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Synthesis of Fercoprolone, a Degraded Prenylated Coumarin[1]

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Abstract: The degraded prenylated coumarin fercoprolone (**1a**) was prepared from 4-hydroxycoumarin in five steps and overall 13% yield. Key steps were the oxidative addition of 4-hydroxycoumarin to an alkene and the Barbier-type allylation of a ketone carbonyl. Natural fercoprolone is racemic. The relative stereochemistry of the glycol moiety was tentatively assigned on the basis of mechanistic considerations, further backed up by the stereospecific and biomimetic synthesis of model compounds.

The oxidative addition of active methylene compounds to alkenes has been extensively investigated.[2] Though the reaction has been employed in the total synthesis of natural products,[3] there is a surprising shortage of examples where natural β-dicarbonyl compounds were used as the active methylene component. We recently reported an expeditious entry to dihydrofurano[3,2-*c*]coumarins based on the oxidative addition of 4-hydroxycoumarin, the enol form of a natural β-dicarbonyl compound, to alkenes.[1] The reaction has great potential for natural product synthesis, owing to its versatility in terms of the substitution and functionalization pattern of the adducts, and to the occurrence of a furanocoumarin moiety in several meroterpenoids.[4] We have now implemented this strategy with the first total synthesis of fercoprolone (**1**), a degraded prenylated coumarin isolated from giant fennel (*Ferula communis* L.).[5]

Fercoprolone was isolated from a Turkish collection of the plant,[5] but has been suggested to be biogenetically related to ferulenol[6] (**2**, Scheme 1), the major toxin from the Sardinian population of *F. communis*.[7] The availability of fercoprolone was important in the context of studies aimed at unraveling the complex ecology of this plant, which is toxic to mammals but hosts an edible mushroom (*Pleurothus eryngii* var. *Ferulae* Lanzi) and is the specific ovoposition site of the Corsican swallowtale butterfly (*Papilio hospiton* Géné), a Sardo-Corsican endemism, considered one of the most endangered insect species in the world.[8]

Fercoprolone was isolated in racemic form, and the stereochemistry of its glycol moiety was not assessed. Our synthesis provided both diastereomers corresponding to the plain formula **1**, and the stereochemical assignment was then tentatively done on the basis of mechanistic considerations, further backed up by the stereospecific and biomimetic synthesis of model compounds. The retrosynthetic plan (Scheme 1) has as a key intermediate the homoallylic alcohol **3**, available from the allylation of the methylketone **4**, in turn prepared from the oxidative adduct of 4-hydroxycoumarin and 3-buten-2-ol.

