Na^+-Glucose Cotransporter (SGLT) Inhibitors as Antidiabetic Agents. 4. Synthesis and Pharmacological Properties of 4′-Dehydroxyphlorizin Derivatives Substituted on the B Ring

Kenji Tsujihara,* Mitsuya Hongu, Kunio Saito, Hiroyuki Kawanishi, Kayoko Kuriyama, Mamoru Matsumoto, Akira Oku, Kiichiro Ueta, Minoru Tsuda, and Akira Saito*

Discovery Research Laboratory, Tanabe Seiyaku Company, Ltd., 2-2-50, Kawagishi, Toda, Saitama 335-8505, Japan

Received April 13, 1999

In our studies of Na^+-glucose cotransporter (SGLT) inhibitors as antidiabetic agents, a series of novel 4′-dehydroxyphlorizin derivatives substituted on the B ring was prepared and their effects on urinary glucose excretion were evaluated in rats. Introduction of only a small alkyl group at the 4′-position increased the activity, and 3-(benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-*β*-D-glucopyranoside (**4**) showed the most potent effect. To overcome hydrolysis of compound **4** by *β*-glucosidase in the digestive tract, the OH groups on the glucose moiety of compound **4** were modified. Three prodrugs (**5**, **42**, and **55**) were more potent than the parent compound **4** by oral administration, and finally 3-(benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-(6-*O*-methoxycarbonyl-*β*-D-glucopyranoside) (**5**) was selected as a new promising candidate. Compound **5** was metabolized mainly by liver esterase to the active form (**4**), which was about 10 times more potent than **5** in inhibiting SGLT. In oral glucose tolerance test in db/db mice, compound **5** dose-dependently suppressed the elevation of glucose levels. Single administration of **5** reduced hyperglycemia concurrently with increase of glucose excretion into urine in diabetic KK-A^y mice. Furthermore, compound **5** suppressed the elevation of blood glucose levels but did not lower it below the normal level even in fasted conditions in KK-A^y mice. Additionally, long-term treatment with **5** dose-dependently reduced hyperglycemia and HbA1c in KK-A^y mice. These pharmacological data strongly suggest that compound **5** has a therapeutic potential in the treatment of NIDDM.

Introduction

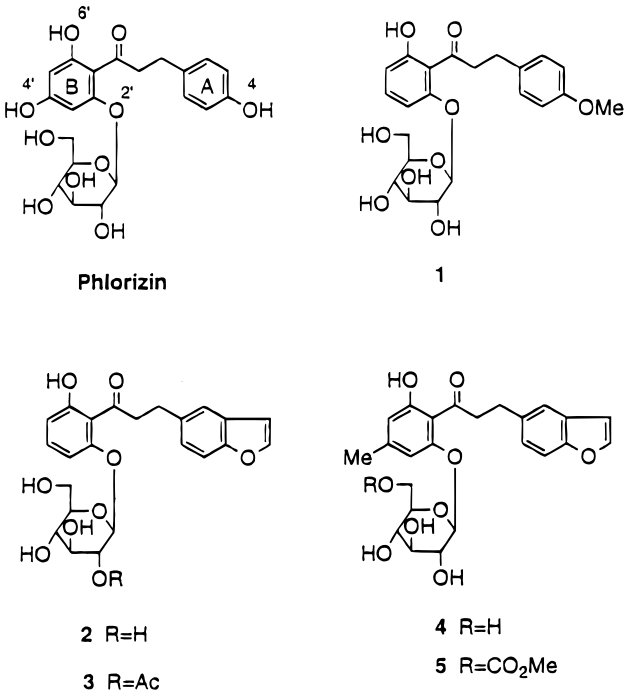
The incidence of noninsulin dependent diabetes mellitus (NIDDM) has been markedly increasing in developed countries.[1] Environmental factors including excessive energy intake and physical inactivity contribute to the occurrence of NIDDM.[1,2] Chronic hyperglycemia is not only a major risk factor for complications, including heart disease, nephropathy, neuropathy, and retinopathy, but also a major cause of impairment of both insulin secretion and insulin sensitivity of peripheral tissues in patients with diabetes (so-called glucose toxicity).[3] The management of NIDDM starts with caloric restriction and increase of physical activity to correct the inadequate energy balance.[1,2,4,5] While antiobesity agents such as appetite suppressants,[6] absorption inhibitors,[7] and thermogenic stimulators[8] are thought to be effective for the treatment of NIDDM, the antidiabetic agent of a new type which can immediately correct hyperglycemia as well as inadequate energy balance is strongly desired.

We have reported the potential of an inhibitor of Na^+-glucose cotransporter (SGLT) as an antidiabetic agent which corrects both hyperglycemia and energy imbalance.[9−11] SGLT, which exists on the chorionic membrane of the intestine and the kidney, actively transports glucose by coupling with Na^+. Suppression of tubular glucose reabsorption by inhibiting renal SGLTs excretes excess plasma glucose into urine and, thus, eliminates hyperglycemia. In diabetic patients, glucose loss by excretion is beneficial since such action can reduce hyperglycemia and glucose-related osmotic dehydration of cells.[12]

In designing structural modifications of phlorizin (Chart 1), a classic inhibitor of renal tubular glucose reabsorption,[13] the following criteria were introduced for the lead optimization: (i) selective and reversible inhibition of SGLTs, (ii) induction of urinary glucose excretion by oral treatment, (iii) suppression of hyperglycemia with oral treatment, (iv) inactivity on the facilitated glucose transporters (GLUTs) by the aglycon produced by hydrolysis, and (v) lack of renal toxicity. Phlorizin itself meets only criteria (i) and (v).[14] In the previous study, we have found 4′-dehydroxyphlorizin derivative **1** as a lead compound which meets roughly the above five criteria.[9] Structure−activity analysis showed that there were strict structural requirements for the activity. Introduction of a small substituent or a flat ring at the 3- and/or 4- position on the A ring was permissible, but any change at the linker part between the A and B rings or in the sugar moiety resulted in complete loss of the activity. In modifying the substituents on the A ring, the benzofuran derivative **2** was found to show a strong effect on urinary glucose excretion and was selected as a new lead compound.[10] To prevent hydrolysis by *β*-glucosidase in the digestive tract, the OH groups on the glucose moiety of **2** were modified. The prodrug **3** was found to be resistant to *β*-glucosidase and was more potent than the parent compound **2** by oral administration.[11]

10.1021/jm990175n CCC: $18.00
Published on Web 12/03/1999

Chart 1



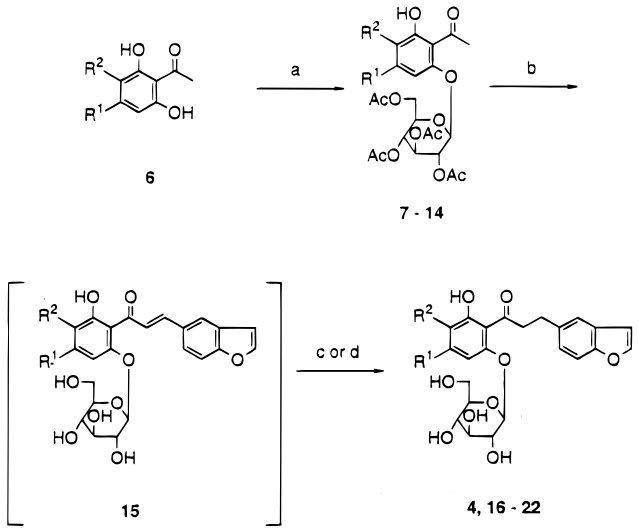
In the present paper we describe the synthesis and the structure−activity relationships (SAR) of phlorizin derivatives with substituents on the B ring of **2**, leading finally to the synthesis of a potent SGLT inhibitor **4** (4′-methyl derivative) and its prodrug **5**. We also describe the pharmacological profile of compound **5** (T-1095) and propose it as a promising new antidiabetic agent.

Chemistry

A series of dihydrochalcone glucosides (**4**, **16**−**22**) was synthesized as shown in Scheme 1. Glucosides **7**−**14** were prepared by the phase-transfer-catalyzed glycosylation of the substituted 2′,6′-dihydroxyacetophenone **6** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in a solid−liquid two-phase system (K_2CO_3/CH_2Cl_2).[15] Condensation of compounds **7**−**14** with benzofuran-5-carboxaldehyde[16] followed by catalytic hydrogenation using Pt on carbon as a catalyst[10] (method A) or reduction with sodium hydrogen telluride (NaTeH)[17] (method B) afforded the desired dihydrochalcone glucosides (**4**, **16**−**22**).

2′,6′-Dihydroxyacetophenone **6** used above was prepared as shown in Scheme 2. Initially, the 4′-substituted derivatives were synthesized according to the method of Desai and Mavani[18] (route 1) by acetylation followed by Fries rearrangement and deacetylation. Alternatively, compounds **6a**−**e** were also prepared in one step by reaction of **24** with $AlCl_3$ in chlorobenzene at 90 °C (route 2). The synthesis of 3′-alkyl derivatives (route 3) was achieved by the method of Russell and Frye.[19] The reaction of **23** with acetoacetate gave coumarin **26**. Acetylation of **26** followed by Fries rearrangement afforded **27**, which was hydrolyzed in alkaline medium to give **6f** (R^2 = Et) and **6g** (R^2 = Me). The 4′-OMe (**6h**) and 4′-OMOM (**6i**) derivatives were prepared from 2′,4′,6′-trihydroxyacetophenone **28**. Triisopropylsilylation of **28** gave 4′-*O*-silylated compound **29**, from which the glucoside was obtained only in low yield. Therefore, more stable MOM group was introduced to prepare 4′-OH derivative **21** (Scheme 2).

Scheme 1[a]



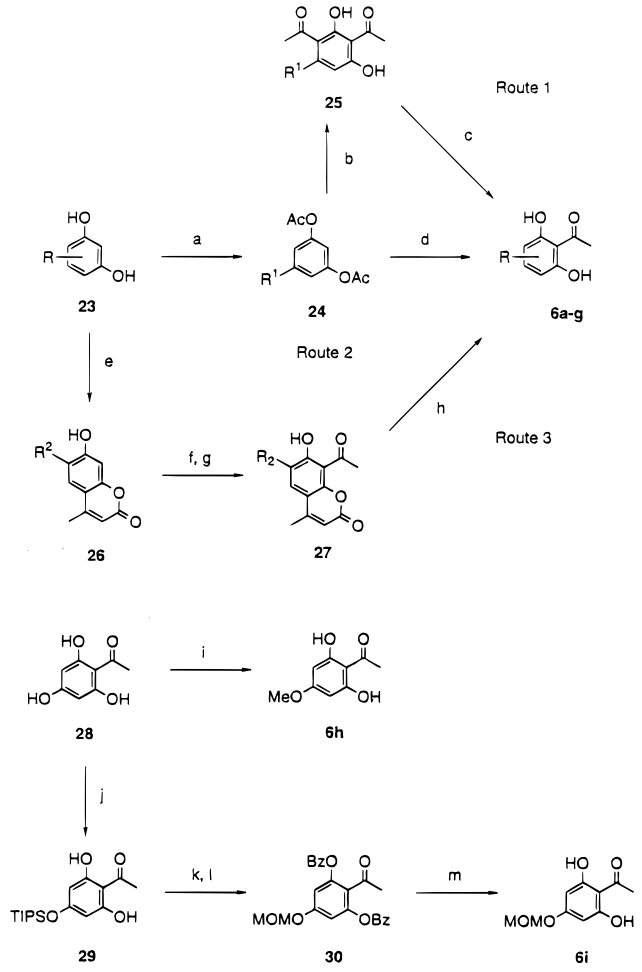
compound	R^1	R^2
6a, **7**, **4**	Me	H
6b, **8**, **16**	Et	H
6c, **9**, **17**	^{n}Pr	H
6d, **10**, **18**	^{i}Pr	H
6e, **11**, **19**	Cl	H
6f, **12**, **22**	H	Et
6h, **13**, **20**	OMe	H
6i, **14**, (**21**)	OMOM (OH)	H

[a] Reagents and conditions: (a) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, K_2CO_3, $BnBu_3NCl$, $CHCl_3$; (b) benzofuran-5-carboxaldehyde, 50% aq KOH, EtOH; (c) H_2, 10% Pt−C, 4-(dimethylamino)pyridine, EtOH−H_2O (method A); (d) NaTeH, EtOH (method B).

Alternative synthetic methods used to obtain dihydrochalcone glucosides are illustrated in Scheme 3. The 5′- allyl derivative **32** was prepared by Claisen rearrangement of allyl ether **31**. The 3′-Me derivative **36** was synthesized from **33**, which was obtained by benzoylation of **6g**. Glycosylation of **33** gave **34**, however only in low yield because of the steric hindrance of methyl group. Then crude **34** was condensed with benzofuran-5-carboxaldehyde to give the enone derivative **35** (27% from **33**). Reduction of **35** provided **36**. The 3′,5′- dichloro derivative **39** was prepared by chlorination of **37** with *N*-chlorosuccinimide (NCS) followed by aldol reaction and hydrogenation as shown in Scheme 3. The yield and physicochemical data of the dihydrochalcone glucosides are listed in the Table 1.

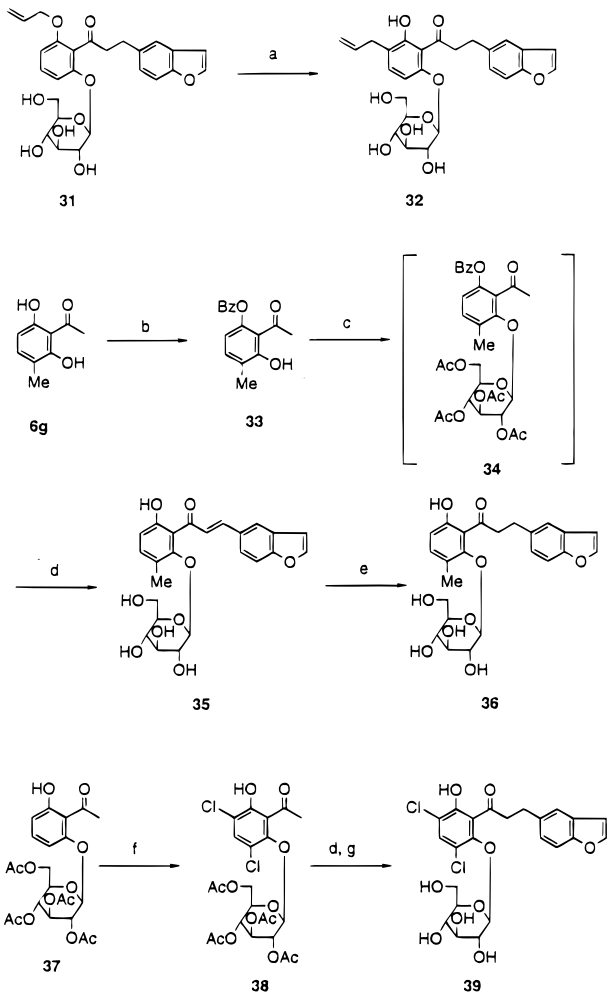
Next, various prodrugs of the most potent 4′-Me derivative **4** were prepared according to the method described in the previous paper.[11] Benzylidenation of **4** (**40**; 92%) followed by acetylation gave **41** (95%), and subsequent removal of the benzylidene group yielded the triacetyl derivative **42**. Treatment of **41** with $NaHCO_3$ selectively removed the acetyl group at the phenolic OH group, providing **43** which gave diacetate **44** on removal of the protecting group (Scheme 4). The 2- or 6-*O*-acyl derivatives (**46**, **47**, **5**, and **49**−**53**) were

Scheme 2[a]



[a] Reagents and conditions: (a) Ac_2O, pyridine; (b) $AlCl_3$, neat, 150 °C; (c) 85% H_2SO_4; (d) $AlCl_3$, chlorobenzene, 90 °C; (e) ethyl acetoacetate, H_2SO_4; (f) Ac_2O, reflux; (g) $AlCl_3$, neat, 170 °C; (h) NaOH, H_2O; (i) $TMSCHN_2$, MeOH−$CHCl_3$; (j) TIPSCl, imidazole, DMF; (k) BzCl, pyridine; (l) MOMCl, *n*-Bu_4NF, THF, 0 °C; (m) K_2CO_3, MeOH−THF.

