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Note

An improved procedure for nucleoside synthesis using glycosyl trifluoroacetimidates as donors

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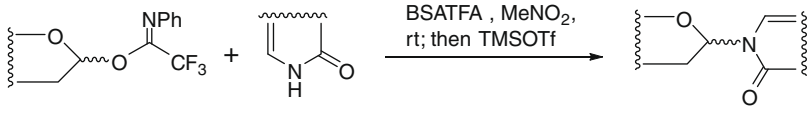
ABSTRACT

Using glycosyl trifluoroacetimidates as donors and nitromethane (or acetonitrile) as solvent, silylation and subsequent glycosylation were realized in a 'one-pot' procedure to provide the corresponding nucleosides derivatives in high yields.



Nucleosides, which are components of nucleic acids, themselves possess many essential functions such as regulating enzyme and cell activities and controlling physiological blood pressure.[1] Analogs of nucleosides have been used as therapeutic agents such as antitumor and antiviral agents.[2,3] Moreover, with the development of RNA interference and antisense oligonucleotides technologies, the importance of unnatural oligonucleotides increased dramatically. They can provide an oligonucleotide mimic that binds to mRNA in a complimentary fashion and meanwhile tolerate degradation pathways. Other reasons for modification of the nucleic acids include the desire to expand the genetic code and to understand the scope and limits of the Watson–Crick base-pairing. Modifications at the sugar portion (e.g., use of a hexose instead of the pentose) or at the nucleobase portion (e.g., through expanding the size of the naturally occurring bases) will go a long way in addressing these questions.[4]

The exceptional importance of nucleic acids in life science has fueled the development of chemical synthesis methodologies of nucleosides. To date, three types of chemical synthesis strategies have been employed: (1) condensation of the sugar moiety and the base directly; (2) construction of the base moiety after introduction of a functional group at the anomeric position of the sugar moiety; (3) derivatization of naturally occurring nucleosides.[5] Compared to the last two, the first method is the most frequently adopted approach for the synthesis of nucleosides, in that this method is highly convergent and flexible.[6,7] Nevertheless, in this method the activation of bases to trimethylsilyl ethers is usually required; the resulting trimethylsilyl ethers are either purified by distillation or used directly after evaporation of the solvent in the subsequent glycosylation.[8] The highly hydrolyzable property of the activated bases makes their handling quite difficult. If the activation and glycosylation steps could be conducted in the same vessel and same solvent, nucleoside synthesis would become much more convenient. By choosing the appropriate silylating reagent and solvent and trifluoroacetimidates as donors, we realized such a one-pot procedure for nucleosides synthesis.[9] Herein, we report the results on this matter.

Recently, we have found that *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) was a better silylating reagent when glycosyl trifluoroacetimidates were used as donors in nucleoside synthesis.[10] Using the N-glycosylation reaction between 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl *N*-phenyl-2,2,2-trifluoroacetimidate **1a** and uracil **2a** as a model, different solvents and amounts of TMSOTf were examined (Table 1). 1,2-Dichloroethane, the common solvent that is used in Vorbrüggen's method, was tested first. However, the silylation step did not proceed in this solvent at room temperature; thus, no desired glycosylation product was detected in the presence of donor **1a** and TMSOTf (entry 1). To our delight, when acetonitrile was used as solvent, the silylation proceeded smoothly. Upon addition of 1 equiv of TMSOTf, the glycosylation took place to provide the desired nucleoside **3aa** in a satisfactory 75% yield (entry 2). When the amount of the promoter was reduced to a catalytic amount of 0.1 equiv, there was no evident decrease in yield, but a longer reaction time (24 h) was required to secure an acceptable yield (70%; entry 3). The reaction rate and yield could be fur-

