HETEROCYCLES, Vol. 75, No. 5, 2008, pp. 1213 - 1223. © The Japan Institute of Heterocyclic Chemistry
Received, 5th December, 2007, Accepted, 1st February, 2008, Published online, 5th February, 2008. COM-07-11289

APPLICABILITY OF METHYL 2,3,4-TRI-*O*-BENZOYL-1-METHANE-SULFONYL-α-D-GLUCOPYRANURONATE AS A NOVEL QUATERNARY GLUCURONYL REAGENT FOR TERTIARY AMINES

Ichiro Araya[*a,b] and Hiroyuki Akita[b]

[a] Research Center, Kyorin Pharmaceutical Co, Ltd., 1848, Nogi, Nogi-machi, Shimotsuga-Gun, Tochigi, 329-0114, Japan.
E-mail: ichirou.araya@mb.kyorin-pharm.co.jp

[b] Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan.

Abstract – Applicability of a methyl 2,3,4-tri-*O*-benzoyl-1-methanesulfonyl-α-D-glucopyranuronate **3** as a novel quaternary glucuronyl reagent was investigated. The reaction of **3** with an aromatic tertiary amines such as pyridine derivatives or imidazole derivatives proceeded to give quaternary *N*-glucuronides in a moderate yields, but the reaction of **3** with an aliphatic tertiary amine did not occur. In case of the reaction of **3** with nicotine which has aromatic and aliphatic tertiary amines in the molecule, the reaction proceeded selectively on the pyridine ring to give the corresponding *N*-glucuronide. The present reagent was considered to be useful for the formation of *N*-quaternary glucuronide from aromatic tertiary amines.

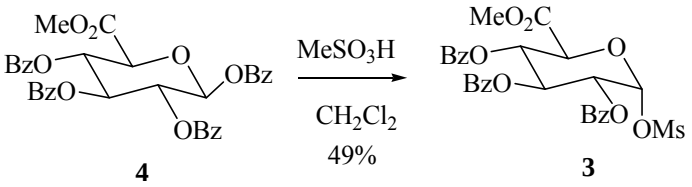
INTRODUCTION

In a study of metabolites of pharmaceuticals, quaternary glucuronidation of tertiary amines is a significant role in the metabolic eliminations of pharmaceuticals containing a tertiary amine group. It is important to synthesize an authentic sample of glucuronate derived from candidate compounds for drugs in order to confirm its structure and pharmacological activities. There have been many reports concerning the synthesis of β-*N*-quaternary glucuronide of tertiary amines using methyl 2,3,4-tri-*O*-acetyl-1-bromo-α-D-glucopyranuronate (**1**). In this case, the preparation of *α*-*N*-glucuronides is not reported.[1] The reaction of **1** with aliphatic tertiary amines such as H_1 antihistamine and tricyclic antidepressant drugs gave β-*N*-glucuronides in moderate yield after deprotection of protecting groups.[2] In contrast, in case of the reaction of **1** with aromatic tertiary amines, there are a few report of chemical synthesis. The reaction of **1**

with pyridine,[3] 1-phenylimidazole[4] and nicotine derivatives[5] is reported to give the corresponding *N*-glucuronide, respectively in low yields. These results seem to be low reactivity and stability of **1**, and less basicity of aromatic tertiary amine. In our initial investigation, 4-(2-methyl-1*H*-imidazol-1-yl)-2,2-diphenylbutanamide (**2**) possessing an imidazole moiety as a new type of treatment for urinary incontinence was not reacted with **1** in many reaction conditions, but **2** was reacted with methyl 2,3,4-tri-*O*-benzoyl-1-methanesulfonyl-α-D-glucopyranuronate (**3**) in $CHCl_3$ under reflux condition to afford the corresponding *N*-glucuronide in moderate yields.[6] In addition, compound **3** is stable under the room temperature for 3 months, while compound **1** was necessarily stored in the refrigerator. In the present study, we describe applicability of this newly prepared compound **3** for *N*-glucuronidation.

RESULTS AND DISCUSSION

First, synthesis of methyl 2,3,4-tri-*O*-benzoyl-1-methanesulfonyl-*α*-D-glucopyranuronate (**3**) as a new glycosyl donor is shown in Chart 1. By applying the reported method,[7] 1,2,3,4-tetra-*O*-benzoyl-β-D-glucopyranouronate (**4**) was synthesized from D-(+)-glucurono-3,6-lactone. Compound (**4**) was treated with methansulfonic acid in CH_2Cl_2 to afford α-methansulfonate (**3**) as a white powder in 49% yield.



4 **3**

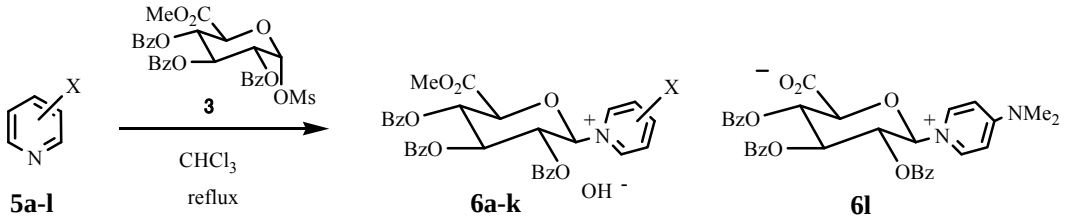
Chart 1

Next, we examined the quaternary glucuronidation reaction of aromatic tertiary amines using 1.2 equivalent of **3** in $CHCl_3$ under reflux for 24 h. Counter ion of the generated *N*-quanternary compounds might be hydroxyl ion because the reaction mixture was treated with water. Elemental analysis of the products was not successful, while molecular weight of N^+-quaternary part of the each compound was determined by Electrospray Ionization Mass spectrum (ESI-MS). The results were summarized Table 1.

