Na^+-Glucose Cotransporter Inhibitors as Antidiabetic Agents. II.[1] Synthesis and Structure–Activity Relationships of 4′-Dehydroxyphlorizin Derivatives

Mitsuya HONGU, Takashi TANAKA, Nobuyuki FUNAMI, Kunio SAITO, Kenji ARAKAWA, Mamoru MATSUMOTO, and Kenji TSUJIHARA*

Lead Optimization Research Laboratory, Tanabe Seiyaku Co., Ltd., 2–2–50 Kawagishi, Toda, Saitama 335, Japan.
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A novel series of 4′-dehydroxyphlorizin derivatives was synthesized and the effects of these compounds on urinary glucose excretion were evaluated in rats. There was a strict structural requirement for activity. Introduction of a small substituent or a flat ring at the 3- and/or the 4-position on the A ring was permissible, but any change at the bridge part between the A and B rings or in the sugar moiety resulted in complete loss of activity. The 6′-OH group on the B ring was also necessary, and even small structural modifications of the 6′-OH group reduced the activity considerably. Among the compounds synthesized, the 5-benzofuryl derivative 25 was the most potent and was selected as a new lead for further structure–activity relationship investigations.

Key words antidiabetic; Na^+-glucose cotransporter inhibitor; 4′-dehydroxyphlorizin; structure–activity relationship

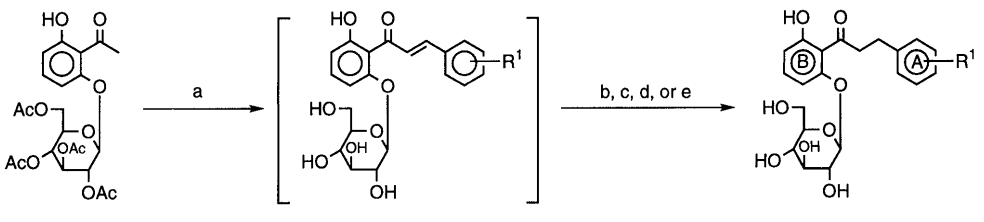
The Na^+-glucose cotransporter (SGLT) existing on the chorionic membrane of the intestine and the kidney plays important roles in the absorption of glucose from the digestive tract and its reabsorption from urine.[2] We consider that inhibitors of SGLT might be useful as antidiabetic agents in preventing chronic hyperglycemia.[1] Phlorizin is known to cause renal diabetes, and this effect has been attributed to its SGLT-inhibitory activity.[3] Therefore, we designed some analogues of phlorizin, synthesized them, and examined their pharmacological properties related to antidiabetic activity. Among them, 4′-dehydroxy-4-*O*-methylphlorizin (**1**) has a strong SGLT-inhibitory effect *in vitro* and prevented the elevation of blood glucose levels on a glucose tolerance test in normal mice after oral administration. Compound **1** also reduced the blood glucose level in diabetic rats, but caused no apparent renal pathological change.[1] Thus, compound **1** seems to be a promising lead for further structure–activity relationship (SAR) studies on antidiabetic agents.

In this paper, we describe the synthesis of various kinds of 4′-dehydroxyphlorizin derivatives and their effect on urinary glucose excretion, and we discuss the SARs of these compounds.

Chemistry

In order to investigate SARs, we first synthesized 4′-dehydroxyphlorizin derivatives **2**—**34** having various substituents on the A ring. By using the method described in the previous paper,[1] most of these compounds were conveniently prepared in a one-pot procedure. The acetophenone **35** was condensed with appropriate aldehydes using KOH as a base in aqueous EtOH. Subsequent hydrogenation of the resulting chalcones **36** over Pd on carbon afforded the desired dihydrochalcone derivatives **2**—**17**, **20**, **22**—**24**, and **32** (method A, Chart 1).

Some compounds were prepared by modified procedures. In the case of the 4-Cl derivative **18**, compound **7** (R^1 = H) was also generated as a by-product (**18** : **7** = 3 : 1) and could not be separated by chromatography. Thus, pure **18** was prepared by catalytic hydrogenation in acetic acid (method B). This procedure was employed when strong hydrogenation conditions were required (**26** and **33**). Although the catalytic hydrogenation did not proceed in the case of compounds containing sulfur, selective 1,4-reduction of the enone intermediates was attained by sodium hydrogen telluride (NaTeH)[4] to afford the desired compounds **19**, **21**, and **30** (method C). The same procedure was used in the case of the compounds containing substituents susceptible to catalytic hydrogenation, such as bromide (**27**) and olefins (**29** and **34**). Although the benzofuran derivative **25** was obtained by reduction with NaTeH (47%), hydrogenation over Pt on carbon in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) gave a better yield (58%) (method D). Therefore, the 2-methylbenzofuran derivative **28** was similarly prepared. The yields and the physicochemical data of these dihydro-



35 **36** **2 — 34**

Chart 1

a) R^1-C$_6$H$_4$-CHO, 50% aq. KOH, EtOH; b) H_2/10% Pd–C, EtOH–H_2O (method A); c) H_2/10% Pd–C, AcOH (method B); d) NaTeH, EtOH (method C); e) H_2/10% Pt–C, DMAP, EtOH–H_2O (method D)

* To whom correspondence should be addressed.

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chalcone derivatives are listed in Tables 1 and 2.

The commercially unavailable aldehydes were synthesized as shown in Chart 2. 2,3-Dibromo-2,3-dihydrobenzofuran-5-carboxaldehyde (**38**) was prepared from benzofuran-5-carboxaldehyde (**37**)[5] by the method of Okuyama *et al.*[6] During the condensation of the acetophenone **35** with **38**, dehydrobromination occurred and the 3-bromobenzofuran derivative **27** was obtained. 2-Methylbenzofuran-5-carboxaldehyde (**42**) was synthesized by the same procedure as reported for the preparation of **37**.[5] Benzothiophene-5-carboxaldehyde (**44**) was prepared from 5-bromobenzothiophene (**43**).[7] The *ortho*-formylation[8] of *p*-hydroxybenzaldehyde (**45**) after acetalization of the aldehyde, followed by reaction with triphenylvinylphosphonium bromide,[9] afforded 2*H*-1-benzopyran-6-carboxaldehyde (**47**). Although we tried to synthesize indene-5-carboxaldehyde (**50**) from the Grignard reagent of 5-bromo-1*H*-indene (**49**),[10] a mixture of **50** and indene-6-carboxaldehyde (**51**) was obtained in only 9% yield. On the other hand, the reaction of the Grignard reagent of the bromide **52**, prepared by the tetrahydropyranylation of **48**, with *N*,*N*-dimethylformamide (DMF) gave the aldehyde **53** (50%). Condensation of the acetophenone **35** with the aldehyde **53** followed by reduction with NaTeH afforded the dihydrochalcone derivative **54** (54%) in the same manner as shown in Chart 1, method C. Peracetylation and removal of the tetrahydropyranyl (THP) group of **54** gave the alcohol **55** (75%). Dehydration of **55** with *p*-toluenesulfonyl chloride (TsCl) in pyridine followed by deacetylation afforded the indene derivative **31** (65%) as a mixture of indene-5-yl and 6-yl regioisomers (Chart 3).

Next, we synthesized compounds modified at the 6′-OH group on the B ring and at the bridge part linking the A

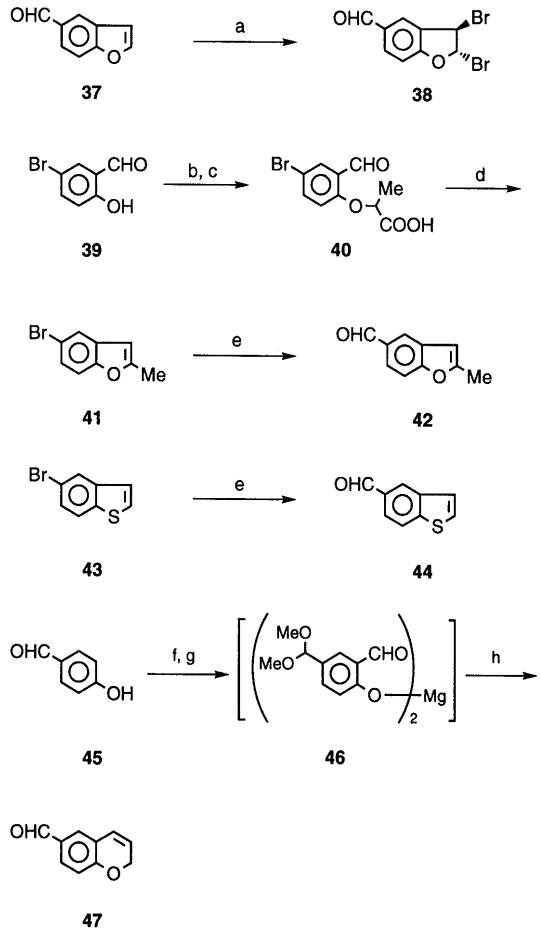

Chart 2

a) Br_2, AcOH; b) ethyl 2-bromopropionate, K_2CO_3; c) aq. NaOH; d) Ac_2O, NaOAc, AcOH; e) Mg, THF then DMF; f) $HC(OMe)_3$, TsOH; g) $Mg(OMe)_2$, $(CH_2O)_n$; h) triphenylvinylphosphonium bromide, K_2CO_3

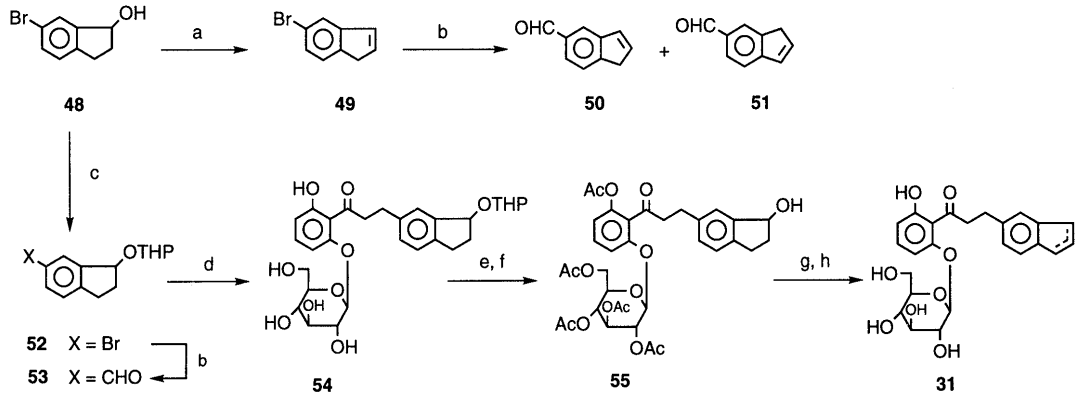

Chart 3

a) TsOH, benzene; b) Mg, THF then DMF; c) DHP, PPTS; d) **35**, 50% aq. KOH, EtOH then NaTeH, EtOH; e) Ac_2O, pyridine; f) AcOH, H_2O; g) TsCl, pyridine; h) K_2CO_3, MeOH

