Biomimetic Synthesis of the Flavanone Leridol, Revision of the Structure of the Natural Product

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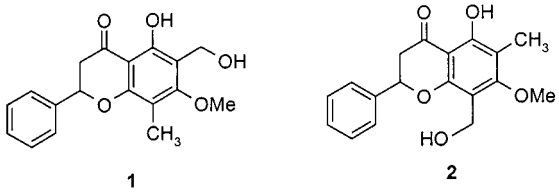
Two independent syntheses of 5-hydroxy-6-hydroxymethyl-7-methoxy-8-methylflavanone (**1**), which was supposed to be natural leridol, demonstrated that this structure assignment was wrong and that the natural flavanone leridol was indeed 5-hydroxy-8-hydroxymethyl-7-methoxy-6-methylflavanone (**2**).

Our interest in finding new access to aromatic natural products[1] prompted us to investigate a biomimetic synthesis of natural flavanones. The candidate we selected was leridol, a natural product isolated in 1992 from the leaves of *Petiveria alliacea*,[2] a shrub used in traditional medicine in South America. The structure **1** was proposed for this natural product.[2]

We report in this paper a biomimetic synthesis of compounds **1** and **2** showing that natural leridol has indeed the structure **2** and not **1**, a result which is confirmed by a second independent synthesis described also in this paper. The synthesis of enantiomerically pure 5-hydroxy-6-hydroxymethyl-7-methoxy-8-methylflavanone (**1**) will be reported in the near future.

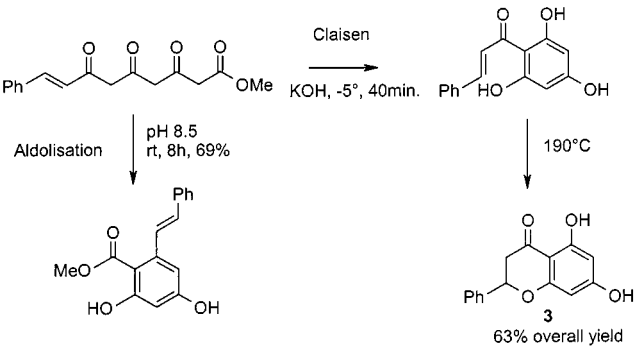


Scheme 1

A biomimetic synthesis of pinocembrin (**3**), a flavanone having the basic skeleton of the target **1**, was already described by Harris.[3] This approach was based on the cyclization of a 3,5,7-trioxo ester, which can give aromatic compounds in two ways: The first route involves an aldol condensation to form a resorcylic ester and the second an internal Claisen condensation to form pinocembrin (**3**).

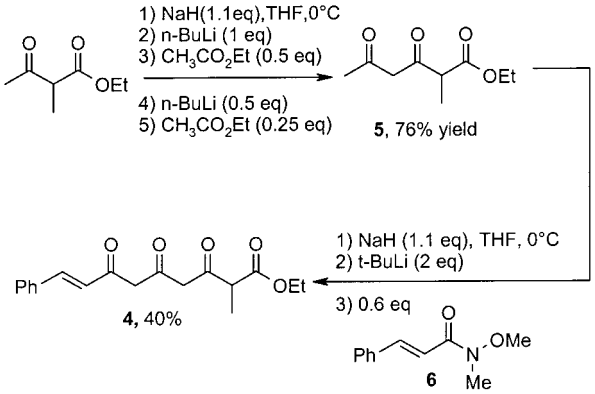
This β-polycarbonyl approach could be applied to the synthesis of **1**. That requires the synthesis of the methyl-substituted trioxo ester **4** and the experimental conditions for Claisen condensation.

The synthesis of the oxo ester **4** started from the condensation of the dianion of ethyl 2-methylacetoacetate to ethyl acetate (Scheme 3). The dianion was prepared with sodium



Scheme 2

hydride and *n*BuLi but, because the hydrogen atoms of the condensation product are more acidic than those of the terminal methyl group of ethyl 2-methylacetoacetate, the following procedure was used: addition of 0.5 equiv. of ethyl acetate to the dianion, regeneration of the dianion by addition of base (0.5 equiv.) and finally addition of 0.25 equiv.



Scheme 3

of ester. These conditions usually gave yields around 70%.[4]

It was shown by ^{1}H-NMR spectroscopy that the δ-carbonyl group of **5** was enolized at 85%. The next step was the condensation of the trianion of **5** to a cinnamic acid derivative. Preliminary experiments showed that cinnamic esters in such a reaction gave a complex mixture of products; the presence of a methyl group α to the ester in **5** increases the formation of secondary products. A result

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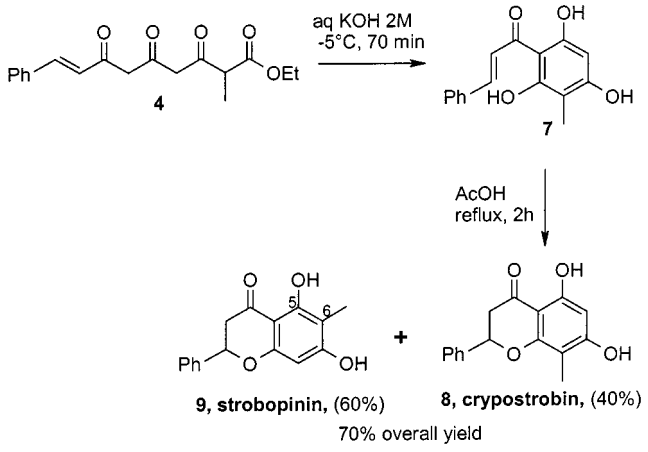
from literature[5] showed that the condensation of ethyl acetoacetate dianion gave much better results with the Weinreb derivative **6** (49% yield), which did not give any dicondensation of the nucleophile to the α,β-unsaturated carbonyl compound, a reaction observed with *N*,*N*-dimethyl cinnamide. In our case we obtained a 40% yield of pure **4** after chromatography on demetalated (acid-washed[11]) silica gel. Inverse addition gave a similar result.

