8, 96.0, 126.2, 133.2, 167.7, 169.8, 170.1, 170.5, 170.6. Positive ion HR-FABMS (NBA) (*m/z*) Calcd for $C_{22}H_{34}NO_{11}$ $[M+H]^+$: 488.2132, Found 488.2147.

5-Acetamido-2-benzyloxy-6-(1,2,3-triacetoxypropyl)-5,6-dihydro-2*H*-pyran-2-carboxylic acid methylester (7f): The reaction was carried out using **5** (50 mg, 0.12 mmol) and $Bi(OTf)_3$-montmorillonite K-10 (20 mg, 30% w/w) in a mixture of 1.0 mL of MeCN and 0.1 mL of benzyl alcohol in a manner similar to the preparation of **7a**, to give **7f** (26 mg, 41%). β-**7f**: ^{1}H-NMR ($CDCl_3$) δ: 1.95 (3H, s), 1.97, 2.04, 2.17 (each 3H, s), 3.76 (3H, s), 4.15 (1H, dd, *J* = 10.3, 2.3 Hz), 4.25 (1H, dd, *J* = 12.8, 6.5 Hz), 4.48 (1H, d, *J* = 12.0 Hz), 4.64 (1H, d, *J* = 12.0 Hz), 4.67 (1H, m), 4.70 (1H, dd, *J* = 2.0, 12.8 Hz), 5.32 (1H, m), 5.41 (1H, dd, *J* = 5.3, 2.3 Hz), 5.71 (1H, br d), 5.91 (1H, d, *J* = 10.0 Hz), 6.02 (1H, dd, *J* = 2.6, 10.0 Hz), 7.35 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 20.7, 20.8, 23.2, 30.3, 38.6, 43.0, 50.8, 52.8, 62.3, 66.5, 68.3, 70.7, 71.4, 96.0, 125.8, 127.5, 127.8, 128.4, 133.4, 136.9, 167.6, 170.0, 170.1, 170.6, 170.7. Positive ion MS (ESI) *m/z*: 544 $(M+Na)^+$. HR-MS (ESI) Calcd for $C_{25}H_{31}O_{11}NNa$ $(M + Na)^+$: 544.17948; Found: 544.18228.

5-Acetamido-2-dodecylsulfanyl-6-(1,2,3-triacetoxypropyl)-5,6-dihydro-2*H*-pyran-2-carboxylic acid methyl ester (7g): The reaction was carried out using **5** (50 mg, 0.12 mmol), 1-dodecanethiol (98 mg, 0.48 mmol) and $BF_3{\cdot}OEt_2$ (34 mg, 0.24 mmol) in 1.0 mL of CH_2Cl_2 in a manner similar to the preparation of **7a**, to give **7g** (30 mg, 40%). α-**7g:** ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.9 Hz), 1.30 (18H, m), 1.48 (2H, q, *J* = 7.3 Hz), 1.98 (3H, s), 2.05, 2.10, 2.15 (each 3H, s), 2.57 (2H, m), 3.82 (3H, s), 4.28 (1H, dd, *J* = 12.3, 7.2 Hz), 4.36 (1H, dd, *J* = 10.0, 2.4 Hz), 4.64 (1H, m), 4.68 (1H, dd, *J* = 2.3, 12.3 Hz), 5.21 (1H, ddd, *J* = 4.4, 7.2, 2.3 Hz), 5.40 (1H, dd, *J* = 2.4, 4.4 Hz), 5.48 (1H, br d), 5.75 (1H, d, *J* = 10.3, Hz), 6.13 (1H, dd, *J* = 2.6, 10.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 14.1, 20.7, 21.0, 22.6, 23.3, 24.6, 28.3, 29.0, 29.3, 29.4, 29.5, 29.6, 31.8, 34.0, 42.8, 52.8, 62.5, 68.5, 70.7, 85.4, 126.4, 130.5, 167.3, 169.7, 170.2, 170.5. Positive ion MS (ESI) *m/z*: 638 $(M+Na)^+$. HR-MS (ESI) Calcd for $C_{30}H_{49}O_{10}NSNa$ $(M+Na)^+$: 638.29749; Found: 638.29845.

5-Acetamido-2-methoxy-6-(1,2,3-trihydroxypropyl)-5,6-dihydro-2*H*-pyran-2-carboxylic acid (4a): To a solution of compound **7a** (65 mg, 0.15 mmol) in dry MeOH (1.0 mL) was added NaOMe (2

drops, 25% w/w MeOH solution) and the mixture was stirred for 1 h at 0 °C under Ar, and then Amberlite IRC-50 (0.5 g) resin was added to remove sodium ions, after which the sample was filtered and concentrated to dryness. The residue was dissolved in MeOH (1.0 mL) and to the mixture was added 5 drops of 1.0 M NaOH aqueous solution at room temperature: the mixture was then stirred overnight, made neutral with Amberlite IR-120 (H^+ form) (0.2 g) resin, filtered, and the filtrate was concentrated to dryness. The residue was purified by silica gel column chromatography using $CHCl_3$-MeOH-H_2O (6:6:1) to give **4a** (27 mg, 60%). FT-IR (neat) 1734, 1616, 1373, 1080 cm^{-1}; ^{1}H-NMR (D_2O) δ: 1.84 (3H, s), 3.12 (3H, s), 3.47-3.51 (2H, m), 3.64 (1H, dd, *J* = 2.9, 12.0 Hz), 3.74-3.78 (1H, m), 3.83 (1H, d, *J* = 10.4 Hz), 4.58 (1H, d, *J* = 10.4 Hz), 5.77 (2H, s). MS (ESI) *m/z*: 328 $(M+Na)^+$. HR-MS (ESI) Calcd for $C_{12}H_{19}O_8NNa$ $(M+Na)^+$: 328.10084; Found: 328.09663.

