A Straightforward Entry into Polyketide Monoprenylated Furanocoumarins and Pyranocoumarins[1]

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A regioselective synthesis of 5-methyl- and 5-ethyl-4-hydroxycoumarin (**1b** and **1c**, respectively) is described. Starting from these compounds, several prenylated polyketide coumarins of limited availability from natural sources and important taxonomic relevance were prepared.

Coumarin derivatives are widespread in nature, especially in higher plants,[2] and the coumarin system is a versatile template, amenable by appropriate molecular decoration to a great variety of applications within the realm of pharmaceuticals,[3] asymmetric syntheses,[4] and chiral separations.[5] Many biologically active coumarins bear an oxygen function at C-4, with pre-eminent examples being the hemorrhagic toxin ferulenol[6] and the topoisomerase inhibitor novobiocin[7] from plant and mold sources, respectively.[8] In sharp contrast to 7-hydroxycoumarins, 4-hydroxycoumarins can originate either from the shikimate or from the polyketide route,[9] and the presence of a substituent at C-5 (methyl-, ethyl-) is the hallmark of this pathway. Although 4-hydroxycoumarin (**1a**) is an inexpensive commercial chemical, its 5-methyl- and 5-ethyl-derivatives (**1b** and **1c**) are only available through multistep, low-yielding, and generally nonregioselective syntheses.[10]

Polyketide coumarins have a narrow distribution in plants and are almost invariably prenylated. The attachment is generally bidentate, resulting in the formation of a pyranocoumarin or a furanocoumarin system. These compounds are common within the Mutisieae tribe of the Compositae families[2c,d] but are otherwise very rare and, therefore, of exceptional taxonomic value.[11] The structural complexity of polyketide coumarins has sparked intense synthetic activity culminating in several elegant syntheses, mainly by Bohlmann's group.[12] Paradoxically, many simpler members of the class have never been synthesized. This is even more surprising when one considers that these compounds, available by isolation only in minute amounts, are the most useful from a chemotaxonomic point of view, having been found also in the "difficult" and complex family of the Meliaceae.[11] The pharmacology of these compounds is virtually unexplored, notwithstanding their isolation from plants used in traditional medicine[13] and the powerful antiprotozoal activity displayed by certain sesquiterpene polyketide coumarins.[14]

The availability of an expeditious synthesis of these compounds should prompt a systematic investigation on their occurrence and pharmacological potential. With this aim in mind, we have developed a straightforward synthesis of 5-methyl- and 5-ethyl-4-hydroxycoumarins. These compounds were then reacted with commercially available prenyl building blocks to afford, after further modification, all of the core pyranocoumarins and furanocoumarins of the monoprenyl type. Their corresponding 5-*nor* derivatives, hitherto unknown as natural products, were also synthesized for comparison.

Results and Discussion

Ethyl 6-methyl-(**2b**) and 6-ethylsalicylate (**2c**) were identified as suitable starting materials for the synthesis of **1b** and **1c**, respectively. Compounds **2b** and **2c** are not commercially available, but an expeditious procedure for the preparation of **2a** from crotonaldehyde and ethyl acetoacetate via Robinson annulation and aromatization has been reported (Scheme 1).[15] We modified the reported procedure (see Experimental Section) and extended it to the preparation of **2c** by replacement of crotonaldehyde with its homologue (pent-2-enal). 4-Hydroxy-5-methylcoumarin (**1b**) was next prepared by reacting **2b** with the lithium enolate of *tert*-butyl acetate (Rathke salt),[16] generated in the presence of an excess LDA (lithium diisopropylamide) to avoid its re-protonation by the phenolic hydroxyl of **2b**. After considerable optimization, a protocol employing 5.5 equiv LDA and 3.5 equiv Rathke salt was established. The excess *tert*-butyl acetate is necessary to suppress the formation of *N*,*N*-diisopropyl-6-methylsalicylamide, the result of competitive nucleophilic attack by LDA on the ester carbonyl of **2b.** The use of alternate hindered bases (LiHDMS, LiTMP) did not substantially increase the yield. The crude Claisen adduct **3a** was next stirred with neat trifluoroacetic acid to affect the cyclization to **1b**, eventually obtained in overall 85% yield from **2b**. A similar procedure from **2c** afforded **1c** in comparable yield.

The methyl group of **2b** provided a handle for functionalization, paving the way to chain extension. As an example of these possibilities, an alternate preparation of **2c**, using **2b** as the starting material, was executed. Thus, after protection of the phenolic hydroxyl of **2b** as a BOC (butoxycarbonyl) derivative and metalation with LDA in the presence of TMEDA (*N*,*N*,*N*′-trimethylenediamine),[17] the deep-orange solution of the 6-lithiomethyl anion of BOC-protected **2b** was quenched with methyl iodide. Deprotection with neat formic acid afforded directly **2c**.

With a source of **1b** and **1c** secured, we moved on to the introduction of the prenyl residues. The synthesis of the pyranocoumarins **4a**−**c** capitalized on a domino Knoevenagel−electrocyclic reaction, using 3-methyl-2-butenal as a bidentate prenyl synthon.[18] Thus, starting from 4-hydroxycoumarin and its 5-methyl and 5-ethyl derivatives,

