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TETRAHEDRON: *ASYMMETRY*

Synthesis of (+)-(*R*)-5-hydroxy-6-hydroxymethyl-7-methoxy-8-methylflavanone

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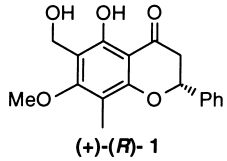
Abstract

The synthesis of (+)-(*R*)-5-hydroxy-6-hydroxymethyl-7-methoxy-8-methylflavanone is described. A new chromylation method of β-ketosulfoxide **9** leading to the Michael acceptor **12** has been developed. Dilithium tetrachlorocuprate was shown to be a very efficient catalyst for the conjugate addition reaction of phenyl magnesium bromide to the α,β-unsaturated sulfoxide **12**. The instability of the obtained adducts **10** represents a limitation in terms of yield. It was confirmed that the natural flavanone leridol does not possess the structure of title compound **1**.

In the course of our studies directed towards biomimetic syntheses of natural flavanones,[1] we have been faced with the preparation of (+)-(*R*)-**1** in enantiomerically pure form, a structure which was erroneously assigned to natural leridol.[1,2]



(+)-(*R*)- 1

Recently, Wallace[3] reported the synthesis of enantiomerically pure (*S*)-2-methylchroman-4-one **2** based on the following procedure: transformation of methyl salicylate into the corresponding β-ketosulfoxide, formylation and cyclodehydration to sulfinylchromone and finally diastereoselective conjugate addition of lithium dimethyl cuprate giving one diastereomer in 24% isolated yield after chromatographic separation. After desulfurization and partial reduction of the carbonyl with aluminium amalgam, a PDC oxidation gave (−)-(*S*)-chromanone **2** in 59% yield (Scheme 1). Without separation of the diastereomeric intermediates, Wallace[3] obtained the cuprate adduct **2** in 88% ee and 65% yield (for the last three steps).

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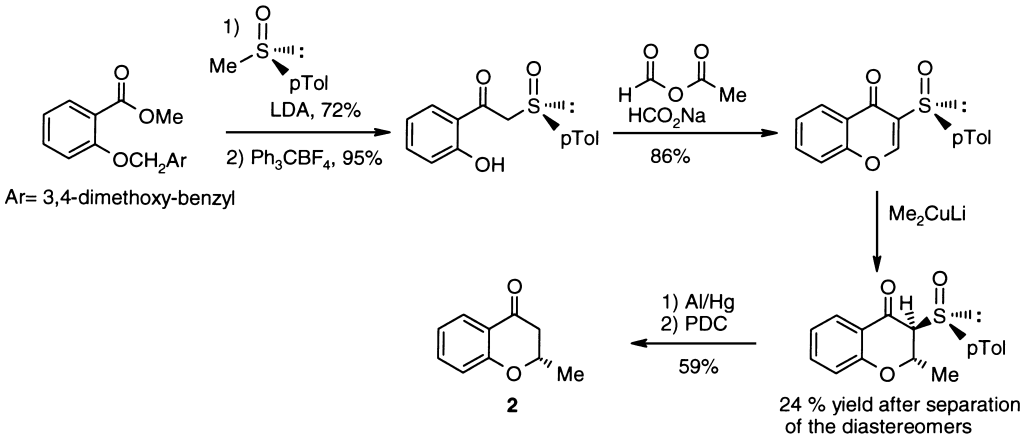
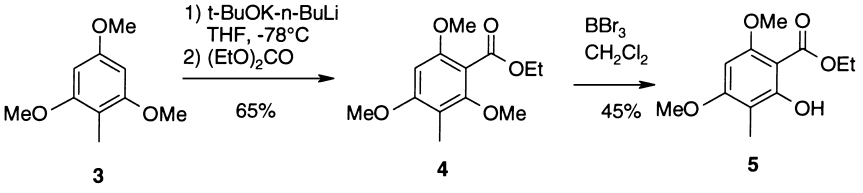


Scheme 1.

Direct application of this method to the synthesis of compound **1** very quickly raised several problems. 2,4,6-Trimethoxytoluene **3** was orthometallated with the complex base of Schlosser (a mixture of *t*-BuOK and *n*-BuLi)[4] and quenched with ethyl carbonate to obtain the ester **4** in 65% yield (Scheme 2). Monodemethylation with BBr_3 in dichloromethane gave a mixture of ethyl 6-hydroxy-2,4-dimethoxy-3-methylbenzoate (33% isolated yield) and ethyl 2-hydroxy-4,6-dimethoxy-3-methylbenzoate **5** (45% isolated yield) which was separated by chromatography and identified by NOE experiments. Unfortunately, all the attempts to obtain the corresponding β-ketosulfoxide by reaction of the ester **5** with an excess of methyl *p*-tolylsulfoxide anion failed, probably because of steric hindrance and ester deactivation by the aromatic oxygens.

