SYNTHESIS OF (±)-3-(1′,1′-DIMETHYLALLYL)DECURSINOL AND 3-(1′,1′-DIMETHYLALLYL)-XANTHYLETIN

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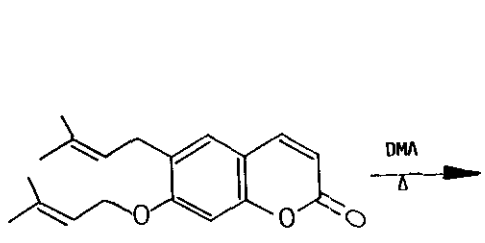
Abstract -- (±)-3-(1′,1′-Dimethylallyl)decursinol (1) and 3-(1′,1′-dimethylallyl)-xanthyletin (2) were synthesized from umbelliferone (3) in each 6.9% overall yield.

As a part of our continuing efforts toward synthesis of 3-(1′,1′-dimethylallyl)coumarin derivatives[1] we describe herein the synthesis of (±)-3-(1′,1′-dimethylallyl)decursinol (1) and 3-(1′,1′-dimethylallyl)xanthyletin (2), the latter is a natural product previously isolated from Boenninghausenia albiflora[2] (Rutaceae). Because of their biological activity[3,4] and because their small quantities from natural sources, we undertook their synthesis in order to obtain sufficient quantities for study their further pharmacological effects.

1 and 2 were obtained each in 6.9% overall yield from umbelliferone (3). The key step involves sigmatropic rearrangements in dimethylaniline (DMA), of 6-(3′,3′-dimethylallyl)-7-(3″,3″-dimethylallyloxy)coumarin (4) to gravelliferone (5, 26%) and 6-(3′,3′-dimethylallyl)-8,8,9-trimethyl-8,9-dihydroangelicin (6, 57%), as reported previously[1]. Simultaneously this reaction has been described[5] using diethylaniline as solvent but the yields in the C-3 prenylated compound (5, 20%), and in 6 (8%) were not improved.

Treatment of 5 with MCPBA in $CHCl_3$ led to (±)-3-(1′,1′-dimethylallyl)decursinol (1, 64%). When 1 was treated with p-toluensulphonylchloride (TsCl) afforded the p-toluensulphonate ester 7 (49.8%) accompanied by the starting product 1 (48.1%). It has been reported[6] that the best way to prepare pyranocoumarins by dehydration of the corresponding alcohols is by refluxing their p-toluensulphonate ester in collidine. So refluxing 7 in collidine the elimination product 3-(1′,1′-dimethylallyl)xanthyletin (2) was obtained in quantitative yield.



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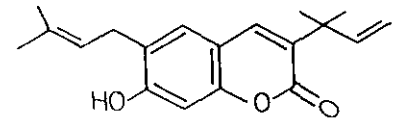

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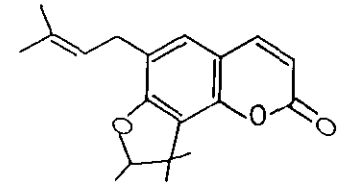

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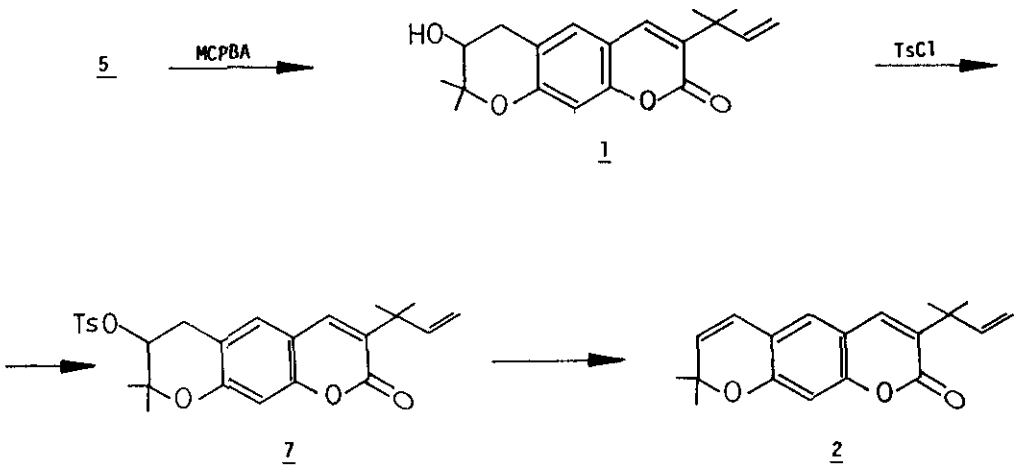

EXPERIMENTAL

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 Brucker Spectrospin 200 MHz using TMS as internal reference; chemical shifts are given in δ and coupling constants in Hz. Mass spectra were measured with a VG 12250. 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 in column chromatography and elution was carried out with mixtures of hexane and ethyl acetate.
Gravelliferone (5) was obtained from umbelliferone (3), through 8-iodoumbelliferone, 7-(1',1'-dimethylpropynyloxy)-8-iodocoumarin, 7-(1',1'-dimethylallyloxy)-8-iodocoumarin, demethylsuberosin and 6-(3',3'-dimethylallyl)-7-(3'',3''-dimethylallyloxy)coumarin, in a 10.3% overall yield, as reported previously[1].