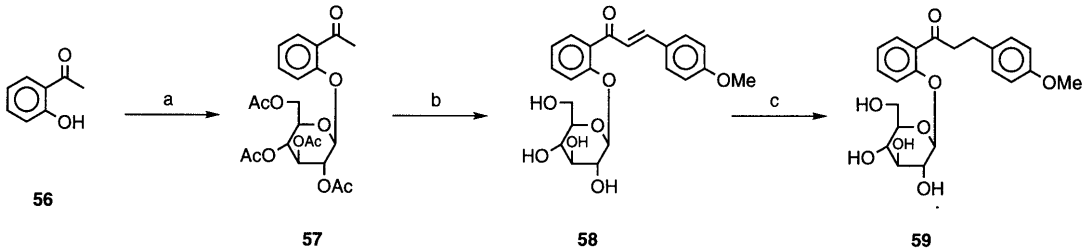

Chart 4

a) acetobromoglucose, $PhCH_2NBu_3Cl$, CH_2Cl_2/5% aq. NaOH; b) *p*-anisaldehyde, 50% aq. KOH, EtOH; c) NaTeH, EtOH

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and B rings. The 6′-dehydroxy derivative **59** was prepared as shown in Chart 4. The reaction of 2′-hydroxyacetophenone (**56**) with acetobromoglucose in the presence of $CdCO_3$, by the same method as described in the previous paper,[1] afforded the glucoside **57** in only 7% yield. On the other hand, the glucoside **57** was obtained in 31% yield by glycosylation using a phase-transfer catalyst.[11] The condensation of **57** with *p*-anisaldehyde gave the chalcone **58** (71%), but catalytic hydrogenation failed. Diedrich has also reported that attempts to prepare the dihydrochalcone derivative from 4,2′,4′-trihydroxychalcone 2′-*O*-*β*-D-glucopyranoside by catalytic hydrogenation were not successful because of over-reduction.[12] Therefore **58** was reduced with NaTeH to give the desired dihydrochalcone **59** (68%). The reaction of compound **1** with appropriate alkyl iodides in the presence of K_2CO_3 in DMF gave the alkoxides **60** (75%) or **61** (74%). Compound **1** was reduced with sodium borohydride ($NaBH_4$) in MeOH to give the alcohol **62** (81%), which was a 1:1 diastereomeric mixture of the carbinols (^{1}H-NMR spectrum), but these diastereomers could not be separated by chromatography. The reaction of compound **1** with hydroxylamine afforded a mixture (2:1 as judged from the ^{1}H-NMR spectrum) of *E* and *Z* oximes **63** (61%) (Chart 5). Compound **66** was prepared as shown in Chart 6. The reaction of 2′,6′-dihydroxypropiophenone (**64**)[13] with acetobromoglucose in the presence of $CdCO_3$ in toluene afforded the glucoside **65** (55%), which was converted to compound **66** in the same manner as shown in Chart 1, method A (64%). Compound **66** was a 1:1 diastereomeric mixture (^{1}H-NMR spectrum) owing to the asymmetric *α* carbon to the ketone. Next, the *p*-methoxyphenoxyacetophenone derivative **70** was prepared. Compound **67**, the benzyl ether of **35**, was treated with $CuBr_2$ in the presence of $CaCO_3$ in $CHCl_3$–AcOEt[14] to give the bromoketone **68** (43%). The reaction of **68** with *p*-methoxyphenol followed by catalytic hydrogenation in an alkaline medium gave compound **70** (33%) (Chart 7). The physicochemical data for **59**—**63**, **66**, and **70** are listed in Table 3.

Compounds with another sugar moiety instead of

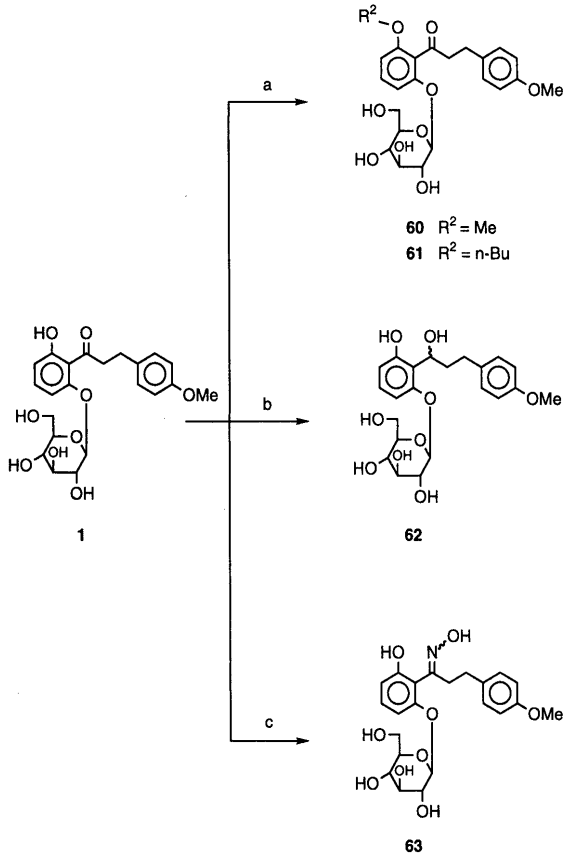

Chart 5

a) R^2-I, K_2CO_3, DMF; b) $NaBH_4$, MeOH; c) $H_2NOH \cdot HCl$, pyridine, EtOH

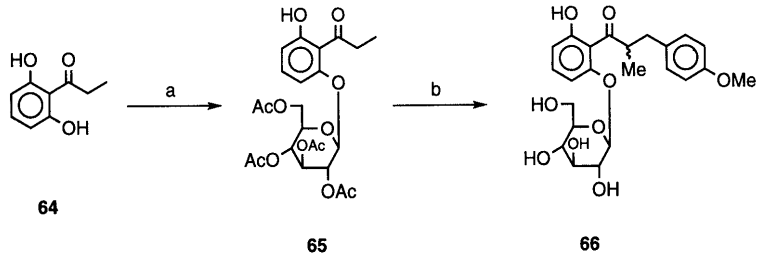

Chart 6

a) acetobromoglucose, $CdCO_3$, toluene, reflux; b) *p*-anisaldehyde, 50% aq. KOH, EtOH then H_2/10% Pd–C

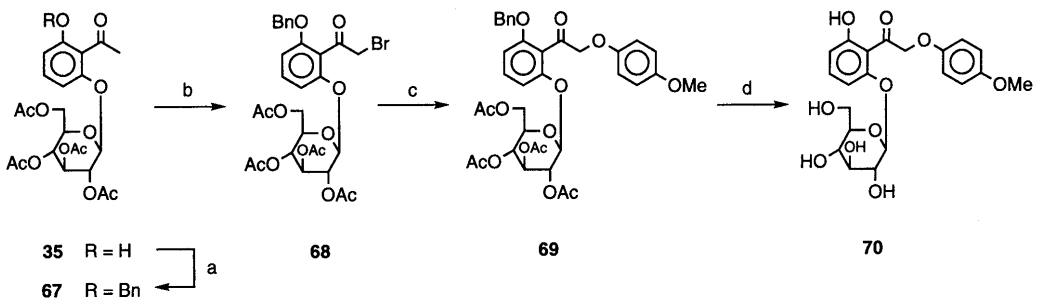

Chart 7

a) $PhCH_2Br$, NaH, DMF; b) $CuBr_2$, $CaCO_3$, $CHCl_3$–AcOEt, reflux; c) *p*-methoxyphenol, K_2CO_3, DMF; d) H_2/10% Pd–C, 25% aq. KOH, EtOH–THF

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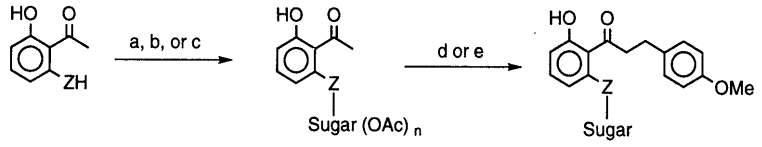
glucose were prepared (Chart 8). The reaction of 2′,6′-dihydroxyacetophenone (**72**) with appropriate acetobromosugars afforded the corresponding glycosides **74**—**77**. The galactoside **74** (62%), maltoside **76** (62%), and lactoside **77** (63%) were prepared by glycosylation using $CdCO_3$ as a base by the same method as shown in Chart 6, but the xyloside **75** could not be prepared by this method because of the instability of the acetobromoxylose under

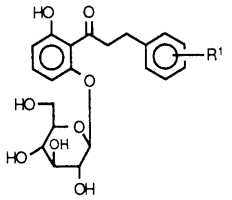


72 Z = O
73 Z = S
74 ~ 78
79 ~ 83

Chart 8

a) acetobromosugar, $CdCO_3$, toluene, reflux; b) acetobromoxylose, Bu_4NHSO_4, CH_2Cl_2/4% aq. NaOH then K_2CO_3; c) pentaacetylglucose, $SnCl_4$, CH_2Cl_2; d) *p*-anisaldehyde, 50% aq. KOH, EtOH, then H_2/10% Pd–C; e) *p*-anisaldehyde, 50% aq. KOH, EtOH, then NaTeH, EtOH

Table 1. Physical and Biological Properties of 4′-Dehydroxyphlorizin Derivatives (**1**)



No.	R^1	Method	Yield[a] (%)	mp (°C) (Recryst. solvent)	Formula	*Anal.* Calcd (Found) C	H	N	Urinary glucose excretion[b] (mg/24 h) *p.o.*	i.p.
1	4-OMe[c]								340±18	204± 8
2	3-OMe	A	31	105—107 (iso-Pr_2O)	$C_{22}H_{26}O_9$	60.82 (60.87	6.03 6.29)		66±12	88± 6
3	2-OMe	A	52	Amorphous	$C_{22}H_{26}O_9 \cdot 1/4H_2O$	60.20 (60.37	6.08 6.06)		8± 1	11± 2
4	4-OEt	A	46	76.5—78 (MeO-H_2O)	$C_{23}H_{28}O_9 \cdot 3/4H_2O$	59.77 (59.55	6.44 6.42)		124±27	77± 9
5	3-OH	A	54	127—130 (Et_2O)	$C_{21}H_{24}O_9 \cdot 5/4H_2O$	56.95 (57.05	6.03 5.96)		3± 0	NT
6	2-OH	A	53	128—132 (Et_2O)	$C_{21}H_{24}O_9 \cdot 1/2H_2O$	58.74 (58.45	5.87 5.69)		2± 1	14± 3
7	H	A	54	126—129 (Et_2O–iso-Pr_2O)	$C_{21}H_{24}O_8 \cdot 1/4H_2O$	61.68 (61.88	6.04 5.91)		217±18	160± 8
8	2-Me	A	32	Amorphous	$C_{22}H_{26}O_8 \cdot 1/4H_2O$	62.48 (62.37	6.32 6.28)		21±11	9± 3
9	3-Me	A	49	78—81 (Acetone-H_2O)	$C_{22}H_{26}O_8 \cdot 3/4H_2O$	61.17 (61.18	6.39 6.42)		299±35	160±11
10	4-Me	A	49	105— (iso-Pr_2O)	$C_{22}H_{26}O_8 \cdot 1/4H_2O$	62.48 (62.76	6.32 6.24)		344±84	144±10
11	4-Et	A	51	127.5—129.5 (Et_2O–iso-Pr_2O)	$C_{23}H_{28}O_8$	63.88 (63.59	6.53 6.51)		277±64	76± 6
12	4-*i*-Pr	A	33	109—112 (Et_2O–iso-Pr_2O)	$C_{24}H_{30}O_8$	64.56 (64.28	6.77 6.64)		31± 6	8± 3
13	4-Ph	A	42	Amorphous	$C_{27}H_{28}O_8$	67.49 (67.19	5.87 6.03)		NT	1± 1
14	4-NMe_2	A	32	Amorphous	$C_{23}H_{29}NO_8 \cdot 1/4H_2O$	61.12 (60.99	6.58 6.82	3.10 2.81)	178±22	122± 8
15	4-COOH	A	43	200.5—204 (MeOH–iso-Pr_2O)	$C_{22}H_{24}O_{10} \cdot 3/4H_2O$	57.20 (57.21	5.56 5.47)		4± 1	1± 0
16	4-$CONH_2$	A	35	178—181 (MeOH–iso-Pr_2O)	$C_{22}H_{25}NO_9 \cdot 1/2H_2O$	57.89 (57.81	5.74 5.66	3.07 2.99)	2± 1	83±23
17	4-CN	A	28	155—156.5 (MeOH–iso-Pr_2O)	$C_{22}H_{23}NO_8 \cdot H_2O$	59.06 (59.19	5.63 5.46	3.13 3.01)	4± 0	10± 1
18	4-Cl	B	48	142—144 (iso-Pr_2O)	$C_{21}H_{23}ClO_8$	57.47 (57.47	5.28 5.57)		253±23	115± 9
19	4-SMe	C	42	135—136 (CH_2Cl_2–iso-Pr_2O)	$C_{22}H_{26}O_8S \cdot 1/4H_2O$	58.07 (58.18	5.88 5.75)		101±21	NT

a) Isolated yield from **35**. *b*) Urinary glucose level was measured after two administrations of the test compound (*p.o.*, 100 mg/kg; i.p., 10 mg/kg),[1] NT: not tested. *c*) Reference 1.

