Synthesis of Virgatol and Virgatenol, Two Naturally Occurring Coumarins from *Pterocaulon virgatum* (L.) DC, and 7-(2,3-Epoxy-3-methylbutoxy)-6-methoxycoumarin, Isolated from *Conyza obscura* DC

Jan Demyttenaere,[a] Stijn Vervisch,[a] Silvia Debenedetti,[b] Jorge Coussio,[c] Dominick Maes,[a] Norbert De Kimpe*[a]

[a] Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure links 653, 9000 Ghent, Belgium
Fax +32(9)2646243; E-mail: norbert.dekimpe@ugent.be

[b] Department of Biological Sciences, University of La Plata, Calle 115 and 47, 1900 La Plata, Argentina

[c] IQUIMEFA, Faculty of Pharmacy, University of Buenos Aires, Junin 956, 1113 Buenos Aires, Argentina

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Abstract: The synthesis of a number of naturally occurring coumarins from *Pterocaulon virgatum* (L.) and *Conyza obscura* DC is described for the first time. It concerns the synthesis of 7-(2-hydroxy-3-methoxy-3-methylbutoxy)-6-methoxycoumarin (virgatol, **1**), 7-(2-hydroxy-3-methyl-3-butenyloxy)-6-methoxycoumarin (virgatenol, **2**) and 7-(2,3-epoxy-3-methylbutoxy)-6-methoxycoumarin (**3**). In addition, a straightforward synthesis of scopoletin (**4**) (7-hydroxy-6-methoxycoumarin) is reported and the synthesis of a new coumarin derivative, 6-methoxy-7-(2-oxo-3-methylbutoxy)coumarin (**7**), is described.

Keywords: virgatol, virgatenol, coumarins, natural products, Wittig reactions, epoxides

A very large number of coumarins has been isolated from plants. Several comprehensive reviews deal with the occurrence, chemistry and biochemical properties of simple and complex natural coumarins.[1–4] However, to date, most of the pharmacological and biochemical studies have been carried out on coumarin itself and on mono- and dihydroxycoumarins or methoxycoumarins.[5,6] Since the 1990's, a large number of in vivo and in vitro studies has revealed a diverse array of pharmacological and biochemical properties, some of which are of potential pharmaceutical interest, e.g. antibacterial,[7] antimutagenic and antitumor activity,[8–13] inhibitory properties on human platelet aggregation,[14] anti-HIV-PR activity,[15] effect on cell growth and differentiation.[16]

An important classification of the numerous coumarins is based on an arbitrary but biogenetically related system of the number of nuclear oxygen atoms. Thus coumarins are commonly subdivided in classes depending on their oxygenation pattern. 7-(2-Hydroxy-3-methoxy-3-methylbutoxy)-6-methoxycoumarin (virgatol, **1**), 7-(2-hydroxy-3-methyl-3-butenyloxy)-6-methoxycoumarin (virgatenol, **2**) and 7-(2,3-epoxy-3-methylbutoxy)-6-methoxycoumarin (**3**) are examples of dioxygenated coumarins derived from scopoletin (**4**) (Figure 1). The absolute optical configuration of substances **1**–**3** is not known.

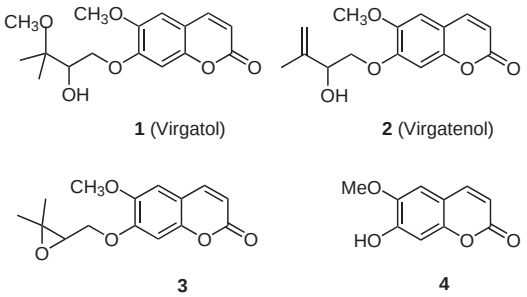

Figure 1

The former two coumarins, virgatol (**1**) and virgatenol (**2**) have been described as new isolated compounds from *Pterocaulon virgatum* (L.) DC and *P. polystachium* DC,[17,18] while the latter coumarin **3** has been isolated from *Conyza obscura* DC.[19] Although 6,7-dioxygenated coumarins are quite common in plants, the synthesis of compounds **1**–**3** has not been reported to date.

