# SYNTHESIS OF C-8 PRENYLATED AND ANGULAR 3-(1′,1′-DIMETHYLALLYL)COUMARINS

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Abstract- The natural coumarins ramosinin (1) and 3-(1′,1′-dimethylallyl)-8-(3″,3″-dimethylallyl)xanthyletin (2) have been synthesized from umbelliferone. The synthesis of the angular derivatives 3-(1′,1′-dimethylallyl)columbianetin (9) and 3-(1′,1′-dimethylallyl)lomatin (10) was also achieved.

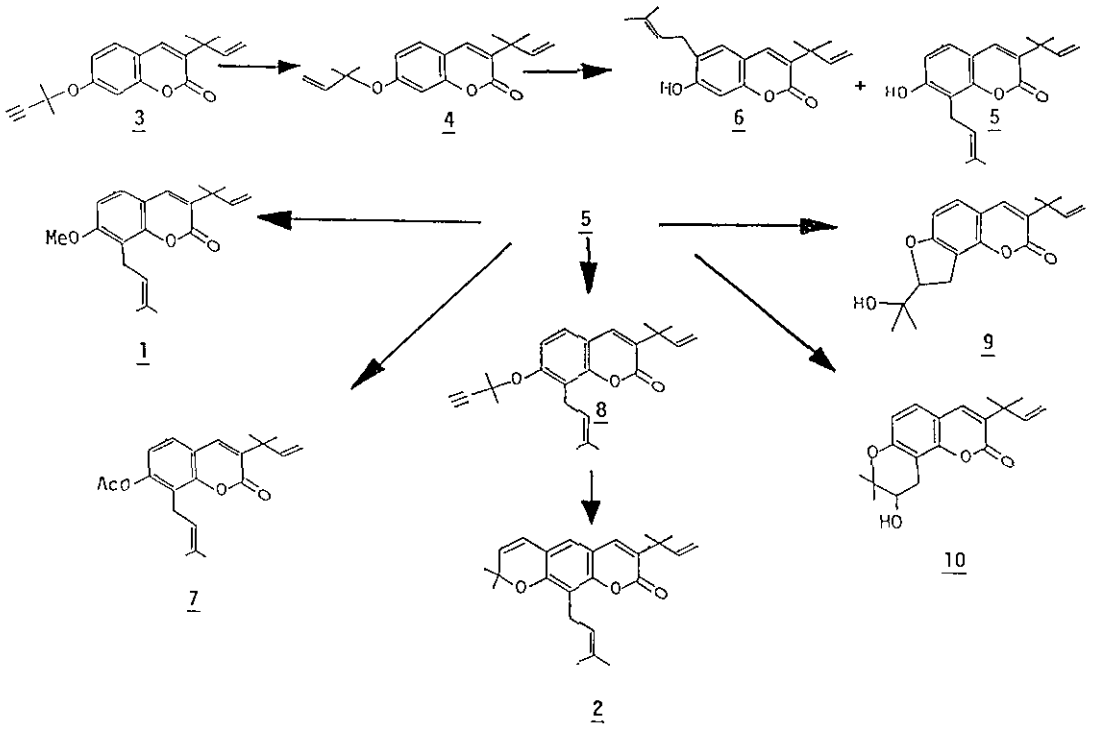
We previously reported an efficient synthetic procedure for 3-(1′,1′-dimethylallyl)coumarins alkylated at C-6 and their dihydrofuran and dihydropyran derivatives starting from umbelliferone. This reaction involves the sigmatropic rearrangement of the 3,3-dimethylallyl ether of 6-(3′,3′-dimethylallyl)umbelliferone.[1,2] However, this methodology could not be succesfully applied to prepare 3-(1′,1′-dimethylallyl)coumarins alkylated on C-8. Therefore an alternative aproach based on a previous rearrangement to C-3 followed by further prenylation[3] has been carried out.

In the present paper we report the synthesis of 3,8-dialkylated coumarins and their corresponding angular cyclized derivatives. Two of them, ramosinin (1) and 3-(1′,1′-dimethylallyl)-8-(3″,3″-dimethylallyl)xanthyletin (2), represent natural products.[4,5]

Catalytic hydrogenation of 3-(1′,1′-dimethylallyl)-7-(1″,1″-dimethylpropynyloxy)coumarin (3) yielded 3-(1′,1′-dimethylallyl)-7-(1″,1″-dimethylallyloxy)coumarin (4, quantitative). When the ether 4 was heated at 150°C in N,N-diethylaniline (DEA) a mixture of demethylramosinin (5) and gravelliferone (6) was obtained in 80 and 10% yields, respectively. Treatment of 5 with methyl iodide in acetone afforded 1, the melting point and spectroscopic data of which were identical with those described for the natural product.[4] 5 by treatment with acetic anhydride in pyridine afforded the acetate (7).