The next step was the cyclization of this intermediate **4** (Scheme 4). We used the conditions described by Harris.[3] In the presence of aqueous potassium hydroxide we observed aromatization by Claisen condensation giving the chalcone **7** as well as some (15%) of the two flavanones **8** and **9**. We did not observe any aldolization reaction. This crude product was cyclized by heating in acetic acid. An overall 70% yield in a mixture of the two isomers **8** and **9** was obtained. The structure identification was done by NOE experiments: Irradiation of the methyl protons in the main isomer **9** increased the intensity of the phenolic hydrogen atom in 5-position (which is engaged in an intramolecular hydrogen bonding with the carbonyl group). The signal of the other phenolic proton (7-OH) was not visible. Irradiation of 6-H in compound **8** led to an NOE to both phenolic hydrogen atoms. In addition these two compounds are known and showed the same physical data: cryptostrobin (**8**), m.p. 198−201°C (ref.[6] 202−103°C), strobopinin (**9**), m.p. 228−230°C (ref.[6] 225−227°C).

By changing the cyclization conditions we tried to favour the formation of the isomer **8** which is indeed the precursor of the flavanone **1**. As shown in Table 1, all attempts increased the percentage of the other isomer **9** which can be obtained in high proportion in basic medium.



Scheme 4

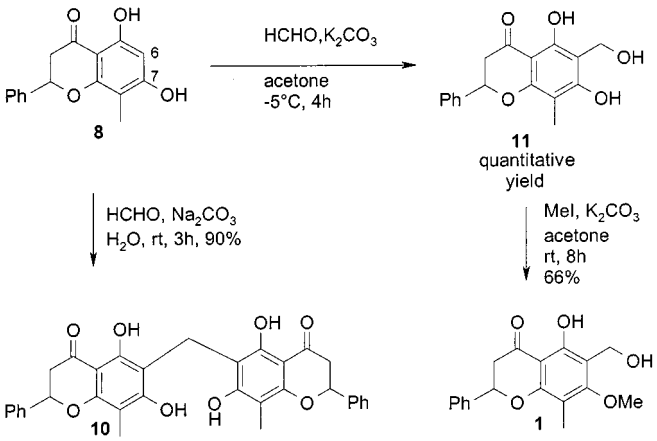
Table 1. Cyclization of the chalcone 7

Catalyst	Solvent	Temperature	Reaction time	**9**/**8**[a]
acetic acid	acetic acid	reflux	2 h	60:40
$ZnCl_2$	THF	reflux	16 h	55:45
NaOMe	ether	room temp.	4 d	82:18

[a] Determined by ^{1}H NMR.

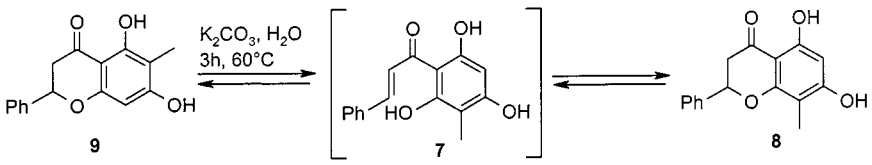
Starting from literature results that report isomerization of these two products during paper chromatography,[7] we could equilibrate the isomer **9** in basic medium into a 1:1 mixture of **8** and **9** with only traces of the chalcone intermediate, but some degradation products (30%) were also observed (Scheme 5). A separation by column chromatography allowed to increase the yield in compound **8**. After two cycles (equilibration, separation) the isolated yield of **8** increased from 28 to 49%.

The next step of the synthesis was the hydroxymethylation of the electron-rich aromatic ring of **8**. Reaction of **8** with formaldehyde in the presence of a base in water surprisingly gave the diarylmethane **10** in good yield, a reaction usually observed in acidic medium (Scheme 6). The hydroxymethyl derivative **11** was obtained from **8** in quantitative yield by changing the solvent water by acetone. Finally, regioselective methylation of **11** gave the flavanone **1**.

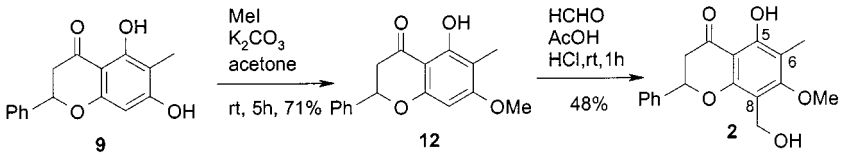


Scheme 6

The melting point of the synthetic compound **1** was lower than the melting point of natural leridol (97−99°C instead of 139−140°C[2]). The ^{1}H NMR spectrum was very similar to the spectrum of natural leridol except for the methylenic



Scheme 5



Scheme 7

proton signals of the primary alcohol; we observed the expected doublet at δ = 4.73 while for natural leridol one surprising quadruplet at δ = 4.82 was reported.[2] In the ^{13}C-NMR spectrum the differences in chemical shifts were between 1 and 2 ppm for four signals with respect to the spectrum reported in literature.[2]

In order to rule out any isomerization of the flavanone **1** to its isomer **2** at the end of the synthesis, we confirmed the structure **1** by NOE experiments: Irradiation of the signal at δ = 4.73 (corresponding to 6-CH_2OH) gave an increase of the intensity of the signals of 7-OMe and 5-OH.

In the biomimetic route to the flavanone **1** from the trioxo ester **4**, the main isomer formed was **9**, which is a precursor of the flavanone **2**. We carried out the final steps to prepare this compound. Since compound **9** did not react under the conditions employed to hydroxymethylate the flavanone **8**, we inverted the last two steps (Scheme 7).