In previous publications we described the isolation and structural elucidation of a number of di- and trioxygenated coumarins from Argentine medicinal plants.[18,20,21] Our recent findings on interesting physiological activities, such as the determination of antiproliferation and differentiation activity[22] of these coumarins, encouraged us to initiate a program for synthesis of a whole range of coumarins isolated from the *Asteraceae* family.

The present report deals with the synthesis of these three coumarins virgatol (**1**), virgatenol (**2**) and 7-(2,3-epoxy-3-methylbutoxy)-6-methoxycoumarin (**3**) via a synthesis of the coumarin scopoletin (**4**) which holds a fundamental position in coumarin chemistry.

This research has been carried out in the framework of the synthesis of derivatives of natural coumarins in view of planned structure–activity studies. For the synthesis of the above-mentioned 6,7-dioxygenated coumarins it was decided to develop routes via scopoletin (**4**). Several syntheses of scopoletin have been reported in the literature.[23–25] The Pechmann synthesis of 2,4-dihydroxyanisol with ethyl 3,3-diethoxypropionate[26] afforded scopoletin in 73%. However, 2,4-dihydroxyanisol is less accessible as it needs to be synthesized in low yield from 4-nitroguaiacol acetate[23] or by the Baeyer–Villiger oxidation of isovanil-

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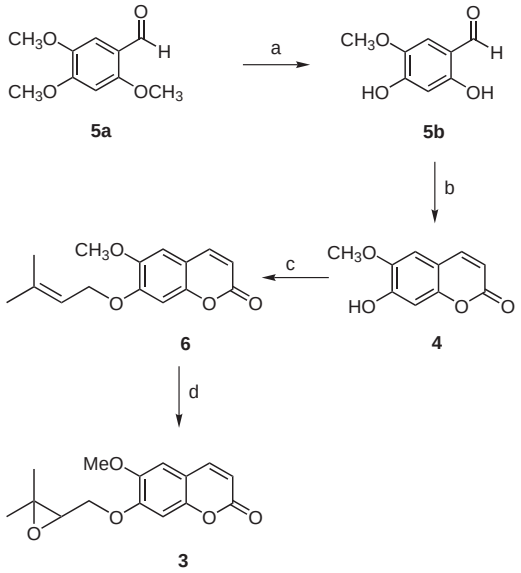
lin with peracetic acid.[26] The Gattermann reaction of this pivotal 2,4-dihydroxyanisol leads to 2,4-dihydroxy-5-methoxybenzaldehyde[23,27] which can undergo the classical coumarin synthesis. This important 2,4-dihydroxy-5-methoxybenzaldehyde (**5b**) is now readily accessible in a one-step reaction from the commercially available 2,4,5-trimethoxybenzaldehyde (**5a**) by reaction with aluminium(III) chloride in dichloromethane, followed by acid hydrolysis (Scheme 1).[28]



Scheme 1 Conditions and reagents: (a) $AlCl_3$ (8 equiv), CH_2Cl_2, r.t., 20 h, 71%; (b) $(C_6H_5)_3P{=}CHCOOCH_3$ (1.2 equiv), $Et_2NC_6H_5$, N_2, Δ, 4 h, 62%; (c) $(CH_3)_2C{=}CHCH_2Br$ (1.4 equiv), K_2CO_3, acetone, Δ, 15 h, 96%; (d) MCPBA, CH_2Cl_2, r.t., 30 min, 70%.