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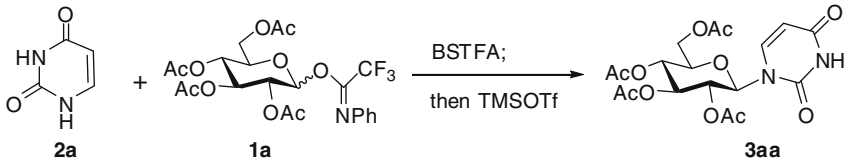
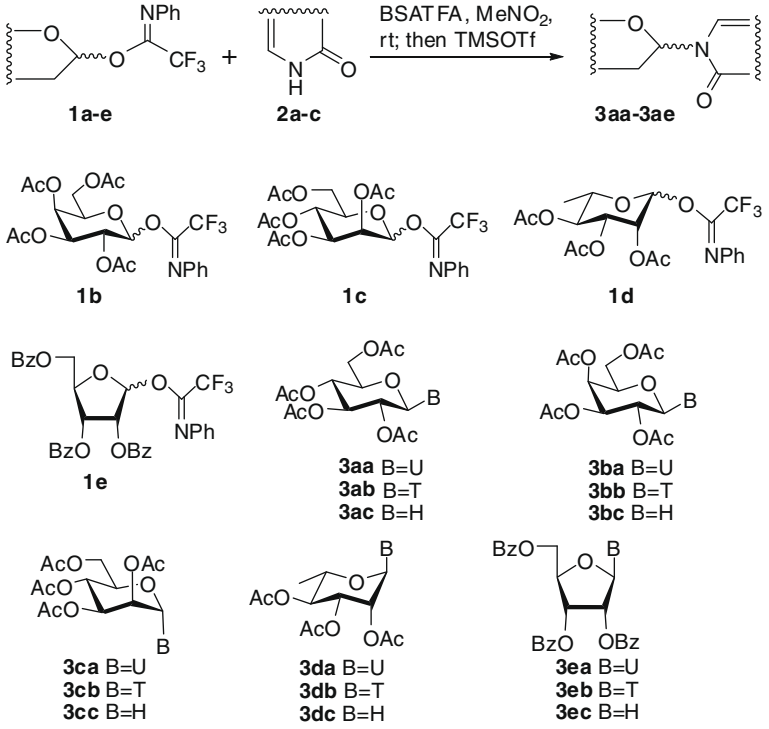
Table 1
Attempts at one-pot N-glycosylation of uracil **2a** and glucosyl trifluoroacetimidates **1a**



Entry	Solvent	Amount of TMSOTf (equiv)	Reaction time (h)	Yield[a] (%)	α:β
1	$ClCH_2CH_2Cl$	1.0	12	0	—
2	CH_3CN	1.0	6	75	β
3	CH_3CN	0.1	24	70	β
4	CH_3NO_2	1.0	4	81	β
5	CH_3NO_2	0.1	24	75	β

[a] Isolated yield.



Scheme 1. Nucleoside synthesis employing a one-pot procedure.

ther improved when nitromethane was used as solvent (entry 4). As was the case in acetonitrile, a reduction of the amount of the promoter slowed down the rate of the reaction (entry 5). These preliminary results demonstrate that the combined use of nitromethane as solvent and 1 equiv of TMSOTf as the promoter is optimal to provide the desired nucleoside expeditiously.

Next, the substrate scope of this one-pot procedure was investigated. Thus, the frequently occurring bases uracil (**2a**), thymine (**2b**), and 2-hydroxypyridine (**2c**) were selected as glycosylation acceptors to react with pyranosyl and furanosyl trifluoroacetimidates **1a–e** (Scheme 1).[10–12] In all these coupling reactions, very high yields of the glycosylation products (**3aa–ec**) were isolated (79–99%, Table 2). In particular, when 2-hydroxypyridine **3c** was used as the base, no O-glycosylation products were detected.[13] It is also worth noting that the activity of the silylated 2-hydroxypyridine is much higher than that of uracil (**2a**) and thymine (**2b**); thus, 0.2 equiv of TMSOTf is sufficient to promote the glycosylation to proceed completely (entries 3, 6, 9, and 12). In addition, for the furanosyl donor **1e**, acetonitrile proved to be the better solvent for the glycosylation (entries 13–15).

