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CONJUGATE ADDITION TO 3-(*p*-TOLYLSULPHINYL)CHROMONE: A ROUTE TO 2-SUBSTITUTED CHROMONES AND CHIRAL 2-SUBSTITUTED CHROMAN-4-ONES

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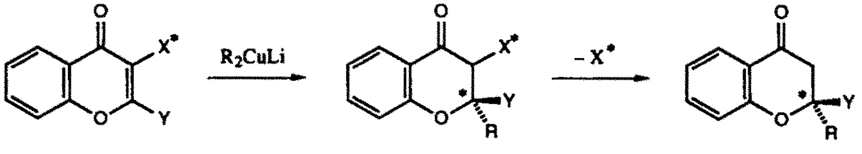
Abstract: 3-(*p*-Tolylsulphinyl)chromone **3a** undergoes diastereoselective conjugate addition of lithium dimethylcuprate, producing a mixture of 2-methyl-3-(*p*-tolylsulphinyl)chroman-4-ones. Heating the mixture to 140 °C gives 2-methylchromone in quantitative yield. Desulphurisation of the mixed products from (*S*)-**3a** gives (*S*)-2-methylchroman-4-one with 90% e.e. Chelation of the carbonyl and sulphoxide oxygens during methyl addition accounts for the diastereoselection.

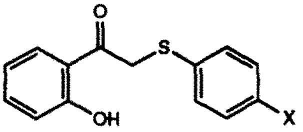
We previously described a route to 2-substituted chroman-4-ones based on the conjugate (1,4-) addition of cuprates to chromones (4-oxo-4*H*-1-benzopyrans) activated by electron-withdrawing groups at C-3.[1] In seeking a means of inducing chirality at C-2 during this reaction, we were attracted by the possibility that the substituent X responsible for activating the chromone towards the addition might also serve as a removable chiral auxiliary, as indicated in Scheme 1. The successful use of a *p*-tolylsulphinyl substituent in a similar role by Posner and coworkers[2] prompted us to investigate the reactions of 3-(*p*-tolylsulphinyl)chromone with lithium dimethylcuprate and other organometallic reagents, and our findings are herein reported in detail.[3]



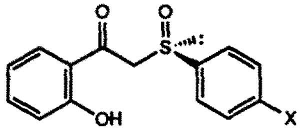
SCHEME 1

Preparation of Racemic 3-(Arylsulphinyl)chromones

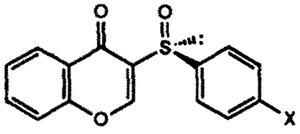
A general route to racemic 3-(arylsulphinyl)chromones was established. Thus, treatment of 2-bromo-2'-hydroxyacetophenone with the sodium salt of *p*-thiocresol gave 2'-hydroxy-2-(*p*-tolylthio)acetophenone **1a** in 83% yield. Oxidation of **1a** with *m*-chloroperoxybenzoic acid (*m*-CPBA) gave the corresponding sulphoxide (±)-**2a** (95%), which was condensed with acetic-formic anhydride and sodium formate to obtain the desired chromone sulphoxide (±)-**3a** (56%) as a colourless crystalline solid. Analogous sequences provided the 3-(phenylsulphinyl)- and 3-(4-chlorophenylsulphinyl)chromones (±)-**3b** and (±)-**3c** respectively.



1 **a** X = Me
b X = H
c X = Cl



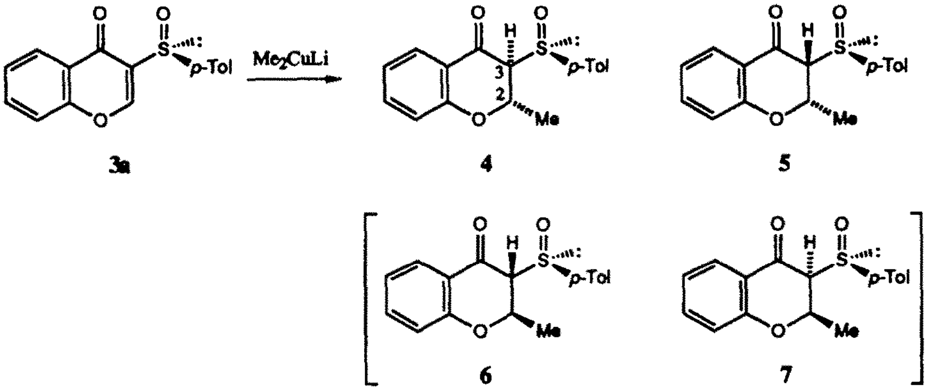
2 **a** X = Me
b X = H
c X = Cl



3 **a** X = Me
b X = H
c X = Cl

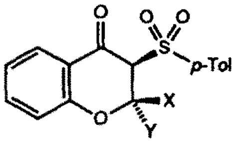
Diastereoselective Conjugate Addition to Racemic 3-(p-Tolylsulphinyl)chromone

The conjugate addition of a methyl group to a chromone (±)-**3** could in principle generate up to four pairs of diastereoisomeric chromanones, as indicated in Scheme 2. In the event, treatment of (±)-**3a** with lithium dimethylcuprate gave two main products (total 87%) in a ratio of *ca.* 4:1, as judged by n.m.r. spectroscopy. Their relative stereochemistry was not clear from coupling constants (*i.e.* $J_{2,3}$ values), and they were only identified as the respective 2,3-*trans* and 2,3-*cis* isomers (±)-**4** and (±)-**5** after a series of chemical tests.

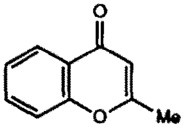


SCHEME 2

Thus, oxidation of the mixed sulphoxides obtained from (±)-**3a** with *m*-CPBA gave a mixture of sulphones **8** and **9** in the same ratio, indicating that the original sulphoxides differed in their C-2/C-3 relative stereochemistry and were not merely epimeric at sulphur. Thermolysis of the mixed sulphoxides at 80 °C resulted in the disappearance (during three hours) of the major component and the simultaneous formation of the chromone **10**, establishing that the major (labile) cuprate adduct was either **4** or **6**, *i.e.* had 2,3-*trans* stereochemistry, since the transition state for *syn*-elimination leading to the chromone **10** is not readily accessible to the 2,3-*cis* diastereoisomers **5** and **7**.