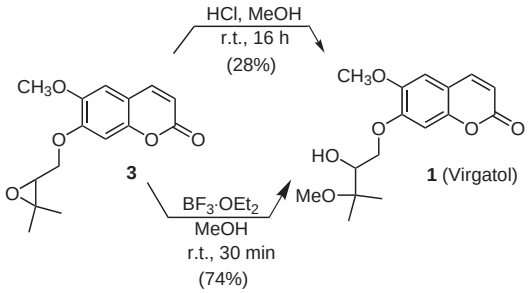
Condensation of 2,4-dihydroxy-5-methoxybenzaldehyde with (methoxycarbonyl)methylene triphenylphosphorane in *N*,*N*-diethylaniline under reflux in a nitrogen atmosphere afforded scopoletin (**4**).[28,29]

The direct purification of the reaction mixture by column chromatography (silica gel; CH_2Cl_2–MeOH, 95:5) left large amounts of product adsorbed on the column (no improvement). A better yield of scopoletin (**4**) (62%) was obtained by crystallization of the reaction mixture from methanol, making it now the preferred synthetic route from 2,4,5-trimethoxybenzaldehyde (**5a**) in two steps.

Scopoletin (**4**) is a suitable substrate for the synthesis of a number of 6,7-dioxygenated coumarins which occur naturally in plants. Scopoletin (**4**) has been converted into 6-methoxy-7-(3-methyl-2-butenyloxy)coumarin (**6**) by prenylation[30,31] which has been synthesized from aesculetin (6,7-dihydroxycoumarin) by selective prenylation at the 7-position, followed by methylation of the hydroxy group at position 6.[25,30–32] Coumarin **6** is a naturally occurring coumarin which was isolated from *Ptaeroxylon obliquum* (sneeze wood),[30,31,33] *Artemisia dracunculoides* Pursh. (from Arizona),[34] *Conyza obscura* DC,[18] *Haplopappus deserticola*[35] and *Carduus tenuiflorus*.[32] Coumarin **6** together with virgatenol (**2**) has been isolated from *Bupleurum fruticosum* roots as well.[36] Bupleurum species have a major interest in Chinese traditional medicine as Bupleuri Radix, i.e. the dried roots are one of the most frequently occurring crude drugs in the prescriptions of Chinese traditional medicine.

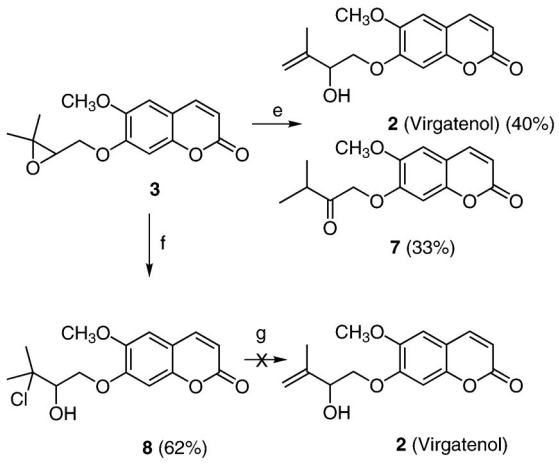
6-Methoxy-7-(3-methyl-2-butenyloxy)coumarin (**6**) was epoxidized with meta-chloroperoxybenzoic acid in dichloromethane at room temperature to afford 7-(2,3-epoxy-3-methylbutoxy)-6-methoxycoumarin (**3**) in 70% yield. This is the first synthesis of the natural coumarin **3** which has been isolated from *Conyza obscura* DC.[18]

Reaction of epoxide **3** with anhydrous hydrogen chloride in methanol at room temperature for 16 h afforded 7-(2-hydroxy-3-methoxy-3-methylbutoxy)-6-methoxycoumarin (virgatol, **1**) in 28% yield (Scheme 2). The yield of coumarin **1** could be drastically improved to 74% by reaction of coumarin **3** with boron(III) fluoride etherate in methanol at room temperature for 30 minutes.



