Regular Article

O-Glycosylation of 4-(Substituted benzyl)-1,2-dihydro-3*H*-pyrazol-3-one Derivatives with 2,3,4,6-Tetra-*O*-acyl-*α*-D-glucopyranosyl Bromide *via* N_1-Acetylation of the Pyrazole Ring

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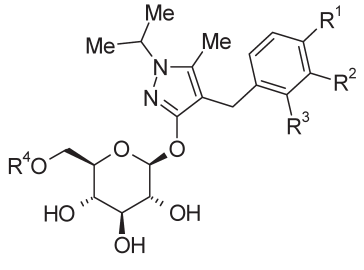
A practical preparation of 4-(substituted benzyl)-3-(2,3,4,6-tetra-*O*-acyl-*β*-D-glucopyranosyloxy)-1*H*-pyrazole derivative 2 is described. *O*-Glycosylation of 4-(substituted benzyl)-1,2-dihydro-3*H*-pyrazol-3-one derivative 3 was facilitated by introduction of electron-withdrawing substituents, such as an acetyl group, at the N_1-position of the pyrazole ring. 1-Acetyl-4-(substituted benzyl)-1,2-dihydro-3*H*-pyrazol-3-one 10 reacted with 2,3,4,6-tetra-*O*-acyl-*α*-D-glucopyranosyl bromide 5 in the presence of potassium carbonate in acetonitrile to provide the 1-acetyl-4-(substituted benzyl)-3-(2,3,4,6-tetra-*O*-acyl-*β*-D-glucopyranosyloxy)-1*H*-pyrazole derivative 11 in high yield. When 2,3,4,6-tetra-*O*-pivaloyl-*α*-D-glucopyranosyl bromide (5b) was used as a glycosyl donor, the resulting *O*-glycosylated product 11 was N_1-deacetylated in the presence of potassium bicarbonate in methanol without unfavorable deprotection of the glycosyl moiety to provide 2 in excellent yield. The synthetic intermediate 2b of Remogliflozin etabonate (1b) was synthesized using this strategy.

Key words *O*-glycosylation; 1,2-dihydro-3*H*-pyrazol-3-ones derivative; N_1-acetylation; glucopyranosyloxypyrazole derivative; Remogliflozin etabonate

Some glucopyranosyloxypyrazole derivatives such as **1a**–**d** (Fig. 1) have been demonstrated to inhibit the low-affinity Na^+-dependent glucose co-transporter SGLT2.[1–3] Two types of SGLT are known, SGLT1 and SGLT2, both of which act as transmembrane glucose transporters. Although SGLT1 (high-affinity Na^+-dependent glucose co-transporter) is expressed to some extent in the kidney and contributes to glucose reabsorption, it is mainly expressed in the small intestine, where it plays an important role in glucose absorption.[4,5] SGLT2 is specifically expressed in the kidney and plays an important role in renal glucose reabsorption in the proximal tubule.[6] Remogliflozin (**1a**), discovered at Kissei Pharmaceutical Co., Ltd., exhibits an inhibitory activity that is highly selective for SGLT2.[7,8] Remogliflozin etabonate (**1b**), a prodrug of **1a**, is metabolized to its active form **1a** in the body, and may therefore be useful as a preventive or therapeutic agent for diseases attributable to hyperglycemia such as diabetes, complications related to diabetes, and obesity.[9,10]



1a (Remogliflozin): R^1=O*i*-Pr, R^2=H, R^3=H, R^4=H
b (Remogliflozin etabonate): R^1=O*i*-Pr, R^2=H, R^3=H, R^4=C(O)OEt
c: R^1=OMe, R^2=F, R^3=H, R^4=C(O)OEt
d: R^1=OMe, R^2=H, R^3=F, R^4= H

Fig. 1. Glucopyranosyloxypyrazole Derivatives **1** Having an SGLT2 Inhibitory Activity

The synthetic strategy for **1b**, given in Chart 1, shows that the 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acyl-*β*-D-glucopyranosyloxy)-1*H*-pyrazole derivative **2** is an important intermediate. *O*-Glycosylation of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-1,2-dihydro-3*H*-pyrazol-3-one (**3a**) with a glycosyl donor (**4** or **5**) is therefore a key step in the production of **1b**. Various *O*-glycosylation methods of 1,2-dihydro-3*H*-pyrazol-3-one derivatives **3** have been reported, including the Koenigs–Knorr reaction, which employs a phase-transfer catalyst, and the Mitsunobu reaction.[1,2,11–13] Although we also evaluated these methods for the preparation of **2**, no successful results were obtained. Therefore, developing an efficient *O*-glycosylation method is strongly desired to establish scalable synthesis of **1b**. We report here a convenient and practical method for the *O*-glycosylation of **3** with 2,3,4,6-tetra-*O*-acyl-*α*-D-glucopyranosyl bromide **5** *via* N_1-acetylation of the pyrazole ring.

Results and Discussion

4-(Substituted benzyl)-1,2-dihydro-3*H*-pyrazol-3-one derivatives **3a**–**c** were prepared by a two-step sequence starting from benzyl halide derivatives **6a**–**c**, as shown in Table 1. Compounds **6a**–**c** were reacted with methyl acetoacetate (**7**) in the presence of lithium halide and *N*,*N*-diisopropylethylamine to yield the corresponding alkylated *β*-keto ester derivatives **8a**–**c**.[14] The crude products of **8a**–**c** were treated with hydrazine monohydrate in toluene to provide **3a**–**c** as white solids.[15]

The various precedent methods for direct *O*-glycosylation of the 5-methylpyrazole derivative **3a** with glycosyl donors **4** and **5a**, **b** were first evaluated. The results are summarized in

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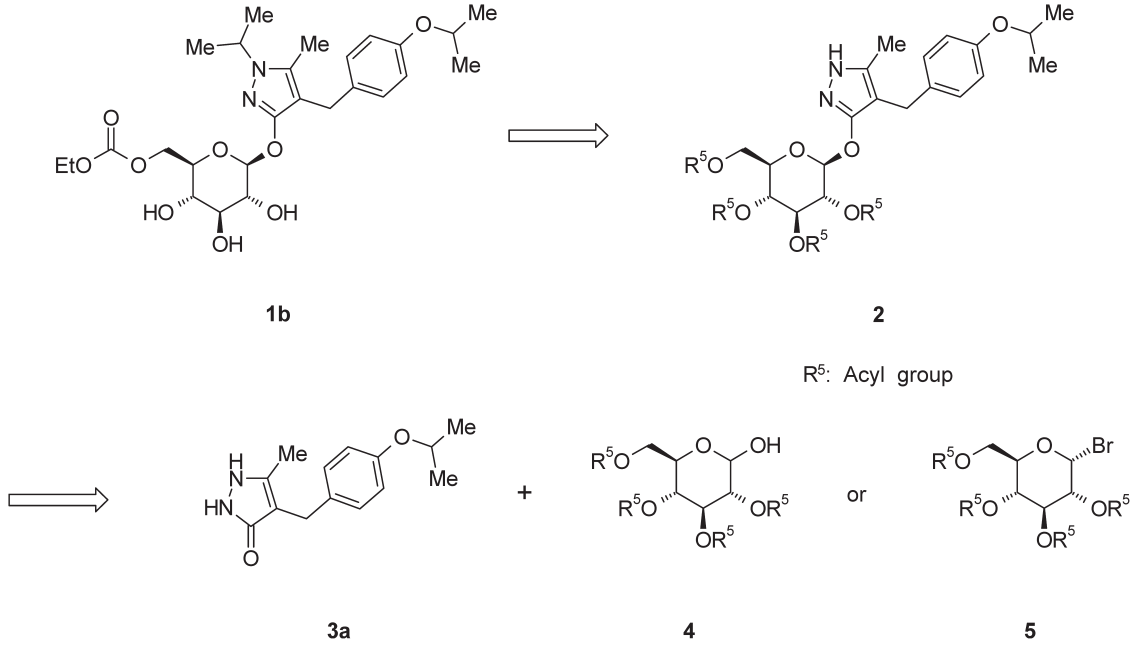
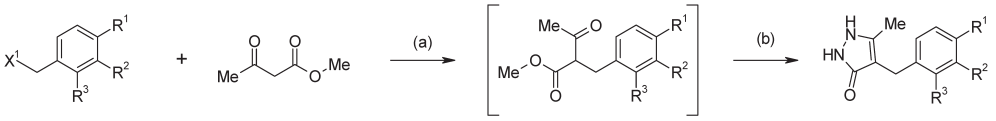


Chart 1. Synthetic Strategy for **1b**

Table 1. Preparation for Pyrazole Derivative **3**

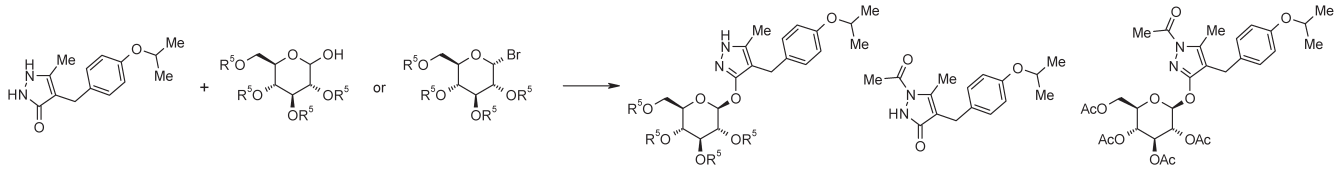


Reagents: (a) *i*-Pr$_2$NEt, lithium halide, toluene, DMF; (b) Hydrazine monohydrate, toluene.