8 X = H Y = Me
9 X = Me Y = H



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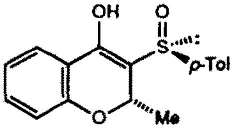

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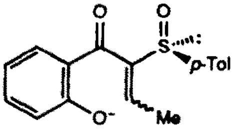
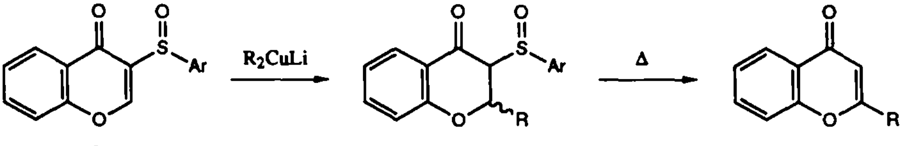


12

Thermolysis of the mixture of **4** and **5** at 140 °C generated the chromone **10** quantitatively, so the conjugate addition/thermolysis sequence (Scheme 3) constitutes a potentially general route to 2-substituted chromones. Presumably at 140 °C the *trans*- and *cis*-sulphoxides **4** and **5** can equilibrate *via* the enol tautomer **11**.



SCHEME 3

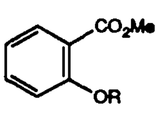
To determine whether the chromanones obtained from (±)-**3a** possessed the same relative stereochemistry with respect to sulphur and C-2, the *trans*-isomer (±)-**4** [δ_H 1.46 (d, J 7 Hz, 2-Me)] was isolated and treated with d_5-pyridine in deuteriochloroform. This gave rise to the characteristic ^{1}H n.m.r. signals of the previously observed *cis*-isomer (±)-**5** [δ_H 1.92 (d, J 7 Hz, 2-Me)]. It is reasonable to assume that this equilibration (**4**:**5** ratio 87:13 after 16 h at room temperature) proceeds *via* the anion of the enol **11**, and confirms that **4** and **5** differ in stereochemistry only at C-3. Equilibration of (±)-**4** under more vigorous conditions (NaOMe, tetrahydrofuran, room temperature, 14 h, aq. HCl quench; recovery 82%) generated a mixture containing all four of the diastereoisomers **4**, **5**, **6** [δ_H 1.465 (d, J 7 Hz, 2-Me)], and **7** [δ_H 1.88 (d, J 7 Hz, 2-Me)] in the proportions 55:8:19:18. The lability of **6** at 80 °C indicated its 2,3-*trans* arrangement as it had for **4**. Having located the signals from traces of **6** and **7** in the ^{1}H n.m.r. spectrum of the original cuprate addition mixture, the diastereoisomeric excess (d.e.) of (**4** + **5**) relative to (**6** + **7**) was estimated by integration to be *ca*. 90%.

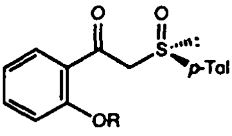
Presumably **6** and **7** are formed from **4** *via* the anion **12** in a retro-Michael/Michael process,[4] and from a synthetic viewpoint it is significant that the conditions required to generate **12** appear to be considerably more severe than those of the cuprate addition reaction itself, and that the latter should therefore provide a stereochemically secure route to chiral non-racemic 2-substituted chroman-4-ones.

The reactions of (±)-**3a** with other organometallic methylating agents was also briefly investigated. Use of the methylcopper - boron trifluoride - tributylphosphine system[5] gave a product mixture essentially the same as that obtained using the cuprate reagent, whereas with methylmagnesium iodide the product composition was similar but the overall yield and d.e. were both slightly reduced.

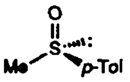
Enantioselective Preparation of (*S*)-(−)-2-Methylchroman-4-one

In order to establish the absolute stereochemical course of cuprate addition reaction, the chromone sulphoxide (*S*)-(−)-**3a** was prepared. Initial experiments showed that the hydroxyl function of methyl salicylate could be protected using various alkyl groups, and the products **13** converted into the corresponding ketosulphoxides (±)-**14** *via* treatment with the lithium derivative of (±)-methyl *p*-tolyl sulphoxide (±)-**15**. However, it was found that only the 3,4-dimethoxybenzyl[6] compound (±)-**14a** could be efficiently deprotected in order to obtain the chromone precursor **2a**. The chromone (*S*)-**3a** was therefore prepared from **13a**. Acylation of the lithium derivative of (*R*)-(+)-methyl *p*-tolyl sulphoxide (*R*)-**15** with **13a** afforded the ketosulphoxide (*R*)-**14** in 72% yield. Deprotection with trityl fluoroborate gave the chromone precursor (*R*)-**2a** (95%), which was converted into the chromone (*S*)-**3a** (86%) in the conventional manner, with acetic-formic anhydride/sodium formate.





13	R	14
a	3,4-dimethoxybenzyl	a
b	4-methoxybenzyl	b
c	methyl	c



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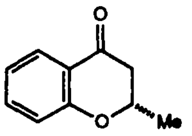
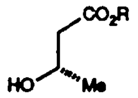


(*S*)-16



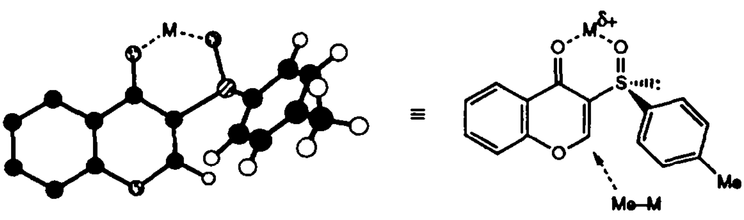
(*S*)-17 R = H
(*S*)-18 R = Me

Treatment of (*S*)-**3a** with lithium dimethylcuprate gave the expected mixture of chromanones **4** - **7** from which the *cis*-isomer (+)-**5** was isolated in 24% yield by chromatography followed by crystallisation from ethanol - pyridine.[7] Removal of the sulphoxide moiety from (+)-**5** was effected with aluminium amalgam, but this also caused some carbonyl reduction which necessitated re-oxidation with pyridinium dichromate. This gave (*S*)-2-methylchroman-4-one (*S*)-**16** (59% over two steps), $[\alpha]_D^{22}$ –50° ±4° (*c* 1.2, chloroform). When another sample of (*S*)-**3a** was carried through the above sequence but without separation of the intermediate cuprate adducts, the (*S*)-**16** so obtained (65% over three steps) had $[\alpha]_D^{21}$ –44° ±2° (*c* 2.0, chloroform), indicating an enantiomeric excess (e.e.) of 88%. This is in close agreement with the 90% d.e. estimated for the cuprate addition step *via* ^{1}H n.m.r. spectroscopy.