Scheme 3[a]



[a] Reagents and conditions: (a) *N*,*N*-diethylaniline, 230 °C; (b) BzCl, collidine; (c) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, K_2CO_3, $BnBu_3NCl$, $CHCl_3$; (d) benzofuran-5-carboxaldehyde, 50% aq KOH, EtOH; (e) H_2, 10% Pd−C, piperizine, EtOH−H_2O−DMA; (f) NCS, DMF, 50 °C; (g) H_2, 10% Pt−C, *N*,*N*-(dimethylamino)pyridine, EtOH−H_2O.

prepared as shown in Scheme 5. The reaction of **40** with TBS chloride afforded bissilylated derivative **45** in 76% yield. Acetylation of **45** followed by deprotection yielded the 2-*O*-acetyl derivative **46**. The derivative having two acetyl groups at the phenolic OH and glucose 6-*O*-position (**47**) was prepared by acetylation of **4** with acetyl chloride in the presence of Et_3N in *N*,*N*-dimethylacetamide (DMA). The 6-*O*-acyl derivatives (**5**, **49**−**53**) were obtained by selective acylation of allyl ether **48** at the glucose 6-*O*-position[20] followed by deallylation.[21]

The 4-*O*-methoxycarbonyl derivative **55** and 4,6-*O*-methoxyethylidene derivative **56** were prepared as shown in Scheme 6. The reaction of **4** with *p*-nitrophenyl chloroformate in collidine gave the 4,6-*O*-carbonyl derivative **54** in 68% yield. Methanolysis of **54** in the presence of *p*-toluenesulfonic acid (*p*-TsOH) afforded **55** (43%) along with **5** (39%). The reaction of **4** with trimethyl orthoacetate yielded the 4,6-*O*-methoxyethylidene derivative **56**. The yield and physicochemical data of the prodrugs of **4** are listed in the Table 2.

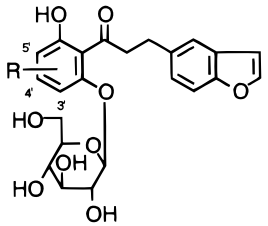
Results and Discussion

SAR. At first, the effect of the substituents on the B ring on urinary glucose excretion[9−11] was investigated in rats and results are shown in Table 1. Among the 4′-substituted derivatives, the methyl derivative **4** and ethyl derivative **16** were nearly 3 times as potent as that of unsubstituted compound **2**. But substituents larger than ethyl showed only reduced activity (**17**, **18**). Similarly, compounds with the substituent such as Cl (**19**), OMe (**20**), or OH (**21**) showed an unsatisfactory effect. Introduction of substituents on the 5′-position (**22**, **32**) as well as 3′-position (**36**) caused loss of the activity. Therefore, in the modification at the B ring, only the introduction of the small alkyl group such as methyl (**4**) and ethyl group (**16**) to the 4′-position markedly increased the activity.

Next, we examined the effects of modification of the OH groups on the glucose moiety of the most potent compound **4**, because these modifications were expected to enhance the stability against hydrolysis by β-glucosidase in the digestive tract and thus to increase the activity.[11] Results are summarized in Table 2.

As expected, the triacetyl derivative **42** was 1.5 times more efficacious than **4**. However, the 2,3-*O*-diacetyl (**44**) and the 2-*O*-acetyl (**46**) derivatives were less potent, although the reason of these results is not yet clear.

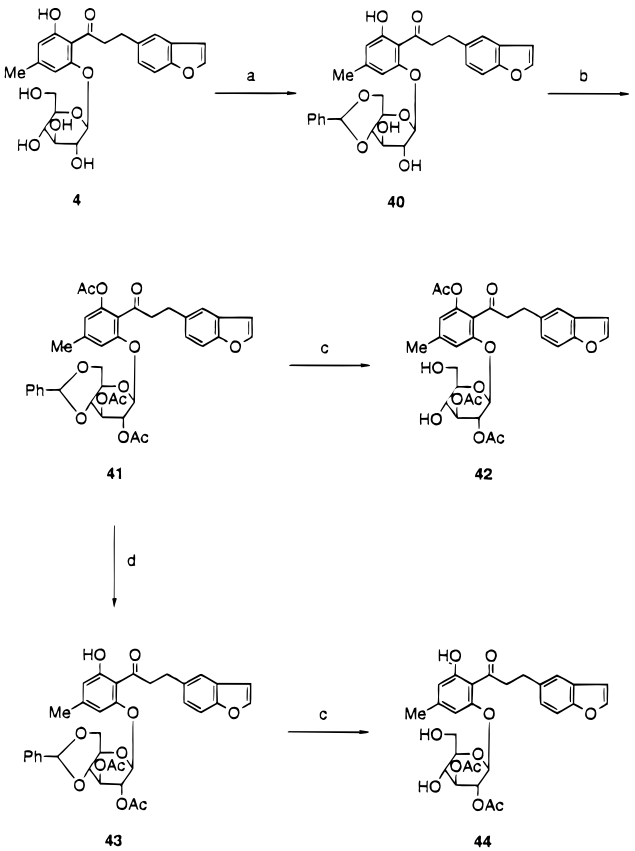
Table 1. Physical and Biological Properties of Dihydrochalcone Glucosides



no.	R	method[a]	yield (%)[b]	mp (°C) (recryst. solvent)	formula[c]	urinary glucose excretion[d] (mg/24 h) po (100 mg/kg)
2	H[e]					321 ± 29
4	4′-Me	A	78	155−157 (EtOH−H_2O)	$C_{24}H_{26}O_9$	935 ± 18
16	4′-Et	B	83	155−155.5 (AcOEt−*iso*-Pr_2O)	$C_{25}H_{28}O_9$	864 ± 159
17	4′-*n*-Pr	B	72	amorphous	$C_{26}H_{30}O_9$[g]	27 ± 11
18	4′-*iso*-Pr	B	86	amorphous	$C_{26}H_{30}O_9$[g]	128 ± 21
19	4′-Cl	A	48	106−107 (EtOH−*iso*-Pr_2O)	$C_{23}H_{23}ClO_9 \cdot {}^1/_2H_2O$	8 ± 2
20	4′-OMe	B	39	161−164 (EtOH−H_2O)	$C_{24}H_{26}O_{10}$	38 ± 7
21	4′-OH[f]	B	50	85−88 (EtOH−H_2O)	$C_{23}H_{24}O_{10} \cdot H_2O$	38 ± 24
22	5′-Et	B	54	84−87 (EtOH−H_2O)	$C_{25}H_{28}O_9 \cdot H_2O$	1 ± 1
32	5′-allyl		57	amorphous	$C_{26}H_{28}O_9$[g]	5 ± 2
36	3′-Me		22	amorphous	$C_{24}H_{26}O_9$[g]	5 ± 2
39	3′,5′-Cl_2	A	54	106−109 (toluene)	$C_{23}H_{22}Cl_2O_9 \cdot {}^1/_2H_2O$	5 ± 0

[a] Method A: the enone intermediate was reduced by catalytic hydrogenation over Pt on carbon. Method B: reduction by NaTeH. [b] Isolated yield from **7**−**14**. [c] Analyses (C, H, N) were within ±0.4% of theoretical values. [d] See Experimental Section. [e] Reference 10. [f] Compound **21** was prepared by deprotection of the 4′-OMOM derivative. [g] HR-MS were measured (see Experimental Section).

Scheme 4[a]



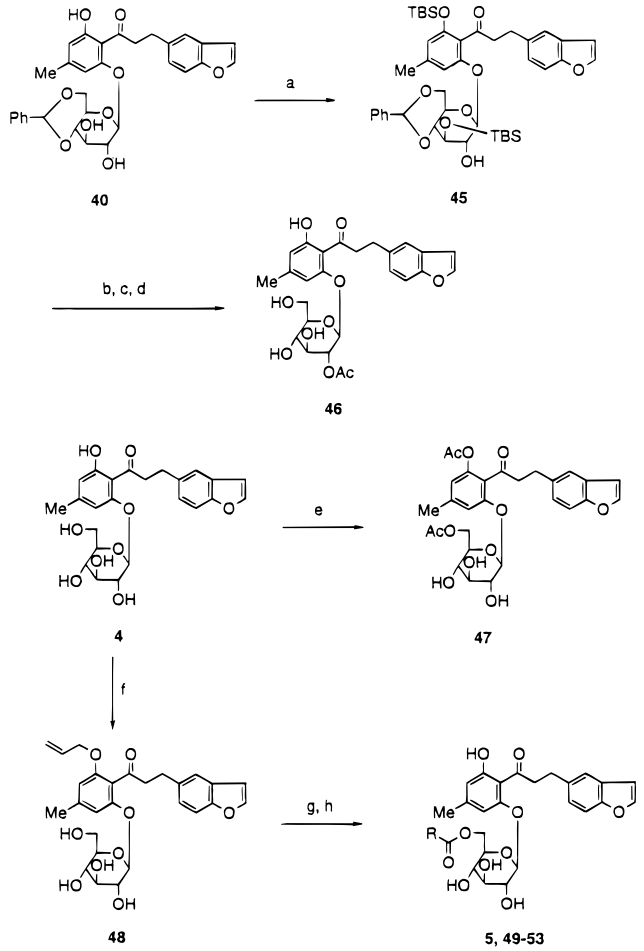
[a] Reagents and conditions: (a) benzaldehyde dimethylacetal, *p*-TsOH, CH_2Cl_2; (b) Ac_2O, pyridine; (c) *p*-TsOH, AcOH−H_2O; (d) $NaHCO_3$, MeOH−THF−H_2O.

Among the glucose 6-*O*-acyl derivatives, the 6-*O*-methoxycarbonyl derivative **5** was 1.3 times more potent than **4**. With increased bulk of alkoxycarbonyl moiety (**51**−**53**), the biological effect was attenuated and the activity of the diacylated compound at the phenolic OH and glucose 6-*O*-position (**47**) was weaker than the 6-*O*-acylated compound **49**. The 4-*O*-methoxycarbonyl derivative **55** was 1.5 times more potent than **4**, but the glucose 4,6-cyclic ortho ester **56** did not exhibit the improved activity.

In summary, investigations of the SAR of the dihydrochalcone glucosides substituted on the B ring revealed that only the introduction of a small alkyl group at the 4′-position enhanced the activity and among them compound **4** (4′-Me) was the most potent. In the series of prodrugs of **4**, we found three compounds more potent than **4**: triacetyl (**42**), 6-*O*-methoxycarbonyl (**5**), and 4-*O*-methoxycarbonyl (**55**) derivatives. Because of ease of synthesis, physical characteristics including crystallinity and stability, and metabolism by esterases in vivo, we selected compound **5** (T-1095) as a new promising candidate for the treatment of diabetes.

Pharmacological Profile of Compound 5. In dogs and humans, compound **5** was metabolized to its active form **4** mainly by liver esterase (Figure 1). We first determined the inhibitory effect of **4**, **5**, phlorizin, and 1,2-dihydro-4-[[4-(methylthio)phenyl]methyl]-5-(trifluoromethyl)-3*H*-pyrazol-3-one (WAY-123783), which was proposed as an inhibitor of renal glucose reabsorption,[22] on SGLT in rat renal brush border membrane vehicles (BBMVs). Compound **4** and phlorizin were about 10 times more potent than **5** in inhibiting SGLT, while WAY-123783 had no effect (Figure 2). Next, the effect of compound **5** on hyperglycemia was determined in an oral glucose tolerance test in db/db mice, and it suppressed the elevation of glucose levels in a dose-dependent manner (Figure 3). Under fed conditions, single administration of compound **5** reduced hyperglycemia concurrently with an increase of glucose excretion into urine in diabetic KK-A^y mice. The Na^+ content of the urine was not increased although an SGLT inhibitor would inhibit the reabsorption of Na^+ in proximal tubules (Figure 4). There are many other types

Scheme 5[a]

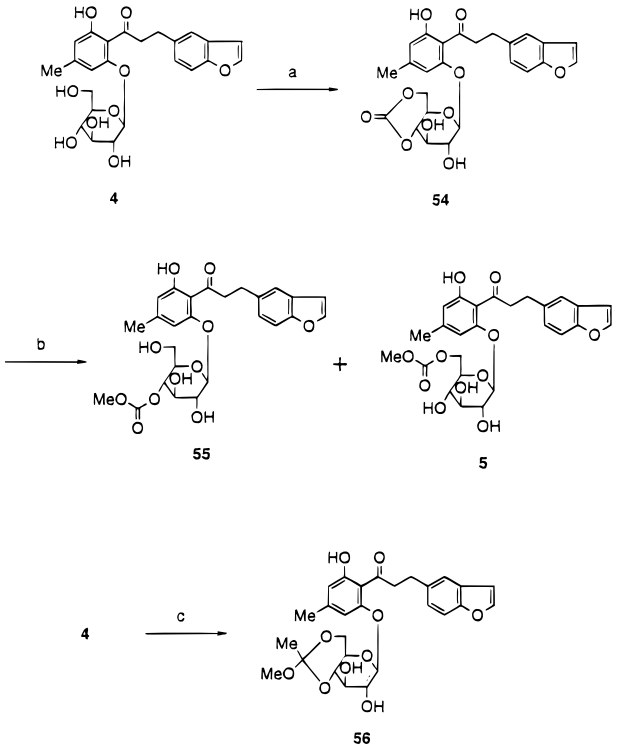


[a] Reagents and conditions: (a) TBSCl, imidazole, DMF; (b) Ac_2O, pyridine; (c) *n*-Bu_4NF, THF, AcOH; (d) *p*-TsOH, AcOH−H_2O; (e) AcCl, Et_3N, DMA; (f) allyl bromide, K_2CO_3, DMF; (g) RCOCl, collidine; (h) $PdCl_2(PPh_3)_2$, HCO_2NH_4, acetonitrile.

of Na^+-coupled transporters in renal tubules, and Na^+ would be reabsorbed by these transporters. The plasma osmolarity and the contents of electrolytes were determined in the diabetic KK-A^y mice. There was no difference in the plasma osmolarity between control KK-A^y and compound **5**-treated KK-A^y mice. In control KK-A^y mice, the plasma Na^+ and Cl^- contents were lower than those of normoglycemic mice, while the plasma Na^+ and Cl^- contents of compound **5**-treated mice were close to those of normal mice (Figure 5). This may be due to a compensation of the plasma osmolarity counteracting the reduction of high blood glucose levels.

In the drug therapy of diabetes, one of the most serious adverse side effects is induction of hypoglycemia in fasting conditions. Compound **5** suppressed the elevation of blood glucose levels, but the blood glucose level was not lowered below the normal level. Even in fasted conditions, there was no sign of hypoglycemia in KK-A^y mice (Figure 6). Lack of hypoglycemia in fasting conditions is explained as follows. Plasma glucose is continuously filtered in the glomerulus and then reabsorbed in proximal tubules.[12,23] In normoglycemic conditions, the glucose content in the glomerular filtrate is below the level of maximal absorptive capacity (TmG) and glucose is completely restored into peritubular capillary vessels. When the concentration exceeds the TmG, the reabsorption process is saturated and urinary

Scheme 6[a]



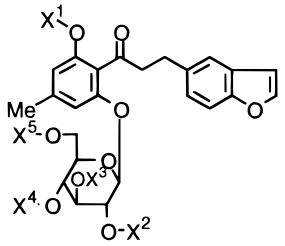
[a] Reagents and conditions: (a) *p*-nitrophenyl chloroformate, collidine; (b) *p*-TsOH, MeOH; (c) $MeC(OMe)_3$, PPTS.

glucose excretion increases linearly.[12] While inhibition of SGLTs lowers the TmG, glucose excretion would not occur if the glucose level is below the TmG. Since renal tubules possess about 3.5-fold capacity for absorption of glucose in normoglycemia,[12,23] partial suppression of the reabsorption process is effective on increasing glucose excretion only in hyperglycemia but not in normoglycemia. Thus SGLT inhibitors would efficiently suppress the reabsorption and increase the urinary excretion of glucose only when the glucose concentration is increased above the normal level in hyperglycemic conditions (Figure 7).

Next, we tested the effect of long-term treatment with compound **5**. KK-A^y mice were fed with compound **5**-mixed chow for 12 weeks, and the result is shown in Figure 8. Long-term treatment with **5** dose-dependently reduced hyperglycemia and HbA1c similar to acarbose, an α-glucosidase inhibitor, which causes a variety of abdominal side effects because of dyspepsia of carbohydrates. Since it was anticipated that inhibition of intestinal SGLT might cause similar abdominal side effects, the effects on the absorption of carbohydrates were determined. Figure 9 shows the effects of compound **4**, **5**, and acarbose following the sucrose load. In acarbose-treated animals, there was nonabsorbed sucrose left throughout the small and large intestines. In contrast, compound **4** and **5** did not significantly inhibit the sugar absorption even when 10 times larger dose was given compared to acarbose. Therefore, inhibition of intestinal SGLT by compound **4** and **5** are not sufficient to suppress the net absorption of glucose, probably because compound **4** and **5** are promptly absorbed or hydrolyzed in intestine.