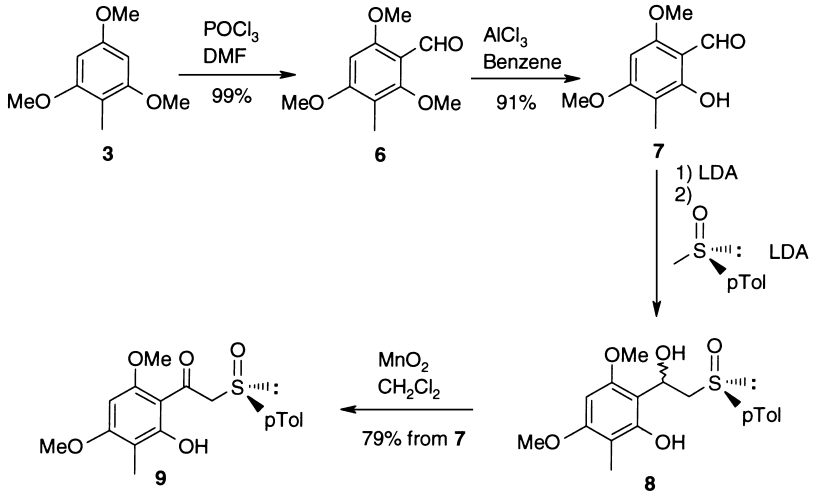


Scheme 2.

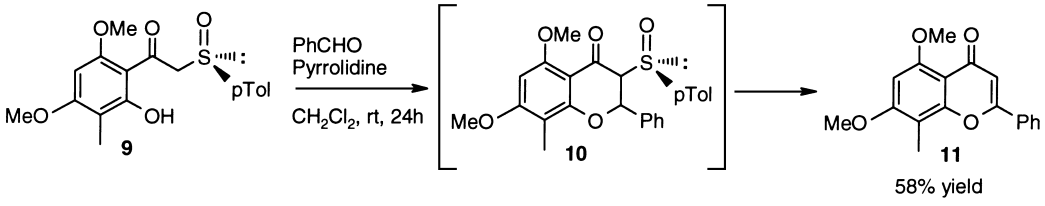
The strategy was modified and the required β-ketosulfoxide **9** was prepared via the aldehyde **7** which was synthesized by Vilsmeier–Haack formylation of trimethoxytoluene[5] and regioselective demethylation with $AlCl_3$ (Scheme 3). Yields were much higher than those obtained for the ester **5**.

Addition of methyl *p*-tolylsulfoxide anion to the phenolate of the aldehyde **7** afforded a diastereomeric mixture (60/40) of the crude and almost pure β-hydroxysulfoxide **8** which was oxidized with MnO_2 to the corresponding β-ketosulfoxide **9**. Compound **9** was obtained from the commercial **3** in excellent yields and without any chromatographic purification.

Reaction of the β-ketosulfoxide **9** with benzaldehyde in the presence of pyrrolidine should give the sulfinylflavanone **10** via a Knoevenagel condensation followed by a cyclization step. However, we isolated only the flavone **11** formed by spontaneous *syn* elimination of *p*-tolylsulfenic acid (Scheme 4). This reaction was already reported for the attempted synthesis of *trans*-3-(phenylsulfinyl)flavanone by *m*-CPBA oxidation of the corresponding sulfide. In contrast, the isomer having the sulfinyl and phenyl groups *cis* was stable and could be obtained in a good yield.[6] In our case, no sulfinylflavanone **10** could be isolated, probably due to a rapid interconversion of the four possible diastereomers under the reaction conditions.

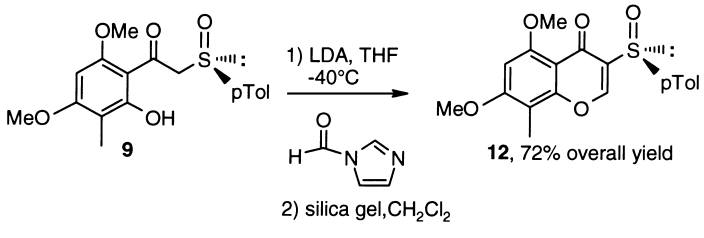


Scheme 3.



Scheme 4.

