Tetrahedron Letters,Vol.27,No.18,pp 2015-2018,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

STRUCTURE AND SYNTHESIS OF WF 3681, A NOVEL ALDOSE REDUCTASE INHIBITOR

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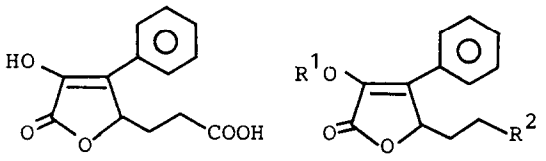
Summary: The structure of WF 3681 (1), an aldose reductase inhibitor isolated from a *Chaetomella* species, has been determined on the basis of its physical and chemical properties and confirmed by a total synthesis.

WF 3681 (1) is a fungal metabolite with potent aldose reductase-inhibitory activity. Herein we report the structure elucidation and the synthesis of this novel natural product.

WF 3681 was isolated from *Chaetomella raphigera* Swift No.3681 as colorless needles[1]: $C_{13}H_{12}O_5$ (high-resolution EIMS: obsd. m/z 248.066; calcd. 248.068. Anal. Calcd: C, 62.90; H, 4.87 %. Found: C, 63.13; H, 4.98 %); mp 177-179°C. Treatment of 1 with CH_2N_2 in MeOH gave the dimethyl derivative 2 (EIMS, m/z 276 (M^+)), while acetylation of 1 with Ac_2O in pyridine gave monoacetate 3 (EIMS, m/z 290 (M^+)), indicating the presence of a carboxyl group and an enol function in 1. The absorption bands at 3400-2500 and 1700 cm^{-1} in the IR spectrum (Nujol) of 1 were attributed to these functionalities. In the ^{13}C NMR spectrum (CD_3OD) of 1, the signal corresponding to the carboxyl group was observed at δ 176.2 (s).



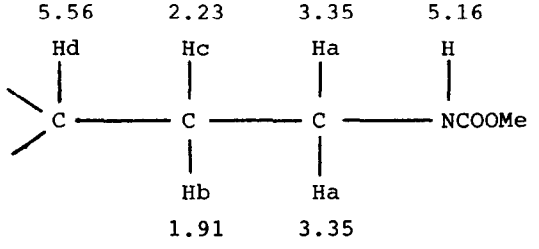
1

2 R^1=CH_3, R^2=$COOCH_3$
3 R^1=$COCH_3$, R^2=COOH
4 R^1=$COCH_3$, R^2=CH_2OH
5 R^1=H, R^2=CH_2OH
6 R^1=$COCH_3$, R^2=CH_2OCOCH_3
7 R^1=$COCH_3$, R^2=$CH_2NHCOOCH_3$

The UV spectra (λmax (MeOH) 285 nm (ε, 17,900); λmax (MeOH-NaOH) 320 (14,900)), together with the IR data (1735 cm^{-1}), argued the presence of an α-hydroxybutenolide chromophore. The 45-50 nm bathochromic shifts from the

UV absorptions of the typical α-hydroxybutenolides[2] in both neutral and basic media showed a conjugation of the lactonic diosphenol with a phenyl ring (e.g. as shown in 1). The presence of the phenyl group was also suggested by the ^{1}H and ^{13}C NMR spectra (CD_3OD) of 1 (δ7.75 (brd, J = 7.5 Hz, 2 H), 7.44 (brt, J = 7.5 Hz, 2 H), 7.35 (brt, J = 7.5 Hz, 1 H); δ130.8 (s) (or 131.6 (s)), 128.4 (d)x2, 129.6 (d)x3). The carbons which constitutes the butenolide ring system were observed in the ^{13}C NMR spectrum of 1 at δ 171.0 (s, C-2), 139.1 (s, C-3), 131.6 (s, C-4) (or 130.8 (s)), and 79.2 (d, C-5), respectively, and the poroton on C-5 was observed at δ5.51 (dd, J=2, 8.5 Hz, 1 H) in the ^{1}H NMR spectrum of 1.