There are concerns that the increased urinary glucose excretion may induce polyuria and dehydration. Fol-

Table 2. Physical and Biological Properties of the Modified Compounds of **4**



no.	X^1	X^2	X^3	X^4	X^5	yield[a] (%)	mp (°C) (recryst. solvent)	formula[b]	urinary glucose excretion[c] (mg/24 h) po (100 mg/g)
4	H	H	H	H	H				935 ± 18
42	Ac	Ac	Ac	H	H	85	amorphous	$C_{30}H_{32}O_{12}$[d]	1450 ± 126
44	H	Ac	Ac	H	H	54	151−153 (*iso*-Pr_2O)	$C_{28}H_{30}O_{11}\cdot{}^1/_4H_2O$	349 ± 40
46	H	Ac	H	H	H	63	160−163 (AcOEt−*iso*-Pr_2O)	$C_{26}H_{28}O_{10}\cdot{}^1/_2H_2O$	482 ± 34
47	Ac	H	H	H	Ac	51	amorphous	$C_{28}H_{30}O_{11}$[d]	183 ± 61
49	H	H	H	H	Ac	74	86−89 (AcOEt−*iso*-Pr_2O)	$C_{26}H_{28}O_{10}\cdot{}^3/_4H_2O$	540 ± 33
50	H	H	H	H	$MeOCH_2CO^-$	59	65−68 (EtOH−H_2O)	$C_{27}H_{30}O_{11}\cdot H_2O$	721 ± 60
5	H	H	H	H	$MeOCO^-$	86	78−80 (MeOH−H_2O)	$C_{26}H_{28}O_{11}\cdot H_2O$	1192 ± 103
51	H	H	H	H	$EtOCO^-$	80	72−75 (EtOH−H_2O)	$C_{27}H_{30}O_{11}\cdot H_2O$	805 ± 36
52	H	H	H	H	*iso*-$PrOCO^-$	63	82−85.5 (EtOH−H_2O)	$C_{28}H_{32}O_{11}\cdot H_2O$	980 ± 47
53	H	H	H	H	$MeOCH_2CH_2OCO^-$	62	amorphous	$C_{28}H_{32}O_{12}$[d]	817 ± 74
55	H	H	H	$MeOCO^-$	H	43	amorphous	$C_{26}H_{28}O_{11}$[d]	1407 ± 199
56	H	H	H	−CMe(OMe)−		71	amorphous	$C_{27}H_{30}O_{10}$[d]	729 ± 53

[a] Yields are based on compound **4** or the protected derivatives **43**, **48**, or **53**. [b] Analyses (C, H, N) were within ±0.4% of theoretical values. [c] See Experimental Section. [d] HR-MS were measured (see Experimental Section).

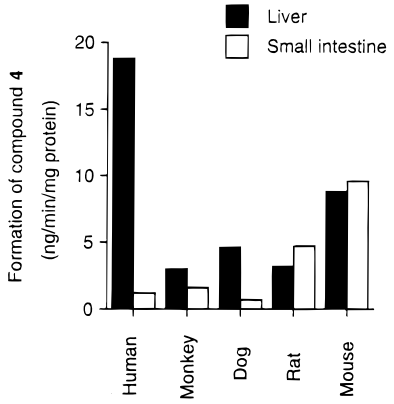


Figure 1. Metabolic conversion of compound **5** to **4** by S9 fraction of liver and intestine. The figure gives the data from pooled S9 fraction prepared from several animal and human tissues.

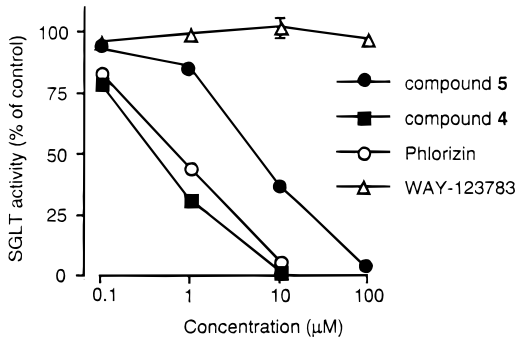


Figure 2. Inhibition of SGLT activity by compound **4**, **5**, and phlorizin in BBMVs of rat kidney. Data are the mean ± SEM of three experiments.

lowing the single administration of compound **5**, there was an increase of urinary volume as well as urinary glucose excretion. However, during the long-term treatment of diabetic animals with **5**, both urine volume and urinary glucose excretion were decreased along with the

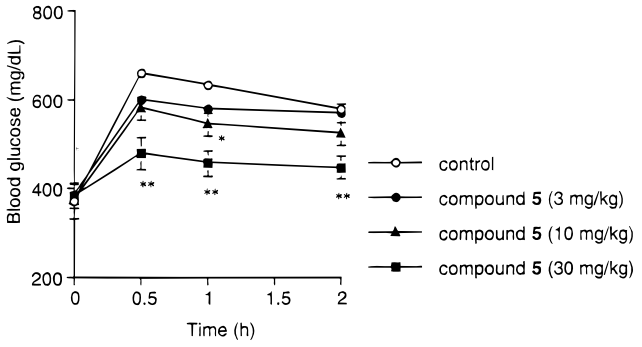


Figure 3. Effect of compound **5** (3−30 mg/kg) on blood glucose levels in oral glucose tolerance tests (OGTT) in db/db mice. Each value indicates the mean ± SEM of five animals. * $P < 0.05$. ** $P < 0.01$.

correction of hyperglycemia (the details will be reported elsewhere). Therefore, the concerns that compound **5** may lead to polyuria and dehydration are expected not to be serious.

In diabetic patients, glucose loss by excretion is beneficial since more severe hyperglycemia is prevented and glucose-related osmotic dehydration of cells is limited.[12] A decade ago, glycosuria had been suspected as a risk factor for the urinary tract infections in diabetic patients. However, normal urine contains 2−20 mg/dL glucose which is above the optimal level for bacterial growth (50 μM = 0.9 mg/dL).[24] Now the most important factor for urinary tract infection in diabetic patients is thought not to be glycosuria but a bladder dysfunction due to diabetic neuropathy.[25] Furthermore, there have been reports on type O glycosuria patients who completely lack renal glucose reabsorption without any serious symptoms.[26,27] Thus it seems likely that inhibition of renal SGLT activity causes no serious adverse side effects through induction of glycosuria. At present, there has been no adverse side effect up to 6 months treatment of diabetic animals with compound

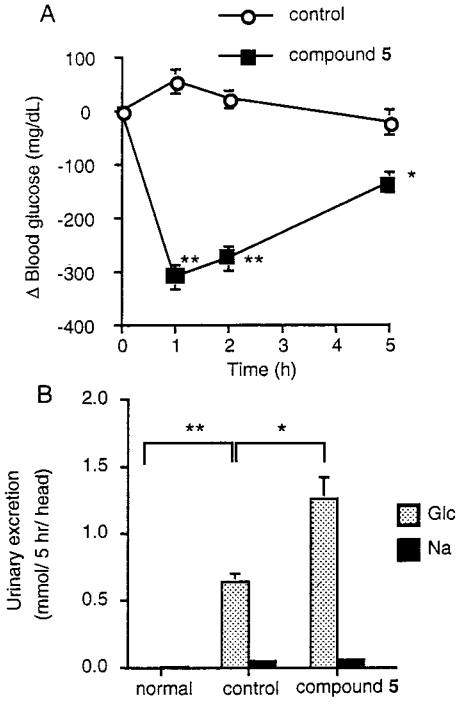


Figure 4. Effect of compound **5** (100 mg/kg, po) on fed glucose levels and urinary excretion of glucose in KK-A^y mice. Each value indicates the mean ± SEM of four animals. * $P < 0.05$. ** $P < 0.01$.

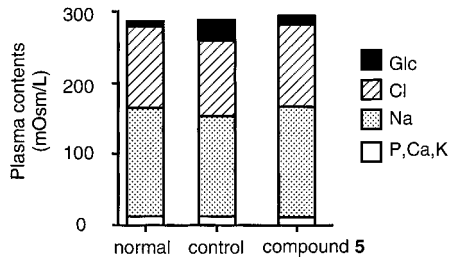


Figure 5. Glucose and electrolyte contents in plasma of KK-A^y mice 1 h after po administration of compound **5** (100 mg/kg, po). Contents were expressed as milli osmole (mOsm/L). Each value indicates the mean of four animals.

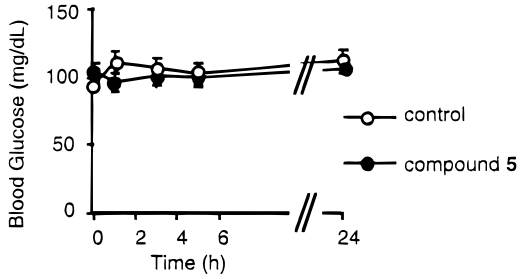


Figure 6. Lack of hypoglycemic effect of compound **5** (100 mg/kg, po) in fasted KK-A^y mice. Each value indicates the mean ± SEM of six animals.

5 except a slight reduction in the body weight (unpublished observations). Therefore, an orally active SGLT inhibitor, compound **5**, has a novel therapeutic potential for the treatment of NIDDM. Further detailed pharmacological results will be reported soon.[28]

Experimental Section

All melting points were determined on a Büchi 535 digital melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on an Analect FX-6200 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM-FX200, a Varian Gemini 300 spectrometer, or a JEOL JNM-GSX400. Mass spectra were recorded on a JEOL JMS-HX100 mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 C, H, N analyzer and were within ±0.4% of the calculated values.

2′,6′-Dihydroxy-4′-methylacetophenone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-*β*-D-glucopyranoside (7). A mixture of 2′,6′-dihydroxy-4′-methylacetophenone (**6a**) (100 g, 0.60 mol), 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (419 g, 1.02 mol), benzyltributylammonium chloride (37 g, 0.12 mol), K_2CO_3 (414 g, 3.00 mol), H_2O (29 mL), and $CHCl_3$ (1.3 L) was stirred at room temperature for 27 h. The reaction mixture was neutralized with 10% HCl, and the organic layer was separated. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated. The residue was triturated in MeOH to give **7** (239.75 g, 81%) as a colorless solid, mp 140−142.5 °C: IR (Nujol) 1755, 1725, 1650 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.96 (s, 3H), 2.02 (s, 9H), 2.26 (s, 3H), 2.39 (s, 3H), 4.06−4.32 (m, 3H), 5.00 (dd, 1H, J = 9.5, 9.9 Hz), 5.10 (dd, 1H, J = 7.9, 9.7 Hz), 5.39 (t, 1H, J = 9.5 Hz), 5.64 (d, 1H, J = 7.9 Hz), 6.46 (s, 1H), 6.48 (s, 1H), 11.60 (s, 1H); ESI-MS m/z 519 (M + Na$^+$).

Compounds **8**−**14** were prepared by the same procedure as described above.

4′-Ethyl-2′,6′-dihydroxyacetophenone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-*β*-D-glucopyranoside (8): 73% yield as colorless needles, mp 125−127 °C; IR (Nujol) 1755, 1740, 1640 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.17 (t, 3H, J = 7.5 Hz), 1.96 (s, 3H), 2.00 (s, 3H), 2.02 (s, 6H), 2.40 (s, 3H), 2.55 (q, 2H, J = 7.5 Hz), 4.09 (dd, 1H, J = 2.5, 12.0 Hz), 4.16 (dd, 1H, J = 5.5, 12.0 Hz), 4.31 (m, 1H), 5.00 (t, 1H, J = 9.5 Hz), 5.11 (dd, 1H, J = 8.0, 9.5 Hz), 5.40 (t, 1H, J = 9.5 Hz), 5.64 (d, 1H, J = 8.0 Hz), 6.48 (d, 1H, J = 2.0 Hz), 6.51 (d, 1H, J = 2.0 Hz), 11.60 (s, 1H); ESI-MS m/z 528 (M + NH$_4^+$).

2′,6′-Dihydroxy-4′-*n*-propylacetophenone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-*β*-D-glucopyranoside (9): 78% yield as colorless needles, mp 122−123 °C; IR (Nujol) 1755, 1725, 1645 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.91 (t, 3H, J = 7.5 Hz), 1.60 (m, 2H), 1.96 (s, 3H), 2.00 (s, 3H), 2.02 (s, 6H), 2.39 (s, 3H), 2.49 (t, 2H, J = 7.5 Hz), 4.08 (dd, 1H, J = 2.5, 12.0 Hz), 4.15 (dd, 1H, J = 6.0, 12.0 Hz), 4.31 (ddd, 1H, J = 2.5, 6.0, 9.5 Hz), 5.00 (t, 1H, J = 9.5 Hz), 5.11 (dd, 1H, J = 7,5, 9.5 Hz), 5.41 (t, 1H, J = 9.5 Hz), 5.69 (d, 1H, J = 7.5 Hz), 6.46 (d, 1H, J = 1.5 Hz), 6.49 (d, 1H, J = 1.5 Hz), 11.62 (s, 1H); ESI-MS m/z 542 (M + NH$_4^+$).

2′,6′-Dihydroxy-4′-*iso*-propylacetophenone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-*β*-D-glucopyranoside (10): 73% yield as colorless needles, mp 142−143 °C; IR (Nujol) 1760, 1745, 1725, 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.19 (d, 6H, J = 6.5 Hz), 1.97 (s, 3H), 2.00 (s, 3H), 2.02 (s, 6H), 2.39 (s, 3H), 2.81 (m, 1H), 4.07 (dd, 1H, J = 2.0, 11.5 Hz), 4.14 (dd, 1H, J = 5.0, 11.5 Hz), 4.35 (ddd, 1H, J = 2.0, 5.0, 9.5 Hz), 5.00 (t, 1H, J = 9.5 Hz), 5.11 (dd, 1H, J = 8.0, 9.5 Hz), 5.42 (t, 1H, J = 9.5 Hz), 5.74 (d, 1H, J = 8.0 Hz), 6.50 (d, 1H, J = 1.0 Hz), 6.52 (d, 1H, J = 1.0 Hz), 11.64 (s, 1H); ESI-MS m/z 542 (M + NH$_4^+$).

4′-Chloro-2′,6′-dihydroxyacetophenone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-*β*-D-glucopyranoside (11): 48% yield as colorless needles, mp 144.5−145.5 °C; IR (Nujol) 1760, 1740, 1640 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.96 (s, 3H), 2.02 (s, 6H), 2.04 (s, 3H), 2.33 (s, 3H), 4.10 (dd, 1H, J = 2.5, 10.5 Hz), 4.15 (m, 1H), 4.29 (m, 1H), 4.97 (t, 1H, J = 9.5 Hz), 5.05 (dd, 1H, J = 8.0, 9.5 Hz), 5.36 (t, 1H, J = 9.5 Hz), 5.59 (d, 1H, J = 8.0 Hz), 6.68 (d, 1H, J = 2.0 Hz), 6.71 (d, 1H, J = 2.0 Hz), 11.05 (s, 1H); ESI-MS m/z 539 (M + Na$^+$), 541 (M + 2+ Na$^+$).

