Na^+–Glucose Cotransporter Inhibitors as Antidiabetic Agents. III.[1] Synthesis and Pharmacological Properties of 4′-Dehydroxyphlorizin Derivatives Modified at the OH Groups of the Glucose Moiety

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To overcome hydrolysis by β-glucosidase present in the digestive tract, the OH groups on the glucose moiety of the 4′-dehydroxyphlorizin derivatives (1, 2, 3) were modified with various kinds of patterns, and then the effects of the modified compounds on urinary glucose excretion were evaluated in rats. Among them, triacetyl (9), 2,3-*O*-diacetyl (17), 6-*O*-methoxycarbonyl (34), 4-*O*-methoxycarbonyl (38), and 2-*O*-acetyl (41) derivatives showed more potent effect than the parent compound 2 by oral administration (*p.o.*). The stabilities of the compounds 34, 38, and 41 against β-glucosidase were higher than that of 2. The increase in oral activity was found to correlate with the enhancement of the stability against β-glucosidase.

Key words antidiabetic; Na^+–glucose cotransporter; 4′-dehydroxyphlorizin; β-glucosidase

The Na^+–glucose cotransporter (SGLT) present on the chorionic membrane of the intestine and kidney plays an important role in the absorption and reabsorption of glucose.[2] We thought that inhibitors of SGLT would be useful as antidiabetic agents in preventing chronic hyperglycemia, since they would be able not only to inhibit glucose uptake at the intestine but also to stimulate glucose excretion into urine directly at the kidney. On the basis of this new concept, some analogues of phlorizin, which is known to cause renal diabetes by inhibition of SGLT,[3] were designed, synthesized, and examined for various pharmacological properties related to antidiabetic activity. Among them, we found that 4′-dehydroxy-4-*O*-methylphlorizin (**1**) lowers high blood glucose levels by oral administration (*p.o.*).[4] Furthermore, we tried various structural modifications of compound **1** and studied the structure–activity relationships on the urinary glucose excretion. All modifications, such as the replacement of the glucose moiety to other sugars, the alkylation of the phenolic OH group (B ring) or the changing the bridge part between the A and the B rings, resulted only in reduction of the activity. But finally we found that the benzofuran derivative **2** showed a more potent effect than **1**.[1]

Evans and Diedrich reported that phlorizin and its analogues (4′-dehydroxyphlorizin (**3**) and 4-*O*-methylphlorizin) were easily hydrolyzed to the aglycons and glucose by β-glucosidase present on the intestinal brush border membranes[5] and the aglycons had almost no SGLT-inhibitory activity.[4] We found that the compound **3** and phlorizin had strong SGLT-inhibitory effect *in vitro* and markedly increased urinary glucose by intraperitoneal injection (i.p.), but showed weak or almost no effect by *p.o.*[4] These data suggest that the oral activity of these compounds relates closely to their stability against β-glucosidase. So it was expected that the enhancement of their stability against β-glucosidase in the digestive tract would increase the potency of these compounds by *p.o.* We tried some modifications of the OH groups on the glucose moiety of the compounds **1**, **2**, and **3** with some protective groups, which would be removed metabolically after absorption.

In this paper, we describe the synthesis and the effect on the urinary glucose excretion of the compounds modified at the OH groups on the glucose moiety and the phenolic OH groups with various kinds of patterns.

Chemistry

First, the peracetylated compound **4** was prepared from the compound **1** by acetylation using acetic anhydride (Ac_2O) in pyridine. Then, the triacetyl derivatives (**8**, **9**) were synthesized as follows. The compounds **1** and **2** were reacted with benzaldehyde dimethylacetal in the presence of *p*-toluenesulfonic acid (*p*-TsOH) to give the glucose 4,6-*O*-benzylidene derivatives **5** and **6** in 95 and 92% yield, respectively. Then **5** and **6** were acetylated and then the benzylidene groups were removed by heating in AcOH–H_2O (8 : 1) at 70 °C to give the triacetyl derivatives **8** (86%) and **9** (79%) (Chart 1).

The glucose 2,3-*O*-diacyl derivatives (**10**—**19**, **22**, **23**) were prepared by the method shown in Chart 2. The benzylidene derivatives **5** and **6** were acylated and then treated with $NaHCO_3$ in MeOH at room temperature or at 40 °C to remove the undesired acyl groups at the phenolic OH group selectively. The subsequent debenzylidenation of the products in the same manner as shown in Chart 1 yielded the glucose 2,3-*O*-diacyl derivatives of **1** (**10**—**16**) and those of **2** (**17**—**19**), respectively. Acetylation of the benzylidene derivative **7**, prepared from **3** by the benzylidenation in 60% yield (Chart 1), followed by treatment with $NaHCO_3$ at 40 °C for 1.5 h afforded the triacetyl derivative **20** (36%) and the diacetyl derivative **21** (46%). Debenzylidenation gave compounds **22** and **23**. The yield and the physicochemical data are listed in the tables (**4**, **8**, **10**—**16**, **22**, **23** (Table 1); **9**, **17**—**19** (Table 2)).

Next, the glucose 4,6-*O*-diacyl derivatives of compound **1** were synthesized (Chart 3). Carbobenzyloxy (Z)-protection of the three OH groups of the benzylidene derivative **5** with Z-Cl in pyridine failed, but the method using phase transfer catalyst in a two-phase system (10% aq. NaOH–CH_2Cl_2) was found to be suitable for Z-protection. Thus, the Z-protection of **5** followed by debenzylidenation gave **24** in 72% yield. Compound **24** was acylated and then the Z groups were removed by catalytic hydrogenolysis to afford the desired 4,6-

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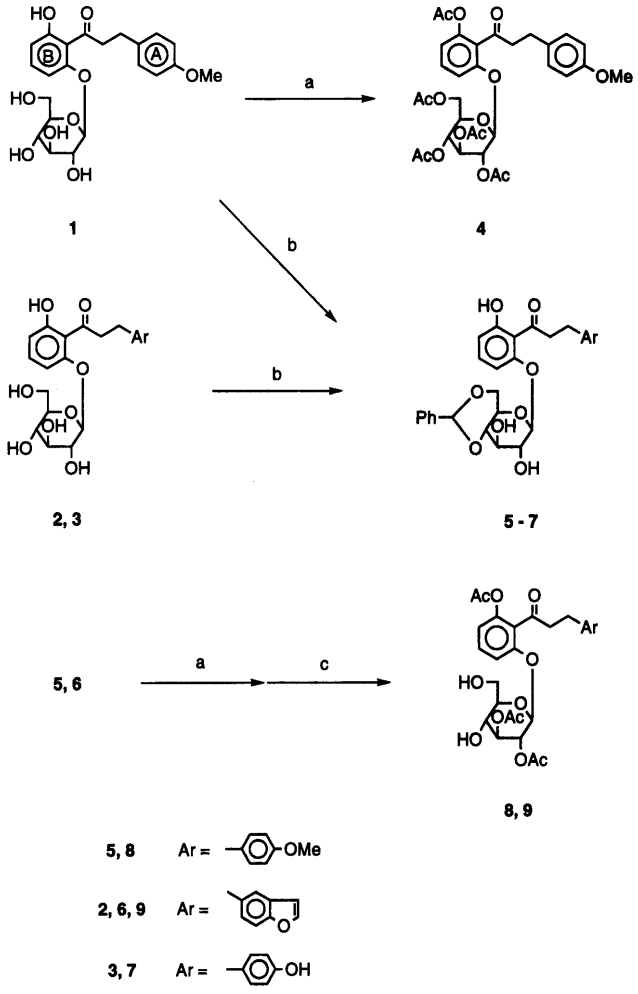


Chart 1

a) Ac_2O, pyridine; b) benzaldehyde dimethylacetal, *p*-TsOH, CH_2Cl_2; c) AcOH, H_2O.

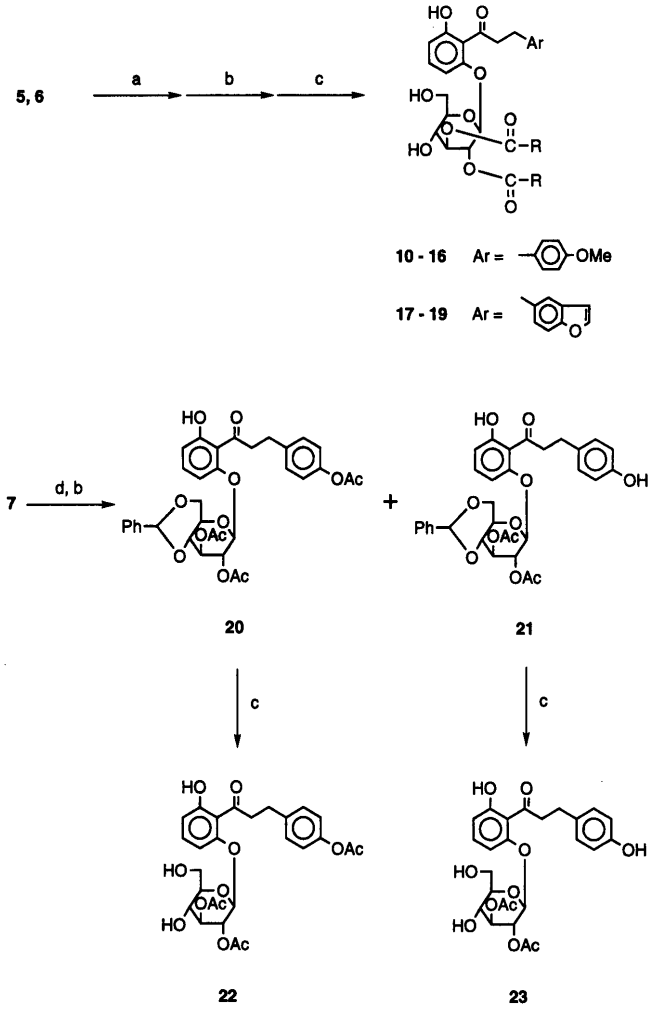


Chart 2

a) RCOCl or Ac_2O, pyridine; b) $NaHCO_3$, MeOH; c) AcOH, H_2O; d) Ac_2O, pyridine.

O-diacyl derivatives (**25**, **26**) (Table 1).

The glucose 6-*O*-acyl derivatives of **1** were prepared by the method shown in Chart 4. Compound **1** was benzoylated in pyridine at 0 °C to give the 6-*O*-benzoyl derivative **27** in 49% yield. Since the 6-*O*-ethoxyacetylated compound **29** could not be obtained in the usual manner, the phenol-protected compound **28** prepared from **1** was used for its synthesis. Thus, **28** was condensed with ethoxyacetic acid using bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl)[6] to afford the 6-*O*-acyl derivative. After removal of the benzyl group, **29** was obtained in 55% yield (Table 1). The glucose 6-*O*-acyl derivatives of **2** were prepared by acylation in 2,4,6-collidine, according to the procedure of Yamamoto and his co-workers.[7] Although, even in these conditions, the phenolic OH group was partially acylated, these acyl groups could be removed by treatment with $NaHCO_3$ (**30**—**32**). In the case of the methoxycarbonyl and the *N*-phenylcarbamoyl derivatives, it was difficult to selectively remove these groups at the phenols by solvolytic procedures. So the allylated compound **33** was used for their preparation. Thus, methoxycarbonylation or *N*-phenylcarbamoylation of **33** in the same manner as described above followed by removal of the allyl group,[8] gave the desired compounds (**34**, **35**). The diacyl derivative at the phenol and glucose 6-*O*-position (**36**) was prepared by acylation in the presence of triethylamine (Et_3N) in *N*,*N*-di-

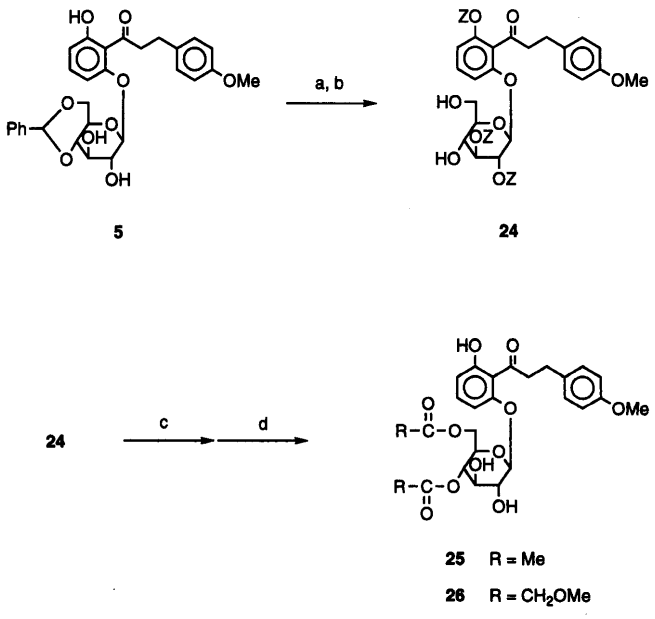


Chart 3

a) Z-Cl, *n*-Bu_4NHSO_4, 10% aq. NaOH, CH_2Cl_2; b) AcOH, H_2O; c) Ac_2O or RCOCl, pyridine; d) H_2/10% Pd–C, EtOH.

