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Conjugate addition to 3-arylsulfinylchromones as a synthetic route to homochiral 2-substituted chromanones: scope and limitations

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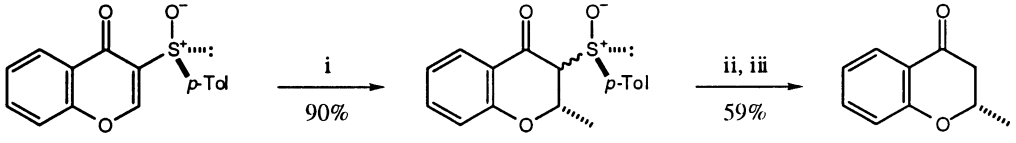
Abstract—A route to homochiral 2-substituted chromanones via the diastereoselective conjugate addition of organocopper reagents to 3-(*p*-tolylsulfinyl)chromones has been improved and used to prepare 2,6-dimethylchromanone (*S*)-**4** and LL-D253α methyl ether (*S*)-**6**. The attempted preparation of a 2-phenylchromanone (flavanone) using this strategy was unsuccessful due to the lability of the intermediate 2-phenyl-3-(*p*-tolylsulfinyl)chromanone, which underwent sulfoxide elimination at room temperature to give the corresponding 2-phenylchromone (flavone).

The chroman ring system features in a wide variety of compounds of biological and medicinal interest,[1] and new examples continue to emerge.[2] From a synthetic viewpoint, substituted chroman-4-ones (2,3-dihydro-4-oxo-4*H*-1-benzopyrans)[3] are valued both as functional intermediates and as targets in their own right.[4,5] Our interest in such compounds prompted us to explore a conjugate addition approach to 2-substituted chromanones,[6] and we established that the treatment of (*S*)-3-(*p*-tolylsulfinyl)chromone **1** with lithium dimethylcuprate provides the chromanones **2** diastereoselectively, and that their subsequent reductive desulfurisation generates (2*S*)-methylchromanone **3** without racemisation (Scheme 1).[7]

We recently applied this methodology to three chromanone targets with the objective of exploring its scope and limitations, and herein describe our findings. The first target was (*S*)-2,6-dimethylchroman-4-one **4**, which has been isolated from the essential oil produced by natural roots (and also from genetically transformed root cultures) of *Leontopodium alpinum* (Edelweiss).[8] The second was (*R*)-5,7-dimethoxyflavanone **5**, the dimethyl ether of the uncommon (+)-antipode of pinocembrin, which was recently isolated from the pine tree *Pseudotsuga wilsoniana*.[9] The third target was the methyl ether **6** of the antibiotic LL-D253α **7**, a fungal metabolite isolated from a culture of *Phoma pigmentivora* by a group at Lederle.[10] The metabolite and methyl derivative were originally assigned the respective structures **8** and **9**, but doubt was cast on these constitutions by Takahashi et al. following their isolation of the same metabolite from other microorganisms.[11] The issue was eventually resolved by Simpson and coworkers, who synthesised both **7** and **8** in racemic form.[12]



1 **2** (d.e. 90%) **3**

Scheme 1. *Reagents*: (i) Me_2CuLi, Et_2O–THF, −78 to 0°C; (ii) Al–Hg, THF–H_2O; (iii) PDC, CH_2Cl_2.

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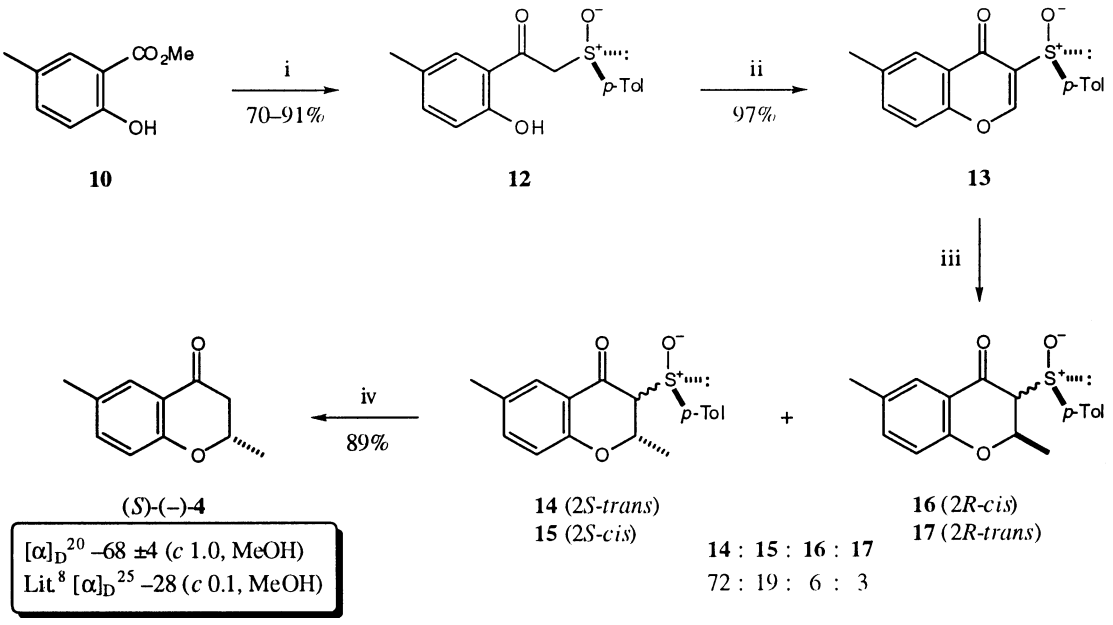
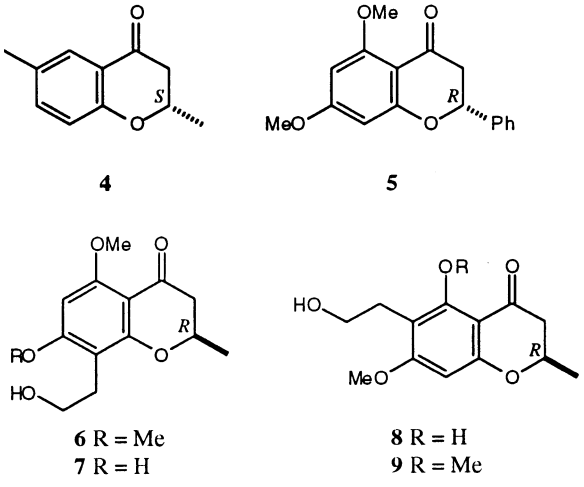


Scheme 2. *Reagents and conditions*: (i) (*R*)-(+)-Methyl *p*-tolyl sulfoxide **11**, LDA, THF, −78 to 20°C; (ii) AcOCHO, HCO_2Na, toluene, 60°C, 3 h; (iii) Me_2CuLi, Et_2O–THF, −78 to 0°C, then chromatography (**14**+**15**, 78%); (iv) Zn, NH_4Cl, THF–H_2O, 20°C, 3 h.

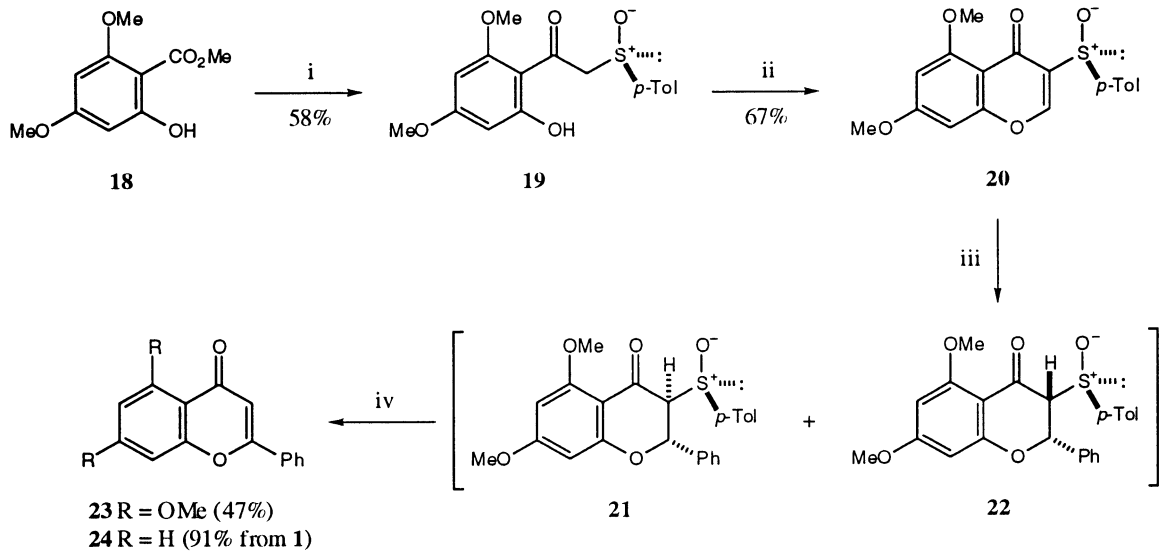


Our approach to the chromanone (*S*)-**4** was analogous to that which gave **3**, but with two significant refinements which made the overall sequence shorter and more efficient (Scheme 2). Firstly, the protection of the starting salicylate as an ether[7] proved unnecessary. Treating methyl 5-methylsalicylate **10** with an excess of lithium diisopropylamide (LDA) followed by the lithium derivative of (*R*)-(+)-methyl *p*-tolyl sulfoxide **11** gave the desired ketosulfoxide (*R*)-**12** directly and in good yield. This strategy was used by Solladié and coworkers in an application of the sulfoxide-cuprate approach to a flavanone,[13] and by others for related enolate anion additions to salicylates.[14] The formation of the chromone **13** was achieved conventionally using acetic formic anhydride[15] and sodium formate. The reaction of **13** with 3 equiv. of lithium dimethylcuprate at −78°C gave the two desired products **14** [δ 1.43 (d, 2-Me)] and **15** [δ 1.90 (d, 2-Me)] (≥91% of the mixture) and two minor products, **16** [δ 1.86 (d, 2-Me)] and **17** [δ 1.445 (d, 2-Me)] (≤9% of the mixture) indicating that the conjugate addition step had again proceeded with high diastereoselectivity. The relative stereochemistry of the products **14**–**17** was assigned by comparison of the ^{1}H NMR data of the products with those of the homologues **2** described previously.[7] Purification of the mixture by flash chromatography gave a mixture of the *trans*- and *cis*-(2*S*,6)-dimethyl-3-(tolylsulfinyl)chromanones **14** and **15** in 78% overall yield.