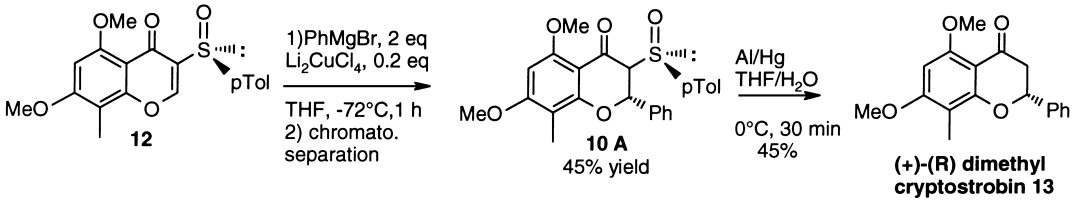
Direct formylation–cyclodehydration of **9** under the conditions of Allan–Robinson proposed by Wallace[3] (acetic formic anhydride, sodium formate, reflux 3 h) gave the sulfinylchromen-4-one **12** in only 22% yield. We finally obtained a yield of 72% by using in situ formed *N*-formylimidazole[7] as formylating agent. The reaction of the dianion of **9** and the imidazolide carried out between −40°C and room temperature gave a mixture of the chromone **12** and a not fully identified intermediate which was transformed into **12** by treatment with silica gel in dichloromethane (Scheme 5). The described conditions represent a new general method for preparation of 3-substituted chromones of type **12**.



Scheme 5.

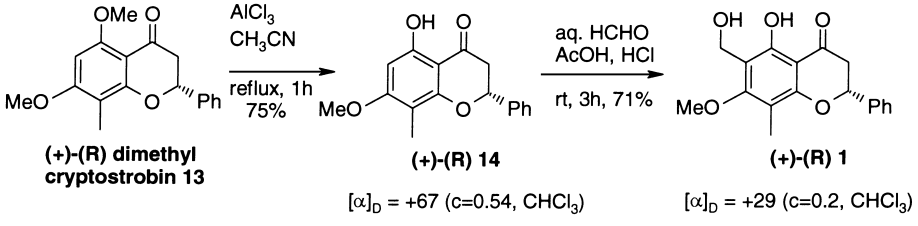
Addition of lithium diphenyl cuprate, phenyl magnesium bromide or phenyl lithium to the chromone **12** gave only traces of addition product **10** and its elimination product **11**. We finally solved this problem by adding the phenylmagnesium bromide in the presence of a catalytic amount of lithium tetrachlorocuprate, a compound used till now only for Würtz type coupling reactions.[8] Under these conditions, a very clean reaction was observed, leading immediately after work-up to a mixture of three diastereomers of **10** and to **11** in the ratio 5:2:2:2, the main diastereomer being **10A** which was isolated by chromatography in 45% yield. The relative stereochemistry of **10A** was not clear from the

coupling constant ($J_{2,3}$=2 Hz). Isomers **10B** and **10C** could not be separated by chromatography, but they showed very different stabilities. Isomer **10C** disappeared almost completely within 24 h, while isomer **10B** seemed to be stable at room temperature in $CDCl_3$. On this basis, it is reasonable to attribute the *trans* stereochemistry to **10C** and *cis* to **10B**. Stability of **10A** was between those of **10B** and **10C**. The main isomer **10A** could be 2,3-*trans* or 2,3-*cis*, the latter suffering from slow epimerization to 2,3-*trans* and rapid elimination of *p*-tolylsulfenic acid. Due to its low stability, **10A** was desulfurized as quickly as possible. The yield with aluminium amalgam was only 45% because some decomposition occurred before running the reaction. The flavanone **13** was identified as (+)-(*R*)-dimethylcryptostrobin, enantiomer of a known natural product (Scheme 6).[9]



Scheme 6.

Finally **13** was regioselectively demethylated with aluminium chloride and hydroxymethylated with formaldehyde, a reaction sequence already used in racemic form **1**, to obtain the flavanone (+)-(*R*)-**1** (Scheme 7).



Scheme 7.

The (+)-enantiomer of **1** exhibited all the characteristics of racemic **1**[1] showing particularly a different melting point (98–100°C) with respect to natural leridol (139–140°C).[2] This is good confirmation that natural leridol does not have the structure **1**. The enantiomerically pure flavanone (+)-(*R*)-**1** could be synthesized in nine steps with an overall yield of 6.1% starting from trimethoxytoluene **3**.

1. Experimental

1.1. General remarks

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer at 200 and 50 MHz, respectively. Chemical shifts δ were 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}. Melting points: Reichert uncorrected. Elemental analysis: Microanalytical Service of CNRS of Strasbourg. Optical rotations: Perkin–Elmer 241 MC polarimeter between 20 and 23°C. 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. Work-up: organic solutions were dried using magnesium sulfate monohydrate ($MgSO_4 \cdot H_2O$), filtered over sintered glass and concentrated by rotary evaporation at water aspirator pressure, unless otherwise stated.