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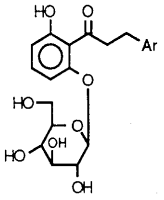
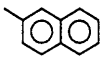
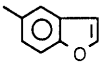
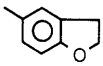
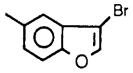
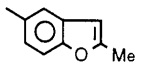
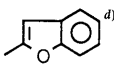
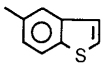
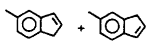
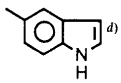
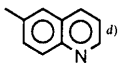
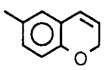
the reaction conditions. Therefore we examined the glycosylation using a phase-transfer catalyst.[11] The tetrabutylammonium phenoxide of compound **72** in CH_2Cl_2, prepared from **72** and tetrabutylammonium hydrogensulfate (1.2 mol eq) by stirring in the two-phase system of CH_2Cl_2 and aqueous NaOH, was reacted with aceto-

Table 2. Physical and Biological Properties of 4′-Dehydroxyphlorizin Derivatives (**2**)



No.	Ar	Method	Yield[a] (%)	mp (°C) (Recryst. solvent)	Formula	*Anal.* Calcd (Found) C	H	N	Urinary glucose excretion[b] (mg/24 h) *p.o.*	i.p.
20		A	22	150—153 (CH_2Cl_2–iso-Pr_2O)	$C_{19}H_{22}O_9 \cdot 1/2H_2O$	56.57 (56.68	5.75 5.50)		39±14	NT
21		C	43	62—70 (iso-Pr_2O)	$C_{19}H_{22}O_8S \cdot 5/4H_2O$	52.71 (52.61	5.70 5.45)		53±11	NT
22		A	17	157—159 (MeOH–iso-Pr_2O)	$C_{20}H_{23}NO_8 \cdot 1/2H_2O$	57.97 (57.75	5.84 5.80	3.38 3.29)	3± 1	9± 4
23		A	54	97—100 (Et_2O–iso-Pr_2O)	$C_{25}H_{26}O_8$	66.07 (66.03	5.77 5.78)		224±36	350±46
24		A	64	80— (iso-Pr_2O)	$C_{25}H_{26}O_8 \cdot 1/2H_2O$	64.79 (65.00	5.87 5.85)		3± 1	NT
25		D	58	73— (EtOH–H_2O)	$C_{23}H_{24}O_9 \cdot 1/2H_2O$	60.92 (61.07	5.56 5.51)		591±105	NT
26		B	91[c]	59— (CH_2Cl_2–iso-Pr_2O)	$C_{23}H_{26}O_9 \cdot 1.5H_2O$	58.35 (58.32	6.17 5.89)		149±10	NT
27		C	47	175—176.5 (AcOEt)	$C_{23}H_{23}BrO_9$	52.79 (52.85	4.43 4.40)		6± 1	NT
28		D	65	170—172 (Et_2O–iso-Pr_2O)	$C_{24}H_{26}O_9$	62.88 (62.60	5.72 5.77)		17± 8	NT
29	 [d]	C	22	78— (iso-Pr_2O)	$C_{23}H_{24}O_9 \cdot 1/4H_2O$	61.53 (61.74	5.50 5.80)		88±31	NT
30		C	57	63— (iso-Pr_2O)	$C_{23}H_{24}O_8S \cdot 3/4H_2O$	58.28 (58.37	5.42 5.40)		307±13	NT
31	 (1 : 1 mixture)	C	[e]	Amorphous	$C_{24}H_{26}O_8 \cdot 1/2H_2O$	63.85 (63.61	6.30 6.30)		327±43	NT
32	 [d]	A	63	124—126 ($CHCl_3$–AcOEt)	$C_{23}H_{25}NO_8 \cdot 1.5H_2O$	58.72 (58.42	6.00 6.06	2.98 2.70)	67±13[f]	NT
33	 [d]	B	42	179.5—180.5 (AcOEt)	$C_{24}H_{25}NO_8 \cdot 1/4H_2O$	62.67 (62.68	5.59 5.54	3.05 2.98)	21± 8[f]	NT
34		C	35	68— (Et_2O–iso-Pr_2O)	$C_{24}H_{26}O_9 \cdot 1/2H_2O$	61.66 (61.44	5.82 5.71)		96±68[f]	NT

a) Isolated yield from **35**. *b*) Urinary glucose level was measured after two administrations of the test compound (*p.o.*, 100 mg/kg; i.p., 10 mg/kg),[11] NT: not tested. *c*) Isolated yield from **25**. *d*) The appropriate aldehydes used for the condensation were prepared according to the literature.[18–20] *e*) See experimental section. *f*) Urinary glucose level was measured after a single administration of the test compound (*p.o.*, 100 mg/kg). Under this condition, urinary glucose was 334±32 mg/24 h when compound **25** was administered.

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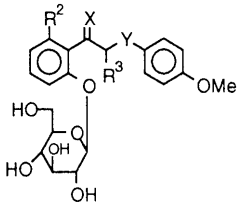
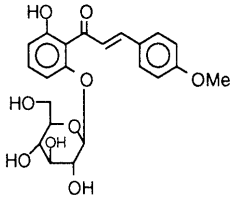
bromoxylose in the presence of excess K_2CO_3 at room temperature to give the xyloside **75** in 61% yield. The condensation of the glycosides **74**—**77** with *p*-anisaldehyde followed by catalytic hydrogenation, in the same manner as shown in Chart 1, method A, afforded the dihydrochalcone derivatives **79**—**82** (Chart 8, Table 4). Compound **83**, a thioglucoside analogue of **1**, was also prepared. The reaction of 6′-hydroxy-2′-mercaptoacetophenone (**73**)[15] with pentaacetyl-β-D-glucose in the presence of $SnCl_4$ in CH_2Cl_2 at room temperature[16] gave the pentaacetyl thioglucoside **78** (89%). The condensation of **78** with *p*-anisaldehyde followed by reduction with NaTeH afforded the desired thioglucoside **83** in the same manner as shown in Chart 1, method C, (Chart 8, Table 4).

Biological Results and Discussion

The effect of the compounds thus prepared on urinary glucose excretion[1] was investigated in rats and the results are summarized in Tables 1—4. First we focused our

Table 3. Physical and Biological Properties of Analogues of Compound **1**



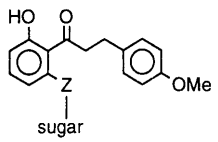


71

No.	R^2	X	R^3	Y	mp (°C) (Recryst. solvent)	Formula	*Anal.* Calcd (Found)			Urinary glucose excretion[a] (mg/24 h)	
							C	H	N	*p.o.*	i.p.
59	H	O	H	CH_2	Oil	$C_{22}H_{26}O_8$[c]				1± 0	NT
60	OMe	O	H	CH_2	Amorphous	$C_{23}H_{28}O_9 \cdot 3/4H_2O$	59.80 (59.82	6.44 6.34)		118±23	NT
61	OBu^n	O	H	CH_2	104—107 (EtOH–Et_2O)	$C_{26}H_{34}O_9 \cdot 1/4H_2O$	63.08 (63.11	7.02 6.99)		17± 3	NT
62	OH	H, OH	H	CH_2	90—93 (iso-PrOH–iso-Pr_2O)	$C_{22}H_{28}O_9 \cdot 1/2H_2O$	59.32 (59.61	6.56 6.86)		2± 0	4±3
63	OH	NOH	H	CH_2	98—105 (iso-PrOH–iso-Pr_2O)	$C_{22}H_{27}NO_9 \cdot 1/4H_2O$	58.21 (58.05	6.11 6.40	3.09 2.81)	2± 0	12±2
66	OH	O	Me	CH_2	Amorphous	$C_{23}H_{28}O_9 \cdot 3/4H_2O$	59.80 (60.07	6.44 6.70)		3± 1	NT
70	OH	O	H	O	Amorphous	$C_{21}H_{24}O_{10} \cdot 3/4H_2O$	56.06 (55.97	5.71 5.88)		4± 1	NT
71[b]										1± 2	NT

a) Urinary glucose level was measured after two administrations of the test compound (*p.o.*, 100 mg/kg; i.p., 10 mg/kg),[1] NT: not tested. *b*) Reference 1. *c*) HR FAB-MS *m/z*: 441.1532 (Calcd for $C_{22}H_{26}NaO_8$: 441.1526).

Table 4. Physical and Biological Properties of Analogues Modified at the Sugar Moiety



No.	Z	Sugar	Yield[a] (%)	mp (°C) (Recryst. solvent)	Formula	*Anal.* Calcd (Found)		Urinary glucose excretion[b] (mg/24 h)	
						C	H	*p.o.*	i.p.
79	O	β-D-Galactopyranoside	72	163.5—166 (iso-Pr_2O)	$C_{22}H_{26}O_9 \cdot H_2O$	58.40 (58.57	6.24 6.19)	5±1	NT
80	O	β-D-Xylopyranoside	60	77— (iso-PrOH–Et_2O)	$C_{20}H_{24}O_8 \cdot 1/4H_2O$	60.52 (60.49	6.22 6.37)	3±0	NT
81	O	β-Maltoside	57	92— (EtOH–Et_2O)	$C_{28}H_{36}O_{14} \cdot 3/4H_2O$	55.12 (55.28	6.20 6.36)	157±15	110±13
82	O	β-Lactoside	17	212—215 (EtOH)	$C_{28}H_{36}O_{14} \cdot 3/4H_2O$	55.12 (55.24	6.20 6.11)	3±2	NT
83	S	β-D-Glucopyranoside	41	Amorphous	$C_{22}H_{26}O_8S$	57.96 (57.79	5.88 6.03)	2±1	NT

a) Isolated yield from **74**—**78**. *b*) Urinary glucose level was measured after two administrations of the test compound (*p.o.*, 100 mg/kg; i.p., 10 mg/kg),[1] NT: not tested.

