A Short Synthesis of Hirsutene using the de Mayo Reaction

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A short synthesis of the fungal metabolite hirsutene is described in which the key steps are photochemical cycloaddition of the enol of 5,5-dimethylcyclohexane-1,3-dione to 2-methylcyclopent-2-enol, followed by low-valent titanium reduction of the silylated adducts.

Hirsutene (**1**) is the simplest member of a group of fungal metabolites possessing the *cis–anti–cis*-tricyclo[6.3.0.0^{4,8}]-undecane ring system.[1] Because of the interesting physiological activity of members of this class of compounds the development of routes to this ring system[2] and to hirsutene itself[3] has attracted the attention of synthetic chemists. Described here is a new, short route to (±)-hirsutene.

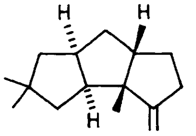
U.v. (254 nm) irradiation of a 1% methanolic solution of 5,5-dimethylcyclohexane-1,3-dione and 2-methylcyclopent-2-enol (obtained by $LiAlH_4$ reduction of 2-methylcyclopent-2-enone[4]) resulted in addition of the alkene to the triplet excited state of the enol form of the dione (the de Mayo reaction[5]). The major products were the adducts (**2**) and (**3**) (86% combined yield) generated by spontaneous retro-aldol opening of the initially formed cyclobutanols[5] and differing in the regiochemistry of alkene addition and the stereochemistry of the alcohol function.

The adduct (**2**) was found to be unstable with respect to retro-aldol reaction of the β-hydroxy-ketone function and so the adducts were separated in 89% combined yield as the t-butyldimethylsilyl derivatives (**4**) and (**5**) by column chromatography following silylation of the crude reaction mixture. Three of the four possible adducts were separated in the ratio 1 : 1 : 1. Two of these adducts were assigned the structure (**5**) and differ in the stereochemistry of the siloxy function; the third adduct was assigned as one of the alternative regioisomeric products (**4**).

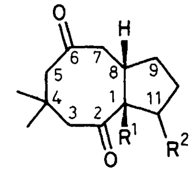
The regiochemistries of the adducts were determined by comparison of their ^{13}C n.m.r. spectra with those of the two major adducts, compounds (**6**) and (**7**), separated in 38 and 49% yields, respectively, following photocycloaddition of cyclopent-2-enol to 5,5-dimethylcyclohexane-1,3-dione. The regiochemistries of these adducts were assigned by ^1H n.m.r. decoupling experiments; irradiation of the hydroxy methine [*i.e.* the hydrogen at position 11 in (**6**) and that at position 9 in (**7**)] revealed the chemical shift and splitting pattern of the ring fusion methine at position 1 in (**6**) and position 8 in (**7**). The methine hydrogen at position 8 in the isomer assigned as (**7**) appeared at δ 2.95 as a multiplet (*J* 1.5, 4, 6, and 10 Hz) split by the four adjacent hydrogen atoms; the methine at position 1 in the isomer assigned structure (**6**) appeared at δ 2.85 and was split into three lines (*J* 8 Hz) by the adjacent hydrogen atoms. The ^{13}C n.m.r. shifts of the tertiary carbon atoms at position 1 in (**6**) and position 8 in (**7**) were then unambiguously assigned (δ 65.8 and 46.8, respectively) and correlated with the chemical shifts of the corresponding quaternary carbon atoms of (**4**) and (**5**) [δ 70.6 in (**4**), and 47.5 and 47.9 for the two stereoisomers of (**5**)].

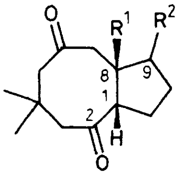
The stereochemistry of the ring fusion was assigned as *cis* in adducts (**2**)—(**7**) on the basis of the known course of the cycloaddition reaction in closely related analogues.[2,5]

Treatment of the silylated adducts (**4**) and (**5**) (as a 1 : 2 mixture) with a refluxing tetrahydrofuran (THF) solution of a low-valent titanium reagent obtained by reduction of titanium trichloride with potassium metal (the McMurry reagent[6]) gave the products of reductive cyclisation of the ketone groups,[2] compounds (**8**) and (**9**), in isolated yields of 17 and 38%, respectively following column chromatography. The structural assignment was confirmed by the ^{13}C n.m.r. spectrum and by ozonolysis of the major isomer which regenerated (**5**). Desilylation of (**8**) and (**9**) as a mixture ($Bu^n_4N^+F^-$ in dry CH_2Cl_2) followed by hydrogenation over platinum and oxidation of the products (Jones' reagent) gave (**10**) and (**11**) in the ratio 1 : 2 (62% overall, isolated yield). Hydrogenation of the double bond in (**8**) proceeded from the more hindered side, presumably because the hydroxy group holds this side of the molecule on the catalyst surface; similar stereoselectivity has been observed in other synthetic hirsutene precursors.[7] The isomer (**10**) possessed spectra (^1H and ^{13}C n.m.r.; mass) identical with those of an authentic sample which has been



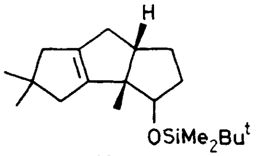
(**1**)



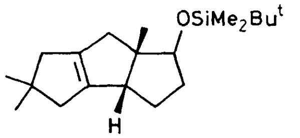


(**2**) R^1=Me, R^2=OH
(**4**) R^1=Me, R^2=OSiMe$_2$Bu^t
(**6**) R^1=H, R^2= OH

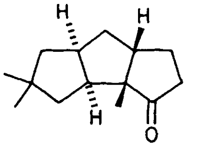
(**3**) R^1= Me, R^2=OH
(**5**) R^1= Me, R^2= OSiMe$_2$Bu^t
(**7**) R^1= H, R^2=OH



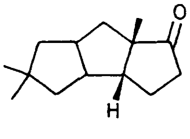
(**8**)



(**9**)



(**10**)



(**11**)

previously obtained by other routes to hirsutene and converted into the latter in one step using the Wittig reaction.[3,7]

The synthesis described offers the advantages of brevity coupled with ready availability of the starting materials; it also offers the possibility of preparation of optically pure hirsutene by using resolved 2-methylcyclopent-2-enol. The mildness of the procedures should also allow its extension to the preparation of other members of the hirsutene family bearing more sensitive functionality.

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