Entry	Benzyl halide	R^1	R^2	R^3	X^1	Product	Yield (%)
1	**6a**	O*i*-Pr	H	H	Cl	**3a**	71
2	**6b**	OMe	F	H	Cl	**3b**	69
3	**6c**	OMe	H	F	Cl	**3c**	64

a) The formation of α-anomer was not observed.

Table 2. Direct *O*-Glycosylation of **3a** with **4** or **5**

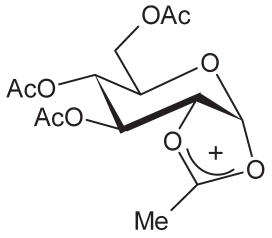


Entry	Glycosyl donor	R^5	Reagent	Solvent	Temp. (°C)	Products	Yield (%)
1	**4**	Ac	PPh_3, DEAD	THF	rt	**2a**	29 (α-anomer: 2.5)
2	**5a**	Ac	Ag_2CO_3	THF	rt	**2a**	44 (α-anomer: 0.7)
3	**5a**	Ac	NaOH, BnN(*n*-Bu)$_3$Cl	CH_2Cl_2–H_2O	rt	**2a**	25 (**10a**: 21, **11a**: 19)[a]
4	**5a**	Ac	K_2CO_3, BnN(*n*-Bu)$_3$Cl	CH_2Cl_2–H_2O	rt	**2a**	32 (**10a**: 18, **11a**: 23)[a]
5	**5a**	Ac	K_2CO_3	MeCN	60	**2a**	36 (**10a**: 10, **11a**: 26)[a]
6	**5b**	Piv	K_2CO_3	MeCN	60	**2b**	47[a]

a) The formation of α-anomer was not observed.

Table 2. In the Mitsunobu reaction, the desired product was provided, but with moderate β-selectivity (β:α ratio of 92:8) and only 29% yield (Table 2, entry 1). The Koenigs–Knorr reaction was more effective than the Mitsunobu reaction. The desired product was provided with high β-selectivity (β:α ratio of 98:2) due to the anchimeric assistance *via* intermediacy of **9** in Fig. 2; however, a satisfactory yield was not provided (44%, entry 2). In addition to low yield, these two methods are known to have several other disadvantages in terms of scalability. It is difficult to remove triphenylphos-

phine oxide from the Mitsunobu reaction mixture, especially at larger scales. The Koenigs–Knorr reaction has a high likelihood of contamination from silver-related elemental impurities in the final drug substance and coating of reaction vessels by the silver mirror reaction. Entries 3–5 indicate that the desired reaction did not proceed completely, with recovery of significant amounts of **3a** and side reactions that resulted in the N_1-acetylated product **10a** and its *O*-glycosylated product **11a**, causing low yields. When the reaction was performed with 2,3,4,6-tetra-*O*-pivaloyl-*α*-D-glucopyranosyl bromide (**5b**), N_1-acylation of **3a** did not occur. However, a satisfactory yield was not provided with concurrent recovery of **3a** (47%, entry 6). Formation of an *α*-anomer was not observed in entries 3–6.

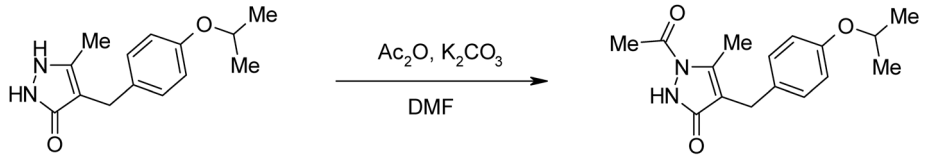


9

Fig. 2. Oxonium Intermediate **9**

To improve the yield of *O*-glycosylation, we attempted the *O*-glycosylation reaction of 1-substituted-1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one **10**. 1-Acetyl-1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one (**10a**), which has an acetyl group as an electron-withdrawing group at the N_1-position of the pyrazol ring, was prepared in an 81% yield by reacting **3a** with acetic anhydride in the presence of potassium carbonate (K_2CO_3) in *N*,*N*-dimethylformamide (DMF) at 70°C, as shown in Chart 2. As a different type of pyrazole derivative, 1-methyl-1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one (**10b**), having a methyl group as an electron-donating group at the N_1-position of the pyrazole ring, was prepared by a four-step sequence starting from **10a**, as shown in Chart 3. **10a** was reacted with benzyl bromide in the presence of K_2CO_3 in acetonitrile (MeCN) to provide **12** in a 69% yield. **12** was treated with potassium bicarbonate ($KHCO_3$) in MeOH to provide **13**. The crude product of **13** was reacted with iodomethane (MeI) in the presence of sodium hydride (NaH) to provide **14** in an 85% yield from **12**. Then, **14** was debenzylated in the presence of 10% Pd/C in tetrahydrofuran (THF) under a H_2 atmosphere to provide **10b** in a 99% yield.

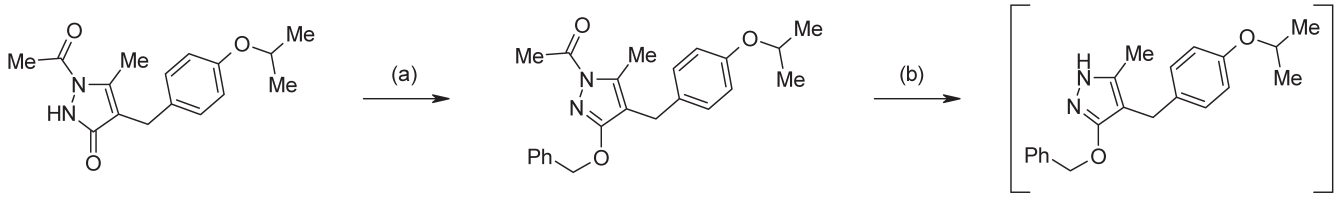
The *O*-glycosylation of **10a** with **5a** in the presence of



3a **10a**

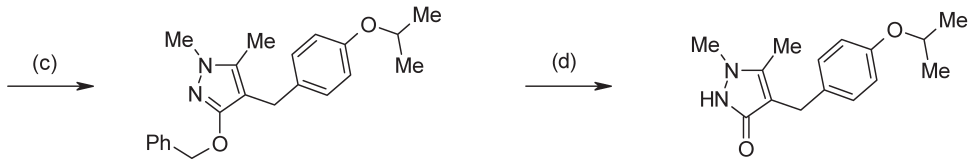
Yield 81%

Chart 2. Preparation for **10a**



10a **12** **13**

Yield 69%



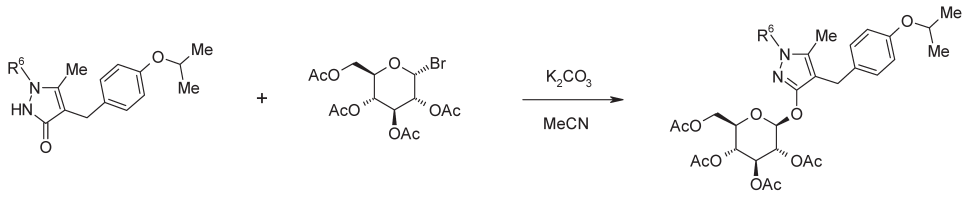
14 **10b**

Yield 85% (2 Steps) Yield 99%

Reagents: (a) Benzyl bromide, K_2CO_3, MeCN; (b) $KHCO_3$, MeOH; (c) MeI, NaH, *N*,*N*-dimethylacetamide (DMAc); (d) 10% Pd/C (wet), H_2, THF.

Chart 3. Preparation for **10b**

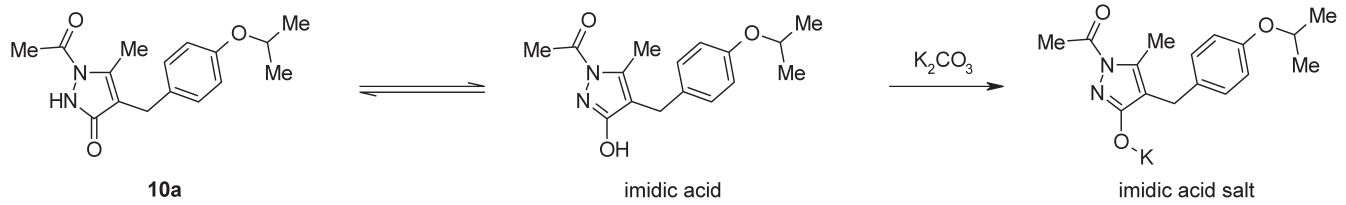
Table 3. *O*-Glycosylation of **10** with **5a**



10 **5a** **11**

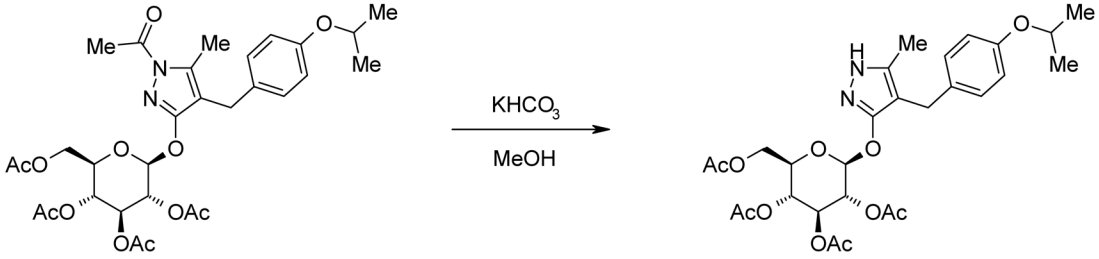
Entry	Aglycon	R^6	*O*-Glycosylation	
			Product	Yield (%)[a]
1	**10a**	Ac	**11a**	90[b]
2	**10b**	Me	**11b**	26[b]

a) Isolated by column chromatography. *b*) The formation of α-anomer was not observed.