Selective methylation of phenol **9** with methyl iodide and potassium carbonate gave **12** in 71% yield. The final hydroxymethylation was carried out with formalin in acetic acid in the presence of hydrochloric acid giving probably first a chloromethylated intermediate which is hydrolysed during the workup. The flavanone **2** and natural leridol showed very similar ^{1}H-NMR spectra (except for the methylenic proton signals of 8-CH_2OH showing as for **1** a doublet at δ = 4.69). In the ^{13}C-NMR spectra the chemical shifts of all signals of compound **2** are virtually identical to those of leridol, the differences do not exceed 0.1 ppm. This is strongly in favour of structure **2** for leridol. Electron impact mass spectrometry of **2** is consistent with that of natural leridol, whereas the spectrum of **1** showed several differences: The peaks at *m*/*z* 181 and 182 have comparable intensities in leridol and **2** but a much weaker intensity in **1**; the peaks at *m*/*z* 192 and 177 are not mentioned for leridol and are very weak in **2** but rather high in **1** (Table 2). Finally, the melting point of racemic **2** is closer to that of optically active leridol (120−123°C for **2**, 139−140°C for leridol and 97−99°C for **1**).

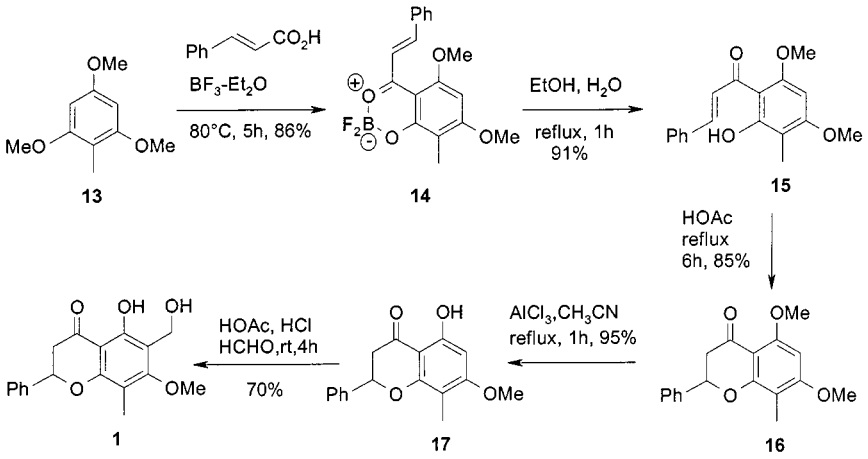
Table 2. Mass spectra of natural leridol and synthetic compounds **1** and **2** (rel. intensities in %)

m/*z*	Natural leridol[2]	**1**	**2**	*m*/*z*	Natural leridol[2]	**1**	**2**
314	100	100	100	193	–	18	21
296	36	22	26	**192**	**–**	**48**	**18**
295	–	22	29	191	–	34	11
281	12	10	12	**182**	**41**	**10**	**41**
263	7	6	8	**181**	**23**	**10**	**27**
253	8	5	6	**177**	**–**	**35**	**14**
237	7	5	7	104	33	22	17
219	52	50	58	103	26	15	19
209	20	19	26	77	22	9	15
205	13	14	17				

All these results are in favour of structure **2** for natural leridol.

However another synthesis of the flavanone **1** was carried out to confirm the preceding results.

This new synthesis started from the chalcone **15** which was prepared according to a known procedure.[8] 2,4,6-Trimethoxytoluene (**13**) was acylated with cinnamic acid in the presence of BF_3·Et_2O leading to the cyclic borate **14**, which is then hydrolysed to the chalcone. Cyclization to the flavanone **16** was carried out in acetic acid with a 70% yield (this yield can be increased to 85% by recycling the unchanged starting material). The methyl ether β to the carbonyl group could be selectively cleaved with $AlCl_3$ in 95%



Scheme 8

yield. The attempted hydroxymethylation of the aromatic ring of **17** with formaldehyde in basic medium gave only aldolization products of the ketone with formaldehyde. Under acidic conditions the hydroxymethylation was obtained on the aromatic ring yielding **1**. A small amount (15%) of the dimeric diarylmethane was also formed. The resulting flavanone **1** showed exactly the same characteristics as the molecule prepared in Scheme 8.

In conclusion we have reported in this paper results supporting the structure **2** for natural leridol and ruling out the isomeric structure **1**.

Experimental Section

General Remarks: ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AC-200 spectrometer at 200 and 50 MHz respectively. Chemical shifts δ in ppm relative to solvent signal (residual proton signal for proton spectra or carbon signal for carbon spectra). − IR spectra: Perkin−Elmer 257 spectrophotometer in cm^{-1}. − UV spectra: Kontron Instruments Uvikon 933; absorption in nm and intensity in lg ε. − Melting points: Reichert apparatus; uncorrected values. − Mass spectrometry: AutoSpecE (FAB) or Fisons Instruments (EI at 70 eV); *m*/*z* (rel. intensities in %). − Elemental analyses: Microanalytical Service of CNRS of Strasbourg. − Analytical TLC: precoated Merck silica gel 60F-254 glass plates; detection by UV (λ = 254 nm or 365 nm) and/or visualization by spray reagents (ethanolic vanillin/H_2SO_4, *p*-anisaldehyde/H_2SO_4 or phosphomolybdic acid). − Preparative (column) chromatography: Silica gel Geduran Si 60 (40−63 μm; 70−230 mesh) from E. Merck. − Workup*:* Organic solutions were dried with magnesium sulfate monohydrate ($MgSO_4 \cdot H_2O$), filtered through sintered glass and concentrated by rotary evaporation at water aspirator pressure, unless otherwise stated.