*1.2. Ethyl 2,4,6-trimethoxy-3-methylbenzoate **4***

A 1.5 M solution of *n*-butyllithium in hexane (1.46 ml, 2.19 mmol, 2.0 equiv.) was slowly added to a stirred suspension of *t*-BuOK (246 mg, 2.19 mmol, 2.0 equiv.) in THF (7 ml) at −78°C. To this mixture was added a solution of 2,4,6-trimethoxytoluene **3** (200 mg, 1.10 mmol, 1.0 equiv.) in THF (2 ml). After 30 min, diethyl carbonate (0.63 ml, 2.19 mmol, 2.0 equiv.) was added dropwise. The solution was stirred for 30 min before being quenched with water (10 ml). The two phases were separated and the aqueous phase was extracted with ether (3×20 ml). The combined organic phases were washed with brine (20 ml), dried, filtered and concentrated. The crude product was purified on silica gel to give 182 mg (yield 65%) of **4**. R_f=0.22 (hexane:AcOEt, 4:1); ^{1}H NMR ($CDCl_3$): δ 1.37 (t, 3H, *J*=7 Hz, CH_3 ester), 2.08 (s, 3H, 3-Me), 3.80, 3.82, 3.84 (3s, 9H, 3×OMe), 4.37 (q, 2H, CH_2 ester), 6.24 (s, 1H, H-5).

*1.3. Ethyl 2-hydroxy-4,6-dimethoxy-3-methylbenzoate **5***

To a solution of benzoate **4** (100 mg, 0.393 mmol, 1.0 equiv.) in CH_2Cl_2 (1 ml) was added a 1 M solution of boron tribromide (0.39 mg, 0.39 mmol, 1.0 equiv.) in CH_2Cl_2 at −78°C. The solution was stirred for 1 h before being quenched with water (5 ml). Ethyl acetate was added and the emulsion was broken by adding brine and 10% hydrochloric acid. The two phases were separated and the aqueous phase was extracted with ethyl acetate (3×5 ml). The combined organic phases were dried, filtered and concentrated. The crude product was purified on silica gel to give 42 mg (yield 45%) of **5** as well as 31 mg (yield 33%) of its 6-hydroxy isomer. R_f=0.32 (hexane:AcOEt, 4:1); ^{1}H NMR ($CDCl_3$): δ 1.40 (t, 3H, *J*=7 Hz, CH_3 ester), 2.02 (s, 3H, 3-Me), 3.85, 3.86 (2s, 6H, 2×OMe), 4.38 (q, 2H, *J*=7 Hz, CH_2 ester), 5.99 (s, 1H, H-5), 11.94 (s, 1H, 2-OH); ethyl 6-hydroxy-2,4-dimethoxy-3-methylbenzoate: R_f=0.44 (hexane:AcOEt, 4:1); ^{1}H NMR ($CDCl_3$): δ 1.43 (t, 3H, *J*=7 Hz, CH_3 ester), 2.04 (s, 3H, 3-Me), 3.71, 3.83 (2s, 6H, 2×OMe), 4.42 (q, 2H, *J*=7 Hz, CH_2 ester), 6.27 (s, 1H, H-5), 11.70 (s, 1H, 6-OH).

*1.4. 2,4,6-Trimethoxy-3-methylbenzaldehyde **6***[10]

To a solution of 2,4,6-trimethoxytoluene **3** (5.0 g, 27.4 mmol, 1.0 equiv.) in DMF (15 ml) was slowly added freshly distilled $POCl_3$ (3.0 ml, 32.2 mmol, 1.17 equiv.) at 0°C. The mixture was allowed to reach room temperature and the solution was stirred for a further 2 h before being poured into ice and water (40 ml). Next day the fine white needles were filtered, washed with water and dried overnight at reduced pressure to give 5.221 g (yield 90%) of **6**. The filtrate was extracted with ethyl acetate (3×15 ml). The extracts were dried, filtered and concentrated to give a further 534 mg (yield 9%) of **6**. Total yield: 99%. R_f=0.17 (hexane:AcOEt, 2:1); mp=79–82°C (lit.[10]: 84°C); ^{1}H NMR ($CDCl_3$): δ 2.05 (s, 3H, 3-CH_3), 3.77, 3.89, 3.90 (3s, 9H, 3×OMe), 6.23 (s, 1H, H-5), 10.31 (s, 1H, CHO).

