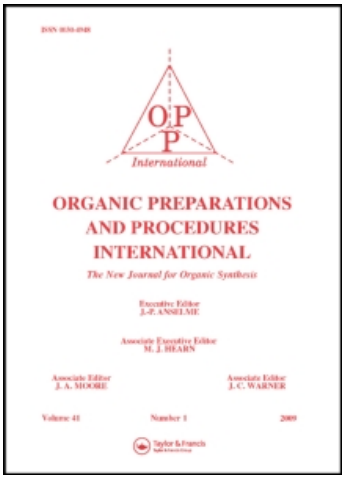

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OPPI BRIEFS

NEW SYNTHESIS OF HYDRANGETIN AND COLLININ

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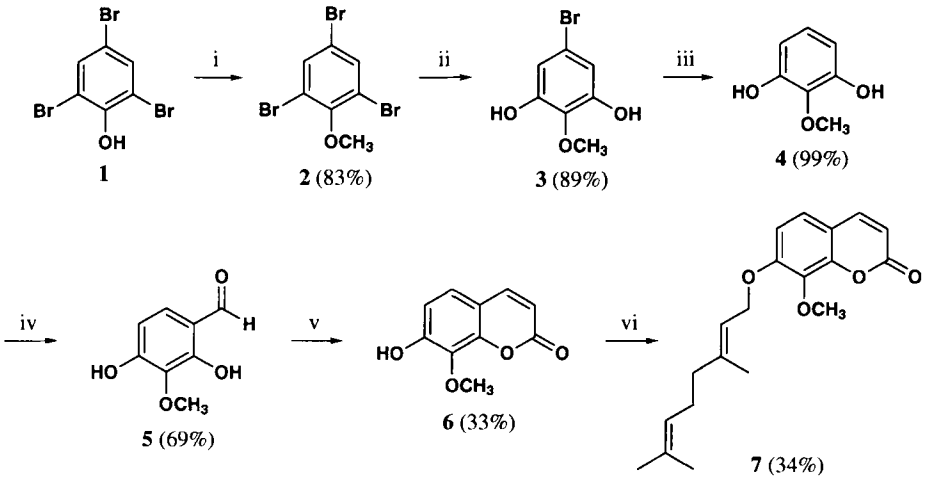
Hydrangetin (**6**) is a natural constituent of a number of plant species including *Hydrangea macrophylla*[1,2] and *Zanthoxylum schinifolium*.[3] Collinin (**7**) occurs, among others, in *Hydrangea macrophylla*,[1,2] *Zanthoxylum schinifolium*,[3] *Flindersia collina*,[4] *Flindersia maculata*[5] and *Haplophyllum alberti-regelli*.[6] The latter coumarin has received much attention and has been proven to exert anti-platelet aggregation[3,7] and anti-hepatitis B virus[3] activities. These interesting properties make this coumarin a useful target for organic synthesis. A synthesis of collinin starting from pyrogallol and propiolic acid has been reported.[8] We now describe an alternative synthetic strategy for collinin (**7**) starting from readily available 2,4,6-tribromoanisole (**2**). This pathway also offers a new synthetic route towards hydrangetin (**6**).

2,4,6-Tribromoanisole (**2**) was prepared in 83% yield by reaction of 2,4,6-tribromophenol **1** with one equivalent of dimethyl sulfate and 1.5 equivalent of sodium hydroxide in water under reflux. Lithiation of **2** with *n*-butyllithium in pentane at –20°C, followed by quenching with trimethyl borate and oxidation of the resulting borane with a 32% solution of peracetic acid in acetic acid yielded 4-bromo-2,6-dihydroxyanisole **3** in 89% yield.[9] Debromination of **3** with H_2 in MeOH containing 10w% palladium on activated carbon (5w% palladium relative to carbon) at 50°C gave 2,6-dihydroxyanisole (**4**) in quantitative yield.[9] 2,4-Dihydroxy-3-methoxybenzaldehyde (**5**) was subsequently obtained by formylation of **4** with zinc(II) cyanide, zinc(II) chloride and dry hydrogen chloride according to the Gattermann method.[10] The synthesis of **5** had been described earlier by selective demethylation of 2,3,4-trimethoxybenzaldehyde with a combination of sodium *p*-thiocresolate and hexamethylphosphoric triamide in refluxing toluene.[13] Our synthesis of **5** by formylation of **4** provides an alternative for this reaction and avoids the use of unpleasantly smelling thiocresol. The synthesis of **6** was then completed by Wittig reaction of **5** with methyl (triphenylphosphoranylidene)acetate in *N,N*-diethylaniline.[14-17] Further reaction of **6** with geranyl bromide and potassium carbonate gave pure **7** in 34% yield *(Scheme 1)*. The yield of this reaction is rather low, despite the use of excess base