In the above one-pot procedure, O-glycosylation of 2-hydroxypyridine was not detected. In fact, the 2-pyridyl-*O*-glycosides have been used as glycosyl donors for the synthesis of biologically relevant oligosaccharides.[19] The previous synthesis of these glycosyl donors employed glycosyl halides as precursors and gave only moderate yields of the products.[20] Selective O-glycosylation of 4-pyridone has been reported,[13,21] but not that of 2-pyridone. Here we found that selective O-glycosylation of 2-pyridone could be successfully realized with CH_2Cl_2 as the solvent in the glycosylation step. Under the action of a catalytic amount of TMSOTf

Table 2
One-pot synthesis of nucleosides with glycosyl trifluoroacetimidates as donors[a]

Entry	Donor	Acceptor	Product	TMSOTf (equiv)	Yield[b] (%)	α:β
1	**1a**	**2a**	**3aa**[14]	1.0	81	β
2	**1a**	**2b**	**3ab**[15]	1.0	98	β
3	**1a**	**2c**	**3ac**[10]	0.2	95[c]	β
4	**1b**	**2a**	**3ba**[14]	1.0	98	β
5	**1b**	**2b**	**3bb**[16]	1.0	88	β
6	**1b**	**2c**	**3bc**	0.2	94[c]	β
7	**1c**	**2a**	**3ca**	1.0	83	α
8	**1c**	**2b**	**3cb**	1.0	91	α
9	**1c**	**2c**	**3cc**	0.2	80[c]	α
10	**1d**	**2a**	**3da**	1.0	79	α
11	**1d**	**2b**	**3db**	1.0	97	α
12	**1d**	**2c**	**3dc**	0.2	86[c]	α
13	**1e**	**2a**	**3ea**[17]	1.0	88[c]	β
14	**1e**	**2b**	**3eb**[18]	1.0	98[c]	β
15	**1e**	**2c**	**3ec**[9]	1.0	99[c]	β

[a] Unless otherwise mentioned, reactions were conducted in $MeNO_2$.
[b] Isolated yield.
[c] MeCN was used as solvent.

(0.2 equiv), glycosyl trifluoroacetimidates reacted smoothly with the silylated 2-hydroxypyridine to provide the *O*-glycosides **4a–d** in good to excellent yields (77–90%; Table 3). The structures of **4a–d** could be definitely determined from ^{13}C spectrum with the anomeric ^{13}C chemical shift being above 90 ppm (93.2, 93.8, 91.8, and 91.7 ppm, respectively), while those of the N-glycosylation counterparts are below 80 ppm (79.0, 79.4, 75.6, and 73.8 ppm, respectively).

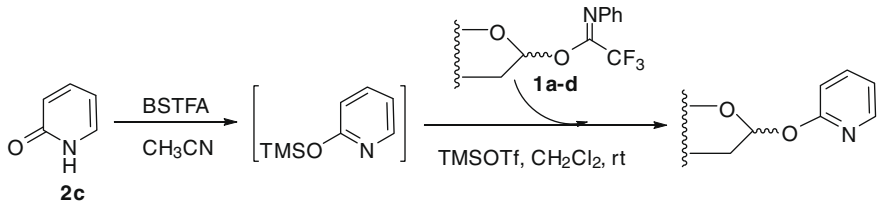
In conclusion, by employing glycosyl trifluoroacetimidates as donors, a highly efficient one-pot procedure for nucleoside synthesis was developed using nitromethane (or acetonitrile) as the solvent, BSTFA as silylating reagent, and TMSOTf as the glycosylation promoter. In contrast to conventional methods, the present procedure avoids handling of the silylated bases prior to glycosylation. In addition, selective O-glycosylation of 2-hydroxypyridine was achieved by treatment of the silylated 2-hydroxypyridine with glycosyl trifluoroacetimidates and TMSOTf in CH_2Cl_2.

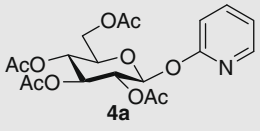
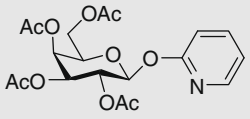
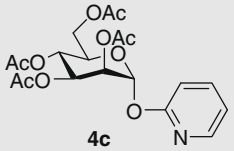
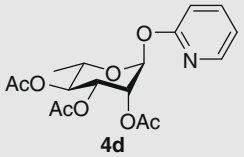
1. Experimental

1.1. General methods

Solvents were purified in the usual way. Thin layer chromatography (TLC) was performed on precoated plates of Silica Gel HF254 (0.5 mm, Yantai, China). Flash column chromatography was performed on Silica Gel H (10–40 μ, Yantai, China). Optical rotations were determined with a Perkin–Elmer Model 241 MC polarimeter. NMR spectra were recorded on a Bruker AM 300 spectrometer with Me_4Si as the internal standard. *J* values were given in hertz. Mass spectra were obtained on a HP5989A or a VG Quatro mass spectrometer.