3-(1′,1′-Dimethylallyl)-8-(3″,3″-dimethylallyl)xanthyletin (2) was isolated from Ruta graveolens.[5] The synthesis of 2 was carried out via demethylramosinin (5). Treatment of 5 with 3-chloro-3-methyl-1-butyne afforded 3-(1′,1′-dimethylallyl)-7-(1″,1″-dimethylpropynyloxy)-8-(3‴,3‴-dimethylallyl)coumarin (8, 75%). The desired product 2 was obtained refluxing a solution of 8 in DEA (90%). The spectroscopic data of 2 are identical with those given in literature for the natural product.[5]

Synthesis of 3-(1′,1′-dimethylallyl)columbianetin (9) and 3-(1′,1′-dimethylallyl)lomatin (10) was achieved by controlled oxidation of the corresponding phenol (5) by the commonly used synthetic method for dihydrofurano- and dihydropyranocoumarins.[6] Treatment of 5 with m-chloroperbenzoic acid (MCPBA) in $Et_2O$ and $CHCl_3$ led to 9 and 10 in 73 and 66% yields, respectively.



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 spectra were registered in a Shimadzu MPS-2000, dissolved in MeOH, and are given in nm. The nmr spectra were recorded in a Varian XL-200 MHz or in a Bruker 400 MHz using TMS as internal reference; chemical shifts are given in $\delta$ and coupling constans in Hz. Mass spectra were measured with a VG 12250 or with a ZAB7070 Finningan. 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.

3-(1',1'-Dimethylallyl)-7-(1",1"-dimethylallyloxy)coumarin (4): 3 (0.3 mmol) was dissolved in 12 ml of toluene. $Pd/BaSO_4$ (10%) (4 mg) was added, and the mixture was subjected to hydrogenation at 0.4 atm. pressure of $H_2$. When the starting material disappeared, as ascertained by tlc, the reaction was stopped (10 min). The catalyst was filtered through celite. Evaporation of solvent by distillation under reduced pressure furnished 0.3 mmol (quantitative yield) of 3-(1',1'-dimethylallyl)-7-(1",1"-dimethylallyloxy)coumarin (4): oil, uv $\lambda_{max}$ 320, 210; ir (film) 1712, 1603, 1245, 1119, 994; H-nmr (400 MHz, $CDCl_3$): 7.48 (s, H-4), 7.25 (d, J= 8.5, H-5), 6.92 (d, J= 2.3, H-8), 6.82 (dd, J= 8.5 and 2.3, H-6), 6.14 (dd, J= 17.2 and 10.4, H-2'), 6.09 (dd, J= 17.7 and 10.8, H-2"), 5.20 (d, J= 17.7, H-3" trans), 5.18 (d, J= 10.8, H-3" cis), 5.06 (d, J= 10.4, H-3' cis), 5.04 (d, J= 17.2, H-3' trans), 1.48 (s, $Me_2$-C-1"), 1.44 (s, $Me_2$-C-1'); ms m/z 298 (19), 283 (25), 230 (75), 203 (45); hrms 298.1553 ($C_{19}H_{22}O_3$ requires 298.1569).

Claisen rearrangement of 3-(1′,1′-dimethylallyl)-7-(1″,1″-dimethylallyloxy)coumarin (4): 4 (0.3 mmol) was dissolved in 5 ml of DEA and the solution was heated at 150°C for 2 h. After cooling $Et_2O$ and 10% HCl were added and the organic layer was washed with saturated $NaHCO_3$ solution, then with brine, and finally dried over anhydrous $Na_2SO_4$. Evaporation of the solvent led to 114 mg of crude products. Column chromatography of the mixture on silica gel using mixtures of increasing polarity from hexane to AcOEt gave gravelliferone (7) (0.03 mmol, 10%): mp 160-162°C (hexane:EtOAc) (lit.[7] 166-168°C) and demethylramosinin (5) (0.24 mmol, 80%): mp 114-116°C (hexane: EtOAc); uv$\lambda_{max}$ 320, 260, 225; ir (film) 3310, 1668, 1578, 1453, 1263, 1042; H-nmr (200 MHz,$Cl_3CD$): 7.49 (s, H-4), 7.17 (d, J=8.4, H-5), 6.77 (d, J=8.4, H-6), 6.16 (dd, J=18.0 and 10.4, H-2′), 5.25 (tt, J=7.2 and 1.4, H-2″), 5.06 (dd, J=18.0 and 1.2, H-3′trans), 5.06 (dd, J=10.4 and 1.2, H-3′cis), 3.56 (d, J=7.2, H-1″), 1.82 (s, Me-C-3″), 1.71 (s, Me-C-3″), 1,46 (s, $Me_2$-C-1′); ms m/z 298 (74), 283 (93), 243 (55), 227 (100), 199 (61); hrms 298.1580 ($C_{19}H_{22}O_3$ requires 298.1569).

