[Chem. Pharm. Bull. 36(4)1404—1414(1988)]

Synthesis and Aldose Reductase-Inhibitory Activities of Structural Analogues of WF-3681, a Novel Aldose Reductase Inhibitor

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(Received September 17, 1987)

Various analogues of WF-3681 (**1a**), a novel aldose reductase inhibitor, were synthesized and examined for aldose reductase-inhibitory activity. It was found that the carboxylic acid function is necessary and the side-chain length is important for the activity. Furthermore, the lipophilicities of the benzene ring and the enol ether group are significant for increasing the activity.

Keywords——natural product; aldose reductase inhibitor; α-hydroxybutenolide; aldol condensation; structure–activity relationship

Diabetic complications, *e.g.* neuropathy, nephropathy, retinopathy, and cataract, have become more critical in recent years. It has been suggested that aldose reductase, which catalyzes the reduction of glucose to sorbitol, may be implicated in the pathogenesis of these complications and an increased intracellular accumulation of sorbitol under nonphysiological conditions of hyperglycemia may result in an osmotic imbalance and subsequent cellular damage, leading to development of diabetic complications. It has been expected, therefore, that inhibition of the enzyme activity may provide a pharmacological approach to treatment of these complications. Numerous investigators have been concerned in finding effective aldose reductase inhibitors, among which a few compounds have been subjected to clinical trials.[2]

In the preceding papers, we reported the isolation, structure elucidation, and total synthesis of WF-3681 (**1a**), a novel aldose reductase inhibitor isolated from *Chaetomella* species.[3,4] We also reported an efficient total synthesis of WF-3681 which further facilitated chemical modifications of this natural product.[5]

As part of a program of research on aldose reductase inhibitors, we were interested in studying the structure–activity relationship of WF-3681 and also in preparing more active compounds by chemical modifications. Herein we report the syntheses and biological activities of compounds of this series.

Chemistry

For an approach of the structural alteration of WF-3681, we attempted to alter the three substituents, phenyl (A), hydroxy (B), and carboxyethyl (C) groups, of its molecule as depicted in Fig. 1.

For the syntheses of compounds having various substituents on the phenyl group (A part) of WF-3681, we adopted the synthetic methods developed for the synthesis of WF-3681 itself as described in the preceding communication.[5] Although the syntheses of some representatives of the compounds related to WF-3681 were also described in the communication,[5] this paper includes those compounds together with the other related com-

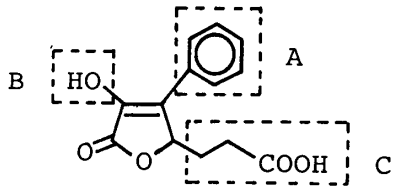
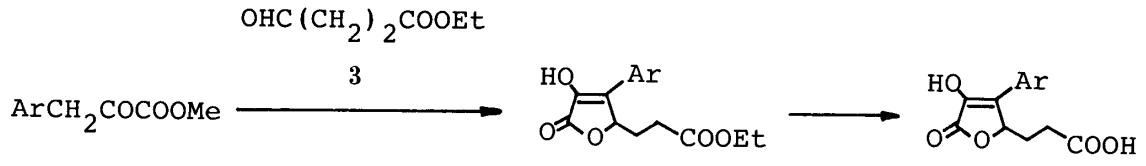


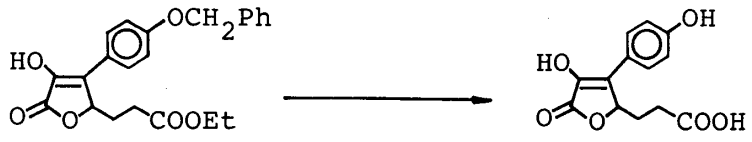
Fig. 1

1a

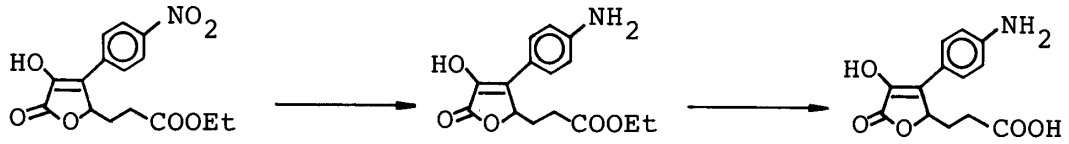


2 **4** **1**

Chart 1

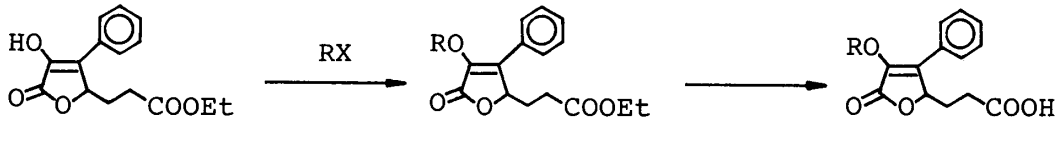


4g **1i**



4j **4k** **1k**

Chart 2



4a **5** **6**

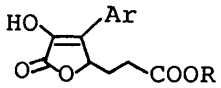
Chart 3

pounds. Namely, the corresponding methyl arylpyruvates **2** were allowed to react with ethyl 3-formylpropionate (**3**)[6] in the presence of 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) in dimethylformamide (DMF) to give the desired compounds **4**. The products were then hydrolyzed by acid treatment to give the carboxylic acids **1** (Chart 1).

