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TOTAL SYNTHESIS OF dl-HIRSUTIC ACID

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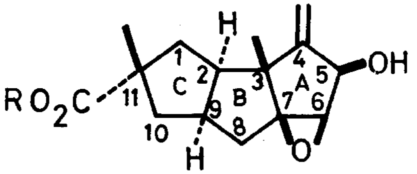
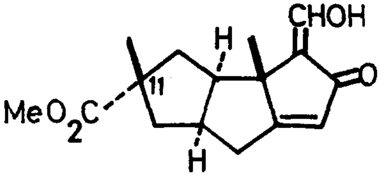
Although the skeleton of hirsutic acid (**1**)[1,2], a highly oxygenated fungal sesquiterpenoid, has already been synthesized[3,4], the total synthesis of the acid has remained unsettled, because of the difficulty of constructing the densely functionalized system. Herein we describe a stereospecific conversion of the previously reported[3] α-hydroxymethylene ketone **2** to racemic hirsutic acid.



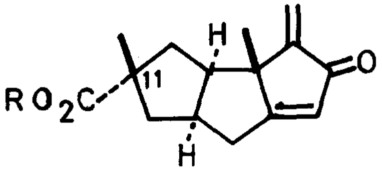
1 R=H
1a R=Me
1' 11-epimer(R=H)

Treatment of ketone **2** with 38% formalin and K_2CO_3 in acetone[5] (rt, 2 hr) gave dienone ester **3**[6] [oil, ν 1695, 1645, 1625 cm^{-1}; δ 1.18, 1.38, 3.64 (each 3H, s), 5.14 (1H, s), 5.86 (2H, s)], smoothly in 85% yield. The corresponding acid **4**[6,7] [oil, δ 1.20, 1.42 (each 3H, s), 5.13 (1H, s), 5.86 (2H, s)] was obtained by refluxing the ester in DMF in the presence of a large excess (15 eq.) of LiI[8] (16 hr, under Ar, 60%). Regio- and stereospecific epoxidation at the <u>endo</u> double bond of **4** was effected with basic



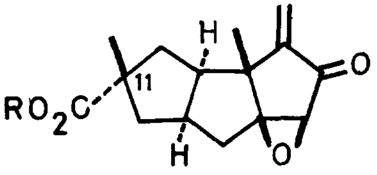
2

2' 11-epimer



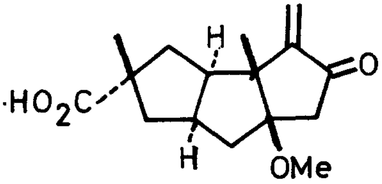
3 R=Me 3' 11-epimer

4 R=H 4' 11-epimer



5 R=H 5' 11-epimer

5a R=Me



6

30% H_2O_2-MeOH (-36°C, 3 eq. of 1N NaOH, 40 min) to give epoxyketone 5[6,9] [oil, δ 1.18, 1.42 (each 3H, s), 3.39, 5.24, 6.03 (each 1H, s)] in 60% yield. As a by-product (20%), a MeOH adduct 6[6,10] [mp 128-129°C, δ 2.48 (2H, s), 3.21 (3H, s)] was obtained. The adduct could be reverted to the starting compound 4 on treatment with 95% sulfuric acid (CH_2Cl_2, 0°C, 30 min) or with dilute NaOH. Finally reduction of epoxyketone 5 with $NaBH_4$ in EtOH (0°C, 15 min) afforded selectively dl-hirsutic acid (1) [80% yield, mp 168-169°C]. Mass, ir and nmr spectral data [m/e 264 (M^+), ν 3450, 3400-2400, 1700, 1670, 915, 890 cm^{-1}; δ 1.04, 1.38 (each 3H, s), 3.46 (1H, d, J = 2.0 Hz), 4.60 (1H, m), 4.99 (1H, d, J = 2.5 Hz), 5.26 (1H, d, J = 2.0 Hz)] of the synthetic acid were practically in complete agreement with those reported[1] for the optically active form.