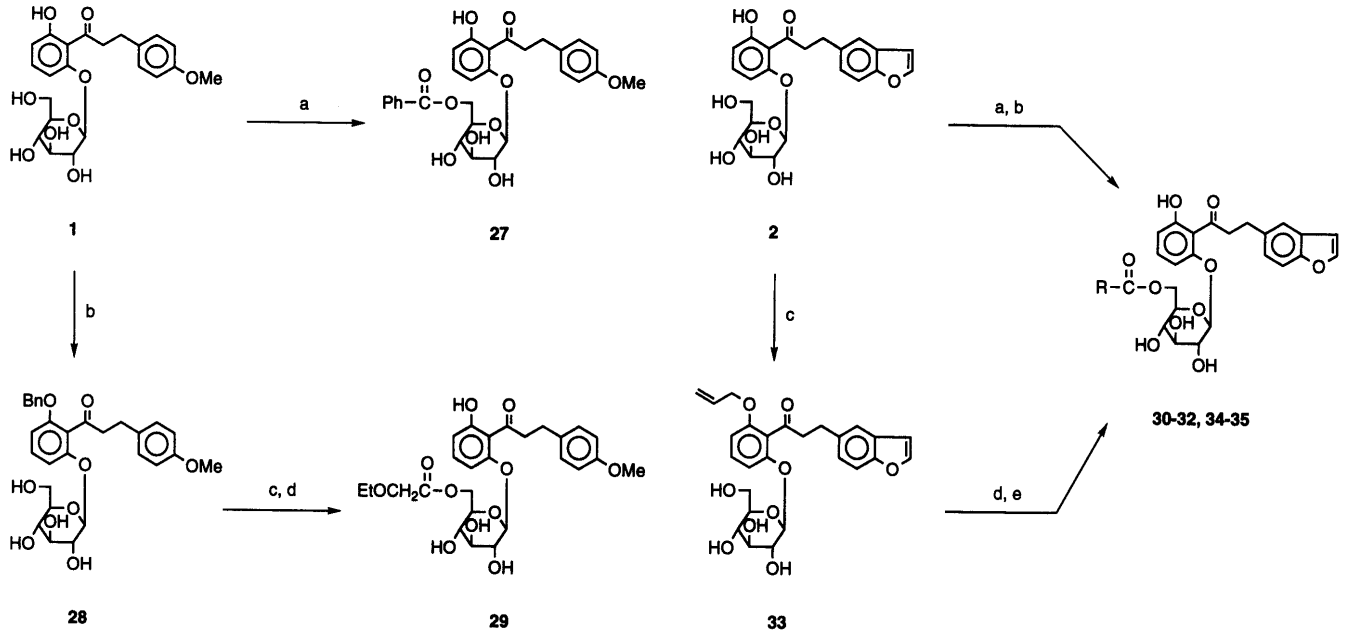


Chart 4

a) PhCOCl, pyridine; b) BnBr, K_2CO_3, acetone; c) ethoxyacetic acid, BOP–Cl, pyridine; d) H_2/10% Pd–C, EtOH.

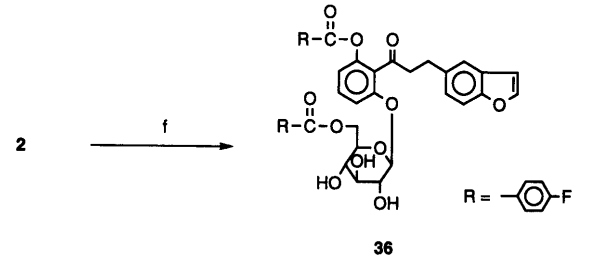


Chart 5

a) RCOCl, collidine; b) $NaHCO_3$, MeOH–THF; c) allyl bromide, K_2CO_3, acetone; d) MeOCOCl or PhNCO, collidine; e) $PdCl_2(PPh_3)_2$, HCO_2NH_4, acetonitrile, reflux; f) *p*-fluorobenzoyl chloride, Et_3N, DMA.

methylacetamide (DMA) (Chart 5).

The glucose 4-*O*-alkoxycarbonyl derivatives (**38**, **39**) and 2-*O*-acetyl derivative **41** were synthesized by the method shown in Chart 6. In the reaction of **2** with *p*-nitrophenyl chloroformate in 2,4,6-collidine, the glucose 6-*O*-*p*-nitrophenyloxycarbonyl derivative was first generated and then cyclized by heating (50 °C) to give the glucose 4,6-cyclic carbonate derivative **37** (69%). The ring-opening reaction of the cyclic carbonate moiety in **37** with *p*-TsOH in MeOH or EtOH afforded the desired 4-*O*-alkoxycarbonyl derivatives (**38**: R=Me, 46%; **39**: R=Et, 19%) and the 6-*O*-alkoxycarbonyl derivatives (**34**: R=Me, 35%; **40**: R=Et, 58%), respectively. The glucose 2-*O*-acetyl derivative **41** was obtained by deacetylation of **17** in the presence of *p*-TsOH in MeOH at 40 °C in 42% yield accompanied by the 3-*O*-acetyl derivative **42** (8%), **2** (29%), and recovered **17** (20%). The yield and the physicochemical data of compounds **30**—**32**, **34**—**39**, and **41** are listed in Table 2.

Next, the compounds having a cyclic acetal moiety at the 4,6-*O*-positions of the glucose part were prepared (Chart 7, 8). The reaction of **1** with acetaldehyde dimethylacetal in the presence of *p*-TsOH in CH_2Cl_2 gave the ethylidene derivative **43** as a single isomer. The treatment of **1** with trimethyl orthoformate followed by cleavage of the excessive orthoesters by addition of MeOH at 0 °C afforded the glucose 4,6-cyclic orthoformate **44**. Compound **44** was a diastereomeric mixture (5.4 : 1 as judged from the ^{1}H-NMR spectrum) owing to the asymmetric orthoester moiety, but these diastereomers could not be separated by silica gel chromatography. The configuration at the asymmetric center of the orthoester part of **44** was determined as follows. The acetylation of **44** gave **45** (67%) and **46** (11%). Nuclear Overhauser effect (NOE) enhancement was observed between the methine proton of the orthoformate and the axial proton at the 6-position of the glucose part in the minor product **46**, but not in the major product **45**. Therefore, the methoxy group is oriented axial in **45** and equatorial in **46**. The cyclic orthoester (**47**, **48**, and **49**) and orthocarbonate (**50**) derivatives of **2** were prepared by a similar procedure as employed for **44**. The orthoformate **47** was a 3.7 : 1 diastereomeric mixture (^{1}H-NMR spectrum), while the orthoacetate **48** and the orthobenzoate **49** were each obtained as a single diastereomer. The glucose 4,6-*O*-methylene derivative **52** was not obtained by the treatment of the triacetyl derivative **9** with dimethoxymethane in the presence of *p*-TsOH and LiBr,[9] but only the 6-*O*-methyoxymethyl derivative **51** was isolated (69%). So, compound **51** was further treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in 2,6-lutidine[10] for cyclization, and then deacetylated to afford the desired 4,6-*O*-methylene derivative **52** (47%). The yield and the physicochemical data of **43**, **44** (Table 1) and **47**—**50**, **52** (Table 2) are listed.

Finally, the glucose 6-*O*-methyl derivative **57** was synthesized by the procedure as shown in Chart 9. According to the method of Bayle and Gadelle,[11] methyl 6-deoxy-6-iodo-α-D-glucopyranoside **53**[12] was converted to the 6-*O*-methyl derivative, which was acetylated to yield **54** (42%). The reaction of bromosugar **55** with 2′,6′-dihydroxyacetophenone afforded glycoside **56** (33%) by the same method as described in the previous papers.[1,4] The condensation of **56** with benzo[*b*]furan-5-carboxaldehyde followed by catalytic hydrogenation over 10% Pt on carbon[1] gave desired **57** in 72% yield (Table 2).

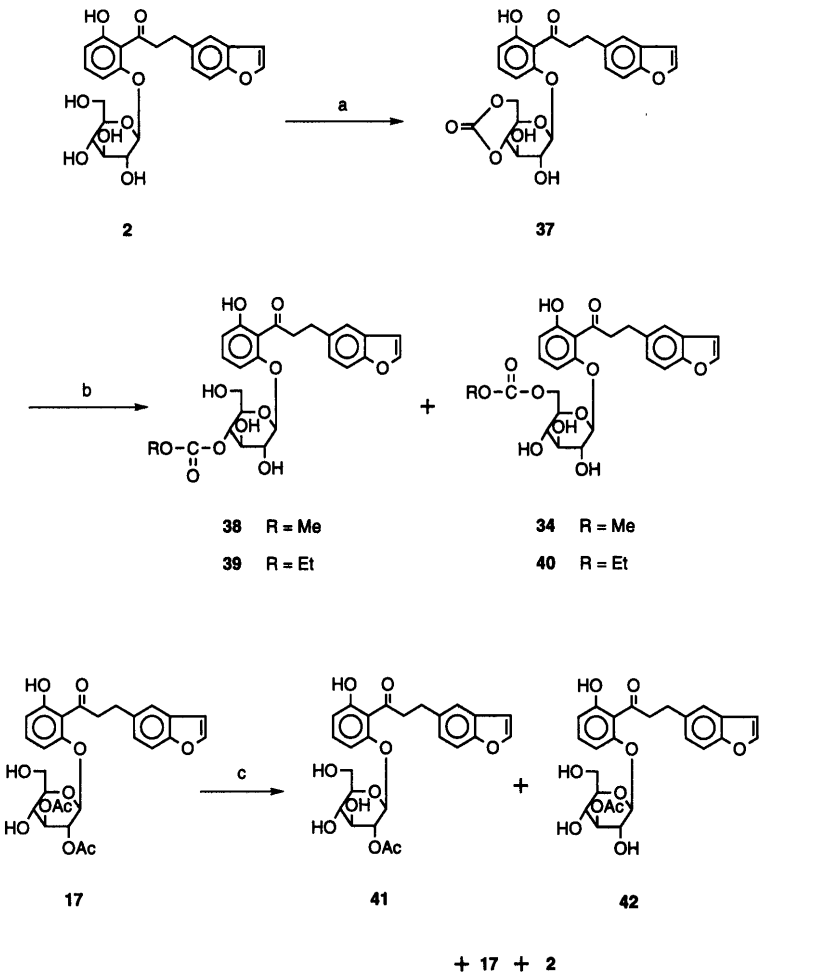


Chart 6

a) *p*-nitrophenyl chloroformate, collidine; b) ROH, *p*-TsOH; c) *p*-TsOH, MeOH.

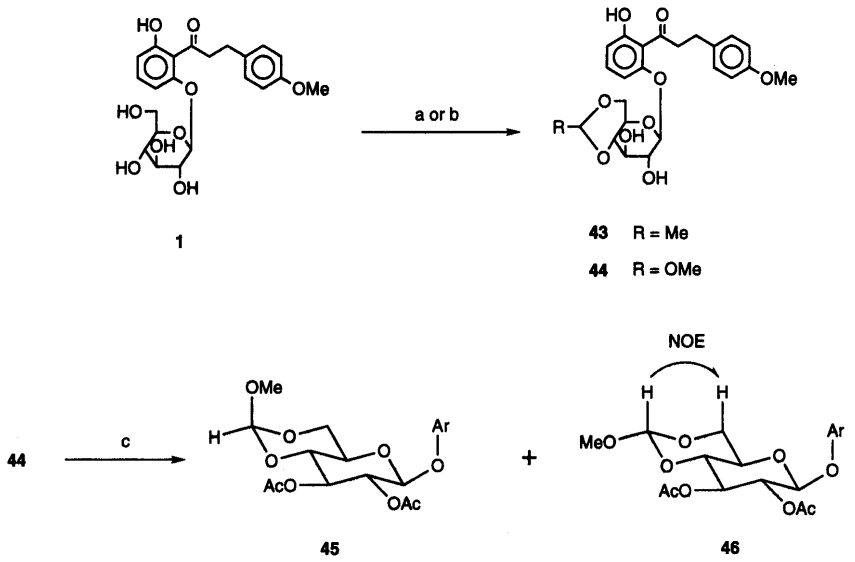


Chart 7

a) $MeCH(OMe)_2$, *p*-TsOH; b) $HC(OMe)_3$, PPTS then MeOH; c) Ac_2O, pyridine.