The (*S*)-configuration at C-2 of (–)-**16** was initially assigned from its c.d. spectrum (see Experimental), there being a reliable relationship between the signs of the Cotton effects due to the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions of such ketones and their absolute stereochemistry.[8] The assignment was confirmed by ozonolytic degradation of a sample of (–)-**16** into (*S*)-3-hydroxybutanoic acid **17**, which was isolated as the known methyl ester (*S*)-(+)-**18** after treatment with diazomethane.

Mechanistic Considerations

The observed results are consistent with a mechanistic model analogous to one advanced previously by Posner and coworkers,[2] based on the principle that chelation of the two oxygens of the substrate (*S*)-**3a** by a metallic species M results in shielding of the *re* face of the reacting enone by the tolyl substituent, as depicted in **19**. As a result, the incoming methyl group preferentially attacks the unhindered *si* face, and (2*S*) chirality is induced.



19

In principle, acylation of the ketosulphoxide (*R*)-**2a** offers a general route to 2-substituted homologues of the chromone (*S*)-**3a**, and hence to chiral non-racemic 2,2-disubstituted chroman-4-ones. The scope and limitations of this synthetic method are currently under investigation.

EXPERIMENTAL

All compounds are racemic unless signs of rotation are indicated in the text. Melting points were determined using an Electrothermal apparatus and are uncorrected. Unless otherwise stated, i.r. spectra were of liquid paraffin mulls on sodium chloride plates, recorded on Pye-Unicam SP3-100, Perkin-Elmer 297, or Perkin-Elmer 1710FT spectrometers. N.m.r. spectra were measured for solutions in deuteriochloroform unless otherwise indicated, with tetramethylsilane as the internal standard, on Varian EM 360 (60 MHz), Varian CFT-20 (80 MHz), Perkin-Elmer R32 (90 MHz), or Bruker (300, 360 and 400 MHz) instruments. U.v. spectra were recorded using a Pye-Unicam SP800 spectrometer. Mass spectra were measured on a Kratos MS30 instrument with a 70 eV electron impact source. Optical rotations were measured on an Optical Activity AA-10 polarimeter.

Starting materials and solvents were routinely purified by conventional techniques.[9] Distillation of liquid products was performed using a bulb-to-bulb (Kugelrohr) apparatus, and the temperatures quoted are those of the oven. Organic solutions were dried using anhydrous magnesium sulphate and concentrated by rotary evaporation. Analytical thin layer chromatography (t.l.c.) was carried out on Camlab Polygram SIL G/UV$_{254}$ plates. Preparative (column) chromatography was carried out using 60H silica gel (Merck 7736 and hand-bellows pressure, or Merck 9385 and the flash technique[10]). Compositions of solvent mixtures are quoted as ratios of volume. 'Petroleum' refers to a light petroleum fraction, b.p. 40–60 °C, unless otherwise stated. 'Ether' refers to diethyl ether.

1-(2-Hydroxyphenyl)-2-[(4-methylphenyl)thio]ethanone **1a**. – A solution of sodium 4-methylbenzenethiolate [from sodium (0.35 g, 15.2 mmol) and 4-methylbenzenethiol (1.88 g, 15.2 mmol)] in absolute ethanol (10 ml) was added dropwise at room temperature to a solution of 2-bromo-2'-hydroxyacetophenone[11] (3.2 g, 15 mmol) in 1,4-dioxane (5 ml). After stirring for a further hour the mixture was treated with water (30 ml) and the resulting precipitate collected by filtration. Washing with water, drying by suction, and crystallisation from petroleum gave the *title compound* **1a** (3.2 g, 83%), which formed colourless prisms, m.p. 66–67 °C (dichloromethane - petroleum) (Found: C, 69.75; H, 5.5. $C_{15}H_{14}O_2S$ requires C, 69.7; H, 5.5%); ν_{max} 1635 and 1610 cm^{-1}; δ (60 MHz) 2.37 (3 H, s, Me), 4.22 (2 H, s, CH$_2$), 6.8–7.9 (8 H, m, ArH), and 12.05 (1 H, s, exchanges with D$_2$O, OH); *M*$^+$, 258.

1-(2-Hydroxyphenyl)-2-(phenylthio)ethanone **1b**.[12] – This was prepared by the procedure described above for the homologue **1a**, using 4-methylbenzenethiol (1.88 g, 15.2 mmol). The title compound **1b** (2.8 g, 77%) formed colourless needles, m.p. 52–54 °C (lit.[12] 55 °C); ν_{max} 1625 and 1605 cm^{-1}; δ (60 MHz) 5.13 (2 H, s, CH$_2$), 7.6–8.75 (9 H, m, ArH), and 11.95 (1 H, s, exchanges with D$_2$O, OH).

The preparations of compounds **1c**, **2c**, and **3c** have been described.[13]

1-(2-Hydroxyphenyl)-2-[(4-methylphenyl)sulphinyl]ethanone **2a**. – Method A: To a stirred solution of the acetophenone **1a** (1.29 g, 5 mmol) in dichloromethane (10 ml) was added dropwise at 0 °C a solution of *m*-CPBA (1.1 g, 6.4 mmol) in dichloromethane (20 ml). The mixture was kept at 0 °C for 5 h and water (30 ml) then added. The dichloromethane layer was separated and the aqueous layer extracted with dichloromethane (3 x 30 ml). The combined organic phase was washed successively with water (2 x 50 ml), saturated aqueous sodium hydrogen carbonate (50 ml), and brine. The solution was evaporated and the residue crystallised to obtain the pure *title compound* **2a** (1.30 g, 95%), m.p. 118–119 °C (ether - dichloromethane) (Found: C, 65.55; H, 5.1. $C_{15}H_{14}O_3S$ requires C, 65.7; H, 5.1%); ν_{max} 1660, 1600, and 980 cm^{-1}; δ (60 MHz) 2.4 (3 H, s, Me), 4.2 and 4.5 (each 1 H, d, *J* 14 Hz, CH_2), 6.6–7.8 (8 H, m, ArH), and 11.75 (1 H, s, exchanges with D_2O, OH); *M*$^+$, 274.