In a similar fashion, 11-epi-hirsutic acid(1')[1] [mp 157.5-159°C, m/e 264 (M^+), ν 1700, 1665 cm^{-1}; δ 1.09, 1.24 (each 3H, s), 3.51 (1H, d, J = 2.0 Hz), 4.64 (1H, m), 5.03 (1H, d, J = 2.6 Hz), 5.29 (1H, d, J = 2.0 Hz) was synthesized[11], starting from the known 11-epimeric hydroxymethylene ketone

2'[3,11]. As expected, the signal due to the 11-methyl group of hirsutic acid appears at lower field than that of the epimer, reflecting the equatorial nature[1b] of the methyl group.

dl-Methyl hirsutate **1a**[6] [mp 137-138°C, ν 3420, 1720, 1660 cm^{-1}; δ 1.04, 1.33, 3.65 (each 3H, s), 3.45 (1H, d, J = 1.9 Hz), 4.60 (1H, m), 4.98 (1H, d, J = 2.6 Hz), 5.24 (1H, d, J = 2.2 Hz)] was also obtained similarly through $NaBH_4$ reduction (100% yield) of epoxyketone methyl ester **5a**[6] [oil, ν 1725, 1640 cm^{-1}; δ 1.18, 1.36, 3.63 (each 3H, s), 3.40, 5.25, 6.03 (each 1H, s)] which in turn prepared by direct epoxidation of the exomethylene ester **3**. Spectral data of synthetic dl-ester are also in good agreement with those reported in the literature[1].

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REFERENCES AND FOOTNOTES

(1) a) F.W. Comer, F. McCapra, I.H. Qureshi and A.I. Scott, *Tetrahedron*, **23**, 4761 (1967); b) X-ray crystallographic analysis; F.W. Comer and J. Trotter, *J. Chem. Soc.*, **B**, 11 (1966); c) In the present paper, the numbering system of Scott was adopted. For the C.A. name and numbering, see *Chem. Abstr.*, **76**, Index Guide (1972).

(2) Biosynthesis; T.C. Feline and G. Mellows, *J.C.S. Chem. Comm.*, 63 (1974).

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(5) A.J. Manson and D. Wood, *J. Org. Chem.*, **32**, 3434 (1967).

(6) Satisfactory exact mass, ir ($\nu_{max}^{CHCl_3}$) and nmr ($\delta_{TMS}^{CDCl_3}$) data have been obtained for this compound. Only important values were given in the text. Homogenity of the product was checked by tlc and/or glc.

(7) Attempted basic hydrolysis of **3** under usual conditions afforded an intractable mixture.

(8) P.D.G. Dean, *J. Chem. Soc.*, 6655 (1965); For the O-alkyl cleavage by nucleophilic displacement reaction, see F. Elsinger, J. Schreiber and A. Eschenmoser, *Helv. chim. Acta*, **63**, 113 (1960); P.A. Bartlett and W.S. Johnson, *Tetrahedron Letters*, 4459 (1970).

(9) The compound **5** (complicatic acid) has recently been isolated from *Stereum complicatum*, G. Mellows, P.G. Mantle, T.C. Feline and D.J. Williams, *Phytochemistry*, **12**, 2717 (1973).

(10) Equilibration experiments indicated **6** to be a thermodynamically controlled product. The A/B *cis* structure is much more strain free than the *trans* counterpart.

(11) All epimeric intermediates[6] were oil and obtained in quite similar yields. The δ values characteristic for these compounds are as follows; **4'**[12] [1.25, 1.30 (each 3H, s), 5.17 (1H, s), 5.92 (2H, s)]; **5'**[12] [1.23, 1.26 (each 3H, s), 3.45, 5.27, 6.06 (each 1H, s)].

(12) Dash denotes the 11-epimer.