In case of the reaction of **3** with many aromatic tertiary amines, the reaction proceeded to give the corresponding *N*-glucuronides in moderate yield. In case of methylpyridine derivatives, effect of substitution patterns of methyl group of pyridine was not found (entries 2~4) and the reaction proceeded even in 2-methylpyridine with steric hindrance. In addition, pyridine congeners possessing electron-donating group such as the hydroxyl or hydroxylmethyl groups (entries 5-6), and the electron-withdrawing groups such as the ethoxycarbonyl group and the amide group (entries 9-10) were reacted with **3** to give the corresponding *N*-glucuronides. However, in case of CN group (entry 11), the reaction did not proceed and only 3-cyanopyridine (**5k**) was recovered. This was considered due to the

low basicity of **5k**. In case of the reaction of **3** with 4-dimethylaminopyridine (**5l**), the reaction exclusively proceeded to afford *N*-glucuronide (**6l**) along with hydrolysis of ester group in 87% yield.

Table 1. *N* -Glucuronidation of pyridine derivatives



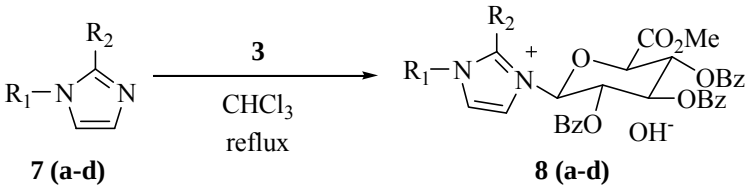
Entry		X	Time(h)		Yield (%)	Anomeric proton	Config.
1	**5a**	H	24	**6a**	52	8.21 (d, 9.2Hz)	β
2	**5b**	2-Me	24	**6b**	42	7.74 (d, 7.3Hz)	β
3	**5c**	3-Me	24	**6c**	50	8.32 (d, 9.2Hz)	β
4	**5d**	4-Me	24	**6d**	54	8.26 (d, 9.2Hz)	β
5	**5e**	3-OH	24	**6e**	80	7.27 (d, 8.0Hz)	β
6	**5f**	3-CH_2OH	24	**6f**	63	7.66 (d, 9.2Hz)	β
7	**5g**	3-Cl	24	**6g**	70	-[1)]	–
8	**5h**	3-F	24	**6h**	32	8.53 (d, 8.8Hz)	β
9	**5i**	3-CO_2Et	24	**6i**	70	8.53 (d, 9.2Hz)	β
10	**5j**	3-$CONH_2$	24	**6j**	70	-[1)]	-
11	**5k**	3-CN	48	**6k**	-(N.R)	-	-
12	**5l**	4-NMe_2	24	**6l**	87	6.01 (d, 9.0Hz)	β

1) Anomeric proton of this compound is not able to assign.

The β-configuration at the anomeric position of the *N*-glucuronide was determined by using ^{1}H-NMR analysis. For eight compounds (entries 1-6,8,9) examined in the present work, a doublet at δ 6.01-8.53 (J = 7.3-9.2 Hz) was seen on the ^{1}H-NMR spectrum and was assigned to the anomeric proton (C_1-H) of the glucuronate moiety. Because coupling constant for α- and β-anomers of various types of glucuronides are reported to appear in the range of about 2 to 4 Hz and about 7 to 10 Hz, respectively.[1] The experimentally determined coupling constants indicate that these compounds have a β-configuration at the anomer center. The reaction of **3** with 1-butylimidazole (**7a**), 1-phenylimidazole (**7b**), 1-benzyl-2-methylimidazole (**7c**) gave the corresponding *N*-glucuronides (**8a**, **8b**, **8c**), respectively in good yields. (Table 2) Furthermore the reaction of **3** with imidazole (**7d**) afforded the tertiary *N*-glucuronide (**8d**) in 88% yields. The

conjugated position of the glucuronide moiety on the imidazole ring of **8c** was confirmed by a heteronuclear multiple bond connectivity (HMBC) spectrum as shown in Figure 1. The HMBC method demonstrated two connectivities 1) C(5)-carbon atom of the imidazole ring and the anomeric proton (C_1-H), 2) C(4)-carbon atom of the imidazole ring and methyene proton of the benzyl moiety. These results were consistent with the above structure. (Figure 1) Applicability for other compounds such as heterocycles

Table 2. *N*-Glucuronidation of imidazole derivatives



7 (a-d) **8 (a-d)**

	R_1	R_2	Yield (%)	Anomeric Proton
7a	*n*-Bu	H	**8a** 72	7.43 (d, 9.4Hz)
7b	Ph	H	**8b** 78	7.71 (d, 9.4Hz)
7c	Bn	CH_3	**8c** 47	7.74 (d, 9.3Hz)
7d	H	H	**8d** 88	5.67 (d, 9.2Hz)

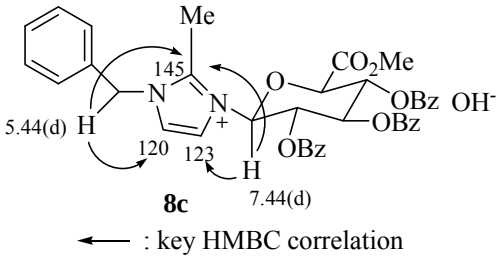
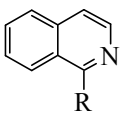
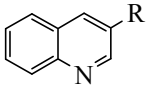
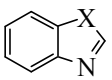
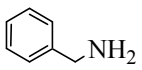
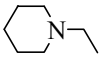