Ethyl 2-Methyl-3,5-dioxohexanoate (5):[9] Ethyl 2-methylacetoacetate (10.85 g, 75.3 mmol, 1.0 equiv.), diluted in THF (10 mL), was added slowly to a stirred suspension of sodium hydride (55−65% in oil, 3.60 g, 82 mmol, 1.1 equiv.) in THF (280 mL) at 0°C. After 15 min, a solution of *n*-butyllithium (1.55 M in hexane, 48 mL, 74.4 mmol, 1.0 equiv.) was added over 10 min to the formed white precipitate and the obtained yellow-orange solution was stirred for a further 15 min before addition of the first portion of ethyl acetate (3.6 mL, 36.8 mmol, 0.5 equiv.). After a reaction period of 15 min, additional *n*-butyllithium (24 mL, 37.2 mmol, 0.25 equiv.) was added. A further period of 15 min was allowed to elapse before the second portion of ethyl acetate (2.0 mL, 20 mmol, 0.27 equiv.) was added and the reaction stirred for a final 15 min before being quenched with concentrated hydrochloric acid (20 mL). The reaction was worked up by addition of water (60 mL) and ether (100 mL). The aqueous phase was separated and further extracted with ether (3 × 50 mL). The ethereal extracts were combined, washed with a saturated $NaHCO_3$ solution (100 mL) and with a saturated NaCl solution (100 mL), dried, filtered and concentrated. The crude product was distilled under vacuum through a Vigreux column to give 8.05 g (43.2 mmol, yield 76%) of **5** as a liquid. R_f = 0.45 (hexane/AcOEt, 3:1). − B.p. 60−63°C (0.5 Torr). − ^{1}H NMR ($CDCl_3$): The spectrum indicates about 85% of enolic and 15% of ketonic form. Enol: δ = 1.26 (t, 3 H, *J* = 7 Hz, CH_3 ester), 1.38 (d, 3 H, *J* = 7 Hz, C2−CH_3), 2.06 (s, 3 H, 6-H), 3.36 (q, 1 H, *J* = 7 Hz, 2-H), 4.18 (q, 2 H, *J* = 7 Hz, CH_2 ester), 5.58 (s, 1 H, 4-H), 15.13 (br. s, 1 H, OH). Keto: δ = 1.2−1.4 (m, 6 H, CH_3 ester and C2−CH_3), 2.24 (s, 3 H, 6-H), 3.62 (q, 1 H, *J* = 7 Hz, 2-H), 3.71 (AB, 2 H, 4-H), 4.18 (q, 2 H, *J* = 7 Hz, CH_2 ester).

***N*-Methoxy-*N*-methylcinnamide (6):** Pyridine (18 mL, 223 mmol, 2.2 equiv.) was slowly added to a well-stirred slurry of cinnamoyl chloride (16.66 g, 100 mmol, 1.0 equiv.) and *N*,*O*-dimethylhydroxylamine hydrochloride (10.16 g, 104.2 mmol, 1.04 equiv.) in CH_2Cl_2 (150 mL) at 0°C. The cooling bath was removed after 15 min and stirring continued for further 2 h, at which time a solution of 5% hydrochloric acid (40 mL) was added. The two phases were separated and the aqueous phase was extracted with ether (3 × 20 mL). The combined organic phases were washed with a saturated $NaHCO_3$ solution (50 mL) and with a saturated NaCl solution (50 mL), dried, filtered and concentrated to give 18.23 g (yield 95%) of **6** as a white solid. R_f = 0.35 (hexane/AcOEt, 1:1). − ^{1}H NMR ($CDCl_3$): δ = 3.32 (s, 3 H, NCH_3), 3.77 (s, 3 H, OCH_3), 7.04 (d, 1 H, *J* = 16 Hz, α-H), 7.36−7.42 (m, 3 H, ArH), 7.55 −7.60 (m, 2 H, ArH), 7.74 (d, 1 H, *J* = 16 Hz, β-H). − ^{13}C NMR ($CDCl_3$): δ = 32.6 (NCH_3), 62.0 (OCH_3), 115.8 (C-α), 128.1, 128.9, 129.9 (CArt), 135.2 (CArq), 143.5 (C-β), 167.0 (C=O).

Ethyl 2-Methyl-3,5,7-trioxo-9-phenyl-8-nonenoate (4): Dioxo ester **5** (4.216 g, 22.64 mmol, 1.0 equiv.), diluted in THF (10 mL), was transferred by cannula to a stirred suspension of oil-free sodium hydride (650 mg, 27.1 mmol, 1.2 equiv.) in THF (100 mL) at 0°C. After 30 min of stirring, a solution of *tert*-butyllithium (ca. 1.4 M in pentane, 32 mL, 45 mmol, 2.0 equiv.) was slowly added over 10 min. The solution was stirred for 20 min before a solution of amide **6** (2.34 g, 12.2 mmol, 0.54 equiv.) in THF (10 mL) was added. The solution was stirred for a final 30 min before being quenched with 3 M hydrochloric acid (40 mL). The two phases were separated and the aqueous phase was extracted with ether (3 × 30 mL). The combined organic phases were washed with a saturated $NaHCO_3$ solution (50 mL) and with a saturated NaCl solution (50 mL), dried, filtered and concentrated. The crude product was chromatographed on demetalated (acid-washed)[11] silica gel (eluant: hexane/acetone, 88:12) to give 1.550 g (yield 40%) of **4** as an orange solid which could be crystallized from hexane/ether (1:1). R_f = 0.26 (hexane/AcOEt, 5:1). − M.p. 47−64°C (prisms). − ^{1}H NMR ($CDCl_3$): δ = 1.2−1.5 (m, 6 H, *J* = 7 Hz, CH_3 ester and C2−CH_3), 3.29 (q, ca. 0.65 H, 2-H), 3.6−3.8 (m, ca. 1.0 H), 4.19 (m, 2 H, CH_2 ester), 5.37 and 5.38 (2 s, ca. 1.3 H), 5.71−5.75 (m, ca. 0.4 H), 6.44 (d, ca. 0.65 H, *J* = 16 Hz, α-H), 6.46 (d, ca. 0.3 H, *J* = 16 Hz, α-H), 6.85 (d, ca. 0.05 H, *J* = 16 Hz, α-H), 7.3−7.7 (m, 6 H, ArH and β-H), 13.5−15.5 (3 br. s, ca. 1.6 H, enolic OH). − IR ($CHCl_3$): $\tilde{\nu}$ [$^{-1}$] = 3690, 3610, 3450 (O−H), 3000 (C−H); 2400; 1735, 1625, 1590 (C=O, C=C); 1450, 1405, 1140, 1085, 1030, 970, 915, 865. − $C_{18}H_{20}O_5$ (316.35): calcd. C 68.34, H 6.37; found C 68.33, H 6.38.