10a imidic acid imidic acid salt

Chart 4. Tautomeric Forms and the Reactive Species of **10a**



11a **2a**

Yield 45%

Chart 5. Deacetylation of **11a**

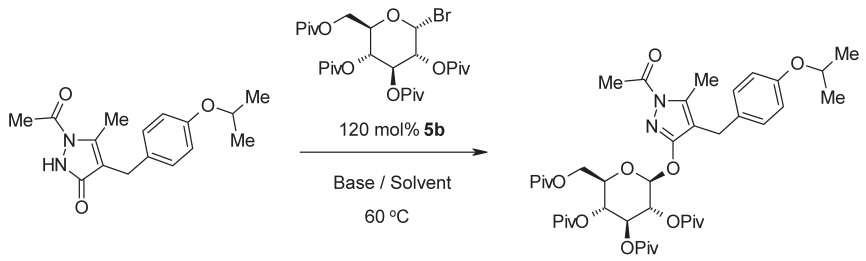
K_2CO_3 in MeCN was evaluated at 60°C. Under this condition, *O*-glycosylation proceeded efficiently and provided **11a** with a 90% yield (Table 3, entry 1). However, under the same condition, *O*-glycosylation of **10b** with **5a** provided **11b** in only 26% yield (entry 2). Formation of the α-anomer and glucoside-orthoester was not observed in either case. Based on these results, the suggested reaction mechanism is that *O*-glycosylation proceeds through a direct S_N2-type displacement in the presence of K_2CO_3 in MeCN, and formation of the oxonium intermediate **9** does not occur. The reactive species in this reaction is the imidic acid of **10**, and the electron-withdrawing acetyl group at the N_1-position of the pyrazole ring in **10a** increases the acidity of the 3-OH group of this imidic acid. Therefore, the formation of the imidic acid salt of **10a** is facilitated under mildly basic conditions such as K_2CO_3, as shown in Chart 4.

The acetyl group at the N_1-position of the pyrazole ring was easily removed under N_1-deacetylation conditions, that is, in the presence of $KHCO_3$ in MeOH. Unfortunately, treatment of **11a** under the above conditions provided **2a** in a low yield (45%) because of the low selectivity of *O*- and N_1-deacetylation in the presence of $KHCO_3$ in MeOH, as shown in Chart 5.

To prevent undesired *O*-deacetylation of the glucosyl moiety, we attempted to introduce a pivaloyl group as the *O*-protective group of the glucosyl moiety, which is more stable than the acetyl group under basic conditions. The results are summarized in Table 4. The *O*-glycosylation of **10a** with **5b** in the presence of K_2CO_3 in MeCN provided **11c** with a 92% yield (entry 1). On the other hand, sodium carbonate (Na_2CO_3) and potassium *t*-butoxide (*t*-BuOK) as a base were less efficient (entries 2, 3). With regard to solvents, THF was less efficient (entry 4). The best overall condition for *O*-glycosylation was therefore observed using K_2CO_3 and MeCN. The *O*-glycosylation of **10a** with **5b** provided the desired product **11c** in a high yield.

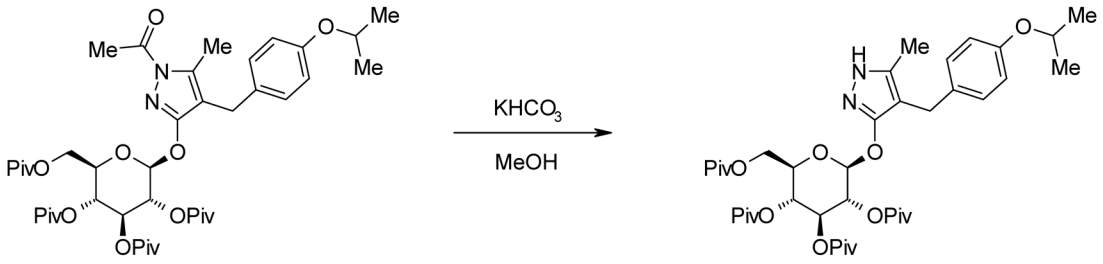
Furthermore, introducing a pivaloyl group as the *O*-protective group of the glucosyl moiety effectively led to N_1-deacet-

Table 4. *O*-Glycosylation of **10a** with **5b**



10a **11c**

Entry	Base	(mol%)	Solvent	Yield (%)
1	K_2CO_3	(140)	MeCN	92
2	Na_2CO_3	(140)	MeCN	75
3	*t*-BuOK	(110)	MeCN	77
4	K_2CO_3	(140)	THF	73



11c **2b**

Yield 98%

Chart 6. Deacetylation of **11c**

ylation with high selectivity without unfavorable deprotection of the glucosyl moiety, providing the desired product **2b** in a 98% yield, as shown in Chart 6. **5b** is easily prepared from D-glucose by a known synthetic method, and is commercially available and inexpensive.[16,17] In addition, **5a** is an unstable compound that requires storage below −20°C; **5b** is stable and can be stored at room temperature without special caution. These characteristics make **5b** the more suitable glycosyl donor for this method.

Implementation of the above results made it possible to proceed with *O*-glycosylation of **10a** with **5b** and N_1-deacetylation in a high yield. Therefore, the crude product of **11c** after *O*-glycosylation was treated with $KHCO_3$ in MeOH, and then the resulting crude product of **2b** was crystallized from 2-PrOH to provide **2b** in an 81% yield from **10a**, as shown in Chart 7. This method represents an easily scalable process for the efficient synthesis of **2b**.

An even more efficient pathway to **2b** was attempted in a one-pot synthesis without isolation of **10a** and **11c**. The results are summarized in Table 5. Compound **3a** was acetylated by acetic anhydride in the presence of K_2CO_3 in DMF. MeCN, aqueous K_2CO_3, and **5b** were then added to the reaction mixture and the reaction was allowed to proceed at 60°C. The resulting crude product of **11c** was treated with $KHCO_3$ in MeOH. In this way, the desired product **2b** was provided, with a high yield of 86%, from **3a** (entry 1).

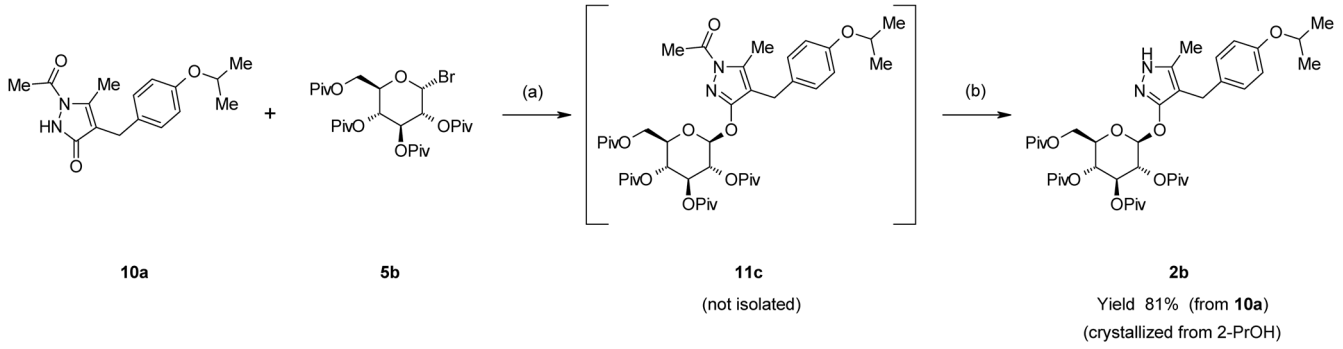
The same methodology was then applied to other 5-methylpyrazole derivatives **3b**, **c**, and the corresponding products **2c**, **d** were provided in high yields (entries 2, 3). These results demonstrate the applicability of this method for *O*-glycosylation of various 5-methylpyrazole derivatives.