Figure 1

nitrogen-containing aromatic bicyclic heterocycles and aliphatic amines was carried out and the results were shown in Table 3. In case of aromatic bicyclic heterocycles, isoquinoline (**9a**) and 1-methylbenz-imidazole (**12**) was reacted with **3** to give the *N*-glucuronides **10a** (53% yield) and **13** (73% yield). However, in case of the electron-withdrawing groups binding isoquinoline, the reaction of **3** with **9b** did not proceed. In case of the reaction of **3** with aliphatic amines including primary (**16**), secondary (**17**) and tertiary amines (**18**, **19**), compound **3** was decomposed to afford a complex mixture at 0 °C. (Table 3)

Table 3. *N*-Glucuronidation of other amines

Substrate		X	R	Yield (%)	Anomeric Proton
	**9a**	-	H	**10a** 53	6.64 (d, J=8.9Hz)
	9b	-	CN	N.R.	
	**11a**	-	H	complex mixt.	
	11b	-	CN	N.R.	
	**12**	NMe	-	**13** 73	7.48 (d, J=9.4Hz)
	14	O	-	complex mixt.	
	15	S	-	complex mixt.	

Substrate		Yield (%)
	**16**	complex mixt.
	**17**	complex mixt.
	**18**	complex mixt.
	**19**	complex mixt.

These results indicate that moderate basicity of substrates is important to proceed the reaction. Then we investigated the reaction of **3** with nicotine (**20**) which has aromatic and aliphatic tertiary amines in the molecule. The reaction selectively proceeded on the pyridine ring to give *N*-glucuronide (**21**) along with hydrolysis of ester group in 61% yield. (Chart 2)

In the present study, we investigated the scope and limitation of the *N*-glucuronidation using a newly synthesized quaternary glucuronyl reagent **3** for tertiary amines. This reagent **3** is available from glucurono-D-lactone in three steps and can be safely stored at room temperature. The *N*-glucuronidation is not applicable to aliphatic tertiary amines because **3** is susceptible to decomposition in the present of strong basic amines. The *N*-glucuronidation using **3** is applicable to many aromatic tertiary amines having moderate basicity. Finally, it is possible to obtain *N*-glucuronides of aromatic tertiary amines by removing the protective group of quaternary salt thus obtained under alkaline conditions.[6]

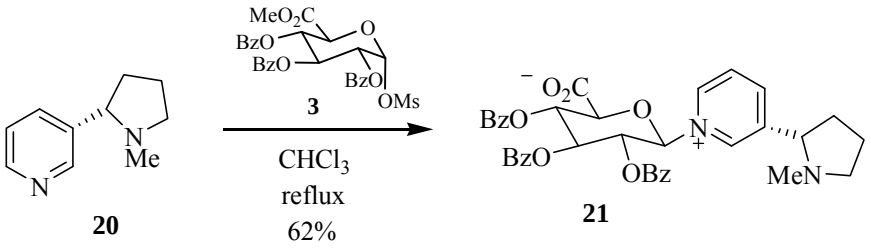


Chart 2

EXPERIMENTAL

Melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. Elemental analyses are within ±0.3% of the theoretical values and were determined by a Yanaco CHN coder MT-5. Infrared spectra were recorded with a JASCO FT/IR-5300 spectrometer. Mass spectrometry (MS) and high-resolution MS (HRMS) were performed with JEOL JMS SX-102A or JEOL JMS-T100LP mass spectrometer. ^{1}H-NMR spectra were obtained on a JEOL EX-400 (400 MHz) spectrometer. Spectra were run in either $CDCl_3$ or CD_3OD using TMS as internal standard. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Columm chromatography was performed with silica gel (Merck: silica gel 60 with particle size 0.040–0.063 mm).

Methyl 2,3,4-tri-*O*-benzoyl-1-methanesulfonyl-α-D-glucopyranuronate (3)

To a solution of methyl 1,2,3,4-tetra-*O*-benzoyl-β-D-glucopyranouronate **4**[7] (44.3 g, 72.4 mmol) in anhydrous CH_2Cl_2 (300 mL) was added methansulfonic acid (55.8 g, 581 mmol) and the whole mixture was stirred for 45 min at rt. The reaction was quenched with 5 % aqueous sodium hydrogen carbonate (1400 mL). The organic layer was separated, and the aqueous layer was extracted two times with CH_2Cl_2. The combined organic solution was washed with water, dried over sodium sulfate (Na_2SO_4), and

concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: hexane: AcOEt=10:5:1) and crystallized from a mixed solvent of CH_2Cl_2/hexane (1:2) to give a colorless solid **3** (20.6 g, 49%). **3**: mp 139-140 °C (decomp). $[\alpha]_D^{25}$ 63.7 (*c* 0.3, $CHCl_3$). IR (KBr) cm^{-1}: 1763, 1731, 1272, 707. ^{1}H-NMR ($CDCl_3$) δ: 3.11 (3H, s), 3.70 (3H, s), 4.79 (1H, d, *J*=9.8 Hz), 5.54 (1H, dd, *J*=3.4, 9.8 Hz), 5.75 (1H, t, *J*=9.8 Hz), 6.17 (1H, t, *J*=9.8 Hz), 6.41 (1H, d, *J*=3.4 Hz), 7.31-7.57 (9H, m), 7.88-7.99 (6H, m). ^{13}C-NMR ($CDCl_3$) *δ*: 39.5, 53.1, 68.7, 69.1, 69.5, 70.8, 95.9, 128.4, 128.4, 128.5, 128.5, 128.5, 128.6, 129.7, 129.8, 129.9, 133.5, 133.6, 133.8, 165.0, 165.2 165.3, 166.7. FAB-MS *m/z*: 597 $(M-H)^-$. *Anal*. Calcd for $C_{29}H_{26}O_{12}S$ (MW: 598.58): C, 58.19; H, 4.38. Found: C, 58.20; H, 4.30.