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attention upon the substituent on the A ring (Table 1). The non-substituted derivative (**7**) and the compounds containing some electron-donating substituent at the 3- or 4-position (**1**, **9**, **10**, **11**, and **14**) showed strong activity after oral administration (*p.o.*) or intraperitoneral injection (i.p.). The compounds containing an electron-withdrawing substituent (**15**—**17**) were almost inactive *p.o.*, but the 4-Cl derivative **18** was exceptionally active. As the alkyl or alkoxy group became larger, the activity tended to be reduced (**1** *vs.* **4**; **10**—**12**). On the other hand, the compounds possessing the substituent at the 2-position (**3**, **6**, and **8**) were almost inactive. In the previous paper,[1] we reported that the activity was greatly reduced as the number of the substituents on the A ring was increased, as follows: 4-OMe derivative (**1**) > 3,4-$(OMe)_2$ derivative > 3,4,5-$(OMe)_3$ derivative. Therefore we assume that the binding pocket for the A ring is restricted, especially at the region corresponding to the 2-position of the phenyl group.

We further examined compounds in which the A-benzene ring was replaced with other aromatic moieties (Table 2). The 2-furyl derivative **20** and the 2-thienyl derivative **21** showed weak activity and the 4-pyridyl derivative **22** was almost inactive. Interestingly, the 2-naphthyl derivative **23** showed a strong effect on urinary glucose excretion. On the other hand, the 1-naphthyl derivative **24**, corresponding to the 2,3-substituted derivative on the A ring, and the biphenyl derivative **13** having almost the same lipophilicity, were inactive. These results suggest that a coplanar ring fusion at the 3,4-positions of the A ring is permissible with retention of the activity. In further investigations of the fused-bicyclic analogues (**25**—**34**), we found that the 5-benzofuryl (**25**), 5-benzothienyl (**30**), and 5- and/or 6-indenyl (**31**) derivatives showed strong activities. In particular, **25** was more active than compound **1**. However, the activity was reduced in the dihydro and the substituted derivatives of **25** (**26**, **27**, and **28**) or the 2-benzofuryl derivative **29**.

We examined the inhibitory effects of the 4′-dehydroxyphlorizin derivatives on SGLT using rat renal brush border membrane vesicles (BBMV),[1] and the results are shown in Fig. 1. Compound **25** showed the most potent inhibitory effect and compound **11** was less potent. These results showed a good correlation with the effects on urinary glucose excretion.

Next, we examined the modification of the 6′-OH group on the B ring and at the bridge part linking the A and B rings (Table 3). The 6′-dehydroxy derivative **59** was inactive. While compound **60** methylated at the 6′-OH group showed moderate activity, the *n*-butylated compound **61** had very weak activity. These results suggest that the 6′-OH group is essential for the activity. The conversion of the ketone to the alcohol (**62**) or the oxime (**63**) resulted in loss of the activity. Accordingly, the ketone on the bridge part is necessary to exhibit the activity. Compound **66** having a methyl group at the α position to the ketone, compound **70** in which the carbon atom is replaced with an oxygen atom, and the enone derivative (**71**)[1] were completely inactive. Diedrich has already reported that the 4′-hydroxy analogue of **71** (phlorizin chalcone) had no effect on the renal reabsorption of

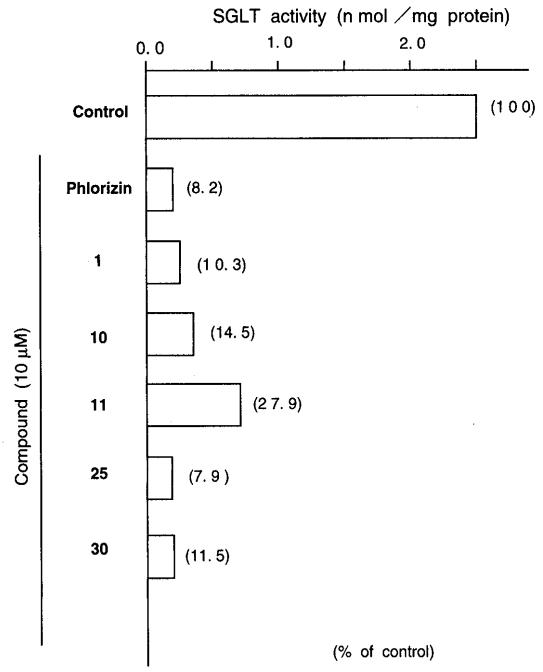

Fig. 1. Inhibitory Effect of 4′-Dehydroxyphlorizin Derivatives on Rat Kidney SGLT

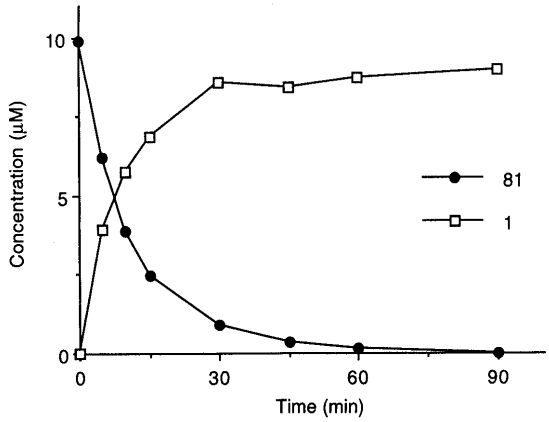

Fig. 2. Metabolism of the Maltoside **81** to the Glucoside **1** in Rat Plasma

glucose.[17] These results suggest that the bridge structure is extremely important and any modification at this part may reduce the activity.

Finally, we examined analogues in which the sugar moiety was modified (Table 4). The galactoside **79**, the xyloside **80**, and the lactoside **82** were inactive. The maltoside **81**, however, showed comparatively strong activity. When the maltoside **81** was incubated in rat plasma, it was converted quickly to the glucoside **1** (90% conversion after 90 min) as shown in Fig. 2. This result suggests that **81** is metabolized to the glucoside **1** in the body and then shows activity. Therefore, the glucose moiety is necessary to exhibit the activity. On the other hand, the thioglucoside **83** had no effect. This result suggests that **83** is not recognized by SGLT, because of the considerable change in the distance or the conformation between the aglycon and the sugar moiety due to the conversion of *O*-glucoside to *S*-glucoside.

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Conclusions

We synthesized a new series of 4′-dehydroxyphlorizin derivatives and examined their effect on the urinary glucose excretion. Studies on SARs revealed that there is a fairly strict conformational requirement for activity. Compounds possessing an electron-donating substituent at the 3- or 4-position on the A ring were potent (**1**, **7**, **9**, **10**, **11**, and **14**), but the introduction of the substituent at the 2-position resulted in loss of the activity (**3**, **6**, and **8**). The strong activity of the 2-naphthyl derivative **23** showed that coplanar ring fusion at the 3,4-positions was allowed. In a further investigation of fused-bicyclic analogues, we found that the 5-benzofuryl derivative **25** was the most potent among them. We also found that the 6′-OH group on the B ring and the bridge structure linking the A and B rings were essential for the activity. Finally, β-D-glucose was necessary as a sugar moiety for the activity.

We found that the 5-benzofuryl derivative **25** was superior to compound **1**. Thus compound **25** has been selected as a new lead for further investigation.

Experimental

All melting points were determined on a Büchi 535 digital melting point apparatus without correction. Infrared (IR) spectra were taken on an Analect FX-6200 FT-IR spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-FX-200 or a Varian Gemini 300 spectrometer. Mass spectra were recorded on a JEOL JMS-HX100 mass spectrometer. Microanalyses were performed on a Perkin–Elmer 2400 C, H, N analyzer.

2′,6′-Dihydroxy-3-methoxydihydrochalcone 2′-*O*-β-D-Glucopyranoside (2) (Method A) A 50% aqueous KOH solution (3 ml) was added to a suspension of **35**[1] (1.20 g, 2.49 mmol) in EtOH (12 ml) and the mixture was stirred at room temperature for 10 min. Then *m*-anisaldehyde (0.51 g, 3.73 mmol) was added and the whole was stirred at room temperature for 15 h. The reaction mixture containing the chalcone **36** was diluted with water and washed with toluene to remove excess aldehyde. The aqueous layer was hydrogenated over 10% Pd–C (0.5 g) at room temperature for 1 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 the residue was purified by column chromatography on silica gel using $CHCl_3$–MeOH (9 : 1) as an eluent and triturated in iso-Pr_2O to give **2** (0.34 g, 31%). IR (Nujol): 3600—3000, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.88 (2H, t, J=7.3 Hz), 3.2—3.6 (6H, m), 3.47 (1H, dd, J=5.9, 11.5 Hz), 3.6—3.8 (4H, m), 4.56 (1H, t, J=5.9 Hz), 4.91 (1H, d, J=6.8 Hz), 5.03 (1H, d, J=5.4 Hz), 5.10 (1H, d, J=4.4 Hz), 5.23 (1H, d, J=4.9 Hz), 6.55 (1H, d, J=7.8 Hz), 6.68 (1H, d, J=8.3 Hz), 6.7—6.8 (3H, m), 7.1—7.3 (2H, m), 11.00 (1H, s). FAB-MS *m/z*: 457 $(M+Na)^+$.

Compounds **3**—**17**, **20**, **22**—**24**, and **32** were prepared by the same procedure as employed for the preparation of **2**. Physical data of these compounds are listed in Tables 1 and 2.

4-Chloro-2′,6′-dihydroxydihydrochalcone 2′-*O*-β-D-Glucopyranoside (18) (Method B) **35** (1.17 g, 2.42 mmol) was condensed with *p*-chlorobenzaldehyde (0.51 g, 3.63 mmol) by the same procedure as described for the synthesis of **2**. The reaction mixture was neutralized with 10% HCl and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue containing the chalcone was hydrogenated over 10% Pd–C (0.4 g) in AcOH (15 ml) at room temperature for 1 h. The catalyst was removed and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel ($CHCl_3$–MeOH (9 : 1)) and triturated in iso-Pr_2O to give **18** (0.51 g, 48%). IR (Nujol): 3400, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.90 (2H, t, J=7.3 Hz), 3.1—3.4 (6H, m), 3.45 (1H, m), 3.70 (1H, dd, J=4.9, 11.2 Hz), 4.57 (1H, t, J=5.4 Hz), 4.91 (1H, d, J=6.8 Hz), 5.04 (1H, d, J=3.9 Hz), 5.11 (1H, br), 5.26 (1H, d, J=4.4 Hz), 6.55 (1H, d, J=8.3 Hz), 6.68 (1H, d, J=8.3 Hz), 7.24 (1H, t, J=8.3 Hz), 7.30 (4H, s), 10.95 (1H, s). FAB-MS *m/z*: 461/463 $(M+Na)^+$.

Compound **33** was prepared by the same procedure as described above. Compound **26** was prepared by the reduction of **25** under the same conditions.

2′,6′-Dihydroxy-4-methylthiodihydrochalcone 2′-*O*-β-D-Glucopyranoside (19) (Method C) Compound **35** (1.20 g, 2.49 mmol) was condensed with *p*-(methylthio)benzaldehyde (0.57 g, 3.74 mmol) by the same procedure as used in method B. The resultant residue containing the chalcone was dissolved in EtOH (1.2 ml) and added to a suspension of NaTeH[4] (3.74 mmol) in EtOH (5 ml) at −20 °C. The whole was stirred at room temperature for 3 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 (9 : 1)) and triturated in CH_2Cl_2–iso-Pr_2O to give **19** (0.47 g, 42%). IR (Nujol): 3600—3200, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.44 (3H, s), 2.86 (2H, t, J=7.4 Hz), 3.1—3.4 (6H, m), 3.45 (1H, dd, J=5.8, 11.7 Hz), 3.70 (1H, ddd, J=1.7, 5.1, 10.5 Hz), 4.56 (1H, t, J=5.7 Hz), 4.91 (1H, d, J=7.4 Hz), 5.03 (1H, d, J=5.2 Hz), 5.10 (1H, d, J=4.7 Hz), 5.24 (1H, d, J=5.3 Hz), 6.55 (1H, d, J= 8.2 Hz), 6.68 (1H, d, J=8.2 Hz), 7.16 (2H, d, J=8.5 Hz), 7.22 (2H, d, J=8.5 Hz), 7.24 (1H, t, J=8.3 Hz), 11.00 (1H, s). FAB-MS *m/z*: 473 $(M+Na)^+$.