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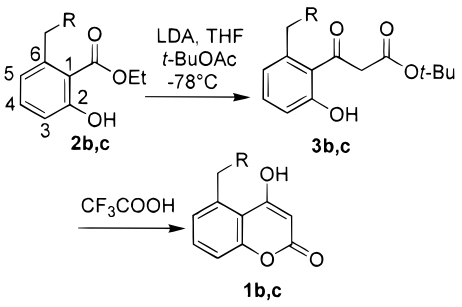
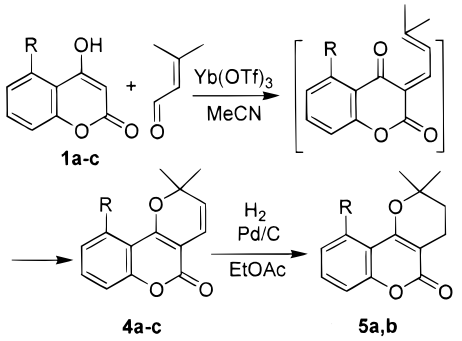
Scheme 1. Synthesis of 5-Methyl- and 5-Ethyl-4-hydroxycoumarin (**1b,c**)



(**b** R:H; **c** R:Me)

Scheme 2. Synthesis of the Pyranocoumarins **4a**−**c** and **5a,b**



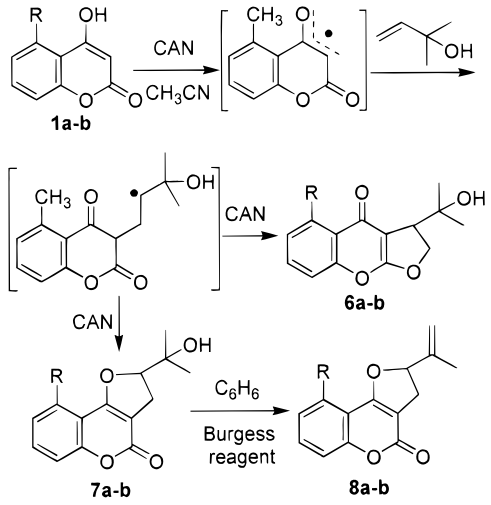
(**a** R:H; **b** R:Me; **c** R:Et)

nor-bothrioclinin (**4a**), bothrioclinin (**4b**),[19] and homobothrioclinin (**4c**)[19] were obtained (Scheme 2). The spectroscopic data on **4b** and **4c** were identical to those reported for the natural products.[19] Ytterbium triflate proved superior to the Tietze base (diethylendiammonium diacetate) to promote the reaction.[20] Catalytic hydrogenation of the pyranocoumarin adducts afforded the corresponding 2,3-dihydroderivatives, one of which is known as a natural product (pterophyllin III, **5b**).[11]

To synthesize the prenylated coumarins of the furano-type, we relied on the cerium [IV]ammonium nitrate (CAN)-mediated oxidative addition of **1a,b** to 2-methyl-3-buten-2-ol (Scheme 3).[21] The reaction was regioselective in the carbon−carbon-forming step, but poorly discriminating in the following carbon−oxygen-formation step, because the oxygen of both the ketone- and the lactone-carbonyl could be involved. As a result, a mixture of linear (**6a,b**) and angular adducts (**7a,b**) was obtained (Scheme 3). These compounds were easily separated by column chromatography, with the linear adduct being eluted first from Si gel column chromatography in all cases. The spectroscopic assignment of **6a,b** and **7a,b** relied on diagnostic differences in the chemical shift of the atom at C-5 (deshielding *peri*-effect of the ketone carbonyl in the linear adducts **7a,b**) and in the frequency of the carbonyl stretching (lactone vs enone).[21,22] Compound **6b** was identical to the natural product isoerlangeafusciol.[23] The adducts from the furano series could be regioselectively dehydrated using either the Burgess[24] or the sulfurane Martin reagent.[25] In this way pterophyllin I (**8b**)[11] as well as its *nor*-derivative (**8a**), yet unreported as a natural product, could be obtained.

In conclusion, a straightforward entry into the most elementary members of the pyrano- and furano-polyketide prenylated coumarins has been achieved. The increased availability of these important taxonomic markers should spur studies aimed at a better evaluation of their puzzling, scattered distribution in plants and of their biological activity.

Scheme 3. Synthesis of the Furanocoumarins **7a,b** and **8a,b**



(**a** R:H; **b** R:Me)

Experimental Section

General Experimental Procedures. Anhydrous conditions were achieved (when indicated) by flame-drying flasks and equipment. Reactions were monitored by TLC on Alugram Sil−Macherey Nagel (F_{254}, 0.25 mm) plates, and spots were detected by UV inspection or staining with 5% aqueous $KMnO_4$ or 5% H_2SO_4 in EtOH and heating. Merck Si gel was used for open-column chromatography and MPLC (70−230 mesh and 230−440 mesh, respectively). MPLC was carried out on a Büchi instrument B 680A, equipped with a B 685-type column. Waters microPorasil 7.8−300 and Merck Hibar 25−250 columns were used for semipreparative HPLC, with detection by a Gilson 133 refractive index refractometer. Melting points were obtained on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H NMR (300 and 200 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AC-300 and Bruker AC-200 spectrometers at 25 °C. ^{1}H and ^{13}C NMR chemical shifts refer to C*H*Cl$_3$ at 7.26 ppm, and *C*DCl$_3$ at 77.0 ppm, respectively. LRMS were performed on a Finnigan-MAT TSQ70 in chemical ionization with isobutane as reactant gas. Commercially available reagents and solvents were used without further purification unless otherwise stated. CH_2Cl_2 was dried by distillation from P_4O_{10} and THF by distillation from Na−benzophenone.

Ethyl 6-Methylsalicylate (**2b**). The condensation between ethyl acetoacetate (132 mL, 1.04 mol) and crotonaldehyde (85.8 mL, 1.04 mol) in the presence of sodium ethoxide (30 mmol) was carried out according to Hauser and Pogany[15a]. After the aromatization with $CuCl_2$ and LiCl in DMF at 90 °C, the dark brown reaction mixture was cooled to room temperature, diluted with ice-water and poured on a Celite-Si gel bed previously prepared on a sintered glass funnel (180 mm, 100 g Celite and 150 g Si gel). After filtration with suction and washing with H_2O (1 L) to remove DMF, **2b** was eluted with petroleum ether. Further purification was achieved with fractional distillation under vacuum (80 °C, 0.66 kPa) and a normal air condenser, occasionally heated to avoid clogging from lumps of solidified distillate. Compound **2b** (86 g, 46%) was obtained as pale yellow crystals; **2b** could alternatively be purified by MPLC (petroleum ether−EtOAc 95:5): R_f (hexane−EtOAc 7:3) 0.64.