and geranyl bromide. This low yield after chromatography might be due to hydrolytic cleavage of the geranyloxy side-chain of **7** on the silica gel.



i) Me_2SO_4, NaOH, H_2O, r.t., 2 h; ii) a. *n*-BuLi, pentane, –20°C to –10°C, 15 min, b. $B(OMe)_3$, –30°C to 0°C, 30 min, c. AcOOH (32%) in AcOH, –10°C to 0°C, 30 min; iii) H_2, 5% Pd on carbon (10 w%), MeOH, 50°C, 17 h; iv) a. $Zn(CN)_2$, HCl, Et_2O, r.t., b. H_2O, H_2SO_4, Δ, 30 min; v) $(C_6H_5)_3P$=CHCOOMe, $Et_2NC_6H_5$, N_2-atm, Δ, 4 h; vi) $(CH_3)_2C$=$CHCH_2CH_2C(CH_3)$=$CHCH_2Br$, K_2CO_3, acetone, 50°C, 15 h

Scheme 1

EXPERIMENTAL SECTION

^1H NMR spectra (270 MHz) and ^{13}C NMR spectra (68 MHz) were recorded on a Jeol JNM-EX 270 spectrometer. IR spectra were taken with a Perkin-Elmer Spectrum One spectrophotometer. Mass spectra were obtained on an Agilent 1100 Series VL mass spectrometer (ES 70 eV). Melting points were measured with a Büchi B-450 apparatus. Flash chromatography was performed with ACROS silica gel (particle size 0.035-0.070, pore diameter ca. 6 nm) using a glass column.

2,4,6-Tribromoanisole (2).- 2,4,6-Tribromophenol (**1**) (200 mmol, 66.16 g) was dissolved in a solution of 12.0 g (300 mmol) sodium hydroxide in water (125 mL). The solution was cooled to 0°C, dimethyl sulfate (200 mmol, 25.23 g) was slowly added, and then the solution was kept at 0°C for 1 h. Subsequently, the mixture was refluxed for 2 h to complete the methylation. Upon cooling to 0°C, the crystals formed were collected. Recrystallization from ethanol afforded 57.24 g (83%) of pure **2**. mp 87°C (*lit.*[18] 87-88°C). ^1H NMR (270 MHz, $CDCl_3$): δ 3.87 (3 H, s, OCH_3); 7.65 (2 H, s, 3-CH and 5-CH).

4-Bromo-2,6-dihydroxyanisole (3)[9].- 89% yield; mp 124-126°C (*lit.*[9] 124-126°C). The spectroscopic data correspond to those reported in literature.[9]

2,6-Dihydroxyanisole (4)[9].- 99% Yield; mp 85-87°C (*lit.*[9] 89-90°C). The spectroscopic data correspond to those reported in literature.[9]