(±)-3-(1',1'-Dimethylallyl)decursinol (1): Gravelliferone (5) (36 mg) was dissolved in 5 ml of $CHCl_3$ previously acidified (2 drops HCl conc. in 10 ml $CHCl_3$) and the solution was cooled at 0°C. MCPBA (25 mg) dissolved in 5 ml of the acidified $CHCl_3$ was added. After agitating for 6 h the reaction mixture was monitored by TLC, showing that the starting material had disappeared. After evaporating the solvent the reaction mixture was chromatographied on a silica gel column separating 24 mg (64%) of 1 (overall yield 6.9%), mp 181-183°C ($CHCl_3$). $(\alpha)_D^{25°}$ 0° (c, 0.12; $CHCl_3$), uv λ_{max} 330, 258, ir (KBr) 3340, 1700, 1630, 1570, 1500, 1275, H-nmr (200 MHz, $CDCl_3$) 7.44 (s, H-4); 7.13 (s, H-5); 6.72 (s, H-8); 6.13 (dd, J=17 and 11, H-2'); 5.06 (d, J=11, H-3'cis); 5.04 (d, J=17, H-3'trans); 3.83 (t, J=6, H-3''); 3.08 (dd, J=17 and 6, H-4''); 2.79 (dd, J=17 and 6, H-4''); 1.44 (s, Me_2-C-1'); 1.36 (s, Me-C-2''); 1.33 (s, Me-C-2''), ms m/z 314 (7); 299 (7); 243 (8); 69 (86); 57 (100).

(±)-3-(1′,1′-Dimethylallyl)decursinol p-Toluensulphonate Ester (7): To 1 (27 mg) dissolved in 3 ml of dry pyridine, 20 mg of p-toluensulphonyl chloride in 3 ml of pyridine was added. The mixture was stirred at room temperature for 7 days after which it was taken to dryness and separation over silica gel column afforded: 7 (16 mg, 49.8%) and 1 (13 mg, 48.1%) 7, oil, $(\alpha)_D^{25°}$ 0° (c, 0.12; $CHCl_3$), uv λ_{max} 326, ir (KBr) 1730, 1620, 1570, 1500, 1370, 1285, 1180, H-nmr (200 MHz, $CDCl_3$) 7.57 (d, J=8, H-2‴ and H-6‴); 7.41 (s, H-4); 7.31 (d, J=8, H-3‴ and H-5‴); 7.03 (s, H-5); 6.67 (s, H-8); 6.12 (dd, J=17 and 11, H-2′); 5.05 (d, J=11, H-3′cis); 5.03 (d, J=17, H-3′trans); 4.63 (t, J=6, H-3″); 3.13 (dd, J=18 and 6, H-4″); 2.99 (dd, J=18 and 6, H-4″); 2.43 (s, Me-C-4‴); 1.43 (s, Me_2-C-2′); 1.24 (s, Me-C-2″); 1,20 (s, Me-C-2″), ms m/z 468 (9.5); 453 (4.5); 296 (10); 281 (46); 69 (100).

3-(1′,1′-Dimethylallyl)xanthyletin (2): 7 (16 mg) was dissolved in collidine and refluxed (200°C) for 24 h. The reaction mixture was monitored by TLC and showed total abscense of starting material. Et_2O and 5% HCl were added. The organic layer was neutralized with saturated $NaHCO_3$ solution, washed with brain and dried over anhydrous Na_2SO_4. Evaporation of the solvent furnished 10 mg (quantitative yield) of 3-(1′,1′-dimethylallyl)xanthyletin (2) (overall yield 6.9%), mp, 93-95°C (hexane/AcOEt) (lit[2] 98-100°C, petrol/acetone), uv λ_{max} 347, 304, 267, ir (KBr) 1710,1620, 1600, 1500, 1270, H-nmr (200 MHz, $CDCl_3$) 7.45 (s, H-4); 7.00 (s, H-5); 6.66 (s, H-8); 6.33 (d, J=10, H-4″); 6.13 (dd, J=17 and 11, H-2′); 5.64 (d, J=10, H-3″); 5.06 (d, J=11, H-3′cis); 5.04 (d, J=17, H-3′trans); 1.44 (s, Me_2-C-1′ and Me_2-C-2″), ms m/z 296 (22), 281 (100).

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