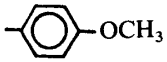
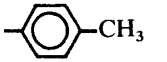
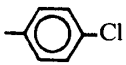
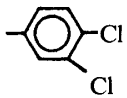
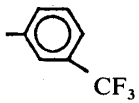
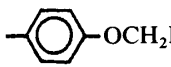
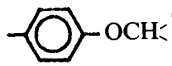
The 4-hydroxyphenyl derivative **1i** was prepared by heating **4g** with 3 N hydrochloric acid (HCl) in acetic acid (AcOH). The 4-aminophenyl derivative **1k** was prepared by acid hydrolysis of the product **4k** obtained by reduction of **4j** with anhydrous stannous chloride ($SnCl_2$) in ethanol (EtOH)[7] (Chart 2). The yields and physical data of the compounds (**1a**—**r**) thus obtained are listed in Table I.

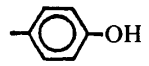
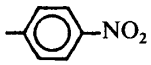
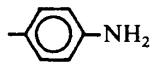
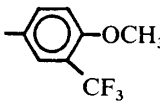
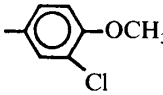
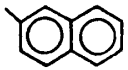
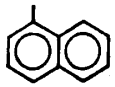
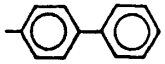
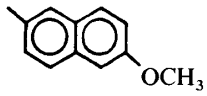
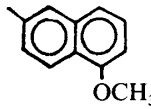
The modification of the enol hydroxy group (B part) was achieved by alkylation of the

TABLE I. 3-Aryl Derivatives



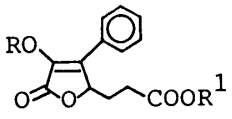
4: R = Et
1: R = H

Ar	Compd.	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	Compd.	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
	**4a**	72	116—118	$C_{15}H_{16}O_5$	65.21 (65.51	5.84 5.73)		**1a**	100	177—179	$C_{13}H_{12}O_5$	62.90 (62.77	4.87 4.93)	
	**4b**	59	120—121	$C_{16}H_{18}O_6$	62.74 (62.63	5.92 5.89)		**1b**	82	173—174	$C_{14}H_{14}O_6$	60.43 (60.42	5.07 5.13)	
	**4c**	61	108—109	$C_{16}H_{18}O_5$	66.20 (66.41	6.25 6.27)		**1c**	100	168—169	$C_{14}H_{14}O_5$	64.12 (63.94	5.38 5.45)	
	**4d**	60	121—122	$C_{15}H_{15}ClO_5$	57.98 (58.16	4.87 4.81)		**1d**	96	181—182	$C_{13}H_{11}ClO_5$	55.24 (55.06	3.92 4.18)	
	**4e**	70	109—111	$C_{15}H_{14}Cl_2O_5$	52.19 (52.05	4.09 3.91)		**1e**	86	179—180	$C_{13}H_{10}Cl_2O_5$	49.24 (49.34	3.18 3.32)	
	**4f**	61	104—105	$C_{16}H_{15}F_3O_5$	55.82 (55.50	4.39 4.37)		**1f**	89	188—189	$C_{14}H_{11}F_3O_5$	53.17 (53.14	3.51 3.60)	
	**4g**	72	130—131	$C_{22}H_{22}O_6$	69.10 (69.47	5.80 5.73)		**1g**	60	198—199	$C_{20}H_{18}O_6$	67.79 (67.99	5.12 5.21)	
	**4h**	66	126—127	$C_{18}H_{22}O_6$	64.66 (64.84	6.63 6.49)		**1h**	66	178—179	$C_{16}H_{18}O_6$	62.74 (62.59	5.92 5.89)	

								**1i**	57	251—253	$C_{13}H_{12}O_6$	59.09 (58.80	4.58 4.70)	
	**4j**	41	149—151	$C_{15}H_{15}NO_7$	56.08 (55.92	4.71 4.47	4.36 4.51)	**1j**	78	198—200	$C_{13}H_{11}NO_7$	53.25 (53.55	3.78 3.81	4.78 4.66)
	**4k**	59[b]	131—132	$C_{15}H_{17}NO_5$	61.85 (62.04	5.88 5.87	4.81 4.85)	**1k**	58	212—213[c]	$C_{13}H_{13}NO_5$	59.31 (59.09	4.98 5.02	5.32 5.02)
	**4l**	51	168—169	$C_{17}H_{17}F_3O_6$	54.55 (54.35	4.58 4.34)		**1l**	87	224—226	$C_{15}H_{13}F_3O_6$	52.03 (52.27	3.78 3.85)	
	**4m**	46	126—129	$C_{16}H_{17}ClO_6$	56.40 (56.66	5.03 4.84)		**1m**	77	208—211	$C_{14}H_{13}ClO_6$	53.77 (53.46	4.19 4.08)	
	**4n**	44	115—116	$C_{19}H_{18}O_5$	69.93 (69.85	5.56 5.47)		**1n**	82	185—186	$C_{17}H_{14}O_5$	68.45 (68.57	4.73 4.52)	
	**4o**	48	Oil					**1o**	30	168—170	$C_{17}H_{14}O_5$	68.45 (68.21	4.73 4.56)	
	**4p**	48	131—132	$C_{21}H_{20}O_5$	71.58 (71.87	5.72 5.63)		**1p**	86	217—218	$C_{19}H_{16}O_5$	70.36 (70.23	4.97 4.77)	
	**4q**	54	146—147	$C_{20}H_{20}O_6$	67.41 (67.47	5.66 5.51)		**1q**	41	202—204	$C_{18}H_{16}O_6$	65.85 (65.67	4.91 4.79)	
	**4r**	24	133—134	$C_{20}H_{20}O_6$	67.41 (67.55	5.66 5.54)		**1r**	72	215—216	$C_{18}H_{16}O_6$	65.85 (65.55	4.91 4.88)	

a) Recrystallized from a mixture of ethyl acetate and *n*-hexane. *b*) Yield of reduction. *c*) Recrystallized from ethanol.