1-(2,3,4-Tri-*O*-benzoyl-6-methyl–β-D-glucopyranuronosyl)pyridinium hydroxide (6a)

A solution of pyridine (15.8 mg, 0.20 mmol) and **3** (144 mg, 0.24 mmol) in anhydrous $CHCl_3$ (1 mL) was refluxed for 24 h under argon. After cooling, the reaction mixture was diluted with CH_2Cl_2 (2 mL), then washed with water (2 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH=5:1) to give the title compound **6a** as a white powder (62.0 mg, 52%). **6a**: mp 140-144 °C (decomp). $[\alpha]_D^{25}$ -5.0 (*c* 0.4, $CHCl_3$). IR (KBr) cm^{-1}: 3422, 1734, 1261, 710. ^{1}H-NMR ($CDCl_3$) δ: 3.65 (3H, s), 5.31 (1H, d, *J*=9.9 Hz), 5.79 (1H, t, *J*=9.3 Hz), 5.90 (1H, t, *J*=9.6 Hz), 6.45 (1H, t, *J*=9.4 Hz), 7.24-7.28 (2H, m), 7.35 (2H, t, *J*=7.8 Hz), 7.40-7.45 (3H, m), 7.49-7.54 (1H, m), 7.54-7.59 (1H, m), 7.87-7.80 (4H, m), 8.01-8.09 (4H, m), 8.34 (1H, d, *J*=9.2 Hz), 8.52 (1H, t, *J*=7.8 Hz), 9.86 (2H, d, *J*=5.6 Hz). MS (ESI) *m/z*: 582$[M-OH]^+$. HR-MS (ESI) *m/z*: 582.17577 (Calcd for $C_{33}H_{28}NO_9$: 582.17641).

1-(2,3,4-Tri-*O*-benzoyl-6-methyl– β-D-glucopyranuronosyl)-2-methylpyridinium hydroxide (6b)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**6b**) from 2-methylpyridine (18.6 mg, 0.20 mmol) to give **6b** (42.0 mg, 42%) as pale brownish amorphous foam. **6b**: $[\alpha]_D^{25}$ -6.9 (*c* 0.4, $CHCl_3$). IR (KBr) cm^{-1}: 3415, 1734, 1258, 711. ^{1}H-NMR ($CDCl_3$) δ: 3.40 (3H,s), 3.62 (3H, s), 5.76 (1H, t, *J*=9.4 Hz), 5.89 (1H, t, *J*=9.8 Hz), 6.07 (1H, d, *J*=10.0 Hz), 6.59 (1H, t, *J*=9.5 Hz), 7.24-7.31 (2H, m), 7.34-7.43 (5H, m), 7.51-7.57 (2H, m), 7.74 (1H, d, *J*=7.3Hz), 7.80-7.82 (4H, m), 8.01-8.03 (3H, m), 8.37-8.40 (2H, m), 9.42 (1H, br s). MS (ESI) *m/z*: 596$[M-OH]^+$. ESI-MS *m/z*: 596.19188 (Calcd for $C_{34}H_{30}NO_9$: 596.19206).

1-(2,3,4-Tri-*O*-benzoyl-6-methyl–β-D-glucopyranuronosyl)-3-methylpyridinium hydroxide (6c)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**6c**) from 3-methylpyridine (18.6 mg, 0.20 mmol) to give **6c** (61.0 mg, 50 %) as white powder. **6c**: mp 133-136 °C (decomp). $[\alpha]_D^{25}$ -23.6 (*c* 0.3, $CHCl_3$). IR (KBr) cm^{-1}: 3415, 1734, 1258, 711. ^{1}H-NMR ($CDCl_3$) δ: 2.53 (3H,s), 3.64 (3H, s), 5.32 (1H, d, *J*=9.9 Hz), 5.72 (1H, t, *J*=9.3 Hz), 5.86 (1H, t, *J*=9.6 Hz), 6.47 (1H, t, *J*=9.3 Hz), 7.25-7.29 (1H, m), 7.32-7.44 (6H, m), 7.50-7.58 (2H, m), 7.82 (2H, d, *J*=7.3 Hz), 7.89-7.93 (3H, m), 8.02 (2H, d, *J*=7.3 Hz), 8.27 (1H, d, *J*=7.8 Hz), 8.32 (1H, d, *J*=9.2 Hz), 9.60 (1H, s), 9.68 (1H, d,

J=6.1 Hz). MS (ESI) *m/z*: 596 $[M\text{-}OH]^+$.ESI-MS *m/z*: 596.19148 (Calcd for $C_{34}H_{30}NO_9$: 596.19206).