2′,4′,6′-Trihydroxy-3′-methylchalcone (7): A solution of trioxo ester **4** (1.835 g, 5.80 mmol, 1.0 equiv.) in methanol (40 mL) was added to a well-stirred aqueous 2 M KOH solution (400 mL) at −5°C. The solution was stirred for 70 min before being poured into ice-cooled 5 M hydrochloric acid (200 mL). The yellow precipitate was extracted with ether (3 × 100 mL). The combined organic phases were washed with a saturated NaCl solution (80 mL), dried, filtered and concentrated. The crude orange solid was used in the next reaction step without purification (see below). In a further experiment, the chromatographic separation of the crude product on demetalated silica gel (eluant: hexane/AcOEt, 3:1) gave chalcone **7** (yield 57%) as an orange solid besides a mixture of flavanones **8** and **9** (yield 13%). Data for **7**: R_f = 0.52 (hexane/AcOEt/AcOH, 10:10:1). − ^{1}H NMR ([D_6]acetone): δ = 2.00 (s, 3 H, $ArCH_3$), 6.13 (s, 1 H, 5′-H), 7.40−7.44 (m, 3 H, ArH), 7.66−7.74 (m, 2 H, ArH), 7.78 (d, 1 H, *J* = 16 Hz, α-H), 8.28 (d, 1 H, *J* = 16 Hz, β-H), 9.5 (br. s, 2 H, ArOH), 14.2 (s, 1 H, chelated ArOH). − ^{13}C NMR ([D_6]acetone): δ = 7.6 (3′-Me), 95.3 (C-5′), 103.8 and 105.6 (C-1′

and C-3′), 128.8, 129.2, 129.8, 130.9, 136.7, 142.4 (C-1 to C-6, C-α and C-β), 160.3, 163.4, 165.9 (C-2′, C-4′ and C-6′), 193.4 (C=O).

5,7-Dihydroxy-8-methylflavanone (Cryptostrobin) (8): Crude chalcone **7** was refluxed in acetic acid (50 mL) for 2 h. The solvent was evaporated at reduced pressure and the residue was purified by column chromatography on silica gel to give 436 mg (yield 28%) of flavanone **8** and 665 mg (yield 42%) of **9**. Data for **8**: R_f = 0.32 (toluene/AcOEt, 12:1). − M.p. 198−201°C (ref.[6]: m.p. 202−203°C). − ^{1}H NMR ([D$_6$]acetone): δ = 2.00 (s, 3 H, 8-Me), 2.98 (*AB*X, 2 H, J_{AB} = 17 Hz, J_{AX} = 12 Hz, J_{BX} = 3 Hz, Δν = 54 Hz, 3-H), 5.57 (dd, AB*X*, 1 H, J_{AX} = 12 Hz, J_{BX} = 3 Hz, 2-H), 6.05 (s, 1 H, 6-H), 7.35−7.62 (m, 5 H, ArH), 9.56 (s, 1 H, ArOH), 12.12 (s, 1 H, chelated ArOH). − ^{13}C NMR ([D$_6$]acetone): δ = 7.9 (8-Me), 43.6 (C-3), 79.6 (C-2), 96.4 (C-6), 103.3, 104.1 (C-8, C-10), 127.1 (C-2′, C-6′), 129.3 (C-4′), 129.5 (C-3′, C-5′), 140.4 (C-1′), 161.0, 162.9, 165.3 (C-5, C-7, C-9), 197.2 (C-4).

5,7-Dihydroxy-6-methylflavanone (Stropopinin) (9): A mixture of chalcone **7** (45 mg) and sodium methoxide (54 mg) in ether (10 mL) and methanol (10 mL) was stirred at room temperature for 4 d. Water (5 mL) and 3 M hydrochloric acid (2 mL) were added and the aqueous phase was extracted with ether (3 times). The combined organic phases were washed with a saturated NaCl solution, dried, filtered and concentrated to give 49 mg of the two regioisomers **9** and **8** in an 82:18 ratio (determined by ^{1}H NMR). Data for **9**: R_f = 0.41 (toluene/AcOEt, 12:1). − M.p. 228−230°C (ref.[6]: m.p. 225−227°C). − ^{1}H NMR ([D$_6$]acetone): δ = 1.99 (s, 3 H, 6-Me), 2.97 (*AB*X, 2 H, J_{AB} = 17 Hz, J_{AX} = 12.5 Hz, J_{BX} = 3 Hz, Δν = 69 Hz, 3-H), 5.52 (dd, AB*X*, 1 H, J_{AX} = 12.5 Hz, J_{BX} = 3 Hz, 2-H), 6.08 (s, 1 H, 8-H), 7.38−7.58 (m, 5 H, ArH), 9.52 (s, 1 H, ArOH), 12.44 (s, 1 H, chelated ArOH). − ^{13}C NMR ([D$_6$]acetone): δ = 7.1 (6-Me), 43.8 (C-3), 79.9 (C-2), 95.2 (C-8), 103.1, 104.9 (C-6, C-10), 127.3 (C-2′, C-6′), 129.4 (C-4′), 129.5 (C-3′, C-5′), 140.2 (C-1′), 161.6, 162.5, 165.1 (C-5, C-7, C-9), 196.9 (C-4).