Remogliflozin etabonate (**1b**) was prepared by a four-step sequence starting from **2b**, as shown in Chart 8. Introduction of an isopropyl group to **2b** with 2-iodopropane in the presence of NaH in 1,3-dimethyl-2-imidazolidinone (DMI) provided 4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-*O*-acyl-*β*-D-glucopyranosyloxy)-1*H*-pyrazole derivative (**15**) in an 86% yield. The depivaloylation of **15** in the presence of sodium methoxide (MeONa) in MeOH provided Remogliflozin (**1a**) in a 99% yield. The reaction of **1a** with ethyl chloroformate in the presence of 2,6-lutidine and pyridine in MeCN provided **16** as an ethanol solvate of **1b** in a 72% yield. **16** was crystallized from a mixed solvent of methyl *t*-butyl ether (MTBE) and *n*-heptane to provide **1b** in a 98% yield.

In conclusion, an efficient and practical method for the synthesis of **2b**, an important intermediate in the synthesis of **1b**, was established. These results suggest that this *O*-glycosylation method could be applied in syntheses of additional glucopyranosyloxypyrazole derivatives exhibiting SGLT2 inhibitory activity such as **1c**, **d**.

Experimental

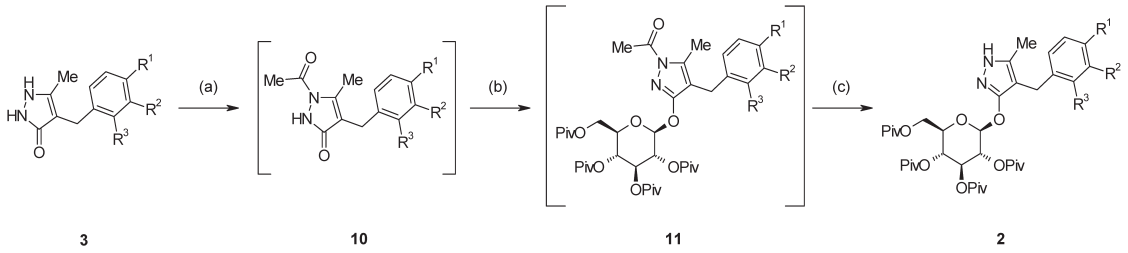
All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Optical rotations were recorded on a JASCO P-2300 polarimeter. IR spectra



Reagents: (a) K_2CO_3, MeCN; (b) $KHCO_3$, MeOH.

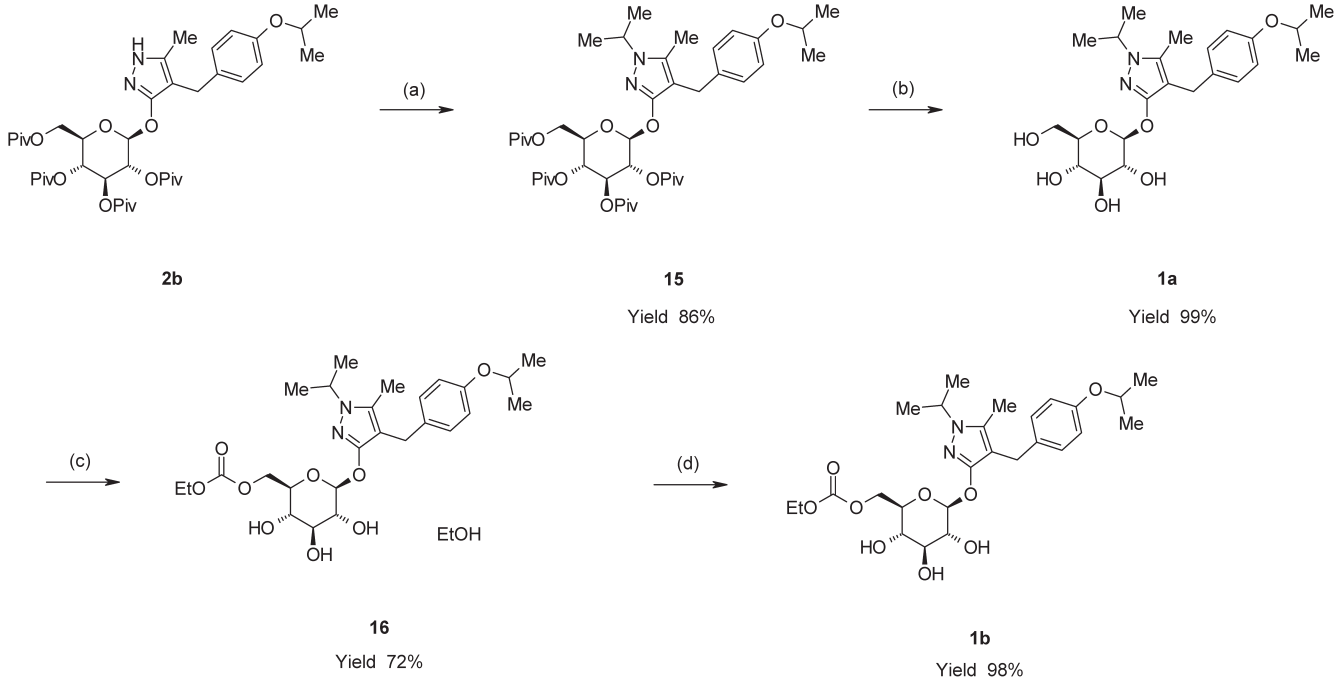
Chart 7. Preparation for **2b** without Isolation of **11c**

Table 5. A One-Pot Synthesis for **2** from **3**



Reagents: (a) AC_2O, K_2CO_3, DMF; (b) **5b**, K_2CO_3, MeCN; (c) $KHCO_3$, MeOH.

Entry	Aglycon	R^1	R^2	R^3	**5b** (mol%)	Product	Yield (%)
1	**3a**	O*i*-Pr	H	H	(130)	**2b**	86
2	**3b**	OMe	F	H	(130)	**2c**	85
3	**3c**	OMe	H	F	(130)	**2d**	87



Reagents: (a) 2-Iodopropane, NaH, DMI; (b) MeONa, MeOH; (c) Ethyl chloroformate, 2,3-lutidine, pyridine, MeCN; (d) MTBE, *n*-heptane.

Chart 8. Preparation for **1b** from **2b**

were recorded on a Nicolet AVATAR 320 FT-IR spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AV-400M (400 MHz) or DRX-500 (500 MHz) spectrometer using tetramethylsilane as the internal standard. High-resolution (HR)-MS were recorded on an Agilent Technologies Q-TOF 6520 mass spectrometer.

General Procedure for the Preparation of 4-(Substituted benzyl)-1,2-dihydro-5-methyl-3*H*-pyrazol-3-ones (3a–c) *N*,*N*-Diisopropylethylamine (12.9 g, 100 mmol) was added dropwise to a mixture of an appropriate benzyl chloride **6a–c** (50 mmol), methyl acetoacetate (**7**) (6.39 g, 55 mmol), lithium chloride (2.33 g, 55 mmol), and potassium iodide (0.896 g, 5.4 mmol) in a mixed solvent of toluene (20 mL) and DMF (20 mL) at 50°C with stirring. The reaction mixture was stirred at 70°C for 12 h and then cooled to room temperature. After the addition of toluene (20 mL), the resulting mixture was washed successively with water (30 mL), 2 M HCl (30 mL), water (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and water (30 mL). The organic layer was concentrated under reduced pressure. Hydrazine monohydrate (3.25 g, 65 mmol) was added dropwise to the residual solution in toluene (30 mL) at room temperature. The reaction mixture was stirred for 12 h at 70°C and then cooled to room temperature. *n*-Hexane (30 mL) and 2-propanol (5 mL) were then added to the mixture in that order. The resulting slurry was stirred for 1 h at room temperature and for an additional 1 h at 0°C. The precipitate was filtered off and dried *in vacuo* to provide **3a–c**.

1,2-Dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one (**3a**)

White solid (71% from **6a**). mp 227–234°C (decomp.). IR (KBr) cm^{-1}: 2977, 1609, 1543, 1507, 1477, 1420, 1383, 1372. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (6H, d, J=6.0 Hz), 2.00 (3H, s), 3.46 (3H, s), 4.46–4.55 (1H, m), 6.77 (2H, d, J=8.8 Hz), 7.04 (2H, d, J=8.8 Hz), 10.02–10.46 (2H, brs). ^{13}C-NMR (DMSO-d_6) δ: 9.86 (q), 21.77 (q×2), 26.28 (t), 68.87 (d), 100.30 (s), 115.26 (d×2), 128.83 (d×2), 133.60 (s), 136.65 (s), 155.22 (s), 159.55 (s). HR-MS (electrospray ionization (ESI)) *m*/*z*: 247.1448 $[M+H]^+$ (Calcd for $C_{14}H_{19}N_2O_2$: 247.1441).

1,2-Dihydro-4-[(3-fluoro-4-methoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one (**3b**)

White solid (69% from **6b**). mp 216–220°C (decomp.). IR (KBr) cm^{-1}: 1609, 1518, 1435, 1275. ^{1}H-NMR (DMSO-d_6) δ: 2.01 (3H, s), 3.49 (2H, s), 3.78 (3H, s), 6.90–6.97 (2H, m), 7.02 (1H, t, J=8.7 Hz), 10.39 (2H, brs). ^{13}C-NMR (DMSO-d_6) δ: 9.79 (q), 26.17 (t), 55.85 (q), 99.74 (s), 113.55 (d, J_{CF}=1.5 Hz), 115.22 (d, J_{CF}=17.6 Hz), 123.68 (d, J_{CF}=2.9 Hz), 134.98 (d, J_{CF}=5.8 Hz), 136.83 (s), 144.83 (d, J_{CF}=10.3 Hz), 151.17 (d, J_{CF}=244.3 Hz), 159.55 (s). HR-MS (ESI) *m*/*z*: 237.1030 $[M+H]^+$ (Calcd for $C_{12}H_{14}FN_2O_2$: 237.1034).