Ethyl 6-Ethylsalicylate (**2c**). To a cooled (0 °C) two-necked round-bottomed flask, equipped with a pressure-equalizing addition funnel, magnetic stirrer, and nitrogen inlet, 37.8 mL

(287 mmol) of ethyl acetoacetate and 57 mL of sodium ethoxide (8.57 mmol) in EtOH were sequentially added. 2-Pentenal (29 mL, 0.297 mmol) was then added over 5 min. After stirring 30 min at 0 °C, the solution was allowed to warm to room temperature for 48 h, and saturated by bubbling HCl (15 min at 0 °C). After stirring two further days at room temperature, the solution was freed of HCl by stripping under vacuum (water pump) and mild heating. The dark brown residue obtained in this way was dissolved in DMF (50 mL) and heated at 90 °C under magnetic stirring. Then, 32.93 g (0.297 mol) $CuCl_2$ and 17.30 g (0.408 mol) LiCl were added, and the flask was immediately connected to a Drechsel bottle containing 3N NaOH. After 3 h, the dark reaction mixture was cooled to room temperature and treated as described for **2b**. The crude reaction mixture was purified by column chromatography using petroleum ether as the eluent, affording 31 g of **2c** (54%) as a straw-colored oil: IR (liquid film) 3350, 1662, 1608, 1451, 1248, 1209 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.25 (1H, s, OH), 7.32 (1H, t, J = 7.9 Hz, H-4), 6.86 (1H, d, J = 7.9 Hz, H-5), 6.75 (1H, d, J = 7.9 Hz, H-3), 4.46 (2H, q, J = 7.1 Hz, CH_2-1′), 2.97 (2H, q, J = 7.4 Hz, H-7), 1.45 (3H, t, J = 7.1 Hz, CH_3-2′), 1.23 (3H, t, J = 7.4 Hz, H-8);^{13}C NMR ($CDCl_3$) δ 171.4 (s, C=O), 162.35 (s, C-2), 147.40 (s, C-6), 134.13 (d, C-4), 121.57 (d, C-5), 115.49 (d, C-3), 111.83 (s, C-1), 61.52 (t, C-1′), 29.49 (t, C-7), 16.15 and 13.90 (2 q, C-2′ and C-8); LRMS 195 (MH^+, CIMS); R_f (hexane−EtOAc 9:1) 0.57; *anal.* calcd for $C_{11}H_{14}O_3$; C 68.02, H 7.26; found C 67.99, H 7.28.

Ethyl 6-Ethylsalicylate by Homologation of 2b. (a) Protection of the phenolic hydroxyl. In a two-necked round-bottomed flask equipped with magnetic stirrer and nitrogen inlet, **2b** (6.312 g, 35 mmol) was dissolved in 30 mL of anhydrous CH_2Cl_2 at room temperature. To this solution, 7.19 mL (42.07 mmol) *N*-ethyl diisopropylamine (Hünig base), 9.191 g (42.07 mmol) di-(*t*-butyl)dicarbonate, and a few crystals DMAP (4-(dimethylamino)pyridine) were added. After stirring overnight, the reaction was diluted with 100 mL of $CHCl_3$, washed with 2N HCl (3 × 50 mL) and brine (2 × 50 mL), and dried over $MgSO_4$. Removal of the solvent left a yellow oil, purified by column chromatography (100 g Si gel, petroleum ether−EtOAc 19:1 as eluent) to afford 9.52 g (97% yield) of a pale yellow oil: IR (liquid film) 1763, 1731, 1468, 1379, 1235, 1152, 872 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (1H, t, J = 7.8 Hz, H-4), 7.11 (1H, d, J = 7.8 Hz, H-5), 7.03 (1H, d, J = 8.1 Hz, H-3), 4.38 (2H, q, J = 7.2 Hz, CH_2-1′), 2.42 (3H, s, H-7), 1.53 (9H, s, *t*-Bu), 1.39 (3H, t, J = 7.1 Hz, H-2′); LRMS 281 (MH^+, CIMS); R_f (hexane−EtOAc 8:2) 0.35.

(b) Homologation. To a 100-mL, three-necked round-bottomed flask equipped with a pressure-equalizing addition funnel, magnetic stirrer, nitrogen inlet, and a thermometer, dry THF (10 mL), TMEDA (650 μL, 4.37 mmol), diisopropylamine (775 μL, 8.63 mmol), and *N*-benzylbenzamide (3 mg) were added. The solution was cooled (−78 °C), and *n*-BuLi (1.6M in hexanes, 5.16 mL, 8.22 mmol) was added slowly. After 30 min, a solution of 1.441 g (5.14 mmol) ethyl 2-*O*-BOC-6-methylsalicylate in 10 mL of THF was added over 5 min, during which the solution turned from dark blue to red and then to orange. The solution was then stirred at −78 °C for 40 min, and a solution of methyl iodide (2.56 mL, 41.12 mmol) in THF (5 mL) was added, causing the reaction mixture to turn yellow. The solution was allowed to warm to room temperature overnight, and then quenched by the addition of ice-cooled saturated aqueous NH_4Cl (40 mL) and EtOAc (40 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered, and then concentrated under reduced pressure. The crude yellow oil obtained in this way was purified by column chromatography (25 g Si gel, petroleum ether−EtOAc 19:1 as eluent) to afford 1.027 g (68%) ethyl *O*-2-BOC-6-ethylsalicylate as a colorless oil: IR (liquid film) 1768, 1735, 1460, 1369, 1281, 1236, 1185, 733 cm^{-1}; ^1H NMR ($CDCl_3$ δ 7.35 (1H, t, J = 7.9 Hz, H-4), 7.13 (1H, d, J = 7.3 Hz, H-5), 7.03 (1H, d, J = 8.3 Hz, H-3), 4.38 (2H, q, J = 7.1 Hz, CH_2-1′), 2.72 (2H, q, J = 7.5 Hz, H-7), 1.53 (3H, s, *t*-Bu), 1.37 (3H, t, J = 7.0 Hz, H-8); 1.23 (3H, t, J = 7.5, H-2′); LRMS 295 (MH^+, CIMS); R_f (hexane/EtOAc 8:2) 0.46.