Scheme 2

Virgatol (**1**), virgatenol (**2**) together with compound **6** and scopoletin (**4**) have been isolated from the aerial parts of *Pterocaulon virgatum* and *P. polystachium*.[16] Both *Pterocaulon* species are widely distributed in north eastern Argentina, southern Brazil and Paraguay. Aerial parts of this plant are used in Argentine traditional medicine as a digestive, emenagogue, insecticide and as agent against snake bites.[37–40]



Scheme 3 Conditions and reagents: (e) TsOH (1.5 equiv), CH_2Cl_2, r.t., 1.5 h; (f) HCl (15 equiv), Et_2O, –10 °C, 45 min; (g) *t*-BuOK, THF.

Attempts were then made to perform a synthesis of 7-(2-hydroxy-3-methyl-3-butenyloxy)-6-methoxycoumarin (**2**) (Scheme 3), a natural product from the Argentine plant *Pterocaulon virgatum* DC.[22] The reaction of 7-(2,3-epoxy-3-methylbutoxy)-6-methoxycoumarin (**3**) with a catalytic amount of *para*-toluenesulfonic acid in a two phase system of dichloromethane–water at reflux did not lead to a conversion, while the reaction with aq HCl (2 M) in the same biphasic system resulted in the formation of a mixture of unidentified products. However, when 7-(2,3-epoxy-3-methylbutyloxy)-6-methoxycoumarin (**3**) was treated with *para*-toluenesulfonic acid (1.5 equiv) in dichloromethane at room temperature for 1.5 h, a mixture of 7-(2-hydroxy-3-methyl-3-butenyloxy)-6-methoxycoumarin (**2**) (55%) and 6-methoxy-7-(2-oxo-3-methylbutoxy)coumarin (**7**) (45%) was obtained. Purification by column chromatography led to the isolation of both compounds **2** and **7** in 40 and 33% yield, respectively. It is the first time that a synthesis of the naturally occurring coumarin **2** has been described. In addition, the synthesis of a new coumarin **7**, giving a full spectroscopic characterization, is described here for the first time.

An alternative approach to the synthesis of coumarin **2** was tried via the chlorohydrin **8**. Reaction of 7-(2,3-epoxy-3-methylbutoxy)-6-methoxycoumarin (**3**) with a large excess of saturated hydrogen chloride in diethyl ether at 0 °C for 15 min afforded a complex mixture of products. The reaction of this epoxide with hydrogen chloride (5 equiv) in diethyl ether for 15 minutes gave coumarin **8** and starting material, while the reaction of hydrogen chloride (15 equiv) in diethyl ether at –10 °C for 45 min resulted in the isolation of 7-(3-chloro-2-hydroxy-3-methylbutoxy)-6-methoxycoumarin (**8**) in 62% yield. All attempts to perform a dehydrochlorination of coumarin **8** with potassium *tert*-butoxide in THF at different temperatures did not give rise to 7-(2-hydroxy-3-methyl-3-butenyloxy)-6-methoxycoumarin (**2**).

Several research works dealing with the structural determination of new isolated coumarins from natural sources are incomplete and, as a consequence, several wrong structures have been proposed. Thus, the synthesis of natural coumarins is not only a necessary tool to obtain large quantities of these compounds for biological purposes but it is a must for the unambiguous confirmation of the identity of the new isolated coumarins.

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 NMR spectrometer, operating at 270 MHz and 67.5 MHz, respectively. GC analytical and preparative separations were done with a DELSI Intersmat IGC 120 ML gas chromatograph. FT-IR spectra were recorded on a Perkin–Elmer model 1310 spectrophotometer. The Electron Impact (EI) mode mass spectra were obtained with a Varian MAT 112 mass spectrometer, operating at 70 eV. THF was distilled over sodium benzophenone ketyl prior to use. CH_2Cl_2 was distilled over calcium hydride prior to use. Et_2O was dried and distilled over sodium wire. Chromatographic separations were done using Merck Kieselgel 60 (230–400 mesh ASTM). Reactions were monitored with Merck Kieselgel 60 F_{254} precoated TLC plates (0.25 mm thickness). All other solvents and chemicals were used as supplied. (Methoxycarbonyl)methylenetriphenylphosphorane was synthesized according to the literature.[41]