TABLE II. 4-Alkoxy and 4-Aralkoxy Derivatives



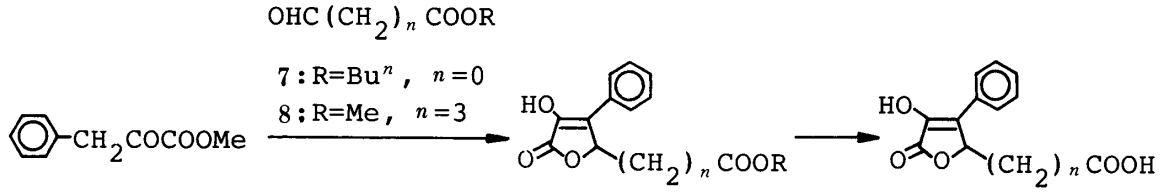
5: $R^1 = Et$
6: $R^1 = H$

R	Compd.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	Compd.	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found) C	H
$-CH_3$	**5a**	77	41—42[b]	$C_{16}H_{18}O_5$	66.20 (66.37	6.25 6.49)	**6a**	90	129—130	$C_{14}H_{14}O_5$	64.12 (64.23	5.38 5.40)
$-C_2H_5$	**5b**	81	Oil				**6b**	78	114—116	$C_{15}H_{16}O_5$	64.97 (65.04	6.18 5.82)
$-C_3H_7$	**5c**	96	Oil				**6c**	84	123—125	$C_{16}H_{18}O_5$	66.20 (66.44	6.25 6.26)
$-C_4H_9$	**5d**	94	Oil				**6d**	59	94—96	$C_{17}H_{20}O_5$	67.09 (67.15	6.62 6.77)
$-C_5H_{11}$	**5e**	100	Oil				**6e**	80	86—87	$C_{18}H_{22}O_5$	67.91 (68.11	6.96 6.91)
$-C_7H_{15}$	**5f**	100	Oil				**6f**	82	85—86	$C_{20}H_{26}O_5$	69.34 (69.62	7.56 7.34)
$-C_{10}H_{21}$	**5g**	82	36—37[c]	$C_{25}H_{36}O_5$	72.09 (72.39	8.71 8.76)	**6g**	38	82—84	$C_{23}H_{32}O_5$	71.11 (70.81	8.30 8.29)
$-CH_2-C_6H_5$	**5h**	100	Oil				**6h**	38	115—116	$C_{20}H_{18}O_5$	71.00 (70.65	5.36 5.53)
$-CH_2-C_6H_4-Cl$	**5i**	60	59—60[a]	$C_{22}H_{21}ClO_5$	65.92 (66.02	5.28 5.22)	**6i**	67	125—128	$C_{20}H_{17}ClO_5$	64.44 (64.44	4.60 4.43)
$-CH_2-C_6H_3Cl_2$	**5j**	67	71—72[a]	$C_{22}H_{20}Cl_2O_5$	60.70 (60.61	4.63 4.43)	**6j**	85	148—150	$C_{20}H_{16}Cl_2O_5$	58.99 (58.83	3.96 3.93)
$-CH_2-C_6H_4-OCH_3$	**5k**	91	Oil				**6k**	40	110—115	$C_{21}H_{20}O_6$	68.47 (68.35	5.47 5.59)
$-CH_2-C_6H_4-CH_3$	**5l**	74	42—43[d]	$C_{23}H_{24}O_5$	72.61 (72.86	6.36 6.33)	**6l**	37	117—120	$C_{21}H_{20}O_5$	71.58 (71.77	5.72 5.68)

a) Recrystallized from a mixture of ethyl acetate and *n*-hexane. *b*) Recrystallized from isopropyl ether. *c*) Crystallized from petroleum ether. *d*) Crystallized from *n*-hexane.

hydroxy group of **4a** with various alkyl or aralkyl halides in the presence of potassium carbonate (K_2CO_3) in DMF, followed by acid hydrolysis for **5a—j** and alkaline hydrolysis for **5k** and **5l** to yield the alkoxy and aralkoxy derivatives **6a—l** (Chart 3). The yields and physical data of these derivatives are listed in Table II.

In order to modify the carboxylic acid side-chain (C part) of WF-3681, we attempted aldol condensation of methyl phenylpyruvate (**2a**) and various ω-formylalkanoates according to the method described above. The condensations of **2a** with *n*-butyl glyoxalate (**7**)[8] and methyl 4-formylbutylate (**8**)[9] were successful and the products **9** and **10** were converted to **11** and **12** by hydrolysis with 1 N sodium hydroxide (NaOH) in tetrahydrofuran (THF) and 3 N HCl in AcOH, respectively (Chart 4). Since we were unable to achieve the condensation of **2a** and ethyl formylacetate[10] as described in the preceding paper,[5] we undertook, for the preparation of **18**, a more reliable but rather roundabout approach using 3-benzyloxy-