Compounds **21**, **27**, **29**, **30**, and **34** were prepared by the same procedure as described above.

2-(Benzo[*b*]furan-5-yl)-2′,6′-dihydroxypropiophenone 2′-*O*-β-D-Glucopyranoside (25) (Method D) Compound **35** (1.00 g, 2.07 mmol) was condensed with benzofuran-5-carboxaldehyde (**37**)[5] (0.33 g, 2.28 mmol) by the same procedure as described for the synthesis of **2**. DMAP (0.25 g, 2.07 mmol) was added to the reaction mixture and the whole was hydrogenated over 10% Pt–C (0.20 g) at room temperature for 6 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, then the residue was chromatographed on silica gel ($CHCl_3$–MeOH (9 : 1)) and crystallized from EtOH–H_2O to give **25** (0.67 g, 71%). IR (Nujol): 3380, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.00 (2H, t, J=7.5 Hz), 3.1—3.4 (6H, m), 3.47 (1H, m), 3.71 (1H, ddd, J=1.7, 5.1, 11.4 Hz), 4.56 (1H, t, J=5.7 Hz), 4.93 (1H, d, J=7.3 Hz), 5.03 (1H, d, J=5.2 Hz), 5.10 (1H, d, J=4.5 Hz), 5.25 (1H, d, J=5.3 Hz), 6.55 (1H, dd, J=0.7, 8.4 Hz), 6.68 (1H, d, J=8.0 Hz), 6.88 (1H, dd, J=1.0, 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=8.4 Hz), 7.53 (1H, d, J=1.4 Hz), 7.92 (1H, d, J=2.2 Hz), 10.98 (1H, s). FAB-MS *m/z*: 467 $(M+Na)^+$.

Compound **28** was prepared by the same procedure as described above.

2,3-Dibromo-2,3-dihydrobenzo[*b*]furan-5-carboxaldehyde (38) A mixture of benzofuran-5-carboxaldehyde (**37**) (146 mg, 1 mmol), Br_2 (160 mg, 1 mmol) and AcOH (1 ml) was stirred under argon at 100 °C for 30 min. The reaction mixture was diluted with AcOEt–Et_2O, washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (hexane–AcOEt (4 : 1)) to give **38** (215 mg, 70%) as a yellow oil. IR (Neat): 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.77 (1H, s), 6.95 (1H, s), 7.20 (1H, d, J=8.3 Hz), 7.94 (1H, dd, J=8.4 Hz), 8.07 (1H, d, J=1.8 Hz), 9.96 (1H, s). MS *m/z*: 304/306/308 (M^+).

5-Bromo-2-methylbenzo[*b*]furan (41) A mixture of 5-bromosalicylaldehyde (**39**) (5.00 g, 24.87 mmol), ethyl 2-bromopropionate (4.95 g, 27.36 mmol), K_2CO_3 (10.30 g, 74.61 mmol) and acetone (75 ml) was stirred at room temperature for 15 h and at 50 °C for 3.5 h. The reaction mixture was diluted with AcOEt and filtered through a plug of Celite, then the filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH (50 ml). An 8% aqueous NaOH solution (15 ml) was added to the above solution under ice-cooling and the whole was stirred for 1 h. It was concentrated *in vacuo*, acidified with 10% HCl and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$, and evaporated to give 2-(4-bromo-2-formylphenoxy)propionic acid (**40**, 7.42 g) as a crude product.

Acetic anhydride (13 ml) was added dropwise to a mixture of **40** (7.42 g), sodium acetate (13 g) and AcOH (35 ml) under reflux for 2 h and the whole was stirred under reflux for another 1 h. It was cooled to 80 °C, then H_2O (25 ml) was added and the mixture was refluxed for 1 h. After cooling, H_2O (150 ml) and hexane (150 ml) were added. The organic layer was separated, washed with water and water saturated with $NaHCO_3$, dried over $MgSO_4$, and evaporated to give 5-bromo-2-methylbenzo[*b*]furan (**41**) (2.58 g, 49%) as a pale yellow oil. IR (Neat): 1600, 1455, 1260, 1050, 790 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, d, J=1.1 Hz), 6.31 (1H, t, J=1.1 Hz), 7.25 (1H, d, J=8.6 Hz), 7.29 (1H, dd, J=1.8, 8.6 Hz), 7.58 (1H, d, J=1.8 Hz). MS *m/z*: 210/212 (M^+).

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5-Formyl-2-methylbenzo[*b*]furan (42) A mixture of Mg (318 mg, 13.08 mmol), a catalytic amount of I_2, and tetrahydrofuran (THF) (4 ml) was heated at 50 °C under argon for 10 min. A solution of **41** (2.58 g, 12.22 mmol) in THF (6 ml) was added dropwise and the whole was stirred for 30 min. It was cooled to 5 °C and DMF (1.16 g, 15.89 mmol) was added over 15 min. The reaction mixture was stirred under ice-cooling for 1 h, then 10% HCl (10 ml) and brine (6 ml) were added. The whole was stirred for 1 h and extracted with AcOEt and the organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel ($CHCl_3$) to give **42** (1.18 g, 60%) as a yellow oil. IR (Neat): 1690, 1610, 1440, 1260 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.49 (3H, d, J=1.1 Hz), 6.49 (1H, m), 7.51 (1H, d, J=8.4 Hz), 7.78 (1H, dd, J=1.7, 8.5 Hz), 8.01 (1H, d, J=1.6 Hz), 10.04 (1H, s). MS m/z: 160 (M^+).

Benzo[*b*]thiophene-5-carboxaldehyde (44) Compound **44** was prepared from 5-bromobenzo[*b*]thiophene (**43**)[7] (5.57 g, 26.14 mmol) by the same procedure as described for the synthesis of **42** in 62% yield as yellow prisms, mp 56—57 °C (iso-Pr_2O). IR (Nujol): 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.48 (1H, dd, J=0.9, 5.6 Hz), 7.57 (1H, d, J=5.5 Hz), 7.87 (1H, dd, J=1.5, 8.4 Hz), 8.00 (1H, dd, J=0.7, 8.4 Hz), 8.31 (1H, d, J=1.5 Hz), 10.11 (1H, s). MS m/z: 162 (M^+).

2*H*-1-Benzopyran-6-carboxaldehyde (47) A mixture of *p*-hydroxybenzaldehyde (**45**) (1.22 g, 10 mmol), *p*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$) (95 mg, 0.5 mmol) and trimethyl orthoformate (5.5 ml) was stirred under argon at room temperature for 1.5 h. A 9.5% MeOH solution of $Mg(OMe)_2$ (11 ml) and toluene (20 ml) were added to the reaction mixture and the whole was refluxed with removal of MeOH in a Dean–Stark apparatus until the inner temperature rose to 95 °C. Paraformaldehyde ($(CH_2O)_n$) (1.20 g) was added in small portions and the reaction mixture was stirred at 95 °C for 1 h. Triphenylvinylphosphonium bromide (5.54 g, 15 mmol) and K_2CO_3 (1.38 g, 10 mmol) were added and the whole was heated at reflux for 13 h. Further triphenylvinylphosphonium bromide (3.69 g) and K_2CO_3 (1.38 g) were added. The mixture was refluxed for 8 h, cooled in an ice-bath, acidified with 10% HCl and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (hexane–AcOEt (9 : 1)) to give **47** (289 mg, 18%) as a yellow oil. IR (Neat): 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.97 (2H, dd, J=1.9, 3.4 Hz), 5.83 (1H, td, J=3.4, 9.9 Hz), 6.46 (1H, td, J=1.9, 9.9 Hz), 6.85 (1H, d, J=8.2 Hz), 7.48 (1H, d, J=2.0 Hz), 7.63 (1H, dd, J=2.0, 8.2 Hz), 9.82 (1H, s). MS m/z: 160 (M^+).

1*H*-Indene-5-carboxaldehyde (50) and 1*H*-Indene-6-carboxaldehyde (51) A 1 : 1 mixture of **50** and **51** was prepared from 5-bromo-1*H*-indene (**49**)[10] (1.95 g, 10 mmol) by the same procedure as described for the synthesis of **42** in 9% yield as a yellow oil. IR (Neat): 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.49 (3H, m), 6.67 and 6.83 (1H, td, J=2.0, 5.5 Hz), 6.95 (1H, m), 7.53 and 7.61 (1H, d, J=7.7 Hz), 7.73 and 7.81 (1H, dd, J=1.5, 7.7 Hz, and m), 7.90 and 7.98 (1H, d, J=1.5 Hz and m), 10.02 and 10.04 (1H, s). MS m/z: 144 (M^+).

6-Bromo-1-tetrahydropyranyloxyindane (52) A mixture of 6-bromoindanol (**48**)[10] (3.01 g, 14.13 mmol), dihydropyran (DHP) (1.78 g, 21.20 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (178 mg, 0.71 mmol) in CH_2Cl_2 (50 ml) was stirred at room temperature for 1.5 h. The reaction mixture was washed with saturated $NaHCO_3$, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (hexane–AcOEt (9 : 1)) to give **52** (4.10 g, 98%) as a colorless oil. IR (Neat): 2930, 1470, 1200, 1030, 870 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.9 (6H, m), 2.00 and 2.16 (1H, m), 2.43 (1H, m), 2.74 (1H, m), 2.99 (1H, m), 3.59 (1H, m), 3.98 (1H, m), 4.83 (1H, dd, J=2.9, 4.0 Hz), 5.11 and 5.27 (1H, dd, J=5.5, 6.6 Hz, and 5.9, 6.2 Hz), 7.09 and 7.12 (1H, d, J=7.7 Hz, and 7.3 Hz), 7.34 and 7.35 (1H, dd, J=2.2, 8.1 Hz), 7.47 and 7.58 (1H, d, J=1.8 Hz, and 1.5 Hz). MS m/z: 296/298 (M^+).

1-Tetrahydropyranyloxyindane-6-carboxaldehyde (53) Compound **53** was prepared from **52** (2.60 g, 8.75 mmol) by the same procedure as described for the synthesis of **42** in 50% yield as a pale yellow oil. IR(Neat): 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.9 (6H, m), 2.06 and 2.24 (1H, m), 2.49 (1H, m), 2.87 (1H, m), 3.12 (1H, m), 3.61 (1H, m), 4.00 (1H, m), 4.88 (1H, m), 5.20 and 5.36 (1H, dd, J=5.2, 6.6 Hz and t, J=6.1 Hz), 7.38 and 7.41 (1H, d, J=7.3 Hz, and 7.0 Hz), 7.77 and 7.78 (1H, dd, J=1.5, 7.7 Hz). 7.86 and 7.97 (1H, br s), 10.00 and 10.01 (1H, s). MS m/z: 246 (M^+).