Scopoletin (4)

Scopoletin (**4**) was synthesized from 2,4,5-trimethoxybenzaldehyde (**5**) as described recently by our group.[28] As an alternative for the recrystallization from MeOH or MeOH–hexane, the filtrate was treated in high vacuo (0.01 mmHg) at 60–70 °C to remove *N*,*N*-diethylaniline. The residual brown oil was dissolved in MeOH from which scopoletin crystallized. The total yield of scopoletin **4** mounted to 62%, as compared to 27% when the previous work-up procedure was applied.[28]

Mp 205–206 °C (Lit.[24] mp 204 °C, Lit.[26] 198–200 °C).

6-Methoxy-7-(3-methyl-2-butenyloxy)coumarin (6)

To a solution of scopoletin (**4**) (1.0 g, 5.20 mmol) in acetone (50 mL) was added K_2CO_3 (0.89 g, 6.44 mmol) and prenyl bromide (1.11 g, 7.45 mmol). The mixture was heated at 50 °C for 15 h. After filtration and evaporation of the solvent in vacuo, the residue was dissolved in EtOAc (50 mL) and this solution was washed with sat. aq $NaHCO_3$ (2 × 50 mL) and water (2 × 50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo to afford 6-methoxy-7-(3-methyl-2-butenyloxy)coumarin (**6**).

Yield: 1.30 g (96%); mp ($CHCl_3$–hexane) 82 °C (Lit.[24] mp 80–82 °C).

IR (KBr): 1705 (C=O), 1605, 1555 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.78 and 1.79 [each 3 H, each s, $(CH_3)_2$C=], 3.90 (3 H, s, OCH_3), 4.65 (2 H, d, *J* = 6.6 Hz, CH_2O), 5.49 (1 H, tt, J_1 = 6.6, J_2 = 1.3 Hz, =C*H*CH2), 6.25 (1 H, d, *J* = 9.2 Hz, CH=C*H*CO), 6.80 (1 H, s, 8-C*H*), 6.88 (1 H, s, 5-C*H*), 7.64 (1 H, d, *J* = 9.2 Hz, C*H*=CHCO).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 18.4 and 25.8 [each $(CH_3)_2$C=], 56.3 (OCH_3), 66.2 (CH_2O), 101.0 (8-CH), 108.0 (5-CH), 111.3 (C-4_a), 113.2 (CH=*C*HCO), 118.7 (=*C*HCH$_2$O), 139.0 [$(CH_3)_2$*C*=], 143.5 (*C*H=CHCO), 146.6 (C-6), 149.9 (C-8_a), 152.1 (C-7), 161.5 (C=O).

MS (70 eV): *m*/*z* (%) = 260 (M^+, 4), 245 (0.3), 217 (0.4), 204 (1), 193 (11), 192 (100), 191 (6), 177 (28), 164 (15), 149 (12), 135 (2), 121 (5), 92 (3), 79 (7), 69 [$(CH_3)_2C{=}CH{-}CH_2^+$, 50], 67 (11), 53 (11), 43 (13).

7-(2,3-Epoxy-3-methylbutoxy)-6-methoxycoumarin (3)

To a solution of coumarin **6** (1.90 g, 7.30 mmol) in CH_2Cl_2 (25 mL) was added MCPBA (1.50 g, 8.75 mmol; purity 70–75%). The mixture was stirred at r.t. for 30 min, after which the mixture was poured into sat. aq $NaHCO_3$ (25 mL). Extraction with CH_2Cl_2 (3 × 25 mL), drying ($MgSO_4$), filtration and evaporation afforded 7-(2,3-epoxy-3-methylbutoxy)-6-methoxycoumarin (**3**) (1.41 g, 70%). Column chromatography (benzene–$CHCl_3$, 1:1) could be used as well.

R_f = 0.06; mp ($CHCl_3$) 123–124 °C (Lit.[18] mp 125 °C).