Method B: To a stirred solution of the sulphoxide (±)-**14a** (0.42 g, 1.0 mmol) in dichloromethane (10 ml) at 0 °C was added dropwise a solution of triphenylcarbenium tetrafluoroborate (0.40 g, 1.2 mmol) in dichloromethane (10 ml). After 2 h at 0 °C followed by 0.5 h at room temperature, the reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate (20 ml). The organic phase was washed with water (2 x 10 ml) and brine (10 ml), dried, and evaporated. Flash chromatography of the residue, eluting with ethyl acetate - petroleum (2:3), gave triphenylmethane followed by the sulphoxide **2a** (0.22 g, 81%), identical to the material prepared by Method A.

1-(2-Hydroxyphenyl)-2-(phenylsulphinyl)ethanone **2b**. – This was prepared in the same manner as the homologue **2a** (Method A), using the acetophenone **1b** (1.22 g, 5 mmol) and *m*-CPBA (1.1 g, 6.4 mmol). The *title compound* **2b** (1.17 g, 90%) had m.p. 117–118 °C (Found: C, 64.6; H, 4.7. $C_{14}H_{12}O_3S$ requires C, 64.6; H, 4.65%); ν_{max} 1630, 1600, and 1040 cm^{-1}; δ (60 MHz) 4.22 and 4.53 (each 1 H, d, *J* 14 Hz, CH_2), 6.7–7.85 (9 H, m, ArH), and 11.52 (1 H, s, exchanges with D_2O, OH); *M*$^+$, 260.

*3-[(4-Methylphenyl)sulphinyl]-4*H*-1-benzopyran-4-one (±)*-**3a**. – A mixture of the sulphoxide **2a** (1.10 g, 4.0 mmol), acetic-formic anhydride[14] (3.5 g, 40 mmol), and anhydrous sodium formate (2.8 g, 40 mmol) was heated to 70–75 °C for 3 h and allowed to stand at room temperature for a further hour. Water (20 ml) was then added and the mixture extracted with dichloromethane (3 x 20 ml). The combined extracts were washed with water and brine, dried, and evaporated to obtain the crude product, which was crystallised from ethanol to afford the *title compound* (±)-**3a** (0.64 g, 56%) as colourless crystals, m.p. 173–174 °C (Found: C, 67.6; H, 4.3; S, 11.4. $C_{16}H_{12}O_3S$ requires C, 67.6; H, 4.25; S, 11.3%); ν_{max} 1640, 1610, and 1040 cm^{-1}; δ (60 MHz) 2.37 (3 H, s, Me), 7.1–8.2 (8 H, m, ArH), and 8.38 (1 H, s, 2-H); *M*$^+$, 284.

*3-(Phenylsulphinyl)-4*H*-1-benzopyran-4-one* **3b**. – This was prepared in the same manner as **3a**, starting with the sulphoxide **2b** (1.04 g, 4.0 mmol). The *title compound* **3b** (0.60 g, 56%) formed colourless crystals, m.p. 183 °C (ethanol) (Found: C, 66.4; H, 3.85; S, 12.3. $C_{15}H_{10}O_3S$ requires C, 66.65; H, 3.7; S, 11.9%); ν_{max} 1640, 1605, and 1050 cm^{-1}; δ (60 MHz) 7.25–8.25 (9 H, m, ArH), and 8.44 (1 H, s, 2-H); *M*$^+$, 270.

Conjugate Addition of Lithium Dimethylcuprate to the Chromone (±)-**3a**. – To a stirred solution of lithium dimethylcuprate, prepared from copper(I) iodide (0.61 g, 3.2 mmol) in ether (10 ml) and methyllithium (1.6 M; 4.0 ml, 6.4 mmol) at 0 °C under nitrogen, was added dropwise at –78 °C a solution of the sulphoxide (±)-**3a** (0.57 g, 2.0 mmol) in tetrahydrofuran (15 ml). After 0.5 h at –78 °C the mixture was allowed to warm up to 0 °C over *ca.* 1 h and then quenched by the addition of saturated aqueous ammonium chloride solution (15 ml). The organic layer was separated and the aqueous layer washed with ethyl acetate (3 x 20 ml). The combined extracts were washed successively with 2 M hydrochloric acid (20 ml), water (2 x 20 ml), and brine (20 ml), and the solution dried and evaporated. Flash chromatography (elution with dichloromethane - ethyl acetate 19:1) yielded a mixture of **4** and **5** (0.36 g, 60%), and crystallisation gave pure trans-*2,3-dihydro-2-methyl-3-[(4-methylphenyl)sulphinyl]-4*H*-1-benzopyran-4-one* **4** (170 mg, 28%) as colourless needles, m.p. 114–115 °C (methanol) (Found: C, 67.9; H, 5.45. $C_{17}H_{16}O_3S$ requires C, 68.0; H, 5.4%); ν_{max} 1680, 1610, and 1060 cm^{-1}; δ (400 MHz) 1.46 (3 H, d, *J* 6.9 Hz, 2-Me), 2.42 (3 H, s, 4'-Me), 3.53 (1 H, d, *J* 2.0 Hz, 3-H), 5.50 (1 H, dq, *J* 2.0, 6.9 Hz, 2-H), 7.00–7.05 (2 H, m, 6-H, 8-H), 7.31 (2 H, d, *J* 8 Hz, 3'-H, 5'-H), 7.40 (2 H, d, *J* 8 Hz, 2'-H, 6'-H), 7.56 (1 H, ddd, *J* 2, 7, 8.5 Hz, 7-H), and 7.74 (1 H, ddd, *J* 1, 2, 7.5 Hz, 5-H); *M*$^+$, 300.

The *cis*-isomer **5** had characteristic signals at δ (400 MHz) 1.92 (3 H, d, *J* 6.7 Hz, 2-Me), 3.44 (1 H, d, *J* 2.7 Hz, 3-H), and 4.93 (dq, *J* 2.7, 6.7 Hz, 2-H).