2,4-Dihydroxy-3-methoxybenzaldehyde (5).- This compound was synthesized using the Gattermann procedure. Anisole (**4**) (60 mmol, 8.41 g), zinc cyanide (90 mmol, 10.57 g), zinc chloride (15 mmol, 2.03 g) and a trace (5 mg) amount sodium chloride were introduced in a two-necked flask. Diethyl ether (200 mL) was added and the flask was fitted with an ice-water cooler to avoid evaporation of the HCN formed *in situ*. Dry HCl gas was bubbled through the reaction mixture under continuous stirring. When a green precipitate appeared, stirring was continued for an additional 30 min. The ethereal layer was carefully decanted under the hood and the precipitate was rinsed thoroughly with diethyl ether to remove all traces of intermediate HCN and **4** present in the reaction mixture. Subsequently, the intermediate iminium salt was dissolved in boiling water (140 mL). A few drops of concentrated sulfuric acid were added and the resulting mixture was refluxed for 30 minutes. The reaction mixture was left at room temperature overnight after which 2,4-dihydroxy-3-methoxybenzaldehyde **5** crystallized. The crystals were collected and dissolved in dichloromethane (200 mL). After drying over magnesium sulfate, filtration and evaporation of the solvent, 6.96 g (69%) of pure **5** was obtained as colorless crystals, mp 85-86°C (*lit.*[12] 85.5-86.5°C). ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.01 (3 H, s, OCH_3); 6.62 (1 H, d, J = 8.6 Hz, 5-C<u>H</u>); 6.80 (1 H, broad s, 4-O<u>H</u>); 7.21 (1 H, d, J = 8.6 Hz, 6-C<u>H</u>); 9.70 (1 H, s, C<u>H</u>O); 11.53 (1 H, s, 2-O<u>H</u>).

Hydrangetin (7-Hydroxy-8-methoxycoumarin) (6).- A solution of **5** (20 mmol, 3.36 g) and methyl (triphenylphosphoranylidene)acetate (24 mmol, 8.02 g) in *N,N*-diethylaniline (100 mL) was refluxed under a nitrogen atmosphere for 4 h. After cooling to room temperature, the reaction mixture was diluted with 2.5 N hydrochloric acid (300 mL) and extracted with diethyl ether (3 x 300 mL). The organic phase was washed with brine and dried over magnesium sulfate. After filtration and evaporation of the solvent, the resulting solid was further purified by column chromatography on silica gel (eluent: dichloromethane/methanol 9/1; RF 0.21) to give 1.27 g (6.6 mmol, 33%) of pure **6** as a colorless solid, mp 184-185°C (*lit.*[1] 186.5°C). ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.02 (3 H, s, OCH_3); 6.21 (1 H, d, J = 9.6 Hz, CH=C<u>H</u>CO); 6.94 (1 H, d, J = 8.6 Hz, 6-C<u>H</u>); 7.06 (1 H, d, J = 8.6 Hz, 5-C<u>H</u>); 7.65 (1 H, d, J = 9.6 Hz, C<u>H</u>=CHCO); 8.4 (1 H, broad s, O<u>H</u>).

Collinin (7).- To a solution of hydrangetin (**6**) (0.62 mmol, 0.12 g) in acetone (50 mL), potassium carbonate (0.81 mmol, 0.11 g) and geranyl bromide (0.88 mmol, 0.20 g) were added with stirring. The reaction mixture was heated for 15 h at 50°C. After filtration and evaporation of the solvent a brown oil was obtained, which after chromatography using hexane/ethyl acetate 80/20 as eluent, yields pure **7** (0.07 g, 34%) as a colorless solid, mp 68°C (*lit.*[4-5] 67-68°C). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.60 and 1.66 (each 3 H, each s, $(C\underline{H}_3)_2C$=); 1.75 (3 H, s, $C\underline{H}_3C$=$CHCH_2O$); 2.05-2.15 (4 H, m, =$CH_2C\underline{H}_2C$=); 3.98 (3 H, s, OCH_3); 4.70 (2 H, d, J = 6.3

Hz, =CHC$\underline{H}_2$O); 5.04-5.10 (1 H, m, $(CH_3)_2$C=C$\underline{H}$CH_2-); 5.49 (1 H, td, J_t = 6.4 Hz, J_d = 1.3 Hz, CH_3C=C$\underline{H}$CH_2O); 6.25 (1 H, d, J = 9.6 Hz, CH=C$\underline{H}$CO); 6.87 (1 H, d, J = 8.7 Hz, 6-C$\underline{H}$); 7.15 (1 H, d, J = 8.7 Hz, 5-C$\underline{H}$); 7.63 (1 H, d, J = 9.6 Hz, C$\underline{H}$=CHCO).

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