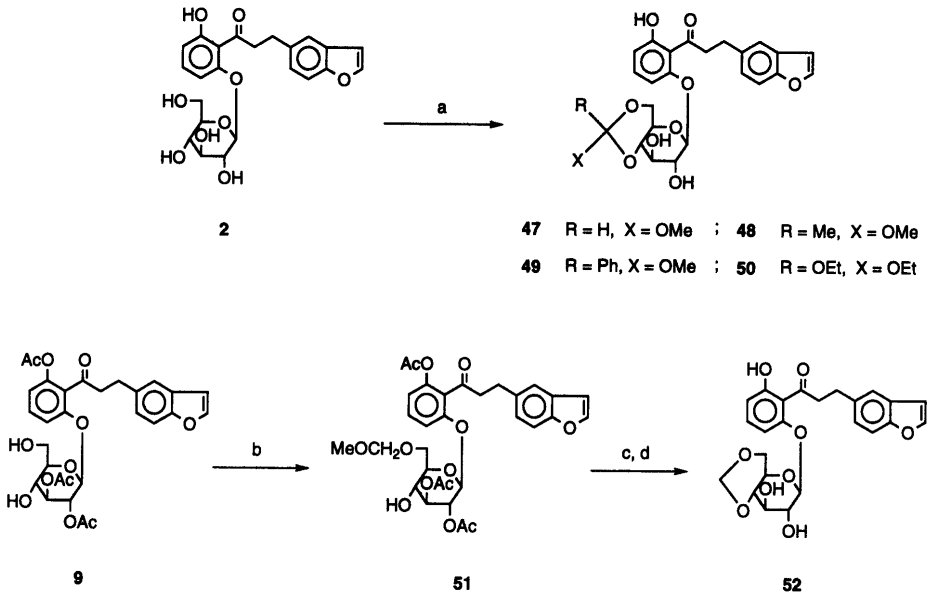


Chart 8

a) $RC(OMe)_3$ or $C(OEt)_4$, PPTS then MeOH; b) $CH_2(OMe)_2$, *p*-TsOH, LiBr, reflux; c) TMSOTf, lutidine; d) K_2CO_3, MeOH, H_2O.

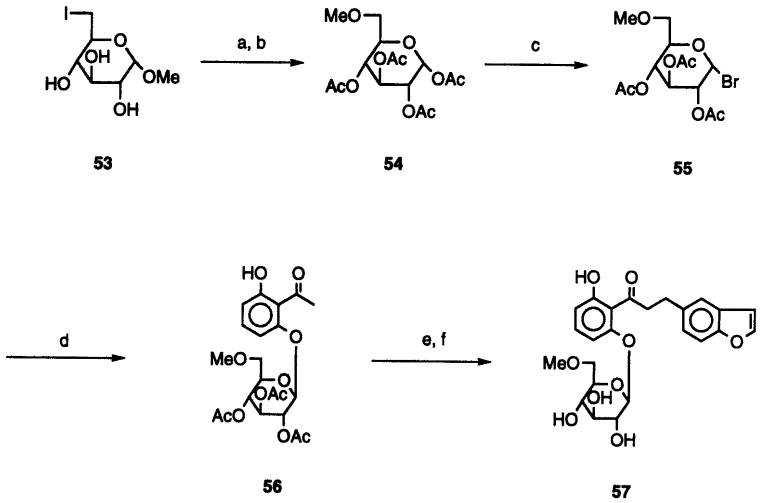


Chart 9

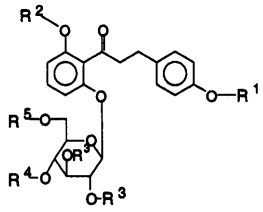
a) Cl_2, MeOH; b) Ac_2O, AcOH, H_2SO_4; c) HBr, AcOH; d) 2′,6′-dihydroxyacetophenone, $CdCO_3$, toluene, reflux; e) benzo[*b*]furan-5-carboxaldehyde, 50% aq. KOH, EtOH; f) H_2/10% Pt–C, DMAP, EtOH–H_2O.

Biological Results and Discussion

The effect of the compounds thus prepared on urinary glucose excretion[1,4] was investigated in rats and the results are summarized in Tables 1 and 2. First, we examined the derivatives of compound **1** (Table 1). The pentaacetyl derivative **4** was almost inactive and the triacetyl derivative **8** showed comparable activity to **1** by *p.o.* These results suggest that excessive acylation at the OH groups of the glucose moiety is undesirable for potent activity. However, the 2,3-*O*-diacyl derivatives, such as diacetyl (**10**), dimethoxyacetyl (**13**), and diethoxyacetyl (**14**), showed a more potent effect than **1** by *p.o.* Even in this case, when the acyl groups were large, the activity was reduced (**11**, **12**, **15**). The diethoxycarbonyl derivative **16** showed moderate effect by *p.o.*, but was inactive by i.p. Probably compound **16** is hydrolyzed to the active compound **1** in the digestive tract but not after absorption into the body. The 4,6-*O*-dimethoxyacetyl derivative (**26**) and the 6-*O*-acyl derivatives (**27**, **29**) exhibited considerable activity, but not so potent as **10**, **13**, and **14**. The 4,6-*O*-ethylidene derivative **43** was inactive, while the 4,6-cyclic orthoformate **44** showed considerable activity by *p.o.* It is likely that compound **44** is converted to compound **1** after administration, but **43** is not converted. In contrast, the derivatives of compound **3** (**22**, **23**) showed only weak activity (Table 1).

Next, we examined the derivatives of compound **2** (Table 2). The triacetyl (**9**) and the 2,3-*O*-diacetyl (**17**) derivatives exhibited markedly strong effects as observed in the derivatives of **1**. However, being different from the derivatives of **1**, the diethoxyacetyl (**18**) and the diethoxycarbonyl (**19**) derivatives did not increase the activity. The 6-*O*-acyl derivatives were all effective. Among them, the 6-*O*-methoxycarbonyl derivative **34** was the most active compound. The carbamoyl derivative **35** was inactive. Presumably the carbamoyl group of **35** would not be removed metabolically. Compound **36**, having another acyl group on the phenolic OH, showed a weaker effect than that of the phenol-free compound **32**. The

Table 1. Physical and Biological Properties of the Modified Compounds of **1** and **3**



No.	R^1	R^2	R^3	R^4	R^5	Yield[a] (%)	mp (°C) (Recryst. solvent)	Formula	*Anal.* Calcd (Found) C	H	Urinary glucose excretion[e] (mg/24 h) *p.o.* (100 mg/kg)	i.p. (10 mg/kg)
1	Me	H	H	H	H						340±18	204± 8
3	H	H	H	H	H						60± 9	329± 7
4	Me	Ac	Ac	Ac	Ac	82	Amorphous	$C_{32}H_{36}O_{14}$ $\cdot 1/4H_2O$	59.21 (59.12	5.67 5.57)	14± 3	1± 1
8	Me	Ac	Ac	H	H	86	Amorphous	$C_{28}H_{32}O_{12}$ $\cdot 1/4H_2O$	59.52 (59.40	5.80 5.81)	319±111	NT
10	Me	H	Ac	H	H	62	136—138 (Et_2O–iso-Pr_2O)	$C_{26}H_{30}O_{11}$	60.23 (60.39	5.83 5.82)	406±70	33±10
11	Me	H	$CH_3CH_2CH_2CO$–	H	H	47	126—127 (iso-Pr_2O–hexane)	$C_{30}H_{38}O_{11}$	62.71 (62.61	6.67 6.64)	46±21	4± 1
12	Me	H	PhCO–	H	H	40	Amorphous	$C_{36}H_{34}O_{11}$ $\cdot 1/4H_2O$	66.81 (66.84	5.37 5.64)	132±31	4± 1
13	Me	H	$MeOCH_2CO$–	H	H	70	103—105 (iso-Pr_2O)	$C_{28}H_{34}O_{13}$ $\cdot 1/4H_2O$	57.68 (57.86	5.96 6.05)	376±34	162±18
14	Me	H	$EtOCH_2CO$–	H	H	54	96—99 (EtOH–iso-Pr_2O)	$C_{30}H_{38}O_{13}$	59.40 (59.31	6.31 6.30)	417±17	100±20
15	Me	H	$PhOCH_2CO$–	H	H	61	Amorphous	$C_{38}H_{38}O_{13}$ $\cdot 1/2H_2O$	64.13 (64.24	5.52 5.63)	12± 4	30±10
16	Me	H	EtOCO–	H	H	73	118—119.5 (MeOH–iso-Pr_2O)	$C_{28}H_{34}O_{13}$	58.13 (58.17	5.92 5.95)	255±36	3± 2
22	Ac	H	Ac	H	H	28	127—129 (iso-Pr_2O)	$C_{27}H_{30}O_{12}$	59.34 (59.37	5.53 5.54)	67±19	59± 8
23	H	H	Ac	H	H	38	141.5—143 (Et_2O–iso-Pr_2O)	$C_{25}H_{28}O_{11}$ $\cdot 1/2H_2O$	58.48 (58.75	5.69 5.59)	10± 5	25± 2
25	Me	H	H	Ac	Ac	71[b]	108—112 (iso-Pr_2O)	$C_{26}H_{30}O_{11}$ $\cdot H_2O$	58.20 (58.42	6.01 5.97)	61±31	NT
26	Me	H	H	$MeOCH_2CO$–	$MeOCH_2CO$–	74[b]	54— (EtOH–Et_2O)	$C_{28}H_{34}O_{13}$ $\cdot 1/2H_2O$	57.24 (57.28	6.00 6.16)	172±62	NT
27	Me	H	H	H	PhCO–	49	Amorphous	$C_{29}H_{30}O_{10}$ $\cdot 1/2H_2O$	63.61 (63.64	5.71 5.71)	214±44	7± 1
29	Me	H	H	H	$EtOCH_2CO$–	55[c]	Amorphous	$C_{26}H_{32}O_{11}$[d]			256±11	NT
43	Me	H	H	——CH(Me)——		85	104—107 (EtOH–H_2O)	$C_{24}H_{28}O_9$ $\cdot 3/4H_2O$	60.82 (60.64	6.27 6.42)	1± 1	1± 1
44	Me	H	H	——CH(OMe)——		73	Amorphous	$C_{24}H_{28}O_{10}$[d]			206±10	NT

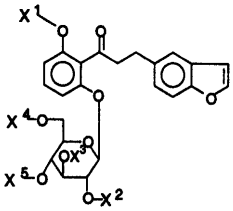
a) Yields are based on compound **1** or the benzylidene derivatives **5** or **7**. *b*) Yields are based on **24**. *c*) Yield is based on **28**. *d*) HR-MS were measured (see experimental section). *e*) See experimental section. NT: not tested.

4-*O*-methoxycarbonyl derivative **38** was also effective, whereas the activity of the 4-*O*-ethoxycarbonyl derivative **39** was weak. The 2-*O*-acetyl derivative **41** showed the strongest activity among all compounds prepared. Among the 4,6-cyclic carbonate and orthoesters (**37**, **47**—**50**), the orthoacetate **48** showed strong activity. On the other hand, the 4,6-*O*-methylene derivative **52** was inactive. The 6-*O*-methyl derivative **57** was also inactive. This result suggests that **57** is not recognized by SGLT and is not converted to the active compound **2** in the body.