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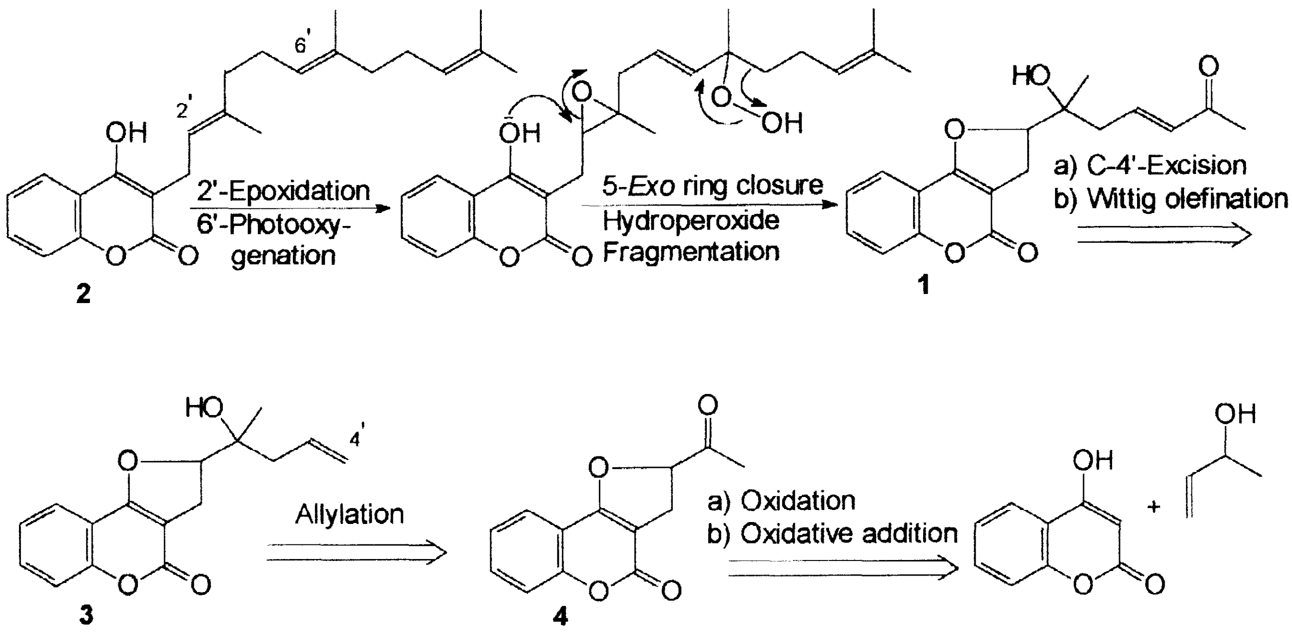
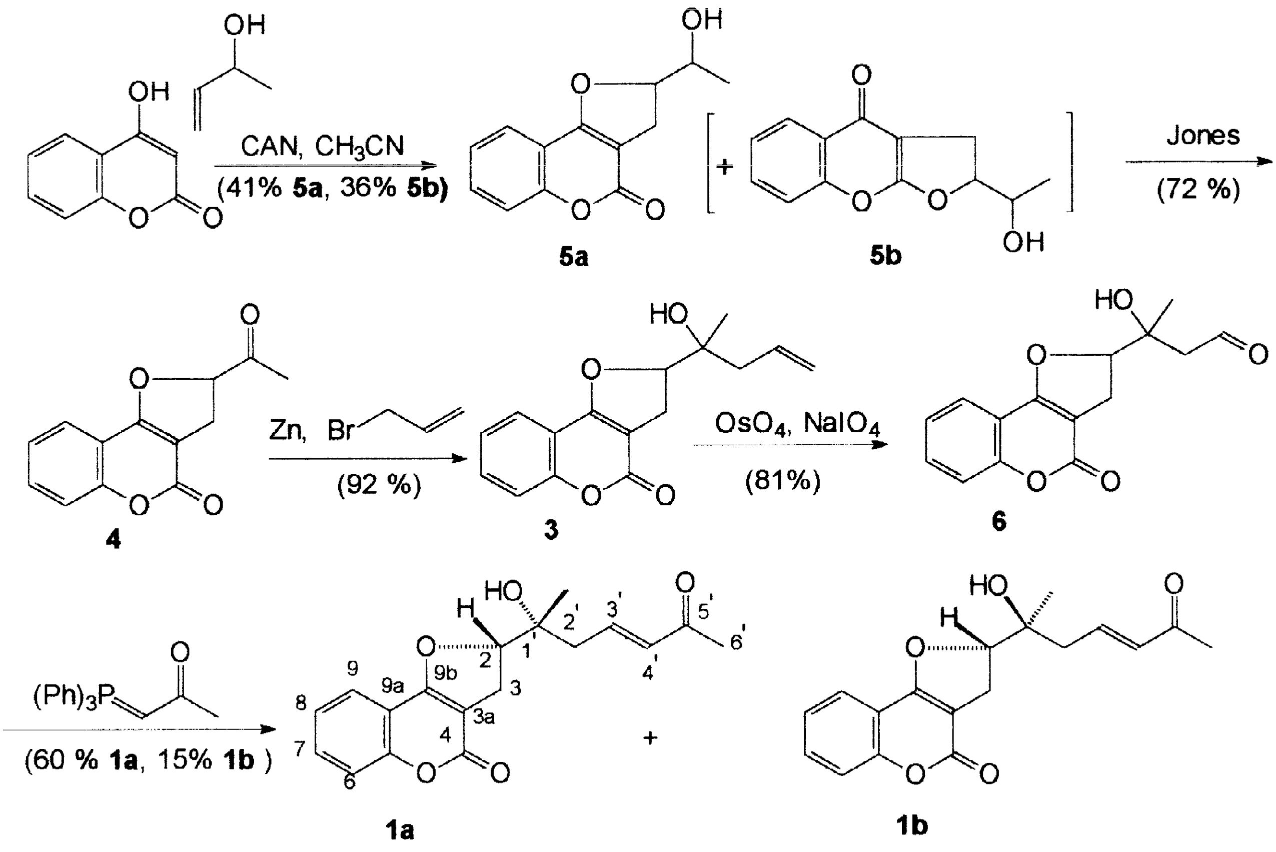


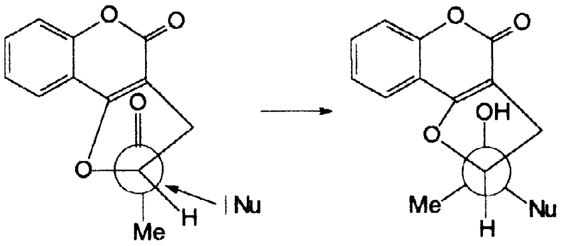
Scheme 1. Possible biogenetic relationship between ferulenol (**2**) and fercoprolone (**1**), and retrosynthetic analysis of fercoprolone.