1-(2,3,4-Tri-*O*-benzoyl-6-methyl–β-D-glucopyranuronosyl)-4-methylpyridinium hydroxide (6d)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**6d**) from 4-methylpyridine (18.6 mg, 0.20 mmol) to give **6d** (66.0 mg, 54 %) as pale brownish powder. **6d**: mp 137-142 °C (decomp). $[\alpha]_D^{24}$ -20.6 (*c* 0.3, $CHCl_3$). IR (KBr) cm^{-1}: 3415, 1734, 1280, 711. ^{1}H-NMR ($CDCl_3$) δ: 2.67 (3H,s), 3.64 (3H, s), 5.28 (1H, d, *J*=10.0 Hz), 5.75 (1H, t, *J*=9.3 Hz), 5.86 (1H, t, *J*=9.6 Hz), 6.43 (1H, t, *J*=9.4 Hz), 7.25-7.29 (2H, m), 7.36 (2H, t, *J*=7.8 Hz), 7.41-7.45 (3H, m), 7.50-7.58 (2H, m), 7.78-7.82(4H, m), 7.88 (2H, dd, *J*=8.3, 1.1 Hz), 8.00-8.02 (2H, m), 8.26 (1H, d, *J*=9.2 Hz), 9.66 (2H, d, *J*=6.7 Hz). MS (ESI) *m/z*: 596 $[M\text{-}OH]^+$. HR-MS (ESI) *m/z*: 596.19222 (Calcd for $C_{34}H_{30}NO_9$: 596.19206).

1-(2,3,4-Tri-*O*-benzoyl-6-methyl-β-D-glucopyranuronosyl)–3-hydroxypyridinium hydroxide (6e)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**6e**) from 3-hydroxypyridine (19.0 mg, 0.20 mmol) to give **6e** (98.0 mg, 80 %) as pale yellow powder. **6e**: mp 149-153 °C (decomp). $[\alpha]_D^{25}$ -7.4 (*c* 0.3, $CHCl_3$). IR (KBr) cm^{-1}: 3423, 1735, 1261, 710. ^{1}H-NMR ($CDCl_3$) δ: 3.67 (3H, s), 5.23 (1H, d, *J*=9.8 Hz), 5.80 (1H, t, *J*=9.2 Hz), 5.89 (1H, t, *J*=9.6 Hz), 6.36 (1H, t, *J*=9.4 Hz), 7.24-7.32 (4H, m), 7.38-7.46 (5H, m), 7.50-7.56 (2H, m), 7.76-7.85 (5H, m), 7.99-8.01 (2H, m), 8.46 (1H, d, *J*=5.6 Hz), 8.78 (1H, s). MS (ESI) *m/z*: 598 $[M\text{-}OH]^+$. ESI-MS *m/z*: 598.17064 (Calcd for $C_{33}H_{28}NO_{10}$: 598.17132).

1-(2,3,4-Tri-*O*-benzoyl-6-methyl-β-D-glucopyranuronosyl)-3-hydroxymethylpyridinium hydroxide (6f)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**6f**) from 3-hydroxymethylpridine (21.8 mg, 0.20 mmol) to give **6f** (79.0 mg, 63 %) as colorless amorphous foam. **6f**: $[\alpha]_D^{25}$ -21.5 (*c* 0.4, $CHCl_3$). IR (KBr) cm^{-1}: 3396, 1734, 1261, 710. ^{1}H-NMR ($CDCl_3$) δ: 3.69 (3H, s), 4.68 (2H, dd, *J*=19.7, 15.1 Hz), 5.36 (1H, d, *J*=10.0 Hz), 5.98-6.04 (2H, m), 6.41 (1H, t, *J*=9.4 Hz), 7.23-7.33 (5H, m), 7.39-7.49(4H, m), 7.53-7.57 (1H, m), 7.66 (1H, d, *J*=9.2 Hz), 7.79 (2H, dd, *J*=8.4, 1.2 Hz), 7.84 (2H, dd, *J*=8.3, 1.2 Hz), 7.90 (1H, dd, *J*=7.8, 6.2 Hz), 8.00 (2H, dd, *J*=8.4, 1.3 Hz), 8.48 (1H, d, *J*=8.1 Hz), 9.40 (1H, d, *J*=6.1 Hz), 9.67 (1H, s). MS (ESI) *m/z*: 612 $[M\text{-}OH]^+$. HR-MS (ESI) *m/z*: 612.18668 (Calcd for $C_{34}H_{30}NO_{10}$: 612.18697).

1-(2,3,4-Tri-*O*-benzoyl-6-methyl-β-D-glucopyranuronosyl)-3-chloropyridinium hydroxide (6g)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**6g**) from 3-chloropyridine (22.7 mg, 0.20 mmol) to give **6g** (89.0 mg, 70 %) as yellow powder. **6g**: mp 122-126 °C (decomp). $[\alpha]_D^{25}$ -37.9 (*c* 0.3, $CHCl_3$). IR (KBr) cm^{-1}: 3405, 1734, 1261, 710. ^{1}H-NMR ($CDCl_3$) δ: 3.65 (3H, s), 5.28 (1H, d, *J*=9.8 Hz), 5.72 (1H, t, *J*=9.3 Hz), 5.89 (1H, t, *J*=9.4 Hz), 6.44 (1H, t, *J*=9.3 Hz), 7.25-7.58 (12H, m), 7.93-7.81 (5H, m), 8.01-8.08 (3H, m), 8.42-8.47 (2H, m), 9.74 (1H, s), 10.15 (1H, d,

J=6.1 Hz). MS (ESI) *m/z*: 616 $[M\text{-}OH]^+$. HR-MS (ESI) *m/z*: 616.13648 (Calcd for $C_{33}H_{27}ClNO_9$: 616.13743).