5′-Ethyl-2′,6′-dihydroxyacetophenone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-*β*-D-glucopyranoside (12): 59% yield as colorless needles, mp 116−116.5 °C; IR (Nujol) 1760, 1750, 1620 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.11 (t, 3H, J = 7.5 Hz), 1.96 (s, 3H), 2.00 (s, 3H), 2.01 (s, 3H), 2.02 (s, 3H), 2.49 (s, 3H), 2.53 (q, 2H, J = 7.5 Hz), 4.07 (dd, 1H, J = 2.5, 12.0 Hz), 4.20 (dd, 1H, J = 6.0, 12.0 Hz), 4.28 (ddd, 1H, J = 2.5, 6.0, 9.5 Hz), 5.02 (t, 1H, J = 9.5 Hz), 5.17 (dd, 1H, J = 8.0, 9.5 Hz), 5.43 (t, 1H, J = 9.5 Hz), 5.73 (d, 1H, J = 8.0 Hz), 6.63 (d, 1H, J = 8.5

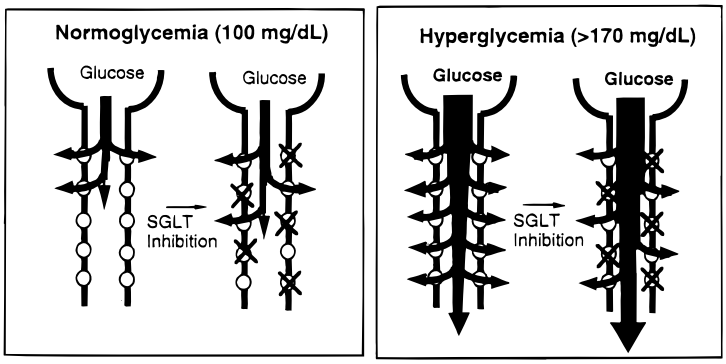


Figure 7. Schematic representation of the effect of the SGLT inhibitor on glucose reabsorption in renal tubules. Plasma glucose is continuously filtered in the glomerulus. Filtered glucose is reabsorbed in renal tubules by the function of SGLTs. In normoglycemic conditions (left panel), there is extra capacity for reabsorption. Partial inhibition of the reabsorption process by the SGLT inhibitor hardly causes glycosuria and hypoglycemia. Because the number of SGLTs is limited, the total reabsorption process becomes saturated when the glucose concentration rises in the filtrate. In contrast to normoglycemic conditions, inhibition of SGLTs excretes glucose into urine and reduces blood glucose levels in hyperglycemic conditions.

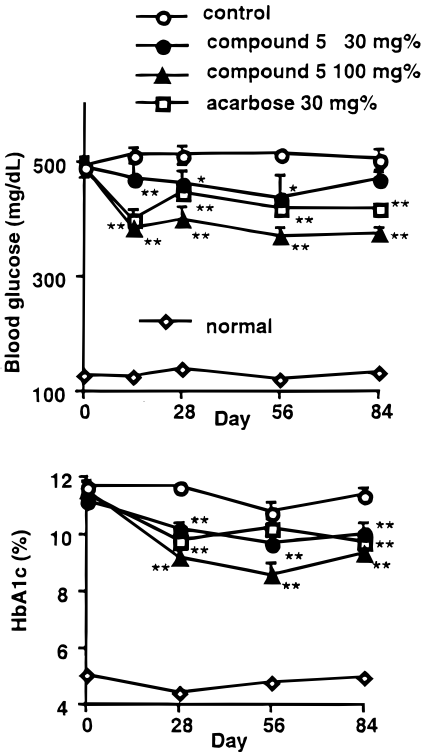


Figure 8. Effect of long-term treatment with compound **5** at 30 and 100 mg/100 g chow (mg%) and acarbose at 30 mg% on blood glucose and hemoglobin A1c levels in KK-A^y mice. Normoglycemic mice (C57BL/6N) served as control. Each value indicates the mean ± SEM of eight animals. * $P < 0.05$. ** $P < 0.01$.

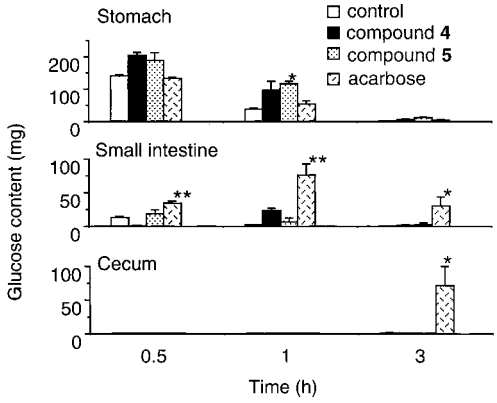


Figure 9. Effect of compound **4** (30 mg/kg), **5** (30 mg/kg), and acarbose (3 mg/kg) on intestinal glucose absorption following sucrose feeding. The remaining sugar in the gastrointestinal tract was determined. There was extensive inhibition of sugar absorption by acarbose but not by compound **4** nor **5**. Each value indicates the mean ± SEM of three animals. * $P < 0.05$. ** $P < 0.01$.

Hz), 7.34 (d, 1H, J = 8.5 Hz), 12.52 (s, 1H); ESI-MS m/z 528 (M + NH_4^+).

2′,6′-Dihydroxy-4′-methoxyacetophenone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-*β*-D-glucopyranoside (13): 62% yield as a colorless solid, mp 181.5−184.5 °C; IR (Nujol) 1755, 1740, 1620 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.97 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 2.03 (s, 3H), 2.42 (s, 3H), 3.81 (s, 3H), 4.07 (dd, 1H, J = 2.4, 12.1 Hz), 4.18 (dd, 1H, J = 6.1, 12.1 Hz), 4.33 (ddd, 1H, J = 2.2, 6.1, 10.1 Hz), 5.02 (dd, 1H, J = 9.3, 10.1 Hz), 5.19 (dd, 1H, J = 8.0, 9.7 Hz), 5.40 (t, 1H, J = 9.5 Hz), 5.78 (d, 1H, J = 7.9 Hz), 6.22 (d, 1H, J = 2.4 Hz), 6.23 (d, 1H, J = 2.6 Hz), 13.32 (s, 1H); ESI-MS m/z 530 (M + NH_4^+).

2′,6′-Dihydroxy-4′-methoxymethyloxyacetophenone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-*β*-D-glucopyranoside (14): 80% yield as a colorless solid, mp 129−132 °C; IR (Nujol) 1755, 1750, 1720, 1650 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.97 (s, 3H), 2.01 (s, 3H), 2.02 (s, 3H), 2.03 (s, 3H), 2.41 (s, 3H), 3.39 (s, 3H), 4.07 (dd, 1H, J = 2.4, 12.3 Hz), 4.18 (dd, 1H, J = 6.2, 12.3 Hz), 4.32 (m, 1H), 5.02 (dd, 1H, J = 9.5, 9.9 Hz), 5.17 (dd, 1H, J = 8.0, 9.7 Hz), 5.21 (d, 1H, J = 6.8 Hz), 5.26 (d, 1H, J = 6.8 Hz), 5.41 (dd, 1H, J = 9.3, 9.7 Hz), 5.75 (d, 1H, J = 8.1 Hz), 6.28 (d, 1H, J = 2.2 Hz), 6.31 (d, 1H, J = 2.2 Hz), 12.92 (s, 1H); ESI-MS m/z 560 (M + NH_4^+).

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-*β*-D-Glucopyranoside (4) (Method A). A 50% aqueous KOH solution (150 mL) was added to a suspension of **7** (124.94 g, 0.25 mol) in EtOH (1.2 L), and the mixture was stirred at room temperature for 10 min. Then benzofuran-5-carboxaldehyde[16] (40.46 g, 0.28 mol) was added, and the whole was stirred at room temperature for 16 h. 4-(Dimethylamino)pyridine (30.75 g, 0.25 mol) was added to the reaction mixture containing the chalcone **15**, and the whole was hydrogenated over 10% Pt−C (12.31 g) at room temperature for 9 h. The catalyst was removed by filtration, and the filtrate was neutralized with 10% HCl and extracted with AcOEt. The organic layer was washed with water and dried over $MgSO_4$. The solvent was removed, and then the residue was purified by crystallization from MeOH−H_2O to give **4** (89.44 g, 78%) as a colorless solid, mp 155−157 °C: IR (Nujol) 3380, 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.24 (s, 3H), 3.00 (t, 2H, J = 7.4 Hz), 3.12−3.53 (m, 7H), 3.71 (ddd, 1H, J = 1.7, 5.5, 11.7 Hz), 4.59 (t, 1H, J = 5.8 Hz), 4.98 (d, 1H, J = 7.3 Hz), 5.05 (d, 1H, J = 5.1 Hz), 5.12 (d, 1H, J = 4.6 Hz), 5.29 (d, 1H, J = 5.3 Hz), 6.40 (d, 1H, J = 0.7 Hz), 6.54 (s, 1H), 6.88 (dd, 1H, J = 0.9, 2.2 Hz), 7.22 (dd, 1H, J = 1.7, 8.5 Hz), 7.46 (d, 1H, J = 8.4

Hz), 7.53 (d, 1H, J = 1.1 Hz), 7.93 (d, 1H, J = 2.2 Hz), 11.90 (s, 1H). ESI-MS m/z 481 ($M + Na^+$). Anal. ($C_{24}H_{26}O_9$) C, H.

Compound **19** was prepared by the same procedure as described above.

3-(Benzo[*b*]furan-5-yl)-4′-chloro-2′,6′-dihydroxypropiophenone 2′-*O*-*β*-D-Glucopyranoside (19): 48% yield as colorless needles, mp 106−107 °C; IR (Nujol) 3350, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.98 (t, 2H, J = 7.5 Hz), 3.10−3.48 (m, 7H), 3.69 (ddd, 1H, J = 1.7, 5.5, 10.0 Hz), 4.61 (t, 1H, J = 5.5 Hz), 4.98 (d, 1H, J = 7.5 Hz), 5.06 (d, 1H, J = 5.5 Hz), 5.14 (d, 1H, J = 5.0 Hz), 5.32 (d, 1H, J = 5.5 Hz), 6.61 (d, 1H, J = 2.0 Hz), 6.76 (d, 1H, J = 2.0 Hz), 6.88 (dd, 1H, J = 1.0, 2.0 Hz), 7.20 (dd, 1H, J = 1.5, 8.5 Hz), 7.46 (d, 1H, J = 8.5 Hz), 7.52 (d, 1H, J = 1.5 Hz), 7.93 (d, 1H, J = 2.0 Hz), 10.09 (s, 1H); FAB-MS m/z 501 ($M + Na^+$), 503 ($M + 2 + Na^+$). Anal. ($C_{23}H_{23}ClO_9 \cdot {}^1/_2H_2O$) C, H.

3-(Benzo[*b*]furan-5-yl)-4′-ethyl-2′,6′-dihydroxypropiophenone 2′-*O*-*β*-D-Glucopyranoside (16) (Method B). Compound **8** (3.00 g, 5.88 mmol) was condensed with benzofuran-5-carboxaldehyde (1.03 g, 7.06 mmol) by the same procedure as used in method A. The resultant residue containing the chalcone was dissolved in THF (18 mL) and added to a suspension of NaTeH[17] (11.76 mmol) in EtOH (50 mL) at −20 °C. The whole was stirred at room temperature for 2 h. The black precipitate was removed by filtration, and the filtrate was diluted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$−MeOH (25:1)) and recrystallized from AcOEt−*iso*-Pr_2O to give **16** (2.31 g, 83%) as colorless needles, mp 155−155.5 °C: IR (Nujol) 3560, 3490, 3350, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.15 (t, 3H, J = 7.5 Hz), 2.55 (q, 2H, J = 7.5 Hz), 3.00 (m, 2H), 3.10−3.50 (m, 7H), 3.72 (m, 1H), 4.61 (t, 1H, J = 5.5 Hz), 4.98 (d, 1H, J = 7.5 Hz), 5.06 (d, 1H, J = 5.5 Hz), 5.14 (d, 1H, J = 5.0 Hz), 5.31 (d, 1H, J = 5.5 Hz), 6.42 (d, 1H, J = 1.5 Hz), 6.57 (d, 1H, J = 1.5 Hz), 6.88 (dd, 1H, J = 1.0, 2.0 Hz), 7.22 (dd, 1H, J = 2.0, 8.5 Hz), 7.46 (d, 1H, J = 8.5 Hz), 7.53 (d, 1H, J = 2.0 Hz), 7.93 (d, 1H, J = 2.0 Hz), 11.90 (s, 1H); ESI-MS m/z 490 ($M + NH_4^+$). Anal. ($C_{25}H_{28}O_9$) C, H.

Compounds **17**−**18** and **20**−**22** were prepared by the same procedure as described above.

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-*n*-propylpropiophenone 2′-*O*-*β*-D-Glucopyranoside (17): 72% yield as a foam; IR (neat) 3400, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.89 (t, 3H, J = 7.5 Hz), 1.58 (m, 2H), 2.47 (t, 2H, J = 7.5 Hz), 3.00 (t, 2H, J = 7.5 Hz), 3.14−3.52 (m, 7H), 3.70 (ddd, 1H, J = 2.5, 5.5, 10.0 Hz), 4.58 (t, 1H, J = 5.5 Hz), 4.98 (d, 1H, J = 7.5 Hz), 5.04 (d, 1H, J = 5.5 Hz), 5.12 (d, 1H, J = 5.0 Hz), 5.29 (d, 1H, J = 5.5 Hz), 6.40 (d, 1H, J = 1.0 Hz), 6.56 (d, 1H, J = 1.0 Hz), 6.88 (dd, 1H, J = 1.0, 2.0 Hz), 7.22 (dd, 1H, J = 2.0, 9.0 Hz), 7.47 (d, 1H, J = 9.0 Hz), 7.53 (d, 1H, J = 2.0 Hz), 7.93 (d, 1H, J = 2.0 Hz), 11.90 (s, 1H); ESI-MS m/z 504 ($M + NH_4^+$); HR-FABMS calcd for $C_{26}H_{30}NaO_9$ ($M + Na^+$) m/z 509.1788, found 509.1785.

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-*iso*-propylpropiophenone 2′-*O*-*β*-D-Glucopyranoside (18): 86% yield as a foam; IR (neat) 3415, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.17 (d, 6H, J = 7.0 Hz), 2.90 (m, 1H), 3.01 (t, 2H, J = 7.5 Hz), 3.17 (m, 1H), 3.30 (t, 2H, J = 7.5 Hz), 3.36−3.52 (m, 4H), 3.72 (ddd, 1H, J = 1.5, 5.5, 11.0 Hz), 4.60 (t, 1H, J = 5.5 Hz), 4.99 (d, 1H, J = 7.5 Hz), 5.04 (d, 1H, J = 5.5 Hz), 5.12 (d, 1H, J = 4.5 Hz), 5.24 (d, 1H, J = 5.0 Hz), 6.44 (d, 1H, J = 1.0 Hz), 6.60 (d, 1H, J = 1.0 Hz), 6.88 (dd, 1H, J = 1.0, 2.0 Hz), 7.22 (dd, 1H, J = 1.5, 8.5 Hz), 7.46 (d, 1H, J = 8.5 Hz), 7.53 (d, 1H, J = 1.5 Hz), 7.93 (d, 1H, J = 2.0 Hz), 11.90 (s, 1H); FAB-MS m/z 509 ($M + Na^+$); HR-FABMS calcd for $C_{26}H_{30}NaO_9$ ($M + Na^+$) m/z 509.1788, found 509.1790.

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methoxypropiophenone 2′-*O*-*β*-D-Glucopyranoside (20): 39% yield as a colorless solid, mp 161−164 °C; IR (Nujol) 3570, 3490, 3350, 3230, 1640 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.01 (t, 2H, J = 7.2 Hz), 3.10−3.80 (m, 8H), 3.79 (s, 3H), 4.62 (t, 1H, J = 5.6 Hz), 5.03 (d, 1H, J = 7.5 Hz), 5.08 (d, 1H, J = 5.3 Hz), 5.16 (d, 1H, J = 4.8 Hz), 5.36 (d, 1H, J = 5.3 Hz), 6.13 (d, 1H, J = 2.4 Hz), 6.30 (d, 1H, J = 2.4 Hz), 6.88 (dd, 1H, J = 0.9, 2.2 Hz), 7.22 (dd, 1H, J = 1.7, 8.6 Hz), 7.46 (d, 1H, J = 8.4 Hz), 7.53 (d, 1H, J = 1.3 Hz), 7.93 (d, 1H, J = 2.0 Hz), 13.33 (s, 1H); ESI-MS m/z 492 ($M + NH_4^+$). Anal. ($C_{24}H_{26}O_{10}$) C, H.

3-(Benzo[*b*]furan-5-yl)-2′,4′,6′-trihydroxypropiophenone 2′-*O*-*β*-D-Glucopyranoside (21): 50% yield as colorless needles, mp 85−88 °C; IR (Nujol) 3520, 3420, 3300, 3200, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.00 (t, 2H, J = 7.4 Hz), 3.15−3.60 (m, 7H), 3.72 (m, 1H), 4.60 (t, 1H, J = 5.7 Hz), 4.95 (d, 1H, J = 7.5 Hz), 5.05 (d, 1H, J = 5.3 Hz), 5.14 (d, 1H, J = 4.2 Hz), 5.32 (d, 1H, J = 5.1 Hz), 5.94 (d, 1H, J = 2.2 Hz), 6.14 (d, 1H, J = 2.2 Hz), 6.88 (dd, 1H, J = 0.9, 2.2 Hz), 7.22 (dd, 1H, J = 1.7, 8.5 Hz), 7.46 (d, 1H, J = 8.4 Hz), 7.53 (d, 1H, J = 1.3 Hz), 7.93 (d, 1H, J = 2.2 Hz), 10.59 (s, 1H), 13.50 (s, 1H); ESI-MS m/z 483 ($M + Na^+$). Anal. ($C_{23}H_{24}O_{10} \cdot H_2O$) C, H.