*1.5. 2-Hydroxy-4,6-dimethoxy-3-methylbenzaldehyde **7***

A mixture of aldehyde **6** (5.75 g, 27.3 mmol, 1.0 equiv.) and aluminium trichloride (5.56 g, 41.7 mmol, 1.52 equiv.) was heated at reflux in benzene (50 ml) for 15 h. After cooling, the supernatant was discarded and the residual viscous oil was dried in vacuo before being hydrolyzed with water (30 ml) and conc.

hydrochloric acid (30 ml). Dichloromethane (200 ml) was added, the two phases were separated and the aqueous phase containing a yellow-orange precipitate was stirred overnight with CH_2Cl_2 (50 ml). The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×30 ml). The combined organic phases were washed with a saturated $NaHCO_3$ solution (40 ml) and brine (40 ml). They were dried, filtered and concentrated to give 4.90 g (yield 91%) of **7** as a solid (virtually pure in ^{1}H NMR) which could be crystallized from ethanol (125 ml) to yield yellowish flakes. R_f=0.34 (hexane:AcOEt, 2:1); mp=168–169°C (lit.[11]: 168–169°C); ^{1}H NMR ($CDCl_3$): δ 1.99 (s, 3H, 3-CH_3), 3.89, 3.91 (2s, 6H, 2×OMe), 5.94 (s, 1H, H-5), 10.14 (s, 1H, CHO), 12.44 (s, 1H, 2-OH).

*1.6. (*R*$_S$)-1-(2-Hydroxy-4,6-dimethoxy-3-methylphenyl)-2-(*p*-tolylsulfinyl)ethanol **8***

Two identical solutions of LDA in THF/hexane (approx. 50 ml, 18.6 mmol, 1.1 equiv.) were prepared. (+)-(*R*)-Methyl *p*-tolylsulfoxide[12] (2.604 g, 16.88 mmol, 1.02 equiv.) dissolved in THF (15 ml) was added to the first solution of LDA at −10°C (solution A). The second solution of LDA was cannulated to a suspension of aldehyde **7** (3.25 g, 16.56 mmol, 1.0 equiv.) in THF (30 ml) at −40°C. The suspension became white and the temperature was allowed to reach 0°C for approx. 1 h (suspension B). Solution A was then cannulated to suspension B at −40°C. The precipitate dissolved during addition and the obtained clear yellow solution was stirred for 1 h while allowing the temperature to reach −25°C. The reaction was quenched with 1 M hydrochloric acid (60 ml) and the pH was adjusted to 2–3. The two phases were separated and the aqueous phase was extracted with ethyl acetate (3×25 ml). The combined organic phases were washed with brine (50 ml), dried, filtered and concentrated. The oily brown crude product was re-evaporated with CH_2Cl_2 (20 ml) to give 5.90 g (mass yield 100%) of **8** as a whitish solid. R_f=0.53 (AcOEt; anisaldehyde: blue; the diastereomeric mixture gave a single spot in TLC); ^{1}H NMR ($CDCl_3$): the spectrum indicated the presence of two diastereomers (83%) in a 60:40 ratio, as well as those of aldehyde **7** (7%) and starting sulfoxide (10%). Yield of crude product was thus estimated to be 92%. Major isomer: δ 1.99 (s, 3H, 3′-CH_3), 2.47 (s, 3H, CH_3 *p*-Tol), 2.59 (dd, 1H, J_{AB}=14 Hz, $J_{1,2}$=1.5 Hz, H-2B), 3.40 (s, 3H, OMe), 3.65 (dd, 1H, J_{AB}=14 Hz, $J_{1,2}$=10.5 Hz, H-2A), 3.74 (s, 3H, OMe), 5.65 (m, 1H, H-1), 5.83 (m, 2H, 1-OH and H-5′), 7.48 (A_2B_2, 4H, J=8 Hz, Δν=26.5 Hz, ArH), 9.58 (s, 1H, 2′-OH); minor isomer: δ 1.99 (s, 3H, 3′-CH_3), 2.41 (s, 3H, CH_3 *p*-Tol), 2.90 (dd, 1H, $J_{1,2}$=2.5 Hz, H-2B), 3.28 (dd, 1H, H-2A), 3.79 (s, 3H, OMe), 3.81 (s, 3H, OMe), 5.83 (m, 1H, 1-OH), 5.99 (s, 1H, H-5′), 6.05 (m, 1H, H-1), 7.43 (A_2B_2, 4H, J=8 Hz, Δν=45 Hz, ArH), 9.44 (s, 1H, 2′-OH); the other coupling constants could not be determined.