(c) Deprotection. A mini-vial was charged with ethyl 2-BOC-6-ethylsalicylate (1.0 g, 3.4 mmol) and HCO_2H (1 mL) and left for 4 h in the refrigerator at 5 °C. The solution was then poured into ice-water (50 mL), neutralized with $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with brine (80 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography (20 g Si gel, petroleum ether−EtOAc 19:1 as eluent) to give 606 mg (92%) of **1c**.

4-Hydroxy-5-methylcoumarin (1b). To a 200-mL three-necked round-bottomed flask equipped with a pressure-equalizing addition funnel, magnetic stirrer, nitrogen inlet, and a thermometer, diisopropylamine (7.08 mL, 50.48 mmol), *N*-benzylbenzamide (5 mg), and dry THF (20 mL) were added. The solution was cooled (−78 °C), and *n*-BuLi (1.6M in hexanes, 30.1 mL, 48.15 mmol) was added slowly. After 30 min, a solution of *tert*-butyl acetate (3.56 g, 30.62 mmol, 3.5 mol. equiv.) in 10 mL of THF was added over 5 min, during which time the solution turned from dark blue to deep yellow. The solution was then stirred at −78 °C for 50 min, and a solution of ethyl 6-methylsalicylate (**2b**) 1.68 g (8.75 mmol) in 10 mL THF was added over 5 min. After warming to room temperature overnight, the reaction was quenched by the addition of ice-cooled saturated aqueous NH_4Cl (50 mL) and EtOAc (80 mL). The organic layer was washed with brine (100 mL), dried ($MgSO_4$), and concentrated. The residue was purified by medium-pressure column chromatography (40 g Si gel; packing with petroleum ether, followed by petroleum ether−EtOAc 9:1) to afford 319 mg (19%) of recovered ethyl 6-methylsalicylate (**2b**) and 942 mg (71%) of **3b** as pale-yellow oil: IR (liquid film) 2980, 1730, 1455, 1148, 1034, 781 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.85 (br s, 1H, OH), 7.27 (1H, t, J = 7.5 Hz, H-4), 6.83 (1H, d, J = 7.5 Hz, H-5), 6.73 (1H, d, J = 7.5 Hz, H-3), 3.91 (2H, s, CH_2CO), 2.53 (3H, s, H-7), 1.45 (9H, s, *t*-Bu); LRMS 251 (MH^+); R_f (hexane−EtOAc 9:1) 0.64; *anal.* calcd for $C_{14}H_{18}O_4$; C 67.18, H 7.25; found C 67.53, H 7.21.

When 1.2 equiv *tert*-butyl acetate was used, the yield dropped to 19%, and *N*,*N*-di(isopropyl)-6-methyl salicylamide was also isolated in 15% yield as colorless needles: mp 212−214 °C; IR (KBr) 2950, 2693, 1600, 1575, 1460, 1369, 1298, 1038, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.58 (1H, br s, 1H, OH), 6.66 (1H, t, J = 7.8 Hz, H-4), 6.33 (2H, m, J = 7.8 Hz, H-3 and H-5), 3.40 and 3.18 (2H, br s, R−C*H*-Me_2), 1.89 (3H, s, Me-aryl), 1.23 (6H, br s, *Me*$_2$−CHR), 0.81 (6H br d, J = 7.0 Hz, *Me*$_2$−CHR); LRMS 236 (MH^+); R_f (hexane−EtOAc 3:7) 0.58; *anal.* calcd for $C_{14}H_{21}NO_2$; C 71.46, H 8.99, N 5.95; found C 71.39, H 8.96, N 5.92. A mini-vial was charged with **3b** (1.0 g, 4 mmol) and trifluoroacetic acid (0.5 mL). The mixture was shaken vigorously (10 min) and allowed to settle at room temperature for 4 h. A pale yellow solid formed, which was collected on a sintered glass filter and washed with a 3:1 mixture of petroleum ether and Et_2O (20 mL). The filtrate was concentrated and cooled (4 °C) to afford a second crop of **1b** as a yellowish powder. The overall yield was (584 mg) 83%: mp: 229−230 °C [lit.[26] 221−223 °C]; IR (KBr) 3384, 1649, 1559, 1344, 1262, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.41 (1H, br s, OH), 7.46 (1H, t, J = 7.9 Hz, H-7), 7.17 (1H, d, J = 8.1 Hz, H-6), 7.09 (1H, d, J = 7.5, H-8), 5.56 (1H, s, H-3), 2.66 (3H, s, Me); ^{13}C NMR ($CDCl_3$) δ 161.5 (s, C-2), 91.3 (d, C-3), 168.7 (s, C-4), 114.4 (s, C-4a), 137.2 (s, C-5), 127.2 (d, C-6), 131.8 (d, C-7), 114.9 (d, C-8), 155.1 (s, C-8a), 22.8 (q, C-9); LRMS 177 (MH^+); R_f ($CHCl_3$−MeOH−H_2O 8:1:1) 0.75; *anal.* calcd for $C_{10}H_8O_3$; C, 68.16, H 4.58; found C 68.20, H 4.5.