1-(2,3,4-Tri-*O*-benzoyl-6-methyl-β-D-glucopyranuronosyl)-3-fluoropyridinium hydroxide (6h)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**6h**) from 3-fluoropyridine (19.4 mg, 0.20 mmol) to give **6h** (40.0 mg, 32 %) as white powder. **6h**: mp 139-143 °C (decomp). $[\alpha]_D^{25}$ -6.4 (*c* 0.4, $CHCl_3$). IR (KBr) cm^{-1}: 3409, 1734, 1278, 710. ^{1}H-NMR ($CDCl_3$) δ: 3.64 (3H, s), 5.26 (1H, d, *J*=9.5 Hz), 5.77 (1H, t, *J*=9.0 Hz), 5.91 (1H, t, *J*=9.2 Hz), 6.41 (1H, t, *J*=9.2 Hz), 7.22-7.57 (9H, m), 7.80 (2H, d, *J*=9.4 Hz), 7.88 (2H, d, *J*=9.4 Hz), 8.01 (2H, d, *J*=8.1 Hz), 8.16-8.21 (1H, m), 8.34-8.37 (1H, m), 8.53 (1H, d, *J*=8.8 Hz), 9.82 (1H, s), 10.06 (1H, d, *J*=5.9 Hz). MS (ESI) *m/z*: 600 $[M\text{-}OH]^+$. HR-MS (ESI) *m/z*: 600.16750 (Calcd for $C_{33}H_{27}FNO_9$: 600.16698).

1-(2,3,4-Tri-*O*-benzoyl-6-methyl-β-D-glucopyranuronosyl)-3-ethoxycarbonylpyridinium hydroxide (6i)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**6i**) from 3-ethoxycarbonylpyridine (30.2 mg, 0.20 mmol) to give **6i** (94.0 mg, 70 %) as pale brownish amorphous foam. **6i**: $[\alpha]_D^{25}$ 3.9 (*c* 0.3, $CHCl_3$). IR (KBr) cm^{-1}: 3444, 1735, 1261, 709. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (3H, t, *J*=7.1 Hz), 3.66 (3H, s), 4.48-4.57 (2H, m), 5.28 (1H, d, *J*=9.7 Hz), 5.73 (1H, t, *J*=9.2 Hz), 5.91 (1H, t, *J*=9.4 Hz), 6.43 (1H, t, *J*=9.2 Hz), 7.26-7.59 (8H, m), 7.81-7.95 (5H, m), 8.03 (2H, d, *J*=7.3 Hz), 8.14 (1H, t, *J*=7.0 Hz), 8.53 (1H, d, *J*=9.2 Hz), 9.01 (1H, d, *J*=8.0 Hz), 9.99 (1H, s), 10.46 (1H, d, *J*=5.9 Hz). MS (ESI) *m/z*: 654 $[M\text{-}OH]^+$. HR-MS (ESI) *m/z*: 654.19653 (Calcd for $C_{36}H_{32}NO_{11}$: 654.19753).

1-(2,3,4-Tri-*O*-benzoyl-6-methyl-β-D-glucopyranuronosyl)-3-carbamoylpyridinium hydroxide (6j)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**6i**) from 3-carbamoylpyridine (24.4 mg, 0.20 mmol) to give **6j** (88.0 mg, 70 %) as white powder. **6j**: mp 147-149 °C (decomp). $[\alpha]_D^{25}$ 27.4 (*c* 0.3, $CHCl_3$). IR (KBr) cm^{-1}: 3406, 1735, 1262, 710. ^{1}H-NMR ($CDCl_3$) δ: 3.66 (3H, s), 5.19 (1H, d, *J*=8.2 Hz), 6.01-6.11 (2H, m), 6.43 (1H, t, *J*=8.1 Hz), 6.71(1H, br), 7.25-7.56 (9H, m), 7.84-7.89 (5H, m), 7.97-7.99(2H, m), 8.12 (1H, br s), 9.38 (2H, br s), 9.61 (1H, br s), 11.09 (1H, br s). MS (ESI) *m/z*: 625 $[M\text{-}OH]^+$. HR-MS (ESI) *m/z*: 625.18268 (Calcd for $C_{34}H_{29}N_2O_{10}$: 625.18222).

1-(2,3,4-Tri-*O*-benzoyl-6-methyl-β-D-glucopyranuronosyl)-4-dimethylaminopyridinium hydroxide (6l)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**6l**) from 4-dimethylaminopyridine (24.4 mg, 0.20 mmol) to give **6l** (109 mg, 87 %) as white powder. **6l**: mp 182-183 °C (decomp). $[\alpha]_D^{25}$ -88.7 (*c* 0.3, $CHCl_3$). IR (KBr) cm^{-1}: 3423, 1730, 1282, 711. ^{1}H-NMR (CD_3OD) δ: 3.23 (6H, s), 4.49 (1H, d, *J*=9.9 Hz), 4.85 (3H, s), 5.86-5.95 (2H, m), 6.01 (1H, d, *J*=9.0 Hz), 6.10 (1H, t, *J*=9.5 Hz), 7.00 (2H, d, *J*=7.9 Hz), 7.29-7.33 (2H, m), 7.37- 7.41 (4H, m), 7.45-7.49 (1H, m),

7.51-7.58 (2H, m), 7.78-7.85 (4H, m), 7.94-7.96 (2H, m), 8.53 (2H, d, *J*=8.1 Hz). MS (ESI) *m/z*: 611 $[M\text{-}OH]^+$. HR-MS (ESI) *m/z*: 611.20368 (Calcd for $C_{34}H_{31}N_2O_9$: 611.20295).