1,2-Dihydro-4-[(2-fluoro-4-methoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one (**3c**)

White solid (64% from **6c**). mp 226–227°C (decomp.). IR (KBr) cm^{-1}: 1628, 1598, 1512, 1466, 1446, 1435, 1409. ^{1}H-NMR (DMSO-d_6) δ: 2.00 (3H, s), 3.48 (2H, s), 3.71 (3H, s), 6.67 (1H, dd, J=2.4, 8.4 Hz), 6.74 (1H, dd, J=2.9, 12 Hz), 7.02 (1H, t, J=8.8 Hz), 10.38 (2H, brs). ^{13}C-NMR (DMSO-d_6) δ: 9.71 (q), 19.41 (d, J_{CF}=2.9 Hz), 55.34 (q), 98.48 (s), 101.00 (d, J_{CF}=25.7 Hz), 109.76 (d, J_{CF}=2.9 Hz), 119.70 (d, J_{CF}=16.1 Hz), 130.58 (d, J_{CF}=7.4 Hz), 136.85 (s), 158.53 (d, J_{CF}=11.0 Hz), 159.68 (s), 160.34 (d, J_{CF}=242.9 Hz). HR-MS (ESI) *m*/*z*: 237.1031 $[M+H]^+$ (Calcd for $C_{12}H_{14}FN_2O_2$: 237.1034).

1-Acetyl-1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one (10a) Acetic anhydride (3.27 g, 32 mmol) was added dropwise to a mixture of **3a** (7.39 g, 30 mmol) and K_2CO_3 (4.56 g, 33 mmol) in DMF (27 mL) at 40°C. The reaction mixture was stirred for 30 min at 40°C and for 1 h at 70°C. The reaction mixture was cooled to 50°C and the inorganic salt was filtered off and washed with DMF (12 mL). Acetic acid (0.180 g, 3.0 mmol) in H_2O (1.8 mL) was added to the combined filtrates and stirred for 30 min at 20°C. H_2O (30 mL) was added to the resulting slurry and the mixture was stirred for 1 h at 20°C. The precipitate was filtered off and dried *in vacuo* at 60°C to provide **10a** (7.01 g, 81%) as a white solid. mp 166–173°C (decomp.). IR (KBr) cm^{-1}: 2978, 2924, 1725, 1626, 1609, 1539, 1507, 1396, 1377, 1318, 1307. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (6H, d, J=6.0 Hz), 2.41 (3H, s), 2.45 (3H, s), 3.52 (2H, s), 4.47–4.56 (1H, m), 6.79 (2H, d, J=8.7 Hz), 7.05 (2H, d, J=8.7 Hz), 10.97 (1H, brs). ^{13}C-NMR (DMSO-d_6) δ: 12.84 (q), 21.77 (q×2), 23.16 (q), 25.75 (t), 68.93 (d), 111.25 (s), 115.46 (d×2), 128.93 (d×2), 131.70 (s), 139.97 (s), 155.62 (s), 161.62 (s), 169.88 (s). HR-MS (ESI) *m*/*z*: 289.1541 $[M+H]^+$ (Calcd for $C_{16}H_{21}N_2O_3$: 289.1547).

1-Acetyl-3-benzyloxy-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole (12) A mixture of **10a** (4.32 g, 15 mmol), benzyl bromide (3.08 g, 18 mmol), and K_2CO_3 (3.11 g, 22.5 mmol) in MeCN (20 mL) was stirred at 60°C for 2 h and the resulting inorganic salt was filtered off. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (eluent AcOEt–*n*-hexane, 1 : 3) to provide **12** (3.89 g, 69%) as a colorless oil. IR (KBr) cm^{-1}: 2975, 2934, 1718, 1612, 1507, 1467, 1453, 1375, 1337. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (6H, d, J=6.0 Hz), 2.84 (3H, s), 2.56 (3H, s), 3.56 (2H, s), 4.44–4.53 (1H, m), 5.26 (2H, s), 6.77 (2H, d, J=8.5 Hz), 7.06 (2H, d, J=8.5 Hz), 7.30–7.35 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 13.14 (q), 22.07 (q×2), 23.37 (q), 26.50 (t), 69.86 (d), 70.07 (t), 111.38 (s), 115.85 (d×2), 127.84 (d×2), 127.93 (d), 128.34 (d×2), 129.17 (d×2), 131.69 (s), 136.83 (s), 141.24 (s), 156.24 (s), 162.54 (s), 170.98 (s). HR-MS (ESI) *m*/*z*: 379.2018 $[M+H]^+$ (Calcd for $C_{23}H_{27}N_2O_3$: 379.2016).

3-Benzyloxy-4-[(4-isopropoxyphenyl)methyl]-1,5-dimethyl-1*H*-pyrazole (14) A mixture of **12** (3.60 g, 9.51 mmol) and $KHCO_3$ (0.286 g, 2.85 mmol) in MeOH (20 mL) was stirred at 50°C for 2 h and the reaction mixture was concentrated under reduced pressure. AcOEt (40 mL) was added to the residue and the mixture was washed with H_2O (20 mL). The organic layer was dried over $MgSO_4$ and the filtrate was concentrated under reduced pressure to provide an oil. The oil was dissolved in DMAc (10 mL) and added dropwise to a suspension of sodium hydride (0.571 g, 14.3 mmol, 60% oil dispersion) in DMAc (5 mL) at 0°C under a N_2 atmosphere and the mixture was stirred for 15 min at 0°C. MeI (2.70 g, 19.0 mmol) was added and the mixture was stirred for 2 h. The reaction mixture was diluted with AcOEt (70 mL) and washed with H_2O (30 mL×2). The resulting organic layer was dried over $MgSO_4$ and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent AcOEt–*n*-hexane, 1 : 2) to provide **14** (2.84 g, 85% yield) as a colorless oil. IR (KBr) cm^{-1}: 2974, 2934, 1738, 1611, 1580, 1506, 1464, 1453, 1383, 1365, 1333. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (2H, d, J=6.0 Hz), 2.07 (3H, s), 3.60 (2H, s), 3.62 (3H, s), 4.43–4.52 (1H, m), 5.21 (2H, s), 6.74 (2H, d, J=8.6 Hz), 7.08 (2H, d, J=8.6 Hz), 7.26–7.39 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 9.88 (q), 22.10 (q×2), 27.21 (t), 35.56 (q), 69.86 (d), 69.97 (t), 102.40 (s), 115.76 (d×2), 127.45 (d×2), 127.55 (d), 128.28 (d×2), 129.10 (d×2), 133.52 (s), 137.45 (s), 137.77 (s), 155.93 (s), 160.17 (s). HR-MS (ESI) *m*/*z*: 351.2071 $[M+H]^+$ (Calcd for $C_{22}H_{27}N_2O_2$: 351.2067).

1,2-Dihydro-4-[(4-isopropoxyphenyl)methyl]-1,5-dimeth-

yl-3*H*-pyrazol-3-one (10b) A solution of **14** (2.70 g, 7.70 mmol) in THF (30 mL) was hydrogenated over 10% Pd/C (50% wet, 0.30 g) for 10 h at room temperature under atmospheric pressure. The Pd–C was filtered off and the filtrate was concentrated under reduced pressure to provide **10b** (1.98 g, 99%) as a white solid. mp 160–162°C. IR (KBr) cm^{-1}: 1613, 1540, 1511, 1372, 1300. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (6H, d, J=6.0 Hz), 2.03 (3H, s), 3.45 (2H, s), 3.47 (3H, s), 4.46–4.55 (1H, m), 6.76 (2H, d, J=8.5 Hz), 7.03 (2H, d, J=8.5 Hz), 9.37 (1H, br s). ^{13}C-NMR (DMSO-d_6) δ: 9.31(q), 21.76 (q×2), 26.56 (t), 34.97 (q), 68.87 (d), 100.95 (s), 115.27 (d×2), 128.76 (d×2), 133.59 (s), 136.22 (s), 155.24 (s), 157.91 (s). HR-MS (ESI) *m/z*: 261.1609 $[M+H]^+$ (Calcd for $C_{15}H_{21}N_2O_2$: 261.1598).