4-Hydroxy- 5-ethylcoumarin (1c). The same procedure described for the preparation of **1b** from **2c** was employed. Compound **1c** was obtained in 60% overall yield. Data for (**3c**): colorless oil, IR (KBr) 3400, 1732, 1698, 1466, 1323, 1286, 1255, 1152 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (1H, t, J = 7.8 Hz, H-4), 6.82 and 6.79 (2 × 1H, 2 × d, J = 8.0 Hz, H-3 and H-5), 3.89 (2H, s, H-10), 2.74 (2H, q, J = 7.6 Hz, H-4), 1.42 (9H, s, *t*-Bu), 1.29 (3H, t, Me); ^{13}C NMR ($CDCl_3$) δ 205.2 (s, C-9), 132.8 (d, C-4), 120.8 and 114.9 (d, d, C-3 and C-5), 51.8 (t, C-10), 27.75 (q, C- *t*Bu), 27.1 (t, C-7), 15.9 (q, C-8); LRMS 264 (MH^+, CIMS); R_f (hexane−EtOAc 9:1) 0.52; *anal.* calcd for $C_{15}H_{20}O_4$; C 68.16, H 7.63; found C 68.10, H 7.69. Data for Compound **1c**: IR (KBr) 3380, 1638, 1597, 1344, 1302, 821 cm^{-1}; ^1H NMR

($CDCl_3$) δ 12.37 (1H, br s, OH), 7.45 (1H, t, J = 7.8 Hz, H-7), 7.13 (1H, d, J = 7.8 Hz, H-6), 7.07 (1H, d, J = 7.8 Hz, H-8), 5.57 (1H, s, H-3), 3.08 (2H, q, J = 7.4 Hz, H-9), 1.18 (3H, t, H-10); ^{13}C NMR ($CDCl_3$) δ 168.32 (s, C-4), 161.56 (s, C-2), 155.16 (s, C-8a), 143.61 (s, C-5), 131.82 (d, C-7), 125.96 (d, C-6), 114.82 (d, C-8), 113.70 (s, C-4a), 91.59 (d, C-3), 28.31 (t, C-9), 16.74 (q, C-10); LRMS 191 (MH^+, CIMS); R_f ($CHCl_3$−MeOH−H_2O 8:1:1) 0.75; *anal.* calcd for $C_{11}H_{10}O_3$; C 69.46, H 5.30; found C 69.48, H 5.22.

2,2,10-Trimethyl-2*H*,5*H*-pyrano [3,2-*c*][1]benzopyran-5-one (**Bothrioclinin, 4b**). 4-Hydroxy-5-methylcoumarin (**1b**) (200 mg, 1.14 mmol) and 3-methyl-2-butenal (120 μL, 1.25 mmol) were dissolved in MeOH (5 mL), and a catalytic amount of diethylendiammonium diacetate (5 mg) was added. The reaction was stirred for 3 h at room temperature. Removal of the solvent left an oily residue, then purified by column chromatography (15 g Si gel, petroleum ether−EtOAc 8:2) to afford 200 mg **4b** (73%) as a white powder: mp 135−137 °C (diethyl ether); IR (KBr) 1713, 1595, 1464, 1234, 1055, 980, 871 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33 (1H, dd, J = 8.1 Hz, J'= 7.4, H-8), 7.14 (1H, d, J = 8.1 Hz, H-9), 7.00 (1H, d, J = 7.4 Hz, H-7), 6.54 and 5.36 (2H, AB syst., J = 10.0, H-4 and H-3), 2.71 (3H, s, Me-10), 1.56 (6H, s, 6H, Me_2CR_2); ^{13}C NMR ($CDCl_3$) δ 80.5 (q, C-2), 125 (d, C-3), 117.3 (d, C-4), 100.6 (s, C-4a), 160.7 (s, C-5), 154.0 (s, C-6a), 115.3 (d, C-7), 131.3 (d, C-8), 127.4 (d, C-9), 137.0 (s, C-10), 114.3 (s, C-10a), 161.5 (s, C-10b), 28.4 (q, C-11), 28.4 (q, C-12), 20 (q, C-13); LRMS 243 (MH^+); R_f (hexane−EtOAc 7:3) 0.44; *anal.* calcd for $C_{15}H_{14}O_3$; C 74.36, H 5.82; found C 74.37, H 5.77.

2,2-dimethyl-pyrano[3,2-*c*][1]benzopyran-5-one (**4a**) was prepared in a similar way from 4-hydroxycoumarin (**1a**) in 77% yield. For data, see Appendino et al.[18]

2,2-Dimethyl-10-ethyl-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-5-one (Methylbothrioclinin, 4c). The same procedure used to prepare **4b** was employed, but 4-hydroxy-5-ethylcoumarin (**1c**) was used as starting material, $Yb(OTf)_3$ (5 mg) as the catalyst, and MeCN as the solvent. Compound **4c** was obtained as colorless crystals in 87% yields; mp 83 °C; IR (KBr) 3455, 1709, 1593, 1466, 1045, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38 (1H, t, J = 7.8 Hz, H-8), 7.15 (1H, d, J = 7.7 Hz, H-9), 7.04 (1H, d, J = 7.7 Hz, H-7), 6.56 (1H, d, J = 10.0 Hz, H-4), 5.49 (1H, d, J = 10.0 Hz, H-3), 3.11 (2H, q, J = 7.4 Hz, H-11), 1.58 (6H, s, Me_2CR_2), 1.26 (3H, t, J = 7.4 Hz, H-12); ^{13}C NMR ($CDCl_3$) δ 80.5 (q, C-2), 117.2 (d, C-3), 115.2 (d, C-4), 100.4 (s, C-4a), 160.9 (s, C-5), 154.4 (s, C-6a), 125.0 (d, C-7), 126.3 (d, C-8), 131.4 (d, C-9), 143.4 (s, C-10), 113.5 (s, C-10a), 169.2 (s, C-10b), 28.9 (q, C-11), 17.0 (t, C-12), 28.2 (q, C-13); LRMS 257 (MH^+, CIMS); R_f (hexane−EtOAc 7:3) 0.65; *anal.* calcd for $C_{16}H_{16}O_3$; C 74.98, H 6.29; found C 74.77, H 6.35.