1-Butyl-3-(2,3,4-tri-*O*-benzoyl-6-methyl-β-D-glucopyranuronosyl)imidazolium hydroxide (8a)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**8a**) from 1-butylimidazole (24.8 mg, 0.20 mmol) to give **8a** (93.0 mg, 72 %) as pale brownish amorphous foam. **8a**: $[\alpha]_D^{25}$ 36.9 (*c* 0.5, $CHCl_3$). IR (KBr) cm^{-1}: 3419, 1734, 1262, 711. ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, t, *J*=7.3 Hz), 1.09–1.17 (2H, m), 1.67–1.74 (2H, m), 3.63 (3H, s), 4.12–4.24 (2H, m), 4.99 (1H, d, *J*=9.9 Hz), 5.79 (1H, t, *J*=8.5 Hz), 5.84 (1H, t, *J*=9.5 Hz), 6.27 (1H, t, *J*=9.5 Hz), 7.26–7.31 (2H, m), 7.36-7.46 (6H, m), 7.50–7.58 (2H, m), 7.81–7.83 (3H, m), 7.92-7.99 (4H, m), 11.18 (1H, s). IR (KBr) cm^{-1}: 3419, 1734, 1262, 711. MS (ESI) *m/z*: 627 $[M\text{-}OH]^+$. HR-MS (ESI) *m/z*: 627.23415 (Calcd for $C_{35}H_{35}N_2O_9$: 627.23425).

1-Phenyl-3-(2,3,4-tri-*O*-benzoyl-6-methyl-β-D-glucopyranuronosyl)imidazolium hydroxide (8b)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**8b**) from 1-phenylimidazole (28.8 mg, 0.20 mmol) to give **8b** (104 mg, 78 %) as white powder. **8b**: mp 151-153 °C (decomp). $[\alpha]_D^{25}$ 32.0 (*c* 0.3, $CHCl_3$). IR (KBr) cm^{-1}: 3407, 1734, 1260, 711. ^{1}H-NMR ($CDCl_3$) δ: 3.63 (3H, s), 5.09 (1H, d, *J*=9.9 Hz), 5.82 (1H, t, *J*=9.6 Hz), 5.95 (1H, t, *J*=9.4 Hz), 6.33 (1H, t, *J*=9.3 Hz), 7.28–7.64 (18H, m), 7.71 (1H, d, *J*=9.4 Hz), 7.83 (2H, d, *J*=7.4 Hz), 7.94-8.03 (6H, m), 11.77 (1H, s). MS (ESI) *m/z*: 6487$[M\text{-}OH]^+$. HR-MS (ESI) *m/z*: 647.20274 (Calcd for $C_{37}H_{31}N_2O_9$: 647.20295).

Benzyl-2-methyl-3-(2,3,4-tri-*O*-benzoyl-6-methyl-β-D-glucopyranuronosyl)imidazolium hydroxide (8c)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**8c**) from 1-benzyl-2-methylimidazole (34.4 mg, 0.20 mmol) to give **8c** (65.0 mg, 47 %) as pale brownish amorphous foam. **8c**: $[\alpha]_D^{25}$ -4.4 (*c* 0.1, $CHCl_3$). IR (KBr) cm^{-1}: 3406, 1733, 1279, 711. ^{1}H-NMR ($CDCl_3$) δ: 3.04 (3H, s), 3.58 (3H, s), 5.44 (2H, dd, *J*=21.5, 15.6 Hz), 5.56 (1H, d, *J*=10.1 Hz), 5.69 (1H, t, *J*=9.5 Hz), 5.78 (1H, t, *J*=9.8 Hz), 6.40 (1H, t, *J*=9.6 Hz), 7.12 (2H, dd, *J*=7.9, 1.5 Hz), 7.24-7.44 (12H, m), 7.49-7.56 (3H, m), 7.74 (1H, d, *J*=9.3 Hz), 7.82-7.79 (4H, m), 7.90 (1H, d, *J*=2.3 Hz), 7.98-8.00 (2H, m). MS (ESI) *m/z*: 675 $[M\text{-}OH]^+$. HR-MS (ESI) *m/z*: 675.23330 (Calcd for $C_{39}H_{35}N_2O_9$: 675.23425).

1-(2,3,4-Tri-*O*-benzoyl-6-methyl-β-D-glucopyranuronosyl)imidazole (8d)

A solution of imidazole (27.2 mg, 0.40 mmol) and **3** (120 mg, 0.20 mmol) in anhydrous $CHCl_3$ (1 mL) was refluxed for 48 h under argon. The reaction mixture was diluted with CH_2Cl_2 (2 mL), then washed with water (2 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt:hexane=1:1) to give the title compound **8d** as a white powder (100 mg, 88 %).**8d**: mp 211-213 °C (decomp). $[\alpha]_D^{25}$ 19.3 (*c* 0.3, $CHCl_3$). IR (KBr) cm^{-1}: 3445, 1734, 1263, 707. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (3H, s), 4.55 (1H, d, *J*=9.9 Hz), 5.67 (1H, d, *J*=9.2 Hz), 5.83 (1H, t, *J*=9.7 Hz), 5.93 (1H, t, *J*=9.4 Hz), 6.06 (1H, t, *J*=9.6 Hz), 7.07 (1H, s), 7.25-7.56 (11H, m), 7.70

(1H, s), 7.77 (2H, d, *J*=7.4 Hz), 7.84 (2H, t, *J*=7.6 Hz), 7.95 (2H, d, *J*=7.3 Hz). MS (ESI) *m/z*: 571 $[M+H]^+$. HR-MS (ESI) *m/z*: 571.17154 (Calcd for $C_{31}H_{27}N_2O_9$: 571.17165).