Treatment of 4-hydroxycoumarin with 3-buten-2-ol and cerium (IV) ammonium nitrate (CAN) in acetonitrile at room temperature gave as the major reaction product (41%) the angular adduct **5a**, obtained as a *ca* 2.5:1 mixture of diastereomers (Scheme 2). A more polar mixture of linear adducts (**5b**) was also obtained (36% yield), resulting from the trapping of the addition radical by the lactone carbonyl. This unusual reaction course is unprecedented in β-ketoesters, but had already been observed with 4-hydroxycoumarin.[1] No substantial improvement of the ratio between angular and linear adducts could be achieved changing solvent or metal oxidant (manganese (III) acetate hydrate, MAH)[3] and varying the temperature. These studies highlighted the critical role of the solvent and the concentration, since reproducible yields could only be obtained in acetonitrile and with diluted solutions (*ca* 1%) of 4-hydroxycoumarin. The mixture of angular adducts was then oxidized with Jones reagent, affording the crystalline ketone **4**. Allylation of **4** with Grignard or organolithium reagents gave mixtures of products owing to competitive attack on the lactone carbonyl, but complete chemoselectivity was observed under Barbier-type conditions.[9] Thus, treatment of **4** with allyl bromide and activated zinc in sat. aq. NH_4Cl-THF at room temperature gave, in excellent yield, the homoallylic alcohol **3** as an inseparable 4:1 mixture of diastereomers. Attempts to improve the diastereomeric ratio by changing the allyl metal reagent failed, since allyltrimethylsilane and allyltributyltin gave an almost equimolar mixture of diastereomers under a variety of conditions ($MgBr_2$, $BF_3.Et_2O$, $SnCl_4$ catalysis; normal or inverse addition). Oxidative sacrifice of the terminal olefin carbon *via* a tandem hydroxylation-oxidative fragmentation with OsO_4-$NaIO_4$[10] was followed by a stereoselective Wittig olefination of the aldehyde **6** with 1-triphenylphosphoranylidene-2-propanone, eventually affording fercoprolone as a mixture of *E*-diastereomers. Their observed ratio (4:1, ^1H NMR) reflected the diastereoselection of the Barbier allylation, and the two isomers could be separated by multiple elution preparative TLC. The NMR spectra of **1a** and **1b** were very similar, but diagnostic differences could be observed for the ^1H-NMR signals of H-2'a,b, and the 1'-methyl ($\Delta\delta$ = 0.11 ppm). In the ^{13}C NMR spectrum, the major differences regarded the resonances of C-2' ($\Delta\delta$ = 1.0 ppm) and the 1'-methyl ($\Delta\delta$ = 0.8 ppm). Comparison of the spectroscopic data with those reported for the natural product,[5] identified the major isomer with fercoprolone.



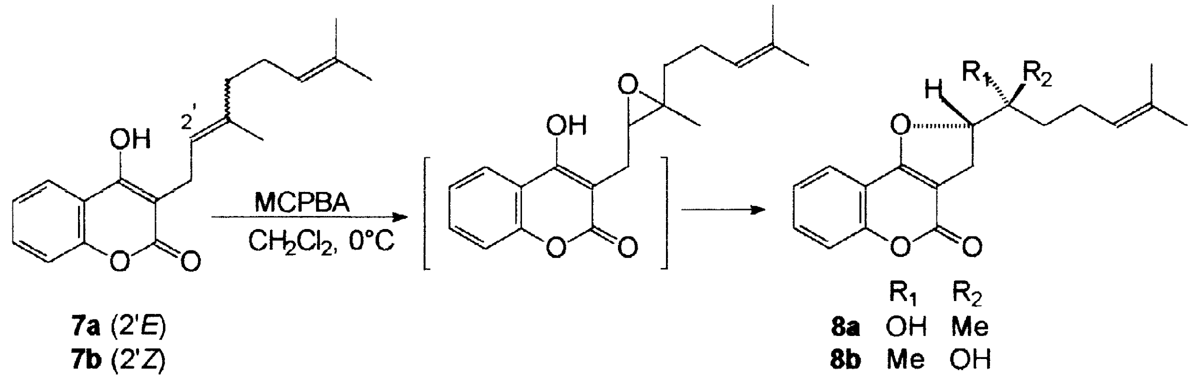
Scheme 2. Synthesis of fercoprolone (**1a**)

Attempts to prepare derivatives of the natural product amenable to X-ray analysis failed, but clues to its configuration could be obtained by mechanistic considerations. The stereochemical aspects of Barbier-type allylations have been the subject of many studies, which have highlighted the role of the non-chelate Felkin-Anh[11] transition state for the addition to α-alkoxycarbonyl compounds.[12] This especially holds in aqueous solution, where water solvation of metal ions competes with chelate formation.[12] For the allylation of **4**, the mesomeric effect of the coumarin carbonyl should deplete electron density from the ethereal oxygen, further reinforcing the attainment of a non-chelate transition state and favoring the formation of an *anti*-(= *erythro*) adduct (Scheme 3). This suggested that natural fercoprolone had an *anti* stereochemistry.



Scheme 3. Felkin-Anh model for the nucleophilic attack to methylketone **4** (Nu=allyl group).

In order to confirm these mechanistic insights, we synthesized in a stereospecific way model compounds of the dihydrofuranocoumarin moiety of fercoprolone. Our starting materials were 3-geranyl- and 3-neryl-4-hydroxycoumarin (**7a** and **7b**, respectively, scheme 4). Epoxidation of the "proximal" 2'-double bond would give an epoxide which might undergo intramolecular opening by action of the nucleophilic enol hydroxyl, overall translating the *trans-cis* geometry of **7a,b** into *anti/syn* stereoisomerism of the furanocoumarin products (Scheme 4). A reaction of this type is presumably involved in the formation of fercoprolone from ferulenol (Scheme 1), and we hoped that the spectroscopic differences between the adducts would parallel those observed between the synthetic fercoprolone isomers, allowing a tentative stereochemical assignment. The oxidative cyclization of meroterpenoids of the prenyl-type has been extensively investigated in connection with the synthesis of hemiterpenoid quinolone alkaloids from prenyl derivatives of 4-hydroxy-2-quinolinone, an isoster of 4-hydroxycoumarin.[13] In these compounds, treatment with peracids gives an unstable epoxide, which undergoes *in situ* intramolecular cyclization induced by the lactam oxygen, eventually affording a mixture of linear furano- and pyranoquinolones. The lack of regioselectivity in epoxide opening as well as the involvement of the lactam oxygen were points of concern for our scheme, further compounded by problems of chemoselectivity in the epoxidation, due to the greater π-nucleophilicity of the terminal double bond of prenyl residues compared to the internal ones.[14]



Scheme 4. Synthesis of the model furanocoumarins **8a,b**.