3,4-Dihydro-2,2,10-trimethyl-2*H*,5*H*-pyrano [3,2-*c*][1]benzopyran-5-one (Pterophyllin III, 5b). To a solution of **4b** (100 mg, 0.41 mmol) in EtOAc (5 mL), 20% palladium hydroxide on carbon (25 mg) was added. The flask was evacuated and purged with dry nitrogen three times, and then placed under an atmosphere of hydrogen (101.32 kPa). After 3 h, the reaction mixture was filtered through a pad of Celite, and the residue was washed with EtOAc (100 mL). The filtrate and the washings were evaporated, and the residue was purified by column chromatography (5 g Si gel, hexane−EtOAc 19:1) to give **5b** (74 mg, 75%) as a colorless solid: mp 110−112 °C (diethyl ether) [lit.[11] gum, 58−60 °C]; IR (KBr) 1699, 1618, 1443, 1323 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31 (1H, t, J = 7.8 Hz, H-8), 7.14 (1H, d, J = 7.7 Hz, H-9), 7.00 (1H, d, J = 7.4 Hz, H-7), 2.68 (3H, s, Me-10), 2.59 (2H, t, J = 6.7 Hz, H-3), 1.84 (2H, t, J = 6.7 Hz, H-4), 1.44 (6H, s, Me-12 and 13); ^{13}C NMR ($CDCl_3$) δ 78.1 (q, C-2), 31.4 (t, C-3), 17.5 (t, C-4), 99.3 (s, C-4a), 163.0 (s, C-5), 158.6 (s, C-6a), 115.1 (d, C-7), 130.8 (d, C-8), 127.3 (d, C-9), 138.4 (s, C-10), 114.9 (s, C-10a), 161.8 (s, C-10b), 23.5 (q, C-11), 26.7 (q, C-12 and q, C-13); LRMS 245 (MH^+); R_f (hexane−EtOAc 7:3) 0.47; *anal.* calcd for $C_{15}H_{16}O_3$; C 73.75, H 6.60; found C 73.78, H 6.58.

2-(1-Hydroxy-1-methylethyl)-9-methyl-2,3-dihydrofuro-[3,2-*c*][1]benzopyran- 2(3*H*)-one (Isoerlangeafusciol, 7b). 5-Methyl-4-hydroxycoumarin (**1b**) (200 mg, 1.14 mmol) was suspended in dry MeCN (15 mL) in the presence of 2-methyl-3-buten-2-ol (98 mg, 1.14 mmol). The suspension was cooled to 0 °C, and a solution of CAN (1.557 g, 2.84 mmol) in MeCN (15 mL) was added. After stirring 1 h at 0 °C, the reaction mixture was diluted with 30 mL of H_2O and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3 (20 mL) and brine (20 mL). After drying ($MgSO_4$) and removal of the solvents, the dark residue was purified by column chromatography (20 g Si gel, hexanes−EtOAc 7:3 as eluent) to provide, in order of elution, 133 mg (45%) isoerlangeafusciol (**7b**) as colorless solid, and its linear isomer (allo-isoerlangeafusciol, **6b**) (48 mg, 21%). Data for **7b**: IR (KBr) 3432, 1693, 1603, 1485, 1169, 1057, 799 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.42 (1H, t, J = 8.0 Hz, H-7), 7.18 (1H, d, J = 8.0 Hz, H-8), 7.03 (1H, d, J = 8.0 Hz, H-6), 4.91 (1H, t, J = 9.6 Hz, H-2), 3.10 (2H, d, J = 9.6 Hz, H-3), 2.68 (3H, s, Me-9), 2.0 (1H, br s, OH), 1.48 (s) and 1.43 (s) (6H, Me_2−C); ^{13}C NMR ($CDCl_3$) δ 92.7 (d, C-2), 27.0 (t, C-3), 102.7 (s, C-3a), 166.5 (s, C-4), 155.7 (s, C-5a), 117.2 (d, C-6), 135.7 (d, C-7), 126.2 (d, C-8), 131.5 (d, C-9), 114.9 (s, C-9a), 160.5 (s, C-9b), 71.5 (s, C-1′), 25.6−24.5 (q, q, C-2′ and C-3′) 21.1 (s, C-10); LRMS 261 (MH^+); R_f (hexane−EtOAc 3:7) 0.46; *anal.* calcd for $C_{15}H_{16}O_4$; C 69.22, H 6.20; found C 69.43, H 6.19. Data for **6b**: IR (KBr) 3310, 1643, 1605, 1468, 1265, 1130, 937, 794 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40 (1H, t, J = 7.9, H-7), 7.19 (d) and 7.13 (d) (2H, J = 8.1, 7.4 Hz, H-6 and H-8), 4.83 (1H, t, J = 8.9 Hz, H-2), 3.11 (2H, d, J = 8.9 Hz, H-3), 2.88 (3H, s, Me-5), 2.31 (1H, br s, OH), 1.37 (s) and 1.28 (s) (6H, Me_2−CR_2); ^{13}C NMR ($CDCl_3$) δ 90.7 (d, C-2),), 26.1 (t, C-3), 95.7 (s, C-3a), 177.5 (s, C-4), 121.7 (s, C-4a), 141.0 (s, C-5), 128,6 (d, C-6), 131,1 (d, C-7), 115.1 (d, C-8), 154.9 (s, C-8a), 167.3 (s, C-9a), 71.4 (s, C-10), 25.2−23.9 (q, q, C-11, C-12), 22.5 (q, C-13); LRMS 261 (MH^+); R_f (hexane−EtOAc 3:7) 0.32; *anal.* calcd for $C_{15}H_{16}O_4$; C 69.22, H 6.20; found C 69.36, H 6.17.

