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Synthesis of Collinin, an Antiviral Coumarin

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Collinin (1), a geranyloxycoumarin, has been synthesized in three steps and 24.6% overall yield from pyrogallol (2) and propiolic acid (3).

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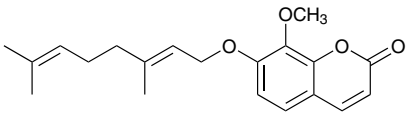
Collinin (1) (Diagram 1) is a geranyloxycoumarin isolated for the first time from *Flindersia maculata* (Rutaceae) by Ritchie[1] and coworkers in 1954, and from *Haplophyllum alberti-regelli* (Rutaceae) by Tikhomirova and coworkers in 1977.[2] About twenty years later, collinin was also isolated by Chen and coworkers from the root bark of *Zanthoxylum schinifolium* (Rutaceae).[3–5] These latter authors showed that collinin exerted anti-platelet aggregation ($50\,\mu g\,mL^{-1}$, 100% inhibition) and anti-hepatitis B virus (HBV) replication activities ($IC_{50} = 17.1\,\mu g\,mL^{-1}$) associated with inhibition of the DNA-synthesis step of virus life-cycles.[4,5]

Unfortunately, only *Z. schinifolium* is a good source of collinin and in other plants it is present in traces ranging from 278 to 139 ppm.[3–5] Therefore, huge quantities of plant material would be needed to isolate collinin in sufficient quantities to carry out experiments to better define its biological profile. Up to now the biological profile of collinin has not been adequately characterized, especially when compared with that of other naturally occurring coumarins.

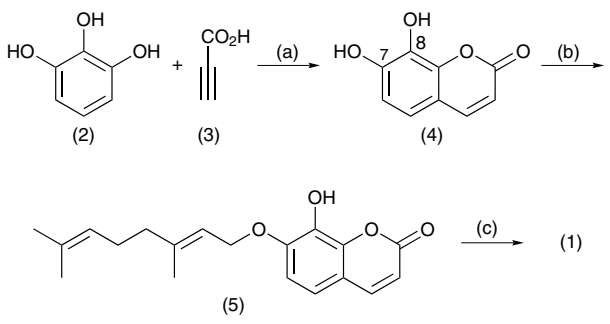
In connection with projects devoted to study the in vitro and in vivo anti-inflammatory activity of natural and semi-synthetic prenylated coumarins, we wish to report here a simple and short synthesis of collinin (1) from pyrogallol (2) and propiolic acid (3) (Scheme 1) that make available sufficient quantities of this compound in pure form for biological testing. To the best of our knowledge, only a partial synthesis of (1) from 7-hydroxy-8-methoxy-chromen-2-one and 1-chloro-3,7-dimethyl-octa-2,6-diene using sodium ethylate in ethanol has been reported to date.[6]



(1)

Diagram 1.

The coumarin nucleus, 7,8-dihydroxycoumarin (4) (daphnetin), was made using a concentrated H_2SO_4 catalyzed Pechmann-type condensation between pyrogallol (2) and propiolic acid (3) under solvent-free conditions at 120°C for 30 min. Daphnetin (4) was obtained in 59% yield after crystallization (Et_2O). Subsequent geranylation of (4) with geranyl bromide and K_2CO_3 in refluxing acetone for 5 h or NaH in THF at 0°C for 3 h was not selective. In both cases an equimolar, inseparable mixture of 7- and 8-geranylated products was obtained in 70 and 74% overall yield, respectively, along with a small amount (5% yield) of the 7,8-dialkylated compound. However, the 7-OH was selectively geranylated by employing sterically-hindered amines. Reaction of (4) with $(^iPr)_2EtN$ (Hünig's base) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetone at room temperature for 3 h gave the desired 7-geranyloxy-8-hydroxy-coumarin (5) in 32 and 65% yield, respectively. This selectivity may be explained by a preferential hydrogen abscission by bulky amines from the more accessible 7-OH. Finally, methylation of 8-OH with



Scheme 1. (a) conc. H_2SO_4 (cat.), 120°C; (b) geranyl bromide, DBU, rt; (c) MeI, NaH 60%, DMF, rt.

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methyl iodide and NaH in *N*,*N*-dimethylformamide at room temperature for 2 h gave collinin (1) in 64% yield. Although we were not able to obtain authentic samples of the natural material, our analytical data for (1) was in full agreement with those previously reported.[3–5]

In conclusion, we have developed an easy and short synthesis of collinin (1) in three steps and 24.6% overall yield, which provides an alternative and valuable route to obtain collinin for biological testing purposes. Studies to synthesize suitably functionalized analogues and to further explore the biological activity of (1) in order to define a structure–activity relationship profile are now in progress.