The above experiment was repeated with the sulphoxide **3a** (0.142 g, 0.5 mmol) in tetrahydrofuran (5 ml) and lithium dimethylcuprate (1.5 mmol). Chromatography, eluting with ether - petroleum 4:1, yielded a mixture of **4** and **5** (0.13 g, 87%). By comparison of the integrals of the 2-Me signals of **4** and **5** with those of the minor *trans*- and *cis*-diastereoisomers **6** and **7**, located by treatment of **4** with sodium methoxide (*vide infra*), in the 400 MHz ^{1}H n.m.r. spectrum of the crude reaction mixture, the ratio (**4** + **5**):(**6** + **7**) was calculated to be *ca.* 95:5.

Oxidation of the mixture of sulphoxides **4** *and* **5**. – To a stirred solution of a mixture of **4** and **5** (4:1; 75 mg, 0.25 mmol) in dichloromethane (2 ml) at 0 °C was added dropwise a solution of *m*-CPBA (60 mg, 0.35 mmol) in dichloromethane (2 ml). After 1 h at 0 °C the mixture was treated with water (5 ml) and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 5 ml), and the combined organic phases washed successively with water (2 x 10 ml), saturated aqueous sodium hydrogen carbonate (20 ml), and brine (20 ml). Drying, evaporation, and flash chromatography of the residue (elution with dichloromethane) gave a mixture of the sulphones **8** and **9** (67 mg, 85%; 4:1 by 60 MHz ^{1}H n.m.r. spectroscopy). Fractional crystallisation gave the pure *title compound* **8** (42 mg, 54%) as colourless crystals, m.p. 118–119 °C (ether - petroleum) (Found: C, 64.7; H, 5.2. $C_{17}H_{16}O_4S$ requires C, 64.5; H, 5.1%); ν_{max} 1670, 1605, and 1150 cm^{-1}; δ (90 MHz) 1.45 (3 H, d, *J* 7 Hz, 2-Me), 2.3 (3 H, s, ArMe), 3.85 (1 H, d, *J* 1 Hz, 3-H), 5.65 (1 H, dq, *J* 1, 7 Hz, 2-H), and 6.75–7.85 (8 H, m, ArH); M^+, 316.

The *cis*-isomer **9** had δ (60 MHz) 1.95 (1 H, d, *J* 7 Hz, 2-Me), 4.2 (1 H, d, *J* 3 Hz, 3-H), and 5.1 (1 H, dq, *J* 3, 7 Hz, 2-H).

Thermolysis of the mixture of sulphoxides **4** *and* **5**

(i) Analytical – A solution of **4** and **5** (20 mg, 0.15 mmol)) in $CDCl_3$ (1 ml) was heated at 80 °C in a sealed n.m.r. tube for 3 h, and the progress of the reaction monitored by 60 MHz ^{1}H n.m.r. spectroscopy. The major component of the initial mixture [δ 1.45 (d)] was consumed within 3 h, with the concomitant formation of 2-methyl-4*H*-1-benzopyran-4-one **10**. At 80 °C the minor component [δ 1.9 (d)] disappeared only after heating for 20 h.

(ii) Preparative – A solution of **4** and **5** (30 mg, 0.1 mmol) in $CDCl_3$ (1 ml) was heated at 140 °C for 1 h. Evaporation, followed by chromatography of the residue, eluting with dichloromethane - ethyl acetate (9:1), gave 2-methyl-4*H*-1-benzopyran-4-one **10** (16 mg, 100%) as colourless needles, m.p. 70–71 °C (petroleum) (lit.[15] 71 °C), identical (n.m.r., i.r.) to an authentic sample.

Equilibration of the benzopyranones **4** *and* **5**. – The benzopyranone **4** (5 mg, 0.017 mmol) in $CDCl_3$ (0.5 ml) at room temperature was treated with one drop of d_5-pyridine, and the ^{1}H n.m.r. spectrum of the mixture recorded at intervals. The signal due to the 2-methyl group of the *cis*-isomer **5** [δ (360 MHz) 1.92 (d, *J* 6.7 Hz)] was apparent within a few minutes. After 3 h the ratio **4**:**5** was 87:13, and it remained at this value after 16 and 24 h. At no point were signals due to the diastereoisomers **6** [δ 1.465 (d, *J* 6.8 Hz)] and **7** [δ 1.88 (d, *J* 6.8 Hz)] visible in the spectra.

Equilibration of the benzopyranone **4** *with sodium methoxide*. – To a stirred solution of the benzopyranone **4** (40 mg, 0.13 mmol) in dry tetrahydrofuran (3 ml) under nitrogen at room temperature was added dropwise a solution of sodium methoxide (15 mg, 0.28 mmol) in methanol (2 ml). The resulting yellow solution was stirred for 24 h, quenched with 1 M hydrochloric acid (5 ml), and extracted with ether (3 x 20 ml). The extract was washed with water (20 ml) and brine (20 ml), dried, and evaporated. Chromatography of the residue, eluting with ether - petroleum (4:1), gave a mixture of the diastereoisomers **4**, **5**, **6**, and **7** (total 33 mg, 82%), ratio *ca.* 55:8:19:18 by ^{1}H n.m.r. spectroscopy. The *trans*-isomer **6** had δ (360 MHz) 1.465 (3 H, d, *J* 6.8 Hz, 2-Me), 3.90 (1 H, d, *J* 2.5 Hz, 3-H), and 5.25 (1 H, dq, *J* 2.5, 6.8 Hz, 2-H), and the *cis*-isomer **7** had δ (360 MHz) 1.88 (3 H, d, *J* 6.8 Hz, 2-Me), 3.89 (1 H, d, *J* 3.0 Hz, 3-H), and 5.00 (1 H, dq, *J* 3.0, 6.8 Hz, 2-H).