The removal of the sulfoxide auxiliary from the mixed isomers **14** and **15** was initially attempted with aluminium amalgam, but as before[7] this caused some carbonyl reduction which necessitated a reoxidation with pyridinium dichromate. This final step of the sequence was much improved by the use of zinc and ammonium chloride,[16] which produced the chromanone (−)-**4** cleanly and in high yield. For the most part the ^{1}H NMR spectrum of our material coincided with the reported data,[8] but our material was a crystalline solid (rather than an oil) with a specific rotation of more than twice that reported. The issue of the homogeneity of the natural material is discussed later.

Our proposed route to the flavanone (*R*)-**5** began with the acylation of the lithium derivative of the sulfoxide (*R*)-**11** using methyl 2-hydroxy-4,6-dimethoxybenzoate **18**[17] (Scheme 3). However, this reaction was rather sluggish, and gave the ketoester (*R*)-**19** in only moderate yield together with unreacted starting materials. We assume, as did Solladié and coworkers,[13] that the two methoxy substituents in **18** electronically deactivate the carbonyl substituent towards nucleophilic attack, and that 2,6-disubstitution also imposes an adverse steric effect on this process. The formylation of **19** also required more forcing conditions, but gave an acceptable yield of the desired chromone (*S*)-(−)-**20** as a yellow crystalline solid, mp 151–152°C.

In an attempt to effect the conjugate addition of a phenyl group to **20**, a racemic sample was prepared from (±)-**11**[18]



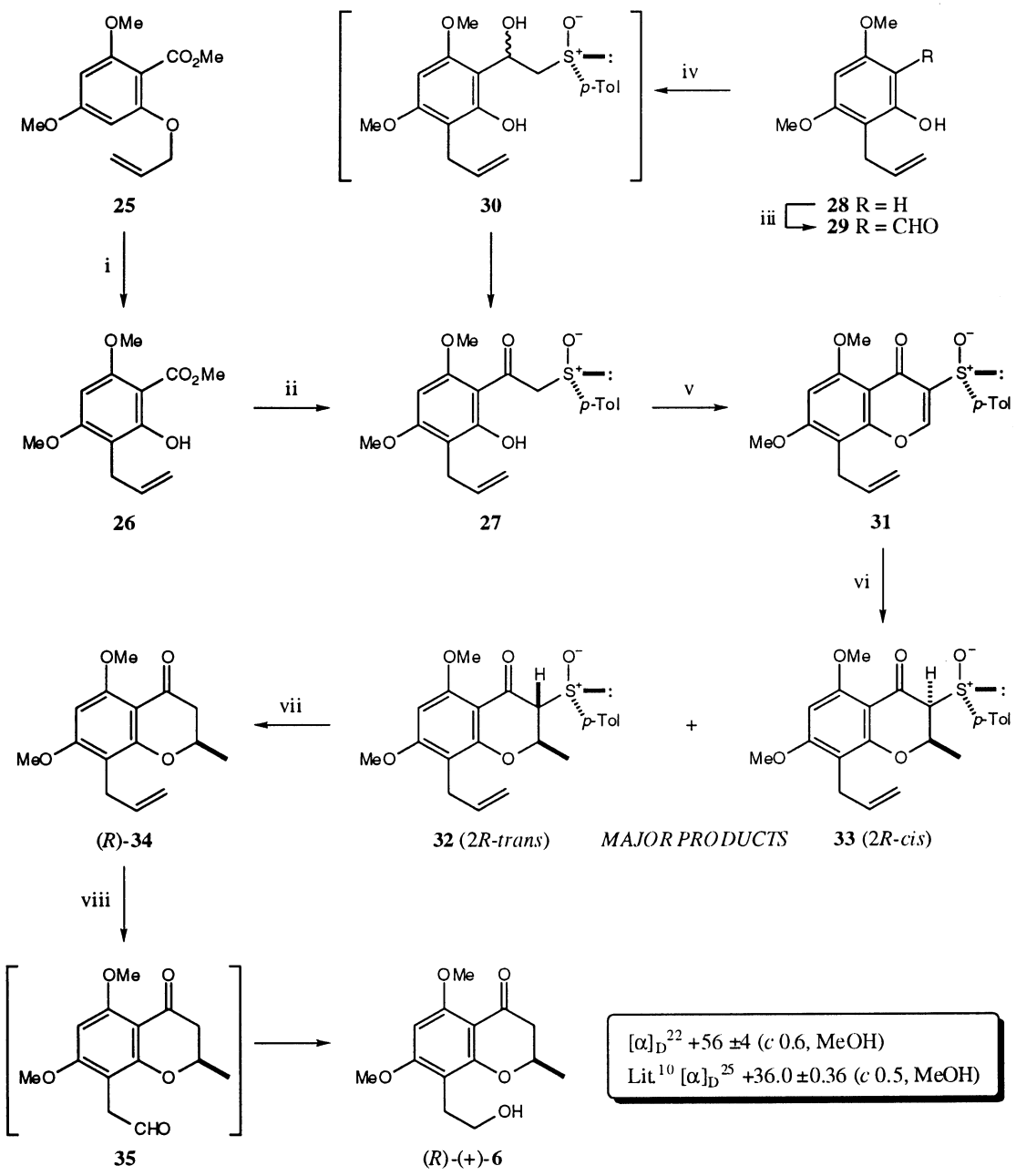
Scheme 3. *Reagents and conditions*: (i) (*R*)-(+)-**11**, LDA, THF, −78 to 20°C; (ii) AcOCHO, HCO_2Na, 70–80°C, 12 h; (iii) PhMgBr, CuBr·SMe_2, Et_2O–THF, −78 to 0°C; (iv) room temperature.

as per Scheme 3, and treated with an excess of phenylmagnesium bromide and copper(I) bromide–dimethyl sulfide complex. However, the major product isolated after conventional work-up and chromatography was neither of the desired tolylsulfinylchromanones **21** or **22**, but chrysin dimethyl ether **23**.[19] This would be expected to arise most readily via the thermal *syn*-elimination of *p*-toluenesulfenic acid from the anticipated major (*trans*) product **21**. Such eliminations can be effected at 80°C in the corresponding 2-methyl series,[7] but its occurrence at room temperature or below was unexpected. It appears that the activation barrier to the elimination process is significantly lower when the eliminating (C-2) hydrogen is benzylic. Solladié also encountered this facile elimination in a similar system,[13] and it represents a significant limitation to the effectiveness of the sulfoxide–cuprate methodology as a route to flavanones. However, it does offer a direct route from 3-(arylsulfinyl)chromones to flavones, as exemplified by the copper(I)-assisted addition of phenylmagnesium bromide to the sulfoxide (±)-**1**, which provided the parent system **24** in 91% yield.

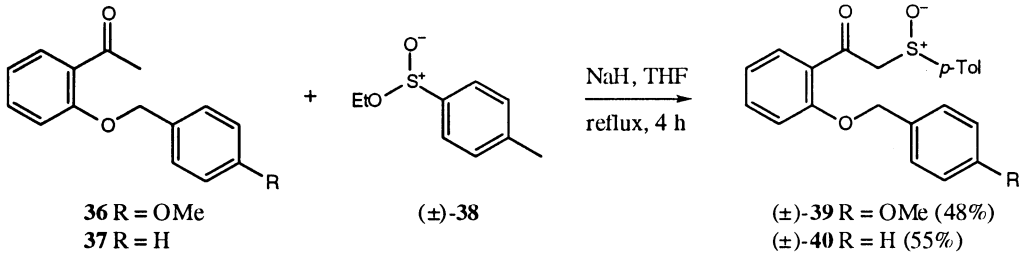
Our attempts to prepare the LL-D253α derivative (*R*)-**6** began with the heat-induced Claisen rearrangement[20] of the allyl ether **25** to the salicylate **26**, which proceeded almost quantitatively and established the requisite aromatic substitution pattern (Scheme 4). However, the reaction of the ester **26** with the lithium derivative of methyl *p*-tolyl sulfoxide **11** gave, at best, only a trace of the desired product **27** after several attempts, and it appeared that the deactivating electronic and steric effects first encountered with the ester **18** were now prohibitive. Fortunately the corresponding aldehyde **29**, prepared from the allylphenol **28**[21] by Vilsmeier formylation, proved more reactive towards the sulfoxide nucleophile and the chromone precursor **27** was accessible in moderate overall yield via sulfoxide addition, producing the mixed alcohols **30**, followed by oxidation with manganese dioxide. Following a protocol developed for use in a similar context by Solladié et al.,[13] formylation of **27** was in this instance effected using in situ-generated 1-formylimidazole,[22] which was more convenient and effective than acetic formic anhydride, and provided the chromone **31** in good yield.