Equilibration of 8 and 9: The flavanone **9** (1.03 g, 3.81 mmol, 1.0 equiv.) was dissolved in sat. Na_2CO_3 solution (120 mL, ca. 80 mmol) under heating and the mixture was kept at 60−65°C for 3 h. Then the solution was cooled and poured into 3 M hydrochloric acid (140 mL) under stirring. The aqueous phase was extracted with ethyl acetate (4 × 50 mL). The combined organic phases were washed with a saturated NaCl solution (50 mL), dried, filtered and concentrated to give 374 mg (yield 36%) of flavanone **8** and 338 mg (yield 33%) of **9** after chromatographic purification. This equilibration sequence was repeated to give a further 132 mg of **8**.

5,7-Dihydroxy-6-hydroxymethyl-8-methylflavanone (11): To a solution of flavanone **8** (285 mg, 1.05 mmol, 1.0 equiv.) in acetone (15 mL) were successively added potassium carbonate (270 mg, 1.95 mmol, 1.85 equiv.) and formalin (37 wt-%, 3.0 mL, ca. 38 mmol, 36 equiv.) at −5°C. The mixture was stirred for 5 h between 0 and −5°C before being quenched with an aqueous solution of 1 M NaH_2PO_4 (3.5 mL) and water (10 mL). The aqueous phase was extracted with ether (4 × 10 mL). The combined organic phases were washed with water (5 mL), dried, filtered and concentrated to give 320 mg (yield 100%) of **11** as a white solid. R_f = 0.32 (hexane/AcOEt, 5:2; vanillin: red). − ^{1}H NMR ([D$_6$]acetone): δ = 1.99 (s, 3 H, 8-Me), 2.8 (br. s, 1 H, OH), 2.99 (*AB*X, 2 H, J_{AB} = 17 Hz, J_{AX} = 12 Hz, J_{BX} = 3.5 Hz, Δν = 51.5 Hz, 3-H), 4,93 (s, 2 H, 6−CH_2O), 5,58 (dd, AB*X*, 1 H, J_{AX} = 12 Hz, J_{BX} = 3.5 Hz, 2-H), 7.38−7.62 (m, 5 H, ArH), 10.2 (br. s, 1 H, ArOH), 12.47 (s, 1 H, chelated ArOH). − ^{13}C NMR ([D$_6$]acetone): δ = 7.6 (8-Me), 43.5 (C-3), 57.9 (6-CH_2O), 79.6 (C-2), 102.6, 104.4, 104.9 (C-6, C-8, C-10), 127.1 (C-2′, C-6′), 129.3 (C-4′), 129.5 (C-3′, C-5′), 140.4 (C-1′), 158.8, 159.9, 165.5 (C-5, C-7, C-9), 197.5 (C-4).

6-Methylenebis(5,7-dihydroxy-8-methylflavanone) (10): To a suspension of flavanone **8** (27 mg, 0.1 mmol, 1.0 equiv.) in a saturated Na_2CO_3 solution (1 mL, 0.6 mmol) was added formalin (37 wt-%, 0.2 mL, ca. 2.4 mmol, 24 equiv.) at room temperature. The mixture was stirred for 4 h before being quenched with 10% sulfuric acid (5 mL). The aqueous phase was extracted with ethyl acetate (4 times). The combined organic phases were washed with a saturated NaCl solution, dried, filtered and concentrated to give 25 mg (yield 90%) of **10**. R_f = 0.52 (toluene/AcOEt, 12:1; vanillin: red). − ^{1}H NMR ($CDCl_3$): δ = 2.06 (s, 6 H, 8-Me), 2.95 (*AB*X, 4 H, J_{AB} = 17 Hz, J_{AX} = 12 Hz, J_{BX} = 3.5 Hz, Δν = 32.5 Hz, 3-H), 3.80 (s, 2 H, 6-CH_2), 5.41 (dd, AB*X*, 2 H, J_{AX} = 12 Hz, J_{BX} = 3.5 Hz, 2-H), 7.33−7.49 (m, 10 H, ArH), 9.15 (br. s, 2 H, ArOH), 13.59 (s, 2 H, chelated ArOH). − ^{13}C NMR ($CDCl_3$): δ = 8.1 (8-Me), 15.0 (6-CH_2), 43.0 (C-3), 78.7 (C-2), 102.2, 105.9 (C-8, C-10), 125.9 (C-2′, C-6′), 128.7 (C-4′), 128.9 (C-3′, C-5′), 138.7 (C-1′), 156.8, 158.7, 163.0 (C-5, C-7, C-9), 196.7 (C-4).