1-(2,3,4-Tri-*O*-benzoyl-6-methyl-β-D-glucopyranuronosyl)isoquinolinium hydroxide (10a)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**10a**) from isoquinoline (25.8 mg, 0.20 mmol) to give **10a** (69.0 mg, 53 %) as pale brownish powder. **10a**: mp 138-140 °C (decomp). $[\alpha]_D^{25}$ -28.1 (*c* 0.3, $CHCl_3$). IR (KBr) cm^{-1}: 3422, 1732, 1261, 709. ^{1}H-NMR (CD_3OD) δ: 3.66 (3H, s), 5.06 (1H, d, *J*=10.0 Hz), 6.01 (1H, t, *J*=9.8 Hz), 6.14 (1H, t, *J*=9.3 Hz), 6.40 (1H, t, *J*=9.6 Hz), 6.64 (1H, t, *J*=8.9 Hz), 7.26–7.31 (4H, m), 7.36-7.51 (4H, m), 7.56–7.60 (1H, m), 7.66–7.68 (2H, m), 7.78–7.80 (2H, m), 7.93–7.95 (2H, m), 8.06–8.10 (1H, m), 8.30–8.31 (2H, m), 8.51 (2H, t, *J*=7.1 Hz), 8.98–8.96 (1H, m), 10.38 (1H, s). MS (ESI) *m/z*: 632 $[M-OH]^+$. HR-MS (ESI) *m/z*: 632.19163 (Calcd for $C_{37}H_{30}NO_9$: 632.19206).

3-Methyl-1-(2,3,4-tri-*O*-benzoyl-6-methyl-β-D-glucopyranuronosyl–1-yl)benzimidazolium hydroxide (13)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**13**) from 1-methylbenzimidazole (26.4 mg, 0.20 mmol) to give **13** (95.0 mg, 73 %) as pale brownish amorphous foam. **13**: $[\alpha]_D^{25}$ -49.0 (*c* 0.4, $CHCl_3$). IR (KBr) cm^{-1}: 3413, 1734, 1258, 710. ^{1}H-NMR ($CDCl_3$) δ: 3.65 (3H, s), 4.10 (3H, s), 5.10 (1H, d, *J*=9.6 Hz), 5.91 (1H, t, *J*=9.5 Hz), 6.07 (1H, t, *J*=9.3 Hz), 6.32 (1H, t, *J*=9.3 Hz), 7.26–7.35 (4H, m), 7.41–7.58 (6H, m), 7.49 (1H, d, *J*=8.9 Hz), 7.66-7.89 (8H, m), 8.01 (2H, t, *J*=4.2 Hz), 8.37 (1H, d, *J*=8.3 Hz), 11.88 (1H, s). MS (ESI) *m/z*: 635 $[M-OH]^+$. HR-MS (ESI) *m/z*: 635.20369 (Calcd for $C_{36}H_{31}N_2O_9$: 635.20295).

1-(2,3,4-Tri-*O*-benzoyl-6-methyl-β-D-glucopyranuronosyl)-3-((S)-1-methyl-pyrrolidin-2-yl)-pyridinium hydroxide (21)

The same procedure as the synthesis of **6a** was applied for the synthesis of the title compound (**21**) from (*S*)-nicotine (24.4 mg, 0.20 mmol) to give **21** (80.0 mg, 62 %) as pale yellow powder. **21**: mp 134-137 °C (decomp). $[\alpha]_D^{25}$ -78.7 (*c* 0.3, $CHCl_3$). IR (KBr) cm^{-1}: 3419, 1732, 1280, 710. ^{1}H-NMR (CDCl3) δ: 1.46-1.55 (1H, m), 1.70-1.87 (2H, m), 1.98-2.11 (4H, m), 3.13 (1H, t, *J*=7.6 Hz), 3.37 (1H, t, *J*=8.1 Hz), 4.93 (1H, d, *J*=7.9 Hz), 5.89 (1H, t, *J*=9.0 Hz), 6.06 (1H, d, *J*=7.6 Hz), 6.18 (1H, t, *J*=8.1 Hz), 6.72 (1H, d, *J*=9.2 Hz), 7.25-7.29 (4H, m), 7.36-7.51 (5H, m), 7.74 (2H, d, *J*=7.3 Hz), 7.87-7.90 (3H, m), 8.08 (2H, d, *J*=7.2 Hz), 8.34 (1H, d, *J*=8.1 Hz), 9.35(1H, s), 9.90 (1H, d, *J*=6.1 Hz). MS (ESI) *m/z*: 651 $[M-OH]^+$. HR-MS (ESI) *m/z*: 651.23405 (Calcd for $C_{37}H_{35}N_2O_9$: 651.23425).

REFERENCES

1. F. M. Kasperson and V. Boeckel, *Xenobiotica*, 1987, **17**, 1451.
2. H. Luo, E. M. Hawes, G. Mckay, and K. K. Midha, *J. Pharm. Sci.*, 1992, **81**, 1079.

3. L. Dalgaard, *Acta Chem. Scand. B*, 1983, **37**, 923.
4. S. C. vashishita, E. M. Hawes, G. Mckay, and D. J. Mckay, *Drug Metabolism and Disposition*, 2000, **28**, 1009.
5. M. J. Seaton, E. S. Vesell, H. Luo, and E. M. Haws*, J. Chromatography*, 1993, **621**, 49.
6. I. Araya, T. Tsubuki , T. Saito, M. Numata, and H. Akita, *Chem. Pharm. Bull*., 2007, **55**, 1039.
7. F. Scheinmann, K. W. Lumbard, R. T. Brown, S. P. Mayalarp, and N. E. Caeter, WO patent 9303051(1993).