Finally, we examined the stability of the parent compound **2** and its modified compounds against β-glucosidase (Table 3). Judging from the amount of the generated aglycon (2-(benzo[*b*]furan-5-yl)-2′,6′-dihydroxypropiophenone), when **2** was incubated in a dog jejunum homogenate at 37 °C for 15 min, about 60% of **2** was hydrolyzed at the glycosyl bond. On the other hand, the glucose 6-*O*-methoxycarbonyl (**34**), 4-*O*-methoxycarbonyl (**38**), and 2-*O*-acetyl (**41**) derivatives were hardly hydrolyzed under the same experimental conditions. These results reveal that the modification of the 2-, 4-, or 6-OH group on the glucose ring of the parent compound **2** increases the stability against β-glucosidase, which correlates with the enhancement of the oral activity in the compounds **34**, **38**, and **41** (Table 2).

Although compound **41** was 2.7 times more potent than **2** on urinary glucose excretion by *p.o.* (Table 2), **41** showed only weak SGLT-inhibitory activity (9.1%) at 10 μM *in vitro*. In contrast, the parent compound **2** showed 94.9% inhibitory effect *in vitro*. Therefore, the present compounds modified at the glucose OH groups should exhibit good oral activity after their metabolic hydrolysis to the parent compounds **1**, **2**, and **3** in the body. So it is expected that these prodrugs would be

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



No.	X^1	X^2	X^3	X^4	X^5	Yield[a] (%)	mp (°C) (Recryst. solvent)	Formula	*Anal* Calcd (Found) C	H	Urinary glucose excretion[g] (mg/24 h) *p.o.* (100 mg/kg)
2	H	H	H	H	H						591±105
9	Ac	Ac	Ac	H	H	79	Amorphous	$C_{29}H_{30}O_{12}\cdot 1/2H_2O$	60.10 (60.07)	5.39 5.31)	1282±137
17	H	Ac	Ac	H	H	65	127—129 (Et_2O)	$C_{27}H_{28}O_{11}$	61.36 (61.37)	5.34 5.36)	1199±102
18	H	$EtOCH_2CO$–	$EtOCH_2CO$–	H	H	71	93—97 (Et_2O–hexane)	$C_{31}H_{36}O_{13}\cdot 1/2H_2O$	59.51 (59.45)	5.96 5.92)	583± 18
19	H	EtOCO–	EtOCO–	H	H	48	65— (Et_2O–iso-Pr_2O)	$C_{29}H_{32}O_{13}\cdot 1/2H_2O$	58.29 (58.01)	5.57 5.65)	18± 8
30	H	H	H	Ac	H	30	Amorphous	$C_{25}H_{26}O_{10}\cdot 1/4H_2O$	61.16 (61.24)	5.44 5.70)	728± 88
31	H	H	H	$EtOCH_2CO$–	H	36	Amorphous	$C_{27}H_{30}O_{11}$[f]			688± 48
32	H	H	H	*p*-F–C_6H_4CO–	H	55	68—71 (EtOH–H_2O)	$C_{30}H_{27}FO_{10}\cdot 3/2H_2O$	60.70 (60.99)	5.09 4.94)	544± 35
34	H	H	H	MeOCO–	H	35	55— (MeOH–H_2O)	$C_{25}H_{26}O_{11}\cdot 3/4H_2O$	58.19 (58.09)	5.37 5.32)	929±110
35	H	H	H	PhNHCO–	H	68	Amorphous	$C_{30}H_{29}NO_{10}$[f]			0± 0[h]
36	*p*-F–C_6H_4CO–	H	H	*p*-F–C_6H_4CO–	H	54	Amorphous	$C_{37}H_{30}F_2O_{11}\cdot 3/4H_2O$	63.29 (63.23)	4.52 4.51)	224± 5
38	H	H	H	H	MeOCO–	46[b]	Amorphous	$C_{25}H_{26}O_{11}$[f]			853±172
39	H	H	H	H	EtOCO–	19[b]	104— (EtOH-H_2O)	$C_{26}H_{28}O_{11}\cdot 1/4H_2O$	59.94 (59.87)	5.51 5.37)	195± 60[h]
41	H	Ac	H	H	H	42[c]	152—156 (EtOH–H_2O)	$C_{25}H_{26}O_{10}\cdot 1/2H_2O$	60.60 (60.36)	5.49 5.40)	1581±129
37	H	H	H	——CO——		69	70— (Et_2O–iso-Pr_2O)	$C_{24}H_{22}O_{10}\cdot 1/2H_2O$	60.13 (60.28)	4.84 5.13)	487± 48
47	H	H	H	——CH(OMe)——		44	Amorphous	$C_{25}H_{26}O_{10}$[f]			501±237
48	H	H	H	——CMe(OMe)——		79	Amorphous	$C_{26}H_{28}O_{10}$[f]			858± 51
49	H	H	H	——CPh(OMe)——		85	Amorphous	$C_{31}H_{30}O_{10}$[f]			387±103
50	H	H	H	——$C(OEt)_2$——		62	Amorphous	$C_{28}H_{32}O_{11}$[f]			335± 43
52	H	H	H	——CH_2——		32[d]	162.5—165.5 (EtOH–H_2O)	$C_{24}H_{24}O_9\cdot 1/4H_2O$	62.54 (62.69)	5.36 5.26)	1± 1[h]
57	H	H	H	Me	H	72[e]	Amorphous	$C_{24}H_{26}O_9$[f]			2± 1[h]

a) Yields are based on compound **2** or the protected derivatives **6** or **33**. *b*) Yields are based on **37**. *c*) Yield is based on **17**. *d*) Yield is based on **9**. *e*) Yield is based on **56**. *f*) HR-MS were measured (see experimental section). *g*) See experimental section. *h*) Urinary glucose level was measured after single administration of the test compound. In this condition, the amount of glucose was 334±32 mg/24 h when compound **2** was administered.

Table 3. Hydrolysis of the Modified Compounds by Incubation in Dog Jejunum Homogenate[a]

Compound	Amount of the Aglycon (nmol/ml)
2	30.40
34	0.47
38	0.93
41	0.95

a) After incubation in dog jejunum homogenate at 37 °C for 15 min (the initial concentration of the compounds: 50 nmol/ml), the concentration of the aglycon was measured.

more potent than the parent compounds in diabetic animal models.

Further investigations on the compounds having strong activity on urinary glucose excretion are ongoing.

Experimental

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. Microanalyses were performed on a Perkin-Elmer 2400 C, H, N analyzer.

6′-Acetoxy-2′-hydroxy-4-methoxydihydrochalcone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-β-D-glucopyranoside) (4) A mixture of 2′,6′-dihydroxy-4-methoxydihydrochalcone 2′-*O*-β-D-glucopyranoside **1**[4] (1.00 g, 2.30 mmol), Ac_2O (5 ml), and pyridine (20 ml) was stirred at room temperature for 2 d. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in AcOEt. The solution was washed with 10% HCl, water and brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography on silica gel ($CHCl_3$–AcOEt (9 : 1)) to give **4** (1.21 g, 82%) as an amorphous powder. IR (Nujol): 1750 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.94 (3H, s), 1.97 (3H, s), 2.01 (6H, s), 2.06 (3H, s), 2.75 (2H, m), 2.89 (2H, m), 3.71 (3H, s), 4.06—4.31 (3H, m), 5.01 (1H, dd, *J*=9.3, 9.8 Hz), 5.06 (1H, dd, *J*=8.2, 9.8 Hz), 5.41 (1H, dd, *J*=9.3, 9.8 Hz), 5.63 (1H, d, *J*=7.8 Hz), 6.84 (2H, ddd, *J*=2.0, 2.9, 8.8 Hz), 6.93 (1H, d, *J*=8.3 Hz), 7.10 (1H, d, *J*=7.8 Hz), 7.14 (2H, d, *J*=8.7 Hz), 7.48 (1H, t, *J*=8.3 Hz). FAB-MS *m/z*: 667 $(M+Na)^+$.

2′,6′-Dihydroxy-4-methoxydihydrochalcone 2′-*O*-(4, 6-*O*-Benzylidene-β-D-glucopyranoside) (5) A mixture of **1** (5.00 g, 11.51 mmol), benzaldehyde dimethylacetal (2.63 g, 17.27 mmol), *p*-TsOH·H_2O (220 mg, 1.15 mmol), CH_2Cl_2 (200 ml), and dioxane (40 ml) was stirred at room temperature for 15 h. The reaction mixture was washed with water saturated with $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed. The residue was purified by column chromatography on silica gel ($CHCl_3$–acetone (9 : 1)) and triturated in iso-Pr_2O to give **5** (5.71 g, 95%) as a white powder, mp 126—130 °C. IR (Nujol): 3440, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.84 (2H, t, *J*=7.6 Hz), 3.19 (2H, t, *J*=7.6 Hz), 3.3—3.7 (5H, m), 3.72 (3H, s), 4.21 (1H, d, *J*=4.9 Hz), 5.16 (1H, d, *J*=7.8 Hz), 5.48 (1H, d, *J*=5.4 Hz), 5.59 (1H, d, *J*=5.4 Hz), 5.60 (1H, s), 6.57 (1H, d, *J*=7.8 Hz), 6.72 (1H, d, *J*=8.3 Hz), 6.84 (2H, ddd, *J*=2.0, 2.9, 8.8 Hz), 7.17 (2H, ddd, *J*=2.0, 2.7, 8.3 Hz), 7.25 (1H, t, *J*=8.3 Hz), 7.40 (5H, m), 10.85 (1H, s). FAB-MS *m/z*: 523 $(M+H)^+$.

The benzylidene derivatives **6** and **7** were prepared from compounds **2**[1] and **3**[4] by the same procedure as described for the synthesis of **5**.

6: Yield 92% as a white powder, mp 114—118 °C. IR (Nujol): 3400, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.00 (2H, t, *J*=7.5 Hz), 3.2—3.7 (7H, m), 4.20 (1H, m), 5.17 (1H, d, *J*=7.7 Hz), 5.50 (1H, d, *J*=5.2 Hz), 5.58 (1H, s), 5.62 (1H, d, *J*=5.7 Hz), 6.57 (1H, d, *J*=7.7 Hz), 6.72 (1H, d, *J*=8.1 Hz), 6.90 (2H, dd, *J*=1.0, 2.2 Hz), 7.21 (1H, dd, *J*=1.8, 8.4 Hz), 7.24 (1H, t, *J*=8.3 Hz), 7.35—7.55 (7H, m), 7.94 (1H, d, *J*=2.2 Hz), 10.73 (1H, s). FAB-MS *m/z*: 555 $(M+Na)^+$.

7: Yield 60% as a white powder, mp 77 °C–gradually melted. IR (Nujol): 3360, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.78 (2H, t, *J*=7.3 Hz), 3.16 (2H, t, *J*=7.6 Hz), 3.3—3.7 (5H, m), 4.20 (1H, d, *J*=4.9 Hz), 5.16 (1H, d, *J*=7.8 Hz), 5.48 (1H, d, *J*=4.9 Hz), 5.58 (1H, d, *J*=4.9 Hz), 5.60 (1H, s), 6.57 (1H, d, *J*=7.8 Hz), 6.67 (2H, d, *J*=8.3 Hz), 6.71 (1H, d, *J*=8.3 Hz), 7.04 (2H, d, *J*=8.3 Hz), 7.25 (1H, t, *J*=8.3 Hz), 7.36—7.49 (5H, m), 9.12 (1H, s), 10.87 (1H, s). FAB-MS *m/z*: 531 $(M+Na)^+$.

6′-Acetoxy-2′-hydroxy-4-methoxydihydrochalcone 2′-*O*-(2,3-*O*-Diacetyl-β-D-glucopyranoside) (8) A mixture of **5** (1.86 g, 3.56 mmol), Ac_2O (10 ml), and pyridine (40 ml) was stirred at room temperature for 3 h and then the reaction mixture was evaporated *in vacuo*. The residue was dissolved in AcOH (24 ml)–H_2O (3 ml) and the whole was stirred at 70 °C for 2 h. The reaction mixture was concentrated and the residue was chromatographed on silica gel ($CHCl_3$–MeOH (20 : 1)) to give **8** (1.69 g, 85%) as an amorphous powder. IR (Nujol): 3440, 1750, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.89 (3H, s), 2.00 (3H, s), 2.06 (3H, s), 2.77 (2H, m), 2.88 (2H, m), 3.4—3.8 (4H, m), 3.71 (3H, s), 4.76 (1H, t, *J*=5.9 Hz), 4.88 (1H, dd, *J*=7.8, 9.8 Hz), 5.11 (1H, dd, *J*=9.3, 9.8 Hz), 5.50 (1H, d, *J*=7.8 Hz), 5.59 (1H, d, *J*=5.9 Hz), 6.84 (2H, ddd, *J*=2.0, 2.9, 8.3 Hz), 6.88 (1H, d, *J*=8.3 Hz), 7.13 (2H, ddd, *J*=2.0, 2.9, 8.3 Hz), 7.15 (1H, d, *J*=7.8 Hz), 7.44 (1H, t, *J*=8.3 Hz). FAB-MS *m/z*: 583 $(M+Na)^+$.

