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A SYNTHESIS OF NATURALLY OCCURRING (-) ISOAVENACIOLIDE

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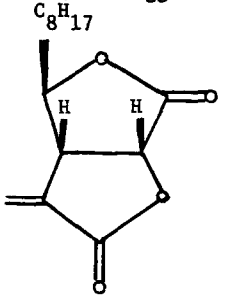
Avenaciolide[1] (1), isoavenaciolide[2] (2), ethisolide[2] (3) and canadensolide[3] (4) form an interesting quartet of antifungal metabolites, three of which (1,2,4) have been synthesized in racemic form[4,5,6]. The absolute stereochemistry of 1 was determined by degradation and correlation of the derived fragments with compounds of known stereochemistry[1]. However this process led to an incorrect assignment, as we showed recently by synthesising the optically pure material[7]. In order to clarify the situation for other members of the series, we undertook a synthesis of 2 from D-glucose and we report herein that the chirality of the naturally occurring material is (3aR, 4S, 6aR) and not the opposite as previously determined[2]. In view of the fact that naturally-occurring isoavenaciolide (2) and ethisolide (3) are both levorotatory[2], we suggest that the latter compound also has the same absolute configuration.



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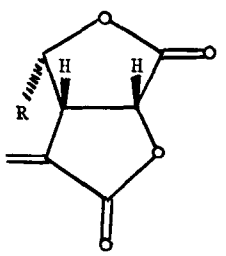
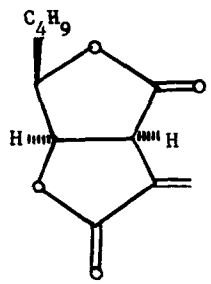


2 R = C_8H_{17}; 3 R = C_2H_5



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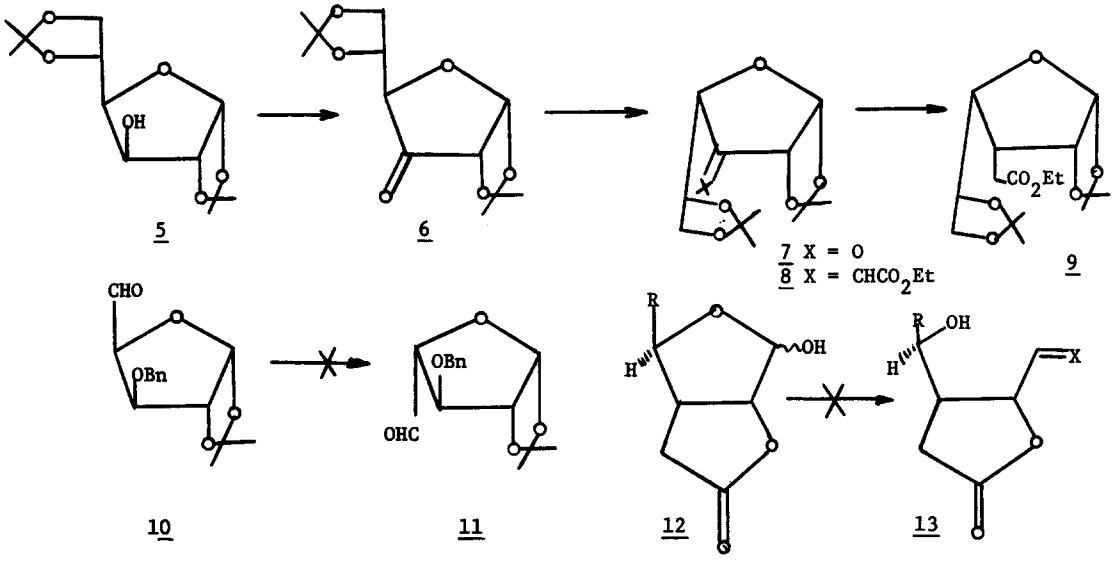
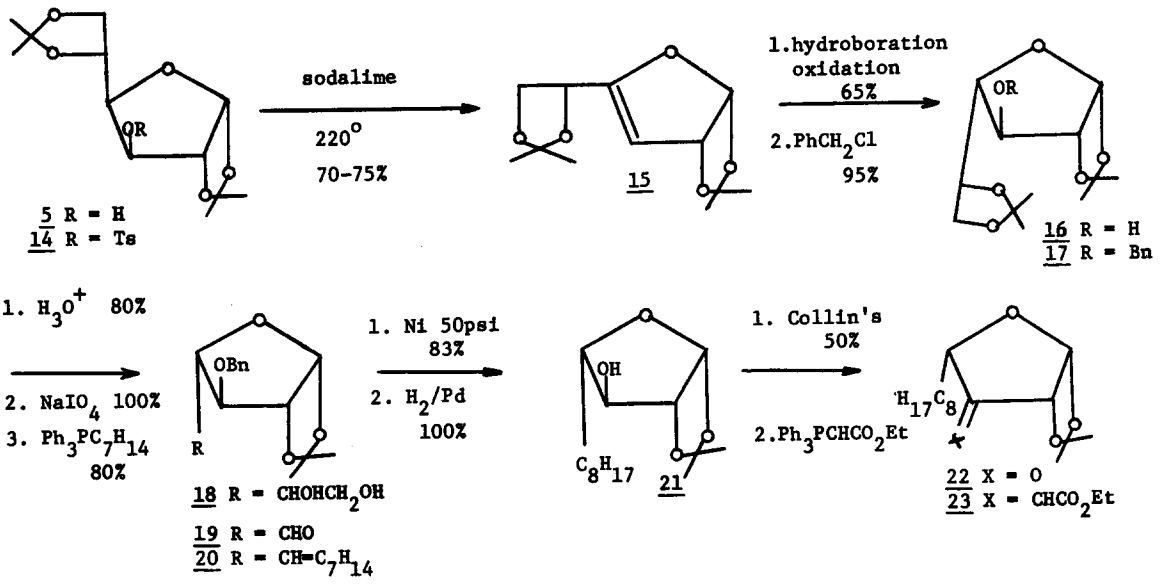
Our route to avenaciolide (1) employed "diacetone glucose" (5) as starting material, and compounds 6[7], 10[7] and 12[7] were intermediates. These were considered to be potential candidates for epimerisation at carbon-4, thereby providing an entry into the isoavenaciolide skeleton. However treatment of 6 with base caused destruction of the molecule[8]. The formation of 7 from 6 has been reported in the literature[8], but the ester 9 obtained from