IR (NaCl): 1720 (br, C=O), 1620, 1563, 1513 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.36 and 1.37 [each 3 H, each s, $(CH_3)_2$C], 3.17 (1 H, dd, J_1 = 6.3, J_2 = 4.0 Hz, OC*H*CH$_2$O), 3.87 (3 H, s, OCH_3), 4.08 and 4.30 (each 1 H, AMX, J_{AM} = 11.4, J_{AX} = 6.3, J_{MX} = 4.0 Hz, OCHC*H*$_2$O), 6.24 (1 H, d, *J* = 9.2 Hz, CH=C*H*CO), 6.83 (1 H, s, 8-C*H*), 6.88 (1 H, s, 5-C*H*), 7.55 (1 H, d, *J* = 9.2 Hz, C*H*=CHCO).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 19.1 and 24.6 [each $(CH_3)_2$C], 56.4 (OCH_3), 58.3 [$(CH_3)_2$*C*], 60.9 (O*C*HCH$_2$), 68.5 (OCH*C*H$_2$O), 101.5 (8-CH), 108.6 (5-CH), 112.0 (C-4_a), 113.6 (CH=*C*HCO), 143.4 (*C*H=CHCO), 146.6 (C-6), 149.7 (C-8_a), 151.8 (C-7), 161.4 (C=O).

MS (70 eV): *m*/*z* (%) = no M^+, 158 (6), 156 (20), 141 (6), 139 (19), 111 (10), 91 (2), 88 (7), 86 (42), 85 (25), 84 (68), 83 (36), 75 (6), 59 (7), 51 (31), 50 (9), 49 (100), 48 (10), 47 (20), 43 (23).

7-(2-Hydroxy-3-methoxy-3-methylbutoxy)-6-methoxycoumarin (Virgatol, 1)

To a solution of 7-(2,3-epoxy-3-methylbutoxy)-6-methoxycoumarin (**3**) (0.16 g, 0.58 mmol) in anhyd MeOH (5 mL) was added an excess of a solution of anhyd hydrogen chloride in anhyd MeOH. The mixture was stirred at r.t. for 16 h. After evaporation of the solvent in vacuo, the residue was column chromatographed with toluene–*i*-PrOH (96:4) to give 7-(2-hydroxy-3-methoxy-3-methylbutoxy)-6-methoxycoumarin (**1**).

Yield: 0.05 g (28%).

An alternative procedure for the synthesis of 7-(2-hydroxy-3-methoxy-3-methylbutoxy)-6-methoxycoumarin (**1**) consists of the treatment of a solution of 7-(2,3-epoxy-3-methylbutoxy)-6-methoxycoumarin (**3**) (0.14 g, 0.51 mmol) in anhyd MeOH (7 mL) with $BF_3{\cdot}OEt_2$ (0.10 mL). The reaction mixture was stirred at r.t. for 30 min. The mixture was evaporated to half of its volume, and then diluted with aq NaOH (0.1 M) (5 mL). After extraction with Et_2O (2 × 10 mL), drying ($MgSO_4$), filtration and evaporation, 7-(2-hydroxy-3-methoxy-3-methylbutoxy)-6-methoxycoumarin (**1**) was obtained. No further purification was needed.

Yield: 0.12 g (77%); mp ($CHCl_3$) 60–61 °C (Lit.[16] mp 60–62 °C).