Table 3
Selective O-glycosylation of 2-hydroxypyridine **2c**



Entry	Donor	Acceptor	Product	Promoter (equiv)	Yield[a] (%)	α:β
1	**1a**	**2c**	 **4a**	0.2	90[10]	β
2	**1b**	**2c**	 **4b**	0.2	79	β
3	**1c**	**2c**	 **4c**	0.2	86	α
4	**1d**	**2c**	 **4d**	0.2	77	α

[a] Isolated yield.

1.2. General procedure for the one-pot nucleoside synthesis

To a stirred suspension of base, glycosyl *N*-phenyltrifluoroacetimidate, and 4 Å MS in dry CH_3NO_2 was added BSTFA (1.5 equiv to base). The mixture was stirred at rt for 30 min and then TMSOTf was added. Stirring was continued at rt until the glycosyl donor was consumed as monitored by TLC. After Et_3N was added to quench the reaction, the 4 Å MS were removed by filtration. Evaporation of the solvent gave a residue that was further purified by chromatography.

1.2.1. 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-1,2-dihydropyridin-2-one (3bc)

$[\alpha]_D^{25}$ +107.8 (*c* 1.1, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 6.0 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 1H), 6.51 (d, *J* = 9.3 Hz, 1H), 6.32–6.23 (m, 2H), 5.53 (d, *J* = 2.7 Hz, 1H), 5.39 (dd, *J* = 9.0, 10.2 Hz, 1H), 5.23 (dd, *J* = 3.3, 10.2 Hz, 1H), 4.19–4.10 (m, 3H), 2.20, 2.04, 1.99, 1.94 (s each, 4 × 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.7, 169.5, 169.4, 140.0, 132.8, 120.1, 106.4, 79.4, 73.5, 70.7, 68.1, 66.9, 61.1, 20.4, 20.3, 20.1. HRMS (ESI) Calcd for $C_{19}H_{23}NO_{10}Na$ [M+Na$^+$]: 448.1214. Found: 448.1221.

1.2.2. 1-(2,3,4,6-Tetra-*O*-acetyl-D-mannopyranosyl) uracil (3ca)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (br s, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 6.16 (d, *J* = 9.9 Hz, 1H), 5.80 (d, *J* = 8.1 Hz, 1H), 5.49 (t, *J* = 3.3 Hz, 1H), 5.37 (dd, *J* = 3.3, 9.9 Hz, 1H), 4.98 (d, *J* = 3.3 Hz, 1H), 4.67 (dd, *J* = 9.6, 13.2 Hz, 1H), 4.37–4.31 (m, 2H), 2.21 (s, 3H), 2.18 (s, 3H), 2.09 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 169.3, 169.1, 168.8, 163.0, 150.3, 139.6, 103.2, 75.7, 75.0, 67.9, 67.7, 65.6, 60.0, 20.6, 20.53, 20.47, 20.2. HRMS (ESI) Calcd for $C_{18}H_{22}NO_{11}Na$: 465.1116. Found: 465.1116.

1.2.3. 1-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl) thymine (3cb)

$[\alpha]_D^{25}$ +27.6 (*c* 1.0, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 7.15 (s, 1H), 6.17 (d, *J* = 9.6 Hz, 1H), 5.50 (t, *J* = 3.3 Hz, 1H), 5.37 (dd, *J* = 3.3, 9.9 Hz, 1H), 4.98 (d, *J* = 2.7 Hz, 1H), 4.65 (m, 1H), 4.39–4.26 (m, 2H), 2.21, 2.20, 2.09, 1.97, 1.95 (s, 5 × 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 169.5, 169.2, 168.9, 163.5, 135.0, 111.9, 75.9, 74.8, 68.2, 68.0, 65.7, 60.2, 20.9, 20.7, 20.6, 20.4, 12.5. HRMS (ESI) Calcd for $C_{19}H_{24}N_2O_{11}Na$ [M+Na$^+$]: 479.1270. Found: 479.1270.