3-(Benzo[*b*]furan-5-yl)-5′-ethyl-2′,6′-dihydroxypropiophenone 2′-*O*-*β*-D-Glucopyranoside (22): 54% yield as a colorless solid, mp 84−87 °C; IR (Nujol) 3600, 3510, 3465, 1650 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.10 (t, 3H, J = 7.5 Hz), 2.52 (q, 2H, J = 7.5 Hz), 3.04 (t, 2H, J = 7.5 Hz), 3.14−3.65 (m, 7H), 3.72 (ddd, 1H, J = 2.0, 5.5, 11.5 Hz), 4.60 (t, 1H, J = 5.5 Hz), 4.99 (d, 1H, J = 7.5 Hz), 5.06 (d, 1H, J = 5.0 Hz), 5.14 (d, 1H, J = 5.5 Hz), 5.34 (d, 1H, J = 5.0 Hz), 6.68 (d, 1H, J = 8.5 Hz), 6.88 (dd, 1H, J = 1.0, 2.0 Hz), 7.23 (dd, 1H, J = 2.0, 8.5 Hz), 7.30 (d, 1H, J = 8.5 Hz), 7.47 (d, 1H, J = 8.5 Hz), 7.54 (d, 1H, J = 2.0 Hz), 7.93 (d, 1H, J = 2.0 Hz), 12.70 (s, 1H); ESI-MS m/z 490 ($M + NH_4^+$). Anal. ($C_{25}H_{28}O_9 \cdot H_2O$) C, H.

2′,6′-Dihydroxy-4′-methylacetophenone (6a) (Route 1). A mixture of 1,3-diacetoxy-5-methylbenzene (**24a**) (37.24 g, 0.18 mol) and $AlCl_3$ (82.10 g, 0.62 mol) was stirred at 145−150 °C for 1.5 h. After cooling, the reaction mixture was poured into ice and 10% HCl, and the whole was stirred for 30 min. The mixture was extracted with AcOEt, and the extract was dried over $MgSO_4$ and evaporated to give crude 2,6-diacetyl-5-methylresorcinol (**25a**) (36.95 g). The crude **25a** was stirred in 85% H_2SO_4 at room temperature for 2 h. Ice was added to the reaction mixture, and the whole was stirred for 30 min and then extracted with AcOEt, dried over $MgSO_4$, and evaporated. The resultant residue was purified by trituration in $CHCl_3$ to give **6a** (19.25 g, 66%) as a pale yellow solid, mp 145.5−149 °C: ^1H NMR (DMSO-d_6) δ 2.17 (s, 3H), 2.62 (s, 3H), 6.20 (d, 2H, J = 0.7 Hz), 11.90 (s, 2H); EI-MS m/z 166 (M^+).

Compounds **6b** and **6e** were prepared by the same procedure as described above.

4′-Ethyl-2′,6′-dihydroxyacetophenone (6b): 62% yield as pale yellow prisms, mp 121.5−122.5 °C; IR (Nujol) 3200, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H, J = 7.5 Hz), 2.53 (q, 2H, J = 7.5 Hz), 2.71 (s, 3H), 6.25 (s, 2H), 9.15−9.30 (br, 2H); ESI-MS m/z 181 ($M + H^+$).

4′-Chloro-2′,6′-dihydroxyacetophenone (6e): 53% yield as a pale brown solid, mp 145.5−146.5 °C; IR (Nujol) 3270, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.70 (s, 3H), 6.43 (s, 2H), 11.81 (s, 2H); EI-MS m/z 186 (M^+), 188 ($(M + 2)^+$).

Compound 6a (Route 2). A solution of **24a** (10.00 g, 48 mmol) in chlorobenzene (8 mL) was added dropwise to the suspension of $AlCl_3$ (19.20 g, 144 mmol) in chlorobenzene (50 mL) at 90 °C during 35 min. The whole was stirred at 90 °C for 1 h and then poured into ice−10% HCl and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by trituration in hexane to give **6a** (5.90 g, 74%).

Compounds **6c** and **6d** were prepared by the same procedure as described above.

2′,6′-Dihydroxy-4′-*n*-propylacetophenone (6c): 70% yield as pale yellow needles, mp 99.5−100 °C; IR (Nujol) 3300, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.5 Hz), 1.61 (m, 2H), 2.46 (t, 2H, J = 8.0 Hz), 2.72 (s, 3H), 6.23 (s, 2H), 9.20−9.70 (br, 2H); ESI-MS m/z 195 ($M + H^+$).

2′,6′-Dihydroxy-4′-*iso*-propylacetophenone (6d): 77% yield as a pale yellow solid, mp 91.5−93 °C; IR (Nujol) 3230, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (d, 6H, J = 7.0 Hz), 2.71 (s, 3H), 2.76 (m, 1H), 6.27 (s, 2H), 9.00−10.00 (br, 2H); ESI-MS m/z 195 ($M + H^+$).

3′-Ethyl-2′,6′-dihydroxyacetophenone (6f). A mixture of 4-ethylresorcinol (2.00 g, 14.47 mmol) and ethyl acetoacetate (1.88 g, 14.47 mmol) was added dropwise to concentrated H_2SO_4 (15 mL) under ice-cooling, and the whole was stirred at room temperature for 14 h. The reaction mixture was poured into ice−water, and the pale yellow precipitate was collected, washed with water, and dried. The precipitate was dissolved in 5% NaOH and the insoluble materials were removed by filtration. The filtrate was acidified with 10% citric acid, and the resultant colorless needles were collected by filtration, washed with water, and dried to give 6-ethyl-7-hydroxy-4-methylcoumarin (**26**) (2.66 g, 90%), mp 215.5−216.5 °C: IR (Nujol) 3165, 1710 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.16 (t, 3H, J = 7.5 Hz), 2.38 (d, 3H, J = 1.5 Hz), 2.60 (q, 2H, J = 7.5 Hz), 6.10 (d, 1H, J = 1.5 Hz), 6.73 (s, 1H), 7.45 (s, 1H), 10.60 (s, 1H); ESI-MS m/z 205 ($M + H^+$).

Compound **26** (2.59 g, 12.68 mmol) was heated under reflux in Ac_2O for 3 h. After cooling, the reaction mixture was poured into ice−water. The precipitates were collected, washed with water, and dried to give 7-acetoxy-6-ethyl-4-methylcoumarin (2.93 g, 94%), mp 147.5−148.5 °C: IR (Nujol) 3165, 1735 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.16 (t, 3H, J = 7.5 Hz), 2.35 (s, 3H), 2.45 (d, 3H, J = 1.0 Hz), 2.57 (q, 2H, J = 7.5 Hz), 6.38 (d, 1H, J = 1.0 Hz), 7.24 (s, 1H), 7.69 (s, 1H); ESI-MS m/z 247 ($M + H^+$).

A mixture of 7-acetoxy-6-ethyl-4-methylcoumarin (2.83 g, 11.49 mmol) and $AlCl_3$ (5.36 g, 40.22 mmol) was stirred at 170 °C for 1 h. After cooling, the reaction mixture was poured into ice−water. The precipitates were collected, washed with water, and dried. The crude product was recrystallized from EtOH to give 8-acetyl-6-ethyl-7-hydroxy-4-methylcoumarin (**27**) (2.16 g, 76%), mp 138.5−139.5 °C: IR (Nujol) 1735, 1615 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.18 (t, 3H, J = 7.5 Hz), 2.43 (d, 3H, J = 1.5 Hz), 2.60 (q, 2H, J = 7.5 Hz), 2.81 (s, 3H), 6.27 (d, 1H, J = 1.5 Hz), 7.76 (s, 1H), 13.30 (s, 1H); ESI-MS m/z 247 ($M + H^+$).

Under argon atmosphere, a solution of NaOH (1.64 g, 40.90 mmol) in H_2O (7 mL) was added to a suspension of **27** (2.12 g, 8.61 mmol) in H_2O (6.3 mL), and the whole was refluxed for 3 h. After cooling, the reaction mixture was acidified with 10% HCl. The precipitates were collected, washed with H_2O, and dried to give brown solid. The solid was dissolved in AcOEt, washed with H_2O, and dried over Na_2SO_4. The solvent was removed in vacuo, and the resultant residue was recrystallized from $CHCl_3$−hexane to give desired 3′-ethyl-2′,6′-dihydroxyacetophenone (**6f**) (1.26 g, 81%) as yellow prisms, mp 128−129 °C: IR (Nujol) 3210, 1690, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (t, 3H, J = 7.5 Hz), 2.57 (q, 2H, J = 7.5 Hz), 2.74 (s, 3H), 6.26 (d, 1H, J = 8.0 Hz), 7.01 (s, 1H), 7.14 (d, 1H, J = 8.0 Hz), 11.80 (s, 1H); EI-MS m/z 180 (M^+).

Compound **6g** was prepared by the same procedure as described above.

2′,6′-Dihydroxy-3′-methylacetophenone (6g): yellow needles, mp 138−139.5 °C; IR (Nujol) 3290, 1630, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (d, 3H, J = 1.0 Hz), 2.74 (s, 3H), 2.74 (s, 3H), 6.25 (d, 1H, J = 8.0 Hz), 7.13 (dd, 1H, J = 1.0, 8.0 Hz), 7.43 (s, 1H), 11.44 (s, 1H); APCI-MS m/z 167 ($M + H^+$).

2′,6′-Dihydroxy-4′-methoxyacetophenone (6h). TMSCHN$_2$ (2.0 M hexane solution) (15 mL, 30 mmol) was added to a solution of 2′,4′,6′-trihydroxyacetophenone (1.86 g, 10 mmol) in $CHCl_3$ (20 mL)−MeOH (10 mL) under ice-cooling, and the whole was stirred at room temperature for 14 h. AcOH (5 drops) was added to the reaction mixture under ice-cooling, and the mixture was stirred for 30 min and then concentrated. The residue was chromatographed on silica gel ($CHCl_3$−AcOEt (9:1)) and triturated in toluene to give **6h** (811 mg, 45%) as a pale yellow solid, mp 144−147.5 °C: IR (Nujol) 3125, 3080, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.58 (s, 3H), 3.74 (s, 3H), 5.95 (s, 2H), 12.30 (s, 2H); EI-MS m/z 182 (M^+).

2′,6′-Dihydroxy-4′-methoxymethyloxyacetophenone (6i). A mixture of 2′,4′,6′-trihydroxyacetophenone (186 mg, 1 mmol), TIPSCl (483 mg, 2.5 mmol), imidazole (205 mg, 3 mmol), and DMF (5 mL) was stirred at room temperature for 24 h. MeOH (0.5 mL) was added to the reaction mixture, and the whole was stirred at room temperature for 2 h. The mixture was diluted with AcOEt and washed with 10% HCl, water, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel ($CHCl_3$−AcOEt (19:1)) to give 2′,6′-dihydroxy-4′-triisopropylsilyloxyacetophenone (**29**) (180 mg, 56%) as pale yellow needles, mp 133−135.5 °C: IR (Nujol) 3260, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (d, 18H, J = 7.0 Hz), 1.25 (m, 3H), 2.58 (s, 3H), 5.90 (s, 2H), 12.20 (s, 2H); APCI-MS m/z 325 ($M + H^+$).

BzCl (0.47 mL, 4.05 mmol) was added dropwise to a solution of **29** (526 mg, 1.62 mmol) in pyridine (4 mL) under ice-cooling, and the whole was stirred at room temperature for 1.5 h. The mixture was diluted with AcOEt and washed with 10% HCl, water, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was triturated in hexane to give 2′,6′-dibenzoyloxy-4′-triisopropylsilyloxyacetophenone (704 mg, 82%) as colorless needles, mp 129−132 °C: IR (Nujol) 1745, 1730, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (d, 18H, J = 7.0 Hz), 1.29 (m, 3H), 2.43 (s, 3H), 6.72 (s, 2H), 7.52 (m, 4H), 7.65 (m, 2H), 8.17 (m, 4H); ESI-MS m/z 550 ($M + NH_4^+$).

n-Bu_4NF (1.0 M THF solution) (4.94 mL, 4.94 mmol) was added to a solution of 2′,6′-dibenzoyloxy-4′-triisopropylsilyloxyacetophenone (2.19 g, 4.12 mmol) and MOMCl (1.10 mL, 14.48 mmol) in THF (20 mL) under ice-cooling, and the whole was stirred at room temperature for 1.5 h. The mixture was diluted with AcOEt and washed with 10% HCl, water, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel ($CHCl_3$−AcOEt (19:1)) to give 2′,6′-dibenzoyloxy-4′-methoxymethyloxyacetophenone (**30**) (1.43 g, 83%) as pale yellow needles, mp 137−140 °C: IR (Nujol) 1745, 1730, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H), 3.50 (s, 3H), 5.22 (s, 2H), 6.90 (s, 2H), 7.52 (m, 4H), 7.65 (m, 2H), 8.17 (m, 4H); ESI-MS m/z 438 ($M + NH_4^+$).

A mixture of **30** (1.41 g, 3.34 mmol), K_2CO_3 (2.31 g, 16.70 mmol), MeOH (30 mL), and THF (30 mL) was stirred at room temperature for 1 h. The reaction mixture was neutralized with 10% HCl and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$−AcOEt (9:1)) to give desired 2′,6′-dihydroxy-4′-methoxymethyloxyacetophenone (**6i**) (632 mg, 92%) as a pale yellow solid, mp 125−128 °C: IR (Nujol) 3300, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59 (s, 3H), 3.37 (s, 3H), 5.18 (s, 2H), 6.03 (s, 2H), 12.26 (s, 2H); FAB-MS m/z 213 ($M + H^+$).

5′-Allyl-3-(benzo[*b*]furan-5-yl)-2′,6′-dihydroxypropiophenone 2′-*O*-*β*-D-Glucopyranoside (32). A solution of 6′-allyloxy-3-(benzo[*b*]furan-5-yl)-2′-hydroxypropiophenone 2′-*O*-*β*-D-glucopyranoside (**31**)[11] (200 mg, 0.413 mmol) in *N*,*N*-diethylaniline (2 mL) was stirred at 230 °C for 2 h. After cooling, the reaction mixture was diluted with AcOEt and washed with 10% citric acid, water, and brine. The organic layer was dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel ($CHCl_3$−MeOH (9:1)) to give **32** (114 mg, 57%) as a colorless foam: IR (Nujol) 3345, 1610 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.36 (t, 2H, J = 7.5 Hz), 3.17 (m, 1H), 3.28 (m, 2H), 3.32−3.64 (m, 4H), 3.70 (ddd, 1H, J = 2.0, 5.5, 11.5 Hz), 4.59 (t, 1H, J = 5.5 Hz), 4.98−5.05 (m, 5H), 5.06 (d, 1H, J = 5.5 Hz), 5.15 (d, 1H, J = 5.0 Hz), 5.36 (d, 1H, J = 5.5 Hz), 5.92 (ddt, 1H, J = 6.5, 10.5, 16.5 Hz), 6.70 (d, 1H, J = 8.5 Hz), 6.88 (dd, 1H, J = 1.0, 2.0 Hz), 7.23 (dd, 1H, J = 2.0, 8.5 Hz), 7.26 (d, 1H, J = 8.5 Hz), 7.47 (d, 1H, J = 8.5 Hz), 7.54 (d, 1H, J = 2.0 Hz), 7.93 (d, 1H, J = 2.0 Hz), 12.70 (s, 1H); ESI-MS m/z 507 ($M + NH_4^+$); HR-FABMS calcd for $C_{26}H_{28}NaO_9$ ($M + Na^+$) m/z 507.1631, found 507.1632.

