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A Synthesis of the Hirsutane Skeleton

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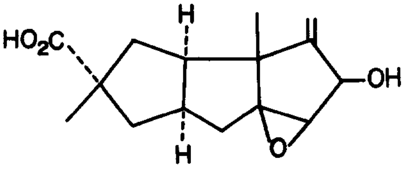
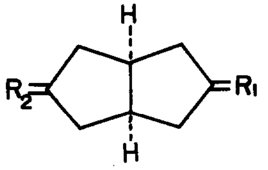
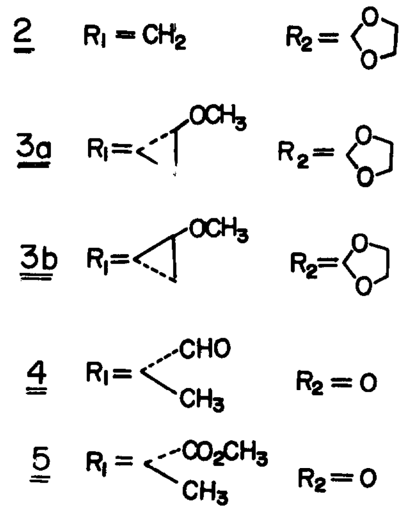
A fungal sesquiterpenoid hirsutic acid has been shown to have the structure **1** by Scott et al[3]. We wish to report here a stereochemically controlled synthesis of the skeleton[4] suitably functionalized for the total synthesis of hirsutic acid[5].

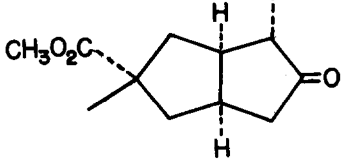
A methylene compound **2**[6] (ν_{max}^{neat} 1655, 1020, 880 cm^{-1}) was prepared from mono ketal[6] of _cis_-bicyclo [3,3,0] octane-3,7-dione[7] by the action of the Wittig reagent. Addition of methoxycarbene[8] (dichloromethyl methyl ether/methyl lithium-lithium iodide/ether) to **2** afforded an epimeric mixture of methoxycyclopropane derivatives **3** (60% yield, _exo_ : _endo_ = 2 : 1). Column chromatography of this mixture on silica gel separated the exo adduct, **3a**[6] (δ^{CCl_4} 0.38, 0.60, 2.78 (each 1H; ABX) from the _endo_ one, **3b**[6,9] (δ^{CCl_4} 0.27, 0.44, 2.95 (each 1H; ABX)). Acid cleavage of the cyclopropane ring of **3a** gave exclusively an aldehyde **4**[6], which was converted to an ester **5**[6,10](δ^{CCl_4} 1.30, 3.60 (each 3H, s)) (Jones reagent, diazomethane, 35% overall yield from 3a). _n_-Butylthiomethylene derivative [6a] of **5** was prepared in the usual manner and was reduced with Raney nickel to give a single product **6**[6,11] (δ^{CCl_4} 1.05 (3H, d, J = 7Hz), 1.32, 3.65 (each 3H, s)) in 35% overall yield from **5**. The configuration of the newly formed methyl group in **6** was assigned on the basis of alkaline equilibration experiment.