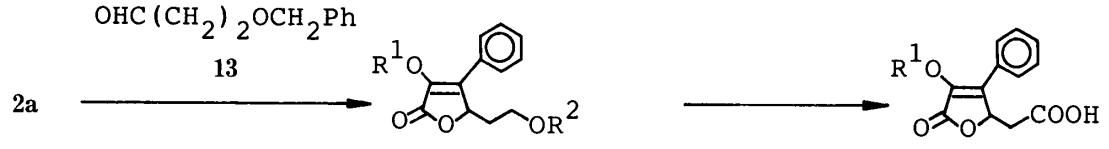


2a

9 : R=Bu^n, n=0
10 : R=Me, n=3

11 : n=0
12 : n=3

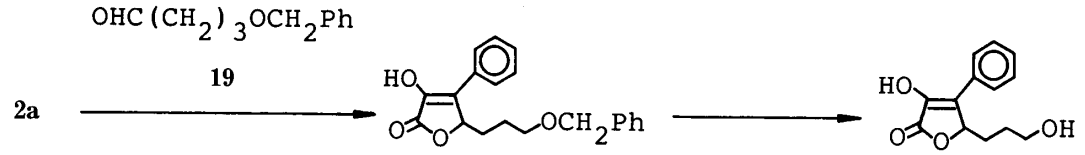
Chart 4



14 : R^1=H, R^2=CH_2Ph
15 : R^1=Me, R^2=CH_2Ph
16 : R^1=Me, R^2=H

17 : R^1=Me
18 : R^1=H

Chart 5



20 **21**

1a **22**

Chart 6

propionaldehyde (**13**)[11] as the starting material. Thus, condensation of **2a** and **13** under the same conditions produced α-hydroxybutenolide **14** in good yield. After protection of the hydroxy group in **14** by methylation with diazomethane (CH_2N_2), the benzyl group in the product **15** was removed by hydrogenolysis using palladium black (Pd black) in the presence of formic acid to give **16**, which was then subjected to Jones' oxidation and the resulting product **17** was treated with boron tribromide (BBr_3) in methylene chloride (CH_2Cl_2) to yield the desired compound **18** (Chart 5).

In connection with the variation of the carboxylic acid side-chain, we also prepared the alcohol **21** and amide **22** as derivatives of WF-3681. The alcohol **21** was prepared by aldol condensation of methyl phenylpyruvate (**2a**) and 4-benzyloxybutyraldehyde (**19**),[12] followed by catalytic reduction (Pd black). The amide **22** was prepared from WF-3681 itself by a mixed anhydride method using isobutyl chloroformate and ammonia (Chart 6).

Results and Discussion

The aldose reductase-inhibitory activities of the compounds described above were examined using rabbit lens aldose reductase,[3] and the results are given in Tables III, IV, and V in comparison with the activity of the parent compounds, WF-3681 (**1a**).

As shown in Table III, the inhibitory activities of the substituted benzene derivatives were all higher than that of **1a**. As can be seen from the data of **1b**, **1g**, and **1h**, introduction of lipophilic substituents at the 4-position of the benzene ring enhanced the activity by *ca.* 5-fold as compared with the parent compound. Furthermore, the compounds with the naphthalene and biphenyl systems (**1n**, **1p**, **1q**, and **1r**) showed increased inhibitory effects by *ca.* 10-fold, except for compound **1o**. These results suggested that the introduction of lipophilicity tends to

TABLE III. Inhibitory Effect of 3-Aryl Derivatives on Rabbit Lens Aldose Reductase

Compound	IC_{50} (M)	Compound	IC_{50} (M)
1a	2.5×10^{-7}	**1k**	2.7×10^{-7}
1b	5.4×10^{-8}	**1l**	5.1×10^{-8}
1c	8.4×10^{-8}	**1m**	8.0×10^{-8}
1d	9.2×10^{-8}	**1n**	4.3×10^{-8}
1e	9.8×10^{-8}	**1o**	6.7×10^{-7}
1f	1.7×10^{-7}	**1p**	1.5×10^{-8}
1g	4.9×10^{-8}	**1q**	4.6×10^{-8}
1h	5.2×10^{-8}	**1r**	2.2×10^{-8}
1i	1.6×10^{-7}	Sorbinil[a]	4.2×10^{-7}
1j	1.1×10^{-7}		

a) See reference 13.

TABLE IV. Inhibitory Effect of 4-Alkoxy and 4-Aralkoxy Derivatives on Rabbit Lens Aldose Reductase

Compound	IC_{50} (M)	Compound	IC_{50} (M)
6a	2.2×10^{-7}	**6g**	9.5×10^{-7}
6b	2.0×10^{-7}	**6h**	1.4×10^{-7}
6c	1.5×10^{-7}	**6i**	1.4×10^{-7}
6d	1.6×10^{-7}	**6j**	1.2×10^{-7}
6e	5.0×10^{-8}	**6k**	1.5×10^{-7}
6f	5.5×10^{-8}	**6l**	1.3×10^{-7}

TABLE V. Inhibitory Effect of Derivatives with Modified Carboxylic Side-Chains on Rabbit Lens Aldose Reductase

Compound	IC_{50} (M)	Compound	IC_{50} (M)
11	$>1.0\times10^{-5}$ a)	**21**	$>1.0\times10^{-5}$ c)
18	$>1.0\times10^{-5}$ b)	**22**	$>1.0\times10^{-5}$ d)
12	1.0×10^{-5}		

a) A 45% inhibition at 1.0×10^{-5}. b) A 44% inhibition at 1.0×10^{-5}. c) A 34% inhibition at 1.0×10^{-5}. d) A 37% inhibition at 1.0×10^{-5}.

increase the activity.

Table IV shows that the alkyl ether derivatives generally have enhanced inhibitory activity. As the alkyl chain length was increased, the inhibitory potency was enhanced. The maximum potency was observed in the medium alkyl derivatives, *n*-pentyl (**6e**) and *n*-heptyl (**6f**). The benzyl derivatives (**6h**—**l**) also exhibited enhanced potencies. These data suggested that increased lipophilicity of the alkyl and aralkyl substituents is also important for increasing the activity.