1.2.4. 1-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl)-1,2-dihydropyridin-2-one (3cc)

$[\alpha]_D^{25}$ −42.6 (*c* 1.0, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 1.8, 6.9 Hz, 1H), 7.32 (dt, *J* = 1.8, 9.3 Hz, 1H), 6.62 (d, *J* = 9.6 Hz, 1H), 6.52 (d, *J* = 8.7 Hz, 1H), 6.24 (dt, *J* = 1.5, 7.8 Hz, 1H), 5.50 (dd, *J* = 3.6, 3.0 Hz, 1H), 5.43 (dd, *J* = 3.6, 9.3 Hz, 1H), 5.02 (dd, *J* = 1.8, 3.6 Hz, 1H), 4.62–4.34 (m, 3H), 2.22, 2.19, 2.08, 1.91 (s, 4 × 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 169.3, 169.1, 169.0, 161.9, 139.7, 132.7, 120.7, 106.3, 75.6, 74.0, 68.2, 68.0, 66.7, 60.3, 20.7, 20.6, 20.5, 20.2. HRMS (ESI) Calcd for $C_{19}H_{23}NO_{10}Na$ [M+Na$^+$]: 448.1214. Found: 448.1224.

1.2.5. 1-(2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl) uracil (3da)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 7.40 (d, *J* = 9.1 Hz, 1H), 6.23 (d, *J* = 9.6 Hz, 1H), 5.80 (d, *J* = 9.1 Hz, 1H), 5.45 (s, 1H), 5.30 (dd, *J* = 3.3, 9.6 Hz, 1H), 4.84 (d, *J* = 1.8 Hz, 1H), 4.30 (dd, *J* = 9.6, 14.4 Hz, 1H), 2.20, 2.17, 1.99 (s, 3 × 3H), 1.57 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 169.3, 169.1, 163.2, 150.6, 139.6, 103.2, 74.1, 73.5, 71.2, 68.5, 65.9, 20.8, 20.7, 20.3, 15.6. HRMS (ESI) Calcd for $C_{16}H_{20}N_2O_9Na$ [M+Na$^+$]: 407.1067. Found: 407.1061.

1.2.6. 1-(2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl) thymine (3db)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.17 (s, 1H), 6.24 (d, *J* = 9.9 Hz, 1H), 5.46 (dd, *J* = 2.4, 3.0 Hz, 1H), 5.30 (dd, *J* = 3.6, 9.9 Hz, 1H), 4.84 (d, *J* = 2.4 Hz, 1H), 4.30 (dd, *J* = 9.9, 14.4 Hz, 1H), 2.19, 2.18, 1.94, 1.91 (s, 4 × 3H), 1.56 (d, *J* = 4.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 169.4, 169.1, 163.7, 150.8, 134.9, 111.7, 74.1, 73.2, 71.3, 68.6, 65.9, 20.9, 20.7, 20.4, 15.7, 12.4. HRMS (ESI) Calcd for $C_{17}H_{22}N_2O_9Na$ [M+Na$^+$]: 421.1217. Found: 421.1218.

1.2.7. 1-(2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl)-1,4-dihydropyridin-2-one (3dc)

$[\alpha]_D^{25}$ +99.8 (*c* 1.0, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 6.6 Hz, 1H), 7.32 (dt, *J* = 2.1, 6.6 Hz, 1H), 6.72 (d, *J* = 9.9 Hz, 1H), 6.53 (d, *J* = 9.0 Hz, 1H), 6.24 (t, *J* = 6.9 Hz, 1H), 5.47 (t, *J* = 3.0 Hz, 1H), 5.37 (dd, *J* = 3.6, 9.6 Hz, 1H), 4.87 (d, *J* = 2.4 Hz, 1H), 4.33 (q, *J* = 7.5 Hz, 1H), 2.21, 2.18, 1.91 (s each, 3 × 3H), 1.61 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 169.2, 169.0, 161.8, 139.5, 132.6, 120.5, 106.1, 73.8, 72.3, 71.3, 68.5, 66.9, 20.7, 20.6, 20.1, 15.6. HRMS (ESI) Calcd for $C_{17}H_{21}NO_8Na$ [M+Na$^+$]: 390.1159. Found: 390.1167.