2-(1-Hydroxy-1-methylethyl)-2,3-dihydrofuro[3,2-c][1]-benzopyran-2(3*H*)-one (*nor*-Isoerlangeafusciol, 7a). This compound and its linear isomer (**6a**) were obtained from 4-hydroxycoumarin (**1a**) using the same procedure employed for the synthesis of **7b**. The yield was 51% for the angular isomer, and 24% for the linear one. Data for **7a**: IR (KBr) 3432, 1709, 1647, 1418, 1032, 908, 754, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.66 (1H, dd, J = 7.7 Hz, J'= 1.5 Hz, H-9), 7.52 (1H, t, J = 7.7 Hz, H-7), 7.32 (1H, d, J = 7.7 Hz, H-8), 7.25 (1H, t, J = 7.7 Hz, H-6), 4.93 (2H, t, J = 9.4 Hz, H-3), 2.38 (1H, br s, OH), 1.38 (s), and 1.27 (s), (6H, Me_2−C); ^{13}C NMR ($CDCl_3$) δ 93.1 (d, C-2), 27.7 (t, C-3), 102.6 (s, C-3a), 166.5 (s, C-4), 154.7 (s, C-5a), 116.8 (d, C-6), 132.2 (d, C-7), 122.5 (d, C-8), 123.8 (d, C-9), 112.2 (s, C-9a), 160.6 (s, C-9b), 71.5 (s, C-1′), 25.4−24.3 (q, q, C-2′ and C-3′); LRMS 247 (MH^+); R_f (hexane−EtOAc 3:7) 0.45. Data for **6a**: IR (KBr) 3328, 1701, 1620, 1466, 1414, 1213, 756, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.74 (1H, m, H-5), 7.50 (1H, m, H-7), 7.35 (1H, m, H-6), 7.28 (1H, m, H-8), 4.80 (1H, t, J = 9.0 Hz, H-2), 3.10 (2H, d, J = 9.0 Hz, H-3), 2.28 (1H, br s, OH), 1.33 (s) and 1.25 (s), (6H, Me_2−CR_2); LRMS 247 (MH^+); R_f (hexane−EtOAc 2:8) 0.34.

2-(1-Methylethenyl)-9-methyl-2,3-dihydrofuro[3,2-*c*][1]-benzopyran-2(3*H*)-one (**Pterophyllin I, 8b**): A solution of the angular adduct **(7b)** (100 mg, 0.38 mmol) in anhydrous C_6H_6 (4 mL) was refluxed for 30 min in the presence of Burgess reagent (methoxycarbonylsulfamoyl−triethylammonium hydroxide inner salt) (100 mg, 0.42 mmol). The solution was diluted with H_2O and extracted with EtOAc, washing the organic phase with brine and then drying it over Na_2SO_4. The residue was purified by column chromatography (hexanes−EtOAc 8:2 as eluent) to give 44.2 mg (48%) **8b** as a colorless gum: mp 58−60 °C [lit.[11] 61°-63 °C]; IR (KBr) 1720, 1632, 1601, 1454, 1049, 1018, 792 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.42 (1H, t, J = 7.9 Hz, H-7), 7.24 (1H, d, J = 8.3 Hz, H-8), 7.07 (1H, d, J = 7.5 Hz, H-6), 5.51 (1H, dd, J = 10.4, 8.2 Hz, H-2), 5.14 (1H, s, H-2′a), 5.02 (1H, s, H-2′b), 3.33 (1H, dd, J = 15.3, 10.6 Hz, H-3a), 2.98 (1H, dd, J = 8.2, 15.3 Hz, H-3b), 2.70 (3H, s, Me-1′), and 1.84 (3H, s, Me-9); ^{13}C NMR ($CDCl_3$) δ 89.09 (d, C-2), 31.06 (t, C-3), 128.8 (s, C-3a), 168.3 (s, C-4), 156.0 (s, C-4a),115.0 (d,C-6), 131.6 (d, C-7), 126.3 (d, C-8), 136.2 (s, C-9), 111.9 (s, C-9a), 163.0 (s, C-9b), 142.4(s, C-1′), 113.0 (t, C-2′), 17.1 (q, C-3′), 21.3 (s, C-10); LRMS 243 (MH^+); R_f (hexane−

EtOAc 4:6) 0.68; *anal.* calcd for $C_{15}H_{14}O_3$; C 74.36, H 5.82; found C 74.40, H 5.81.

2-(1-Methylethenyl)-2,3-dihydrofuro[3,2-*c*][1]benzopyran-2(3*H*)-one (*nor*-Pterophyllin I, 8a). The same procedure described above, but using **7a** as the starting material, gave the title compound in 51% yield: IR (KBr) 1720, 1630, 1600, 1452, 1040, 1016, 788 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (1H, d, J = 7.8 Hz, H-9), δ 7.58 (1H, t, J = 7.8 Hz, H-7), 7.40 (1H, d, J = 8.3 Hz, H-6), 7.30 (1H, t, J = 7.5 Hz, H-8), 5.53 (1H, dd, J = 10.2 Hz, J' = 8.4, H-2), 5.16 (1H, s, H-2′a), 5.02 (1H, s, H-2′b), 3.36 (1H, dd, J = 15.4, 10.4 Hz, H-3a), 3.02 (1H, dd, J = 8.1, 15.3 Hz, H-3b), 1.82 (3H, s, Me-2′); LRMS 243 (MH^+); R_f (hexane−EtOAc 4:6) 0.65; *anal.* calcd for $C_{14}H_{12}O_3$; C 73.67, H 5.30; found C 73.62, H 5.30.