The addition of lithium dimethylcuprate to the chromone **31**, carried out as before, yielded a mixture of products which was analysed by ^{1}H NMR spectroscopy. The major component was assigned the 2*R-trans* structure **32** on the basis of characteristic signals [δ_H (300 MHz) 1.32 (3H, d, J=6.5 Hz, 2-Me), 2.31 (3H, s, 4″-Me), 3.42 (1H, d, J=2 Hz, 3-H), 5.31 (1H, dq, J=2, 6.5 Hz, 2-H)] which were analogous to those of **14**. A second isomer, assigned the 2*R-cis* structure **33**, was also evident [δ_H (300 MHz) 1.67 (3H, d, J=6.5 Hz, 2-Me)], but neither of the minor (2*S*) isomers could be distinguished. Reductive desulfurisation[16] of the crude mixture, followed by chromatography, gave the chromanone (+)-**34** as a crystalline solid, mp 101–103°C. The values for the specific rotation of this material before and after recrystallisation were consistent with a minimum of 90% diastereoselectivity in the cuprate addition step. The transformation of (+)-**34** into the target molecule was accomplished via Lemieux–Johnson cleavage[23] of the side-chain to obtain the aldehyde **35**, followed by borohydride reduction, which gave (*R*)-(+)-**6** as a colourless crystalline solid whose properties (mp, ^{1}H NMR spectrum) corresponded to those previously described.[10] An exception to this was the specific rotation, which had the correct sign but was considerably higher than the published value (see Scheme 4). Such a discrepancy was observed with the simpler analogue (*S*)-(−)-**4**, and invites some speculation as to the optical purity of the materials isolated from natural sources. There are various reasons why chiral compounds of biosynthetic origin might not be enantiomerically pure,[24] but for chromanones such as **4** and **6** there is the possibility of partial racemisation via the reversible (retro-Michael) elimination of the pyran oxygen, either in vivo or during isolation. The conditions under which this process can be induced (or avoided) have been discussed.[25]

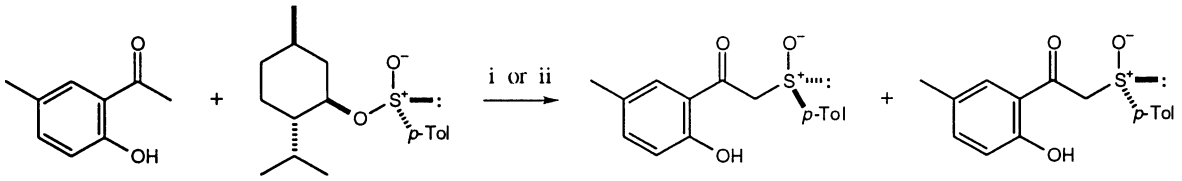
The sluggish reaction of the lithiated sulfoxide **11** with the



Scheme 4. *Reagents and conditions*: (i) 215°C, 12 h (98%); (ii) LDA, THF–DMPU, (*S*)-(−)-**11**, −78 to 20°C (trace); (iii) $POCl_3$, DMF, MeCN, 0–20°C, 7 h (83%); (iv) LDA, THF, (*S*)-(−)-**11**, −78 to 20°C, then MnO_2, CH_2Cl_2, 20°C, 48 h (57%); (v) LDA, THF, 1-formylimidazole, −78 to 20°C, 18 h, then SiO_2, CH_2Cl_2, 20°C, 16 h (73%); (vi) Me_2CuLi, Et_2O–THF, −78 to −10°C, HOAc quench; (vii) Zn, NH_4Cl, THF–H_2O, 20°C, 3 h (54% over two steps); (viii) cat. OsO_4, $NaIO_4$, THF–water, 20°C, 3 h, then $NaBH_4$, THF, 20 min (53% over two steps).



Scheme 5.



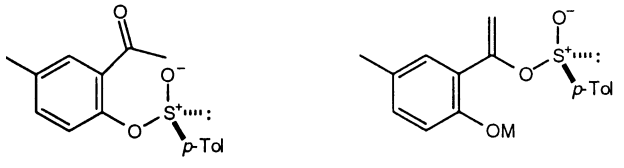
41 42 (*R*)-**12** (*S*)-**12**

Scheme 6. *Reagents*: (i) LDA, CuI, THF, −78°C, then room temperature, 2 h (42%, ee 66±9% *R*); (ii) KH, THF, −78°C, then room temperature, 3 h (31%, ee 23±6% *S*).

ester **26**, circumvented using the aldehyde **29**, prompted us to examine another potential route to intermediate ketosulfoxides. Some time ago we established that this type of molecule is accessible via the sulfinylation of ketone enolates.[26] Thus, reacting the acetophenones **36** and **37**[27] with sodium hydride and ethyl *p*-toluenesulfinate (±)-**38**[28] gave fair yields of the corresponding ketosulfoxides **39** (48%) and **40** (55%), together with unreacted starting material in each case (Scheme 5).

In seeking to extend this approach to homochiral targets, we attempted to prepare (*R*)-**12** from the acetophenone **41** using (−)-menthyl (*S*)-*p*-toluenesulfinate **42** as the sulfinylating species. Two different conditions were used, but in each case the procedure was neither efficient nor stereoselective. With LDA in the presence of copper(I) iodide, the sulfinylation proceeded in 42% yield, but although polarimetry indicated a net inversion at sulfur this was only partial. With potassium hydride as the base both the yield and the stereoselectivity were lower, the outcome this time being net retention at sulfur. Extending the reaction times of these sulfinylations did not significantly change the yield or stereoselectivity (Scheme 6).

The divergent mechanistic pathways which would account for these results remain obscure, but there are precedents. Sulfinylation of the sodium enolate of cyclohexanone with methyl *p*-toluenesulfinate proceeds with inversion at sulfur, whereas with the corresponding lithium enolate the net result is retention; the stereoselectivity is only partial (ca. 10%) in each case.[29] In the present case one possibility is the involvement of other potential sulfinylating species derived from **42**, e.g. the aryl sulfinate (*R*)-**43** or enol sulfinate **44**, which could mediate the formation of (*S*)-**12** via two successive inversions at sulfur. The intramolecular transformation of **43** into (*S*)-**12**, essentially a sulfur variant of the Baker–Venkataraman rearrangement,[30] is another intriguing possibility which we are currently investigating.



43 **44**

In summary, a route to homochiral 2-substituted chromanones based on the diastereoselective conjugate addition of organocopper reagents to 3-(*p*-tolylsulfinyl)chromones has been refined and used to prepare (*S*)-2,6-dimethylchromanone **4** and LL-D253α methyl ether **6**. An application of the strategy to 5,7-dimethoxyflavanone (pinocembrin dimethyl ether) **5** was unsuccessful due to the thermal instability of the intermediate 2-phenyl-3-(*p*-tolylsulfinyl)chromanone **21**, which underwent sulfoxide elimination at room temperature to give the corresponding 2-phenylchromone (flavone) **23**.

1. Experimental

1.1. General

All compounds are racemic unless their names are preceded by stereochemical descriptors. Melting points were determined using an Electrothermal apparatus and are uncorrected. Unless otherwise stated, IR spectra were of neat thin films on NaCl plates, recorded on a Perkin–Elmer 1710FT spectrometer. NMR spectra were measured on Varian Gemini-300 (^{1}H at 300 MHz), Bruker AC300 spectrometer (^{1}H at 300 MHz, ^{13}C at 75 MHz), or Varian Unity-400 (^{1}H at 400 MHz) instruments for solutions in deuteriochloroform with tetramethylsilane as the internal standard; coupling constants (*J* values) are quoted to the nearest 0.5 Hz. Mass spectra were measured on Finnegan 4500 or Micromass Trio 2000 (low resolution) and Kratos Concept 1S (high resolution) instruments using the ammonia CI method unless stated. Data for most peaks with an intensity of less than 20% of that of the base peak are omitted. Optical rotations were measured at 589 nm using AA-10 and AA-100 polarimeters (Optical Activity Ltd.).

Starting materials and solvents were routinely purified by conventional techniques[31] and most reactions were carried out under nitrogen or argon. Organic solutions were dried using anhydrous magnesium sulfate and concentrated by rotary evaporation. Analytical thin layer chromatography (TLC) was carried out on Camlab Polygram SIL G/UV$_{254}$ plates. The chromatograms were visualised by the use of UV light or the following developing agents; ethanolic vanillin or potassium permanganate. Unless otherwise indicated, preparative (column) chromatography was carried out on 60H silica gel (Merck 9385) or basic alumina using the flash technique.[32] Compositions of solvent mixtures are quoted as ratios of volume. 'Petroleum' refers to a light petroleum fraction, bp 40–60°C, unless otherwise stated.