In the event, treatment of geranyl- and neryl 4-hydroxycoumarin (**7a** and **7b**, respectively)[6c] with MCPBA in CH_2Cl_2 at room temperature gave a complex mixture, but when the reaction was carried out at 0°C and in the presence of a buffering agent (NaOAc), the angular dihydrofurocoumarins **8a** and **8b** could be obtained in a stereospecific way (Scheme 4). In sharp contrast to the results reported with 3-prenyl-4-hydroxyquinolones,[13] linear adducts and pyranocoumarins could not be detected in the reaction mixture (^1H NMR analysis). The low overall yield (10-14%) of the reaction was due to the formation of mixtures of diepoxides, and to the need to quench the reaction before complete conversion to limit overoxidation. Though linear dihydrofuroquinolines have been reported to rearrange to their corresponding angular isomer in the presence of strong bases,[13] the oxidative cyclization of **7a,b** is all the same remarkable for its stereospecificy and the absence of pyran derivatives. The stereochemical outcome of the cyclization is in accordance with a concerted mechanism of the 5-*exo-trig* type for the epoxide opening. Thus **8a**, derived from 3-geranyl-4-hydroxycoumarin (**7a**), should belong to the *anti* (= *erythro*) series, whereas **8b**, derived from 3-neryl-4-hydroxycoumarin (**7b**), should be the *syn* (= *threo*) isomer. The diastereomeric furocoumarins **8a** and **8b** showed spectroscopic differences which paralleled those observed between fercoprolone and its diastereoisomer, and between the major and the minor isomer of the allylation product **3**.[15] Natural fercoprolone and the major diastereomer of **3** could thus be related to the furanocoumarin obtained from the oxidative cyclization of 3-geranyl-4-hydroxycoumarin, and should belong to the *anti* series (**1a**). Though our evidence for the stereochemical assignment of fercoprolone is circumstantial, both the mechanistic and the spectroscopic argument point to the same result, namely an *anti* stereochemistry for the natural product, in accordance with its speculative biogenetic derivation from ferulenol.[16]

In conclusion, we have developed a concise synthesis of the prenylated coumarin fercoprolone that features as key steps the oxidative addition of 4-hydroxycoumarin to an alkene and the chemoselective Barbier-type allylation of a ketone carbonyl. The remarkable regioselectivity observed in the oxidative cyclization of prenylated 4-hydroxycoumarins with peracids is surprising and is warrant of further investigation to evaluate the stereoelectronic factors responsible for the marked differences with prenylated 4-hydroxy-2-quinolones.

EXPERIMENTAL

General Methods. Anhydrous conditions were achieved (when indicated) by flame-drying flasks and equipments. Reactions were monitored by TLC on Merck 60 F254 (0.25 mm) plates, which were visualized by UV inspection and stained with a 5% $KMnO_4$ solution. Merck silica gel was used for open-column- and medium pressure liquid chromatography (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. A Waters microPorasil column (0.8 x 30 cm) was used for semipreparative HPLC, with detection by a Waters differential refractometer 340. Melting points were obtained on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on a Bruker AC-300 spectrometer at 25°C. CIMS were performed on a Finnigan-MAT TSQ70 with isobutane as reactant gas. Commercially available reagents and solvents were used without further purification, unless otherwise noted. CH_2Cl_2 was dried by distillation from P_4O_{10}, THF by distillation from Na-benzophenone, and DMF by distillation from CaH_2. Zinc powder was activated by stirring with 2% HCl for 120 sec., followed by filtration and sequential washing with water (until pH 7), acetone, and ether.