IR (NaCl): 3670–3160 (br, OH), 2980, 1720 (C=O), 1615, 1560, 1515 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.26 [6 H, s, $(CH_3)_2C$], 3.0 [1 H, br s, CH(O*H*)CH_2O], 3.27 [3 H, s, C(OC*H*$_3$)], 3.88 (3 H, s, ArOC*H*$_3$), 4.01 [2 H, m, C*H*(OH)CH_2O and CH(OH)*H*CHO], 4.26 [1 H, dd, *J* = 9.2, *J* = 2.0 Hz, CH(OH)HC*H*O], 6.27 (1 H, d, *J* = 9.4 Hz, CH=C*H*CO), 6.85 (1 H, s, 8-C*H*), 6.87 (1H, s, 5-C*H*), 7.61 (1 H, d, *J* = 9.4 Hz, C*H*=CHCO).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 20.4 and 21.2 [each (CH_3)$_2$C], 49.3 [C(OCH_3)], 56.4 (ArOCH_3), 70.7 [CH(OH)CH_2O], 74.9 [*C*H(OH)CH_2O], 76.1 [$(CH_3)_2C$], 101.5 (8-CH), 108.4 (5-CH), 111.7 (C-4$_a$), 113.6 (CH=*C*HCO), 143.3 (*C*H=CHCO), 146.7 (C-6), 149.8 (C-8$_a$), 152.2 (C-7), 161.4 (C=O).

MS (70 eV): *m*/*z* (%) = 308 (M^+, 13), 277 (3), 193 (12), 192 (59), 191 (6), 177 (10), 164 (6), 149 (9), 94 (5), 85 (7), 74 (9), 73 (100), 71 (8), 69 (11), 59 (8), 57 (12), 45 (14), 43 (18).

7-(2-Hydroxy-3-methyl-3-butenyloxy)-6-methoxycoumarin (2) (Virgatenol) and 6-Methoxy-7-(2-oxo-3-methylbutoxy)coumarin (7)

To a solution of 7-(2,3-epoxy-3-methylbutoxy)-6-methoxycoumarin (**3**) (0.10 g, 0.36 mmol) in CH_2Cl_2 (10 mL) was added TsOH (0.10 g, 0.54 mmol). The mixture was stirred at r.t. for 1.5 h after which the mixture was poured in aq NaOH (2 M; 5 mL). After extraction with CH_2Cl_2 (3 × 15 mL), drying ($MgSO_4$), filtration and evaporation of the solvent in vacuo, the reaction mixture was found to consist of a mixture of 7-(2-hydroxy-3-methyl-3-butenyloxy)-6-methoxycoumarin (**2**) and 6-methoxy-7-(2-oxo-3-methylbutoxy)coumarin (**7**) in a ratio of 55:45. This mixture was separated by column chromatography (CH_2Cl_2–MeOH, 98.5:1.5) to afford 6-methoxy-7-(2-oxo-3-methylbutoxy)coumarin (**7**) [33 mg (33%); R_f = 0.23] and 7-(2-hydroxy-3-methyl-3-butenyloxy)-6-methoxycoumarin (**2**) [40 mg (40%); R_f = 0.09].

7-(2-Hydroxy-3-methyl-3-butenyloxy)-6-methoxycoumarin (2) (Virgatenol)

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.84 [3 H, s, (C*H*$_3$)C=], 3.90 (3 H, s, OCH_3), 3.93–4.18 (2 H, m, C*H*(OH)CH_2O and CH(OH)*H*CHO], 4.56 (1 H, dd, J_1 = 8.1, J_2 = 3.0 Hz, CH(OH)HC*H*O], 5.04 and 5.18 (each 1 H, each s, C=CH_2), 6.30 (1 H, d, *J* = 9.6 Hz, CH=C*H*CO], 6.87 (2 H, s, 8-CH and 5-CH), 7.62 (1 H, d, *J* = 9.6 Hz, C*H*=CHCO).

MS (70 eV): *m*/*z* (%) = 276(M^+, 36), 245 (1), 206 (7), 201 (12), 199 (15), 193 (14), 192 (100), 191 (10), 190 (8), 185 (7), 183 (12), 177 (35), 164 (17), 152 (8), 149 (29), 113 (7), 86 (21), 79 (7), 71 (18), 71 (24), 69 (21), 58 (8), 57 (31), 56 (7), 55 (13), 51 (16), 47 (6), 44 (40), 43 (40).