Compound **9** was prepared from **6** by the same procedure as described above.

2′,6′-Dihydroxy-4-methoxydihydrochalcone 2′-*O*-(2,3-*O*-Diacetyl-β-D-glucopyranoside) (10) A mixture of **5** (847 mg, 1.62 mmol), Ac_2O (5 ml), and pyridine (20 ml) was stirred at room temperature for 3 h, and then the reaction mixture was evaporated *in vacuo*. The residue was dissolved in MeOH (20 ml) and $NaHCO_3$ (272 mg, 3.24 mmol) was added to the solution, and then the whole was stirred at room temperature for 4 h and at 40 °C for 30 min. The reaction mixture was diluted with AcOEt, washed with water, and dried over $MgSO_4$. The solvent was removed and the residue was dissolved in AcOH (24 ml)–H_2O (3 ml), and the whole was stirred at 70 °C for 2 h. The reaction mixture was concentrated and the residue was chromatographed on silica gel ($CHCl_3$–MeOH (20 : 1)) followed by trituration in Et_2O–iso-Pr_2O to give **10** (512 mg, 61%). IR (Nujol): 3500, 3400, 1750, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.92 (3H, s), 2.00 (3H, s), 2.76 (2H, m), 2.90 (2H, m), 3.4—3.8 (4H, m), 3.71 (3H, s), 4.73 (1H, t, *J*=5.6 Hz), 4.85 (1H, dd, *J*=7.8, 9.8 Hz), 5.09 (1H, dd, *J*=8.8, 9.8 Hz), 5.35 (1H, d, *J*=7.8 Hz), 5.56 (1H, d, *J*=5.4 Hz), 6.57 (1H, d, *J*=7.8 Hz), 6.67 (1H, d, *J*=8.3 Hz), 6.83 (2H, ddd, *J*=2.0, 2.9, 8.8 Hz), 7.13 (2H, ddd, *J*=2.4, 2.9, 8.8 Hz), 7.19 (1H, t, *J*=8.3 Hz), 10.26 (1H, s). FAB-MS *m/z*: 519 $(M+H)^+$.

Compounds **11**—**16** were prepared by the same procedure as described above. According to the same manner, compounds **17**—**19** were also prepared from **6**. Physical data for these compounds are listed in Tables 1 and 2.

Synthesis of 20 and 21 A mixture of **7** (509 mg, 1 mmol), Ac_2O (5 ml), and pyridine (20 ml) was stirred at room temperature for 2.5 h, and the reaction mixture was evaporated *in vacuo*. The residue was dissolved in MeOH (10 ml) and $NaHCO_3$ (420 mg, 5 mmol) was added to the solution, and the whole was stirred at 40 °C for 1.5 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 ($CHCl_3$–acetone (19 : 1)) to give **20** (230 mg, 36%) and **21** (271 mg, 46%).

20: IR (Nujol): 1750, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.97 (3H, s), 2.01 (3H, s), 2.25 (3H, s), 2.86 (2H, m), 2.96 (2H, m), 3.6—4.0 (3H, m), 4.31 (1H, dd, *J*=3.9, 9.8 Hz), 5.05 (1H, dd, *J*=8.1, 9.5 Hz), 5.41 (1H, t, *J*=9.3 Hz), 5.58 (1H, d, *J*=7.8 Hz), 5.64 (1H, s), 6.60 (1H, d, *J*=7.8 Hz), 6.68 (1H, d, *J*=8.3 Hz), 7.03 (2H, ddd, *J*=2.0, 2.9, 8.3 Hz), 7.21 (1H, t, *J*=8.3 Hz), 7.27 (2H, ddd, *J*=2.0, 2.9, 8.3 Hz), 7.38 (5H, s), 10.27 (1H, s). FAB-MS *m/z*: 657 $(M+Na)^+$.

21: IR (Nujol): 3400, 1750, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.96 (3H, s), 2.01 (3H, s), 2.72 (2H, m), 2.88 (2H, m), 3.7—4.0 (3H, m), 4.31 (1H, dd, *J*=4.4, 10.3 Hz), 5.04 (1H, dd, *J*=7.8, 9.3 Hz), 5.41 (1H, dd, *J*=9.3, 9.8 Hz), 5.57 (1H, d, *J*=7.8 Hz), 5.64 (1H, s), 6.59 (1H, d, *J*=7.8 Hz), 6.67 (3H, d, *J*=8.3 Hz), 7.01 (2H, d, *J*=8.8 Hz), 7.20 (1H, t, *J*=8.3 Hz), 7.38 (5H, s), 9.13 (1H, s), 10.24 (1H, s). FAB-MS *m/z*: 615 $(M+Na)^+$.

4-Acetoxy-2′, 6′-dihydroxydihydrochalcone 2′-*O*-(2,3-*O*-Diacetyl-β-D-glucopyranoside) (22) Compound **20** (700 mg, 1.10 mmol) was dissolved in AcOH (16 ml)–H_2O (2 ml), and the whole was stirred at 70 °C for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel ($CHCl_3$–MeOH (9 : 1)) followed by trituration in iso-Pr_2O to give **22** (410 mg, 68%). IR (Nujol): 3520, 3380, 1750, 1720, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.91 (3H, s), 1.99 (3H, s), 2.24 (3H, s), 2.85 (2H, m), 2.95 (2H, m), 3.4—3.8 (4H, m), 4.73 (1H, t, *J*=5.4 Hz), 4.86 (1H, dd, *J*=8.3, 9.8 Hz), 5.09 (1H, dd, *J*=8.8, 9.8 Hz), 5.36 (1H, d, *J*=7.8 Hz), 5.56 (1H, d, *J*=5.4 Hz), 6.57 (1H, d, *J*=7.8 Hz), 6.67 (1H, d, *J*=8.3 Hz), 7.01 (2H, ddd, *J*=1.7, 2.7, 8.3 Hz), 7.19 (1H, t, *J*=8.3 Hz), 7.26 (2H, dd, *J*=2.0, 8.3 Hz), 10.27 (1H, s). FAB-MS *m/z*: 569 $(M+Na)^+$.

Compound **23** was prepared from **21** by the same procedure as above.

6′-Benzyloxycarbonyloxy-2′-hydroxy-4-methoxydihydrochalcone 2′-*O*-(2,3-*O*-Dibenzyloxycarbonyl-β-D-glucopyranoside) (24) Benzyl chloroformate (768 mg, 4.5 mmol) was added dropwise to a mixture of **5** (523 mg, 1 mmol), tetrabutylammonium hydrogen sulfate (68 mg, 0.2 mmol), 10% aq. NaOH (5 ml), and CH_2Cl_2 (10 ml) under ice-cooling and stirred for 1 h. The organic layer was separated, dried over $MgSO_4$, and evaporated. The resultant residue was dissolved in AcOH (8 ml)–H_2O (1 ml) and the whole was stirred at 70 °C for 1.5 h. The reaction mixture was concentrated and the residue was chromatographed on silica gel ($CHCl_3$–MeOH (19 : 1)) to give **24** (609 mg, 73%). IR (Nujol): 3500, 1760, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.6—3.1 (4H, m), 3.4—3.8 (4H, m), 3.65 (3H, s), 4.77 (1H, t, *J*=5.2 Hz), 4.78 (1H, dd, *J*=7.9, 9.8 Hz), 4.9—5.2 (5H, m), 5.23 (2H, s), 5.64 (1H, d, *J*=7.8 Hz), 5.80 (1H, d, *J*=6.0 Hz), 6.78 (2H, dd, *J*=2.2, 8.8 Hz), 7.06 (1H, d, *J*=8.4 Hz), 7.09 (2H, d, *J*=8.8 Hz), 7.18 (1H, d, *J*=8.4 Hz), 7.2—7.4 (15H, m), 7.49 (1H, t, *J*=8.3 Hz). FAB-MS *m/z*: 859 $(M+Na)^+$.

2′,6′-Dihydroxy-4-methoxydihydrochalcone 2′-*O*-(4,6-*O*-Diacetyl-β-D-glucopyranoside) (25) A mixture of **24** (569 mg, 1 mmol), Ac_2O (1 ml), and pyridine (5 ml) was stirred at room temperature for 2 h, and the reaction mixture was evaporated *in vacuo*. The residue was dissolved in EtOH (5 ml)–AcOEt (5 ml) and hydrogenated over 10% Pd–C (200 mg) at room temperature for 1.5 h. The catalyst was removed by filtration and evaporated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH (9 : 1)) followed by trituration in iso-Pr_2O to give **25** (251 mg, 71%). IR (Nujol): 3550, 3410, 3320, 1740, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.94 (3H, s), 2.05 (3H, s), 2.83 (2H, t, *J*=7.1 Hz), 3.18 (2H, m), 3.32 (1H, m), 3.53 (1H, m), 3.71 (3H, s), 3.90 (1H, m), 3.96 (1H, dd, *J*=2.2, 12.4 Hz), 4.09 (1H, dd, *J*=5.7, 12.0 Hz), 4.69 (1H, dd, *J*=9.5, 9.8 Hz), 5.08 (1H, d, *J*=7.8 Hz), 5.47 (1H, d, *J*=5.7 Hz), 5.58 (1H, d, *J*=5.6 Hz), 6.57 (1H, d, *J*=8.1 Hz), 6.66 (1H d, *J*=8.1 Hz), 6.82 (2H, ddd, *J*=2.1, 3.0, 8.7 Hz), 7.16 (2H, ddd, *J*=2.0, 3.0, 8.6 Hz), 7.24 (1H, t, *J*=8.3 Hz), 10.82 (1H s). FAB-MS *m/z*: 519 $(M+H)^+$.

Compound **26** was prepared by the same procedure as described above.

2′,6′-Dihydroxy-4-methoxydihydrochalcone 2′-*O*-(6-*O*-Benzoyl-β-D-glucopyranoside) (27) Benzoyl chloride (0.46 g, 3.3 mmol) was added dropwise to a solution of **1** (1.30 g, 3 mmol) in pyridine (12 ml) under ice-cooling and the whole was stirred at room temperature. After 1 h, additional benzoyl chloride (0.46 g, 3.3 mmol) was added to the reaction mixture and the whole was stirred at room temperature for 30 min. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel ($CHCl_3$–MeOH (10 : 1)) followed by trituration in iso-Pr_2O to give **27** (0.79 g, 49%). IR (Nujol): 3600—3200, 1720, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.7—2.8 (2H, m), 3.1—3.4 (5H, m), 3.70 (3H, s), 3.71 (1H, m), 4.27 (1H, dd, J=7.7, 11.7 Hz), 4.60 (1H, d, J=10.3 Hz), 5.01 (1H, d, J=6.8 Hz), 5.26 (1H, d, J=4.4 Hz), 5.36 (1H, d, J=4.9 Hz), 5.40 (1H, d, J=4.9 Hz), 6.52 (1H, d, J=8.3 Hz), 6.68 (1H, d, J=8.3 Hz), 6.79 (2H, d, J=8.8 Hz), 7.05 (1H, m), 7.13 (2H, d, J=8.8 Hz), 7.5—7.7 (3H, m), 7.95 (2H, dd, J=1.5, 6.8 Hz), 10.86 (1H, s). FAB-MS *m/z*: 561 $(M+Na)^+$.

6′-Benzyloxy-2′-hydroxy-4-methoxydihydrochalcone 2′-*O*-β-D-Glucopyranoside (28) A mixture of **1** (9.22 g, 21, 22 mmol), benzyl bromide (4.36 g, 25.46 mmol), K_2CO_3 (14.64 g, 106.10 mmol), and acetone (50 ml) was heated under reflux for 2.5 h. The reaction mixture was diluted with AcOEt and filtered through a plug of Celite. The filtrate was washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH (9 : 1)) followed by trituration in AcOEt–iso-Pr_2O to give **28** (8.62 g, 77%) as a white powder, mp 137.5—139 °C. IR (Nujol): 3480, 3240, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.79 (2H, t, J=7.7 Hz), 2.9—3.4 (6H, m), 3.45 (1H, m), 3.69 (3H s), 3.70 (1H, m), 4.55 (1H, t, J=5.7 Hz), 4.87 (1H, d, J=7.6 Hz), 5.01 (1H, d, J=5.2 Hz), 5.06 (1H, d, J=4.9 Hz), 5.10 (2H, s), 5.20 (1H, d, J=5.5 Hz), 6.76 (2H, dd, J=2.1, 8.7 Hz), 6.82 (2H, d, J=8.5 Hz), 7.09 (2H, dd, J=2.0, 8.7 Hz), 7.28 (1H, t, J=8.4 Hz), 7.35 (5H, m). FAB-MS *m/z*: 547 $(M+Na)^+$.