1.3. General procedure for O-glycosylation of 2-hydroxypyridine

To a stirred suspension of **2c** (1.5 equiv to the glycosyl donor) in dry acetonitrile was added BSTFA (1 equiv to the base). The mixture was stirred at rt for 30 min, during which time a clear solution was formed. After the solvent was removed under reduced pressure, the silylated base was obtained as a clear oil. Under argon atmosphere, the activated base was dissolved in dry CH_2Cl_2, followed by the addition of activated 4 Å MS and the glycosyl *N*-phenyltrifluoroacetimidate (1.0 equiv). After subsequent addition of TMSOTf, the resulting mixture was stirred at rt until the donor was consumed completely; normally, 4–24 h was required. After quenching the reaction with Et_3N and removing 4 Å MS by filtration, the solvent was removed under reduced pressure. The resulting residue was further purified by column chromatography to give the pure product.

1.3.1. 2-[(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-oxy] pyridine (4b)

$[\alpha]_D^{25}$ +24.7 (*c* 1.0, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 4.2 Hz, 1H), 7.66 (dd, *J* = 7.5, 7.8 Hz, 1H), 7.02 (t, *J* = 6.0 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.21 (d, *J* = 8.4 Hz, 1H), 5.55–5.47 (m, 2H), 5.19 (dd, *J* = 2.4, 10.2 Hz, 1H), 4.16 (s, 3H), 2.19 (s, 3H), 2.02 (s, 6H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.33, 170.28, 170.1, 169.5, 161.3, 146.7, 139.4, 118.9, 111.7, 93.8, 71.1, 71.0, 68.4, 67.0, 61.0, 20.70, 20.69, 20.66, 20.61. HRMS (ESI) Calcd for $C_{19}H_{23}NO_{10}Na$ [M+Na$^+$]: 448.1214. Found: 448.1221.

1.3.2. 2-[(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl)-oxy] pyridine (4c)

$[\alpha]_D^{25}$ +23.6 (*c* 1.0, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 1.5, 4.8 Hz, 1H), 7.69 (dt, *J* = 1.8, 8.4 Hz, 1H), 7.01 (t, *J* = 6.0 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.47 (d, *J* = 1.2 Hz, 1H), 5.58 (dd, *J* = 3.3, 9.9 Hz, 1H), 5.45–5.36 (m, 2H), 4.26 (dd, *J* = 4.8, 12.0 Hz, 1H), 4.16–4.05 (m, 2H), 2.19, 2.06, 2.02, 2.00 (s, 4 × 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 170.0, 169.95, 169.7, 160.4, 147.1, 139.4, 118.7, 111.3, 91.8, 69.6, 69.0, 65.9, 62.2, 20.8, 20.7, 20.6. HRMS (ESI) Calcd for $C_{19}H_{23}NO_{10}Na$ [M+Na$^+$]: 448.1214. Found: 448.1224.

1.3.3. 2-[(2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl)-oxy] pyridine (4d)

$[\alpha]_D^{25}$ −82.1 (*c* 1.0, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 3.9 Hz, 1H), 7.68 (dd, *J* = 6.9, 7.8 Hz, 1H), 6.99 (t, *J* = 6.0 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.39 (s, 1H), 5.53 (dd, *J* = 2.7, 10.5 Hz, 1H), 5.42 (s, 1H), 5.20 (dd, *J* = 9.9, 10.2 Hz, 1H), 4.06 (q, *J* = 5.7 Hz, 1H), 2.18, 2.06, 2.02 (s, 3 × 3H), 1.21 (d, *J* = 5.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 170.0, 169.9, 160.6, 147.0, 139.3, 118.5,

111.2, 91.7, 70.8, 69.2, 69.0, 67.7, 20.7, 20.66, 20.6, 17.3. HRMS (ESI) calcd for $C_{17}H_{21}NO_8Na$ [M+Na$^+$]: 390.1159. Found: 390.1167.

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