5-Acetamido-2-ethoxy-6-(1,2,3-trihydroxypropyl)-5,6-dihydro-2*H*-pyran-2-carboxylic acid (4b): The reaction was carried out using **7b** (13 mg, 0.03 mmol) in a manner similar to the preparation of **4a**, to give **4b** (5 mg, 52%), FT-IR (neat) 1734, 1363, 1217, 648 cm^{-1}; ^{1}H-NMR (D_2O) δ: 1.01 (3H, t, *J* = 6.9 Hz), 1.85 (3H, s), 3.22 (1H, q, *J* = 9.2 Hz), 3.45-3.56 (3H, m), 3.64 (1H, dd, *J* = 2.9, 12.1 Hz), 3.71-3.72 (1H, m), 3.85 (1H, d, *J* = 10.3 Hz), 4.56 (1H, d, *J* = 10.3 Hz), 5.77 (2H, s). MS (ESI) *m/z*: 342 $(M+Na)^+$. HR-MS (ESI) Calcd for $C_{13}H_{21}O_8NNa$ $(M+Na)^+$: 342.11649; Found: 342.11428.

5-Acetamido-2-propoxy-6-(1,2,3-trihydroxypropyl)-5,6-dihydro-2*H*-pyran-2-carboxylic acid (4c): The reaction was carried out using **7c** (19 mg, 0.04 mmol) in a manner similar to the preparation of **4a**, to give **4c** (5 mg, 38%). FT-IR (neat) 1734, 1364, 1217, 632 cm^{-1}; ^{1}H-NMR (D_2O) δ: 0.71 (3H, t, *J* = 7.5 Hz), 1.39 (2H, q, *J* = 6.9 Hz), 1.83 (3H, s), 3.10-3.15 (1H, m), 3.41-3.51 (3H, m), 3.62-3.67 (1H, m), 3.68-3.76 (1H, m), 3.80 (1H, t, *J* = 10.4 Hz), 4.54 (1H, d, *J* = 10.4 Hz), 5.73-5.77 (2H, m). MS (ESI) *m/z*: 356 $(M+Na)^+$. HR-MS (ESI) Calcd for $C_{14}H_{23}O_8NNa$ $(M+Na)^+$: 356.13214; Found: 356.13227.

5-Acetamido-2-isopropoxy-6-(1,2,3-trihydroxypropyl)-5,6-dihydro-2*H*-pyran-2-carboxylic acid (4d): The reaction was carried out using **7d** (43 mg, 0.09 mmol) in a manner similar to the preparation of **4a**, to give **4d** (10 mg, 32%). FT-IR (neat) 2922, 1737, 1624, 1259, 1072 cm^{-1}; ^{1}H-NMR (D_2O) δ: 0.98-1.05 (6H, m), 1.85 (3H, s), 3.17 (1H, t, *J* = 8.0 Hz), 3.43-3.50 (2H, m), 3.65-3.93 (3H, m), 5.78 (1H, dd, *J* = 2.3, 9.8 Hz), 5.86 (1H, dt, *J* = 2.0, 12.4 Hz). MS (ESI) *m/z*: 356 $(M+Na)^+$. HR-MS (ESI) Calcd for $C_{14}H_{23}O_8NNa$ $(M+Na)^+$: 356.13214; Found: 356.13399.

5-Acetamido-2-butoxy-6-(1,2,3-trihydroxypropyl)-5,6-dihydro-2*H*-pyran-2-carboxylic acid (4e): The reaction was carried out using **7e** (28 mg, 0.06 mmol) in a manner similar to the preparation of **4a**,

to give **4e** (14 mg, 65%). FT-IR (neat) 3304, 2924, 1730, 1627, 1541, 1074 cm^{-1}; ^{1}H-NMR (D_2O) δ: 0.66-0.70 (3H, m), 1.12-1.32 (2H, m), 1.28-1.38 (2H, m), 1.82 (3H, s), 3.16-3.20 (1H, m), 3.37-3.43 (2H, m), 3.48-3.56 (1H, m), 3.61-3.82 (2H, m), 3.89 (1H, dd, *J* = 1.1, 10.4 Hz), 4.53 (1H, t, *J* = 9.8 Hz), 5.75-5.80 (2H, m). MS (ESI) *m/z*: 370 $(M+Na)^+$. HR-MS (ESI) Calcd for $C_{15}H_{25}O_8NNa$ $(M+Na)^+$: 370.14779; Found: 370.14971.

5-Acetamido-2-benzyloxy-6-(1,2,3-trihydroxypropyl)-5,6-dihydro-2*H*-pyran-2-carboxylic acid (4f): The reaction was carried out using **7f** (43 mg, 0.08 mmol) in a manner similar to the preparation of **4a**, to give **4f** (9 mg, 28%). FT-IR (neat) 3317, 2924, 1734, 1627, 1541, 1074, 1035 cm^{-1}; ^{1}H-NMR (D_2O) δ: 1.83 (3H, s), 3.42-3.49 (2H, m), 3.65-3.69 (1H, m), 3.81 (1H, dd, *J* = 1.7, 9.8 Hz), 3.89 (1H, d, *J* = 10.0 Hz), 4.42 (2H, s), 4.53-4.56 (1H, m), 5.78-5.85 (1H, m), 5.93 (1H, dd, *J* = 1.7, 8.0 Hz), 7.17-7.25 (5H, m). MS (ESI) *m/z*: 404 $(M+Na)^+$. HR-MS (ESI) Calcd for $C_{18}H_{23}O_8NNa$ $(M+Na)^+$: 404.13214; Found: 404.13361.

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