1.1.1. (*R*)-1-(2-Hydroxy-5-methylphenyl)-2-(4-methylphenylsulfinyl)ethanone (+)-12. A solution of LDA was prepared by adding *n*-butyllithium in hexane (1.6 M, 11.25 ml, 18 mmol) dropwise to a stirred solution of diisopropylamine (1.84 g, 2.55 ml, 18.2 mmol) in THF (15 ml) under nitrogen at 0°C. The solution was stirred for 0.25 h at

0°C prior to use. Meanwhile two separate reaction flasks, A and B, were set up. Flask A contained a stirred solution of (*R*)-(+)-methyl *p*-tolyl sulfoxide (1.0 g, 6.48 mmol) in THF (5 ml) at −78°C. Flask B contained a stirred solution of methyl 2-hydroxy-5-methylbenzoate (1.08 g, 6.50 mmol) in THF (5 ml) at −78°C. To flask A was added a portion (10 ml, ca. 6.8 mmol) of the LDA solution, while to flask B was added a portion (5 ml, ca. 3.43 mmol) of the LDA solution. After 10 min the solution in flask B was added to flask A, and the resulting mixture was stirred for 0.5 h and then allowed to reach 0°C over 0.5 h. The reaction mixture was then quenched by the addition of 3 M hydrochloric acid (10 ml), extracted with ethyl acetate (3×30 ml), and the extract washed with brine (25 ml) and dried. Evaporation gave a yellow solid which was crystallised from ethanol to obtain the *title compound* (+)-**12** (1.70 g, 91%) as a colourless solid, mp 128°C (Found: C, 67.10; H, 5.49; S, 11.29. $C_{16}H_{16}O_3S$ requires C, 66.64; H, 5.59; S, 11.12%) ($M+H^+$, 289.0901. $C_{16}H_{17}O_3S$ requires 289.0898); $[\alpha]_D^{22}=+141\pm7$ (*c* 1.0, $CHCl_3$); ν_{max} 3400–2900 br, 1637 (C=O), 1615, 1591, 1489, 1338, 1298, 1250, 1211, 1169, 1085, 1050 (S–O), 1015, 992, 813 cm^{-1}; δ_H (300 MHz) 2.26 (3H, s, 5-Me), 2.40 (3H, s, 4′-Me), 4.23 (1H, d, *J*=15 Hz, SCH), 4.52 (1H, d, *J*=15 Hz, SCH), 6.87 (1H, d, *J*=8 Hz, 3-H), 7.25–7.35 (4H, m, 4-H, 6-H, 3′-H, 5′-H), 7.55 (2H, d, *J*= 8 Hz, 2′-H, 6′-H), 11.57 (1H, s, OH); *m/z* (peaks ≥10%) 306 (trace), 289 (3), 152 (12), 151 (100).

1.1.2. (*S*)-6-Methyl-3-(4-methylphenylsulfinyl)-4*H*-1-benzopyran-4-one (−)-13. A mixture of the sulfoxide (*R*)-(+)-**12** (884 mg, 3.07 mmol), acetic–formic anhydride[15] (5.77 g, 65.5 mmol), and anhydrous sodium formate (4.5 g, 66.2 mmol) in toluene (10 ml) was heated to 60°C for 3 h and then allowed to cool to room temperature. The resulting yellow solid was partitioned between ethyl acetate (30 ml) and water (30 ml), and the aqueous phase extracted with more ethyl acetate (30 ml). The combined organic extract was washed with brine (30 ml), dried and evaporated to obtain the *title compound* (−)-**13** (890 mg, 97%) as a colourless solid, mp 174°C (EtOH) (Found: C, 68.51; H, 4.67; S, 11.01. $C_{17}H_{14}O_3S$ requires C, 68.44; H, 4.73; S, 10.75%); $[\alpha]_D^{22}=-352\pm11$ (*c* 2.0, $CHCl_3$); ν_{max} 1636, 1617, 1605, 1484, 1298, 1125, 1084, 1044 (S–O), 813, 786 cm^{-1}; δ_H (400 MHz) 2.36 (3H, s, 5-Me), 2.42 (3H, s, 4′-Me), 7.27 (2H, d, *J*=8 Hz, 3′-H, 5′-H), 7.41 (1H, d, *J*= 8.5 Hz, 8-H), 7.51 (1H, dd, *J*=2.5, 8.5 Hz, 7-H), 7.78 (2H, d, *J*=8 Hz, 2′-H, 6′-H), 7.89 (1H, br. s, 5-H), 8.39 (1H, s, 2-H); *m/z* (peaks ≥20%) 316 (6), 299 (70), 283 (74), 163 (24), 161 (100), 58 (46).

1.1.3. Conjugate addition of lithium dimethylcuprate to the chromone (*S*)-(−)-13. 2,3-Dihydro-2,6-dimethyl-3-(4-methylphenylsulfinyl)-4*H*-1-benzopyran-4-ones **14**–**17**. 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*)-(−)-**13** (0.298 g, 1.0 mmol) in THF (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 (30 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×20 ml). The combined organic phases were washed with brine (20 ml), dried and evaporated [the 400 MHz NMR spectrum of the residue indicated that the product consisted of **14** (δ_H 1.43), **15** (δ_H 1.90), **16** (δ_H 1.86) and **17** (δ_H 1.445) (ratio 72:19:6:3 by NMR), assignments being made on the basis of analogy with the previous study[7]]. Flash chromatography (elution with ether–hexane 2:1) gave the mixed (2*S*)-isomers **14** and **15** (245 mg, 78%) as a mixture (ratio 5:1 by 400 MHz ^1H NMR spectroscopy). The (2*S*)-*trans* isomer **14** had δ_H (400 MHz) 1.43 (3H, d, *J*=6.7 Hz, 2-Me), 2.30–2.45 (obscured 2×3H, s, 6-Me, 4′-Me), 3.49 (1H, d, *J*=2.4 Hz, 3-H), 5.46 (1H, dq, *J*= 2.4, 6.7 Hz, 2-H), 6.93 (2H, d, *J*=8.5 Hz, 8-H), 7.25–7.55 (5H, m, $Ar'H_4$ and 7-H) and 7.95 (1H, br. s, 5-H). The (2*S*)-*cis* isomer **15** had characteristic signals at δ_H (400 MHz) 1.90 (3H, d, *J*=6.7 Hz, 2-Me), 3.39 (1H, d, *J*= 2.5 Hz, 3-H) and 4.89 (dq, *J*=2.5, 6.7 Hz, 2-H). The (2*R*)-*cis* isomer **16** had characteristic signals at δ_H (400 MHz) 1.86 (3H, d, *J*=6.7 Hz, 2-Me), 3.85 (1H, d, *J*=2.5 Hz, 3-H) and 4.95 (dq, *J*=2.5, 6.7 Hz, 2-H). The (2*R*)-*trans* isomer **17** was assigned signals at δ_H (400 MHz) 1.445 (3H, d, *J*=6.7 Hz, 2-Me), 3.85 (1H, d, *J*= 2.5 Hz, 3-H) and 5.15 (dq, *J*=2.5, 6.7 Hz, 2-H).

1.1.4. (*S*)-2,3-Dihydro-2,6-dimethyl-4*H*-1-benzopyran-4-one (−)-4. To a vigorously stirred solution of **14**+**15** (157 mg, 0.50 mmol) in THF (7 ml) and saturated aqueous ammonium chloride (7 ml) at room temperature was added activated zinc powder (2 g, 30 mmol).[16] After 3 h the mixture was filtered through Celite® and washed on the filter with ethyl acetate. The filtrate was partitioned and the aquous phase extracted with more ethyl acetate (2×30 ml). The combined organic phase was washed with saturated aqueous sodium hydrogen carbonate (10 ml), dried and evaporated. Flash chromatography of the residue (elution with ether–hexane 1:9) gave the *title compound* (−)-**4** (78 mg, 89%) as a colourless solid, mp 76°C (lit.8 oil) (Found: C, 75.17; H, 6.74. $C_{11}H_{12}O_2$ requires C, 74.98; H, 6.86%); $[\alpha]_D^{20}=-68\pm4$ (*c* 1.0, MeOH); ν_{max} (FT, neat) 1683, 1621, 1576, 1492, 1456, 1420, 1357, 1294, 1229, 1175, 1146, 1031, 949, 890, 867, 823, 791 cm^{-1}; δ_H (300 MHz) 1.48 (3H, d, *J*=6 Hz, 2-Me), 2.28 (3H, s, 6-Me), 2.60–2.70 (2H, m, 3-H_2), 4.47–4.59 (1H, m, 2-H), 6.85 (1H, d, *J*=8.5 Hz, 8-H), 7.26 (1H, br. d, *J*=8.5 Hz, 7-H) and 7.65 (1H, br. s, 5-H); δ_C (75 MHz) observed [lit.8] 20.38 [18.32] (6-Me), 20.98 [19.80] (2-Me), 44.67 [42.6] (C-3), 74.23 [72.3] (C-2), 117.65 [114.5] (C-8), 120.43 [118.6] (C-4a), 126.52 [124.4] (C-5), 130.63 [128.8] (C-6), 137.05 [134.5] (C-7), 159.78 [155.7] (C-8a), 192.74 [190.9] (C-4); *m/z* (peaks ≥10%) 194 (28), 178 (11), 177 (100); *m/z* (EI, peaks ≥20%) 177 (28), 176 (90), 135 (24), 134 (100), 51 (30), 49 (83), 47 (21).