2′,6′-Dihydroxy-2-(1-tetrahydropyranyloxyindan-6-yl)propiophenone 2′-*O*-*β*-D-Glucopyranoside (54) Compound **35** (1925 mg, 3.99 mmol) was condensed with the aldehyde **53** (1081 mg, 4.39 mmol) followed by reduction with NaTeH in the same manner as described for the synthesis of **19** to give **54** (1180 mg, 54%). ^{1}H-NMR (DMSO-d_6) δ: 1.4—1.8 (6H, m), 1.90 and 2.00 (1H, m), 2.30 (1H, m), 2.70 (1H, m), 2.8—3.0 (3H, m), 3.1—3.4 (6H, m), 3.47 (2H, m), 3.70 (1H, m), 3.85 (1H, m), 4.54 (1H, t, J=5.7 Hz), 4.80 (1H, m), 4.90 (1H, d, J=7.4 Hz), 5.01 (1H, d, J=5.4 Hz), 5.04 and 5.14 (1H, dd, J=4.5, 6.7 Hz, and 5.1, 6.6 Hz), 5.07 (1H, d, J=4.6 Hz), 5.19 (1H, m), 6.55 (1H, d, J=7.7 Hz), 6.68 (1H, d, J=8.3 Hz), 7.14 (2H, br s), 7.18 and 7.21 (1H, br s), 7.25 (1H, t, J=8.3 Hz), 11.50 and 11.70 (1H, s). FAB-MS m/z: 567 $(M+Na)^+$.

6′-Acetoxy-2′-hydroxy-2-(1-hydroxyindan-6-yl)propiophenone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-*β*-D-glucopyranoside) (55) A mixture of **54** (1160 mg, 2.13 mmol), Ac_2O (1.63 g, 16 mmol) and pyridine (10 ml) was stirred at room temperature for 13 h. The reaction mixture was concentrated *in vacuo*, diluted with AcOEt, and then washed with 10% HCl, saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and evaporated to give the peracetylated derivative of **54** (1438 mg). The resultant residue was dissolved in AcOH (20 ml), THF (10 ml) and H_2O (5 ml) and heated at 45 °C for 3 h. The reaction mixture was diluted with AcOEt, washed with water and saturated $NaHCO_3$, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$–acetone (9 : 1)) to give **55** (1071 mg, 75%). ^{1}H-NMR (DMSO-d_6) δ: 1.75 (1H, m), 1.93 and 1.95 (3H, s), 1.97 (3H, s), 2.01 (6H, s), 2.07 (3H, s), 2.30 (1H, m), 2.65 (1H, m), 2.7—3.1 (5H, m), 4.09 (1H, br d, J=11.1 Hz), 4.20 (1H, dd, J=5.5, 12.2 Hz), 4.27 (1H, m), 4.9—5.2 (4H, m), 5.41 (1H, t, J=9.6 Hz), 5.61 and 5.62 (1H, d, J=8.0 Hz), 6.93 (1H, d, J=8.1 Hz), 7.05 (1H, dd, J=1.5, 7.7 Hz), 7.10 (1H, d, J=8.1 Hz), 7.12 (1H, d, J=7.7 Hz), 7.18 (1H, br s), 7.48 (1H, t, J=8.3 Hz). FAB-MS m/z: 693 $(M+Na)^+$.

2′,6′-Dihydroxy-2-(indene-5 and 6-yl)propiophenone 2′-*O*-*β*-D-Glucopyranoside (31) A mixture of **55** (1054 mg, 1.57 mmol), TsCl (329 mg, 1.73 mmol) and pyridine (12 ml) was stirred at 75 °C for 15 h. TsCl (150 mg) was added and the whole was heated at reflux for 2 d. It was concentrated *in vacuo*, diluted with AcOEt and then washed with 10% HCl, H_2O, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was dissolved in MeOH (20 ml), and K_2CO_3 (1 g) and H_2O (0.2 ml) were added. This mixture was stirred at room temperature for 1 h, acidified with 10% HCl under ice-cooling and then extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH (9 : 1)) to give **31** (441 mg, 65%). IR (Nujol): 3400, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.94 (2H, t, J=7.5 Hz), 3.1—3.4 (8H, m), 3.46 (1H, m), 3.70 (1H, ddd, J=1.9, 5.3, 11.7 Hz), 4.55 (1H, t, J=5.4 Hz), 4.93 (1H, d, J=7.3 Hz), 5.02 (1H, d, J=5.2 Hz), 5.09 (1H, d, J=4.7 Hz), 5.22 (1H, d, J=5.1 Hz), 6.53 and 6.58 (1H, td, J=2.0, 5.5 Hz), 6.55 (1H, d, J=8.4 Hz), 6.68 (1H, d, J=8.1 Hz), 6.88 (1H, m), 7.07 and 7.14 (1H, dd, J=1.5, 7.6 Hz, and 1.5, 7.8 Hz), 7.25 (1H, t, J=8.3 Hz), 7.29 and 7.36 (1H, d, J=8.0 Hz, and 7.6 Hz), 7.31 and 7.39 (1H, br s), 11.02 (1H, s). FAB-MS m/z: 465 $(M+Na)^+$.

2′-Hydroxyacetophenone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-*β*-D-glucopyranoside) (57) A mixture of 2′-hydroxyacetophenone **56** (681 mg, 5 mmol), acetobromoglucose (2056 mg, 5 mmol), benzyltri-*n*-butylammonium chloride (234 mg, 0.75 mmol), 5% aqueous NaOH (20 ml) and CH_2Cl_2 (10 ml) was stirred at room temperature. After 4 h, further acetobromoglucose (2056 mg) was added and the whole was stirred at room temperature for 24 h. The CH_2Cl_2 layer was separated, washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt–hexane (1 : 2)) and the product was crystallized from MeOH to give **57** (726 mg, 31%) as colorless needles, mp 141.5—142.5 °C. IR (Nujol): 1750, 1740, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.97 (3H, s), 2.01 (6H, s), 2.02 (3H, s), 2.42 (3H, s), 4.05—4.35 (3H, m), 5.04 (1H, dd, J=9.5, 9.9 Hz), 5.18 (1H, dd, J=7.9, 9.7 Hz), 5.43 (1H, dd, J=9.5, 9.7 Hz), 5.74 (1H, d, J=7.9 Hz), 7.16 (1H, m), 7.22 (1H, d, J=8.2 Hz), 7.53—7.62 (2H, m). ESI-MS m/z: 489 $(M+Na)^+$.

2′-Hydroxy-4-methoxychalcone 2′-*O*-*β*-D-Glucopyranoside (58) A mixture of **57** (933 mg, 2 mmol), *p*-anisaldehyde (327 mg, 2.4 mmol), 50% aqueous KOH (2 ml) and EtOH (10 ml) was stirred at room temperature for 16 h. The reaction mixture was neutralized with 10% HCl and extracted 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 (9 : 1)) to give **58** (588 mg, 71%). IR (Nujol): 3370, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.15—3.30 (2H, m), 3.30—3.43 (2H, m), 3.51 (1H, m), 3.72 (1H, m), 3.81 (3H, s), 4.63 (1H,

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t, J=5.7 Hz), 5.08 (1H, d, J=5.5 Hz), 5.12 (1H, d, J=4.8 Hz), 5.18 (1H, d, J=7.7 Hz), 5.28 (1H, d, J=5.3 Hz), 6.99 (2H, dd, J=1.8, 8.8 Hz), 7.12 (1H, m), 7.33 (1H, d, J=8.1 Hz), 7.50—7.58 (3H, m), 7.64 (1H, d, J=15.74 Hz), 7.76 (2H, d, J=8.8 Hz). ESI-MS m/z: 439 $(M+Na)^+$.

2′-Hydroxy-4-methoxydihydrochalcone 2′-*O*-β-D-Glucopyranoside (59) Compound **58** (397 mg, 0.95 mmol) was reduced with NaTeH in the same manner as described for the synthesis of **19** to give **59** (270 mg, 68%). IR (Nujol): 3400, 1675 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.84 (2H, t, J=7.5 Hz), 3.13—3.53 (7H, m), 3.71 (3H, s), 3.72 (1H, m), 4.58 (1H, t, J=5.7 Hz), 5.02 (1H, d, J=7.5 Hz), 5.07 (1H, d, J=5.3 Hz), 5.15 (1H, d, J=4.6 Hz), 5.34 (1H, d, J=5.1 Hz), 6.82 (2H, dd, J=2.1, 8.8 Hz), 7.08 (1H, m), 7.15 (2H, dd, J=2.0, 8.6 Hz), 7.26 (1H, d, J=8.1 Hz), 7.49 (2H, d, J=7.5 Hz). FAB-MS m/z: 441 $(M+Na)^+$.

2′-Hydroxy-4,6′-dimethoxydihydrochalcone 2′-*O*-β-D-Glucopyranoside (60) A mixture of **1** (869 mg, 2 mmol), iodomethane (568 mg, 4 mmol), K_2CO_3 (828 mg, 6 mmol) and DMF (10 ml) was stirred at room temperature for 20 h. The mixture was filtered through a plug of Celite and the solid was washed with AcOEt. The filtrate was washed with water, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH (9 : 1)) and triturated in iso-Pr_2O to afford **60** (673 mg, 75%). IR (Nujol): 3600—3200, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.80 (2H, t, J=8.1 Hz), 2.9—3.3 (7H, m), 3.44 (1H, dd, J=6.1, 11.9 Hz), 3.71 (6H, s), 4.55 (1H, t, J=5.9 Hz), 4.87 (1H, d, J=7.7 Hz), 5.02 (1H, d, J=5.3 Hz), 5.08 (1H, d, J=4.9 Hz), 5.19 (1H, d, J=5.5 Hz), 6.73 (1H, d, J=8.3 Hz), 6.82 (3H, d, J=8.7 Hz), 7.15 (2H, d, J=8.7 Hz), 7.30 (1H, d, J=8.4 Hz). FAB-MS m/z: 471 $(M+Na)^+$.

Compound **61** was prepared by the same procedure as described above.

2-(1-Hydroxy-3-(4-methoxyphenyl)propyl)resorcinol 1-*O*-β-D-Glucopyranoside (62) $NaBH_4$ (207 mg, 5.5 mmol) was added in small portions to an ice-cooled solution of **1** (793 mg, 1.83 mmol) in MeOH (10 ml). The mixture was stirred under ice-cooling for 1 h and then AcOH was added to make pH 3. The mixture was concentrated *in vacuo*, and the residue was dissolved in AcOEt. The solution was washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH (5 : 1)) to give **62** (642 mg, 81%). IR (Nujol): 3350 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.95 (2H, m), 2.60 (2H, m), 3.1—3.5 (5H, m), 3.70 (3H, s), 3.71 (1H, m), 4.53 (1H, m), 4.69 and 4.74 (1H, d, J=7.3 Hz, and 6.8 Hz), 5.00 (2H, br), 5.20 (1H, br), 5.10 and 5.28 (1H, dd, J=5.4, 7.8 Hz, and 5.9, 6.8 Hz), 6.42 and 6.46 (1H, d, J=7.8 Hz, and 8.3 Hz), 6.61 and 6.66 (1H, d, J=8.3 Hz, and 7.8 Hz), 6.81 (2H, d, J=8.8 Hz), 7.00 (1H, t, J=8.3 Hz), 7.10 (2H, d, J=8.3 Hz), 9.0—10.0 (1H, br). FAB-MS m/z: 459 $(M+Na)^+$.