Reaction of 4-hydroxycoumarin and 3-buten-2-ol. To a stirred suspension of 4-hydroxycoumarin (7.5 g, 46 mmol) in acetonitrile (700 mL), 3-buten-2-ol (2.66 g, 37 mmol, 0.8 mol equiv) was added, and a solution of cerium ammonium nitrate (CAN, 63 g, 115 mmol, 2.5 mol equiv) in acetonitrile (300 mL) was then added dropwise during *ca* 15 min. The reaction mixture was concentrated at reduced pressure to *ca* half the original volume, diluted with water (400 ml) and extracted with EtOAc. The organic phase was washed with sat. Na_2CO_3 and brine. After drying (Na_2SO_4) and removal of the solvent, the residue was purified by MPLC. Elution with hexane-EtOAc 6:4 gave 4.32 g **5a** (41%) and 3.25 g **5b** (30%).
2,3-Dihydro-2-(1-hydroxyethyl)-4H-furo[3,2-c][1]benzopyran-4-one (**5a**) (*ca* 2.5:1 mixture of diastereomers): mp 132-135°C (ether); ^{1}H-NMR ($CDCl_3$) (major isomer) δ 7.72 (m, 1H, H-9), 7.52 (m, 1H, H-7), 7.41 (m, 1H, H-6), 7.24 (m, 1H, H-8), 4.96 (ddd, *J* = 10.1, 8.1, 6.3 Hz, 1H, H-2), 3.99 (m , 1H, H-1'), 3.23 (dd, *J* = 15.2, 10.1 Hz, 1H, H-3a), 2.97 (dd, *J* = 15.2, 8.0 Hz,1H, H-3b), 2.23 (br s, 1H, OH), 1.36 (d, *J* = 6.4 Hz, 3H, H-2'); ^{13}C-NMR ($CDCl_3$) (major isomer) δ 90.9 (d, C-2), 28.9 (t, C-3), 102,4 (s, C-3a), 160.5 (s, C-4), 154.9 (s, C-5a), 116.9 (d, C-6), 132.4 (d, C-7), 123.9 (d, C-8), 122.6 (d, C-9), 112.3 (s, C-9a), 166.3 (s, C-9b), 69.4 (d, C-1'), 18.3 (q, C-2'); (minor isomer): δ 90.4 (d, C-2), 26.9 (t, C-3), 102,4 (s, C-3a), 160.5 (s, C-4), 154.9 (s, C-5a), 116.9 (d, C-6), 132.3 (d, C-7), 123.9 (d, C-8), 122.6 (d, C-9), 112.3 (s, C-9a), 166.3 (s, C-9b), 68.0 (d, C-1'), 17.8 (q, C-2'); CIMS: 233 $(M+H)^+$. Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.22; H, 5.21. Found: C, 67.45; H, 5.20.
2,3-Dihydro-2-(1-hydroxyethyl)-5H-furo[3,2-b][1]benzopyran-4-one (**5b**) (*ca* 1:1 mixture of diastereomers): mp 128-130°C (ether); ^{1}H-NMR ($CDCl_3$) (isomer a): δ 8.16 (m, 1H, H-5), 7.52 (m, 1H, H-7), 7.37 (m, 1H, H-6), 7.30 (m, 1H, H-8), 4.17 (ddd, *J* = 10.1, 8.1, 6.3 Hz, 1H, H-2), 4.17 (m , 1H, H-1'), 3.20 (br s, 2H, H-3a + H-3b), 1.26 (d, *J* = 6.4 Hz, 3H, H-2'); (isomer b): δ 8.15 (m, 1H, H-5), 7.55 (m, 1H, H-7), 7.36 (m, 1H, H-6), 7.26 (m, 1H, H-8), 3.96 (ddd, *J* = 10.1, 8.1, 6.3 Hz, 1H, H-1') 3.00 (m, 2H, H-3a + H-3b), 1.31 (d, *J* = 6.4 Hz, 3H, H-2'); ^{13}C-NMR ($CDCl_3$): δ 88.2. 88.8 (d, C-2), 27.2, 27.1 (t, C-3), 95.1 (s, C-3a), 175.0 (s, C-4), 123.7 (s, C-4a), 125.7 (d, C-5), 125.5 (d, C-6), 132.4, 132.5 (d, C-7), 117.2 (d, C-8), 153.0 (s, C-8a), 168.9, 168.8 (s, C-8b), 67.7, 69.1 (d, C-1'), 17.7, 18.1 (q, C-2'); CIMS: 233 $(M+H)^+$.

2,3-Dihydro-2-(1-oxoethyl)-4H-furo[3,2-c][1]benzopyran-4-one (**4**). To a solution of the angular adduct **5a** (100 mg, 0.43 mmol) in acetone (10 mL), Jones reagent was added dropwise (*ca* 15 drops) until a persistent orange colour of the reaction mixture. The reaction was then worked up by the addition of isopropanol to quench the excess of oxidant, diluted with water, and extracted with EtOAc. The organic phase was washed with sat. aq. $NaHCO_3$ and brine. After drying (Na_2SO_4) and removal of the solvent, the residue was crystallized from ether, to give 71 mg **4** (72%) as a white powder. Mp 137-140 °C (ether); IR (KBr) 1717, 1647, 1609, 1497, 1410, 1026, 750, 727 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.75 (dd, *J* = 7.7, 1.4 Hz, 1H, H-9), 7.62 (ddd, *J* = 7.4, 7.0, 1.3 Hz, 1H, H-7), 7.42 (d, *J* = 8.2 Hz, 1H, H-6), 7.35 (dd, *J* = 7.6, 7.5 Hz, 1H, H-8), 5.40 (dd, *J* = 11.5, 7.5 Hz, 1H, H-2), 3.49 (dd, *J* = 15.9, 11.3 Hz, 1H, H-3a), 3.31 (dd, *J* = 15.7, 7.4 Hz,1H, H-3b), 2.38 (s, 3H, H-2'); ^{13}C-NMR ($CDCl_3$) δ 88.1 (d, C-2), 26.0 (t, C-3), 101.7 (s, C-3a), 160.0 (s, C-4), 155.0 (s, C-5a), 117.1 (d, C-6), 132.7 (d, C-7), 124.1 (d, C-8), 122.5 (d, C-9), 112.0 (s, C-8a), 166.0 (s, C-9b), 204.0 (s, C-1'), 29.9 (q, C-2'); CIMS: 231 (M+H)$^+$. Anal. Calcd for $C_{13}H_{10}O_4$: C, 67.81; H, 4.38. Found: C, 67.70; H, 4.39.