1.1.5. (*R*)-1-(2-Hydroxy-4,6-dimethoxyphenyl)-2-(4-methylphenylsulfinyl)ethanone (−)-19. To a stirred solution of diisopropylamine (1.3 ml, 0.94 g, 9.28 mmol) in THF (5 ml) under argon at −78°C was added dropwise *n*-butyllithium (1.3 M; 7.2 ml, 9.36 mmol). After 20 min a solution of (*R*)-(+)-methyl *p*-tolyl sulfoxide **11** (0.90 g, 5.84 mmol) in THF (5 ml) was added dropwise to the stirred solution. The reaction mixture was stirred at −78°C for a further 0.5 h, at which point a solution of methyl 2-hydroxy-4,6-dimethoxybenzoate **18**[17] (1.6 g, 7.54 mmol) in THF (15 ml) and *n*-butyllithium (1.3 M; 5.8 ml, 7.54 mmol) was added

dropwise. After 1 h at −78°C, the reaction mixture was allowed to return to room temperature over 2 h and quenched by addition of 2 M HCl (15 ml). The mixture was extracted with DCM (5×25 ml), and the combined extracts were washed with water (2×20 ml), saturated aq. sodium hydrogen carbonate (20 ml) and brine (20 ml), and then dried and evaporated. Flash chromatography of the residual yellow oil, eluting with DCM–petroleum (6:1), followed by crystallisation from ethanol, gave the *title compound* (−)-**19** (1.13 g, 58%) as pale yellow crystals, mp 107–109°C ($M+H^+$, 335.0957. $C_{17}H_{19}O_5S$ requires 335.0953); $[\alpha]_D^{20}=-30\pm2$ (*c* 1.0, $CHCl_3$); ν_{max} (Nujol) 1615, 1591, 1284, 1219, 1199, 1153, 1125, 1048, 842, 810 cm^{-1}; δ_H (300 MHz) 2.38 (3H, s, Me), 3.81 (3H, s, OMe), 3.84 (3H, s, OMe), 4.31 and 4.70 (each 1H, d, *J*=14 Hz, CH_2), 5.89 (1H, d, *J*=2 Hz, 3-H), 6.03 (1H, d, *J*=2 Hz, 5-H), 7.28 (2H, d, *J*=8 Hz, 3′,5′-H), 7.55 (2H, d, *J*=8 Hz, 2′,6′-H), 13.24 (1H, s, OH); *m/z* 352 ($M+NH_4^+$, 16%), 336 (16), 335 ($M+H^+$, 100), 294 (60), 197 (25); R_f (DCM–ethyl acetate 4:1) 0.40 (brown with vanillin). The chromatography also yielded portions of unreacted sulfoxide **11** (0.2 g, 22%) and ester **18** (0.7 g).

1.1.6. (*S*)-5,7-Dimethoxy-3-(4-methylphenylsulfinyl)-4*H*-1-benzopyran-4-one (−)-20. A mixture of the sulfoxide (−)-**19** (800 mg, 2.39 mmol), acetic–formic anhydride (4.16 g, 47 mmol), and anhydrous sodium formate (3.25 g, 48 mmol) was heated to 70–80°C for 12 h and then allowed to cool to room temperature. Water (30 ml) was added and the mixture was extracted with dichloromethane (3×20 ml). The combined extracts were washed with water (3×20 ml) and brine (20 ml), dried, and evaporated. Flash chromatography of the residual yellow oil, eluting with ethyl acetate–petroleum (1:1), followed by crystallisation from ethyl acetate, gave the *title compound* (−)-**20** (552 mg, 67%) as yellow crystals, mp 151–152°C (Found: C, 62.38; H, 4.59. $C_{18}H_{16}O_5S$ requires C, 62.78; H, 4.68%) ($M+H^+$, 345.0782. $C_{18}H_{17}O_5S$ requires 345.0797); $[\alpha]_D^{20}=-203\pm2$ (*c* 1.0, $CHCl_3$); ν_{max} (Nujol) 1642, 1602, 1586, 1277, 1220, 1157, 1077, 1026, 1012, 825 cm^{-1}; δ_H (300 MHz) 2.33 (3H, s, Me), 3.85 (3H, s, OMe), 3.86 (3H, s, OMe), 6.33 (1H, d, *J*=2.5 Hz, 6-H), 6.46 (1H, d, *J*=2.5 Hz, 8-H), 7.23 (2H, d, *J*=8 Hz, 3′,5′-H), 7.77 (2H, d, *J*=8 Hz, 2′,6′-H), 8.17 (1H, s, 2-H); *m/z* 345 ($M+H^+$, 100), 207 (25); R_f (DCM–ethyl acetate 4:1) 0.30 (yellow with vanillin).

1.1.7. 5,7-Dimethoxy-2-phenyl-4*H*-1-benzopyran-4-one 23. A solution of the chromone (±)-**20** (60 mg, 0.17 mmol) and copper(I) bromide–dimethyl sulfide complex (180 mg, 0.88 mmol) in THF (10 ml) under argon was cooled to −78°C and treated dropwise with a solution of phenylmagnesium bromide in ether (3.0 M, 0.3 ml, 0.9 mmol). The resulting green mixture was stirred at −78°C for 1.5 h and at 0°C for 1 h, after which the reaction was quenched by the addition of saturated aq. ammonium chloride (5 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 ml). The combined organics were washed with 2 M HCl (10 ml), water (2×15 ml), and brine (10 ml), dried and evaporated to a brown oil. Flash chromatography, eluting with DCM–ethyl acetate (4:1) gave 5,7-dimethoxy-2-phenyl-4*H*-1-benzopyran-4-one **23** (23 mg, 47%) as a yellow solid, mp 146–148°C (lit.19 148–149°C); ν_{max} (Nujol) 1648, 1608, 1260, 1099, 1018, 798 cm^{-1}; δ_H (300 MHz) 3.89 (3H, s, OMe), 3.93 (3H, s, OMe), 6.35 (1H, d, *J*=2 Hz, 6-H), 6.55 (1H, d, *J*=2 Hz, 8-H), 6.66 (1H, s, 3-H), 7.45–7.50 (3H, m, 3′,4′,5′-H), 7.83–7.87 (2H, m, 2′,6′-H) [lit.19 δ_H 3.93 (s), 3.97 (s), 6.39 (d, *J*=2 Hz), 6.59 (d, *J*=2 Hz), 6.70 (s), 7.52 (m), 7.90 (m)]; *m/z* (CI) 283 ($M+H^+$, 100%); R_f (DCM–ethyl acetate 4:1) 0.25. The chromatography also yielded a portion of unreacted starting material **20** (15 mg, 25%).

1.1.8. 2-Phenyl-4*H*-1-benzopyran-4-one 24. A solution of the chromone (±)-**1**[7] (200 mg, 0.70 mmol) and copper(I) bromide–dimethyl sulfide complex (576 mg, 2.80 mmol) in THF (20 ml) under argon was cooled to −78°C and treated dropwise with a solution of phenylmagnesium bromide in THF (1.0 M, 2.8 ml, 2.8 mmol). The resulting mixture was stirred at −78°C for 1.5 h and at 0°C for 1 h, after which the reaction was quenched by the addition of saturated aq. ammonium chloride (15 ml). The mixture was extracted with ethyl acetate (3×40 ml). The combined organics were washed with 2 M HCl (40 ml), water (40 ml), and brine (40 ml), dried and evaporated to a yellow oil. Flash chromatography, eluting with petroleum–ethyl acetate (2:1) gave 2-phenyl-4*H*-1-benzopyran-4-one **24** (143 mg, 91%) as a colourless solid, mp 98–99°C, which was identical (TLC, IR, ^1H NMR) with a commercial sample.[33]

1.1.9. Methyl 2-allyloxy-4,6-dimethoxybenzoate 25. To a stirred suspension of methyl 2-hydroxy-4,6-dimethoxybenzoate **18**[17] (1.00 g, 4.7 mmol) and anhydrous potassium carbonate (12 g, 87 mmol) in dry acetone (100 ml) in a conical flask fitted with a powerful stirrer and a drying tube was added allyl bromide (0.5 ml, 0.70 g, 5.8 mmol). The mixture was stirred at room temperature for 24 h, filtered and the filtrate treated with 1 M ammonium hydroxide (100 ml). The mixture was extracted with DCM (3×100 ml) and the combined extract was dried and evaporated to give the crude product as an oil (0.90 g, 3.6 mmol, 76%) which was difficult to purify as it underwent rearrangement when distilled ($M+H^+$, 253.1080. $C_{13}H_{17}O_5$ requires 253.1076); ν_{max} 1729, 1608, 1422, 1267, 1226, 1203, 1161, 1124, 1053, 820 cm^{-1}; δ_H 3.78 (6H, s, 2×OMe), 3.86 (3H, s, CO_2Me), 4.51 (2H, dt, *J*=1.5, 5 Hz, 1′-H_2), 5.22 (1H, dq, *J*=1.5, 10.5 Hz, 3′-H), 5.36 (1H, dq, *J*=1.5, 17.5 Hz, 3′-H), 5.96 (1H, overlapping ddt, *J*=5, 10.5, 17.5 Hz, 2′-H), 6.07, 6.08 (each 1H, d, *J*=2 Hz, 3-H and 5-H); *m/z* 253 ($M+H^+$, 100%).