2-(3-(4-Methoxyphenyl)-1-oximinopropyl)resorcinol 1-*O*-β-D-Glucopyranoside (63) A mixture of **1** (869 mg, 2 mmol), hydroxylamine hydrochloride (287 mg, 4 mmol), pyridine (2 ml) and EtOH (20 ml) was refluxed for 15 h. The mixture was concentrated *in vacuo*, and the residue was dissolved in AcOEt. The solution was washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH (5 : 1)) to afford **63** (549 mg, 61%). IR (Nujol): 3320 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.5—2.9 (4H, m), 3.1—3.5 (5H, m), 3.70 (3H, s), 3.71 (1H, m), 4.54 (1H, m), 4.80 and 4.87 (1H, d, J=7.0 Hz, and 7.3 Hz), 5.00 (3H, m), 6.53 (1H, d, J=8.3 Hz), 6.63 (1H, d, J=8.8 Hz), 6.79 (2H, d, J=8.8 Hz), 7.08 (2H, d, J=8.3 Hz), 7.09 (1H, t, J=8.3 Hz), 9.0—10.8 (2H, br). FAB-MS m/z: 450 $(M+H)^+$.

2′,6′-Dihydroxypropiophenone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-β-D-glucopyranoside) (65) A mixture of 2′,6′-dihydroxypropiophenone **64**[13] (537 mg, 3.23 mmol) and $CdCO_3$ (2.23 g, 12.93 mmol) in toluene (80 ml) was refluxed for 1 h with removal of the generated water in a Dean–Stark apparatus. Then acetobromoglucose (2.66 g, 6.46 mmol) was added and the whole was heated at reflux for 15 h. The hot mixture was filtered through a plug of Celite and the solid was washed with hot $CHCl_3$. The filtrate and washing were combined and evaporated. The residue was chromatographed on silica gel with $CHCl_3$–AcOEt (9 : 1) and triturated in iso-Pr_2O to give **65** (876 mg, 55%) as a white powder, mp 175.5—177.5 °C. IR (Nujol): 1750, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.97 (3H, t, J=7.2 Hz), 1.96 (3H, s), 2.00 (3H, s), 2.01 (3H, s), 2.02 (3H, s), 2.63 (2H, q, J=7.2 Hz), 4.07 (1H, m), 4.1—4.3 (2H, m), 4.98 (1H, dd, J=9.5, 9.6 Hz), 5.00 (1H, dd, J=8.0, 9.8 Hz), 5.39 (1H, dd, J=9.5, 9.6 Hz), 5.49 (1H, d, J=8.0 Hz), 6.59 (1H, d, J=8.2 Hz), 6.61 (1H, d, J=8.2 Hz), 7.20 (1H, t, J=8.3 Hz), 10.30 (1H, s). FAB-MS m/z: 519 $(M+Na)^+$.

2-(2-Methyl-3-(4-methoxyphenyl)propion-1-yl)resorcinol 1-*O*-β-D-Glucopyranoside (66) In the same manner as employed for the preparation of **2** (method A), the condensation of **65** (850 mg, 1.71 mmol) with *p*-anisaldehyde (466 mg, 3.42 mmol) followed by catalytic hydrogenation afforded **66** (489 mg, 64%) as an amorphous powder. IR (Nujol): 3300, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.93 and 0.94 (3H, d, J=7.0 Hz, and 6.9 Hz), 2.43 (1H, m), 3.02 (1H, m), 3.1—3.4 (4H, m), 3.46 (2H, m), 3.69 (1H, m), 3.70 and 3.71 (3H, s), 4.55 (1H, t, J=5.7 Hz), 4.92 and 4.94 (1H, d, J=6.9 Hz, and 7.1 Hz), 5.02 (1H, d, J=5.2 Hz), 5.07 and 5.08 (1H, d, J=3.9 Hz, and 5.3 Hz), 5.15 (1H, d, J=5.5 Hz), 6.53 and 6.54 (1H, d, J=8.0 Hz), 6.66 (1H, d, J=8.2 Hz), 6.80 and 6.81 (2H, d, J=8.7 Hz), 7.10 and 7.12 (2H, d, J=8.6 Hz, and 8.7 Hz), 7.18 (1H, t, J=8.3 Hz), 10.29 and 10.33 (1H, br). FAB-MS m/z: 471 $(M+Na)^+$.

6′-Benzyloxy-2′-hydroxyacetophenone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-β-D-glucopyranoside) (67) Sodium hydride (60% in mineral oil, 0.88 g, 22 mmol) was added to a solution of **35**[1] (9.65 g, 20 mmol) in DMF (100 ml) with stirring in an ice-water bath. After 0.5 h, benzyl bromide (4.10 g, 24 mmol) was added and the mixture was stirred under ice-cooling for 3 h. AcOH (0.1 ml) was added and then the mixture was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ and filtered through a plug of Celite. The filtrate was washed with water, dried over $MgSO_4$, and evaporated. The residue was crystallized from MeOH–iso-Pr_2O to give **67** (9.50 g, 83%), mp 99—101 °C. IR (Nujol): 1750, 1740, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, s), 2.08 (3H, s), 2.11 (3H, s), 2.43 (3H, s), 3.85 (1H, m), 4.25 (2H, m), 4.9—5.4 (4H, m), 5.07 (2H, s), 6.69 (1H, dd, J=0.8, 8.4 Hz), 6.74 (1H, dd, J=0.7, 8.4 Hz), 7.21 (1H, t, J=8.4 Hz), 7.34 (5H, s). FAB-MS m/z: 573 $(M+H)^+$.

6′-Benzyloxy-2-bromo-2′-hydroxyacetophenone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-β-D-glucopyranoside) (68) A mixture of **67** (573 mg, 1 mmol), $CuBr_2$ (447 mg, 2 mmol), $CaCO_3$ (1 g, 10 mmol), $CHCl_3$ (10 ml) and AcOEt (10 ml) was refluxed for 2 d. The mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 2) to give **68** (283 mg, 43%). IR (Nujol): 1760, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.96 (3H, s), 2.00 (3H, s), 2.02 (3H, s), 2.03 (3H, s), 4.0—4.3 (3H, m), 4.44 (2H, s), 5.00 (2H, m), 5.16 (2H, s), 5.39 (1H, t, J=9.5 Hz), 5.54 (1H, d, J=8.0 Hz), 6.83 (1H, d, J=8.3 Hz), 6.94 (1H, d, J=8.5 Hz), 7.2—7.4 (5H, m), 7.42 (1H, t, J=8.5 Hz). FAB-MS m/z: 673/675 $(M+Na)^+$.

6′-Benzyloxy-2′-hydroxy-2-(4-methoxyphenoxy)acetophenone 2′-*O*-(2,3,4,6-*O*-Tetraacetyl-β-D-glucopyranoside) (69) A mixture of **68** (254 mg, 0.39 mmol), *p*-methoxyphenol (97 mg, 0.78 mmol), K_2CO_3 (259 mg, 1.95 mmol) and DMF (5 ml) was stirred at 80 °C for 3 h. The mixture was filtered and the solid was washed with AcOEt. The filtrate and washings were combined, washed with water, dried, and evaporated. The residue was chromatographed on silica gel (AcOEt–hexane (1 : 3)) to give **69** (167 mg, 62%). IR (Nujol): 1760 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.96 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.00 (3H, s), 3.65 (3H, s), 4.0—4.3 (3H, m), 4.81 (1H, d, J=18.4 Hz), 4.88 (1H, d, J=18.4 Hz), 5.00 (2H, m), 5.14 (2H, s), 5.40 (1H, t, J=9.6 Hz), 5.56 (1H, d, J=8.0 Hz), 6.57 (2H, ddd, J=2.4, 3.7, 9.2 Hz), 6.70 (2H, ddd, J=2.4, 3.7, 9.1 Hz), 6.88 (1H, d, J=8.3 Hz), 7.00 (1H, d, J=8.4 Hz), 7.40 (5H, m), 7.45 (1H, t, J=8.5 Hz). FAB-MS m/z: 717 $(M+Na)^+$.

2′,6′-Dihydroxy-2-(4-methoxyphenoxy)acetophenone 2′-*O*-β-D-Glucopyranoside) (70) Compound **69** (1054 mg, 1.52 mmol) was hydrogenated over 10% Pd–C in a mixture of EtOH (20 ml), THF (10 ml) and 25% aqueous KOH (3 ml) at room temperature for 3 h. The mixture was acidified with 10% HCl under ice-cooling. The catalyst was filtered off and washed with MeOH. The filtrate was evaporated, and the residue was chromatographed on silica gel ($CHCl_3$–MeOH (5 : 1)) and crystallized from EtOH–H_2O to afford **70** (220 mg, 33%). IR (Nujol): 3520, 3440, 3360, 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.1—3.4 (4H, m), 3.47 (1H, m), 3.69 (3H, s), 3.70 (1H, m), 4.58 (1H, t, J=5.5 Hz), 4.99 (1H, d, J=7.5 Hz), 5.06 (1H, d, J=5.3 Hz), 5.10 (1H, d, J=3.0 Hz), 5.18 (1H, d, J=18.7 Hz), 5.28 (1H, d, J=18.6 Hz), 5.34 (1H, d, J=4.8 Hz), 6.60 (1H, d, J=7.7 Hz), 6.73 (1H, d, J=8.0 Hz), 6.83 (2H, dd, J=2.8, 9.4 Hz), 6.89(2H, dd, J=2.8, 9.2 Hz), 7.34 (1H, t, J=8.3 Hz), 11.22 (1H, s). FAB-MS m/z: 459 $(M+Na)^+$.

Physical data for **59**—**63**, **66**, and **70** are listed in Table 3.

Using the same procedure as employed for the preparation of **65**, the peracetylgalactoside (**74**), the peracetylmaltoside (**76**), and the peracetyllactoside (**77**) were prepared by the reaction of 2′,6′-dihydroxyacetophenone (**72**) with appropriate acetobromosugars.

74: Yield 62% as a white powder, mp 123—125 °C (iso-Pr_2O). IR (Nujol): 1750, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.94 (3H, s), 2.01 (3H, s), 2.04 (3H, s), 2.14 (3H, s), 2.35 (3H, s), 4.11 (2H, m), 4.44 (1H, t, J=6.4 Hz), 5.1—5.3 (2H, m), 5.33 (1H, dd, J=2.4, 3.9 Hz), 5.45 (1H, d, J=7.3 Hz), 6.60 (1H, d, J=7.8 Hz), 6.61 (1H, d, J=8.8 Hz), 7.26 (1H,

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t, J=8.3 Hz), 10.71 (1H, s). FAB-MS m/z: 505 $(M+Na)^+$.

76: Yield 62% as a white powder, mp 160—162 °C (Et_2O–iso-Pr_2O). IR (Nujol): 1750, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.01 (3H, s), 2.03 (6H, s), 2.04 (3H, s), 2.06 (3H, s) 2.08 (3H, s), 2.10 (3H, s), 2.59 (3H, s), 3.8—4.4 (6H, m), 4.46 (1H, dd, J=2.9, 12.2 Hz), 4.87 (1H, dd, J=4.2, 10.5 Hz), 5.06 (1H, t, J=9.8 Hz), 5.21 (1H, d, J=7.3 Hz), 5.32 (1H, d, J=2.5 Hz), 5.3—5.5 (3H, m), 6.49 (1H, d, J=8.3 Hz), 6.71 (1H, d, J=8.3 Hz), 7.36 (1H, t, J=8.3 Hz), 12.96 (1H, s). FAB-MS m/z: 793 $(M+Na)^+$.

