SIGMATROPIC REARRANGEMENTS IN SYNTHESIS OF C-8 PRENYLATED 3-(1′,1′-DIMETHYLALLYL)COUMARINS: 3-(1′,1′-DIMETHYLALLYL)SESELIN

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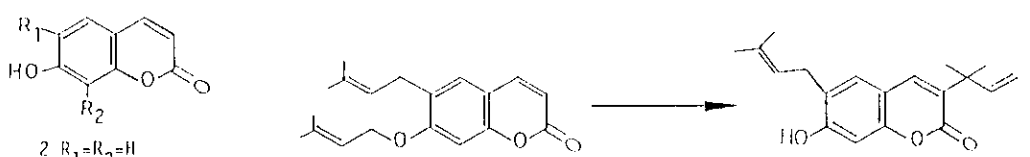
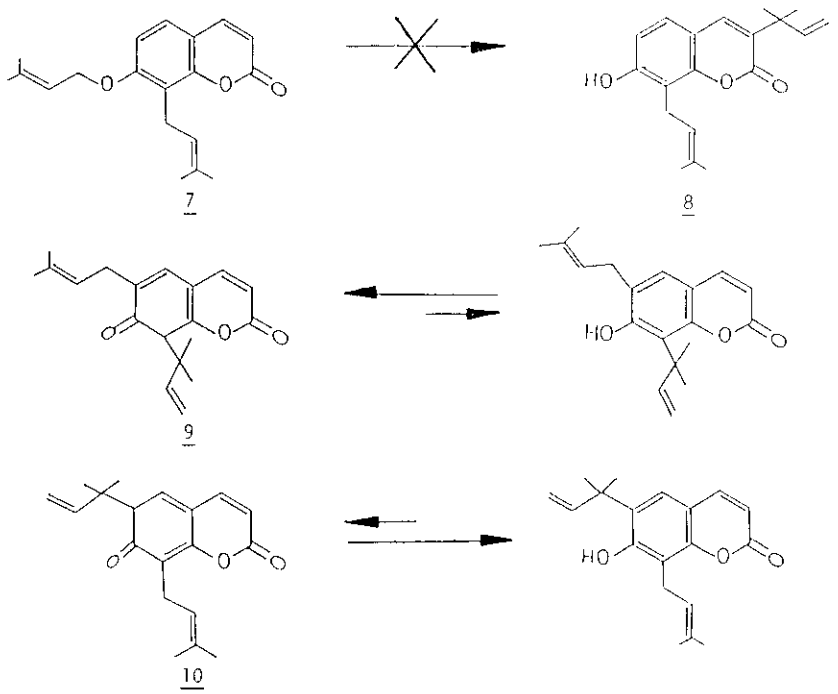
Abstract -- Synthesis of angular pyranocoumarin 3-(1′,1′-dimethylallyl)seselin, via sigmatropic rearrangement and further prenylation of the aromatic ring in good overall yield is described.

In the context of our studies on the synthesis of 3-(1′,1′-dimethylallyl)coumarins we have undertaken the synthesis of 8-isoprenylic derivatives and their corresponding angular cyclized derivatives. Prenylated coumarin systems have shown cytostatic, sometimes selective, effects on leukemic cells[1,2]. In the present paper synthesis of 3-(1′,1′-dimethylallyl)seselin (1) is described.
In earlier works[3,4] we described the synthesis of 3-(1′,1′-dimethylallyl)coumarins prenylated on C-6. The synthetic pathway included the formation of an isoprenylic ether on C-7 of umbelliferone (2) and a thermal rearrangement yielding the o-allylphenols demethylsuberosin (3) and osthenol (4). Prenylation of 3 and thermal rearrangement of the corresponding ether (5) afforded, among other products, the C-3 prenylated derivative gravelliferone (6). To obtain the angular isomer 1 a similar scheme was tried starting from osthenol (4). When the corresponding ether (7) was submitted to the same experimental conditions, a complex mixture of rearranged products was obtained. After silica gel column and HPLC separations, the C-3 alkylated product (8) was not detected. The mainly accepted mechanism[5,6] for this kind of reactions involves a Claisen and subsequently two Cope rearrangements through the C-10 bridge carbon. Our experimental results agree with this explanation. Enolization of the dienone 9, proposed as intermediate, when the rearrangement undergoes through C-8, would be rather inhibited due to the steric hindrance between the methyl groups of the chain and the ortho lactonic group that, as a consequence, additionally restricts the conformational freedom of the ketodienone ring. In such conditions the subsequent Cope rearrangements efficiently compete with the enolization-aromatisation of the system. Similar reasons have been adduced to explain para Claisen rearrangements in xanthones[7]. To what rearrangements through C-6 is concerned, steric restriction due to the chain vanishes because ortho position in the dienone 10 is vacant again. Under these conditions enolization takes place preferentially to Cope rearrangements.