As can be seen in Table V, the modification of the carboxylic acid side-chain, including conversions to the alcohol **21** and amide **22**, considerably decreased the activity. The data thus showed the necessity of the carboxylic acid function and the importance of its length for potent activity.

Experimental

Melting points were measured on a Thomas-Hoover apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-102 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 or a Bruker AM-200 spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were recorded using a ZAB SE instrument (VG Analytical Co.,). Column chromatography was carried out on Silica gel 60 (Merck, 0.063—0.200 mesh).

Methyl 3-Aryl-2-oxopropionates (2)——Method A. Methyl 2-Oxo-3-phenylpropionate (**2a**)[14]: DBU (2.28 ml, 15.2 mmol) and methyl iodide (4.75 ml, 76.3 mmol) were added to a solution of 2-oxo-3-phenylpropionic acid (2.50 g, 15.2 mmol) in dry DMF (80 ml) under stirring at 0°C, and the mixture was stirred for 2.5 h at the same temperature, then poured into a mixture of Et_2O and dilute HCl. The organic layer was separated, washed with H_2O (×2) and saturated NaCl, dried over $MgSO_4$, and evaporated *in vacuo*. The resulting crystalline residue of **2a** (2.35 g, 87%) was used for the following aldol condensation reaction without purification.

Compounds **21** (92%), **2m** (93%), **2n** (87%), **2o** (95%), **2p** (89%), **2q** (93%), and **2r** (94%) were similarly prepared.

Method B. Methyl 3-(4-Methylphenyl)-2-oxopropionate (**2c**): Methyl 2,2-dimethoxy-3-(4-methylphenyl) propionate (4.22 g, 17.7 mmol), prepared from 4-methylbenzylbromide and methyl 2,2-dimethoxyacetate by an application of the procedure described in the literature,[15] was heated under stirring in formic acid (20 ml) for 2 h at 65 to 70 °C. The reaction mixture was cooled and extracted with CH_2Cl_2 (×3). The extract was washed with H_2O (×3), dried over $MgSO_4$, and evaporated *in vacuo*. The resulting crystalline product **2c** (2.95 g, 87%) was used for the following aldol condensation reaction without purification.

Compounds **2b** (90%), **2d** (75%), **2e** (90%), **2f** (82%), **2g** (93%), **2h** (91%), and **2j** (82%) were similarly prepared.

Ethyl 3-(4-Hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furyl)propionate (4a)——DBU (0.80 ml, 5.35 mmol) was added to a mixture of **2a** (0.94 g, 5.28 mmol) and ethyl 3-formylpropionate (**3**) (0.83 ml, 6.83 mmol) in dry DMF (24 ml) with stirring under ice-bath cooling. After 2.5 h of stirring at the same temperature, the reaction mixture was poured into a mixture of Et_2O and dilute HCl. The organic layer was separated and the aqueous layer was extracted with Et_2O (×2). The organic layers were combined, dried over $MgSO_4$, and evaporated *in vacuo*. The resulting crystalline residue was triturated with isopropyl ether and filtered to give 1.05 g (72%) of **4a**. IR (Nujol): 3270, 1740, 1705, 1670 cm^{-1}. NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz), 1.75 (1H, m), 2.32—2.77 (3H, m), 4.16 (2H, q, J=7 Hz), 5.51 (1H, dd, J=2, 9 Hz), 6.74 (1H, s), 7.30—7.60 (3H, m), 7.63—7.90 (2H, m).

Compounds **4b**—**h**, **4j**, and **4l**—**r** were similarly prepared, and their physical data are listed in Table I.

3-(4-Hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furyl)propionic Acid (WF-3681, 1a)——A suspension of **4a** (0.30 g, 1.09 mmol) in a mixture of AcOH (3.4 ml) and 3 N HCl (3.4 ml) was stirred for 1 h at 100 °C. After cooling, the

reaction mixture was poured into a mixture of AcOEt and H_2O. The organic layer was separated and the aqueous layer was extracted with AcOEt (×2). The organic layers were combined, washed with saturated NaCl (×3), dried over $MgSO_4$, and evaporated *in vacuo* to give 0.27 g (100%) of **1a** as a crystalline solid.[3,4]

Compounds **1b**—**h**, **1j**, and **11-r** were similarly prepared, and their physical data are listed in Table I.

3-[4-Hydroxy-3-(4-hydroxyphenyl)-5-oxo-2,5-dihydro-2-furyl]propionic Acid (1i)——This compound was prepared from **4g** in 57% yield by heating for 4 h in the same manner as described for **1a**. IR(Nujol): 3200, 1735, 1700, 1660, 1600 cm^{-1}. NMR (DMSO-d_6) δ: 1.65 (1H, m), 2.00—2.50 (3H, m), 5.48 (1H, dd, J=2, 8 Hz), 6.90 (2H, d, J=9 Hz), 7.60 (2H, d, J=9Hz), 10.33 (2H, br s).