*Ramosinin: $K_2CO_3$ (0.72 mmol), 5 (0.13 mmol), and 5 ml of acetone were mixed. Methyl iodide* (4 mmol) was added and the resulting mixture was refluxed for 40 min. After this time it was cooled, filtered, the solvent evaporated and the residue dissolved in AcOEt, washed with brine and dried over anhydrous $Na_2SO_4$. The reaction product was recrystalized from AcOEt giving 0.12 mmol (92%) of ramosinin (1): mp 82-84°C (lit[4] 85-86°C).

Demethylramosinin acetate (7): Demethylramosinin (5) (0.08 mmol) was dissolved in pyridine (2 ml) and 9 mmol of distilled $Ac_2O$ were added. After the mixture was stirred for 3 h, ice water was added and then stirred for 30 min. The mixture was extracted with AcOEt and the organic layer neutralized with saturated $NaHCO_3$ solution, washed with brine and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent furnished 0.079 mmol (99%) of demethylramosinin acetate (7): oil, uv$\lambda_{max}$ 285; ir (film) 1720, 1593, 1423, 1360, 1188, 1036; H-nmr (200 MHz, $CDCl_3$): 7.47 (s, H-4), 7.22 (d, J=8.4, H-5), 6.89 (d, J=8.4, H-6), 6.10 (dd, J=18.0 and 10.4, H-2′), 5.04 (tt, J=7.2 and 1.2, H-2″), 5.03 (d, J=10.4, H-3′cis), 5.02 (d, J=18.0, H-3′trans), 3.40 (d, J=7.2, H-1″), 2.27 (s, $CH_3CO$), 1.75 (s, Me-C-3″), 1.60 (s, Me-C-3″), 1.47 (s, $Me_2$-C-1′); ms m/z 340 (24), 298 (53), 283 (100), 243 (59); hrms 340.1672 ($C_{21}H_{24}O_4$ requires 340.1675).

3-(1′,1′-Dimethylallyl)-7-(1″,1″-dimethylpropynyloxy)-8-(3‴,3‴-dimethylallyl)coumarin (8): 5 (0.077 mmol) was dissolved in 2 ml of dry acetone and 0.72 mmol of $K_2CO_3$ and 0.87 mmol of 3-chloro-3-methyl-1-butyne were added. The mixture was stirred in glycerin bath at 80°C. The reaction was monitored by tlc and when the starting material disappeared heating was cut off. The mixture was filtered and the solvent was evaporated. The residue was purified by column chromatography eluting with hexane-AcOEt (4:1) to afford 8 (0.057 mmol, 75%): oil, uv$\lambda_{max}$ 335, 232; ir (film) 3281, 2964, 1695, 1122, 1040; H-nmr (200 MHz, $CDCl_3$): 7.52 (d, J=8.0, H-5), 7.49 (s,H-4), 7.20 (d, J=8.0, H-6), 6.17 (dd, J=17.7 and 10.4, H-2′), 5.20 (tt, J=7.2 and 1.3, H-2‴), 5.08 (d, J=10.4, H-3′cis), 5.07 (d, J=17.7, H-3′trans), 3.50 (d, J=7.2, H-1‴), 2.62 (s, H-3″), 1.83 (s, Me-C-3‴), 1.70 (s, $Me_2$-C-1″), 1.66 (s, Me-C-3‴), 1.47 (s, $Me_2$-C-1′); ms m/z 364 (9), 349 (11), 298 (45), 283 (100), 243 (51); hrms 364.2042 ($C_{24}H_{28}O_3$ requires 364.2038).