1-Acetyl-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-1*H*-pyrazole (11a) **5a** (0.987 g, 2.4 mmol) was added to a mixture of **10a** (0.577 g, 2.0 mmol) and K_2CO_3 (0.387 g, 2.8 mmol) in MeCN (5 mL), and the reaction mixture was stirred for 16 h at 60°C. The mixture was diluted with AcOEt (20 mL) and washed with H_2O (5 mL). The resulting organic layer was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent AcOEt–*n*-hexane, 1 : 3) to provide **11a** (1.11 g, 90% yield). An analytical sample of **11a** was obtained as a white solid by recrystallization from Et_2O. mp 68–72°C. $[\alpha]_D^{20}$ −19.3 (c=1.0, dimethyl sulfoxide (DMSO)). IR (KBr) cm^{-1}: 3436, 2977, 2934, 1759, 1611, 1509, 1472, 1431, 1373, 1336. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, dd, J=3.8, 6.2 Hz), 1.86 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.50 (3H, s), 2.55 (3H, s), 3.54 (2H, dd, J=15.6, 19.9 Hz), 3.86–3.91 (1H, m), 4.16 (1H, dd, J=2.3, 12.5 Hz), 4.27 (1H, dd, J=4.8, 12.2 Hz), 4.43–4.52 (1H, m), 5.18 (1H, t, J=9.6 Hz), 5.24–5.33 (2H, m), 5.71 (1H, d, J=7.8 Hz), 6.75 (2H, d, J=8.5 Hz), 7.01 (2H, d, J=8.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 13.12 (q), 20.41 (q), 20.60 (q×2), 20.71 (q), 22.03 (q), 22.09 (q), 23.19 (q), 26.25 (t), 61.82 (t), 68.17 (d), 69.87 (d), 70.62 (d), 72.48 (d), 72.83 (d), 96.67 (d), 111.39 (s), 115.93 (d×2), 129.13 (d×2), 131.30 (s), 141.76 (s), 156.31 (s), 160.45 (s), 169.15 (s), 169.42 (s), 170.23 (s), 170.61 (s), 170.85 (s). HR-MS (ESI) *m/z*: 619.2473 $[M+H]^+$ (Calcd for $C_{30}H_{39}N_2O_{12}$: 619.2498).

4-[(4-Isopropoxyphenyl)methyl]-1,5-dimethyl-3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-1*H*-pyrazole (11b) **5a** (0.987 g, 2.4 mmol) was added to a mixture of **10b** (0.521 g, 2.0 mmol) and K_2CO_3 (0.387 g, 2.8 mmol) in MeCN (5 mL) and the reaction mixture was stirred for 16 h at 60°C. The reaction mixture was diluted with AcOEt (20 mL) and washed with H_2O (5 mL). The resulting organic layer was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent AcOEt–*n*-hexane, 1 : 1) to provide **11b** (0.311 g, 26%). An analytical sample of **11b** was obtained as a white solid by recrystallization from Et_2O-*n*-hexane. mp 65–69°C. $[\alpha]_D^{20}$ −11.2 (c=1.0, DMSO). IR (KBr) cm^{-1}: 2977, 1759, 1751, 1508, 1496, 1371. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (6H, dd, J=1.9, 6.3 Hz), 1.90 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.07 (3H, s), 3.54 (2H, dd, J=16.0, 14.7 Hz), 3.60 (3H, s), 3.82–3.86 (1H, m), 4.09–4.16 (1H, m), 4.30 (1H, dd, J=4.3, 12.5 Hz), 4.42–4.51 (1H, m), 5.17–5.29 (3H, m), 5.53–5.55 (1H, m), 6.74 (2H, d, J=8.7 Hz), 7.02 (2H, d, J=8.7 Hz). ^{13}C-NMR ($CDCl_3$) δ: 9.92 (q), 20.53 (q), 20.62 (q), 20.65 (q), 20.75 (q), 22.07 (q), 22.10 (q), 26.88 (t), 35.77 (q), 61.71 (t), 68.18 (d), 69.85 (d), 70.98 (d), 71.94 (d), 72.96 (d), 97.76 (d), 103.62 (s), 115.78 (d×2), 129.06 (d×2), 133.09 (s), 137.63 (s), 155.97 (s), 157.67 (s), 169.34 (s), 169.45 (s), 170.27 (s), 170.77 (s). HR-MS (ESI) *m/z*: 591.2554 $[M+H]^+$ (Calcd for $C_{29}H_{39}N_2O_{11}$: 591.2548).

4-[(4-Isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-1*H*-pyrazole (2a) A mixture of **11a** (0.618 g, 1.0 mmol) and $KHCO_3$ (0.030 g, 0.30 mmol) in MeOH (3 mL) was stirred at 50°C for 1 h; AcOH (0.018 g, 0.30 mmol) was then added at room temperature. After the reaction mixture was concentrated under reduced pressure, the residue was purified by silica gel chromatography (eluent AcOEt–*n*-hexane, 1 : 2) to provide **2a** (0.259 g, 45% yield). An analytical sample of **2a** was obtained as a white solid by recrystallization from Et_2O. mp 155–156°C. $[\alpha]_D^{20}$ −7.9 (c=1.0, DMSO). IR (KBr) cm^{-1}: 3393, 3222, 2978, 2943, 1751, 1735, 1612, 1509, 1474, 1434, 1374. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, dd, J=2.3, 5.9 Hz), 1.89 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 3.55 (2H, dd, J=15.7, 11.7 Hz), 3.83–3.87 (1H, m), 4.11 (1H, dd, J=2.3, 12.5 Hz), 4.31 (1H, dd, J=4.1, 12.3 Hz), 4.43–4.52 (1H, m), 5.18–5.30 (3H, m), 5.58 (1H, d, J=6.8 Hz), 6.75 (2H, d, J=8.8 Hz), 7.02 (2H, d, J=8.8 Hz), 9.09 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 10.36 (q), 20.48 (q), 20.61 (q), 20.63 (q), 20.72 (q), 22.07 (q), 22.10 (q), 26.50 (t), 61.64 (t), 68.07 (d), 69.89 (d), 70.93 (d), 72.06 (d), 72.92 (d), 97.67 (d), 103.54 (s), 115.84 (d×2), 129.12 (d×2), 132.69 (s), 138.21 (s), 156.05 (s), 159.89 (s), 169.31 (s), 169.44 (s), 170.30 (s), 170.76 (s). HR-MS (ESI) *m/z*: 577.2380 $[M+H]^+$ (Calcd for $C_{28}H_{37}N_2O_{11}$: 577.2392).

1-Acetyl-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-pivaloyl-*β*-D-glucopyranosyloxy)-1*H*-pyrazole (11c) **5b** (1.39 g, 2.4 mmol) was added to a mixture of **10a** (0.577 g, 2.0 mmol) and K_2CO_3 (0.387 g, 2.8 mmol) in MeCN (5 mL), and the mixture was stirred for 16 h at 60°C. The reaction mixture was diluted with AcOEt (20 mL) and washed with H_2O (5 mL). The resulting organic layer was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (eluent AcOEt–*n*-hexane, 1 : 3) to provide **11c** (1.44 g, 92% yield). An analytical sample of **10c** was obtained as a white solid by recrystallization from *n*-hexane. mp 137–140°C. $[\alpha]_D^{20}$ −2.0 (c=1.0, DMSO). IR (KBr) cm^{-1}: 3469, 2975, 2936, 2875, 1747, 1612, 1509, 1480, 1470, 1398, 1370, 1333. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (9H, s), 1.13 (9H, s), 1.16 (9H, s), 1.18 (9H, s), 1.29 (6H, dd, J=2.4, 6.1 Hz), 2.47 (3H, s), 2.54 (3H, s), 3.53 (2H, s), 3.88–3.92 (1H, m), 4.12–4.20 (2H, m), 4.42–4.51 (1H, m), 5.23 (1H, t, J=9.7 Hz), 5.28–5.33 (1H, m), 5.43 (1H, t, J=9.4 Hz), 5.84 (1H, d, J=8.2 Hz), 6.74–6.78 (2H, m), 7.01–7.04 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 13.19 (q), 22.05 (q), 22.10 (q), 23.22 (q), 26.23 (t), 26.88 (q×3), 27.03 (q×6), 27.15 (q×3), 38.66 (s), 38.74 (s), 38.77 (s), 38.83 (s), 61.61 (t), 67.64 (d), 69.83 (d), 70.71 (d), 72.21 (d), 72.89 (d), 97.00 (d), 111.52 (s), 115.96 (d×2), 129.17 (d×2), 131.23 (s), 141.82 (s), 156.30 (s), 160.57 (s), 170.88 (s), 176.38 (s), 176.40 (s), 177.20 (s), 178.03 (s). HR-MS (ESI) *m/z*: 787.4373 $[M+H]^+$ (Calcd for $C_{42}H_{63}N_2O_{12}$: 787.4376).