Ethyl 3-[3-(4-Aminophenyl)-4-hydroxy-5-oxo-2,5-dihydro-2-furyl]propionate (4k)——Anhydrous $SnCl_2$ (0.96 g, 5.00 mmol) was added to a solution of **4j** (0.32 g, 1.00 mmol) in dry EtOH (2 ml), and the mixture was stirred for 0.5 h at 75 to 80 °C under a nitrogen atmosphere. After cooling, the reaction mixture was poured into ice-water and neutralized with 5% $NaHCO_3$. AcOEt was added to the mixture and insoluble materials were removed by filtration. The organic layer was separated and the aqueous layer was extracted with AcOEt (×3). The organic layers were combined, washed with saturated NaCl, dried over Na_2SO_4, and evaporated *in vacuo*. The resulting crystalline residue was recrystallized from a mixture of AcOEt and *n*-hexane to give 0.17 g (59%) of **4k**. IR (Nujol): 3475(sh), 3375, 3250 (sh), 1725, 1710 (sh), 1660, 1630, 1600 cm^{-1}. NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz), 1.73 (1H, m), 2.33—2.72 (3H, m), 4.15 (2H, q, J=7 Hz), 5.40 (1H, d, J=8 Hz), 6.74 (2H, d, J=8.5 Hz), 7.56 (2H, d, J=8.5 Hz).

3-[3-(4-Aminophenyl)-4-hydroxy-5-oxo-2,5-dihydro-2-furyl]propionic Acid (1k)——This compound was prepared from **4k** in 58% yield in the same manner as described for **1a**. IR (Nujol): 3370, 3290, 1735, 1710, 1665, 1605 cm^{-1}. NMR (DMSO-d_6) δ: 1.60 (1H, m), 1.90—2.50 (3H, m), 5.37 (1H, dd, J=2, 8 Hz), 5.47 (2H, br s), 6.60 (2H, d, J=9 Hz), 7.40 (2H, d, J=9 Hz), 10.00 (2H, br s).

Ethyl 3-(5-Oxo-4-pentyloxy-3-phenyl-2,5-dihydro-2-furyl)propionate (5e)——*n*-Pentyl iodide (3.44 g, 17.4 mmol) and K_2CO_3 (2.40 g, 17.4 mmol) were added to a solution of **4a** (4.00 g, 14.5 mmol) in dry DMF (38 ml), and the mixture was stirred for 4 h at room temperature. After concentration of the reaction mixture *in vacuo*, AcOEt was added to the residue and the organic layer was washed with 1 N HCl and saturated NaCl (×3), dried over $MgSO_4$, and evaporated *in vacuo*. The oily residue was subjected to silica gel column chromatography (eluent: benzene and $CHCl_3$) to give 5.01 g (100%) of **5e** as an oil. IR (neat): 1755, 1740 (sh), 1645 cm^{-1}. NMR ($CDCl_3$) δ: 0.77—2.00 (13H, m), 2.17—2.77 (3H, m), 4.17 (2H, q, J=7 Hz), 4.30—4.67 (2H, m), 5.48 (1H, dd, J=2, 8 Hz), 7.37—7.88 (5H, m). MS *m/z*: 346 (M^+).

Compounds **5a**—**d** and **5f**—**l** were similarly prepared, and their physical data are listed in Table II.

3-(5-Oxo-4-pentyloxy-3-phenyl-2,5-dihydro-2-furyl)propionic Acid (6e)——This compound was prepared from **5e** in 80% yield in the same manner as described for **1a**. IR (Nujol): 1755, 1710, 1655 cm^{-1}. NMR ($CDCl_3$) δ: 0.73—2.10 (10 H, m), 2.20—3.00 (3H, m), 4.20—4.70 (2H, m), 5.50 (1H, dd, J=2, 8 Hz), 7.33—7.90 (5H, m), 9.67 (1H, br s).

Compounds **6a**—**d** and **6f**—**j** were similarly prepared, and their physical data are listed in Table II.

3-[4-(4-Methoxybenzyloxy)-5-oxo-3-phenyl-2,5-dihydro-2-furyl]propionic Acid (6k)——A 1 N NaOH solution (0.48 ml) was added to a solution of **5k** (160 mg, 0.40 mmol) in MeOH (2 ml). The mixture was stirred for 2h at room temperature, then poured into a mixture of Et_2O and H_2O. The aqueous layer was separated, acidified with 1 N HCl, and extracted with AcOEt (×3). The extract was washed with saturated NaCl, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was crystallized from *n*-hexane and recrystallized from a mixture of AcOEt and *n*-hexane to give 60 mg (40%) of **6k**. IR(Nujol): 1760, 1720, 1640, 1610 cm^{-1}. NMR ($CDCl_3$) δ: 1.70 (1H, m), 2.12—2.85 (3H, m), 3.78 (3H, s), 5.15—5.62 (3H, m), 6.84 (2H, d, J=9 Hz), 7.12—7.75 (7H, m).

Compound **61** was prepared in a similar manner, and its physical data are listed in Table II.

***n*-Butyl 4-Hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furan-carboxylate (9)**——This compound was prepared from *n*-butyl glyoxalate (**7**) and **2a** in 87% yield in the same manner as described for **4a**, mp 108—109 °C. IR (Nujol): 3275, 1750, 1675 cm^{-1}. NMR ($CDCl_3$) δ: 0.83 (3H, t, J=7 Hz), 1.24 (2H, s, J=7 Hz), 1.54 (2H, q, J=7 Hz), 4.00—4.30 (2H, m), 5.78 (1H, s), 6.81 (1H, br s), 7.32—7.60 (3H, m), 7.65—7.90 (2H, m). *Anal.* Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.35; H, 5.72.