*Conjugate Additions of Other Organometallic Reagents to the chromone (±)-**3a**.*
(i) Methylcopper - boron trifluoride[5] – A stirred suspension of methylcopper (1.5 mmol), prepared by treatment of copper(I) bromide - dimethylsulphide complex (0.31 g, 1.5 mmol) in ether (10 ml) at –10 °C with methyllithium in ether (1.5 M, 1.0 ml, 1.5 mmol), was cooled to –78 °C and treated with tri-*n*-butylphosphine (0.37 ml, 0.30 g, 1.5 mmol). After 10 min boron trifluoride etherate (0.18 ml, 0.21 g, 1.5 mmol) was added and the mixture stirred for a further 0.5 h at –78 °C. A solution of the sulphoxide **3a** (0.142 g, 0.5 mmol) in tetrahydrofuran (5 ml) was then added dropwise. After 1 h at –78 °C the mixture was allowed to warm slowly to room temperature and stirred for 16 h. Quenching with saturated aqueous ammonium chloride (15 ml) followed by isolation as before gave a mixture (0.11 g, 73%) consisting mainly of **4** and **5** (ratio *ca.* 4:1 by 400 MHz ^{1}H n.m.r. spectroscopy). The conversion and diastereoisomeric excess were each essentially the same as had been observed using 3 equivalents of Me_2CuLi.
(ii) Methylmagnesium iodide – To a stirred solution of **3a** (0.142 g, 0.5 mmol) in tetrahydrofuran (5 ml) at –78 °C was added an ethereal solution of methylmagnesium iodide (0.15 M, 10 ml, 1.5 mmol). After 1 h at –78 °C and 1 h at 0 °C, quenching and isolation as before.gave a mixture (0.095 g, 63%) consisting mainly of **4** and **5** (ratio *ca.* 4:1 by 400 MHz ^{1}H n.m.r. spectroscopy). The conversion and diastereoisomeric excess were each at least 10% lower than had been observed using 3 equivalents of Me_2CuLi.

Methyl 2-[(3,4-dimethoxyphenyl)methoxy]benzoate **13a**. – A stirred mixture of methyl salicylate (6.1 g, 40 mmol), 3,4-dimethoxybenzyl chloride[16] (7.4 g, 40 mmol), and anhydrous potassium carbonate (8.3 g, 60 mmol) in acetone (40 ml) was heated under reflux for 2 days. The mixture was then filtered and the filtrate concentrated, diluted with ethyl acetate (60 ml), and the solution washed successively with 6 M sodium hydroxide (3 x 30 ml), water (2 x 30 ml), and brine (30 ml), dried, and evaporated. Bulb-to-bulb distillation (220–230 °C, 0.3 mmHg) of the residual oil afforded the *title compound* **13a** (10.1 g, 84%), which formed colourless needles, m.p. 71–72 °C (ether) (Found: C, 67.2; H, 6.1. $C_{17}H_{18}O_5$ requires C, 67.5; H, 6.0%); ν_{max} 1730 cm^{-1}; δ (60 MHz) 3.8–3.9 (total 9 H, 3 x s, 3 x OMe), 5.1 (2 H, s, CH_2), and 6.85–7.9 (7 H, m, ArH); *M*$^+$, 302.

Methyl 2-[(4-methoxyphenyl)methoxy]benzoate **13b**. – This was prepared by the method used for the analogue **13a**, from methyl salicylate (3.04 g, 20 mmol), 4-methoxybenzyl chloride[17] (3.13 g, 20 mmol), and anhydrous potassium carbonate (4.14 g, 30 mmol) in acetone (20 ml). Bulb-to-bulb distillation (185–190 °C, 0.12 mmHg) of the residual oil gave the *title compound* **13b** (4.02 g, 74%), which formed colourless needles, m.p. 57–58 °C (ether) (Found: C, 70.5; H, 6.0. $C_{16}H_{16}O_4$ requires C, 70.5; H, 5.9%); ν_{max} 1725 cm^{-1}; δ (60 MHz) 3.8 (3 H, s, OMe), 3.9 (3 H, s, OMe), 5.1 (2 H, s, CH_2), and 6.8–8.0 (8 H, m, ArH); *M*$^+$, 272.

1-[2-[(3,4-Dimethoxyphenyl)methoxy]phenyl]-2-[(4-methylphenyl)sulphinyl]ethanone (±)-**14a**. – To a stirred solution of diisopropylamine (1.62 g, 16 mmol) in tetrahydrofuran (10 ml) under nitrogen at –78 °C was added dropwise a solution of *n*-butyllithium in hexane (1.6 M, 10 ml, 16 mmol). The solution was stirred for 0.5 h at –78 °C, and a solution of methyl 4-methylphenyl sulphoxide (±)-**15**[18] (1.54 g, 10 mmol) in tetrahydrofuran (10 ml) then added dropwise. After 10 min at –78 °C the mixture was allowed to warm up to room temperature over 0.5 h, cooled back to –78 °C, and treated dropwise with a solution of the ester **13a** (3.02 g, 10 mmol) in tetrahydrofuran (20 ml). The mixture was stirred for 0.5 h and then allowed to reach 0 °C over 1 h. The solution was quenched with 2 M hydrochloric acid (15 ml), extracted with ethyl acetate (3 x 20 ml), and the extract washed successively with water (2 x 15 ml), saturated aqueous sodium hydrogen carbonate (15 ml), and brine (15 ml). Drying, evaporation, and crystallisation of the residue from ether - dichloromethane gave the *title compound* **14a** (2.35 g, 54%), m.p. 121–122 °C (Found: C, 67.9; H, 5.95. $C_{24}H_{24}O_5S$ requires C, 67.9; H, 5.7%); ν_{max} 1670, 1600, 1050, and 1030 cm^{-1}; δ (60 MHz) 2.4 (3 H, s, ArMe), 3.8 (3 H, s, OMe), 3.9 (3 H, s, OMe), 4.3 (1 H, d, *J* 15 Hz, CH-S), 4.6 (1 H, d, *J* 15 Hz, CH-S), 5.05 (2 H, s, OCH_2Ar), and 6.8–7.9 (11 H, m, ArH); m/z 424 (M$^+$) not observed, main peaks 285 (23%), 151 (100), and 83 (25). Flash chromatography of the mother liquor using dichloromethane - ethyl acetate (4:1) as eluant yielded a further quantity of the sulphoxide **14a** (0.56 g, 13%).