4-[(4-Isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-pivaloyl-*β*-D-glucopyranosyloxy)-1*H*-pyrazole (2b) A mixture of **11c** (0.787 g, 1.0 mmol) and $KHCO_3$ (0.030 g, 0.30 mmol) in MeOH (3 mL) was stirred at 50°C for 1 h; AcOH (0.018 g, 0.30 mmol) was then added at room temperature. After the reaction mixture had been concentrated under reduced pressure, the residue was purified by silica gel chromatography (eluent AcOEt–*n*-hexane, 1 : 2) to provide

2b (0.731 g, 98% yield). An analytical sample of **2b** was obtained as a white solid by recrystallization from 2-PrOH. mp 159–163°C. $[\alpha]_D^{20}$ −10.8 (*c*=1.0, DMSO). IR (KBr) cm^{-1}: 3383, 2975, 2936, 2874, 1746, 1729, 1507, 1482. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (9H, s), 1.12 (9H, s), 1.15 (9H, s), 1.18 (9H, s), 1.30 (6H, dd, *J*=1.2, 6.0 Hz), 2.06 (3H, s), 3.54 (2H, s), 3.84–3.88 (1H, m), 4.11–4.20 (2H, m), 4.41–4.53 (2H, m), 5.23–5.32 (2H, m), 5.38 (1H, t, *J*=9.2 Hz), 5.68 (2H, d, *J*=8.0 Hz), 6.75 (2H, d, *J*=8.8 Hz), 7.04 (2H, d, *J*=8.8 Hz), 8.82 (1H, brs). ^{13}C-NMR ($CDCl_3$) δ: 10.42 (q), 22.07 (q), 22.11 (q), 22.6 (t), 26.95 (q×3), 27.04 (q×3), 27.06 (q×3), 27.14 (q×3), 38.68 (s), 38.72 (s), 38.74 (s), 38.83 (s), 61.53 (t), 67.57 (d), 69.84 (d), 70.94 (d), 72.41 (d), 72.45 (d), 97.72 (d), 103.62 (s), 115.80 (d×2), 129.23 (d×2), 132.68 (s), 138.00 (s), 156.00 (s), 159.83 (s), 176.36 (s), 176.55 (s), 177.24 (s), 178.12 (s). HR-MS (ESI) *m/z*: 745.4262 $[M+H]^+$ (Calcd for $C_{40}H_{61}N_2O_{11}$: 745.4270).

General Procedure for the Preparation of 4-(Substituted benzyl)-5-methyl-3-(2,3,4,6-tetra-*O*-pivaloyl-*β*-D-glucopyranosyloxy)-1*H*-pyrazoles (2b–d) Acetic anhydride (0.325 g, 3.18 mmol) was added dropwise to a mixture of an appropriate 1,2-dihydro-4-(substituted benzyl)-5-methyl-3*H*-pyrazol-3-one (**3a–c**) (3.0 mmol), K_2CO_3 (0.456 g, 3.3 mmol) in DMF (2 mL) at 40°C. The mixture was stirred for 30 min at 40°C and for 1 h at 70°C. The reaction mixture was cooled to 40°C and MeCN (25 mL), and an aqueous solution of 25% K_2CO_3 (3.33 g, 6.0 mmol) and **5b** (2.26 g, 3.9 mmol) were added successively to the mixture. The mixture was stirred for 6 h at 60°C and cooled to room temperature. AcOEt (25 mL) and H_2O (5 mL) were added to the mixture with stirring and the aqueous layer was removed. The organic layer was concentrated under reduced pressure. $KHCO_3$ (0.090 g, 0.90 mmol) was added to a solution of the residue in MeOH (10 mL) and the mixture was stirred for 2 h at 60°C. After the addition of AcOH (0.054 g, 0.90 mmol), the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent AcOEt–*n*-hexane, 1 : 3) to provide **2b**–**d**.

4-[(3-Fluoro-4-methoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-pivaloyl-*β*-D-glucopyranosyloxy)-1*H*-pyrazole (**2c**)

An analytical sample of **2c** was obtained as a white solid by recrystallization from 2-PrOH–*n*-hexane. mp 189–192°C. $[\alpha]_D^{20}$ −11.1 (*c*=1.0, DMSO). IR (KBr) cm^{-1}: 3373, 2970, 2909, 2874, 1747, 1729, 1603, 1516, 1482, 1396, 1365. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (9H, s), 1.12 (9H, s), 1.15 (9H, s), 1.18 (9H, s), 2.07 (3H, s), 3.54 (2H, s), 3.84 (3H, s), 3.84–3.89 (1H, m), 4.11–4.21 (2H, m), 5.23–5.31 (2H, m), 5.39 (1H, t, *J*=9.5 Hz), 5.69 (1H, d, *J*=8.0 Hz), 6.81–6.89 (3H, m), 8.93 (1H, brs). ^{13}C-NMR ($CDCl_3$) δ: 10.36 (q), 26.49 (t), 26.92 (q×3), 27.03 (q×6), 27.14 (q×3), 38.68 (s), 38.72 (s), 38.74 (s), 38.83 (s), 56.32 (q), 61.50 (t), 67.56 (d), 70.93 (d), 72.35 (d), 72.48 (d), 97.76 (d), 102.97 (s), 113.36 (d, J_{CF}=2.2 Hz), 115.88 (d, J_{CF}=18.3 Hz), 123.76 (d, J_{CF}=2.9 Hz), 133.89 (d, J_{CF}=5.9 Hz), 138.04 (s), 145.65 (d, J_{CF}=10.3 Hz), 152.23 (d, J_{CF}=244.9 Hz), 159.75 (s), 176.37 (s), 176.59 (s), 177.25 (s), 178.11 (s). HR-MS (ESI) *m/z*: 735.3844 $[M+H]^+$ (Calcd for $C_{38}H_{56}FN_2O_{11}$: 735.3863).

4-[(2-Fluoro-4-methoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-pivaloyl-*β*-D-glucopyranosyloxy)-1*H*-pyrazole (**2d**)

An analytical sample of **2d** was obtained as a white solid by recrystallization from 2-PrOH–*n*-hexane. mp 167–169°C. $[\alpha]_D^{20}$ −7.1 (*c*=1.0, DMSO). IR (KBr) cm^{-1}: 3381, 2976, 2934, 2910, 1747, 1729, 1626, 1587, 1506, 1482, 1443, 1431, 1394, 1364. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (9H, s), 1.13 (9H, s), 1.15 (9H, s), 1.18 (9H, s), 2.10 (3H, s), 3.54 (2H, dd, *J*=15.6, 20.7 Hz), 3.75 (3H, s), 3.84–3.88 (1H, m), 4.12 (1H, dd, *J*=4.5, 12.3 Hz), 4.17 (1H, dd, *J*=1.8, 12.3 Hz), 5.23–5.32 (2H, m), 5.38 (1H, t, *J*=9.5 Hz), 5.68 (1H, d, *J*=8.0 Hz), 6.52–6.59 (2H, m), 7.07 (1H, t, *J*=8.7 Hz), 8.93 (1H, brs). ^{13}C-NMR ($CDCl_3$) δ: 10.14 (q), 19.70 (d, J_{CF}=3.3 Hz), 26.94 (q×3), 27.04 (q×6), 27.16 (q×3), 38.69 (s), 38.73 (s), 38.75 (s), 38.84 (s), 55.47 (q), 61.52 (t), 67.60 (d), 70.98 (d), 72.43 (d), 72.47 (d), 97.72 (d), 101.28 (d, J_{CF}=25.9 Hz), 102.34 (s), 109.65 (d, J_{CF}=2.8 Hz), 119.27 (d, J_{CF}=16.2 Hz), 131.17 (d, J_{CF}=6.5 Hz), 138.08 (s), 159.00 (s), 159.09 (s), 160.98 (d, J_{CF}=244.3 Hz), 176.37 (s), 176.58 (s), 177.25 (s), 178.10 (s). HR-MS (ESI) *m/z*: 735.3856 $[M+H]^+$ (Calcd for $C_{38}H_{56}FN_2O_{11}$: 735.3863).

4-[(4-Isopropoxyphenyl)methyl]-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-*O*-pivaloyl-*β*-D-glucopyranosyloxy)-1*H*-pyrazole (15) A solution of **2b** (50 g, 0.0671 mol) and 2-iodopropane (45.7 g, 0.269 mol) in DMI (105 g) was added dropwise to a suspension of NaH (8.05 g, 0.201 mol, 60% oil dispersion) in DMI (150 g) while maintaining the internal temperature between 10 and 20°C. The reaction mixture was stirred for 0.5–1 h at this temperature. The reaction mixture was added dropwise to a mixture of H_2O (200 g), glacial acetic acid (8.05 g, 0.134 mol) and toluene (200 g) at 0–30°C, and the layers were separated. The organic layer was washed twice with 1% brine (300 g) and concentrated under reduced pressure. The residue was dissolved in 2-PrOH (250 g) and the solution was concentrated under reduced pressure. The residue was dissolved in 2-PrOH and adjusted to a final weight of 250 g. The 2-propanol solution was stirred at 20°C for 2 h and the resulting slurry was stirred at −8~−2°C for an additional 2 h. The slurry was filtered and the wet cake washed with 2-PrOH (50 g), which was cooled to 0°C. The precipitate was dried *in vacuo* at 60°C to give 45.4 g (86% yield) of **15** as a white solid. mp 137–138°C. $[\alpha]_D^{20}$ −2.2 (*c*=1.0, DMSO). IR (KBr) cm^{-1}: 2979, 2940, 1747, 1508, 1483, 1398, 1384, 1370. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (9H, s), 1.13 (9H, s), 1.15 (9H, s), 1.19 (9H, s), 1.29 (6H, d, *J*=6.3 Hz), 1.33 (6H, dd, *J*=6.8, 9.3 Hz), 2.04 (3H, s), 3.52 (2H, dd, *J*=15.8, 19.6 Hz), 3.81–3.85 (1H, m), 4.10–4.19 (2H, m), 4.18–4.28 (1H, m), 4.41–4.51 (1H, m), 5.21–5.30 (2H, m), 5.41 (1H, t, *J*=9.6 Hz), 5.74 (1H, d, *J*=8.3 Hz), 6.74 (2H, d, *J*=8.7 Hz), 7.04 (2H, d, *J*=8.7 Hz). ^{13}C-NMR ($CDCl_3$) δ: 9.67 (q), 22.10 (q), 22.12 (q), 22.23 (q), 22.24 (q), 26.90 (t), 26.94 (q×3), 27.05 (q×3), 27.09 (q×3), 27.16 (q×3), 38.68 (s), 38.72 (s), 38.74 (s), 38.84 (s), 49.16 (d), 61.72 (t), 67.72 (d), 69.81 (d), 71.13 (d), 72.49(d), 72.51 (d), 98.02 (d), 102.89 (s), 115.71 (d×2), 129.18 (d×2), 133.43 (s), 135.72 (s), 155.88 (s), 157.69 (s), 176.38 (s), 176.58 (s), 177.27 (s), 178.18 (s). HR-MS (ESI) *m/z*: 787.4740 $[M+H]^+$ (Calcd for $C_{43}H_{67}N_2O_{11}$: 787.4739).