Methyl 4-(4-Hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furyl)butyrate (10)——This compound was prepared from methyl 4-formylbutyrate (**8**) and **2a** in 45% yield in the same manner as described for **4a**, mp 78—79 °C. IR (Nujol): 3350, 3250, 1735, 1720 (sh), 1680 cm^{-1}. NMR ($CDCl_3$) δ: 1.62 (1H, m). 1.80 (2H, q, J=7 Hz), 2.16 (1H, m), 2.35 (2H, t, J=7 Hz), 3.63 (3H, s), 5.42 (1H, dd, J=3, 8 Hz), 6.81 (1H, br s), 7.30—7.53 (3H, m), 7.57—7.68 (2H, m). *Anal.* Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.53; H, 5.70.

4-Hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furan-carboxylic Acid (11)——A 1 N NaOH solution (1 ml) was added to a solution of **9** (100 mg, 0.36 mmol) in THF (1 ml) under ice-bath cooling. The reaction mixture was stirred for 0.5 h at room temperature, acidified with 1 N HCl under ice-bath cooling and extracted with AcOEt. The organic layer was washed with saturated NaCl (×2), dried over $MgSO_4$, and evaporated *in vacuo*. The resulting crystalline residue was recrystallized from a mixture of AcOEt and *n*-hexane to give 36 mg (45%) of **11**, mp 189—190 °C. IR (Nujol): 3325, 1760, 1725, 1670 cm^{-1}. NMR (DMSO-d_6) δ: 6.01 (1H, s), 7.10—8.00 (6H, m), 11.20 (1H, br s). *Anal.* Calcd for $C_{11}H_8O_5$: C, 60.00; H, 3.66. Found: C, 59.70; H, 3.61.

4-(4-Hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furyl)butyric Acid (12)——This compound was prepared from **10** in

88% yield in the same manner as described for **1a**, mp 179—180 °C. IR (Nujol): 3350, 3250, 1740, 1700 cm^{-1}. NMR (DMSO-d_6) δ: 1.25—1.74 (3H, m), 1.93 (1H, m), 2.22 (2H, t, J=7 Hz), 5.60 (1H, m), 7.10—7.90 (5H, m), 10.72 (1H, br s), 11.96 (1H, br s). *Anal.* Calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 63.82; H, 5.15.

5-(2-Benzyloxyethyl)-3-hydroxy-4-phenyl-2(5*H*)-furanone (14)——This compound was prepared from 3-benzyloxypropanal (**13**) and **2a** in 69% yield in the same manner as described for **4a**, mp 112—113 °C. IR (Nujol): 3300, 1740, 1670 cm^{-1}. NMR ($CDCl_3$) δ: 1.70 (1H, m). 2.45 (1H, m), 3.55—3.85 (2H, m), 4.55 (2H, s), 5.63 (1H, dd, J=2, 9 Hz), 6.52 (1H, s), 7.28—7.51 (8H, m), 7.65 (2H, dd, J=2, 8 Hz). *Anal.* Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.33; H, 5.61.

5-(2-Benzyloxyethyl)-3-methoxy-4-phenyl-2(5*H*)-furanone (15)——An ether solution of CH_2N_2 was added to a solution of **14** (2.00 g, 6.44 mmol) in MeOH (20 ml) with stirring at room temperature until the mixture became yellow. The excess CH_2N_2 was decomposed by addition of AcOH, and the mixture was evaporated to give 2.09 g (100%) of **15** as an oil. IR (CH_2Cl_2): 1750 cm^{-1}. NMR($CDCl_3$) δ: 1.65 (1H, ddd, J=4, 9, 18 Hz), 2.32 (1H, dddd, J=2, 6, 12, 18 Hz), 3.50—3.80 (2H, m), 4.07 (3H, s), 4.52 (2H, s), 5.55 (1H, dd, J=2, 9 Hz), 7.33 (5H, s), 7.20—7.70 (5H, m). MS m/z: 324 (M^+).

5-(2-Hydroxyethyl)-3-methoxy-4-phenyl-2(5*H*)-furanone (16)——A 4.4% (v/v) solution of formic acid in MeOH (20 ml) was added to Pd black (1.00 g) under a nitrogen atmosphere and then a solution of **15** (2.06 g, 6.35 mmol) in MeOH (20 ml) was further added. The reaction mixture was stirred at room temperature for 1.5 h, then added to a suspension of Pd black (1.00 g) in a 4.4% (v/v) solution of formic acid in MeOH (20 ml) at room temperature under a nitrogen atmosphere. The whole was stirred for 1 h at the same temperature, then filtered, and the filtrate was evaporated *in vacuo*. The residue was dissolved in AcOEt and the solution was washed with dilute $NaHCO_3$, H_2O and saturated NaCl, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was crystallized from *n*-hexane to give 1.34 g (90%) of **16**, mp 82—84°C. IR (Nujol): 3460, 1720, 1640 cm^{-1}. NMR ($CDCl_3$) δ: 1.53—1.80 (2H, m), 2.26 (1H, m), 3.75—4.02 (2H, m), 4.09 (3H, s), 5.56 (1H, dd, J=2, 10 Hz), 7.30—7.52 (3H, m), 7.54—7.67 (2H, m). *Anal.* Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.88; H, 6.00.

4-Methoxy-5-oxo-3-phenyl-2,5-dihydro-2-furylacetic Acid (17)——Jones' reagent (2 N, 8.00 ml, 16.0 mmol) was diluted with acetone (12.5 ml) and to this solution was added dropwise a solution of **16** (1.25 g, 5.34 mmol) in acetone (12.5 ml) over 50 min with stirring at 5 °C under ice-bath cooling. The reaction mixture was stirred for 15 min at room temperature and then isopropyl alcohol (5 ml) was added. The whole was poured into a mixture of AcOEt and H_2O and the organic layer was separated, washed with H_2O (×2) and saturated NaCl, dried over $MgSO_4$, and evaporated *in vacuo*. The crystalline residue was triturated with Et_2O and filtered to give 0.86 g (65%) of **17**, mp 159—160 °C. IR (Nujol): 1760, 1695, 1655 cm^{-1}. NMR (DMSO-d_6) δ: 2.41 (1H, dd, J=9, 16 Hz), 2.85 (1H, dd, J=3, 16 Hz), 3.96 (3H, s), 5.85 (1H, dd, J=3, 9 Hz), 7.35—7.57 (3H, m), 7.63 (2H, dd, J=2, 8 Hz), 12.58 (1H, br s). *Anal.* Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.93; H, 4.69.