2′,6′-Dihydroxy-4-methoxydihydrochalcone 2′-*O*-(6-*O*-Ethoxyaceyl-β-D-glucopyranoside) (29) BOP-Cl (636 mg, 2.5 mmol) was added to a solution of **28** (525 mg, 1 mmol) and ethoxyacetic acid (135 mg, 1.3 mmol) in pyridine (30 ml) and the whole was stirred at room temperature for 13.5 h. Water saturated with $NaHCO_3$ and AcOEt were added to the reaction mixture. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH (19 : 1)) to give the acylated product (360 mg). This was dissolved in EtOH (10 ml) and hydrogenated over 10% Pd–C (150 mg) at room temperature for 3 h. The catalyst was removed by filtration and the filtrate was evaporated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH (19 : 1)) to give **29** (285 mg, 55%) as an oil. IR (Neat): 3440, 1750, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.07 (3H, t, J=7.0 Hz), 2.82 (2H, t, J=7.5 Hz), 3.19 (2H, t, J=7.5 Hz), 3.2—3.4 (3H, m), 3.43 (2H, q, J=7.2 Hz), 3.62 (1H, m), 3.71 (3H, s), 3.98 (1H, d, J=16.6 Hz), 4.05 (1H, d, J=16.6 Hz), 4.15 (1H, dd, J=6.7, 11.8 Hz), 4.35 (1H, dd, J=1.9, 11.8 Hz), 4.97 (1H, d, J=7.4 Hz), 5.22 (1H, d, J=4.7 Hz), 5.32 (1H, d, J=5.4 Hz), 5.33 (1H, d, J=5.3 Hz), 6.56 (1H, d, J=7.7 Hz), 6.64 (1H, d, J=8.1 Hz), 6.81 (2H, dd, J=2.1, 8.7 Hz), 7.15 (2H, dd, J=2.1, 8.8 Hz), 7.23 (1H, t, J=8.3 Hz), 10.88 (1H, s). FAB-MS *m/z*: 543 $(M+Na)^+$. HR FAB-MS *m/z*: 543.1846 (Calcd for $C_{26}H_{32}NaO_{11}$: 543.1842).

2-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxypropiophenone 2′-*O*-(6-*O*-(*p*-Fluorobenzoyl)-β-D-glucopyranoside) (32) A solution of *p*-fluorobenzoyl chloride (571 mg, 3.60 mmol) in CH_2Cl_2 (1 ml) was added dropwise to a solution of **2** (1333 mg, 3 mmol) in 2,4,6-collidine (10 ml) at −40 °C. The whole was stirred at −30 °C for 1.5 h and at room temperature 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 ($CHCl_3$–MeOH (20 : 1)) to give the acylated product (containing diacylated product **36**) (1.60 g). This was dissolved in MeOH (30 ml)–tetrahydrofuran (THF) (30 ml) and stirred with $NaHCO_3$ (756 mg, 9 mmol) at 40 °C for 2 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 ($CHCl_3$–MeOH (40 : 1)) to give **32** (931 mg, 55%). IR (Nujol): 3480, 3240, 1720, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.97 (2H, t, J=7.3 Hz), 3.2—3.4 (5H, m), 3.80 (1H, m), 4.26 (1H, dd, J=7.5, 11.9 Hz), 4.59 (1H, dd, J=1.8, 11.7 Hz), 5.02 (1H, d, J=7.3 Hz), 5.26 (1H, d, J=4.5 Hz), 5.39 (1H, d, J=5.1 Hz), 5.40 (1H, d, J=5.2 Hz), 6.53 (1H, d, J=8.1 Hz), 6.67 (1H, d, J=8.1 Hz), 6.86 (1H, d, J=2.2 Hz), 7.09 (1H, t, J=8.3 Hz), 7.17 (1H, dd, J=1.8, 8.5 Hz), 7.35 (2H, dd, J=5.5, 8.9 Hz), 7.44 (1H, d, J=8.7 Hz), 7.48 (1H, d, J=1.4 Hz), 7.92 (1H, d, J=2.2 Hz), 7.99 (2H, dd, J=5.5, 8.9 Hz), 10.82 (1H, s). ESI-MS *m/z*: 589 $(M+Na)^+$.

Compounds **30** and **31** were prepared by the same procedure as described above.

Compound **31**: IR (Nujol): 3400, 1740, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.06 (3H, t, J=7.0 Hz), 2.99 (2H, t, J=7.4 Hz), 3.1—3.3 (5H, m), 3.41 (2H, q, J=7.0 Hz), 3.65 (1H, m), 3.96 (1H, d, J=16.6 Hz), 4.03 (1H, d, J=16.6 Hz), 4.15 (1H, m), 4.36 (1H, dd, J=1.8, 11.7 Hz), 4.98 (1H, d, J=7.3 Hz), 5.22 (1H, d, J=4.5 Hz), 5.31 (1H, d, J=5.5 Hz), 5.34 (1H, d, J=5.2 Hz), 6.56 (1H, d, J=8.1 Hz), 6.64 (1H, d, J=8.1 Hz), 6.87 (1H, dd, J=1.0, 2.2 Hz), 7.20 (1H, dd, J=1.8, 8.1 Hz), 7.23 (1H, t, J=8.3 Hz), 7.46 (1H, d, J=8.4 Hz), 7.51 (1H, d, J=1.4 Hz), 7.93 (1H, d, J=2.2 Hz), 10.87 (1H, s). FAB-MS *m/z*: 553 $(M+Na)^+$. HR FAB-MS *m/z*: 553.1683 (Calcd for $C_{27}H_{30}NaO_{11}$: 553.1686).

6′-Allyloxy-2-(benzo[*b*]furan-5-yl)-2′-hydroxypropiophenone 2′-*O*-β-D-Glucopyranoside (33) A mixture of **2** (5.00 g, 11.25 mmol), allyl bromide (2.04 g, 16.88 mmol), K_2CO_3 (4.66 g, 33.75 mmol), and acetone (40 ml) was heated under reflux for 5 h. The reaction mixture was diluted with AcOEt and filtered through a plug of Celite. The filtrate was washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was recrystallized from AcOEt to give **33** (4.87 g, 89%) as colorless needles, mp 117—119.5 °C. IR (Nujol): 3340, 1690 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.9—3.0 (2H, m), 3.05—3.4 (2H, m), 3.46 (1H, m), 3.70 (1H, m), 4.52 (2H, td, J=1.6, 4.9 Hz), 4.54 (1H, t, J=5.9 Hz), 4.88 (1H, d, J=7.5 Hz), 5.01 (1H, d, J=5.1 Hz), 5.07 (1H, d, J=4.8 Hz), 5.17 (1H, ddd, J=1.5, 1.8, 10.6 Hz), 5.22 (1H, d, J=5.5 Hz), 5.26 (1H, tdd, J=1.7, 1.8, 17.2 Hz), 5.89 (1H, tdd, J=5.3, 10.5, 17.3 Hz), 6.72 (1H, d, J=8.5 Hz), 6.82 (1H, d, J=8.2 Hz), 6.87 (1H, dd, J=0.9, 2.2 Hz), 7.18 (1H, dd, J=1.7, 8.5 Hz), 7.27 (1H, t, J=8.4 Hz), 7.45 (1H, d, J=8.6 Hz), 7.50 (1H, d, J=1.3 Hz), 7.92 (1H, d, J=2.2 Hz). ESI-MS *m/z*: 507 $(M+Na)^+$.

2-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxypropiophenone 2′-*O*-(6-*O*-Methoxycarbonyl-β-D-glucopyranoside) (34) A solution of methyl chloroformate (702 mg, 7.43 mmol) in CH_2Cl_2 (3 ml) was added dropwise to a solution of **33** (3.00 g, 6.19 mmol) in 2,4,6-collidine (30 ml) at −40 °C. The whole was stirred at −40 °C for 1.5 h and at room temperature for 3 h. The reaction mixture was poured into ice-cooled 10% HCl and extracted with AcOEt. The organic layer was washed with water saturated with $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH (20 : 1)) to give the acylated product (3.04 g, 91%).

To a solution of this compound (200 mg, 0.369 mmol) in acetonitrile (3 ml) was added dichlorobis (triphenylphosphine) palladium (2.5 mg) and ammonium formate (94 mg, 1.48 mmol). The mixture was heated under reflux for 2 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water saturated with $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH (10 : 1)) to give **34** (178 mg, 96%). IR (Nujol): 3340, 1690 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.99 (2H, t, J=7.5 Hz), 3.1—3.4 (5H, m), 3.63 (1H, m), 4.15 (1H, dd, J=6.4, 11.6 Hz), 4.36 (1H, dd, J=2.0, 11.6 Hz), 4.98 (1H, d, J=7.6 Hz), 5.21 (1H, d, J=4.9 Hz), 5.34 (1H, d, J=5.4 Hz), 5.35 (1H, d, J=5.4 Hz), 6.56 (1H, d, J=8.1 Hz), 6.64 (1H, d, J=8.1 Hz), 6.87 (1H, dd, J=1.0, 2.2 Hz), 7.20 (1H, dd, J=1.8, 8.5 Hz), 7.22 (1H, t, J=8.3 Hz), 7.46 (1H, d, J=8.4 Hz), 7.51 (1H, d, J=1.5 Hz), 7.92 (1H, d, J=2.2 Hz), 10.88 (1H, s). ESI-MS *m/z*: 525 $(M+Na)^+$.

Compound **35** was prepared by the same procedure as described above with phenyl isocyanate instead of methyl chloroformate. **35**: IR (Nujol): 3390, 1710, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.98 (2H, t, J=7.5 Hz), 3.2—3.4 (5H, m), 3.55 (1H, m), 4.21 (1H, dd, J=5.5, 11.5 Hz), 4.37 (1H, dd, J=1.5, 11.5 Hz), 5.00 (1H, d, J=7.5 Hz), 5.25 (1H, d, J=5.0 Hz), 5.32 (1H, d, J=5.5 Hz), 5.35 (1H, d, J=5.5 Hz), 6.53 (1H, d, J=8.5 Hz), 6.67 (1H, d, J=8.5 Hz), 6.86 (1H, dd, J=1.0, 2.5 Hz), 6.97 (1H, m), 7.18—7.28 (2H, m), 7.19 (1H, dd, J=2.0, 8.5 Hz), 7.25 (1H, t, J=8.5 Hz), 7.45 (3H, m), 7.50 (1H, d, J=2.0 Hz), 7.92 (1H, d, J=2.5 Hz), 9.69 (1H, s) 10.81 (1H, s). ESI-MS *m/z*: 586 $(M+Na)^+$. HR FAB-MS *m/z*: 586.1672 (Calcd for $C_{30}H_{29}NaNO_{10}$: 586.1689).

2-(Benzo[*b*]furan-5-yl)-6′-*p*-fluorobenzoyloxy-2′-hydroxypropiophenone 2′-*O*-(6-*O*-(*p*-Fluorobenzoyl)-β-D-glucopyranoside) (36) *p*-Fluorobenzoyl chloride (1.05 g, 6.6 mmol) was added dropwise to a solution of **2** (1333 mg, 3 mmol) and Et_3N (668 mg, 6.6 mmol) in DMA (10 ml) under ice-cooling. The whole was stirred under ice-cooling for 1 h 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 (19 : 1)) to give **36** (1.12 g, 54%). IR (Nujol): 1740, 1603 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.89 (2H, t, J=7.5 Hz), 3.1—3.4 (5H, m,), 3.86 (1H, ddd, J=2.1, 7.7, 9.4 Hz), 4.29 (1H, dd, J=7.3, 12.0 Hz),

4.62 (1H, dd, J=1.6, 12.0 Hz), 5.16 (1H, d, J=7.3 Hz), 5.23 (1H, d, J=5.4 Hz), 5.31 (1H, d, J=4.8 Hz), 5.45 (1H, d, J=5.2 Hz), 6.98 (1H, dd, J=0.2, 2.0 Hz), 6.99 (1H, d, J=7.7 Hz), 7.06 (1H, dd, J=1.7, 8.5 Hz), 7.22 (1H, d, J=8.4 Hz), 7.30 (2H, t, J=8.9 Hz), 7.3—7.4 (5H, m), 7.88 (2H, dd, J=5.4, 8.8 Hz), 7.91 (1H, d, J=1.5 Hz), 8.02 (2H, dd, J=5.6, 7.8 Hz). ESI-MS m/z: 711 $(M+Na)^+$.

