Total Synthesis of (±)-4-Isoavenaciolide, a Metabolite of *Aspergillus avenaceus*

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Summary Starting from an aconic acid (**1**), the total synthesis of 4-isoavenaciolide (**13**) in racemic form is described.

4-ISOAVENACIOLIDE, isolated from *Aspergillus avenaceus* was shown to have the novel bislactonic structure (**13**),[1] and to be an epimer at C-4 of avenaciolide (**12**)[2] obtained from the same source.

We record here the synthesis, in racemic form, of 4-isoavenaciolide (**13**). Reduction of (**1**)[3] with Zn in AcOH gave *trans*-γ-lactone acid (**2**)†‡ (65%), m.p. 91—92°. The acid chloride (**3**) of (**2**) was converted (CH_2N_2–ether) into the diazoketone (**4**), which was treated with AcOH (80°) to give the α-acetoxy-ketone (**5**)†‡ [82% from (**2**)], m.p. 61—62°. Acidic hydrolysis (6N-HCl–dioxan 1:1 v/v, 25°) of (**5**) afforded the α-ketol (**6**)†‡§ (85%), m.p. 53—55°. Treat-

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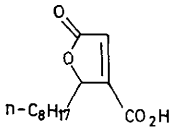
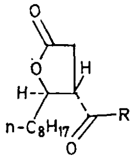
† This compound had i.r., n.m.r., and mass spectra, in agreement with the structure assigned.

‡ Satisfactory microanalytical data were obtained.

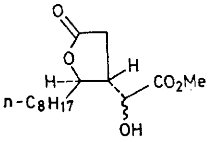
§ Alternatively, the α-ketol (**6**) was formed directly by treatment of (**4**) with aqueous acid in a yield less than 50%.



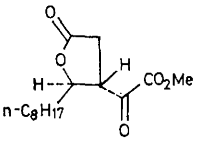
(1)



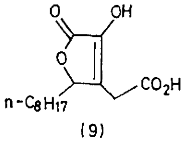
(2) R = OH
(3) R = Cl
(4) R = CHN_2
(5) R = CH_2OAc
(6) R = CH_2OH



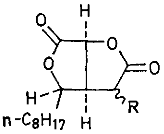
(7)



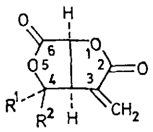
(8)



(9)



(10) R = H
(11) R = CO_2H



(12) $R^1 = n\text{-}C_8H_{17}$, $R^2 = H$
(13) $R^1 = H$, $R^2 = n\text{-}C_8H_{17}$

ment of (**6**) with copper(II) acetate in MeOH (60°, 18 h) gave a mixture (*ca.* 1 : 1) of the two diastereoisomeric hydroxy-esters (**7**)† (65%), which was oxidized with CrO_3 in pyridine to yield the α-keto-ester (**8**)† (80%). Under acidic conditions (2N-HCl–dioxan 1 : 1 v/v, 45°) the α-keto-ester (**8**) was transformed into the α-hydroxy-αβ-unsaturated γ-lactone (**9**)†‡ (75%), m.p. 66—71°. Catalytic hydrogenation (5% Rh on alumina, AcOH) of (**9**), followed by treatment with acid (ether saturated with HCl–glyme 1 : 2 v/v, 45°) afforded, after chromatographic separation with silica gel, the crystalline bis-γ-lactone (**10**)†‡(>40%), m.p. 81—82·5°. As an alternative and short route, alkaline hydrolysis of the mixture of diastereoisomers (**7**) followed by treatment with acid was carried out, resulting in the direct formation of (**10**) though in low yield (*ca.* 10%).¶

Carboxylation of the bislactone (**10**) with Stiles' reagent[4,5] led to the acid (**11**), which without purification, was treated with a mixture of aqueous formaldehyde and diethylamine (25°, 10 min, then 100°, 40 min) to afford, after chromatographic purification with silica gel, crystalline (±)-4-isoavenaciolide (**13**)†‡ [40% from (**10**)], m.p. 99—101°, identical in all respects except for rotation (i.r., n.m.r., m.s., t.l.c. behaviour under various conditions) with natural 4-isoavenaciolide.

We thank Dr. W. B. Turner (Imperial Chemical Industries Limited) for providing a sample of natural 4-isoavenaciolide.

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¶ Since one of the two diastereoisomers (**7**) is able to be converted into the bislactone (**10**), the yield does not exceed 50%. In this sequence of reactions the corresponding acids of (**7**) were obtained as major products.

[1] D. C. Aldridge and W. B. Turner, *J. Chem. Soc.* (*C*), **1971**, 2431.

[2] D. Brookes, B. K. Tidd, and W. B. Turner, *J. Chem. Soc.*, **1963**, 5385; D. Brookes, S. Sternhell, B. K. Tidd, and W. B. Turner, *Austral. J. Chem.*, 1965, **18**, 373; *cf.* the synthesis of (±)-avenaciolide, W. L. Parker and F. Johnson, *J. Amer. Chem. Soc.*, **1969**, **91**, 7208.

[3] The acid (**1**) was prepared using 2-nonylidenesuccinic acid by a procedure (I_2–KI, aqueous $NaHCO_3$) different from that reported: A. Takeda, K. Takahashi, S. Torii, and T. Moriwake, *J. Org. Chem.*, 1966, **31**, 616.

[4] H. L. Finkbeiner and M. Stiles, *J. Amer. Chem. Soc.*, 1963, **85**, 616.

[5] J. Martin, P. C. Watts, and F. Johnson, *Chem. Comm.*, 1970, 27.