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SYNTHESIS OF BRACHYCOUMARIN AND CYCLOBRACHYCOUMARIN

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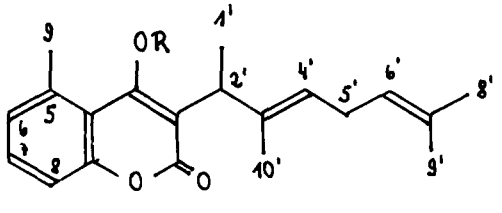
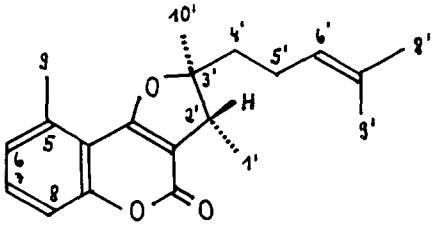
Summary: Starting with 4-hydroxy-5-methyl coumarin two compounds which were isolated from a Brachyclados species have been synthesized.

Brachycoumarin (1) and cyclobrachycoumarin (2) have been isolated from the roots of the Argentinian Compositae Brachyclados megalanthus [1]. These constituents are further representatives of the rapidly growing group of 5-methyl coumarins which in part showed considerable antibiotic activity. Therefore a synthesis of these unusual compounds was of interest.

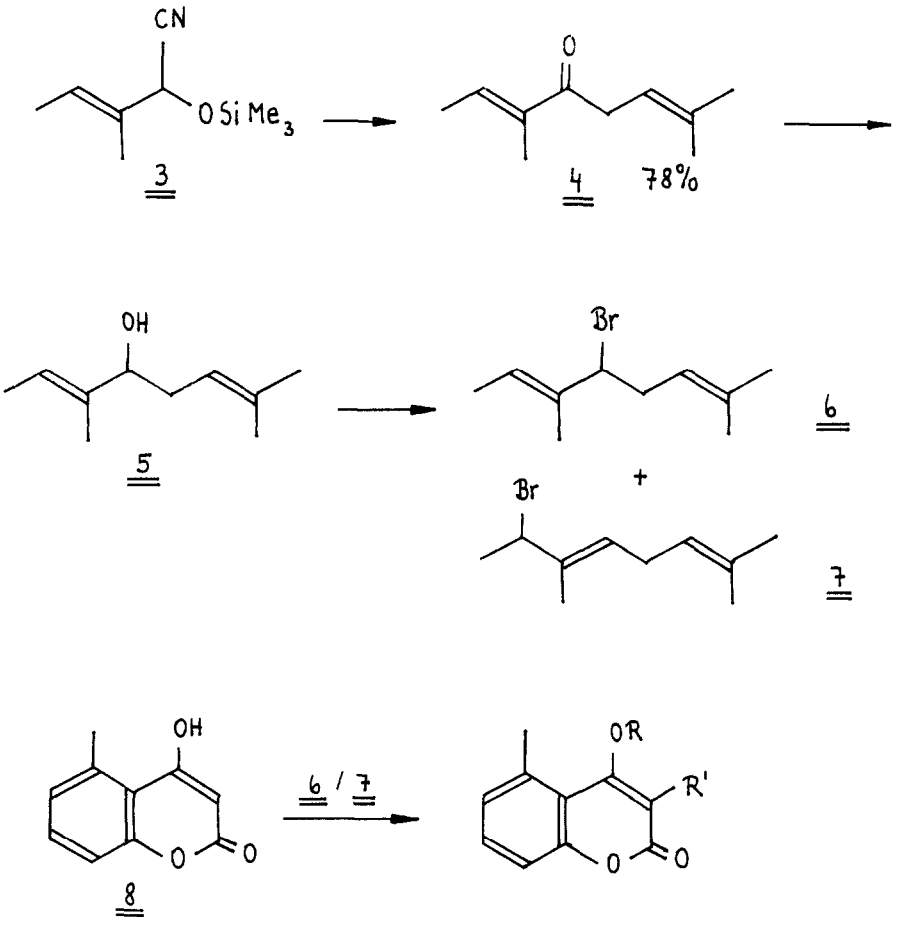


1 R = H 1a R = Ac



2

A suitable starting material for the synthesis of 1 was 4-hydroxy-5-methyl coumarin (8) [2]. The construction of the necessary side chain, which should be introduced in the coumarin skeleton as an allylic bromide, was accomplished by the following sequence. Reaction of tiglic aldehyde with trimethylsilylcyanide in the presence of zinc iodide [3,4] afforded 3. Deprotonation with LDA, alkylation with 3,3-dimethylallylbromide and