*3-(1′,1′-Dimethylallyl)-8-(3″,3″-dimethylallyl)xanthyletin (2):* 8 (0.027 mmol) was dissolved in 3 ml of DEA and the solution was refluxed for 15 h. After cooling AcOEt and 10% HCl were added and the organic layer was washed with saturated $NaHCO_3$ solution, brine and dried over anhydrous $Na_2SO_4$. Chromatographic purification of the crude product eluting with hexane-AcOEt (4:1) afforded

3-(1′,1′-dimethylallyl)-8-(3″,3″-dimethylallyl)xanthyletin (2, 0.027 mmol, quantitative): oil, uv $\lambda_{max}$ 335, 295, 265; ir (film) 2962, 1716, 1580, 1536, 1429, 1251, 1040, 780; H-nmr (400 MHz, $CDCl_3$): 7.44 (s, H-4), 7.01 (s, H-5), 6.30 (d, J=10.0, H-4‴), 6.15 (dd, J=17.8 and 10.3, H-2′), 5.67 (d, J=10.0, H-3‴), 5.23 (tt, J=7.4 and 1.3, H-2″), 5.05 (dd, J=10.3, H-3′cis), 5.04 (d, J=17.8, H-3′trans), 3.25 (d, J=7.4, H-1″), 1.83 (s, Me-C-3″), 1.65 (s, Me-C-3″), 1.44 (s, (s, $Me_2$-C-1′), 1.43 (s, $Me_2$-C-2‴); ms m/z 364 (6),349 (49); hrms 364.2026 ($C_{24}H_{28}O_3$ requires 364.2038).

3-(1′,1′-Dimethylallyl)columbianetin (9): Demethylramosinin (5, 0.074 mmol) was dissolved in 4 ml of $Et_2O$ and the solution was cooled at 0°C. MCPBA (0.087 mmol) dissolved in 3 ml of $Et_2O$ was added. After stirring for 2 h, the reaction mixture was washed with saturated $NaHCO_3$ solution, brine and dried over anhydrous $Na_2SO_4$. The reaction mixture was chromatographed on basic alumina column (eluting with hexane-AcOEt (4:1)) to afford 0.054 mmol (73%) of 9: mp 110-111°C (hexane AcOEt); uv $\lambda_{max}$ 327, 261; ir (film) 3444, 2965, 1700, 1604, 1237, 1123; H-nmr (200 MHz, $CDCl_3$): 7.44 (s, H-4), 7.16 (d, J=8.7, H-5), 6.65 (d, J=8.7, H-6), 6.09 (dd, J=18.0 and 10.0, H-2′), 5.01 (d, J=10.0, H-3′cis), 5.00 (d, J=18.0, H-3′trans), 4.70 (t, J=9.0, H-2″), 3.25 (dd, J=9.0 and 3.0, H-3″), 1.40 (s, $Me_2$-C-1′), 1.29 (s, Me-C-4″), 1.16 (s, Me-C-4″); ms m/z 314 (100), 299 (70), 287 (42), 281 (34), 255 (66); hrms 314.1518 ($C_{19}H_{22}O_4$ requires 314.1517).

3-(1′,1′-Dimethylallyl)lomatin (10): Demethylramosinin (5, 0.13 mmol) was dissolved in 5 ml of acidified $CHCl_3$ (2 drops of conc. HCl in 10 ml of $CHCl_3$) and the solution was cooled at 0°C. MCPBA (0.174 mmol) dissolved in 5 ml of the acidified $CHCl_3$ was added. After stirring for 3 h the reaction mixture was monitored by tlc showing that the starting material had disappeared. After evaporating the solvent the reaction mixture was chromatographed on silica gel (eluting with hexane-AcOEt (4:1)) affording 0.086 mmol (66%) of 10: oil, uv $\lambda_{max}$ 326; ir (film) 3461, 2928, 1687, 1598, 1255, 1130, 1076; H-nmr (400 MHz, $CDCl_3$): 7.44 (s, H-4), 7.15 (d, J=8.6, H-5), 6.68 (d, J=8.6, H-6), 6.10 (dd, J=17.3 and 11.4, H-2′), 5.02 (d, J=11.4, H-3′cis), 5.00 (d, J=17.3, H-3′trans), 3.83 (dd, J=5.2 and 4.9, H-3″), 3.07 (dd, J=17.7 and 4.9, H-4″), 2.88 (dd, J=17.7 and 5.2, H-4″), 1.40 (s, $Me_2$-C-1′), 1.33 (s, Me-C-2″), 1.26 (s, Me-C-2″); ms m/z 314 (100), 299 (60), 281 (36), 244 (68); hrms 314.1498 ($C_{19}H_{22}O_4$ requires 314.1517).

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