5 6 7 X = O 8 X = $CHCO_2Et$ 9 10 11 12 13



5 R = H
14 R = Ts

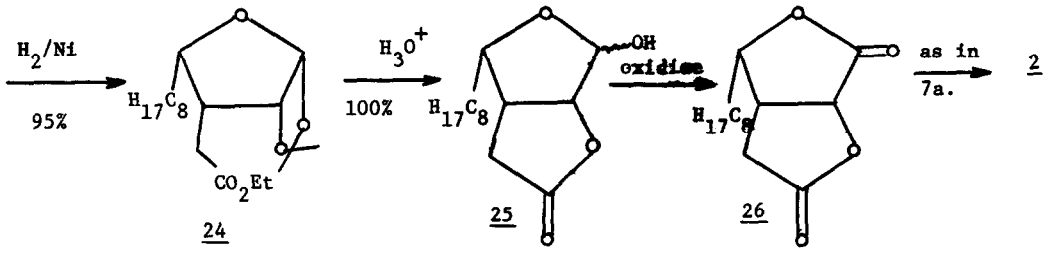
15

16 R = H
17 R = Bn

18 R = $CHOHCH_2OH$
19 R = CHO
20 R = $CH{=}C_7H_{14}$

21

22 X = O
23 X = $CHCO_2Et$



7 via 8 could not be selectively hydrolysed in satisfactory yield[9], rendering this approach unattractive.

The aldehyde 10 was not epimerised to 11 when treated with sodium methoxide in methanol.

Our attention then shifted to the lactone-lactol 12 in the hope that a monocyclic equivalent e.g. 13 could be prepared which would allow the desired epimerisation at carbon-4. However a suitable form of 13 (e.g. x = $(SR)_2$) could not be prepared.

In view of the foregoing failures to employ any avenaciolide intermediates we explored an alternative route. The olefin 15 may be obtained in 70-75 percent yield by careful pyrolysis under high vacuum at 220°, of an intimate mixture of the tosylate 14 and sodalime[10]. Hydroboration of 15 in tetrahydrofuran followed by oxidation gave the known alcohol 16 in better yield than reported in the literature[11]. The recently described benzylation procedure of Czernecki and co-workers[12] gave 17, rapidly and in nearly quantitative yield, and selective hydrolysis gave the diol 18 as a crystalline material (m.p. 104.0-104.5° $[\alpha]_D^{23}$ = 32.6)[13].

The syrupy aldehyde 19 obtained in quantitative yield by periodate cleavage of 18 had an nmr spectrum that was virtually superimposable upon that of its epimer, 10; however the olefin obtained therefrom, 20, was different from that prepared previously.[7b] Conversion of 20 to 21[13] was best done in two steps, and the latter was oxidised to a ketone 22 which was subjected to the Wittig reaction. The material obtained (23) upon hydrogenation gave a single isomer 24 whose stereochemistry became apparent in the next step. Thus hydrolysis gave the lactone 25 quantitatively, and oxidation gave the bis-lactone 26 in 74 percent yield m.p. 110.5-111.5; $[\alpha]_D^{20}$ -7.52[13]. Compound 26 has been prepared in racemic form m.p. 81-82.5.[6a]

Methylenation of 26 according to the published procedure[4a] gave 2 in 40 percent yield m.p. 127-128° $[\alpha]_D^{20}$ -167.2 (c, 1.2 in ethanol). Literature values for naturally occurring 2: m.p. 129-130°, $[\alpha]_D^{27}$ -154° (c, 1.1 in ethanol)[2]. Natural isoavenaciolide therefore has the (3aR, 4S, 6aR) chirality.

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