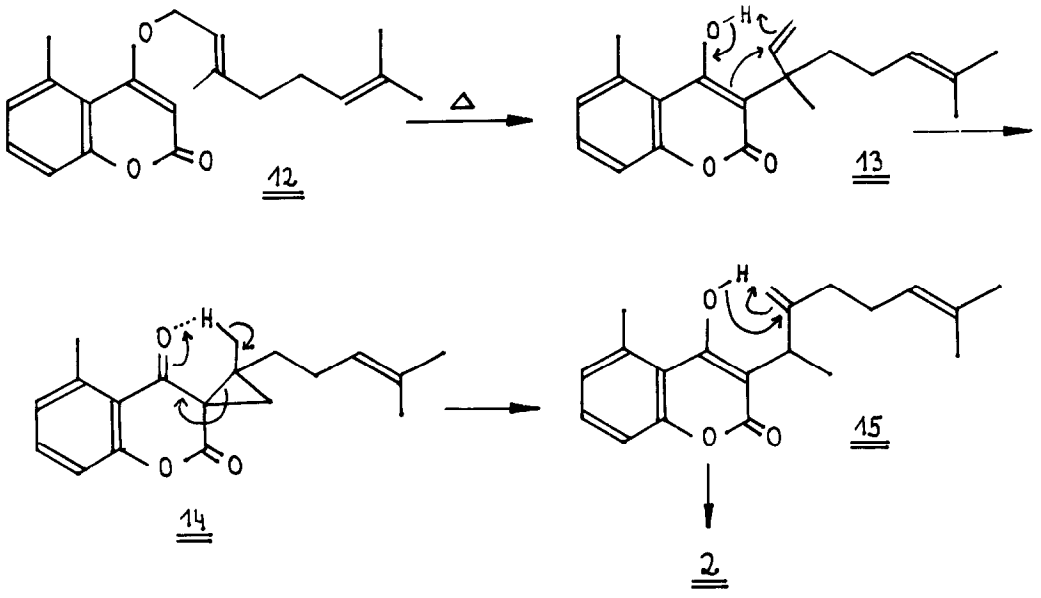
A = -CH(Me)C(Me)=CHCH$_2$CH=CMe$_2$

B = MeCH=C(Me)CHCH$_2$CH=CMe$_2$

	R	R'	
1	H	A	(14 %)
9	H	B	(14 %)
10	B	H	(20 %)
11	A	H	(20 %)

hydrolysis afforded after purification by column chromatography (Et_2O-petrol, 2 : 8) the ketone 4 in 78 % yield. LAH-reduction at 0 °C gave the alcohol 5 in 91 % yield. Reaction with PBr_3/pyridine afforded in 81 % yield a mixture of the bromides 6 and 7 (1 : 1) which could not be separated. All attempts to improve this ratio failed. Other methods mainly led to hydrocarbons formed by elimination. Therefore, the alkylation of the coumarin skeleton was carried out with the mixture of 6 and 7. Due to the ambident nature of the hydroxycoumarin anion [5,6] both O- and C-alkylation was observed. Accordingly, four compounds were obtained which could be separated by column chromatography or HPLC. Brachycoumarin (1) was obtained as a colourless oil in 14 % yield. However, the coumarin 10 also could be transformed to 1. Claisen rearrangement of 10 in acetic anhydride in the presence of sodium acetate gave in 90 % yield 1a which easily could be hydrolyzed to 1. The ^1H NMR data were identical with those of the natural compound [7].

The starting material for the synthesis of cyclobrachycoumarin (2) was 4-geranyloxy-5-methyl coumarin 12. This compound was accessible by O-alkylation of 4-hydroxy-5-methyl coumarin [6] with geranylbromide [8] in triethylamine/2,3-dimethyl-3,4,5-tetrahydro-2(1H)-pyrimidone in 43 % yield after column chromatography (Et_2O-petrol, 4 : 6).



As in similar systems [5,6,9,10] the primary Claisen rearrangement product it not stable under the reaction conditions and it undergoes further rearrangement according to the demonstrated mechanism.

In this way, heating of 12 in N,N-dimethylaniline at 180 °C delivered cyclobrachycoumarin (2) (47 %) together with its 3-epimer (33 %).

Separation could be achieved by preparative thin layer chromatography affording in 47 % yield the coumarin 2 as an colourless oil. The same reaction is possible with brachycoumarin (1) as starting material which gave also 2 in 50 % yield. The spectroscopical data [11] are identical with those of the natural compound.

LITERATURE

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7. 400 MHz - ^{1}H NMR ($CDCl_3$): δ 7.14 br d (H-6), 7.34 t (H-7), 7.01 br d (H-8), 2.66 br s (H-9), 1.37 d (H-1'), 3.88 br q (H-2'), 5.75 br t (H-4'), 2.91 dd (H-5'), 2.85 dd (H-6'), 1.74 br s (H-8'), 1.68 br s (H-9'), 1.76 br s (H-10'); (J [Hz]: 6,7 = 8; 7,8 = 8; 1',2' = 7',5' = 5',6' = 7).
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10. M.M. Ballantyne, P.H. McCabe and R.D.H. Murray (1971) Tetrahedron 27, 871.
11. 400 MHz - ^{1}H NMR ($CDCl_3$): δ 7.19 br d (H-6), 7.37 t (H-7), 7.01 br d (H-8), 2.65 br s (H-9), 1.30 d (H-1'), 3.25 q (H-2'), 1.81 and 1.77 dt (H-4'), 2.13 br dt (H-5'), 5.09 tqq (H-6'), 1.64 br s (H-8'), 1.56 br s (H-9'), 1.45 s (H-10'); (J [Hz]: 6,7 = 4_2',5' = 8; 7,8 = 1',2' = 4_1',5' = 5',6' = 7).

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