3-(*β*-D-Glucopyranosyloxy)-4-[(4-isopropoxyphenyl)-methyl]-1-isopropyl-5-methyl-1*H*-pyrazole (1a) A methanolic solution of 28% MeONa (1.93 g, 10 mmol) was added to a suspension of **15** (7.87 g, 10 mmol) in MeOH (75 mL) at room temperature. The mixture was then heated to 55°C and stirred for 3 h at this temperature. After cooling to 40°C, acetic acid (0.601 g, 10 mmol) was added dropwise to the reaction mixture. The reaction mixture was concentrated under reduced pressure to evaporate the methyl pivalate contained in the mixture. The residue was purified by silica gel chromatography (eluent dichloromethane–MeOH, 10 : 1) to provide **1a** (4.45 g, 99% yield) as a pale yellowish oil. $[\alpha]_D^{20}$ −8.1 (*c*=1.0,

DMSO). IR (KBr) cm^{-1}: 3407, 2975, 2931, 1506, 1466, 1384. ^{1}H-NMR (CD_3OD) δ: 1.26 (6H, d, J=6.0 Hz), 1.36 (6H, dd, J=3.8, 6.8 Hz), 2.09 (3H, s), 3.21–3.26 (1H, m), 3.33–3.43 (3H, m), 3.62–3.72 (3H, m), 3.77 (1H, dd, J=2.5, 12.1 Hz), 4.36–4.46 (1H, m), 4.46–4.55 (1H, m), 5.00–5.05 (1H, m), 6.76 (2H, d, J=8.7 Hz), 7.07 (2H, d, J=8.7 Hz). ^{13}C-NMR (CD_3OD) δ: 8.93 (q), 21.61 (q×2), 21.62 (q), 21.65 (q), 26.79 (t), 49.77 (d), 61.85 (t), 70.25 (d), 70.48 (d), 74.32 (d), 77.24 (d), 77.49 (d), 102.41 (d), 104.50 (s), 116.18 (d×2), 129.39 (d×2), 134.00 (s), 137.53 (s), 156.55 (s), 159.47 (s). HR-MS (ESI) m/z: 451.2444 $[M+H]^+$ (Calcd for $C_{23}H_{35}N_2O_7$: 451.2439).

5-Methyl-4-[4-(1-methylethoxy)benzyl]-1-(1-methylethyl)-1*H*-pyrazol-3-yl-6-*O*-(ethoxycarbonyl)-*β*-D-glucopyranoside Ethanolate (16) A solution of ethyl chloroformate (522 mg, 4.81 mmol) in MeCN (1 mL) was added dropwise to a mixture of **1a** (1.89 g, 4.19 mmol), 2,6-lutidine (672 mg, 6.28 mmol) and pyridine (13 mg, 0.17 mmol) in MeCN (10 mL) while maintaining the temperature between −3 and 3°C. The reaction mixture was stirred at 0°C for 2 h. After addition of glacial acetic acid (113 mg, 1.88 mmol), the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with MTBE (10 mL) and 10% brine (5 mL), and then the layers were separated. The organic layer was washed twice with brine (5 mL), dried over anhydrous $MgSO_4$ (2 g) and concentrated under reduced pressure. The residue was dissolved in EtOH (17 mL) and concentrated again under reduced pressure. EtOH was added to the residue, and the weight was adjusted to 9.3 g. To the EtOH solution, *n*-heptane (6 mL) was added and heated to 60°C to dissolve solids. The mixture was cooled to 45°C and stirred for 1 h at this temperature for an additional 1 h at 0–5°C. The slurry was filtered and the wet cake washed successively with a mixed solvent of EtOH (1.2 mL) and *n*-heptane (2.8 mL), which was cooled to 0°C, and then *n*-heptane (2.8 mL). The precipitate was dried *in vacuo* at room temperature to give 1.72 g (72% yield) of **16** as a white solid. mp 70–74°C. $[\alpha]_D^{20}$ −17.7 (c=1.0, DMSO). IR (KBr) cm^{-1}: 3353, 2980, 2926, 1753, 1731, 1508, 1477, 1467, 1449, 1386, 1371. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz), 1.28 (3H, t, J=7.0 Hz), 1.30 (6H, d, J=6.0 Hz), 1.38 (6H, dd, J=2.3, 6.6 Hz), 2.06 (3H, s), 3.47–3.63 (6H, m), 3.71 (2H, q, J=7.0 Hz), 4.17 (2H, q, J=7.0 Hz), 4.24–4.31 (1H, m), 4.32–4.39 (2H, m), 4.43–4.52 (1H, m), 4.98 (1H, d, J=7.6 Hz), 6.77 (2H, d, J=8.6 Hz), 7.05 (2H, d, J=8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 9.72, 14.21, 18.35, 22.09, 22.21, 22.25, 26.87, 49.44, 58.35, 64.23, 66.48, 69.49, 69.86, 73.65, 74.24, 76.44, 102.32, 104.67, 115.78, 129.10, 133.15, 136.55, 155.46, 155.96, 158.07. HR-MS (ESI) m/z: 523.2648 $[M+H]^+$ (Calcd for $C_{26}H_{39}N_2O_9$: 523.2650).

5-Methyl-4-[4-(1-methylethoxy)benzyl]-1-(1-methylethyl)-1*H*-pyrazol-3-yl-6-*O*-(ethoxycarbonyl)-*β*-D-glucopyranoside (1b) **16** (1.50 g, 2.64 mmol) was dissolved in MTBE (10 mL) at 45°C The solution was concentrated under reduced pressure to evaporate EtOH. MTBE was added to the residue, and the weight was adjusted to 9.0 g. H_2O (0.015 mL) and *n*-heptane (3.6 g) were added to the solution at 40°C and the solution was cooled to 25°C. The solution was seeded with **1a** and stirred at 25°C for 3 h. The resulting slurry was warmed to 40°C, and then a mixed solvent of MTBE (0.44 g) and *n*-heptane (2.4 g) was added dropwise to the slurry while maintaining the temperature between 37 and 43°C. The slurry was stirred at 40°C for 1 h and for an additional 3 h at 10°C. The slurry was filtered and the wet cake washed successively with a mixed solvent of MTBE (1.5 g) and *n*-heptane (1.5 g) followed by *n*-heptane (3.0 g). The product was dried *in vacuo* at room temperature to give 1.35 g (98% yield) of **1a** as a white solid. mp 80–83°C. $[\alpha]_D^{20}$ −19.3 (c=1.0, DMSO). IR (KBr) cm^{-1}: 3414, 2979, 1747, 1506, 1477, 1474, 1466, 1458, 1449, 1382, 1370, 1317. ^{1}H-NMR (CD_3OD) δ: 1.23 (3H, t, J=7.2 Hz), 1.26 (6H, d, J=6.1 Hz), 1.37 (6H, dd, J=2.3, 6.7 Hz), 2.07 (3H, s), 3.34–3.42 (4H, m), 3.61–3.69 (2H, m), 4.12 (2H, q, J=7.2 Hz), 4.21 (1H, dd, J=5.4, 11.5 Hz), 4.35 (1H, dd, J=1.7, 11.6 Hz), 4.35–4.45 (1H, m), 4.45–4.54 (1H, m), 5.04–5.06 (1H, m), 6.75 (2H, d, J=8.6 Hz), 7.06 (2H, d, J=8.6 Hz). ^{13}C-NMR (CD_3OD) δ: 9.70, 14.60, 22.43, 22.49, 22.54, 27.63, 50.53, 65.07, 67.67, 71.07, 71.21, 75.02, 75.56, 77.84, 103.25, 105.62, 116.98, 130.21, 134.81, 138.21, 156.65, 157.33, 159.99. HR-MS (ESI) m/z: 523.2651 $[M+H]^+$ (Calcd for $C_{26}H_{39}N_2O_9$: 523.2650).

Conflict of Interest Masahiro Kobayashi, Hidetoshi Isawa, Junichi Sonehara, Minoru Kubota and Tetsuji Ozawa are employees of Kissei Pharmaceutical Co., Ltd.

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