The remaining portion C_2H_4 of 1, which was observed in the ^{1}H NMR spectrum at δ2.3-2.6 (m, 3 H) and 1.67 (m, 1 H) and in the ^{13}C NMR spectrum at δ30.6 (t) and 29.8 (t), was revealed as follows. $NaBH_4$ reduction of 3, after conversion to the mixed anhydride in situ with EtOCOCl (Et_3N/THF), gave carbinol 4 (EIMS, m/z 276 (M^+)), along with diol 5 (EIMS, m/z 234 (M^+)) which was probably formed via deacylation of 4. Acetylation of 4 with Ac_2O in pyridine gave diacetate 6 (EIMS, m/z 318 (M^+)), in the ^{1}H NMR spectrum of which the newly formed methylene protons were observed at δ4.00 as a triplet (J=7 Hz), indicating the presence of the unit $-CH_2CH_2OAc$ in 6 and hence $-CH_2COOH$ in 1. Curtius rearrangement of 3 (1. EtOCOCl/Et_3N/THF; 2. NaN_3), followed by treatment with MeOH, gave urethane 7. The ^{1}H NMR analysis of 7 with the aid of decoupling experiments revealed ^{1}H-^{1}H relationships of the partial structure $>CHCH_2CH_2NHCOOMe$ as shown in Fig.1. WF 3681 was thus shown to have the unit $>CHCH_2CH_2COOH$ and hence the full structure of 1.

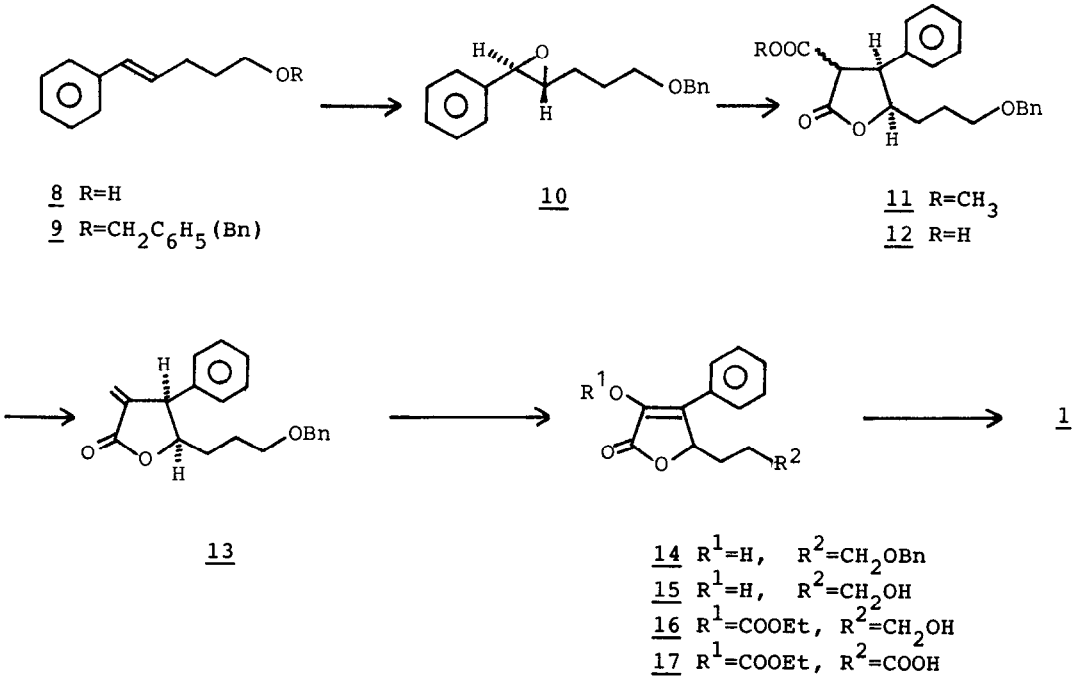


$J_{a,b}$= 6 Hz, $J_{a,c}$= 6 Hz,
$J_{b,c}$= 15 Hz, $J_{b,d}$= 8 Hz,
$J_{c,d}$= 4 Hz, $J_{a,NH}$= 7 Hz,

Fig.1 The Partial Structure of 7 and Its NMR Data (Chemical Shifts in ppm and ^{1}H-^{1}H Relationships).

The presumed structure was further coroborated by the following reactions. Treatment of 1 with MeONa (MeOH, reflux) gave 5-phenyl-4-pentenoic acid (E and Z mixture) (EIMS, m/z 176 (M^+)), whose structure was confirmed by conversion to 5-phenylpentanoic acid by catalytic reduction (Pd-black/MeOH). This fact agreed well with the structure 1.