1.1.10. Methyl 2-hydroxy-3-(prop-2-en-1-yl)-4,6-dimethoxybenzoate 26. Methyl 2-allyloxy-4,6-dimethoxybenzoate **25** (0.90 g, 3.6 mmol) was degassed by exposure to a vacuum (0.01 mmHg) for 0.5 h. The flask was then flushed with argon, fitted for reflux with a short, narrow air condenser, heated on a Woods metal bath at 215°C for 12 h and then allowed to cool. The product could be recrystallised from methanol to give the *title compound* **26** (0.88 g, 98%). The analytical sample, obtained by sublimation, had mp 89°C (Found: C, 62.10; H, 6.31; $C_{13}H_{16}O_5$ requires C, 61.90; H, 6.39%); ν_{max} 3410 br, 1730, 1640, 1613, 1460, 1408, 1278, 1206, 1161, 1121, 996, 952, 909, 814, 780 cm^{-1}; δ_H 3.33 (2H, dt, *J*=1.5, 6 Hz, 1′-H_2), 3.85 (3H, s, OMe), 3.86 (3H, s, OMe), 3.90 (3H, s, CO_2Me),

4.90–5.00 (2H, m, 3′-H_2), 5.86–5.99 (1H, m, 2′-H), 5.99 (2H, s, 3-H, 5-H), 11.31 (1H, s, OH) ppm; δ_C (75 MHz) 26.58 (C-1′), 52.15 (ester OMe), 55.51 (ArOMe), 56.12 (ArOMe), 87.17 (C-5), 96.69 (C-1), 107.87 (C-3), 113.92 (C-3′), 136.56 (C-2′), 161.05, 162.15, 162.71 (C-2′, C-4′, C-6′), 171.86 (C=O); *m/z* 270 ($M+NH_4^+$, 8%), 253 ($M+H^+$, 100), 227 (22), 213 (35), 195 (95).

1.1.11. (*S*)-1-[2-Hydroxy-4,6-dimethoxy-3-(2-propen-1-yl)phenyl]-2-(4-methylphenylsulfinyl)ethanone (+)-27. *Method* 1. In flask A: To a solution of the ester **26** (242 mg, 1 mmol) in THF (3 ml) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (1.5 ml), chilled to −78°C, was added LDA in THF (1.5 M, 1.0 ml, 1.5 mmol). In flask B: to a solution of (*S*)-(−)-methyl *p*-tolyl sulfoxide **11** (200 mg, 1.3 mmol) in THF (3 ml) and DMPU (1.5 ml), chilled to −78°C was added LDA in THF (1.5 M, 2.0 ml, 3 mmol). The contents of flask A were added to flask B at −78°C and the mixture stirred for 0.5 h, then allowed to rise to room temperature and stirred overnight. The mixture was quenched with HCl (2 M, 3 ml), diluted with water (10 ml) and extracted with ethyl acetate (3×20 ml). The combined organics were washed with water (3×30 ml), dried and evaporated. The mixture was freed of excess DMPU by dissolving the solid in methanol–water (1:1; 10 ml) and extracting with hexane (3×10 ml). After drying and evaporation this yielded a solid (10 mg) which TLC and NMR analysis showed to contain a trace of the desired product **27** [δ_H 4.31 (1H, d, *J*=14 Hz, 2-H), 4.74 (1H, d, *J*=14 Hz, 2-H)], but mainly the starting ester **26**.

Method 2. A solution of LDA was prepared by treating diisopropylamine (1.3 ml, 939 mg, 9.28 mmol) in THF (20 ml) at −5 to −10°C (ice/acetone bath) with BuLi in hexane (1.6 M; 5.8 ml, 9.28 mmol). To this was added a solution of (*S*)-(−)-methyl *p*-tolyl sulfoxide **11** (1.30 g, 8.43 mmol) in THF (10 ml), and the resulting pale yellow solution was kept at −10°C until required (solution A). A second solution of LDA was prepared by treating diisopropylamine (1.3 ml, 939 mg, 9.28 mmol) in THF (20 ml) at −5 to −10°C with BuLi in hexane (1.6 M; 5.8 ml, 9.28 mmol). This solution was transferred via a cannula into a suspension of the aldehyde **29** (1.840 g, 8.28 mmol) in THF (20 ml) at −78°C. The mixture was stirred at 0°C for 1 h (suspension B). Suspension B was then cooled to −78° and solution A was added to it via a cannula. The resulting mixture was stirred for 0.5 h at −78°C and the reaction vessel then kept in an ice bath at 0°C for 1 h, during which a clear pale yellow solution was formed. The reaction was then quenched with 1 M hydrochloric acid (60 ml) and extracted with ethyl acetate (3×40 ml). The combined organic phases were washed with brine (2×25 ml), dried, filtered and concentrated. TLC (EtOAc) showed the mixed alcohols **30** as an unresolved spot (R_f 0.63, UV active, blue–green with vanillin), together with traces of **11** (R_f 0.30, UV active, white with vanillin) and **29** (R_f 0.71, brown with vanillin), and an unidentified non-polar by-product (R_f 0.80, pink with vanillin). The crude products **30** (max. 8.2794 mmol) and MnO_2 (Aldrich 21,764-6; dried for 2 h at 130°C/0.1 mmHg; 10.8 g, 124.2 mmol, 15 equiv.) in DCM (80 ml) was stirred at room temperature for 48 h. TLC (EtOAc) indicated that conversion to the product (R_f 0.46; red with vanillin) was complete. The solution was filtered through a pad of Celite® with the aid of more DCM. Evaporation of the filtrate gave an orange solid which was washed with ether and collected on a filter, providing the *title compound* (+)-**27** (1.650 g, 53%) as a pale yellow powder. The ether washings were concentrated, dissolved in ethyl acetate and the solution filtered through a plug of silica gel with the aid of more ethyl acetate. Concentration and trituration with ethanol gave a second crop of (+)-**27** as a yellow solid (123 mg; total 1.773 g, 57%). The analytical sample had mp 150–151°C (EtOH) (Found: C, 64.39; H, 6.00; S, 8.69. $C_{20}H_{22}O_5S$ requires C, 64.15; H, 5.92; S, 8.56%); $[\alpha]_D^{30}=+54\pm2$ (*c* 1.5, $CHCl_3$); ν_{max} 3392 br, 1620, 1587, 1470, 1413, 1292, 1217, 1141, 1048, 809 cm^{-1}; δ_H 2.38 (3H, s, 4‴-Me), 3.27–3.30 (2H, m, 1″-H_2), 3.88 (3H, s, OMe), 3.91 (3H, s, OMe), 4.31 (1H, d, *J*=14 Hz, 2-H), 4.74 (1H, d, *J*=14 Hz, 2-H), 4.89–4.97 (2H, m, 3″-H_2), 5.81–5.93 (1H, m, 2″H), 5.94 (1H, s, 5′-H), 7.28 (2H, d, *J*=8 Hz, 3‴-H, 5‴-H), 7.54 (2H, d, *J*=8 Hz, 2‴-H, 6‴-H), 13.15 (1H, s, OH); δ_C (75 MHz) 21.40 (4‴-Me), 26.19 (C-1″), 55.69 (2×OMe), 72.06 (C-2), 86.17 (C-5′), 105.76, 108.40 (C-1′, C-3′), 114.14 (C-3″ 124.45 (C-2′, C-6‴), 129.83 (C-3‴, C-5‴), 136.11 (C-2″), 141.03, 141.81 (C-1‴, C-4‴), 161.65, 163.80, 164.62 (C-2′, C-4′, C-6′), 194.17 (C-1); *m/z* (CI) 392 ($M+NH_4^+$, <5%), 375 ($M+H^+$, 10), 237 (100) ($M+H^+$, 375.1271. $C_{20}H_{23}O_5S$ requires 375.1266); R_f (EtOAc) 0.46; red with vanillin.

1.1.12. 2-Hydroxy-3-(prop-2-en-1-yl)-4,6-dimethoxybenzaldehyde 29. A stirred solution of DMF (5.0 ml, 4.72 g, 65 mmol) in acetonitrile (20 ml) at room temperature was treated dropwise with phosphoryl chloride (5.0 ml, 8.23 g, 54 mmol). After 1 h the solution was cooled to 0°C and treated dropwise with a solution of the phenol **28**[21] (4.85 g, 25 mmol) in acetonitrile (20 ml). After the addition, which took 10 min, the mixture was left for 1 h at 0°C and the ice-bath then removed. The mixture was then stirred at room temperature for 7 h, and then added slowly to ice (ca. 200 g) in a 250 ml beaker. The mixture was stirred for 30 min and then left to stand overnight (14 h). The aqueous medium contained a mass of beige needles, together with some dark resinous material, the majority of which was stuck to the beaker. The product was collected on a Buchner funnel and washed well with water. The organic material was dissolved in DCM (total 75 ml), dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was dissolved in a small volume of DCM and the solution filtered through a short plug of silica, eluting with more DCM. The eluate was evaporated to a golden yellow oil (4.60 g, 83%) that solidified. Crystallisation from ethanol (25 ml) gave the *title compound* **29** (2.82 g, 51%, in two crops) as cream needles, mp 85–86°C (Found: C, 64.41; H, 6.19. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.19%); ν_{max} (Nujol) 1640, 1618, 1433, 1412, 1298, 1251, 1222, 1204, 1117, 796 cm^{-1}; δ_H (300 MHz) 3.28 (2H, d, *J*=6 Hz, 1′-H_2), 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 4.90–5.02 (2H, m, 3′-H_2), 5.82–5.99 (1H, m, 2′-H), 5.93 (1H, s, 5-H), 10.11 (1H, s, CHO), 10.93 (1H, s, OH); *m/z* (CI) 223 ($M+H^+$, 100%).