6′-Benzoyloxy-2′hydroxy-3′-methylacetophenone (33). Benzoyl chloride (749 mg, 533 mmol) was added to a solution of the compound **6g** (885 mg, 533 mmol) in collidine (4 mL) under ice-cooling, and the whole was stirred at room temperature for 8 h. The reaction mixture was poured into 10% citric acid and extracted with AcOEt. The organic layer was washed with 10% citric acid, water, saturated $NaHCO_3$, brine, dried over Na_2SO_4, and evaporated. The residue was chromato-

graphed on silica gel (hexane−AcOEt (25:1)) to give **33** (811 mg, 56%) as a pale yellow solid. IR (Nujol) 1735, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.27 (d, 3H, J = 0.5 Hz), 2.57 (s, 3H), 6.59 (d, 1H, J = 8.0 Hz), 7.35 (dd, 1H, J = 0.5, 8.0 Hz), 7.56 (m, 2H), 7.69 (m, 1H), 8.23 (dd, 2H, J = 1.5, 7.5 Hz), 13.07 (s, 1H); APCI-MS m/z 271 ($M + H^+$).

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-3′-methylacrylophenone 2′-*O*-*β*-D-Glucopyranoside (35). Compound **33** (805 mg, 2.98 mmol) was glycosylated by the same procedure as described for the synthesis of **7**. The crude glucoside **34** (1.23 g) was obtained. The crude **34** was condensed with benzofuran-5-carboxaldehyde (353 mg, 2.41 mmol) by the same procedure as described for the synthesis of **4**. The reaction mixture was acidified with 10% HCl and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$−MeOH (20:1)) to give **35** (360 mg, 27% from **33**) as a yellow amorphous solid: IR (Nujol) 3350, 1730, 1705, 1635 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.24 (s, 3H), 2.95−3.00 (m, 2H), 3.10−3.15 (m, 2H), 3.29 (m, 1H), 3.55 (dd, 1H, J = 6.0, 11.0 Hz), 4.05 (t, 1H, J = 6.0 Hz), 4.50 (d, 1H, J = 7.5 Hz), 4.91 (d, 1H, J = 5.0 Hz), 4.97 (d, 1H, J = 4.5 Hz), 5.32 (d, 1H, J = 5.0 Hz), 6.65 (d, 1H, J = 8.0 Hz), 6.98 (dd, 1H, J = 1.0, 2.0 Hz), 7.12 (d, 1H, J = 8.0 Hz), 7.20 (d, 1H, J = 16.0 Hz), 7.44 (d, 1H, J = 16.0 Hz), 7.62 (d, 1H, J = 8.5 Hz), 7.69 (dd, 1H, J = 1.5, 8.5 Hz), 8.00 (d, 1H, J = 1.5 Hz), 8.05 (d, 1H, J = 2.0 Hz), 9.88 (s, 1H); ESI-MS m/z 479 ($M + Na^+$).

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-3′-methylpropiophenone 2′-*O*-*β*-D-Glucopyranoside (36). Compound **35** (393 mg, 0.86 mmol) was hydrogenated over 10% Pd−C (40 mg) in the presence of piperazine (74 mg) in 50% aqueous KOH (1 mL), EtOH (3 mL), and DMA (1.5 mL) for 2 h. The catalyst was removed by filtration, and the filtrate was acidified with 10% HCl and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$−MeOH (10:1)) to give **36** (322 mg, 82%) as a pale yellow foam: IR (Nujol) 3400, 1635 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.22 (s, 3H), 2.95 (t, 1H, J = 7.5 Hz), 3.00−3.10 (m, 2H), 3.15−3.25 (m, 2H), 3.28 (t, 1H, J = 7.5 Hz), 3.37 (m, 1H), 3.63 (dd, 1H, J = 5.5, 11.0 Hz), 4.14 (t, 1H, J = 5.5 Hz), 4.46 (d, 1H, J = 7.5 Hz), 4.97 (d, 1H, J = 5.0 Hz), 5.06 (d, 1H, J = 4.5 Hz), 5.48 (d, 1H, J = 4.5 Hz), 6.61 (d, 1H, J = 8.5 Hz), 6.88 (dd, 1H, J = 1.0, 2.0 Hz), 7.06 (d, 1H, J = 8.5 Hz), 7.20 (dd, 1H, J = 1.5, 8.5 Hz), 7.46 (d, 1H, J = 8.5 Hz), 7.52 (d, 1H, J = 1.5 Hz), 7.93 (d, 1H, J = 2.0 Hz), 9.87 (s, 1H); ESI-MS m/z 476 ($M + NH_4^+$); HR-FABMS calcd for $C_{24}H_{26}NaO_9$ ($M + Na^+$) m/z 481.1475, found 481.1488.

3′,5′-Dichloro-2′,6′-dihydroxyacetophenone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-*β*-D-glucopyranoside (38). A mixture of 2′,6′-dihydroxyacetophenone 2′-*O*-(2,3,4,6-*O*-tetraacetyl-*β*-D-glucopyranoside (**37**) (4.84 g, 10 mmol), NCS (3.47 g, 26 mmol), and DMF (50 mL) was stirred at 50 °C for 10 h. After cooling, the reaction mixture was diluted with AcOEt and washed with water and brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (AcOEt−hexane (1:2)) to give **38** (3.46 g, 63%) as pale yellow needles, mp 164.5−165.5 °C: IR (Nujol) 1750, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.97 (s, 3H), 1.98 (s, 6H), 2.06 (s, 3H), 2.50 (s, 3H), 3.87 (m, 1H), 4.00−4.12 (m, 2H), 4.99 (dd, 1H, J = 9.2, 9.5 Hz), 5.05 (dd, 1H, J = 7.9, 9.9 Hz), 5.26 (d, 1H, J = 7.9 Hz), 5.38 (dd, 1H, J = 9.5, 9.7 Hz), 7.80 (s, 1H), 10.86 (s, 1H); ESI-MS m/z 573 ($M + Na^+$), 575 ($M + 2 + Na^+$), 577 ($M + 4 + Na^+$).

3-(Benzo[*b*]furan-5-yl)-3′,5′-dichloro-2′,6′-dihydroxypropiophenone 2′-*O*-*β*-D-Glucopyranoside (39). Compound **39** was prepared from **38** by the same procedure as described for the synthesis of **4**, with a yield of 54%, as a pale yellow solid, mp 107−110 °C: IR (Nujol) 3520, 3310, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.00 (m, 2H), 3.06 (m, 2H), 3.20 (m, 2H), 3.25−3.50 (m, 3H), 3.60 (m, 1H), 4.20 (t, 1H, J = 5.5 Hz), 4.79 (d, 1H, J = 7.3 Hz), 4.99 (d, 1H, J = 5.1 Hz), 5.10 (d, 1H, J = 4.4 Hz), 5.45 (d, 1H, J = 4.7 Hz), 6.89 (dd, 1H, J = 0.9, 2.2 Hz), 7.21 (dd, 1H, J = 1.8, 8.6 Hz), 7.47 (d, 1H, J = 8.6 Hz), 7.53 (d, 1H, J = 1.5 Hz), 7.65 (s, 1H), 7.94 (d, 1H, J = 2.0 Hz), 10.45 (s, 1H); ESI-MS m/z 535 ($M + Na^+$), 537 ($M + 2 + Na^+$), 539 ($M + 4 + Na^+$). Anal. ($C_{23}H_{22}Cl_2O_9 \cdot {}^1/_2H_2O$) C, H.

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-(4,6-*O*-Benzylidene-*β*-D-glucopyranoside) (40). A mixture of **4** (10.00 g, 21.81 mmol), benzaldehyde dimethylacetal (4.98 g, 32.72 mmol), *p*-TsOH·H_2O (415 mg, 2.18 mmol), and CH_2Cl_2 (200 mL) was stirred at room temperature for 1.5 h. The reaction mixture was evaporated, and the residue was dissolved in AcOEt, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed. The residue was purified by column chromatography on silica gel ($CHCl_3$) to give **40** (10.92 g, 92%) as a pale yellow foam: IR (neat) 3450, 1630 cm^{-1}; ^1H NMR(DMSO-d_6) δ 2.09 (s, 3H), 3.00 (t, 2H, J = 7.3 Hz), 3.38 (m, 2H), 3.40−3.47 (m, 2H), 3.54−3.70 (m, 3H), 4.24 (dd, 1H, J = 5.4, 10.4 Hz), 5.22 (d, 1H, J = 7.7 Hz), 5.52 (d, 1H, J = 7.7 Hz), 5.58 (s, 1H), 5.65 (d, 1H, J = 5.7 Hz), 6.42 (s, 1H), 6.59 (s, 1H), 6.90 (dd, 1H, J = 0.9, 2.2 Hz), 7.24 (dd, 1H, J = 1.7, 8.4 Hz), 7.36−7.53 (m, 7H), 7.95 (d, 1H, J = 2.2 Hz), 11.70 (s, 1H); ESI-MS m/z 569 ($M + Na^+$).

6′-Acetoxy-3-(benzo[*b*]furan-5-yl)-2′-hydroxy-4′-methylpropiophenone 2′-*O*-(2,3-*O*-Diacetyl-4,6-*O*-benzylidene-*β*-D-glucopyranoside) (41). A mixture of **40** (2.02 g, 3.70 mmol), Ac_2O (2.1 mL), and pyridine (20 mL) was stirred at room temperature for 4.5 h. The reaction mixture was poured into 10% citric acid and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The residue was triturated in *iso*-Pr_2O to give **41** (2.37 g, 95%) as colorless needles, mp 200−203 °C: IR (Nujol) 1765, 1750, 1700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.94 (s, 3H), 2.01 (s, 3H), 2.02 (s, 3H), 2.34 (s, 3H), 2.87−3.03 (m, 4H), 3.76 (t, 1H, J = 9.9 Hz), 3.90 (t, 1H, J = 9.4 Hz), 3.97 (dd, 1H, J = 4.5, 9.9 Hz), 4.44 (dd, 1H, J = 4.6, 10.0 Hz), 5.07 (dd, 1H, J = 7.9, 8.1 Hz), 5.40 (t, 1H, J = 9.4 Hz), 5.63 (s, 1H), 5.68 (d, 1H, J = 7.9 Hz), 6.74 (s, 1H), 6.91 (dd, 1H, J = 0.9, 2.2 Hz), 7.00 (s, 1H), 7.17 (dd, 1H, J = 1.8, 8.6 Hz), 7.39 (s, 5H), 7.49 (d, 1H, J = 1.3 Hz), 7.51 (d, 1H, J = 8.4 Hz), 7.95 (d, 1H, J = 2.2 Hz); ESI-MS m/z 690 ($M + NH_4^+$).

6′-Acetoxy-3-(benzo[*b*]furan-5-yl)-2′-hydroxy-4′-methylpropiophenone 2′-*O*-(2,3-*O*-Diacetyl-*β*-D-glucopyranoside) (42). A mixture of **41** (2.04 g, 3.03 mmol), *p*-TsOH·H_2O (58 mg, 0.30 mmol), AcOH (60 mL), and H_2O (6 mL) was stirred at room temperature for 20 h. The reaction mixture was poured into ice−water and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$−MeOH (10:1)) to give **42** (1.58 g, 89%) as a colorless foam: IR (Nujol) 3405, 1750 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.87 (s, 3H), 2.00 (s, 6H), 2.31 (s, 3H), 2.84−3.11 (m, 4H), 3.48−3.57 (m, 2H), 3.64−3.77 (m, 2H), 4.77 (t, 1H, J = 5.8 Hz), 4.89 (dd, 1H, J = 8.1, 9.7 Hz), 5.10 (t, 1H, J = 9.7 Hz), 5.50 (d, 1H, J = 8.1 Hz), 5.59 (d, 1H, J = 5.7 Hz), 6.70 (s, 1H), 6.89 (dd, 1H, J = 0.9, 2.2 Hz), 7.00 (s, 1H), 7.16 (dd, 1H, J = 1.5, 8.5 Hz), 7.47−7.50 (m, 2H), 7.94 (d, 1H, J = 2.2 Hz); ESI-MS m/z 602 ($M + NH_4^+$); HR-FABMS calcd for $C_{30}H_{32}NaO_{12}$ ($M + Na^+$) m/z 607.1791, found 607.1782.

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-(2,3-*O*-Diacetyl-4,6-*O*-benzylidene-*β*-D-glucopyranoside) (43). A mixture of **41** (671 mg, 1.00 mmol), $NaHCO_3$ (419 mg, 5.00 mmol), MeOH (5 mL), THF (5 mL), and H_2O (0.1 mL) was stirred at room temperature for 30 h. The reaction mixture was diluted with AcOEt, washed with water, and dried over $MgSO_4$. The solvent was removed, and the residue was chromatographed on silica gel (hexane−AcOEt (2:1)) to give **43** (410 mg, 65%) as colorless needles, mp 187−189 °C: IR (Nujol) 1755, 1635 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.97 (s, 3H), 2.01 (s, 3H), 2.25 (s, 3H), 2.90−2.98 (m, 2H), 3.01−3.09 (m, 2H), 3.76 (t, 1H, J = 9.9 Hz), 3.88 (t, 1H, J = 9.4 Hz), 3.95 (dd, 1H, J = 4.6, 9.5 Hz), 4.32 (dd, 1H, J = 4.6, 10.1 Hz), 5.05 (dd, 1H, J = 7.9, 9.3 Hz), 5.40 (t, 1H, J = 9.3 Hz), 5.63 (s, 1H), 5.63 (d, 1H, J = 7.9 Hz), 6.43 (s, 1H), 6.53 (s, 1H), 6.90 (dd, 1H, J = 0.9, 2.2 Hz), 7.19 (dd, 1H, J = 1.7, 8.6 Hz), 7.39

(s, 5H), 7.50 (m, 2H), 7.95 (d, 1H, J = 2.2 Hz) 10.70 (s, 1H); ESI-MS m/z 648 ($M + NH_4^+$).

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-(2,3-*O*-Diacetyl-*β*-D-glucopyranoside) (44). Compound **44** was prepared from **43** by the same procedure as described for the synthesis of **42**, with a yield of 87%, as colorless needles, mp 151−153 °C: IR (Nujol) 3545, 3240, 1750, 1729 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.91 (s, 3H), 1.99 (s, 3H), 2.23 (s, 3H), 2.89−2.96 (m, 2H), 3.02−3.09 (m, 2H), 3.46−3.80 (m, 4H), 4.75 (t, 1H, J = 5.7 Hz), 4.88 (dd, 1H, J = 8.0, 9.8 Hz), 5.09 (t, 1H, J = 9.4 Hz), 5.43 (d, 1H, J = 8.0 Hz), 5.58 (d, 1H, J = 5.7 Hz), 6.41 (s, 1H), 6.54 (s, 1H), 6.88 (dd, 1H, J = 0.9, 2.2 Hz), 7.17 (dd, 1H, J = 1.8, 8.4 Hz), 7.47 (d, 1H, J = 8.9 Hz), 7.49 (s, 1H), 7.94 (d, 1H, J = 2.2 Hz), 10.84 (s, 1H); ESI-MS m/z 560 ($M + NH_4^+$). Anal. ($C_{28}H_{30}O_{11}\cdot{}^1/_4H_2O$) C, H.

3-(Benzo[*b*]furan-5-yl)-6′-*tert*-butyldimethylsilyloxy-2′-hydroxy-4′-methylpropiophenone 2′-*O*-(4,6-*O*-Benzylidene-3-*O*-*tert*-butyldimethylsilyl-*β*-D-glucopyranoside) (45). A mixture of **40** (1.00 g, 1.83 mmol), TBSCl (827 mg, 5.49 mmol), imidazole (747 mg, 11.00 mmol), and DMF (10 mL) was stirred at room temperature for 13 h. The reaction mixture was poured into ice−water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (hexane−AcOEt (20:1)) to give **45** (1.06 g, 75%) as a colorless foam: IR (Nujol) 3460, 1690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.01 (s, 3H), 0.08 (s, 3H), 0.18 (s, 6H), 0.86 (s, 9H), 0.89 (s, 9H), 2.28 (s, 3H), 2.93−3.02 (m, 2H), 3.04−3.15 (m, 2H), 3.28 (m, 1H), 3.44 (m, 1H), 3.62 (m, 2H), 3.74 (t, 1H, J = 8.8 Hz), 4.18 (m, 1H), 5.18 (d, 1H, J = 7.9 Hz), 5.56 (d, 1H, J = 7.0 Hz), 5.58 (s, 1H), 6.40 (s, 1H), 6.71 (s, 1H), 6.88 (dd, 1H, J = 0.9, 2.2 Hz), 7.17 (dd, 1H, J = 1.8, 8.6 Hz), 7.36−7.49 (m, 7H), 7.93 (d, 1H, J = 2.2 Hz); FAB-MS m/z 797 ($M + Na^+$).