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References and Notes

(1) The Chemistry of Coumarin Derivatives, 10. For Part 9, see Appendino et al.[21b]
(2) Murray, R. D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins*, Wiley: Chichester, UK, 1982. (b) Murray, R. D. H. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, C., Eds.; Springer: New York, 1991; Vol. 58, pp 83−283. (c) Murray, R. D. H., *ibidem*, 1997; Vol. 72, pp 1−119. (d) Estevez-Brown, A.; Gonzales, A. G. *Nat. Prod. Rep.* **1997**, *141*, 465−475.
(3) Zembower, D. E.; Liao, S.; Flavin, M. T.; Xu, Z.; Stup, T. L.; Buckheit, R. W.; Khilevich, A., Jr.; Mar, A. A.; Sheinkman, A. K. *J. Med. Chem.* **1997**, *40*, 1005−1017
(4) Whitesell, J. K.; Apodaca, R. *Tetrahedron Lett.* **1997**, *38*, 2589−2592.
(5) Nagasawa, K.; Yamashita, A.; Katoh, S.; Ito, K.; Wada, K. *Chem. Pharm. Bull.* **1995**, *43*, 344−346.
(6) Isolation: Carboni, S.; Malaguzzi, V.; Marsili, A. *Tetrahedron Lett.* **1964**, 2783−2786. (b) Configurational assignment: Valle, M. G.; Appendino, G.; Nano, G. M.; Picci, V. *Phytochemistry* **1987**, *26*, 253−256. (c) Synthesis: Appendino, G.; Cravotto, G.; Nano, G. M.; Palmisano, G. S*ynth. Commun.* **1992**, *22*, 2205−2212.
(7) Kaczka, E. A.; Wolf, F. G.; Rathe, F. P.; Folkers, K. *J. Am. Chem. Soc.* **1955**, *77*, 6604−6605.
(8) Dicoumarol, the archetypal coumarin anticoagulant, is derived from the microbial transformation of *ortho*-hydroxycinnamic acid and melilotic acid and is therefore of "mixed" origin (see Murray[2a] pp 182−185).
(9) Inoue, T.; Toyonaga, T.; Nagumo, S.; Nagai, M. *Phytochemistry* **1989**, *28*, 2329−2330.
(10) Pasupati, S.; Manju, S.; Pradip, K; Wenkert, E. *J. Indian Chem. Soc.* **1985**, *62*, 916−919. (b) Okogun, J. I.; Enienihi, V. U.; Ekong, D. E. U. *Tetrahedron* **1978**, *34*, 1221−1224. (c) Waterman, P. G.; Zhong, S. M.; Jeffreya, J.A.; Zakaria M. *J. Chem. Res.* **1985**, *1*, 101−144.
(11) Mulholland, D. A.; Iourine, S. E.; Tailor D. A. H.; Dean, F. M. *Phytochemistry* **1988**, *47*, 1641−1644.
(12) Kuhnke, J.; Bohlmann, F. *Liebigs Ann. Chem.* **1988**, 743−748.
(13) Mulholland, D. A., *Anstract O-20*, 39th Annual Meeting of the American Society of Pharmacognosy; Orlando, FL, July 19−24, 1998.
(14) Oketch-Rabah, H. A.; Lemmich, E.; Dossaji, S. F.; Theander, T. G.; Olsen, C. E.; Cornett, C.; Kharazmi, A.; Christensen, S. B. *J. Nat. Prod.* **1997**, *60*, 458−461.
(15) Hauser, F. M.; Pogany, S. A. *Synthesis* **1980**, 814−815. (b) Hamada, Y.; Hara, O.; Kawai, A.; Kohno, Y.; Shioiri T. *Tetrahedron.* **1991**, *47*, 8635−8638.
(16) Rathke, M. W.; Sullivan, D. F. *J. Am. Chem. Soc.* **1973**, *95*, 3050−3051.
(17) Hamada, Y.; Hara, O.; Kawai, A.; Kohno, Y.; Shioiri, T. *Tetrahedron* **1991**, *47*, 8635−8652.
(18) Appendino, G.; Cravotto, G.; Tagliapietra, S.; Nano, G. M.; Palmisano, G. *Helv. Chim. Acta* **1990**, *73*, 1865−1878.
(19) Bohlmann, F.; Zdero, C. *Phytochemistry* **1977**, *16*, 1261−1263.
(20) Kobayashi, S. *Synlett.* **1994**, 689−701.
(21) Appendino, G.; Cravotto, G.; Annunziata R.; Palmisano, G. S*ynth. Commun.* **1996**, *26*, 3359−3371. (b) Appendino, G.; Cravotto, G.; Annunziata R.; Palmisano, G. *Tetrahedron* **1998**, *54*, 10819−10826.
(22) Appendino, G.; Cravotto, G.; Toma, L.; Annunziata R.; Palmisano, G. *J. Org. Chem.* **1994**, *59*, 5556−5564.
(23) Rustaiyan, A.; Nazarians, L.; Bohlmann, F. *Phytochemistry* **1980**, *19*, 1254−1255.
(24) Burgess, E. M.; Penton, Jr., H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26−31.
(25) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327−4329.
(26) Omori, A.; Sonoda, N.; Uchida, Y.; Tsutsumu, S. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3−3237.

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