*1.7. (−)-(*R*$_S$)-1-(2-Hydroxy-4,6-dimethoxy-3-methylphenyl)-2-(p-tolylsulfinyl)ethanone **9***

A mixture of crude hydroxysulfoxide **8** (3.75 g, 10.7 mmol, 1.0 equiv.) and MnO_2 (Fluka 63548 activated at 120°C; 6.12 g, 70 mmol, 6.6 equiv.) in CH_2Cl_2 (30 ml) was stirred at room temperature for 48 h. A second portion of MnO_2 (4.0 g, 46 mmol, 4.3 equiv.) was added and the mixture was stirred for a further 20 h. The reagent was separated by filtration over sintered glass (porosity 4) and well washed with CH_2Cl_2. The filtrate was reduced to 50 ml on the rotary evaporator and washed with 0.3 M hydrochloric acid (10 ml), a saturated $NaHCO_3$ solution (10 ml) and brine (10 ml). The organic phase was dried, filtered and concentrated to give 3.37 g (90%) of crude product. The crude product was crystallized from ethyl acetate (76 ml) to give 2.482 g (yield 67.6%) of **9** as fine yellow needles. The residue of the mother liquor was purified by chromatography on silica gel to give a further 435 mg (11.8%) of **9**. Overall yield: 79% based on aldehyde **7**. R_f=0.30 (AcOEt; anisaldehyde: orange red); mp=170–172°C; $[\alpha]_D$=−44 (*c* 1.0; $CHCl_3$); the optical rotations of the chromatographed and crystallized products, respectively, were

identical. ^{1}H NMR ($CDCl_3$): δ 1.98 (s, 3H, 3′-CH_3), 2.40 (s, 3H, Me *p*-Tol), 3.90 (s, 3H, OMe), 3.92 (s, 3H, OMe), 4.54 (AB, 2H, *J*=14 Hz, Δν=85 Hz, H-2), 5.94 (s, 1H, H-5′), 7.43 (A_2B_2, 4H, *J*=8 Hz, Δν=53 Hz, ArH), 13.17 (s, 1H, 2′-OH); ^{13}C NMR ($CDCl_3$): δ 7.2 (5′-Me), 21.5 (Me *p*-Tol), 55.7, 55.8 (OMe), 72.2 (C-2), 86.0 (C-5′), 105.6, 106.2 (C-1′, C-3′), 124.5, 130.0 (C_{ar}t), 141.0, 141.9 (C_{ar}q), 161.3, 163.9, 164.8 (C-2′, C-4′, C-6′), 194.2 (C-1); IR ($CHCl_3$): ν_{max} (cm^{-1}) 3960, 3920, 2990, 2400, 1630, 1600, 1495, 1470, 1410, 1290, 1145, 1090, 1035, 1015, 940. Anal. calcd for $C_{18}H_{20}O_5S$: C, 62.05; H, 5.79. Found: C, 62.14; H, 5.62.

*1.8. 5,7-Dimethoxy-8-methylflavone **11***

To a solution of ketosulfoxide **9** (55 mg, 0.158 mmol, 1.0 equiv.) in CH_2Cl_2 (2 ml) was added 0.4 ml of a solution prepared from benzaldehyde (1.0 ml, 9.8 mmol), pyrrolidine (0.1 ml, 1.2 mmol) and CH_2Cl_2 (4 ml). The solution was stirred for 22 h before being evaporated to dryness. A mixture of hexane:AcOEt (1:1, 5 ml) was added and the solid product was filtered to give 27 mg (yield 58%) of **11**. The crude product was crystallized from ethanol (1.4 ml) to give fine white needles. $R_f \approx 0.05$ (AcOEt; anisaldehyde: yellow); mp=228–229°C (lit.[13]: 230–232°C); ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H, 8-Me), 3.95, 4.00 (2s, 6H, 2×OMe), 6.42 (s, 1H, H-6), 6.67 (s, 1H, H-2), 7.5 (m, 3H, ArH), 7.9 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$): δ 8.2 (8-Me), 55.9, 56.5 (OMe), 91.5 (C-6), 106.2, 108.4 (C-8, C-10), 126.0 (C-2′, C-6′), 129.1 (C-3′, C-5′), 131.2 (C-4′), 132.0 (C-1′), 156.7, 159.1, 160.5, 161.4 (C-2, C-5, C-7, C-9), 178.4 (C-4).