6-Methoxy-7-(2-oxo-3-methylbutoxy)coumarin (7)

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.20 [6 H, d, *J* = 6.9 Hz, (C*H*$_3$)$_2$CH], 2.89 [1 H, septet, *J* = 6.9 Hz, $(CH_3)_2$C*H*], 3.93 (3 H, s, OCH_3), 4.83 (2 H, s, COCH_2O), 6.30 (1 H, d, *J* = 9.6 Hz, CH=C*H*CO), 6.64 and 6.90 (each 1 H, each s, 8-CH and 5-CH), 7.62 (1 H, d, *J* = 9.6 Hz, C*H*=CHCO).

MS (70 eV): *m*/*z* (%) = 276 (M^+, 2), 261 ($M^+ - CH_3$, 1), 248 (M^+ – CO, 1), 234 (4), 227 (7), 221 (4), 220 (10), 219 (12), 206 (8), 205 (4), 192 (7), 191 (8), 183 (4), 169 (4), 167 (7), 165 (4), 164 (4), 163 (5), 161 (4), 155 (6), 150 (5), 149 (29), 141 (7), 139 (8), 135 (11), 129 (20), 127 (8), 125 (7), 123 (6), 113 (14), 112 (8), 111 (18), 110 (5), 109 (8), 107 (6), 105 (7), 101 (5), 99 (16), 98 (10), 97 (20), 96 (9), 95 (11), 87 (6), 86 (6), 85 (32), 84 (13), 83 (26), 82 (10), 81 (13), 79 (7), 71 (55), 70 (19), 69 (37), 67 (11), 58 (8), 57 (100), 56 (21), 55 (51), 43 (75), 42 (11).

7-(3-Chloro-2-hydroxy-3-methylbutoxy)-6-methoxycoumarin (8)

To a stirred and cooled (–10 °C) solution of 7-(2,3-epoxy-3-methylbutoxy)-6-methoxycoumarin (**3**) (0.10 g, 0.36 mmol) in THF (10 mL) was added a sat. solution of HCl (5.40 mmol) in Et_2O. The mixture was stirred at this temperature for 45 min after which the solvents were evaporated in vacuo. Column chromatography (hexane–EtOAc, 3:7) of the residue gave pure 7-(3-chloro-2-hydroxy-3-methylbutoxy)-6-methoxycoumarin (**8**).

Yield: 0.070 g (62%).

IR (NaCl): 3620–3140 (br, OH), 1720 (br, C=O) cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.68 and 1.69 [each 3 H, each s, (C*H*$_3$)$_2$C], 2.8 (1 H, br s, OH), 3.89 (3 H, s, OCH_3), 4.07–4.16 [2 H, m, C*H*(OH)CH_2O and CH(OH)*H*CHO], 4.41 (1 H, dd, J_1 = 8.6, J_2 = 1.7 Hz, CH(OH)HC*H*O], 6.29 (1 H, d, *J* = 9.2 Hz, CH=C*H*CO), 6.86 and 6.87 (each 1 H, each s, 8-C*H* and 5-C*H*), 7.61 (1 H, d, *J* = 9.2 Hz, C*H*=CHCO).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 28.3 and 29.4 [(CH_3)$_2$C=], 56.4 (OCH_3), 70.7 (OCH_2), 71.0 [$(CH_3)_2C$], 76.3 [CH(OH)], 101.9 (8-CH), 108.4 (5-CH), 112.1 (C-4$_a$), 113.9 (CH=*C*HCO), 143.2 (*C*H=CHCO), 146.7 (C_q), 149.7 (C_q), 151.7 (C_q), 161.2 (C=O).

MS (70 eV) : *m*/*z* (%) = 312/4 (M^+, 19), 235 (5), 193 (15), 192 (100), 191 (11), 190 (5), 177 (29), 164 (15), 149 (12), 79 (6), 71 (9), 69 (15), 57 (9), 55 (7), 51 (5), 44 (5), 43 (26).

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