Communications to the Editor

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AN EFFICIENT SYNTHESIS OF WF-3681, A NOVEL ALDOSE REDUCTASE INHIBITOR, AND ITS RELATED COMPOUNDS

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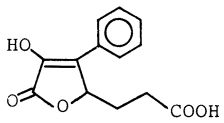
WF-3681 (1a), an aldose reductase inhibitor, and its related compounds (1b-1j) have been synthesized by aldol condensation of phenylpyruvates and ω-formylalkanoates as a key step.

KEYWORDS —— fungal metabolite; aldose reductase inhibitor; aldol condensation; phenylpyruvate; ω-formylalkanoate

We previously described the structure and synthesis of WF-3681 (1a), a novel aldose reductase inhibitor isolated from *Chaetomella* species.[2,3] Here we report an expeditious synthesis of this inhibitor and its related compounds and analyze their biological activity.



1a

We anticipated that the α-hydroxybutenolide ring system of WF-3681 could be constructed by aldol condensation of phenylpyruvate (e.g., 2a) with 3-formylpropionate (e.g., 3a) followed by lactonization of the resulting hydroxy keto ester 4 as depicted in Chart 1.[4] Hydrolysis of the side-chain ester group in the product 5a would afford compound 1a, which was expected to be identical in *all respects* with the natural WF-3681, since the latter had been isolated as *a racemic mixture*.[3]

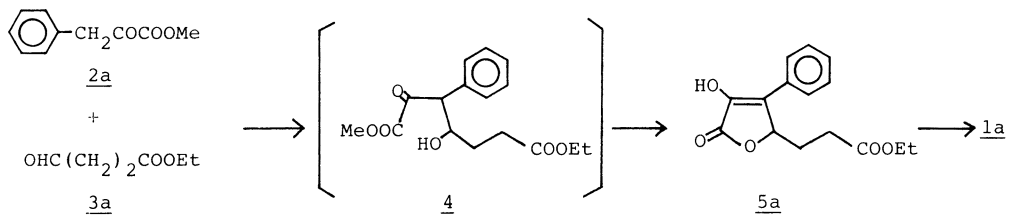
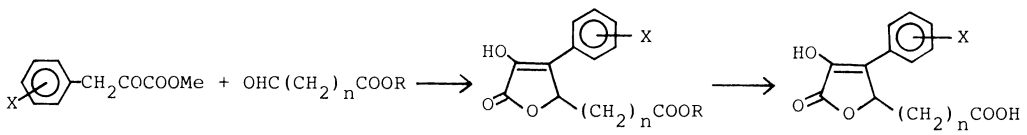


Chart 1

Methyl phenylpyruvate (2a) (mp 55-60°C) was prepared by methylating phenylpyruvic acid (MeI/DBU/DMF, 0°C, 87%).[5] Ethyl 3-formylpropionate (3a) [bp 68-78°C (7mmHg)] was prepared according to the method reported in the literature.[6] The key aldol condensation was conducted by stirring 2a and 3a in the presence of DBU in DMF at 0°C for 2.5 h. Under these conditions, the desired product 5a (mp 116-118°C) was obtained directly in 72% yield. The structure was characterized on the basis of its physical data [EIMS m/z 276 (M^+); IR(nujol) 3270,



2b X=4-Cl
c X=4-Me
d X=4-OCH_2Ph
e X=3,4-diCl
f X=3-CF_3,4-OMe

3b R=Bu^n; n=0
c R=Me; n=3

5b X=4-Cl; R=Et; n=2
c X=4-Me; R=Et; n=2
d X=4-OCH_2Ph; R=Et; n=2
e X=3,4-diCl; R=Et; n=2
f X=3-CF_3,4-OMe; R=Et; n=2
g X=H; R=Bu^n; n=0
h X=H; R=Me; n=3

1b X=4-Cl; n=2
c X=4-Me; n=2
d X=4-OCH_2Ph; n=2
e X=3,4-diCl; n=2
f X=3-CF_3,4-OMe; n=2
g X=H; n=0
h X=H; n=3
i X=4-OH; n=2