A final confirmation for the structure 1 was obtained by a total synthesis starting from (E)-5-phenyl-4-pentenol (8).[3] After protection of the hydroxy group in 8 by alkylation with benzyl bromide (NaH/THF, r.t.), the resulting benzyl ether 9 (oil, 97 %) was oxidized with MCPBA (CH_2Cl_2, r.t.) to give epoxide 10 (oil, 99 %). Reaction of 10 with the enolate anion of methyl malonate (EtONa/EtOH, reflux) brought about a regiospecific opening of the epoxide ring to produce the product 11 (IR ($CHCl_3$) 1780, 1725 cm^{-1}), which, without isolation, was subjected to alkaline hydrolysis (20 % aqueous NaOH, reflux) to provide γ-lactone carboxylic acid 12 (oil, 80 %)[6] as a diastereomeric mixture. Reaction of 12 with CH_2O/Me_2NH (AcONa/AcOH, 100°C) provided, via the Mannich base, methylene lactone 13 (oil, 77 %),[6] which was oxidized with OsO_4-$NaIO_4$ (dioxane, r.t.) to give α-hydroxybutenolide 14 (mp 120-122°C, 42 %).[6] After removal of the benzyl group by catalytic reduction (Pd-black/EtOH), the enol hydroxy group in the product 15 (mp 148-150°C, 96 %)[6] was protected by acylation with EtOCOCl (Et_3N/THF, 0°C) and the partially protected compound 16 (oil, 92 %) was subjected to oxidation with CrO_3 (H_2SO_4/acetone-H_2O, 0°C) to give carboxylic acid 17 (mp 139-141°C, 96 %), which was followed by deprotection (K_2CO_3(5 %)/MeOH-H_2O, r.t.) to yield 1 (mp 177-179°C, 71 %), identical in all respects with the natural product.



8 R=H
9 R=$CH_2C_6H_5$(Bn)

10

11 R=CH_3
12 R=H

13

14 R^1=H, R^2=CH_2OBn
15 R^1=H, R^2=CH_2OH
16 R^1=COOEt, R^2=CH_2OH
17 R^1=COOEt, R^2=COOH

Scheme 1

It is of interest to note that WF 3681 was isolated as a racemic mixture ($[\alpha]_D^{25}0°$(c 1.0, EtOH)) in spite of careful isolation operations.[5] Although we could not completely rule out the racemization during the isolation processes, there might be the possibility that the butenolide formation of WF 3681 is a nonspecific enzymatic reaction or rather a nonenzymatic, chemical process. The fermentation, isolation, and biological activity of WF 3681 will be reported separately.

References and Notes

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4. For the analoguous reaction with styrene oxide, see P. M. G. Bavin, D. P. Hansell, and R. G. W. Spickett, J. Chem. Soc., 4535 (1964); C. H. DePuy, F. W. Breitbeil, and K. L. Eilers, J. Org. Chem., 29, 2810 (1964).
5. Optical resolution of the synthetic product using cinchonidine provided (+)-WS 3681 (mp 179-180°C, $[\alpha]_D^{22}$+132.1° (c 1.0, EtOH)) and (-)-WS 3681 (mp 179-180°C, $[\alpha]_D^{20}$-130.0° (c 1.0, EtOH)). These optically active compounds were stable under some acidic and basic conditions (e.g. at pH 2, r.t. and pH 10, r.t.).
6. Selected spectroscopic data of the synthetic intermediates. 12: IR ($CHCl_3$) 1780, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.89 (m, 1H), 4.3-3.9 (m, 2 H), 3.40 (t, J = 6 Hz, 2 H). 13: IR ($CHCl_3$) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.40 (d, J = 2 Hz, 1 H), 5.58 (d, J = 2 Hz, 1 H), 4.72 (m, 1 H), 4.30 (d, J = 8 Hz, 1 H), 3.37 (t, J = 6 Hz, 2 H). 14: IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.43 (m, 1H), 3.50 (t, J = 6 Hz, 2 H). 15: IR (Nujol) 1725 cm^{-1}; ^1H NMR (CD_3OD) δ 5.48 (dd, J = 2, 7 Hz, 1 H), 3.50 (t, J = 6 Hz, 2 H).

(Received in Japan 4 March 1986)