1-[2-[(4-Methoxyphenyl)methoxy]phenyl]-2-[(4-methylphenyl)sulphinyl]ethanone **14b**. – The sulphoxide **13b** was prepared as described above for **14a**, using lithium diisopropylamide (16 mmol), methyl 4-methylphenyl sulphoxide (±)-**15** (1.54 g, 10 mmol), and the ester **13b** (2.72 g, 10 mmol). Crystallisation gave the *title compound* **14b** (2.5 g, 63%) as colourless needles, m.p. 116–117 °C (ether - dichloromethane) (Found: C, 69.9; H, 5.5. $C_{23}H_{22}O_4S$ requires C, 70.0; H, 5.6%); ν_{max} 1670, 1600, and 1045 cm^{-1}; δ (60 MHz) 2.4 (3 H, s, ArMe), 3.8 (3 H, s, OMe), 4.25 (1 H, d, *J* 15 Hz, CH-S), 4.5 (1 H, d, *J* 15 Hz, CH-S), 5.0 (2 H, s, OCH_2), and 6.7–7.9 (12 H, m, ArH); *M*$^+$, 394.
Attempted debenzylation of 14b using triphenylcarbenium tetrafluoroborate (Method B used for the conversion of (±)-**14a** into (±)-**2a**, above) resulted in an incomplete reaction, as judged by n.m.r. The product **2a** and unreacted starting material **14b** could not be resolved chromatographically using various elution solvents.

1-(2-Methoxyphenyl)-2-[(4-methylphenyl)sulphinyl]ethanone **14c**. – This was prepared as described for **14a**, using diisopropylamine (0.68 g, 6.7 mmol) in tetrahydrofuran (10 ml), *n*-butyllithium in hexane (1.6 M, 4.2 ml, 6.7 mmol), methyl 4-methylphenyl sulphoxide (±)-**15** (0.61 g, 4 mmol), and methyl 2-methoxybenzoate (0.66 g, 4.0 mmol) in tetrahydrofuran (5 ml). The residue was crystallised from ether - dichloromethane to obtain the*title compound* (±)-**14c** (0.88 g, 76%), m.p. 143–144 °C (methanol) (Found: C, 66.6; H, 5.6. $C_{16}H_{16}O_3S$ requires C, 66.6; H, 5.6%); ν_{max} 1655, 1590, and 1040 cm^{-1}; δ (60 MHz) 2.45 (3 H, s, ArMe), 4.0 (3 H, s, OMe), 4.45 (1 H, d, *J* 15 Hz, CH-S), 4.75 (1 H, d, *J* 15 Hz, CH-S), and 6.9–7.9 (8 H, m, ArH).
Attempted demethylation of 14c with boron trichloride (1.1 equivalents, –78 °C to room temperature, 1 h, dichloromethane) or iodotrimethylsilane (1.4 equivalents, room temperature, 1 h, dichloromethane) gave complex mixtures (t.l.c., n.m.r. analysis) in each case.

*(R)-(+)-1-[2-[(3,4-dimethoxyphenyl)methoxy]phenyl]-2-[(4-methylphenyl)sulphinyl]ethanone (R)-(+)-***14a**. – This was prepared in the same manner as (±)-**14a**, using lithium diisopropylamide (3.2 mmol) in tetrahydrofuran (10 ml), (*R*)-methyl 4-methylphenyl sulphoxide (*R*)-(+)-**15**[19] (0.31 g, 2.0 mmol), and the ester **13a** (0.60 g, 2.0 mmol). Chromatography of the crude product using dichloromethane - ethyl acetate (4:1) as eluant yielded the *title compound* (*R*)-(+)-**14a** (0.61 g, 72%), which formed colourless needles, m.p. 107–109 °C (ether - dichloromethane), $[\alpha]_D^{20}$ +112° (*c* 1.0, $CHCl_3$).

*(R)-(+)-1-(2-Hydroxyphenyl)-2-[(4-methylphenyl)sulphinyl]ethanone (R)-(+)-***2a**. – This was prepared as for the racemic material (±)-**2a** (Method B), using (*R*)-(+)-1-[2-[(3,4-dimethoxyphenyl)methoxy]phenyl]-2-[(4-methylphenyl)sulphinyl]ethanone (+)-**14a** (0.212 g, 0.5 mmol) and triphenylcarbenium tetrafluoroborate (0.20 g, 0.6 mmol) in dichloromethane (10 ml). The *title compound* (+)-**2a** (0.13 g, 95%) formed colourless needles, m.p. 125–126 °C (ether - dichloromethane), $[\alpha]_D^{20}$ +156° (*c* 1.0, $CHCl_3$).

*(S)-(–)-3-[(4-Methylphenyl)sulphinyl]-4*H*-1-benzopyran-4-one (S)-(–)-***3a**. – This was prepared in the same manner as the racemic chromone (±)-**3a**, using the sulphoxide (*R*)-(+)-**2a** (274 mg, 1.0 mmol), sodium formate (0.68 g, 10 mmol), and acetic-formic anhydride (0.9 g, 10 mmol). Chromatography, eluting with dichloromethane - ethyl acetate (9:1) afforded the *title compound* (*S*)-(–)-**3a** (244 mg, 86%), which formed colourless needles, m.p. 174–175 °C (dichloromethane - ether), $[\alpha]_D^{21}$ –278° (*c* 1.0, $CHCl_3$).

Conjugate Addition of Lithium Dimethylcuprate to the Chromone (–)-**3a**. – To a stirred solution of lithium dimethylcuprate, prepared from copper(I) iodide (0.95 g, 5 mmol) in ether (20 ml) and methyllithium (1.5 M; 6.7 ml, 10 mmol) at 0 °C under nitrogen, was added dropwise at –78 °C a solution of (*S*)-(–)-3-[(4-methylphenyl)sulphinyl]-4*H*-1-benzopyran-4-one (–)-**3a** (0.284 g, 1.0 mmol) in tetrahydrofuran (10 ml). After 2 h at –78 °C the mixture was allowed to warm up to 0 °C over *ca.* 1 h and then quenched by the addition of saturated aqueous ammonium chloride solution (30 ml). Isolation as described above for the racemic compound, and flash chromatography (elution with ether - petroleum 4:1) gave the *trans*- and *cis*-2,3-dihydro-2-methyl-3-[(4-methylphenyl)sulphinyl]-4*H*-1-benzopyran-4-ones **4** and **5** (0.27 g, 90%) as a mixture (ratio *ca.* 5:1 by 60 MHz ^1H n.m.r. spectroscopy). Trituration with ether and crystallisation of the solid from ethanol yielded *(+)-cis-2,3-dihydro-2-methyl-3-[(4-methylphenyl)sulphinyl]-4*H*-1-benzopyran-4-one* (+)-**5** (10 mg, 3%), m.p. 147–148 °C (dec.); $[\alpha]_D^{21}$ +720° (*c* 0.1, $CHCl_3$) (Found: C, 68.1; H, 5.55. $C_{17}H_{16}O_3S$ requires C, 68.0; H, 5.4%); ν_{max} 1700, 1615, and 1045 cm^{-1}; δ (80 MHz) 1.92 (3 H, d, *J* 7 Hz, 2-Me), 2.43 (3 H, s, 4'-Me), 3.44 (1 H, d, *J* 3 Hz, 3-H), 4.93 (1 H, dq, *J* 3, 7 Hz, 2-H), 6.85–7.6 (7 H, m, ArH), and 7.84 (1 H, dd, *J* 2, 8 Hz, 5-H); M^+, 300. The concentrated mother liquor from the above crystallisation was treated with a small amount of ethanol and one drop of pyridine. After refrigeration a further crop of (+)-**5** (84 mg) was deposited. Recrystallisation from ethanol gave pure (+)-**5** (62 mg, 21%).