4-Hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furylacetic Acid (18)——A 1 N solution of BBr_3 in CH_2Cl_2 (4 ml) was added to a suspension of **17** (496 mg, 2.00 mmol) in dry CH_2Cl_2 (4 ml) with stirring under ice-bath cooling, and the mixture was stirred for 5 d at room temperature, then poured into a mixture of AcOEt and saturated NaCl. The organic layer was separated, washed with saturated NaCl (×2), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was subjected to column chromatography on silica gel [eluent: $CHCl_3$ and $CHCl_3$–MeOH (10:1)]. The fractions containing the product were collected and evaporated *in vacuo*. The crystalline residue was recrystallized from a mixture of AcOEt and *n*-hexane to give 120 mg (26%) of **18**, mp 204—205 °C. IR (Nujol): 3350, 3270, 1740, 1710, 1670 cm^{-1}. NMR (DMSO-d_6) δ: 2.36 (1H, dd, J=9, 16 Hz), 2.94 (1H, dd, J=2, 16 Hz), 5.80 (1H, dd, J=2, 9 Hz), 7.10—8.00 (5H, m), 10.85 (1H, br s). *Anal.* Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.64; H, 4.22.

5-(3-Benzyloxypropyl)-3-hydroxy-4-phenyl-2(5*H*)-furanone (20)——This compound was prepared from 4-benzyloxybutanal (**19**) and **2a** in 78% yield in the same manner as described for **4a**, mp 120—121 °C. IR (Nujol): 3300, 1725, 1680 cm^{-1}. NMR ($CDCl_3$) δ: 1.55—1.85 (3H, m), 2.26 (1H, m), 3.40—3.64 (2H, m), 4.46 (2H, s), 5.45 (1H, dd, J=3, 8 Hz), 6.67 (1H, s), 7.20—7.50 (8H, m), 7.63 (2H, dd, J=2, 8 Hz). *Anal.* Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 73.88; H, 6.00.

3-Hydroxy-5-(3-hydroxypropyl)-4-phenyl-2(5*H*)-furanone (21)——This compound was prepared from **20** in 78% yield in the same manner as described for **16**, mp 149—151°C. IR (Nujol): 3490, 3370, 1740, 1680 cm^{-1}. NMR (DMSO-d_6) δ: 1.20—1.80 (3H, m), 1.80—2.28 (1H, m), 3.36 (2H, m), 4.43 (1H, br s), 5.60 (1H, m), 7.18—7.92 (5H, m), 10.64 (1H, br s). *Anal.* Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.55; H, 5.85.

3-(4-Hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furyl)propanamide (22)——Isobutyl chloroformate (0.29 ml, 2.20 mmol) was added dropwise with stirring to a mixture of WF-3681 (**1a**) (0.248 g, 1.00 mmol) and triethylamine (0.31 ml, 2.20 mmol) in dry CH_2Cl_2 (10 ml) at −20 °C. The reaction mixture was stirred for 1 h at the same temperature, then a 28% solution of ammonia in H_2O (2.5 ml) was added dropwise with stirring at the same temperature. The whole was poured into H_2O and the aqueous layer was separated. After 2 h at room temperature, the aqueous layer was acidified with concentrated HCl under ice-bath cooling. The resulting precipitate was collected by filtration, washed with H_2O, and recrystallized from a mixture of AcOEt and *n*-hexane to give 0.21 g (85%) of **22**, mp 241—242 °C. IR (Nujol): 3460, 3340, 1745, 1665, 1650, 1600 cm^{-1}. NMR (DMSO-d_6) δ: 1.55 (1H, m), 1.90—2.45

(3H, m), 5.55 (1H, d, $J=8$ Hz), 6.80 (1H, s), 7.10—8.00 (6H, m), 10.70 (1H, br s). *Anal.* Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 62.89, H, 5.24; N, 5.71.

Determination of Enzymatic Activity——Aldose reductase activity was measured according to the method described in the preceding paper.[3] Rabbit lenses obtained from male Japanese white rabbits were homogenized in 3 volumes of cold distilled water in a Teflon homogenizer and then centrifuged at 10000 *g* for 60 min to remove insoluble material. The supernatant was dialyzed overnight against 0.05 M sodium chloride. The dialyzed lens homogenate was used in the enzymatic reaction. Oxidation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) to NADP was determined spectrophotometrically at 340 nm. In routine enzymatic assay, the reaction mixture contained 50 mM sodium phosphate buffer (pH 6.2), 0.125 mM NADPH, 400 mM lithium sulfate, enzyme solution, and 3 mM DL-glyceraldehyde as a substrate in a total volume of 1.0 ml. The reaction was started by the addition of DL-glyceraldehyde and NADPH and the reaction rate was measured for 2 min. The effect of an enzyme inhibitor was determined by including a solution of the inhibitor in dimethylsulfoxide (10 μl) in the reaction mixture.

Acknowledgement The authors are grateful to Dr. K. Yoshida, Dr. Y. Notsu, and their colleagues for the biological assays.

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