5-Hydroxy-6-hydroxymethyl-7-methoxy-8-methylflavanone (1): A solution of phenol **11** (100 mg, 0.333 mmol, 1.0 equiv.) in acetone (5 mL) was stirred with K_2CO_3 (75 mg, 0.54 mmol, 1.6 equiv.) and methyl iodide (0.3 mL, 4.8 mmol, 14 equiv.) for 8 h at room temperature and then stored overnight in the refrigerator. The reaction was quenched with an aqueous solution of 1 M NaH_2PO_4 (2 mL) and water (5 mL). The aqueous phase was extracted with ether (3 × 5 mL). The combined organic phases were dried, filtered and concentrated. The crude product was purified on demetalated silica gel to give 69 mg (yield 66%) of **1** as a white solid. R_f = 0.43 (hexane/AcOEt, 1:1; vanillin: red). − M.p. 97−99°C. − ^{1}H NMR ($CDCl_3$): δ = 2.10 (s, 3 H, 8-Me), 2.34 (t, 1 H, *J* = 6.5 Hz, OH), 2.98 (*AB*X, 2 H, J_{AB} = 17 Hz, J_{AX} = 12 Hz, J_{BX} = 3.5 Hz, Δν = 35 Hz, 3-H), 3.85 (s, 3 H, OMe), 4.73 (d, 2 H, *J* = 6.5 Hz, 6-CH_2O), 5.45 (dd, AB*X*, 1 H, J_{AX} = 12 Hz, J_{BX} = 3.5 Hz, 2-H), 7.39−7.50 (m, 5 H, ArH), 12.15 (s, 1 H, chelated ArOH). − ^{13}C NMR ($CDCl_3$): δ = 8.6 (8-Me), 43.5 (C-3), 54.5 (6-CH_2O), 62.0 (7-OMe), 78.8 (C-2), 105.0, 110.3 (C-8, C-10), 114.7, (C-6), 126.0 (C-2′, C-6′), 128.8 (C-4′), 128.9 (C-3′, C-5′), 138.6 (C-1′), 159.8 (magnetic equivalence), 165.7 (C-5, C-7, C-9), 197.5 (C-4). − UV (MeOH): λ_{max} = 283 (4.00), 351 (3.49). − MS (HR-FAB): calcd. for $C_{18}H_{18}O_5$ 314.1154; found 314.1155.

2,2-Difluoro-5,7-dimethoxy-8-methyl-4-(2-phenylvinyl)-1-oxa-3-oxonia-2-boratanaphthalene (14): A mixture of trimethoxytoluene **13** (purchased from Lancaster) (2.055 g, 11.28 mmol, 1.0 equiv.) and cinnamic acid (6.050 g, 40.83 mmol, 3.6 equiv.) in BF_3·Et_2O (50 mL) was heated at 75−85°C for 5 h. After one night at room temperature, the red solid was filtered and dried at reduced pressure to give 3.37 g (yield 86%) of **14**. − M.p. 265−268°C (ref.[8]: m.p. 264−267°C); the crude product could be crystallized from acetone/methanol to yield fine red needles as described in the literature.

2′-Hydroxy-4′,6′-dimethoxy-3′-methylchalcone (Aurentiacin) (15): A suspension of the boron heterocycle **14** (2.385 g, 6.89 mmol) in EtOH/H_2O (4:1, 150 mL) was heated at reflux for 1 h to give a clear orange solution. Heating was stopped and the solution allowed to stand overnight. The formed fine orange needles were filtered and the filtrate was concentrated to about 50 mL giving a suspension which was heated at reflux for a few minutes. Filtration at room temperature and combination with the first solid fraction gave 1.861 g (yield 91%) of chalcone **15**. R_f = 0.34 (hexane/AcOEt, 3:1; phosphomolybdic acid: green). − M.p. 139−140°C (ref.[9]: m.p. 139°C). − ^{1}H NMR ($CDCl_3$): δ = 2.04 (s, 3 H, ArCH_3), 3.89 and 3.94 (2s, 6 H, OMe), 5.98 (s, 1 H, 5′-H), 7.35−7.50 (m, 3 H, ArH), 7.50−7.65 (m, 2 H, ArH), 7.82 (AB, 2 H, *J* = 15.5 Hz, Δν = 22.5 Hz, α-H and β-H), 14.11 (s, 1 H, chelated ArOH). − ^{13}C

NMR ($CDCl_3$): δ = 7.4 (3′-Me), 55.6 and 55.9 (OMe), 86.4 (C-5′), 106.1 and 106.4 (C-1′ and C-3′), 128.0, 128.4, 128.9, 130.0 (C-2 to C-6, C-α), 142.0 (C-β), 135.7 (C-1), 161.2, 163.7, 164.4 (C-2′, C-4′ and C-6′), 193.1 (C=O).

5,7-Dimethoxy-8-methylflavanone (Dimethylcryptostrobin) (16): Chalcone **15** (400 mg, 1.34 mmol) was refluxed in acetic acid (15 mL) for 6 h. The solvent was evaporated at reduced pressure and the residue was purified by column chromatography on silica gel to give 282 mg (yield 70%) of flavanone **16** as a white solid and 98 mg (24%) of unchanged starting material. R_f = 0.29 (hexane/AcOEt, 1:3; phosphomolybdic acid: negative). − M.p. 144−145°C (ref.[10]: m.p. 147°C). − ^{1}H NMR ($CDCl_3$): δ = 2.04 (s, 3 H, 8-Me), 2.89 (*AB*X, 2 H, J_{AB} = 16.5 Hz, J_{AX} = 12 Hz, J_{BX} = 4 Hz, Δν = 22.5 Hz, 3-H), 3.89 and 3.92 (2s, 6 H, OMe), 5.38 (dd, AB*X*, 1 H, J_{AX} = 12 Hz, J_{BX} = 4 Hz, 2-H), 6.11 (s, 1 H, 6-H), 7.3−7.5 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 7.9 (8-Me), 45.8 (C-3), 55.7 and 56.1 (OMe), 78.5 (C-2), 88.5 (C-6), 106.0, 106.3 (C-8, C-10), 125.9, (C-2′, C-6′), 128.4 (C-4′), 128.7 (C-3′, C-5′), 139.4 (C-1′), 160.6, 161.2, 163.6 (C-5, C-7, C-9), 190.0 (C-4).