2,3-Dihydro-2-(1-hydroxy-1-methylbut-3-enyl)-4H-furo[3,2-c][1]benzopyran-4-one (**3**). To a solution of methyl ketone **4** (1.80 g, 7.8 mmol) in a mixture of THF (10 mL) and sat. aq. NH_4Cl (15 mL), activated zinc (1.02 g g, 15.6 mmol, 2 mol equiv) and allyl bromide (1.33 mL, 1.95 g, 15.6 mmol) were added. After stirring at room temp. for 30 min, the reaction was worked up by filtration (synthered glass filter), dilution with brine and extraction with EtOAc. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (hexane-EtOAc 6:4) to give 1.94 g (92%) **6** as a colorless oil. IR (KBr disk) 3435, 1726, 1647, 1500, 1415, 1030, 916, 752 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (major isomer) 7.68 (dd, *J* = 7.7, 1.8 Hz, 1H, H-9), 7.56 (ddd, *J* = 8.7, 7.3, 1.8 Hz, 1H, H-7), 7.36 (br d, *J* = 8.4 Hz, 1H, H-6), 7.28 (ddd, *J* = 9.2, 7.7, 1.5 Hz, 1H, H-8), 5.96 (dddd, *J* = 16.0, 11.0, 8.0, 7.2 Hz, 1H, H-3'), 5.23 (dd, *J* = 10.8, 2.1 Hz, 1H, H-4'a), 5.21 (dd, *J* = 16.3, 2.1 Hz, 1H, H-4'b), 4.97 (dd, *J* = 10.2, 8.7 Hz, 1H, H-2), 3.23 (dd, *J* = 15.4, 8.7 Hz, 1H, H-3a), 3.13 (dd, *J* = 15.4, 10.1 Hz, H-3b), 2.44 (dd, *J* = 19.9, 7.2 Hz, 1H, H-2'a), 2.32 (dd, *J* = 14.0, 8.0 Hz, 1H, H-2'b), 2.05 (br s, 1H, OH), 1.37 (s, 3H, 1'-Me); (minor isomer) 7.69 (dd, *J* = 7.7, 1.8 Hz, 1H, H-9), 7.58 (ddd, *J* = 8.7, 7.3, 1.8 Hz, 1H, H-7), 7.40 (br d, *J* = 8.4 Hz, 1H, H-6), 7.30 (ddd, *J* = 9.2, 7.7, 1.5 Hz, 1H, H-8), 5.92 (dddd, *J* = 16.0, 11.0, 8.0, 7.2 Hz, 1H, H-3'), 5.40 (dd, *J* = 10.8, 2.1 Hz, 1H, H-4'a), 5.20 (dd, *J* = 16.3, 2.1 Hz, 1H, H-4'b), 5.00 (dd, *J* = 10.2, 8.7 Hz, 1H, H-2), 3.47 (dd, *J* = 15.4, 8.7 Hz, 1H, H-3a), 3.28 (dd, *J* = 15.4, 10.1 Hz, H-3b), 2.37 (m, H-2'a,b), 2.05 (br s, 1H, OH), 1.23 (s, 3H, 1'-Me); ^{13}C-NMR ($CDCl_3$) Major isomer: δ 91.9 (d, C-2), 27.4 (t, C-3), 102.5 (s, C-3a), 162.4 (s, C-4), 154.8 (s, C-5a), 116.9 (d, C-6), 132.5 (d, C-7), 124.2 (d, C-8), 122.5 (d, C-9), 112.2 (s, C-9a), 166.3 (s, C-9b), 73.0 (s, C-1'), 42.3 (t, C-2'), 140.6 (d, C-3'), 114.4 (t, C-4'), 22.0 (q, 1'-Me); Minor isomer: δ 91.8 (d, C-2), 27.5 (t, C-3), 102.5 (s, C-3a), 162.4 (s, C-4), 154.8 (s, C-5a), 116.9 (d, C-6), 132.6 (d, C-7), 124.1 (d, C-8), 122.7 (d, C-9), 112.2 (s, C-9a), 166.4 (s, C-9b), 73.3 (s, C-1'), 43.2 (t, C-2'), 140.8 (d, C-3'), 114.5 (t, C-4'), 21.2 (q, 1'-Me); CIMS: 273 (M+H)$^+$. Anal. Calcd for $C_{16}H_{16}O_4$: C,70.56; H, 5.39. Found: C, 70.75; H, 5.37.

2,3-Dihydro-2-(1-Hydroxy-1-methyl-3-oxopropyl)-4H-furo[3,2-c][1]benzopyran-4-one (**6**). To a stirred solution of **3** (230 mg, 0.80 mmol) and OsO_4 (14.3 mg, 0.07 mol equiv) in ether (3 mL), $NaIO_4$ (380 mg, 1.76 mmol, 2.2 mol equiv) was added in small portions over 40 min. After further stirring for 80 min at room temp., the yellow solution was extracted with EtOAc and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromatography (hexane-EtOAc 6:4) to give 182 mg **6** (80%) as an unstable oil, which was directly used the next step. ^{1}H-NMR ($CDCl_3$) (78:22 mixture of diastereomers, major compound) δ 9.93 (t, *J* = 1.6 Hz, 1H, H-3'), 7.70 (m, 1H, H-9), 7.58 (ddd, *J* = 8.7, 7.3, 1.8 Hz, 1H, H-7), 7.30 (m, 1H, H-6), 7.28 (ddd, *J* = 9.2, 7.7, 1.5 Hz, 1H, H-8), 5.08 (t, *J* = 9.3 Hz, 1H, H-2), 3.18 (br s, 2H, H-3a + H-3b), 2.85 (dd, *J* = 16.8, 1.5 Hz, 1H, H-2'a), 2.71 (dd, *J* = 16.7, 2.0 Hz, 1H, H-2'b), 1.42 (s, 3H, 1'-Me); (Minor compound) d 9.98 (t, J = 1.6 Hz, 1H, H-3'), 2.88 (br d, J = 17.0 Hz, 1H, H-2'a), 2.77 (br d, J = 17.0 Hz, 1H, H-2'b), 1.39 (s, 3H, 1'-Me). CIMS: 275 (M+H)$^+$.