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-(2-*O*-Acetyl-*β*-D-glucopyranoside) (46). A mixture of **45** (1.04 g, 1.34 mmol), Ac_2O (2.7 mL), and pyridine (5.4 mL) was stirred at room temperature for 13 h. The reaction mixture was poured into 10% citric acid and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The crude 3-(benzo[*b*]furan-5-yl)-6′-*tert*-butyldimethylsilyloxy-2′-hydroxy-4′-methylpropiophenone 2′-*O*-(2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-*tert*-butyldimethylsilyl-*β*-D-glucopyranoside) (1.09 g) was obtained.

A mixture of the crude product (1.07 g), n-Bu_4NF (685 mg, 2.62 mmol), AcOH (2.3 mL), and THF (23 mL) was stirred at room temperature for 30 min. The reaction mixture was poured into ice−water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The crude 3-(benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-(2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-*tert*-butyldimethylsilyl-*β*-D-glucopyranoside) (968 mg) was obtained.

A mixture of the above product (958 mg), *p*-$TsOH\cdot H_2O$ (50 mg, 0.26 mmol), H_2O (3 mL), and AcOH (35 mL) was stirred at room temperature for 22 h. The reaction mixture was poured into ice−water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$−MeOH (30:1)) and crystallized from AcOEt−*iso*-Pr_2O to give **46** (400 mg, 63% from **45**) as a colorless solid, mp 160−163 °C: IR (Nujol) 3510, 1750 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.99 (s, 3H), 2.22 (s, 3H), 2.90−2.97 (m, 2H), 3.03−3.11 (m, 2H), 3.26 (m, 1H), 3.42−3.53 (m, 3H), 3.72 (m, 1H), 4.67 (t, 1H, J = 5.6 Hz), 4.78 (dd, 1H, J = 8.2, 9.5 Hz), 5.20 (d, 1H, J = 8.1 Hz), 5.28 (d, 1H, J = 5.3 Hz), 5.36 (d, 1H, J = 5.5 Hz), 6.39 (s, 1H), 6.52 (s, 1H), 6.88 (dd, 1H, J = 0.9, 2.2 Hz), 7.18 (dd, 1H, J = 1.7, 8.4 Hz), 7.47 (d, 1H, J = 8.4 Hz), 7.50 (d, 1H, J = 1.3 Hz), 7.93 (d, 1H, J = 2.2 Hz), 10.86 (s, 1H); ESI-MS m/z 518 ($M + NH_4^+$). Anal. ($C_{26}H_{28}O_{10}\cdot{}^1/_2H_2O$) C, H.

6′-Acetoxy-3-(benzo[*b*]furan-5-yl)-2′-hydroxy-4′-methylpropiophenone 2′-*O*-(6-*O*-Acetyl-*β*-D-glucopyranoside) (47). Acetyl chloride (188 mg, 2.40 mmol) was added dropwise to a solution of **4** (500 mg, 1.09 mmol) and Et_3N (242 mg, 2.40 mmol) in DMA (3.5 mL) under ice-cooling. The whole was stirred under ice-cooling for 30 min and at room temperature overnight. The reaction mixture was poured into ice and 10% HCl and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$−MeOH (50:1)) to give **47** (304 mg, 51%): IR (neat) 3420, 1770, 1740, 1695, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.97 (s, 3H), 2.02 (s, 3H), 2.31 (s, 3H), 2.88−2.98 (m, 2H), 3.04−3.32 (m, 5H), 3.66 (m, 1H), 4.03 (dd, 1H, J = 7.2, 14.1 Hz), 4.35 (dd, 1H, J = 1.8, 11.7 Hz), 5.04 (d, 1H, J = 7.5 Hz), 5.25 (d, 1H, J = 4.9 Hz), 5.34 (d, 1H, J = 5.3 Hz), 5.44 (d, 1H, J = 5.5 Hz), 6.67 (s, 1H), 6.88 (dd, 1H, J = 0.9, 2.2 Hz), 6.95 (s, 1H), 7.18 (dd, 1H, J = 1.8, 8.4 Hz), 7.47 (d, 1H, J = 8.4 Hz), 7.50 (d, 1H, J = 1.5 Hz), 7.94 (d, 1H, J = 2.2 Hz); ESI-MS m/z 560 ($M + NH_4^+$); HR-FABMS calcd for $C_{28}H_{30}NaO_{11}$ ($M + Na^+$) m/z 565.1686, found 565.1689.

6′-Allyloxy-3-(benzo[*b*]furan-5-yl)-2′-hydroxy-4′-methylpropiophenone 2′-*O*-*β*-D-Glucopyranoside (48). A mixture of **4** (3.00 g, 6.54 mmol), allyl bromide (989 mg, 8.18 mmol), K_2CO_3 (2.71 g, 19.62 mmol), and DMF (30 mL) was stirred at room temperature for 10 h. The reaction mixture was poured into ice−water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was crystallized from *iso*-PrOH−*iso*-Pr_2O to give **48** (3.05 g, 94%) as colorless needles, mp 83.5−84 °C: IR (Nujol) 3020, 1690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.28 (s, 3H), 2.92−3.02 (m, 2H), 3.04−3.32 (m, 6H), 3.45 (m, 1H), 3.70 (m, 1H), 4.50 (td, 2H, J = 1.5, 5.0 Hz), 4.57 (br, 1H), 4.87 (d, 1H, J = 7.7 Hz), 5.03 (d, 1H, J = 4.8 Hz), 5.09 (br, 1H), 5.16 (tdd, 1H, J = 1.5, 1.7, 10.4 Hz), 5.23 (br, 1H), 5.26 (tdd, 1H, J = 1.5, 1.7, 17.4 Hz), 5.90 (tdd, 1H, J = 5,0, 10.4, 17.4 Hz), 6.56 (s, 1H), 6.66 (s, 1H), 6.88 (dd, 1H, J = 0.9, 2.2 Hz), 7.18 (dd, 1H, J = 1.7, 8.4 Hz), 7.45 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 1.3 Hz), 7.93 (d, 1H, J = 2.2 Hz); ESI-MS m/z 521 ($M + Na^+$).

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-(6-*O*-Methoxycarbonyl-*β*-D-glucopyranoside) (5). A solution of methyl chloroformate (114 mg, 1.20 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to a solution of **48** (500 mg, 1.00 mmol) in 2,4,6-collidine (5 mL) at −40 °C. The whole was stirred at −40 °C for 1 h and at room temperature for 1.5 h. The reaction mixture was poured into ice-cooled 10% HCl and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$−MeOH (30:1)) to give the acylated product (487 mg, 87%).

To a solution of this compound (470 mg, 0.844 mmol) in acetonitrile (7 mL) was added dichlorobis(triphenylphosphine) palladium (11.8 mg) and ammonium formate (213 mg, 3.38 mmol). The mixture was heated under reflux for 3 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$−MeOH (10:1)) and crystallized from MeOH−H_2O to give **5** (410 mg, 94%) as a colorless solid, mp 78−80 °C: IR (Nujol) 3510, 3400, 3170, 1730, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.23 (s, 3H), 2.99 (t, 1H, J = 7.4 Hz), 3.14−3.42 (m, 5H), 3.65 (s, 3H), 3.66 (m, 1H), 4.16 (dd, 1H, J = 6.6, 11.5 Hz), 4.39 (dd, 1H, J = 2.0, 11.5 Hz), 5.02 (d, 1H, J = 7.5 Hz), 5.25 (d, 1H, J = 5.0 Hz), 5.37 (d, 1H, J = 5.3 Hz), 5.39 (d, 1H, J = 5.3 Hz), 6.42 (s, 1H), 6.50 (s, 1H), 6.88 (dd, 1H, J = 0.9, 2.2 Hz), 7.20 (dd, 1H, J = 1.7, 8.4 Hz), 7.47 (d, 1H, J = 8.4 Hz), 7.51 (d, 1H, J = 1.3 Hz), 7.93 (d, 1H, J = 2.2 Hz), 11.80 (s, 1H); ESI-MS m/z 539 ($M + Na^+$). Anal. ($C_{26}H_{28}O_{11}\cdot H_2O$) C, H.

Compounds **49**−**53** were prepared by the same procedure as described above.

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-(6-*O*-Acetyl-*β*-D-glucopyranoside) (49): 74% yield as a colorless solid; IR (Nujol) 3490, 3440, 1740, 1710, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.97 (s, 3H), 2.25 (s, 3H), 2.99 (t, 1H, J = 7.7 Hz), 3.14−3.49 (m, 5H), 3.63 (m, 1H), 4.03 (dd, 1H, J = 7.1, 14.3 Hz), 4.44 (dd, 1H, J = 1.8, 11.7

Hz), 5.01 (d, 1H, J = 7.5 Hz), 5.25 (d, 1H, J = 4.8 Hz), 5.33 (d, 1H, J = 5.5 Hz), 5.39 (d, 1H, J = 5.1 Hz), 6.41 (s, 1H), 6.51 (s, 1H), 6.88 (dd, 1H, J = 0.9, 2.2 Hz), 7.21 (dd, 1H, J = 1.8, 8.4 Hz), 7.47 (d, 1H, J = 8.4 Hz), 7.52 (d, 1H, J = 1.3 Hz), 7.94 (d, 1H, J = 2.2 Hz), 11.77 (s, 1H); ESI-MS m/z 523 ($M + Na^+$). Anal. ($C_{26}H_{28}O_{10}\cdot{}^3/_4H_2O$) C, H.

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-(6-*O*-Methoxyacetyl-*β*-D-glucopyranoside) (50): 59% yield as a colorless solid; IR (Nujol) 3475, 1750, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.25 (s, 3H), 2.99 (t, 1H, J = 7.5 Hz), 3.15−3.42 (m, 5H), 3.24 (s, 3H), 3.67 (m, 1H), 3.96 (d, 1H, J = 16.5 Hz), 4.02 (d, 1H, J = 16.7 Hz), 4.14 (dd, 1H, J = 6.9, 11.7 Hz), 4.42 (dd, 1H, J = 1.7, 11.7 Hz), 5.02 (d, 1H, J = 7.3 Hz), 5.26 (d, 1H, J = 4.8 Hz), 5.36 (d, 1H, J = 5.5 Hz), 5.39 (d, 1H, J = 5.3 Hz), 6.41 (s, 1H), 6.50 (s, 1H), 6.88 (dd, 1H, J = 0.9, 2.2 Hz), 7.20 (dd, 1H, J = 1.7, 8.4 Hz), 7.47 (d, 1H, J = 8.4 Hz), 7.51 (d, 1H, J = 1.5 Hz), 7.94 (d, 1H, J = 2.2 Hz), 11.76 (s, 1H); ESI-MS m/z 548 ($M + NH_4^+$). Anal. ($C_{27}H_{30}O_{11}\cdot H_2O$) C, H.

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-(6-*O*-Ethoxycarbonyl-*β*-D-glucopyranoside) (51): 80% yield as a colorless solid; IR (Nujol) 3520, 3450, 3325, 1730, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.15 (t, 3H, J = 7.1 Hz), 2.24 (s, 3H), 2.99 (t, 1H, J = 7.4 Hz), 3.14−3.44 (m, 5H), 3.66 (m, 1H), 4.02 (q, 2H, J = 7.1 Hz), 4.14 (dd, 1H, J = 6.9, 11.6 Hz), 4.38 (dd, 1H, J = 1.8, 11.5 Hz), 5.02 (d, 1H, J = 7.3 Hz), 5.24 (d, 1H, J = 4.8 Hz), 5.36 (d, 1H, J = 5.3 Hz), 5.39 (d, 1H, J = 5.1 Hz), 6.41 (d, 1H, J = 0.6 Hz), 6.51 (s, 1H), 6.88 (dd, 1H, J = 0.9, 2.2 Hz), 7.20 (dd, 1H, J = 1.7, 8.5 Hz), 7.46 (d, 1H, J = 8.4 Hz), 7.51 (d, 1H, J = 1.3 Hz), 7.93 (d, 1H, J = 2.2 Hz), 11.78 (s, 1H); ESI-MS m/z 548 ($M + NH_4^+$). Anal. ($C_{27}H_{30}O_{11}\cdot H_2O$) C, H.

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-(6-*O*-*iso*-Propyloxycarbonyl-*β*-D-glucopyranoside) (52): 63% yield as a colorless solid; IR (Nujol) 3600, 3490, 3420, 3290, 1710, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.15 (d, 3H, J = 6.5 Hz), 1.17 (d, 3H, J = 6.5 Hz), 2.25 (s, 3H), 2.99 (t, 1H, J = 7.5 Hz), 3.17−3.42 (m, 5H), 3.65 (m, 1H), 4.12 (dd, 1H, J = 7.0, 11.5 Hz), 4.36 (dd, 1H, J = 2.0, 11.5 Hz), 4.71 (m, 1H), 5.02 (d, 1H, J = 7.5 Hz), 5.24 (d, 1H, J = 5.0 Hz), 5.37 (d, 1H, J = 5.5 Hz), 5.40 (d, 1H, J = 5.5 Hz), 6.40 (s, 1H), 6.52 (s, 1H), 6.88 (dd, 1H, J = 1.0, 2.0 Hz), 7.20 (dd, 1H, J = 2.0, 8.5 Hz), 7.46 (d, 1H, J = 8.5 Hz), 7.51 (d, 1H, J = 2.0 Hz), 7.93 (d, 1H, J = 2.0 Hz), 11.80 (s, 1H); ESI-MS m/z 562 ($M + NH_4^+$). Anal. ($C_{28}H_{32}O_{11}\cdot H_2O$) C, H.

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-(6-*O*-Methoxyethoxycarbonyl-*β*-D-glucopyranoside) (53): 62% yield as a pale yellow foam; IR (neat) 3430, 1750, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.24 (s, 3H), 2.99 (t, 1H, J = 7.3 Hz), 3.15−3.45 (m, 5H), 3.21 (s, 3H), 3.48 (m, 2H), 3.63 (m, 1H), 4.14 (m, 3H), 4.40 (dd, 1H, J = 1.9, 11.4 Hz), 5.02 (d, 1H, J = 7.3 Hz), 5.23 (d, 1H, J = 4.9 Hz), 5.36 (d, 1H, J = 5.3 Hz), 5.38 (d, 1H, J = 5.1 Hz), 6.41 (d, 1H, J = 0.7 Hz), 6.52 (d, 1H, J = 0.7 Hz), 6.87 (dd, 1H, J = 1.1, 2.2 Hz), 7.20 (dd, 1H, J = 1.8, 8.4 Hz), 7.46 (d, 1H, J = 8.4 Hz), 7.51 (d, 1H, J = 1.1 Hz), 7.92 (d, 1H, J = 2.2 Hz), 11.80 (s, 1H); ESI-MS m/z 578 ($M + NH_4^+$); HR-FABMS calcd for $C_{28}H_{32}NaO_{12}$ ($M + Na^+$) m/z 583.1791, found 583.1786.

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-(4,6-*O*-Carbonyl-*β*-D-glucopyranoside) (54). A solution of *p*-nitrophenyl chloroformate (1.71 g, 8.51 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of **4** (3.00 g, 6.54 mmol) in 2,4,6-collidine (33 mL) at −40 °C. The whole was stirred at −40 °C for 1.5 h, at room temperature for 1 h, and at 50 °C for 3 h. The reaction mixture was poured into ice and 10% HCl and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$−acetone (4:1)) to give **54** (2.16 g, 68%): IR (Nujol) 3385, 1755, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.25 (s, 3H), 2.99 (t, 1H, J = 7.4 Hz), 3.30−3.40 (m, 3H), 3.64 (m, 3H), 4.09−4.21 (m, 2H), 4.26 (dd, 1H, J = 9.3, 9.7 Hz), 4.49 (dd, 1H, J = 5.3, 9.2 Hz), 5.26 (d, 1H, J = 7.9 Hz), 5.80 (d, 1H, J = 5.9 Hz), 5.86 (d, 1H, J = 5.7 Hz), 6.43 (s, 1H), 6.55 (s, 1H), 6.89 (dd, 1H, J = 0.9, 2.2 Hz), 7.19 (dd, 1H, J = 1.8, 8.6 Hz), 7.49 (d, 1H, J = 8.6 Hz), 7.50 (d, 1H, J = 1.9 Hz), 7.94 (d, 1H, J = 2.2 Hz), 11.60 (s, 1H); FAB-MS m/z 507 ($M + Na^+$).