*(S)-(–)-2,3-Dihydro-2-methyl-4*H*-1-benzopyran-4-one (–)-***16**. – To a stirred solution of (+)-**5** (50 mg, 0.17 mmol) in tetrahydrofuran (9 ml) and water (1 ml) at 0–5 °C was added aluminium amalgam (Al-Hg)[20] (45 mg, 1.7 mmol). After 0.5 h the mixture was allowed to reach room temperature and stirred for a further 14 h. The black precipitate was collected and washed on the filter with ether (25 ml). The filtrate was washed with water (10 ml) and brine (10 ml), dried, and evaporated. The residue was dissolved in dichloromethane (10 ml) and treated with pyridinium dichromate[21] (320 mg, 0.85 mmol). After stirring at room temperature for 4 h, the mixture was filtered. Evaporation of the filtrate and flash chromatography of the residue (elution with ether - petroleum 1:4) gave the *title compound* (–)-**16** (16 mg, 59%) as colourless plates, m.p. 39–40 °C; $[\alpha]_D^{22}$ –50° ±4° (*c* 1.2, $CHCl_3$); ν_{max} (FT, neat) 1695 and 1609 cm^{-1}; λ_{max} (MeOH) 251 nm (ε 10600) and 321 (4260); δ (60 MHz) 1.5 (3 H, d, *J* 6 Hz, 2-Me), 2.7 (2 H, d, *J* 8 Hz, 3-H_2), 4.55 (1 H, dq, *J* 6, 8 Hz, 2-H), 6.8–7.1 (2 H, m, 6-H, 8-H), 7.3–7.6 (1 H, m, 7-H), and 7.9 (1 H, dd, *J* 2, 8 Hz, 5-H); CD spectrum (Figure 1) (*c* 0.788 mg/ml, MeOH) Δε (° cm^2 decimol^{-1}) [nm] –4.15 [342], +4.85 [310], +1.85 [248], and –23.0 [212]. The above sequence was repeated without the separation of the cuprate addition products: A stirred solution of lithium dimethylcuprate (1.8 mmol) in ether (10 ml) was treated with the chromone (–)-**3a** (100 mg, 0.35 mmol) in tetrahydrofuran (5 ml) as described above. The residue on evaporation of the column eluate was dissolved in tetrahydrofuran (9 ml) and water (1 ml), cooled to 0–5 °C and treated with Al-Hg (140 mg, 5.2 mmol), followed by pyridinium dichromate (660 mg, 1.75 mmol) in dichloromethane (10 ml), and the product isolated according to the procedure described above. The chromanone (–)-**16** (37 mg, 65%) thus obtained had $[\alpha]_D^{21}$ –44° ±2° (*c* 2.0, $CHCl_3$).

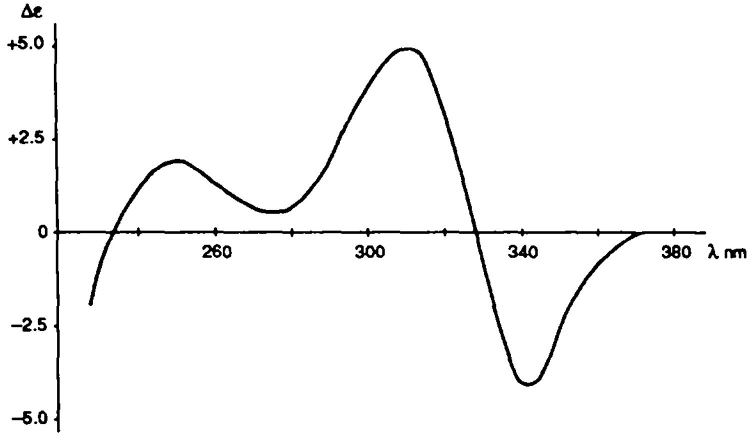


FIGURE 1 C.d. spectrum of (*S*)-(−)-2-methylchroman-4-one **16**

*Ozonolytic Degradation of (−)-2,3-Dihydro-2-methyl-4*H*-1-benzopyran-4-one (−)-***16**. – Ozone (*ca.* 90%) was bubbled through a solution of the chromanone (−)-**16** {$[\alpha]_D^{21}$ −44° ±2° (*c* 2.0, $CHCl_3$); 46 mg, 0.28 mmol} in acetic acid (9 ml) and water (1 ml).[22] When the starting material was no longer detectable by t.l.c. (*ca.* 2 h), the excess of ozone was consumed by the addition of 40% aqueous peracetic acid (2 ml). The solution was diluted with toluene (10 ml) and evaporated to dryness under reduced pressure. Ether (10 ml) was added, the mixture was filtered, and the filtrate was treated with an excess of ethereal diazomethane at room temperature for 10 min. Concentration of the solution, followed by flash chromatography of the residue (elution with ether - petroleum 1:1) gave two unidentified products (22 mg and 16 mg) and (*S*)-(+)-methyl 3-hydroxybutanoate (+)-**18** (11 mg, 33%), $[\alpha]_D^{24}$ +16° (*c* 1.0, $CHCl_3$) {lit.[23] $[\alpha]_D^{23}$ +33.3° (*c* 1.2, $CHCl_3$)}. The i.r. and n.m.r. spectra of the material were identical to those of an authentic racemic sample.

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