E-2,3-Dihydro-2-(1-Hydroxy-1-methyl-5-oxo-3-hexenyl)-4H-furo[3,2c] [1] benzopyran -4-one (Fercoprolone, **1***)*. To a solution of the aldehyde **6** (200 mg, 0.73 mmol) in toluene (20 mL), 1-triphenylphosphoranylidene-2-propanone (Aldrich) (278 mg, 0.87 mmol, 1.2 mol equiv) was added, and the solution was refluxed for 30 min. After evaporation of the solvent, the residue was purified by column chromatography (hexane-EtOAc 6:4) to give 174 mg (75 %) **1** as an oil (80:20 mixture of diastereomers, ^{1}H-NMR). Part of the mixture (100 mg) was separated by prep TLC on alumina (CH_2Cl_2, three elutions) to give 75 mg **1a** and 18 mg **1b**. Major (**1a**, *anti, 2S*, 1'R**) isomer: IR ($CHCl_3$) 1710, 1650, 1200, 1020, 920 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.67 (br d, *J* = 7.8, 1H, H-9), 7.59 (dd, J = 8.1, 7.4 Hz, 1H, H-7), 7.40 (br d, J = 8.3 Hz, 1H, H-6), 7.31 (br d, J = 7.5 Hz, 1H, H-8), 6.92 (dt, J = 16.0, 7.6 Hz, 1H, H-3'), 6.19 (d, J = 15.6 Hz, 1H, H-4'), 4.99 (t, J = 9.4 Hz, 1H, H-2), 3.19 (d, J = 9.4 Hz, 2H, H-3), 2.58 (dd, J = 14.2, 6.9 Hz, 1H, H-2'a), 2.45 (dd, J = 14.2, 8.2 Hz, 1H, H-2'b), 2.26 (s, 3H, H-6), 1.62 (br s, 1H, OH), 1.39 (s, 3H, 1'-Me); ^{13}C-NMR (CDCl$_3$) δ 91.9 (d, C-2), 27.7 (t, C-3), 102.6 (s, C-3a), 160.3 (s, C-4), 154.9 (s, C-5a), 117.0 (d, C-6), 132.5 (d, C-7), 124.0 (d, C-8), 122.5 (d, C-9), 112.0 (s, C-9a), 166.2 (s, C-9b), 73.4 (s, C-1'), 40.7 (t, C-2'), 141.3 (d, C-3'), 134.5 (d, C-4'), 198.0 (s, C-5'), 27.2 (q, C-6'), 22.9 (q, 1'-Me); CIMS: 315 (M+H)$^+$. Anal. Calcd for $C_{18}H_{18}O_5$: C,68.76; H, 5.78. Found: C, 68.88; H, 5.76. Minor (**1b**, *syn, 2S*, 1'S**) isomer: IR (CHCl$_3$) 1710, 1650, 1200, 1020, 920 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 7.68 (br d, J = 7.8, 1H, H-9), 7.59 (dd, J = 8.1, 7.7 Hz, 1H, H-7), 7.40 (br d, J = 8.3 Hz, 1H, H-6), 7.32 (dd, J = 8.4, 7.5 Hz, 1H, H-8), 6.95 (dt, J = 15.8, 7.5 Hz, 1H, H-3'), 6.23 (d, J = 15.8 Hz, 1H, H-4'), 4.99 (t, J = 9.4 Hz, 1H, H-2), 3.19 (d, J = 9.5 Hz, 2H, H-3), 2.71 (dd, J = 14.0, 7.1 Hz, 1H, H-2'a), 2.59 (dd, J = 14.3, 8.0 Hz, 1H, H-2'b), 2.30(s, 3H, H-6), 1.62 (br s, 1H, OH), 1.28 (s, 3H, 1'-Me); ^{13}C-NMR (CDCl$_3$) δ 91.8 (d, C-2), 27.7 (t, C-3), 102.8 (s, C-3a), 160.3 (s, C-4), 154.0 (s, C-5a), 117.0 (d, C-6), 132.5 (d, C-7), 124.0 (d, C-8), 122.5 (d, C-9), 112.0 (s, C-9a), 166.1 (s, C-9b), 73.5 (s, C-1'), 41.7 (t, C-2'), 141.5 (d, C-3'), 134.5 (d, C-4'), 198.0 (s, C-5'), 27.2 (q, C-6'), 22.1 (q, 1'-Me); CIMS: 315 (M+H)$^+$. Anal. Calcd for $C_{18}H_{18}O_5$: C,68.76; H, 5.78. Found: C, 68.89; H, 5.77.