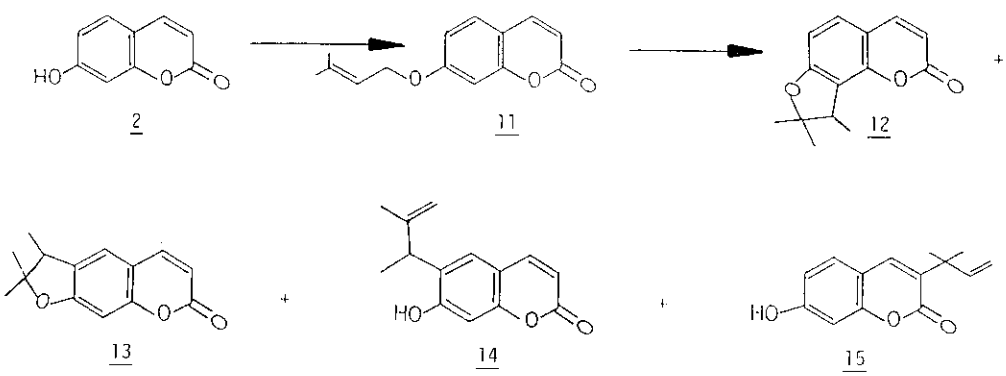


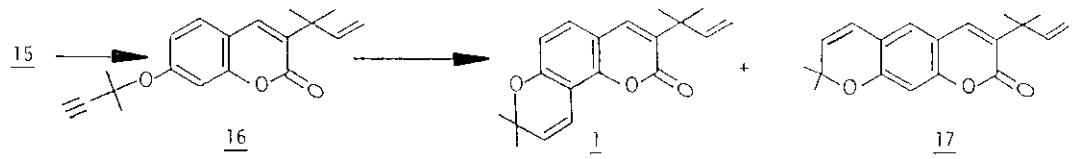
2 $R_1=R_2=H$
3 $R_1=(CH_3)_2C=CH-CH_2-$; $R_2=H$
4 $R_1=H$; $R_2=(CH_3)_2C=CH-CH_2-$

5 6



These results prompted us to use a different synthetic approach, based on a previous rearrangement to C-3 of the umbelliferone ether 11 and further prenylation of the aromatic ring.
Treatment of umbelliferone (2) with 3,3-dimethylallyl bromide in acetone yielded 7-(3',3'-dimethylallyl)umbelliferone (11,95%). Refluxing 11 in DEA (N,N-diethylaniline) gave a mixture of products that after chromatographic separation afforded: 8,8,9-trimethyl-8,9-dihydroangelicin, (12,15%), 2',2',3'-trimethyl-2',3'-dihydropsoralen (13,22%), 8-(1',2'-dimethylallyl)umbelliferone (14,3.2%), angustifolin (15,16%) and umbelliferone (2,39%). Treatment of 15 with 3-chloro-3-methyl-1-butyne afforded the propargylic ether 16 (70%). Refluxing 16 in DEA gave a mixture containing the pyranocoumarins 3-(1',1'-dimethylallyl)seselin (1,75%) and 3-(1',1'-dimethylallyl)xantiletin (17,25%).





15 → 16 → 1 + 17

EXPERIMENTAL

Melting points were determined in a Kofler block Reichert-Jung apparatus and are uncorrected. Ir spectra were recorded in a Perkin-Elmer 257, values being given in cm^{-1}. Uv were registered in a Shimadzu MPS-2000, dissolved in MeOH, and are given in nm. The nmr spectra were recorded with a Hitachi-Perkin-Elmer H-24B 60 MHz instrument or in a Varian XL-200 MHz using TMS as internal reference; chemical shift are given in δ and coupling constans in Hz. Mass spectra were measured with a VG 12250 or with a Micromass ZAB-2F. Elemental analysis were carried out in a Carlo Erba 1106-N apparatus. Thin layer chromatography was done on MN Alugram SIL G/UV 254 plates, 0.25 mm thick. Merck silica gel (0.06-0.2 mm) was used for column chromatography and elution was carried out with mixtures of hexane:ethyl acetate and hexane:chloroform.

7-(3',3'-Dimethylallyloxy)coumarin (11): Umbelliferone (2) (3 g) was dissolved in acetone (100 ml) and 2 ml of 3,3-dimethylallyl bromide were added. The mixture was refluxed at 80° C for 2 h after which it was filtered, taken to dryness, dissolved in AcOEt, washed with a saturated $NaHCO_3$ solution with brine, and dried over anhydrous Na_2SO_4. The reaction product was recrystallized from AcOEt giving 4 g (95%) of 11. Mp 75-77°C (AcOEt) (lit.[8] mp 76-77°C, hexane/AcOEt). Spectroscopic data agree with those given in literature[8].