77: Yield 63% as pale brown amorphous solid. IR (Nujol): 1750, 1630 cm^{-1}. ^{1}H-(DMSO-d_6) δ: 1.90 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.01 (3H, s), 2.02 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 2.50 (3H, s), 3.8—4.4 (7H, m), 4.7—5.3 (6H, m), 5.50 (1H, d, J=7.9 Hz), 6.60 (2H, d, J=8.3 Hz), 7.25 (1H, t, J=8.3 Hz), 10.85 (1H, s). FAB-MS m/z: 793 $(M+Na)^+$.

2′,6′-Dihydroxyacetophenone 2′-*O*-(2,3,4-*O*-Triacetyl-β-D-xylopyranoside) (75) A mixture of **72** (152 mg, 1 mmol), tetra-*n*-butylammonium hydrogensulfate (407 mg, 1.2 mmol), 4% aqueous NaOH (5 ml), and CH_2Cl_2 (5 ml) was stirred at room temperature for 10 min. The yellowish CH_2Cl_2 layer was separated and acetobromoxylose (407 mg, 1.2 mmol) was added to the solution. The mixture was stirred at room temperature for 2 h. Further portions of acetobromoxylose (407 mg) and K_2CO_3 (0.5 g) were added twice at 1 h intervals. After 1 h, the mixture was acidified with 10% HCl to pH 5 and the CH_2Cl_2 layer was separated, washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt–toluene (1 : 4)) and triturated in iso-Pr_2O to give **75** (252 mg, 61%) as a white powder, mp 141—142.5 °C. IR (Nujol): 1760, 1740, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.01 (3H, s), 2.02 (3H, s), 2.03 (3H, s), 2.40 (3H, s), 3.73 (1H, dd, J=9.0, 11.7 Hz), 4.04 (1H, dd, J=5.1, 11.4 Hz), 4.94 (1H, m), 5.04 (1H, dd, J=6.9, 8.9 Hz), 5.28 (1H, t, J=8.7 Hz), 5.53 (1H, d, J=6.9 Hz), 6.60 (1H, d, J=8.5 Hz), 6.63 (1H, d, J=8.8 Hz), 7.26 (1H, t, J=8.3 Hz), 10.94 (1H, s). FAB-MS m/z: 433 $(M+Na)^+$.

Using the same procedure as employed for the preparation of **2** (method A), the β-D-galactopyranoside (**79**), the β-D-xylopyranoside (**80**), the β-maltoside (**81**), and the β-lactoside (**82**) were prepared from **74**—**77** and *p*-anisaldehyde. Yield and physical data of these compounds are listed in Table 4. Spectral data are as follows.

79: IR (Nujol): 3300, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.84 (2H, t, J=7.4 Hz), 3.24 (2H, t, J=7.6 Hz), 3.32 (2H, m), 3.4—3.7 (4H, m), 3.71 (3H, s), 4.55 (1H, d, J=4.5 Hz), 4.64 (1H, t, J=5.2 Hz), 4.87 (2H, d, J=6.6 Hz), 5.05 (1H, d, J=5.4 Hz), 6.54 (1H, d, J=8.2 Hz), 6.69 (1H, d, J=8.2 Hz), 6.82 (1H, d, J=8.4 Hz), 7.17 (2H, d, J=8.4 Hz), 7.24 (1H, t, J=8.2 Hz), 11.04 (1H, s). FAB-MS m/z: 457 $(M+Na)^+$.

80: IR (Nujol): 3520, 3440, 3380, 3280, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.83 (2H, t, J=7.4 Hz), 3.1—3.4 (6H, m), 3.71 (3H, s), 3.74 (1H, dd, J=4.5, 10.7 Hz), 4.93 (1H, d, J=7.0 Hz), 5.08 (1H, d, J=4.7 Hz), 5.13 (1H, d, J=4.5 Hz), 5.28 (1H, d, J=5.1 Hz), 6.55 (1H, d, J=8.2 Hz), 6.64 (1H, d, J=8.0 Hz), 6.82 (2H, dd, J=3.0, 8.7 Hz), 7.15 (2H, dd, J=2.9, 8.6 Hz), 7.23 (1H, t, J=8.3 Hz), 10.91 (1H, s). FAB-MS m/z: 427 $(M+Na)^+$.

81: IR (Nujol): 3340, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.83 (2H, t, J=7.3 Hz), 3.22 (2H, t, J=7.3 Hz), 3.0—3.8 (12H, m), 3.71 (3H, s), 4.55 (2H, m), 4.90 (1H, d, J=4.4 Hz), 4.92 (1H, d, J=5.4 Hz), 4.97 (1H, d, J=7.8 Hz), 5.06 (1H, d, J=3.9 Hz), 5.37 (1H, d, J=5.9 Hz), 5.48 (1H, d, J=5.9 Hz), 5.62 (1H, d, J=2.9 Hz), 6.55 (1H, d, J=7.8 Hz), 6.68 (1H, d, J=8.3 Hz), 6.82 (2H, d, J=2.9, 8.8 Hz), 7.17 (2H, dd, J=2.9, 8.3 Hz), 7.24 (1H, t, J=8.3 Hz), 10.95 (1H, s). FAB-MS m/z: 597 $(M+H)^+$.

82: IR (Nujol): 3480, 3380, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.83 (2H, t, J=7.4 Hz), 3.20 (2H, t, J=7.6 Hz), 3.2—3.8 (12H, m), 3.70 (3H, s), 4.24 (1H, d, J=7.2 Hz), 4.51 (1H, d, J=4.6 Hz), 4.61 (1H, t, J=6.5 Hz), 4.65 (1H, t, J=4.8 Hz), 4.78 (1H, d, J=5.1 Hz), 4.80 (1H, d, J=1.6 Hz), 5.00 (1H, d, J=7.9 Hz), 5.08 (1H, d, J=4.3 Hz), 5.42 (1H, d, J=5.6 Hz), 6.55 (1H, d, J=8.1 Hz), 6.68 (1H, d, J=8.3 Hz), 6.82 (2H, dd, J=2.9, 8.6 Hz), 7.17 (2H, dd, J=2.9, 8.6 Hz), 7.24 (1H, t, J=8.3 Hz), 10.95 (1H, s). FAB-MS m/z: 619 $(M+Na)^+$.

6′-Hydroxy-2′-mercaptoacetophenone 2′-*S*-(2,3,4,6-*O*-Tetraacetyl-β-D-glucopyranoside) (78) A solution of $SnCl_4$ (862 mg, 3.31 mmol) in CH_2Cl_2 (5 ml) was added to a solution of 6′-hydroxy-2′-mercaptoacetophenone (**73**)[15] (556 mg, 3.31 mmol) and pentaacetyl-β-D-glucose (1938 mg, 4.97 mmol) in CH_2Cl_2 (20 ml) under ice-cooling and the whole was stirred at room temperature for 24 h. The mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with water, saturated $NaHCO_3$ and brine, and then dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel ($CHCl_3$–AcOEt (9 : 1)) to afford **78** (1474 mg, 89%) as pale yellow crystals, mp 126—128 °C. IR (Nujol): 3380, 1750, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.94 (3H, s), 1.99 (3H, s), 2.00 (3H, s), 2.01 (3H, s), 2.40 (3H, s), 4.0—4.2 (3H, m), 4.86 (1H, dd, J=9.3, 10.1 Hz), 4.92 (1H, t, J=9.6 Hz), 5.18 (1H, d, J=10.2 Hz), 5.34 (1H, dd, J=9.3, 9.4 Hz), 6.85 (1H, dd, J=1.0, 8.2 Hz), 7.09 (1H, dd, J=1.0, 8.1 Hz), 7.25 (1H, t, J=1.0, 8.0 Hz). FAB-MS m/z: 521 $(M+Na)^+$.

6′-Hydroxy-2′-mercapto-4-methoxydihydrochalcone 2′-*S*-β-D-Glucopyranoside (83) A mixture of **78** (1375 mg, 2.76 mmol), *p*-anisaldehyde (563 mg, 4.14 mmol), 50% aqueous KOH (3 ml), and EtOH (20 ml) was stirred at room temperature for 18 h. The mixture was diluted with water and washed with toluene. The water layer was acidified with 10% HCl to pH 5 under ice-cooling and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and evaporated. The residue containing the crude chalcone was reduced with NaTeH (4.14 mmol) in the same manner as employed for the preparation of **19** (method C) to afford **83** (507 mg, 41%). IR (Nujol): 3320, 1680 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.84 (2H, t, J=7.7 Hz), 3.0—3.3 (6H, m), 3.43 (1H, m), 3.68 (1H, m), 3.71 (3H, s), 4.49 (1H, br), 4.50 (1H, d, J=9.5 Hz), 4.95 (1H, d, J=5.1 Hz), 5.06 (1H, d, J=4.0 Hz), 5.23 (1H, d, J=6.2 Hz), 6.76 (1H, dd, J=3.0, 5.9 Hz), 6.82 (2H, dd, J=1.8, 8.4 Hz), 7.1—7.2 (4H, m), 10.00 (1H, s). FAB-MS m/z: 473 $(M+Na)^+$.

Measurement of Urinary Glucose Excretion Male Sprague–Dawley (SD) rats (6 weeks old) were used. Test compounds were administered once or 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).

Inhibition of Rat Kidney SGLT Activity Male SD rats (10—13 weeks old) were used. BBMV from the rat kidney were prepared according to the method of Nagasawa *et al.*[21] The protein concentration was measured by use of a Coomassie protein assay kit (Pierce) and the preparation was diluted with buffer A (10 mM Hepes/Tris (pH 7.4), 100 mM mannitol) to 4 mg/ml protein concentration.

Assay tubes containing 50 μl of BBMV suspension (0.2 mg, protein) and 100 μl of buffer A containing 1% v/v dimethyl sulfoxide (DMSO) or DMSO solution of the test compounds (final concentration, 10 μM) were preincubated at 37 °C for 2 min. Then 50 μl of buffer A containing 0.4 mM D-glucose (final concentration, 0.1 mM), 400 mM NaSCN (final concentration, 100 mM), and 20 μCi/ml [^{3}H]glucose (final radioactivity, 1 μCi) was added. The assay tubes were incubated at 37 °C for 5 s. The incubation was terminated by addition of 1.5 ml of ice-cold stopping solution (10 mM Hepes/Tris (pH 7.4), 150 mM NaCl, 0.3 mM phlorizin) followed by rapid filtration through a membrane filter (nitrocellulose, 25 mmϕ, pore size 0.45 μm, Advantec). The filter was washed with 4.5 ml of the stopping solution. Then the radioactivity of the pellet was measured with a liquid scintillation counter (Tricarb 2200CA, Packard).

Metabolism of the Maltoside 81 to the Glucoside 1 in Rat Plasma Plasma of a male SD rat was used. The rat plasma containing 10 μM **81** at a final volume of 3 ml was incubated at 37 °C for 0—90 min. After the required time, 300 μl of the incubation mixture was sampled and the reaction was terminated by addition of 300 μl of the chilled water and 5 ml of chilled AcOEt. The mixture was extracted with AcOEt and the organic phase was evaporated. The residue was dissolved in 200 μl of solvent A (H_2O–acetonitrile (90 : 10), containing 0.1% AcOH). HPLC was performed using a Hewlett–Packard 1090 chromatograph equipped with a Hewlett–Packard photodiode array detector (UV wavelength of 268 nm). One hundred μl of residual solution was injected onto a CAPCELL PAC MF C8 column (5 μm, 150 × 4.6 mm; Shiseido Co., Ltd.) and analyzed using a linear gradient of 0—50% solvent B (H_2O : acetonitrile (10 : 90), containing 0.1% AcOH) in solvent A at a flow rate of 1.0 ml/min. Compounds **81** and **1** were determined from calibration curves.

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