(2S, 1'R*) 2,3-Dihydro-2-(1-Hydroxy- 1, 5-dimethyl-4-hexenyl)-4H-furo[3,2-c][1] benzopyran-4-one* (**8a**). To a cooled (0°C) solution of 3-geranyl-4-hydroxycoumarin (400 mg, 1.34 mmol) in dry CH$_2$Cl$_2$ (3 mL), *meta*-chloroperbenzoic acid (85%, 305 mg, 1.48 mmol, 1.1 mol equiv) and NaOAc (300 mg) were added. After stirring at 0°C for 30 min, the reaction was worked up by dilution with EtOAc and sequential washing with 5% aq. Na$_2$S$_2$O$_3$ and sat. aq Na$_2$CO$_3$. After washing with brine, the organic phase was evaporated, and the residue purified by column chromatography (hexane-EtOAc 7:3) to give 42 mg of starting material and 54 mg (13 %) **8a** as a colorless oil. An analytical sample was obtained by HPLC (hexane-EtOAc 8:2 as eluant). IR (CHCl$_3$) 1700, 1650, 1200, 1020, 900 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 7.67 (br d, J = 7.8, 1H, H-9), 7.53 (dd, J = 8.1, 7.0 Hz, 1H, H-7), 7.37 (br d, J = 8.5 Hz, 1H, H-6), 7.27 (dd, J = 8.4, 7.7 Hz, 1H, H-8), 5.13 (br t, J = 6.5 Hz, 1H, H-4'), 4.96 (br d, J = 9.4 Hz, 1H, H-2), 3.13 (d, J = 9.4 Hz, 2H, H-3a + H-3b), 2.17 (m, 2H, H-3'a + H-3'b), 1.68 (br s, 3H, H-6), 1.62 (br s, 3H, 5'-Me), 1.53 (m, 2H, H-2'a,b), 1.35 (s, 3H, 1'-Me); ^{13}C-NMR (CDCl$_3$) δ 92.6 (d, C-2), 25.6 (t, C-3), 102.7 (s, C-3a), 160.6 (s, C-4), 154.9 (s, C-5a), 117.0 (d, C-6), 132.3 (d, C-7), 123.8 (d, C-8), 122.5 (d, C-9), 112.4 (s, C-9a), 166.4 (s, C-9b), 73.6 (s, C-1'), 37.0 (t, C-2'), 27.6 (t, C-3'), 123.7 (d, C-4'), 132.6 (s, C-5'), 22.5 (q, C-6'), 21.9 (q, C-1'-Me), 17.6 (q, C-5'-Me). CIMS: 331 (M+H)$^+$. Anal. Calcd for $C_{19}H_{22}O_5$: C,69.06; H, 6.72. Found: C, 68.90; H, 6.74.

(2S, 1'S*) 2,3-Dihydro-2-(1-Hydroxy- 1, 5-dimethyl-4-hexenyl)-4H-furo[3,2-c][1] benzopyran-4-one* (**8b**). A sample (220 mg, 0.74 mmol) of 3-neryl-4-hydroxycoumarin was epoxidised as described for 3-geranyl-4-hydroxycoumarin. Purification of the reaction mixture by column chromatography (hexane-EtOAc 7:3) gave 36 mg (10 %) **8a** as an oil, along with 56 mg recovered starting material. IR (CHCl$_3$) 1700, 1650, 1200, 1020, 900 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 7.68 (br d, J = 7.8, 1H, H-9), 7.55 (dd, J = 8.1, 7.0 Hz, 1H, H-7), 7.39 (br d, J = 8.5 Hz, 1H, H-6), 7.26 (dd, J = 8.4, 7.7 Hz, 1H, H-8), 5.15 (br t, J = 6.5 Hz, 1H, H-4'), 4.99 (br d, J = 9.4 Hz, 1H, H-2), 3.12 (d, J = 9.4 Hz, 2H, H-3a + H-3b), 2.19 (m, 2H, H-3'a + H-3'b), 1.70 (m, 2H, H-2'a + H-2'b), 1.70 (br s, 3H, H-6'), 1.65 (br s, 3H, 5'-Me), 1.22 (s, 3H, 1'-Me); ^{13}C-NMR (CDCl$_3$) δ 92.4 (d, C-2), 25.7 (t, C-3), 102.8 (s, C-3a), 160.6 (s, C-4), 154.9 (s, C-5a), 117.0 (d, C-6), 132.3 (d, C-7), 123.9 (d, C-8), 122.6 (d, C-9), 112.4 (s, C-9a), 166.4 (s, C-9b), 73.8 (s, C-1'), 38.4 (t, C-2'), 27.8 (t, C-3'), 123.7 (d, C-4'), 132.5 (s, C-5'), 22.2 (q, C-6'), 21.3 (q, C-1'-Me), 17.7 (q, C-5'-Me). CIMS: 331 (M+H)$^+$. Anal. Calcd for $C_{19}H_{22}O_5$: C,69.06; H, 6.72. Found: C, 69.19; H, 6.71.

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15.

Compound	δ 1'-Me (^{1}H)	δ C-2'	δ 1'-Me (^{13}C)
1a	1.39	40.7	22.9
1b	1.28	41.7	22.1
Δδ	+ 0.11	- 1.0	+ 0.8
3 (major)	1.37	42.3	22.0
3 (minor)	1.24	43.6	21.2
Δδ	+ 0.13	- 1.3	+ 0.8
8a	1.35	37.0	21.9
8b	1.22	38.4	21.3
Δδ	+ 0.13	- 1.4	+ 0.7

16. The reactions involved in the putative biogenetic relationship between ferulenol and fercoprolone (double bond photooxygenation/epoxidation and hydroperoxide fragmentation/epoxide opening, Scheme 1) can also be invoked to rationalise the occurrence of other oxidised derivatives of ferulenol, suggesting that a general strategy of oxidative modification underlies the bewildering chemical diversity of the coumarinyl meroterpenoids from *F. communis*.