*1.9. (−)-(S$_S$)-5,7-Dimethoxy-8-methyl-3-(*p*-tolylsulfinyl)chromen-4-one **12***

A solution of LDA (14.9 mmol, 2.6 equiv.) was cannulated to a suspension of ketosulfoxide **9** (2.00 g, 5.75 mmol, 1.0 equiv.) in THF (25 ml) at −40°C, giving an orange solution. The temperature was then allowed to reach −20°C (solution A). At the same time, 1-formyl-1*H*-imidazole was prepared in situ at room temperature by adding formic acid (0.47 ml, 12.3 mmol, 2.13 equiv.; in 5 ml of THF) to a solution of 1,1′-carbonyldiimidazole (2.01 g, 12.4 mmol, 2.16 equiv.) in THF (15 ml) (solution B). Solution B was added to solution A at −60°C and the mixture was allowed to reach room temperature. The solution was stirred overnight before being quenched with 1 M sulfuric acid (15 ml). The organic solvents were evaporated and the residue was taken up with CH_2Cl_2 and washed with brine. The organic phase was dried, filtered and concentrated. The crude product was dissolved in CH_2Cl_2 (35 ml) and stirred in the presence of silica gel (6 g) until disappearance of the intermediate product (2 h). This mixture was poured onto a filled column of silica gel/CH_2Cl_2 and eluted with CH_2Cl_2:AcOEt (3:1) to give 1.490 g (yield 72%) of **12**. The product could be crystallized from AcOEt (25 ml) and CH_2Cl_2 (10 ml). R_f=0.42 (CH_2Cl_2:AcOEt, 1:1); R_f (intermediate product)=0.27 (CH_2Cl_2:AcOEt, 1:1); mp=223–225°C (fine white needles); $[\alpha]_D$=−300 (*c* 1.0; $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 3H, 8-CH_3), 2.35 (s, 3H, Me *p*-Tol), 3.92, 3.93 (2s, 6H, 2×OMe), 6.37 (s, 1H, H-6), 7.51 (AB, 4H, *J*=8 Hz, Δν=108 Hz), 8.24 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$): δ 7.8 (8-Me), 21.5 (Me *p*-Tol), 56.0, 56.4 (OMe), 92.0 (C-6), 106.5, 108.3 (C-8, C-10), 125.7, 129.9 (C_{ar}t), 129.6 (C-3), 140.6, 142.0 (C_{ar}q), 152.8 (C-2), 156.8, 159.4, 162.1 (C-5, C-7, C-9), 173.2 (C-4); IR ($CHCl_3$): ν_{max} (cm^{-1}) 3690, 3620, 2990, 2400, 1645, 1610, 1585, 1500, 1470, 1435, 1395, 1340, 1315, 1270, 1145, 1125, 1080, 1035, 1015, 950, 920. Anal. calcd for $C_{19}H_{18}O_5S$: C, 63.67; H, 5.06. Found: C, 63.69; H, 4.81.

1.10. (2R,S_S)-5,7-Dimethoxy-8-methyl-3-(p-tolylsulfinyl)flavanone **10A**

The sulfoxide **12** (385 mg, 1.08 mmol, 1.0 equiv.) was dissolved in a minimum of THF (20 ml) and a 0.1 M solution of Li_2CuCl_4 in THF (2.2 ml, 0.22 mmol, 0.2 equiv.) was added at −72°C. The formed white precipitate dissolved during the slow addition of a solution of 1 M PhMgBr in THF (2.2 ml, 0.22 mmol, 2.0 equiv.). The solution was stirred for 1 h between −72 and −40°C before being quenched with a saturated NH_4Cl solution. The two phases were separated and the aqueous phase was extracted with ethyl acetate (3×10 ml). The combined organic phases were washed with brine, dried, filtered and concentrated. The crude product was chromatographed on demetalated silica gel to give 211 mg (yield 45%) of **10A**. R_f=0.57 (CH_2Cl_2:AcOEt, 1:1); ^{1}H NMR ($CDCl_3$): δ 2.14 (s, 3H, 8-Me), 2.41 (s, 3H, Me *p*-Tol), 3.84, 3.91 (2s, 6H, 2×OMe), 3.94 (d, 1H, $J_{2,3}$=2 Hz, H-3), 6.07 (s, 1H, H-6), 6.36 (d, 1H, $J_{2,3}$=2 Hz, H-2), 7.2–7.5 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$): δ 8.0 (8-Me), 21.7 (Me *p*-Tol), 55.8 and 56.0 (OMe), 75.7 and 77.3 (C-2, C-3), 88.5 (C-6), 106.4, 106.5 (C-8, C-10), 125.0, 126.0, 128.3, 128.8, 130.0 (C_{ar}t), 136.6, 138.4, 142.5 (C_{ar}q), 158.9, 160.4, 164.7 (C-5, C-7, C-9), 180.6 (C-4). Isomers **10B** and **10C**: R_f=0.42 (CH_2Cl_2:AcOEt, 1:1); ^{1}H NMR ($CDCl_3$): **10B** characteristic signals: δ 3.79 (d, 1H, *J*=2.5 Hz, H-3), 5.85 (d, 1H, *J*=2.5 Hz, H-2), 6.16 (s, 1H, H-6); **10C** characteristic signals: δ 5.91 (s, 1H, H-6), 6.20 (d, H-2).