HO₂C
H
H
OH
O

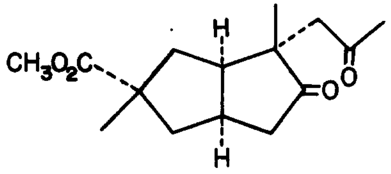
1


H
H
R₂
R₁

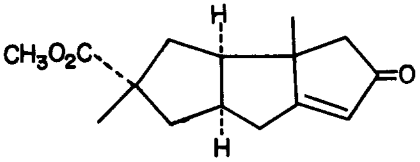

2
R₁ = CH₂
R₂ =
O
O
3a
R₁ =
OCH₃
R₂ =
O
O
3b
R₁ =
OCH₃
R₂ =
O
O
4
R₁ =
CHO
CH₃
R₂ = O
5
R₁ =
CO₂CH₃
CH₃
R₂ = O


CH₃O₂C
H
H
O

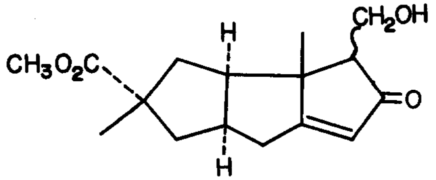
6


CH₃O₂C
H
H
O
O

7


CH₃O₂C
H
H
O

8


CH₂OH
CH₃O₂C
H
H
O

9

Alkylation of 6 with methallyl chloride followed by ozonolysis of the product gave a single diketone 7[6] (δ^{CCl_4} 0.93, 1.28, 2.01, 3.65 (each 3H, s)), in 50% yield in two steps. Cyclization of 7 to a nor-hirsutane derivative 8[6] (δ^{CCl_4} 1.09, 1.31, 3.62 (each 3H, s) 5.57 (1H, s)) was effected by treatment with potassium *t*-butoxide in 85% yield.

In order to introduce one carbon unit to the *nor*-compound 8 was formylated (ethyl formate/sodium methoxide/benzene, 60% yield) and the product[6] was reduced partially with sodium borohydride (1 eq. in water-methanol) to 9[6] (δ^{CCl_4} 1.16, 1.30, 3.60 (each 3H, s), 4.03 (2H, b.m), 5.63 (1H, s), 20% yield). The compound 9 has the suitably functionalized skeleton for the total synthesis of hirsutic acid.

The path leading to hirsutic acid 1 is now under investigation.

References and Notes

1) Present address: Chemical Laboratory, Faculty of Education, Fukui University, Fukui, Japan.

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3) a. F. W. Comer, F. McCapra, I. H. Qureshi and A. I. Scott, *Tetrahedron*, **23**, 4761 (1967).

   b. X ray crystallographic analysis of *p*-bromophenacyl derivative of hirsutic acid; F. W. Comer and J. Trotter, *J. Chem. Soc.*, *(B)*, 11, (1966).

4) a. After completion of the present work, a report concerning the synthesis of a skeleton has appeared; P. T. Lansbury, N. Y. Wang and J. E. Rhodes, *Tetrahedron Letters*, 1829 (1971). The synthesis affords equal amount of epimers at the carbon atom bearing carboxyl group.

   b. More recently an antitumoric compound coriolin has been shown to have the same skeleton; S. Takahashi, H. Naganawa, H. Iinuma,

T. Takita, K. Maeda and H. Umezawa, *Tetrahedron Letters*, 1955 (1971).

5) For the total synthesis of biogenetically related compound illudol see; T. Matsumoto, K. Miyano, S. Kagawa, S. Yu, J. Ogawa and A. Ichihara, *Tetrahedron Letters*, in press.

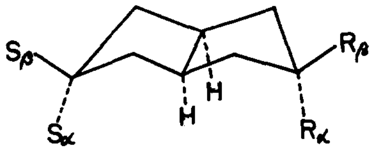
6) Satisfactory a) ir, b) nmr and c) mass spectrometric or analytical data have been obtained for this compound.

7) P. Yates, E. S. Hand and G. B. French, *J. Am. Chem. Soc.*, **82**, 6347 (1960).

8) U. Schöllkopf and J. Paust, *Angew. Chem.*, **75**, 670 (1963).

9) These structures were assigned by taking account of the steric course of the reaction and by comparing the effect of oxygen atoms of the ketal on the chemical shifts of methylene and methine protons on the cyclopropane ring. This conclusion was confirmed at a later stage (see footnote 10).

10) The W_H value of the nmr peak due to the *tert.* Me group of **5** at δ 1.30 is 1.2Hz, while that of the corresponding peak at δ 1.25 of the isomer (**i**)^6 from **3b** is 2.0Hz, indicating axial nature of the methyl group of (**i**). The M type coupling is more pronounced in (**iii**)^6 (δ 1.14, W_H = 2.4Hz), while in (**ii**)^6 a sharp singlet (W_H = 1.0Hz) appears at lower field δ 1.25. All these data are reasonably explained by the assigned stereochemistry.



(**i**) $R_\alpha = CH_3$, $R_\beta = CO_2CH_3$, S_α, S_β = =O

(**ii**) $R_\alpha = CO_2CH_3$, $R_\beta = CH_3$, S_α = H , S_β = OH

(**iii**) $R_\alpha = CH_3$, $R_\beta = CO_2CH_3$, S_α = H , S_β = OH

11) Stereochemically inhomogeneous **6** have been described in ref. 4a.