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-(4-*O*-Methoxycarbonyl-*β*-D-glucopyranoside) (55). A mixture of **54** (2.13 g, 4.40 mmol), *p*-TsOH·H_2O (84 mg, 0.44 mmol), and MeOH (40 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with AcOEt and washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$−acetone (4:1)) to give the 4-*O*-carbonate **55** (986 mg, 43%) and the 6-*O*-carbonate **5** (890 mg, 39%). **55:** IR (neat) 3460, 1750, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.24 (s, 3H), 3.00 (t, 1H, J = 7.4 Hz), 3.32−3.45 (m, 4H), 3.49−3.60 (m, 2H), 3.70 (m, 1H), 3.73 (s, 3H), 4.54 (t, 1H, J = 9.6 Hz), 4.82 (t, 1H, J = 5.6 Hz), 5.12 (d, 1H, J = 7.7 Hz), 5.52 (d, 1H, J = 5.7 Hz), 5.60 (d, 1H, J = 5.7 Hz), 6.44 (d, 1H, J = 0.6 Hz), 6.56 (d, 1H, J = 0.9 Hz), 6.90 (dd, 1H, J = 0.9, 2.2 Hz), 7.22 (dd, 1H, J = 1.7, 8.4 Hz), 7.47 (d, 1H, J = 8.4 Hz), 7.54 (d, 1H, J = 1.3 Hz), 7.93 (d, 1H, J = 2.2 Hz), 11.80 (s, 1H); ESI-MS m/z 534 ($M + NH_4^+$); HR-FABMS calcd for $C_{26}H_{28}NaO_{11}$ ($M + Na^+$) m/z 539.1530, found 539.1540.

3-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone 2′-*O*-(4, 6-*O*-Methoxyethylene-*β*-D-glucopyranoside) (56). A mixture of **4** (400 mg, 0.87 mmol), pyridinium *p*-toluenesulfonate (PPTS) (22 mg, 0.087 mmol), and trimethyl orthoacetate (5 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with AcOEt and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel ($CHCl_3$−MeOH (20:1)) to give **56** (320 mg, 71%) as a pale yellow foam: IR (neat) 3425, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (s, 3H), 2.25 (s, 3H), 2.99 (t, 1H, J = 7.5 Hz), 3.23 (s, 3H), 3.26−3.82 (m, 8H), 5.18 (d, 1H, J = 7.7 Hz), 5.38 (d, 1H, J = 5.3 Hz), 5.61 (d, 1H, J = 5.7 Hz), 6.41 (s, 1H), 6.55 (s, 1H), 6.84 (dd, 1H, J = 0.9, 2.2 Hz), 7.19 (dd, 1H, J = 1.7, 8.4 Hz), 7.47 (d, 1H, J = 8.4 Hz), 7.51 (d, 1H, J = 1.3 Hz), 7.94 (d, 1H, J = 2.2 Hz), 11.70 (s, 1H); ESI-MS m/z 537 ($M + Na^+$).

Conversion of Compound 5 to Compound 4 by S9 Fraction. Livers and small intestines from KK-A^y mice, Sprague−Dawley (SD) rats, beagle dogs, and monkeys were homogenized and centrifuged at 9000*g* for 20 min. The supernatant (S9) fractions were prepared by the method described previously.[29] S9 fractions of human livers and intestines were obtained from IIAM (Exton, PA). Compound **5** (10 μg/mL) was added to the S9 fractions and incubated for 0, 5, 15, 30, 60, and 120 min at 37 °C. Following the termination of esterase reaction with acetonitrile and centrifugation, the supernatant was applied in HPLC to determine the amount of compound **5** and compound **4**.

Inhibition of SGLT Activity in Brush Border Membrane Vehicles (BBMVs). The kidney was obtained from SD rats and BBMVs, prepared by the Ca^{2+} precipitation method,[30] and preincubated at 37 °C for 2 min in assay buffer (10 mM Hepes-Tris, pH 7.4, 100 mM mannitol). The test compounds, D-glucose (0.1 mM), D-[6-^{3}H(N)]-glucose (1 μCi, DuPont/NEN), and NaSCN or KSCN (100 mM) were added for five seconds. The uptake reaction was terminated by addition of 0.3 mM phlorizin in 10 mM Hepes-Tris (pH 7.4). The vehicles were immediately filtered through a nitrocellulose membrane filter (pore size 0.45 μm; Advantec Toyo), and the radioactivity on the membrane was measured by a liquid scintillation counter (Packerd).

Glucose Tolerance Test in db/db Mice. Male db/db mice (13 weeks old, Japan SLC) were given a 20% glucose solution (1 g/kg) orally (OGTT) after 16 h of fasting. Compound **5** (3−30 mg/kg) was orally administered 5 min before the glucose loading. The blood glucose level was measured by a glucose oxidase method (new blood sugar test, Boehringer Mannheim).

Effect of Single Administration of Compound 5 in Vivo. Male KK-A^y mice (12 weeks old) were used. The blood glucose level was measured using a glucose oxidase method (new blood sugar test, Boehringer Mannheim). Urine was

collected for 5 h using metabolic cages, and glucose content was measured with a glucose analyzer (APEC). Electrolyte content in plasma and urine were determined by an autoanalyzer (Hitachi model 710).

Chronic Administration in KK-A^y Mice. KK-A^y mice were fed with a normal (CE-2, Japan CLEA), compound **5**-mixed, or acarbose-mixed diet prepared by Japan CLEA. Blood glucose levels were determined as described above. HbA1c levels were determined by an aminophenyl-boronate-agarose affinity chromatography method (Glyc-Affin. GHb, Seikagaku Kogyo Co.).

Effect on Intestinal Absorption of Sugars. SD rats of 7 weeks old were fasted for 24 h. Sucrose (2.5 g/5 mL/kg) was po administered with either compound **4**, compound **5**, or acarbose. The stomach, mid portion of small intestine (20 cm), and cecum were excised under pentobarbital anesthesia (50 mg/kg) 0.5, 1, and 3 h later. The contents of the gastrointestinal tract were centrifuged at 3000*g* for 10 min after addition of H_2SO_4. Following the hydroxylation by boiling for 2 h, the glucose content was determined by the glucose oxidase method.

Statistics. The data are expressed as the mean ± SEM. Multiple comparisons were performed using Dunnett's tests. A multiple comparison was performed by Dunnett's test to compare the compound **5**-treated group with the diabetic control group.

References

(1) Edelman, S. V. Type II diabetes Mellitus. *Adv. Intern. Med.* **1998**, *43*, 449−500.

(2) Henry, R. R. Glucose control and insulin resistance in noninsulin-dependent diabetes mellitus. *Ann. Intern. Med.* **1996**, *124*, 97−103.

(3) (a) Unger, R. H.; Grundy, S. Hyperglycaemia as an inducer as well as a consequence of impaired islet cell function and insulin resistance: implications for the management of diabetes. *Diabetologia* **1985**, *28*, 119−121. (b) Rossetti, L.; Giaccari, A.; DeFronzo, R. A. Glucose Toxicity. *Diabetes Care* **1990**, *13*, 610−630. (c) Kahn, B. B.; Shulman, G. I.; DeFronzo, R. A.; Cushman, S. W.; Rossetti, L. Normalization of Blood Glucose in Diabetic Rats with Phlorizin Treatment Reverses Insulin-resistant Glucose Transport in Adipose cells without Restoring Glucose Transporter Gene Expression. *J. Clin. Invest.* **1991**, *87*, 561−570. (d) Dimitrakoudis, D.; Vrantic, M.; Klip, A. Effect of Hyperglycemia on Glucose Transporters of the Muscle: Use of the Renal Glucose Reabsorption Inhibitor Phlorizin to Control Glycemia. *J. Am. Soc. Nephrol.* **1992**, *3*, 1078−1091. (e) Brichard, S. M.; Henquin, J. C.; Girard, J. Phlorizin treatment of diabetic rats partially reverses the abnormal expression of genes involved in hepatic glucose metabolism. *Diabetologia* **1993**, *36*, 292−298.

(4) Emilien, G.; Maloteaux, J.-M.; Ponchon, M. Pharmacological management of Diabetes: Recent progress and future perspective in daily drug treatment. *Pharmacol. Ther.* **1998**, *81*, 37−51.

(5) Perfetti, R.; Barnett, P. S.; Mathur, R.; Egan, J. M. Novel therapeutic strategies for the treatment of type 2 diabetes. *Diabetes Metab. Rev.* **1998**, *14*, 207−225.

(6) Hadler, A. J. Mazindol, A New Non-Amphetamine Anorexigenic Agent. *J. Clin. Pharmacol.* **1972**, *12*, 453−458.

(7) (a) Truscheit, E.; Frommer, W.; Junge, B.; Muller, L.; Schmidt, D. D.; Wingender, W. Chemistry and Biochemistry of Microbial α-Glucosidase Inhibitors. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 744−761. (b) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. Synthesis and α-D-Glucosidase Inhibitory Activity of N-Substituted Valiolamine Derivatives as Potential Oral Antidiabetic Agents. *J. Med. Chem.* **1986**, *29*, 1038−1046.

(8) (a) Claus, T. H.; Bloom, J. D. β_3-Selective Adrenergic Receptor Agonists. *Ann. Rep. Med. Chem.* **1995**, *30*, 189−198. (b) Strosberg, A. D.; Pietri-Rouxel, F. Function and regulation of the β_3-adrenoceptor. *Trends Pharmacol. Sci.* **1996**, *17*, 373−381.

(9) Tsujihara, K.; Hongu, M.; Saito, K.; Inamasu, M.; Arakawa, K.; Oku, A.; Matsumoto, M. Na^+-Glucose Cotransporter Inhibitors as Antidiabetics. I. Synthesis and Pharmacological Properties of 4′-Dehydroxyphlorizin Derivatives Based on a New Concept. *Chem. Pharm. Bull.* **1996**, *44*, 1174−1180.

(10) Hongu, M.; Tanaka, T.; Funami, N.; Saito, K.; Arakawa, K.; Matsumoto, M.; Tsujihara, K. Na^+-Glucose Cotransporter Inhibitors as Antidiabetic Agents. II. Synthesis and Structure−Activity Relationships of 4′-Dehydroxyphlorizin Derivatives. *Chem. Pharm. Bull.* **1998**, *46*, 22−33.

(11) Hongu, M.; Funami, N.; Takahashi, Y.; Saito, K.; Arakawa, K.; Matsumoto, M.; Yamakita, H.; Tsujihara, K. Na^+-Glucose Cotransporter Inhibitors as Antidiabetic Agents. III. Synthesis and Pharmacological Properties of 4′-Dehydroxyphlorizin Derivatives Modified at the OH Groups of the Glucose Moiety. *Chem. Pharm. Bull.* **1998**, *46*, 1545−1555.

(12) Deetjen, P.; Baeyer, H. V.; Drexel, H. *Textbook of Nephrology*, 3rd ed.; Massry, S. G., Glassock, R. J., Eds.; Williams & Wilkins: Baltimore, 1995; Vol. 1, pp 90−94.

(13) (a) McKee F. W.; Hawkins W. B. Phlorhizin Glucosuria. *Physiol. Rev.* **1945**, *25*, 255−280. (b) Alvarado F.; Crane R. K. Phlorizin as a competitive inhibitor of the active transport of sugars by hamster small intestine, in vitro. *Biochim. Biophys. Acta* **1962**, *56*, 170−172. (c) Alvarado F.; Crane R. K. Studies on the Mechanism of Intestinal Absorption of Sugars. VII. Phenylglycoside Transport and Its Possible Relationship to Phlorizin Inhibition of the Active Transport of Sugars by the Small Intestine. *Biochim. Biophys. Acta* **1964**, *93*, 116−135. (d) Toggenburger G.; Kessler M.; Semenza G. Phlorizin as a Probe of the Small-Intestinal Na^+, D-Glucose Cotransporter a Model. *Biochim. Biophys. Acta* **1982**, *688*, 557−571.

(14) Phlorizin seems to show no toxicity to the kidney, although it has been reported long time ago to possess kidney toxicity in ref 13a. Gouvea W. L.; Alpert H. C.; Kelley J.; Pardo V.; Vaamonde A. Phlorizin-induced glucosuria does not prevent gentamicin nephrotoxicity in rats. *Kidney Int.* **1989**, 1041−1048.

(15) Hongu M.; Saito K.; Tsujihara K. Solid−Liquid-Phase Transfer Catalyzed Novel Glycosylation Reaction of Phenols. *Synth. Commun.* **1999**, *29*, 2775−2781.

(16) Humphrey G. R.; Madar A. M.; Thompson A. S. Preparation of 4-[N-[(benzofuranylalkyl) carbamoyl] azetidinon-4-yloxy] phenylacetates as elastase inhibitors. U.S. Patent 5149838. [*Chem. Abstr.* **1993**, *118*, 124295].

(17) Yamashita M.; Kato Y.; Suemitsu R. Selective Reduction of α,β-Unsaturated Carbonyl Compounds by Sodium Hydrotelluride. *Chem. Lett.* **1980**, 847−848.

(18) Desai R. D.; Mavani C. K. Heterocyclic Compounds Part XVII. Coumarins from β-Ketonic Esters and 5-Methyl-2-ethyl-, 5-Methyl-2-propyl-, 5-Methyl-2, 4-diethyl-4-Ethyl-2-benzoyl-resorcinols, and Phlorobenzophenone. *Proc. Indian Acad. Sci. Sec. A*, **1947**, *25A*, 341−344.

(19) Rassell A.; Frye J. R. 2,6-Dihydroxyacetophenone. *Org. Synth. Coll. Vol. 3*, **1955**, 281−285.

(20) Ishihara K.; Kurihara H.; Yamamoto H. An Extremely Simple, Convenient, and Selective Method for Acetylating Primary Alcohols in the Presence of Secondary Alcohols. *J. Org. Chem.* **1993**, *58*, 3791−3793.

(21) Tsuji J.; Yamakawa T.; Kaito M.; Mandai T. Formation of a Terminal Conjugated Diene System by the Palladium Catalyzed Elimination Reactions of Allylic Acetates and Phenyl Ethers. *Tetrahedron Lett.* **1978**, 2075−2078.

(22) Kees, K. L.; Fitzgerald, J. J., Jr.; Steiner, K. E.; Mattes, J. F.; Mihan, B.; Tosi, T.; Mondoro, D.; McCaleb, M. L. New potent antihyperglycemic agents in db/db mice: synthesis and structure−activity relationship studies of (4-substituted benzyl) (trifluoromethyl) pyrazoles and -pyrazolones. *J. Med. Chem.* **1996**, *39*, 3920−3928.

(23) Shafer, V. S. *Renal Funct.* **1995**, pp 69−74.

(24) Shehata, T. E.; Marr, A. G. Effect of nutrient concentration on the growth of *Escherichia coli*. *J. Bacteriol.* **1971**, *107*, 210−216.

(25) Patterson, J. E.; Andriole, V. T. Bacterial urinary tract infections in diabetes. *Infect. Dis. Clin. North. Am.* **1995**, *9*, 25−51.

(26) Oenar, B. S.; Byrd, D. J.; Brodehl, J. Complete absence of tubular glucose reabsorption: a new type of renal glucosuria (type O). *Clin. Nephrol.* **1987**, *27*, 156−160.

(27) Bagga, A.; Shankar, V.; Moudgil, A.; Srivastava, R. N. Type O renal glucosuria. *Acta Paediatr. Scand.* **1991**, *80*, 116−119.

(28) Oku, A.; Ueta, K.; Arakawa, K.; Ishihara, T.; Nawano, M.; Kuronuma, Y.; Matsumoto, M.; Saito, A.; Tsujihara, K.; Anai, M.; Asano, T.; Kanai, Y.; Endou, H. T-1095, an inhibitor of renal Na^+-glucose cotransporters, may provide a novel approach to treating diabetes. *Diabetes* **1999**, *48*, 1794−1800.

(29) Prueksaritanont, T.; Gorham, L. M.; Ellis, J. D.; Fernandez-Metzler, C.; Deluna, P.; Gehret, J. R.; Strong, K. L.; Hochman, J. H.; Askew, B. C.; Duggan, M. E.; Gilbert, J. D.; Lin, J. H.; Vyas, K. P. Species and organ differences in first-pass metabolism of the ester prodrug L-751,164 in dogs and monkeys. In vivo and in vitro studies. *Drug Metab. Dispos.* **1996**, *24*, 1263−1271.

(30) Malathi, P.; Preisher, H.; Fairclough, P.; Mallett, P.; Crane, R. K. A rapid method for the isolation of kidney brush border membranes. *Biochim. Biophys. Acta* **1975**, *554*, 259−263.

JM990175N