1.11. (+)-(R)-5,7-Dimethoxy-8-methylflavanone (dimethylcryptostrobin) **13**

Aluminium amalgam (Al/Hg) (90 mg, 3.3 mmol, 9.4 equiv.) was added to a stirred solution of sulfinylflavanone **10A** (155 mg, 0.355 mol, 1.0 equiv.) in THF:H_2O (9:1, 15 ml) at −5°C. The solution was stirred for 35 min before being filtered over sintered glass. The precipitate was washed with THF (3×10 ml), water (5 ml) and brine (10 ml) were added and the product was extracted with ethyl acetate (3×10 ml). The combined organic phases were dried, filtered and concentrated. The crude product was chromatographed on silica gel to give 47.5 mg (yield 45%) of **13**. Mp=139–141°c (lit.[9]: 141–142°C for the (*S*)-isomer); $[\alpha]_D$=+37.5 (*c* 0.93; EtOH); lit.[9]: $[\alpha]_D$=−37.1 (*c* 0.38; EtOH) for the (*S*)-isomer; ^{1}H NMR ($CDCl_3$): δ 2.04 (s, 3H, 8-Me), 2.89 (*AB*X, 2H, J_{AB}=16.5 Hz, J_{AX}=12 Hz, J_{BX}=4 Hz, Δν=22.5 Hz, H-3), 3.89 and 3.92 (2s, 6H, 2×OMe), 5.38 (dd, AB*X*, 1H, J_{AX}=12 Hz, J_{BX}=4 Hz, H-2), 6.11 (s, 1H, H-6), 7.3–7.5 (m, 5H, 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).

1.12. (+)-(R)-5-Hydroxy-7-methoxy-8-methylflavanone **14**

A mixture of **13** (46 mg, 0.154 mmol, 1.0 equiv.) and anhydrous aluminium chloride (75 mg, 0.56 mmol, 3.6 equiv.) in acetonitrile (2.5 ml) was refluxed for 2 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 brine (5 ml), dried, filtered and concentrated. The crude product was purified on silica gel to give the title compound **14** (33 mg, yield 75%). R_f=0.57 (hexane:AcOEt. 3:1, anisaldehyde: orange); mp=143–145°C (lit.[14]: mp=143°C); $[\alpha]_D$=+67 (*c* 0.54; $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.01 (s, 3H, 8-Me), 2.94 (*ABX*, 2H, J_{AB}=17 Hz, J_{AX}=12.5 Hz, J_{BX}=3.5 Hz, Δν=35.5 Hz, H-3), 3.86 (s, 3H, OMe), 5.42 (dd, AB*X*, 1H, J_{AX}=12.5 Hz, J_{BX}=3.5 Hz, H-2), 6.10 (s, 1H, H-6), 7.3–7.5 (m, 5H, ArH), 12.12 (s, 1H, 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).

*1.13. (+)-(*R*)-5-Hydroxy-6-hydroxymethyl-7-methoxy-8-methylflavanone **1***

To a solution of flavanone **14** (26 mg, 0.091 mmol, 1.0 equiv.) in glacial acetic acid (4 ml) were successively added formalin 37 wt% (0.3 ml, ~3.8 mmol, 40 equiv.) and concentrated hydrochloric acid (0.3 ml) at room temperature. The mixture was stirred for 4 h before being quenched with water (20 ml). The aqueous phase was extracted with ethyl acetate (4×10 ml). The combined organic phases were washed with a saturated $NaHCO_3$ solution (10 ml), dried, filtered and concentrated. The crude product was purified on silica gel to give 20.5 mg (yield 71%) of **1** as a white solid. R_f=0.43 (hexane:AcOEt, 1:1, vanillin: red); mp=98–100°C; $[\alpha]_D$=+29 (*c* 0.2; $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.10 (s, 3H, 8-Me), 2.34 (t, 1H, *J*=6.5 Hz, OH), 2.98 (*AB*X, 2H, J_{AB}=17 Hz, J_{AX}=12 Hz, J_{BX}=3.5 Hz, Δν=35 Hz, H-3), 3.85 (s, 3H, OMe), 4.73 (d, 2H, *J*=6.5 Hz, 6-CH_2O), 5.45 (dd, AB*X*, 1H, J_{AX}=12 Hz, J_{BX}=3.5 Hz, H-2), 7.39–7.50 (m, 5H, ArH), 12.15 (s, 1H, 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) and 165.7 (C-5, C-7, C-9), 197.5 (C-4).

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