1.1.13. (*R*)-5,7-Dimethoxy-8-(2-propen-1-yl)-3-(4-methylphenylsulfinyl)-4*H*-1-benzopyran-4-one (+)-31. A solution of LDA was prepared by treating diisopropylamine (1.6 ml, 1.155 g, 11.42 mmol) in THF (25 ml) at −10°C

(ice/acetone bath) with BuLi in hexane (1.6 M; 7.2 ml, 11.52 mmol). This was added to a suspension of keto-sulfoxide (+)-**27** (1.528 g, 4.08 mmol) in THF (20 ml) at −78°C, giving an orange solution. The solution was then allowed to warm up to −10°C and was stirred at that temperature for 10 min (solution A). Meanwhile, 1-formyl-1*H*-imidazole was prepared in situ at room temperature by adding a solution of formic acid (0.36 ml, 439 mg, 9.54 mmol) in THF (4 ml) to a solution of 1,1′-carbonyl-diimidazole (1.560 g, 9.62 mmol) in THF (15 ml) (solution B). Solution A was then cooled back to −78°C, treated with solution B, and the mixture then allowed to warm up to room temperature. The solution was stirred overnight [18 h] and then quenched with 1 M sulfuric acid (15 ml). The organic solvents were evaporated and the residue was taken up with DCM (150 ml) and washed with brine (2×50 ml). The organic phase was dried, filtered and concentrated.[†] The crude product was dissolved in DCM (70 ml) and stirred in the presence of flash silica (5 g) for 16 h. The mixture was then poured on to the top of a column of silica gel–DCM and eluted with DCM–ethyl acetate (3:1) until a yellow fluorescent by-product was about to emerge. Concentration of the eluate and trituration of the residual solid (1.300 g, 83%) with ether gave the *title compound* (+)-**31** (1.147 g, 73%, in two crops) as an off-white solid. Crystallisation from ethyl acetate gave fluffy white needles, mp 180–182°C (Found: C, 65.40; H, 5.23; S, 8.64. $C_{21}H_{20}O_5S$ requires C, 65.61; H, 5.24; S, 8.34%); $[\alpha]_D^{22}=+258\pm5$ (*c* 1.5, chloroform); ν_{max} 1643, 1621, 1598, 1568, 1469, 1386, 1269, 1210, 1128, 1075, 1051, 909, 808 cm^{-1}; δ_H (300 MHz) 2.31 (3H, s, 4″Me), 3.44 (2H, d, *J*=6 Hz, 1′-H_2), 3.88 (3H, s, OMe), 3.89 (3H, s, OMe), 4.88–4.95 (2H, m, 3′-H_2), 5.77–5.91 (1H, m, 2′-H), 6.36 (1H, s, 6-H), 7.21 (2H, d, *J*=8 Hz, 3″-H, 5″H), 7.75 (2H, d, *J*=8 Hz, 2″H, 6″H), 8.18 (1H, s, 2-H); δ_C (75 MHz) 21.41 (4″-Me), 26.68 (C-1′), 56.03 (OMe), 56.38 (OMe), 92.28 (C-6), 108.60, 108.72 (C-4a, C-8), 115.04 (C-3′), 125.59 (C-2″, C-6″ 129.80 (C-3″, C-5″ 129.98 (C-3), 135.26 (C-2′), 140.68, 141.87 (C-1″, C-4″, 152.91 (C-2), 156.86, 160.07, 162.00 (C-5, C-7, C-8a), 173.04 (C-4); *m/z* (CI, peaks >10%) 385 ($M+H^+$, 11%), 251 (10), 249 (57), 248 (14), 247 (100); R_f 0.41 (EtOAc).

1.1.14. (*R*)-2,3-Dihydro-5,7-dimethoxy-2-methyl-8-(2-propen-1-yl)-4*H*-1-benzopyran-4-one (+)-34. To a stirred solution of lithium dimethylcuprate, prepared from copper(I) bromide–dimethylsulfide complex (298 mg, 1.45 mmol) in ether (8 ml) and methyllithium–lithium bromide complex (2.2 M; 1.3 ml, 2.86 mmol) at 0°C under Ar, was added dropwise at −78°C an ice-cold solution of (*R*)-(+)-**31** (267 mg, 0.695 mmol) in THF (10 ml). The yellow solution was kept at −78°C for 1 h, allowed to reach −10°C over 1 h, and then cooled back to −78°C and quenched by the dropwise addition of a solution of glacial acetic acid (0.5 ml) in THF (2 ml). The mixture was partitioned between water (40 ml) and ethyl acetate (40 ml). The organic layer was separated and the water layer was extracted with ethyl acetate (2×20 ml). The combined organic phase was washed with sat. aq. sodium hydrogen carbonate (20 ml), and brine (2×20 ml), dried over anhydrous sodium sulfate and evaporated. The ^1H NMR spectrum of the residue (317 mg) suggested that the major product was (2*R*,3*R*,S_S)-**32** [δ_H (300 MHz) 1.32 (3H, d, *J*=6.5 Hz, 2-Me), 2.31 (3H, s, 4″Me), 3.25 (2H, d, *J*=6.5 Hz, 1′-H_2), 3.42 (1H, d, *J*=2 Hz, 3-H), 3.79 (3H, s, OMe), 3.81 (3H, s, OMe), 4.80–4.95 (2H, m, 3′-H_2), 5.31 (1H, dq, *J*=2, 6.5 Hz, 2-H), 5.75–5.90 (1H, m, 2′-H), 6.03 (1H, s, 6-H), 7.19 (2H, d, *J*=8 Hz, 3″H, 5″H), 7.35 (2H, d, *J*=8 Hz, 2″-H, 6″-H)]. A second product was tentatively identified as (2*R*,3*S*,S_S)-**33** [δ_H (300 MHz) 1.67 (3H, d, *J*=6.5 Hz, 2-Me)]. The ratio **32**–**33** was approximately 6:1 by NMR. Due to the complexity of the spectrum no other isomers were quantifiable. Reductive desulfurisation[16] was effected as follows: To a vigorously stirred solution of the above product mixture (max. 0.695 mmol) in THF (10 ml) and sat. aq. ammonium chloride (10 ml) at room temperature was added activated zinc powder (3 g, 46 mmol). After 3 h the mixture was filtered through Celite® and washed on the filter with ethyl acetate (30 ml). The filtrate was partitioned and the aqueous phase extracted with more ethyl acetate (2×30 ml). The combined organic phase was washed with sat. aq. sodium hydrogen carbonate (30 ml), brine (30 ml), dried and evaporated. Flash chromatography of the residue (elution with DCM–ethyl acetate 9:1) gave the *title compound* (+)-**34** (99 mg, 54% over two steps) as a colourless solid {$[\alpha]_D^{24}=+79\pm2$ (*c* 2.0, chloroform)}. A sample was crystallised by dissolving in the minimum of hot ethyl acetate and adding an excess of petroleum, which gave pale yellow prisms, mp 101–103°C (Found: C, 68.86; H, 6.87. $C_{15}H_{18}O_4$ requires C, 68.68; H, 6.92%); $[\alpha]_D^{24}=+83\pm2$ (*c* 1.8, chloroform); ν_{max} (neat) 1672, 1601, 1571, 1465, 1345, 1267, 1214, 1130, 911, 824 cm^{-1}; δ_H (300 MHz) 1.42 (3H, d, *J*=6.5 Hz, 2-Me), 2.56 (2H, d, *J*=7.5 Hz, 3-H_2), 3.25–3.30 (2H, m, 1′-H_2), 3.85 (3H, s, OMe), 3.88 (3H, s, OMe), 4.44 (1H, apparent dq, ca. *J*=7 Hz, 2-H), 4.86–4.98 (2H, m, 3′-H_2), 5.78–5.92 (1H, m, 2′-H), 6.06 (1H, s, 6-H); δ_C (75 MHz) 20.68 (2-Me), 26.79 (C-1′), 45.84 (C-3), 55.68 (OMe), 56.03 (OMe), 73.66 (C-2), 88.66 (C-6), 106.12, 108.44 (C-4a, C-8), 114.06 (C-3′), 136.56 (C-2′), 160.97, 161.46, 163.19 (C-5, C-7, C-8a), 190.34 (C-4); *m/z* (CI, peaks ≥10%) 264 (11%), 263 ($M+H^+$, 100), 160 (18); R_f (EtOAc) 0.35 (red–orange with vanillin).

In repeat of the above sequence, a fraction containing **32** and **33** (88 mg, 0.22 mmol) was isolated from the cuprate addition product by flash chromatography (elution with DCM–ethyl acetate 9:1). This was dissolved in THF (4 ml) and treated as described above with sat. aq. ammonium chloride (4 ml) and zinc powder (1 g, 15 mmol) for 2 h. Isolation as before followed by flash chromatography (elution with DCM–ethyl acetate 9:1) gave the *title compound* (+)-**34** (43.5 mg, 75%) as a colourless crystalline solid.