2-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxypropiophenone 2′-*O*-(4,6-O-Carbonyl-β-D-glucopyranoside) (37) A solution of *p*-nitrophenyl chloroformate (2.62 g, 13 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a solution of **2** (4.44 g, 10 mmol) in 2,4,6-collidine (50 ml) at −40 °C. The whole was stirred at −40 °C for 1 h, at room temperature for 1 h, and at 50 °C for 5 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 **37** (3.23 g, 69%). IR (Nujol): 3400, 1750, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.98 (2H, t, J=7.5 Hz), 3.23 (2H, m), 3.33 (1H, m), 3.63 (1H, m), 4.13 (1H, m), 4.17 (1H, dd, J=8.9, 9.5 Hz), 4.25 (1H, dd, J=9.5, 9.6 Hz), 4.47 (1H, dd, J=5.5, 9.2 Hz), 5.21 (1H, d, J=7.9 Hz), 5.77 (1H, d, J=5.9 Hz), 5.84 (1H, d, J=5.5 Hz), 6.58 (1H, d, J=8.1 Hz), 6.68 (1H, d, J=8.1 Hz), 6.88 (1H, dd, J=0.9, 2.2 Hz), 7.19 (1H, dd, J=1.8, 8.5 Hz), 7.24 (1H, t, J=8.3 Hz), 7.48 (1H, d, J=8.5 Hz), 7.50 (1H, d, J=1.8 Hz), 7.93 (1H, d, J=2.2 Hz), 10.73 (1H, s). ESI-MS m/z: 493 $(M+Na)^+$.

2-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxypropiophenone 2′-*O*-(4-*O*-Methoxycarbonyl-β-D-glucopyranoside) (38) A mixture of **37** (493 mg, 1.05 mmol), *p*-TsOH·H_2O (19 mg, 0.1 mmol), and MeOH (10 ml) was stirred at room temperature for 2 h. The reaction mixture was diluted with AcOEt and washed with water saturated with $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH (19 : 1)) to give the 4-*O*-carbonate **38** (391 mg, 46%) and the 6-*O*-carbonate **34** (299 mg, 35%). **38**; IR (Nujol): 3420, 1750, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.00 (2H, t, J=7.5 Hz), 3.2—3.4 (4H, m), 3.45—3.6 (2H, m), 3.66 (1H, m), 3.72 (3H, s), 4.51 (1H, t, J=9.5 Hz), 4.79 (1H, t, J=5.5 Hz), 5.06 (1H, d, J=8.1 Hz), 5.51 (1H, d, J=5.9 Hz), 5.57 (1H, d, J=5.9 Hz), 6.56 (1H, d, J=8.1 Hz), 6.69 (1H, d, J=8.1 Hz), 6.89 (1H, dd, J=0.7, 2.2 Hz), 7.21 (1H, dd, J=1.8, 8.4 Hz), 7.24 (1H, t, J=8.4 Hz), 7.47 (1H, d, J=8.4 Hz), 7.53 (1H, d, J=1.5 Hz), 7.93 (1H, d, J=2.2 Hz), 10.89 (1H, s). ESI-MS m/z: 525 $(M+Na)^+$. HR FAB-MS m/z: 525.1371 (Calcd for $C_{25}H_{26}NaO_{11}$: 525.1373).

Compound **39** was prepared by the same procedure as described above.

2-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxypropiophenone 2′-*O*-(2-*O*-Acetyl-β-D-glucopyranoside) (41) A mixture of **17** (529 mg, 1 mmol), *p*-TsOH·H_2O (19 mg, 0.1 mmol), and MeOH (10 ml) was stirred at 40 °C for 22 h. The reaction mixture was diluted with AcOEt and washed with water saturated with $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH (19 : 1)) to give the 2-*O*-acetyl derivative **41** (202 mg, 42%), the 3-*O*-acetyl derivative **42** (37 mg, 8%), **2** (127 mg, 29%), and recovered **17** (105 mg, 20%). **41**: IR (Nujol): 3350, 1745, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.98 (3H, s), 2.88—3.05 (4H, m), 3.26 (1H, m), 3.4—3.55 (3H, m), 3.72 (1H, dd, J=4.1, 10.9 Hz), 4.67 (1H, t, J=5.2 Hz), 4.76 (1H, dd, J=8.2, 9.5 Hz), 5.12 (1H, d, J=8.2 Hz), 5.27 (1H, d, J=5.4 Hz), 5.36 (1H, d, J=5.5 Hz), 6.55 (1H, d, J=8.2 Hz), 6.66 (1H, d, J=8.1 Hz), 6.88 (1H, dd, J=0.9, 2.2 Hz), 7.17 (1H, t, J=8.5 Hz), 7.19 (1H, dd, J=2.0, 8.5 Hz), 7.48 (1H, d, J=8.4 Hz), 7.51 (1H, d, J=1.7 Hz), 7.93 (1H, d, J=2.2 Hz), 10.24 (1H, s). ESI-MS m/z: 509 $(M+Na)^+$.

2′,6′-Dihydroxy-4-methoxydihydrochalcone 2′-*O*-(4,6-*O*-Ethylidene-β-D-glucopyranoside) (43) Compound **43** was prepared by the same procedure as employed for the synthesis of **5** with acetaldehyde dimethylacetal instead of benzaldehyde dimethylacetal. **43**: IR (Nujol): 3380, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (3H, d, J=4.9 Hz), 2.82 (2H, t, J=7.3 Hz), 3.17 (2H, t, J=7.8 Hz), 3.1—3.6 (5H, m), 4.01 (1H, dd, J=5.4, 8.8 Hz), 4.72 (1H, q, J=4.9 Hz), 5.09 (1H, d, J=7.8 Hz), 5.40 (1H, d, J=5.4 Hz), 5.53 (1H, d, J=5.9 Hz), 6.56 (1H, d, J=8.3 Hz), 6.67 (1H, d, J=8.3 Hz), 6.83 (2H, ddd, J=2.0, 2.9, 8.3 Hz), 7.15 (2H, d, J=8.8 Hz), 7.23 (1H, t, J=8.3 Hz), 7.0—8.0 (1H, br). FAB-MS m/z: 461 $(M+H)^+$.

2′,6′-Dihydroxy-4-methoxydihydrochalcone 2′-*O*-(4,6-*O*-Methoxymethylene-β-D-glucopyranoside) (44) A mixture of **1** (434 mg, 1 mmol), pyridinium *p*-toluenesulfonate (PPTS) (25 mg, 0.1 mmol), and trimethyl orthoformate (2 ml) was stirred at room temperature for 4 h. MeOH (0.2 ml) was added to the reaction mixture under ice-cooling and the whole was stirred for 1.5 h. Water saturated with $NaHCO_3$ and AcOEt were added to the mixture. The organic layer was separated, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH (19 : 1)) to give **44** (349 mg, 73%) as an oil. IR (neat): 3430, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6) signals for the major diastereomer are given δ: 2.84 (2H, t, J=7.5 Hz), 3.16 (2H, t, J=7.4 Hz), 3.26 (3H, s), 3.2—3.7 (5H, m), 3.71 (3H, s), 3.79 (1H, dd, J=4.5, 9.5 Hz), 5.12 (1H, d, J=7.7 Hz), 5.36 (1H, d, J=5.6 Hz), 5.44 (1H, s), 5.56 (1H, d, J=5.7 Hz), 6.56 (1H, d, J=8.1 Hz), 6.68 (1H, d, J=7.8 Hz), 6.82 (2H, d, J=8.7 Hz), 7.15 (2H, d, J=8.6 Hz), 7.23 (1H, t, J=8.3 Hz), 10.82 (1H, s). ESI-MS m/z: 499 $(M+Na)^+$. HR FAB-MS m/z: 499.1585 (Calcd for $C_{24}H_{28}NaO_{10}$: 499.1581).

2′,6′-Dihydroxy-4-methoxydihydrochalcone 2′-*O*-(2,3-*O*-Diacetyl-4,6-*O*-methoxymethylene-β-D-glucopyranoside) (45, 46) A mixture of **44** (327 mg, 0.69 mmol), Ac_2O (0.5 ml), and pyridine (2 ml) was stirred at room temperature for 2 h. The reaction mixture was diluted with AcOEt and the solution was washed with 10% HCl, water and brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography on silica gel ($CHCl_3$–acetone (19 : 1)) to give **45** (276 mg, 67%) and **46** (47 mg, 11%).

45: ^{1}H-NMR (DMSO-d_6) δ: 1.94 (3H, s), 2.02 (3H, s), 2.06 (3H, s), 2.76 (2H, m), 2.93 (2H, m), 3.25 (3H, s), 3.72 (3H, s), 3.79 (1H, m, H-6_{ax}), 3.9—4.0 (3H, m), 5.04 (1H, dd, J=7.9, 9.4 Hz), 5.32 (1H, t, J=9.5 Hz), 5.47 (1H, s, CH-OMe), 5.65 (1H, d, J=7.9 Hz), 6.85 (2H, dd, J=2.1, 8.7 Hz), 6.92 (1H, d, J=7.7 Hz), 7.13 (2H, dd, J=2.1, 8.7 Hz), 7.15 (1H, d, J=8.1 Hz), 7.45 (1H, t, J=8.3 Hz). FAB-MS m/z: 625 $(M+Na)^+$.

46: ^{1}H-NMR (DMSO-d_6) δ: 1.94 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.75 (2H, m), 2.90 (2H, m), 3.33 (3H, s), 3.69 (1H, m, H-6_{ax}), 3.71 (3H, s), 3.8—4.0 (2H, m), 4.20 (1H, dd, J=4.5, 10.2 Hz), 5.01 (1H, dd, J=7.9, 9.4 Hz), 5.36 (1H, s, CH-OMe), 5.37 (1H, dd, J=9.3, 9.4 Hz), 5.64 (1H, d, J=7.9 Hz), 6.85 (2H, ddd, J=2.1, 3.0, 8.7 Hz), 6.92 (1H, d, J=7.7 Hz), 7.13 (2H, d, J=8.7 Hz), 7.14 (1H, d, J=8.1 Hz), 7.45 (1H, t, J=8.4 Hz). FAB-MS m/z: 625 $(M+Na)^+$.

Compounds **47**—**50** were prepared from **2** by the same procedure as employed for the synthesis of **44** with the appropriate orthoesters or orthocarbonate.

47: Yield 73% as an amorphous solid. IR (Nujol): 3420, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) signals for the major diastereomer are given δ: 2.98 (2H, t, J=7.7 Hz), 3.26 (3H, s), 3.2—3.75 (7H, m), 3.80 (1H, dd, J=4.6, 9.5 Hz), 5.15 (1H, d, J=7.7 Hz), 5.37 (1H, d, J=5.5 Hz), 5.44 (1H, s), 5.59 (1H, d, J=5.7 Hz), 6.56 (1H, d, J=8.1 Hz), 6.70 (1H, d, J=8.1 Hz), 6.88 (1H, dd, J=0.9, 2.2 Hz), 7.20 (1H, dd, J=1.7, 8.5 Hz), 7.23 (1H, t, J=8.3 Hz), 7.47 (1H, d, J=8.4 Hz), 7.50 (1H, d, J=1.7 Hz), 7.94 (1H, d, J=2.2 Hz), 10.83 (1H, s). ESI-MS m/z: 509 $(M+Na)^+$. HR FAB-MS m/z: 509.1424 (Calcd for $C_{25}H_{26}NaO_{10}$: 509.1424).