Claisen Rearrangement of 7-(3',3'-dimethylallyloxy)coumarin (11) in DEA: 11 (3.5 g) was dissolved in 40 ml of DEA (N,N-diethylaniline) and the mixture was heated at 200°C for 24 h in nitrogen flow and then cooled. AcOEt and 10% HCl were added,and the organic layer was washed with saturated $NaHCO_3$ solution with brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent led to 3.3 g of crude product, TLC of which showed the presence of five products that were separated by column chromatography with elution of hexane:AcOEt mixtures. Separation of compounds 13, 14 and 15 was done using hexane:chloroform (1:1) mixtures as solvent. Thus the following compounds were isolated: 12 (525 mg, 16%) (mp 124-126°C, Et_2O); 13 (770 mg, 22%) (mp 164-165°C, AcOEt); 14 (114 mg, 3.2%) (oil) ; 15 (560 mg, 16%) (mp 129-130°C, hexane:$CHCl_3$) and 2 (960 mg, 39%). The spectroscopic data of compounds 12, 14 and 15 agree with those given in literature[8,9]. 2',2',3'-trimethyl-2',3'-dihydropsoralen (13): Uv λ_{max} 334,239, ir (film) 1715,1618,1266, H-nmr (60 MHz, $CDCl_3$) 7.40 (d, J=10, H-4); 7.00 (s, H-5); 6.50 (s, H-8); 6.00 (d, J=10, H-3); 3.10 (q, J=8, H-3'); 1.40 (s, Me-C-2'); 1.20 (s, Me-C-2'); 1.10 (d, J=8, Me-C-3'). ms m/z (rel. int.) 230.0955 (100), ($C_{14}H_{14}O_3$ requires 230.0943), 215.0693 (86), ($C_{13}H_{11}O_3$ requires 215.0708), 187 (18), 115 (15). (Found: C, 73.78; H, 6.25. $C_{14}H_{14}O_3$ requires C, 73.46; H, 6.10%).

7-(1'',1''-Dimethylpropynyloxy)-3-(1',1'-dimethylallyl)coumarin (16): 15 (100 mg) was dissolved in 10 ml of anhydrous acetone and 0.1 g K_2CO_3 and 0.5 ml of 3-chloro-3-methyl-1-butyne were added. The mixture was stirred in glycerine bath at 80°. The reaction was monitored by TLC and when the starting material had dissapeared heating was cut off. The mixture was filtered and

the solvent evaporated. The product was recrystallized from AcOEt giving 90 mg (70%) of 7-(1″,1″-dimethylpropynyloxy)-3-(1′,1′-dimethylallyl)coumarin (16). Oil, uv λ_{max} 302, 232, ir (film) 3287, 2120, 1713, 1605, 1220. H-Nmr (60 MHz, $CDCl_3$): 7.50 (s, H-4); 7.30 (d, J=9, H-5); 7.25 (d, J=2, H-8); 6.95 (dd, J=9 and 2, H-6); 6.20 (dd, J=17 and 11, H-2′); 5.10 (d, J=17, H-3′trans); 5.05 (d, J=11, H-3′cis); 2.65 (s, H-3″); 1.75 (s, Me_2-C-1″); 1.50 (s, Me_2-C-1′). ms m/z (rel. int.) 296.1392 (14), ($C_{19}H_{20}O_3$ requires 296.1413), 281 (16), 230.0966 (100) ($C_{14}H_{14}O_3$ requires 230.0943), 215 (87), 175 (95).

3-(1′,1′-Dimethylallyl)seselin (1): 15 (80 mg) was dissolved in 10 ml of DEA and the solution was refluxed for 12 h. After cooling Et_2O and 10% HCl were added and the organic layer was washed with saturated $NaHCO_3$ solution with brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent led to 78 mg of the crude product. TLC showed the presence of two products that after chomatographic separation afforded 3-(1′,1′-dimethylallyl)seselin (1, 60 mg, 75%) and 3-(1′,1′-dimethylallyl)xantiletin (17, 18 mg, 22%) (mp 94-96°C, hexane:AcOEt) (lit.[10] mp 98-100°C, hexane: acetone). 3-(1′,1′-Dimethylallyl)seselin (1): overall yield 10.9%. mp 78-80°C (hexane:AcOEt). Uv λ_{max}: 330,293,226, ir (film) 1715,1595,1205. H-Nmr (200 MHz, Cl_3CD): 7.47 (s, H-4); 7.23 (d, J=8.5, H-5); 6.84 (d, J= 10, H-4″); 6.71 (d, J=8.5, H-6); 6.10 (dd, J=17 and 11, H-2′); 5.70 (d, J=10, H-3″); 5.06 (d, J=11, H-3′ cis); 5.02 (d, J=17, H-3′ trans); 1.47 (s, Me_2-C-2″ and Me_2-C-1′). ms m/z (rel. int.) 296.1407 (12), ($C_{19}H_{20}O_3$ requires 296.1412), 281.1206 (100), ($C_{18}H_{17}O_3$ requires 281.1175). (Found: C, 77.12; H, 6.98. $C_{19}H_{20}O_3$ requires C, 77.00; H, 6.80%).

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