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THE SYNTHESIS OF 2-HYDROXY-4-ISOPROPYL-7-METHOXY-1,6-DIMETHYL-NAPHTHALENE, "CHEMICAL PRECURSOR" OF THE BYSSINOTIC AGENT FROM COTTON

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Summary Syntheses of the title compound 9, from carvone 2 and limonene 10, in seven and nine stages respectively, are described

The sesquiterpene 1-Hydroxy-4-isopropyl-7-methoxy-1,6-dimethyl-2(1H)-naphthalenone 1 was isolated from cotton[1] Evidence has been reported suggesting that this compound is responsable for byssinosis disease in textile industry workers[2] Recently, two groups have described the total synthesis of the physiologicaly active compound 1[3]

We report here a very simple synthesis of compound 9, "chemical precursor" of the sesquiterpene 1, starting from carvone 2 or limonene 10, via the aromatic ester 5

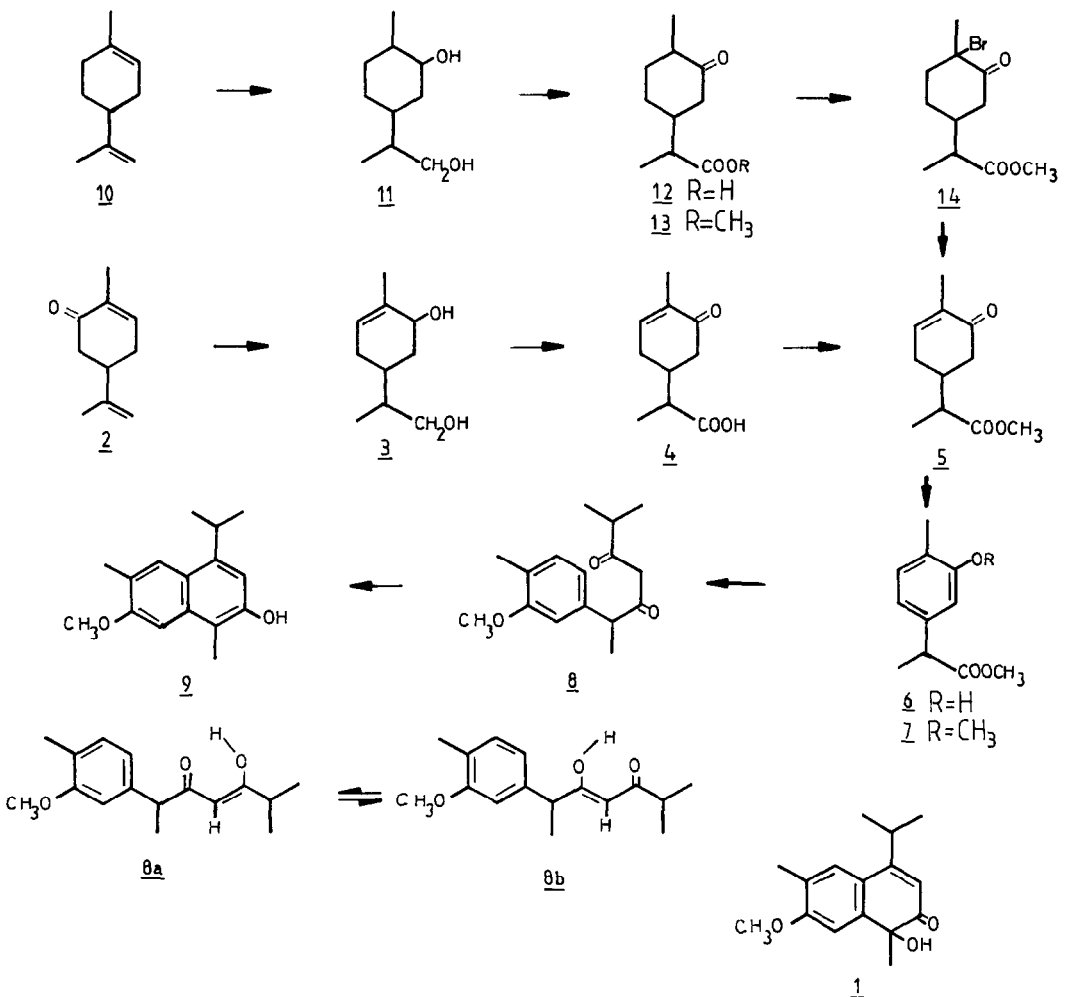
Carvone 2 by hydroboration with 9-BBN in THF at reflux, followed by H_2O_2 in NaOH aq and oxidation with Jones reagent of diol intermediate 3, gave the unsaturated ketocarboxylic acid 4 in an isolated yield of 75% Reaction of 4 with diazomethane ethereal solution, followed by dehydrogenation of ketoester 5 by the Linstead method[4] (Pd/C 10%, 200 ºC 6 hr) afforded the phenolic ester 6 in 75% yield Treatment of 6 with methanol and diazomethane[5] yields the aromatic methoxy methyl ester 7 quantitatively The ketoester 5 can also be obtained easily from limonene 10 Hydroboration with a 1 M solution of Borane in THF of 10 followed by treatment with alkaline hydrogen peroxide gave a mixture of stereoisomeric diols 11[6] which are oxidized with Jones reagent to a mixture of the stereoisomeric ketoacids 12 Esterification with diazomethane of 12 gives 13, which by bromination with $C_5H_5NHBr_3$ in acetic acid at 40 ºC, followed by dehydrohalogenation of the obtained bromoketone 14 with Lithium chloride in DMF at reflux afforded the ketoester 5

From the aromatic methoxy methyl ester 7 we have obtained the target compound 9 in two stages Condensation of 7 with the enolate anion of methyl isopropyl ketone (NaH, monoglyme, reflux 4 hr) gives the diketone 8 in 75% yield The diketone 8 is actually in the ketoenolic form 8a or 8b, IR 1650 cm^{-1}, $-\overset{O}{\overset{\|}{C}}-C=C-\overset{}{\underset{OH}{|}}$, RMN 1,08 (6H, d, J=7 Hz), 1,4 (3H, d, J=7 Hz), 2,15 (3H, s), 2,38 (1H, m), 3,8 (3H, s), 5,4 (1H, s), 6,58-7,18 (3H, m) ppm

Cyclodehydration of compound 8 with concentrated Sulfuric acid at R T [7] afforded almost quantitatively the aromatic methyl ester 9, IR 3600, 3000, 1695, 1250, 1160 cm^{-1},

RMN 1,43 (6H, d, J=7 Hz), 2,35 (3H, s), 2,42 (3H, s), 3,77 (1H, m, J=7 Hz), 3,9 (3H, s) 6,8-7,7 (3H, m) ppm , EM M^+ 244, "chemical precursor" of the byssinosis agent 1

Compound 1 can also be obtained from 9 by several reported methods (phenyl seleninic acid[3], oxygen/IK)



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