48: Yield 79% as an amorphous solid. IR (Nujol): 3430, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.39 (3H, s), 2.98 (2H, t, J=7.4 Hz), 3.22 (3H, s), 3.2—3.8 (8H, m), 5.13 (1H, d, J=7.7 Hz), 5.34 (1H, d, J=5.3 Hz), 5.59 (1H, d, J=5.6 Hz), 6.56 (1H, d, J=7.7 Hz), 6.69 (1H, d, J=8.1 Hz), 6.88 (1H, dd, J=0.9, 2.2 Hz), 7.20 (1H, dd, J=1.8, 8.5 Hz), 7.23 (1H, t, J=8.2 Hz), 7.47 (1H, d, J=8.5 Hz), 7.51 (1H, d, J=1.4 Hz), 7.94 (1H, d, J=2.2 Hz), 10.83 (1H, s). ESI-MS m/z: 523 $(M+Na)^+$. HR FAB-MS m/z: 523.1572 (Calcd for $C_{26}H_{28}NaO_{10}$: 523.1580).

49: Yield 85% as an amorphous solid. IR (Nujol): 3400, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.01 (2H, t, J=7.0 Hz), 3.01 (3H, s), 3.27 (2H, m), 3.4—3.8 (4H, m), 3.89 (1H, dd, J=9.6, 9.8 Hz), 3.97 (1H, dd, J=5.2, 9.8 Hz), 5.19 (1H, d, J=7.7 Hz), 5.45 (1H, d, J=5.5 Hz), 5.63 (1H, d, J=5.7 Hz), 6.57 (1H, d, J=7.7 Hz), 6.72 (1H, d, J=8.1 Hz), 6.89 (1H, dd, J=1.0, 2.2 Hz), 7.22 (1H, dd, J=1.8, 8.5 Hz), 7.24 (1H, t, J=8.3 Hz), 7.40 (3H, m), 7.48 (1H, d, J=8.4 Hz), 7.53 (1H, d, J=1.6 Hz), 7.55 (2H, m), 7.94 (1H, d, J=2.2 Hz), 10.83 (1H, s). ESI-MS m/z: 585 $(M+Na)^+$. HR FAB-MS m/z: 585.1747 (Calcd for $C_{31}H_{30}NaO_{10}$: 585.1736).

50: Yield 62% as an amorphous solid. IR (Nujol): 3400, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.12 (3H, t, J=7.1 Hz), 1.15 (3H, t, J=7.1 Hz), 2.99 (2H, t, J=7.3 Hz), 3.2—3.35 (3H, m), 3.45—3.75 (8H, m), 3.94 (1H, dd, J=3.7, 8.8 Hz), 5.15 (1H, d, J=7.7 Hz), 5.44 (1H, d, J=5.3 Hz), 5.60 (1H, d, J=5.7 Hz), 6.57 (1H, d, J=7.7 Hz), 6.70 (1H, d, J=8.1 Hz), 6.88 (1H, dd, J=1.0, 2.2 Hz), 7.20 (1H, dd, J=1.8, 8.5 Hz), 7.23 (1H, t, J=8.3 Hz), 7.46 (1H, d, J=8.5 Hz), 7.51 (1H, d, J=1.3 Hz), 7.93 (1H, d, J=2.2 Hz), 10.81 (1H, s). ESI-MS m/z: 567 $(M+Na)^+$. HR FAB-MS m/z: 567.1828 (Calcd for $C_{28}H_{32}NaO_{11}$: 567.1842).

6′-Acetoxy-2-(benzo[*b*]furan-5-yl)-2′-hydroxypropiophenone 2′-*O*-(2,3-*O*-Diacetyl-6-*O*-methoxymethyl-β-D-glucopyranoside) (51) A mixture of **9** (1.71 g, 3 mmol), LiBr (52 mg, 0.6 mmol), *p*-TsOH·H_2O (57 mg, 0.3 mmol), and dimethoxymethane (20 ml) was stirred at room temperature for 2.5 h and at 55 °C for 3 h. The reaction mixture was diluted with AcOEt and washed with water saturated with $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$–

acetone (9 : 1)) to give **51** (1.27 g, 69%) as an oil. IR (neat): 3480, 1750, 1705 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.90 (3H, s), 2.00 (3H, s), 2.01 (3H, s), 2.85—3.0 (4H, m), 3.20 (3H, s), 3.45—3.85 (4H, m), 4.53 (1H, d, J=6.4, Hz), 4.56 (1H, d, J=6.4 Hz), 4.91 (1H, dd, J=8.0, 9.9 Hz), 5.12 (1H, dd, J=9.2, 9.7 Hz), 5.54 (1H, d, J=7.9 Hz), 5.73 (1H, br), 6.89 (1H, d, J=8.8 Hz), 6.90 (1H, d, J=2.2 Hz), 7.15 (1H, t, J=8.8 Hz), 7.17 (1H, dd, J=1.6, 8.5 Hz), 7.44 (1H, d, J=8.3 Hz), 7.48 (1H, d, J=1.9 Hz), 7.49 (1H, d, J=8.4 Hz), 7.94 (1H, d, J=2.2 Hz). ESI-MS *m/z*: 637 $(M+Na)^+$.

2-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxypropiophenone 2′-*O*-(4,6-*O*-Methylene-β-D-glucopyranoside) (52) TMSOTf (0.51 ml, 2.64 mmol) was added to a solution of **51** (1.08 g, 1.76 mmol) and 2,6-lutidine (283 mg, 2.46 mmol) in THF (20 ml) under ice-cooling. The whole was stirred under ice-cooling for 2 h and at room temperature for 2 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 ($CHCl_3$–AcOEt (9 : 1)) to give the glucose 4,6-*O*-methylene derivative (634 mg, 62%).

This was dissolved in MeOH (20 ml)–H_2O (0.2 ml) and stirred with K_2CO_3 (579 mg, 1.05 mmol) at room temperature for 2.5 h. The reaction mixture was diluted with AcOEt, washed with 10% HCl, water, and dried over $MgSO_4$. The solvent was removed and the residue was chromatographed on silica gel ($CHCl_3$–MeOH (19 : 1)) to give **52** (399 mg, 93%). IR (Nujol): 3600, 3330, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.88 (2H, t, J=7.6 Hz), 3.1—3.4 (5H, m), 3.50 (2H, m), 4.05 (1H, dd, J=4.6, 9.7 Hz), 4.55 (1H, d, J=6.2 Hz), 4.98 (1H, d, J=6.1 Hz), 5.12 (1H, d, J=7.8 Hz), 5.44 (1H, d, J=5.3 Hz), 5.58 (1H, d, J=5.7 Hz), 6.56 (1H, d, J=8.2 Hz), 6.69 (1H, d, J=8.1 Hz), 6.89 (1H, dd, J=0.9, 2.1 Hz), 7.20 (1H, dd, J=1.7, 8.5 Hz), 7.23 (1H, t, J=8.3 Hz), 7.48 (1H, d, J=8.5 Hz), 7.51 (1H, d, J=1.2 Hz), 7.93 (1H, d, J=2.2 Hz), 10.84 (1H, s). ESI-MS *m/z*: 479 $(M+Na)^+$.

1,2,3,4-*O*-Tetraacetyl-6-*O*-methyl-α-D-glucopyranoside (54) Cl_2 gas was introduced into a solution of methyl 6-deoxy-6-iodo-α-D-glucopyranoside **53**[11] (920 mg, 3.03 mmol) in MeOH (50 ml) at room temperature for 15 min. A basic resin (DIAION PA308) was added to the reaction mixture under ice-cooling and the whole was stirred for 30 min. The resin was removed by filtration and the filtrate was evaporated *in vacuo* to give the crude methyl 6-*O*-methyl-α-D-glucopyranoside (550 mg). This was dissolved in a mixture of Ac_2O, AcOH, and H_2SO_4 (2 : 1 : 0.03; 10 ml) and the whole was stirred at room temperature for 8 h. The reaction mixture was diluted with AcOEt and washed with water, water saturated with $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography on silica gel (AcOEt–hexane (1 : 3)) to give **54** (479 mg, 44%). IR (Nujol): 1750 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.98 (3H, s), 1.99 (3H, s), 2.01 (3H, s), 2.08 (3H, s), 3.22 (3H, s), 3.38 (2H, m), 4.01 (1H, m), 4.97 (1H, dd, J=3.7, 10.3 Hz), 5.04 (1H, dd, J=9.7, 10.3 Hz), 5.32 (1H, t, J=9.9 Hz), 6.15 (1H, d, J=3.7 Hz). ESI-MS *m/z*: 385 $(M+Na)^+$.

2′,6′-Dihydroxyacetophenone 2′-*O*-(2,3,4-*O*-Triacetyl-6-*O*-methyl-β-D-glucopyranoside) (56) Compound **54** (4.52 g, 12.47 mmol) was added to a 25% solution of HBr in AcOH (20 ml) under ice-cooling and the whole was stirred at room temperature for 1.5 h. The reaction mixture was poured into ice and extracted with $CHCl_3$. The organic layer was washed with water and dried over $MgSO_4$. The solvent was removed to give the crude bromosugar **55** (5.11 g). A mixture of 2′,6′-dihydroxyacetophenone (1.90 g, 12.47 mmol) and $CdCO_3$ (8.60 g, 49.88 mmol) in toluene (320 ml) was refluxed for 1 h with removal of the generated water using a Dean–Stark apparatus. Then **55** (5.11 g, 12.47 mmol) was added and the whole was heated at reflux for 15 h. The mixture was filtered through a plug of Celite while hot and the solid was washed with hot $CHCl_3$. The filtrate and washing were combined and evaporated. The residue was triturated in MeOH to give **56** (1.85 g, 33%) as a white powder, mp 174—177 °C. IR (Nujol): 1745, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.95 (3H, s), 2.00 (3H, s), 2.01 (3H, s), 2.36 (3H, s), 3.23 (3H, s), 3.37 (3H, m), 3.45 (1H, dd, J=2.6, 11.2 Hz), 4.14 (1H, ddd, J=2.7, 5.6, 10.0 Hz), 4.94 (1H, dd, J=9.6, 9.9 Hz), 5.02 (1H, dd, J=8.0, 9.8 Hz), 5.36 (1H, t, J=9.6 Hz), 5.55 (1H, d, J=8.1 Hz), 6.60 (1H, d, J=7.6 Hz), 6.63 (1H, d, J=7.6 Hz), 7.26 (1H, t, J=8.3 Hz), 10.86 (1H, s). ESI-MS *m/z*: 477 $(M+Na)^+$.

2-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxypropiophenone 2′-*O*-(6-*O*-Methyl-β-D-glucopyranoside) (57) A 50% aqueous KOH solution (2 ml) was added to a suspension of **56** (909 mg, 2 mmol) in EtOH (10 ml) and the mixture was stirred at room temperature for 10 min. Benzofuran-5-carboxaldehyde[1] (351 mg, 2.4 mmol) was added and the whole was stirred at room temperature for 17 h. 4-*N*,*N*-Dimethylaminopyridine (DMAP) (244 mg, 2 mmol) was added to the reaction mixture and the whole was hydrogenated over 10% Pt–C (0.25 g) at room temperature for 4 h. The catalyst was removed by filtration. 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, then the residue was chromatographed on silica gel ($CHCl_3$–MeOH (9 : 1)) to give **57** (664 mg, 72%). IR (neat): 3410, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.00 (2H, t, J=7.5 Hz), 3.05—3.65 (8H, m), 3.20 (3H, s), 4.96 (1H, d, J=7.5 Hz), 5.15 (1H, d, J=4.6 Hz), 5.17 (1H, d, J=5.3 Hz), 5.31 (1H, d, J=5.2 Hz), 6.55 (1H, dd, J=7.7 Hz), 6.65 (1H, d, J=8.1 Hz), 6.88 (1H, dd, J=0.9, 2.2 Hz), 7.21 (1H, dd, J=1.8, 8.5 Hz), 7.24 (1H, t, J=8.3 Hz), 7.46 (1H, d, J=8.5 Hz), 7.52 (1H, d, J=1.4 Hz), 7.93 (1H, d, J=2.2 Hz), 10.91 (1H, s). ESI-MS *m/z*: 481 $(M+Na)^+$. HR FAB-MS *m/z*: 481.1479 (Calcd for $C_{24}H_{26}NaO_9$: 481.1475).

Measurement of Urinary Glucose Excretion Male Sprague-Dawley (SD) rats (6 weeks old) were used. Test compounds were administered twice with an 8 h interval, at 10 mg/kg, i.p. or 100 mg/kg, *p.o.* The volume of the injection was kept at 5 ml/kg. Urine was collected for 24 h after the first administration and urinary glucose was measured by use of a glucose analyzer (Apec).

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