Chart 2

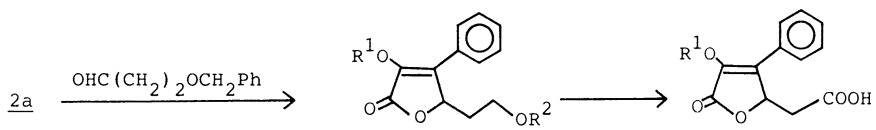
Table I. Synthesis of Compounds Related to WF-3681

Starting material	Aldol condensation			Hydrolysis		
	Product	mp(°C)	Yield(%)	Product	mp(°C)	Yield(%)
2b[a] + 3a	5b	121-122	60	1b	181-182	96
2c[a] + 3a	5c	108-109	61	1c	168-169	100
2d[a] + 3a	5d	130-131	72	1d	198-199	60
2e[a] + 3a	5e	109-111	70	1e	179-180	86
2f[b] + 3a	5f	168-169	51	1f	224-226	87
2a + 3b[c]	5g	108-109	87	1g[d]	189-190	45
2a + 3c[c]	5h	78-79	45	1h	179-180	88
				1i[e]	251-253	57

a) Prepared from methyl 2,2-dimethoxy-3-(substituted phenyl)propionates, synthesized according to the known procedure,[7] by heating in HCO_2H (65-70°C).
b) Prepared in the same way as for 2a.
c) Prepared according to the known procedures.[8]
d) Hydrolysis was achieved by using 1N NaOH/THF at room temp.
e) Prepared by treating 5d with 3N HCl/AcOH(100°C,4h).

1740, 1705 cm^{-1}; NMR($CDCl_3$) δ: 1.27 (3H, t, J=7Hz), 1.75 (1H, m), 2.32-2.77 (3H, m), 4.16 (2H, q, J=7Hz), 5.51 (1H, dd, J=2, 9Hz), 6.74 (1H, s)]. Acid hydrolysis of 5a (3N HCl/AcOH, 100°C, 1h) yielded WF-3681 (1a)(100%), which was identified with the natural product[3] in all respects.

The synthesis of 1a is highly efficient and provides the amounts necessary for detailed biological tests. Moreover, this method is applicable to the preparation of compounds related to 1a. Some compounds having substituents on the benzene ring (1b-1f and 1i) and modified carboxylic acid side-chains (1g and 1h) were thus prepared (Chart 2) and are listed in Table I. However, we were unable to achieve the aldol reaction using ethyl formylacetate,[9] probably due to the formation of an anion on the formylacetate rather than the phenylpyruvate. Therefore, we chose, for the preparation of 1j, 3-benzyloxypropionaldehyde[10] as the starting material and carried out the reaction with methyl phenylpyruvate under the above conditions to obtain α-hydroxybutenolide 6 (mp 112-113°C, 69%). Conversion of 6 to 1j (mp 204-205°C) was achieved via 7 (oil), 8 (mp 82-84°C), and 9 (mp 159-160°C) by a sequence of reactions (1. CH_2N_2/MeOH, 100%; 2. Pd-black/HCO_2H-MeOH, 90%; 3. CrO_3/H_2SO_4/acetone, 65%; 4. BBr_3/CH_2Cl_2, 26%) (Chart 3).



6 R^1=H, R^2=CH_2Ph
7 R^1=Me, R^2=CH_2Ph
8 R^1=Me, R^2=H

9 R^1=Me
1j R^1=H

Chart 3

Table II. Inhibition of Rabbit Lens Aldose Reductase[a)]

Compound	IC_{50} (M)	Compound	IC_{50} (M)
1a	2.5×10^{-7}	1f	5.1×10^{-8}
1b	9.2×10^{-8}	1i	1.6×10^{-7}
1c	8.4×10^{-8}	1g	$>1.0 \times 10^{-5}$ b)
1d	4.9×10^{-8}	1j	$>1.0 \times 10^{-5}$ c)
1e	9.8×10^{-8}	1h	1.0×10^{-5}

a) Enzyme activity was assayed by a modified method[2] described in the literature.[11]
b) A 45% inhibition at 1.0×10^{-5}M.
c) A 44% inhibition at 1.0×10^{-5}M.

The aldose reductase inhibitory activity of the new compounds above are shown in comparison with that of 1a in Table II. All the substituted benzene derivatives were more active than WF-3681, showing that the introduction of the lipophilicity tends to increase the activity. Modification of the carboxylic acid side-chain was found to decrease the activity, indicating that the side-chain length plays an important part in the activity.

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