5-Hydroxy-7-methoxy-8-methylflavanone (17): A mixture of **16** (32 mg, 0.108 mmol, 1.0 equiv.) and anhydrous aluminium chloride (80 mg, 0.6 mmol, 5.6 equiv.) in acetonitrile (2 mL) was refluxed for 1 h. After standing at room temperature for 2 h, the mixture was poured on ice. The volume was reduced by evaporation and 3 M hydrochloric acid (5 mL) was added. The aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with a saturated NaCl solution (5 mL), dried, filtered and concentrated. The crude product (28 mg, yield 95%) was pure according to ^{1}H NMR. R_f = 0.57 (hexane/AcOEt, 3:1; anisaldehyde: orange). − M.p. 143−145°C (ref.[6]: m.p. 143°C). − ^{1}H NMR ($CDCl_3$): δ = 2.01 (s, 3 H, 8-Me), 2.94 (*AB*X, 2 H, J_{AB} = 17 Hz, J_{AX} = 12.5 Hz, J_{BX} = 3.5 Hz, Δν = 35.5 Hz, 3-H), 3.86 (s, 3 H, OMe), 5.42 (dd, AB*X*, 1 H, J_{AX} = 12.5 Hz, J_{BX} = 3.5 Hz, 2-H), 6.10 (s, 1 H, 6-H), 7.3−7.5 (m, 5 H, ArH), 12.12 (s, 1 H, chelated ArOH). − ^{13}C NMR ($CDCl_3$): δ = 7.7 (8-Me), 43.5 (C-3), 56.0 (7-OMe), 78.6 (C-2), 92.3 (C-6), 102.9, 105.0 (C-8, C-10), 126.0 (C-2′, C-6′), 128.6 (C-4′), 128.9 (C-3′, C-5′), 139.1 (C-1′), 158.9, 162.5, 166.1 (C-5, C-7, C-9), 196.3 (C-4).

5-Hydroxy-6-hydroxymethyl-7-methoxy-8-methylflavanone (1): To a solution of flavanone **17** (520 mg, 1.83 mmol, 1.0 equiv.) in glacial acetic acid (40 mL) were successively added formalin (37 wt-%, 3.0 mL, ca. 38 mmol, 20 equiv.) and concentrated hydrochloric acid (3 mL) at room temperature. The mixture was stirred for 4 h before being quenched with water (200 mL). The aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with a saturated $NaHCO_3$ solution (2 × 50 mL), dried, filtered and concentrated. The crude product was purified on silica gel to give 401 mg (yield 70%) of **1** as a white solid. NMR spectra and m.p. are identical to those of product **1** synthesized above.

5-Hydroxy-7-methoxy-6-methylflavanone (12): A solution of phenol **9** (80 mg, 0.296 mmol, 1.0 equiv.) in acetone (3 mL) was stirred with K_2CO_3 (80 mg, 0.58 mmol, 2.0 equiv.) and methyl iodide (0.3 mL, 4.8 mmol, 16 equiv.) for 5 h at room temperature. The reaction was quenched with 2 M hydrochloric acid (5 mL) and the aqueous phase was extracted with ether (3 × 5 mL). The combined organic phases were dried, filtered and concentrated. The crude product was purified on silica gel (eluant hexane/CH_2Cl_2, 1:1) to give 60 mg (yield 71%) of **12**. R_f = 0.59 (hexane/AcOEt, 3:1; anisaldehyde: orange). M.p. 96−98°C (crystallized from MeOH; ref.[7]: m.p. 96−97°C). − ^{1}H NMR ($CDCl_3$): δ = 2.02 (s, 3 H, 6-Me), 2.97 (*AB*X, 2 H, J_{AB} = 17 Hz, J_{AX} = 13 Hz, J_{BX} = 3.5 Hz, Δν = 54.5 Hz, 3-H), 3.84 (s, 3 H, OMe), 5.42 (dd, AB*X*, 1 H, J_{AX} = 13 Hz, J_{BX} = 3.5 Hz, 2-H), 6.10 (s, 1 H, 8-H), 7.3−7.5 (m, 5 H, ArH), 12.07 (s, 1 H, chelated ArOH).

5-Hydroxy-8-hydroxymethyl-7-methoxy-6-methylflavanone (2): To a solution of flavanone **12** (60 mg, 0.211 mmol, 1.0 equiv.) in glacial acetic acid (3 mL) were successively added formalin (37 wt-%, 0.3 mL, ca. 3.8 mmol, 18 equiv.) and concentrated hydrochloric acid (0.3 mL) at room temperature. The mixture was stirred for 1 h before being quenched with water (30 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with a saturated $NaHCO_3$ solution (2 × 5 mL), dried, filtered and concentrated. The crude product was purified on silica gel to give 32 mg (yield 48%) of **2** as a white solid. R_f = 0.26 (hexane/AcOEt, 2:1; anisaldehyde: yellow). − M.p. 120−123°C. − ^{1}H NMR ($CDCl_3$): δ = 2.12 (br. s, 4 H, 6-Me and 8-CH_2OH), 3.00 (*AB*X, 2 H, J_{AB} = 17 Hz, J_{AX} = 12.5 Hz, J_{BX} = 3.5 Hz, Δν = 42 Hz, 3-H), 3.86 (s, 3 H, OMe), 4.69 (br d, 2 H, *J* = 4.5 Hz, 8-CH_2O), 5.46 (dd, AB*X*, 1 H, J_{AX} = 12.5 Hz, J_{BX} = 3.5 Hz, 2-H), 7.3−7.5 (m, 5 H, ArH), 12.18 (s, 1 H, chelated ArOH). − ^{13}C NMR ($CDCl_3$): δ = 8.1 (6-Me), 43.6 (C-3), 54.8 (8-CH_2O), 61.9 (7-OMe), 79.3 (C-2), 105.0, 112.0, 113.2 (C-6, C-8, C-10), 126.1 (C-2′, C-6′), 129.0 (C-4′), 129.0 (C-3′, C-5′), 138.3 (C-1′), 158.3, 161.5, 165.7 (C-5, C-7, C-9), 197.1 (C-4). − UV (MeOH): λ_{max} = 283 (4.00), 351 (3.49). − MS (HR-FAB): calcd. for $C_{18}H_{18}O_5$ 314.1154; found 314.1151.

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