Experimental

7,8-Dihydroxycoumarin (4)

To a mixture of pyrogallol (2) (1.0 g, 7.94 mmol) and propiolic acid (3) (1.1 g, 15.88 mmol) was added one drop of concentrated H_2SO_4. The resulting suspension was stirred at 120°C for 30 min, cooled and dissolved in EtOAc (10 mL). This solution was washed twice with 5% $NaHCO_3$, dried over Na_2SO_4, and evaporated under vacuum. Recrystallization (Et_2O) of this material afforded the title compound (4) (0.83 g, 59%) as a white solid, m.p. 255–256°C (lit.[7] 256–257°C) (Found: C, 60.7; H, 3.4%; $M^{+\bullet}$, 178.0271. $C_9H_6O_4$ requires C, 60.7%; H, 3.4%; $M^{+\bullet}$, 178.0266). ν_{max} (neat)/cm^{-1} 3500, 1730. δ_H (CD_3OD) 7.82 (1 H, d, H4), 7.15 (1 H, d, H3), 6.85 (1 H, d, H5), 6.21 (1 H, d, H6). δ_C see ref. [8].

7-Geranyloxy-8-hydroxycoumarin (5)

To a solution of (4) (0.3 g, 1.68 mmol) in acetone (5 mL) were added DBU (0.255 g, 1.68 mmol) and geranyl bromide (0.365 g, 1.68 mmol), and the resulting solution was stirred at room temperature for 3 h. The mixture was diluted with 2% citric acid (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The collected organic phases were dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to flash chromatography (silica gel, 99 : 1 CH_2Cl_2/MeOH elution) to afford, after concentration of the appropriate fraction (R_F 0.5), the *title compound* (5) (0.34 g, 65%) as a white solid, m.p. 97–99°C (Found: C, 72.6; H, 7.0%; $M^{+\bullet}$, 314.1521. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.1%; $M^{+\bullet}$, 314.1518). ν_{max} (neat)/cm^{-1} 3500, 1726. δ_H ($CDCl_3$) 7.15 (1 H, d, H4), 6.92 (1 H, d, H3), 6.28 (1 H, d, H5), 6.19 (1 H, d, H6), 5.68–5.45 (1 H, m, C*H*CH_2O), 5.10–5.00 (1 H, m, C*H*CH_2CH_2), 4.88 (2 H, d, CH_2O), 2.25–1.87 (4 H, complex m, CH_2CH_2), 1.86–1.29 (6 H, m, CH_3CCH_3), 1.22–1.08 (3 H, m, CH_2CH_3CCH). δ_C ($CDCl_3$) 160.3, 152.8, 147.5, 144.6, 144.2, 131.9, 123.9, 123.5, 118.7, 113.0, 112.5, 111.9, 111.8, 70.2, 39.5, 26.4, 26.2, 17.6, 16.4.

Collinin (1)

To a stirred suspension of NaH (0.011 g of a 60% dispersion in mineral oil, 0.44 mmol), previously washed with *n*-hexane to remove mineral oil, in anhydrous DMF (4 mL) at –10°C under nitrogen was added a solution of (5) (0.12 g, 0.38 mmol) dissolved in anhydrous DMF (3 mL). The resulting solution was stirred at room temperature for 2 h. The solution was again cooled to –10°C, iodomethane (0.05 mL, 0.76 mmol) was added and the stirring was continued at room temperature for 1 h. The reaction mixture was then poured into saturated brine (5 mL) and the aqueous layer was extracted with ether (4 × 15 mL). The collected organic phases were dried over Na_2SO_4 and evaporated. The residue was subjected to flash chromatography (silica, 99 : 1 CH_2Cl_2/MeOH elution) to afford, after concentration of the appropriate fraction (R_F 0.7), the title compound (1) (0.08 g, 64%) as a white solid, m.p. 67–69°C (Found: C, 73.2; H, 7.4%; $M^{+\bullet}$, 328.1677. $C_{20}H_{24}O_4$ requires C, 73.2%, H, 7.4%; $M^{+\bullet}$, 328.1674). ν_{max}(neat)/cm^{-1} 1728. δ_H see ref. [3]. δ_C ($CDCl_3$) 160.5, 156.1, 148.5, 143.6, 142.7, 134.7, 131.6, 123.9, 123.3, 120.1, 113.6, 113.3, 108.3, 69.8, 55.9, 39.6, 26.4, 25.6, 16.4, 14.1.

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