1.1.15. (*R*)-2-(2,3-Dihydro-5,7-dimethoxy-2-methyl-4-oxo-4*H*-1-benzopyran-8-yl)ethanol (+)-6. To a solution of the

[†] NMR analysis at this stage showed the required product **31** and a significant other, possibly a hemiacetal (i.e. 2-hydroxychromanone) precursor of **31** [δ_H (300 MHz) (tentative assignments) 3.32 (2H, d, *J*=6 Hz, 1′-H_2), 5.82 (1H, d, *J*=2.5 Hz, 3-H), 6.07 (1H, s, 6-H), 6.16 (1H, d, *J*= 2.5 Hz, 2-H), 7.08 (2H, d, *J*=8 Hz, 3″H, 5″H), 7.41 (2H, d, *J*=8 Hz, 2″H, 6″H), 8.17 (1H, s, OH).

chromanone (+)-**34** (65 mg, 0.248 mmol) in THF (4 ml) and water (2 ml) was added osmium tetroxide (4% solution in water, 0.2 ml, 0.031 mmol). After the solution had darkened, $NaIO_4$ (125 mg, 0.58 mmol) was added and the mixture was stirred for a further 3 h. The solution was diluted with water (20 ml) and extracted with ethyl acetate (3×20 ml), and the extract was washed with sat. aq. sodium thiosulfate (20 ml) and brine (20 ml). Drying with anhydrous sodium sulfate and evaporation gave **35**, R_f (EtOAc) 0.27. A solution, prepared by stirring sodium borohydride (21 mg, 0.56 mmol) in ethanol (8 ml) at room temperature for 10 min, was added dropwise to a stirred solution of the crude aldehyde **35** prepared as above (max. 65.5 mg, 0.248 mmol) in dry THF (7 ml) under Ar. The reaction, followed by TLC (elution with ethyl acetate), was complete after 20 min. The mixture was poured into 0.2 M hydrochloric acid (40 ml) and the solution extracted with DCM (2×30 ml). The extract was washed with brine (20 ml), dried and evaporated, and the residue chromatographed (elution with ethyl acetate–DCM 1:1) to obtain the title compound (+)-**6** (33 mg, 53%), mp 164–165°C (ethyl acetate); $[\alpha]_D^{22}=+56\pm4$ (*c* 0.63, methanol); ν_{max} 3500–3200 br, 1650, 1606, 1571, 1471, 1350, 1287, 1212, 1124, 1047, 814 cm^{-1}; δ_H (300 MHz) 1.44 (3H, d, *J*=6.5 Hz, 2-Me), 1.80 (1H, br s, OH), 2.57 (2H, apparent d, *J*=7.5 Hz, 3-H_2), 2.86 (2H, t, *J*=6.5 Hz, 2′-H_2), 3.70 (2H, t, *J*=6.5 Hz, 1′-H_2), 3.86 (3H, s, OMe), 3.89 (3H, s, OMe), 4.46 (1H, apparent sextet, ca. *J*=7 Hz, 2-H), 6.07 (1H, s, 6-H); δ_C (75 MHz) 20.71 (2′-Me), 26.26 (C-2), 45.78 (C-3′), 55.67 (OMe), 56.06 (OMe), 62.49 (C-1), 73.85 (C-2′), 88.79 (C-6′), 106.17, 106.92 (C-4a′, C-8′), 161.19, 161.77, 163.59 (C-5′, C-7′, C-8a′), 190.00 (C-4′); *m/z* (CI) 267 ($M+H^+$, 100%), 160 (23); R_f (EtOAc) 0.22 (orange with vanillin). Lit.[10] for the methyl ether **6** prepared from LL-D253α **7**: mp 165–166°C (ethyl acetate); $[\alpha]_D^{25}=+36.0\pm0.36$ (*c* 0.545, MeOH); δ (60 MHz) 1.48 (3H, d, *J*=ca. 7 Hz, 2-Me), 1.85 (1H, s, OH), 2.51 and 2.63 (2H, m, 3-H_2), 2.87 (2H, t, *J*=ca. 7 Hz, benzylic CH_2), 3.73 (2H, t, *J*=ca. 7 Hz, CH_2OH), 3.89 and 3.90 (each 3H, s, OMe), 4.50 (1H, complex quartet, 2-H), 6.12 (1H, s, ArH).

1.1.16. 1-(2-Phenylmethoxy)phenylethanone 36. A stirred mixture of 2-hydroxyacetophenone (2.72 g, 20 mmol), 4-methoxybenzyl chloride (3.13 g, 20 mmol) and anhydrous potassium carbonate (4.14 g, 30 mmol) in acetone (20 ml) was heated under reflux for 48 h. The solid was removed by filtration and the filtrate was concentrated and then diluted with ethyl acetate (30 ml). The solution was washed successively with aq. sodium hydroxide (4 M, 3×30 ml), water and brine, dried and evaporated. The residue was distilled under reduced pressure to obtain the *title compound* **36** (3.9 g, 76%), bp 190–195°C (oven temp.) at 0.12 mmHg, which crystallised from ether as colourless needles, mp 67–68°C (Found: C, 75.08; H, 6.43. $C_{16}H_{16}O_3$ requires C, 74.98; H, 6.29%); ν_{max} 1670, 1620, 1600 cm^{-1}; δ_H (60 MHz) 2.6 (3H, s, COMe), 3.8 (3H, s, OMe), 5.05 (2H, s, OCH_2), 6.8–8.0 (8H, m, ArH); *m/z* (EI) 250 (M^+, 2.5%), 122 (65), 121 (100), 78 (49), 77 (53).

1.1.17. 1-(2-(4-Methoxyphenylmethoxy)phenyl-2-(4-methylphenylsulfinyl)ethanone (±)-39. A stirred solution of the ketone **36** (1.36 g, 5.3 mmol) and ethyl *p*-toluenesulfinate (±)-**38**[28] (0.92 g, 5 mmol) in THF (20 ml) at room temperature under N_2 was treated portionwise with sodium hydride (0.30 g, 80% oil dispersion, 10 mmol). The mixture was heated at reflux temperature for 4 h and water (20 ml) then added. The resulting solution was neutralised with 3 M hydrochloric acid (5 ml) and extracted with ethyl acetate (3×20 ml). The combined extracts were washed with water and brine, dried, filtered and evaporated. Chromatography of the residue on silica gel using ether as eluant gave the title compound **39** (0.95 g, 48%) and the unreacted starting material **36** (0.61 g). The spectra of **39** were identical with those of an authentic sample.[7]

1.1.18. 1-(2-Phenylmethoxy)phenyl-2-(4-methylphenylsulfinyl)ethanone (±)-40. The preparation of **40** was carried out as described above for **39**, using 2′-benzyloxyacetophenone **37**[27] (1.13 g, 5 mmol), ethyl *p*-toluenesulfinate (±)-**38**[28] (0.92 g, 5 mmol) and sodium hydride (0.30 g, 80% oil dispersion, 10 mmol). The *title compound* (±)-**40** (1.0 g, 55%) was isolated as colourless needles, mp 111–113°C (ether–DCM) (Found: C, 72.75; H, 5.66. $C_{22}H_{20}O_3S$ requires C, 72.50; H, 5.53%); ν_{max} 1650, 1590 and 1040 cm^{-1}; δ_H (60 MHz) 2.40 (3H, s, Me), 4.26 (1H, d, *J*=14.5 Hz, 2-H), 4.58 (1H, d, *J*=14.5 Hz, 2-H), 5.13 (2H, s, OCH_2), 6.80–7.95 (13H, m, ArH); *m/z* (EI, peaks ≥20%) 364 (M^+, 29%), 257 (33), 229 (39), 226 (27), 225 (75), 224 (31), 223 (29), 211 (47), 209 (31), 140 (36), 139 (76), 133 (21), 121 (60), 120 (39), 119 (22), 118 (32), 105 (39), 104 (20), 92 (76), 91 (100), 90 (41), 89 (39), 78 (21), 77 (54). A portion of the starting material **37** was also recovered from the column.

1.1.19. 1-(2-Hydroxy-5-methylphenyl)-2-(4-methylphenylsulfinyl)ethanone 12 from the ketone 41. *Using lithium diisopropylamide and copper(I) iodide*. To a stirred solution of 2-hydroxy-5-methylacetophenone **41** (50 mg, 0.33 mmol) and CuI (63 mg, 0.33 mmol) in THF (3 ml) at −78°C was added a solution of LDA in THF (0.25 M, 4.0 ml, 1.0 mmol). The mixture was allowed to warm to room temperature over the course of 0.5 h, then cooled again to −78°C. A solution of (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate **42** (100 mg, 0.34 mmol) in THF (3 ml) was slowly added and the mixture was then allowed to warm to room temperature and stirring continued for 2 h. The mixture was quenched with sat. aq. ammonium chloride (15 ml) and extracted with ethyl acetate (3×15 ml). The extract was washed with water (2×10 ml) and 0.5 M hydrochloric acid (10 ml), dried and evaporated. The products were separated on a short silica column, eluting with ether. Evaporation of the eluate gave a sample of the ketosulfoxide **12** (40 mg, 0.14 mmol, 42%) which was identical (TLC, ^1H NMR) with the material obtained as described earlier and had $[\alpha]_D^{22}=+93\pm8$ (*c* 0.58, $CDCl_3$). On repeating the above sequence with an increased reaction time of 48 h, the isolated ketosulfoxide **12** (ca. 40%) had $[\alpha]_D^{22}=+74\pm6$ (*c* 1.54, $CDCl_3$).

Using potassium hydride. To a stirred suspension of KH (35% dispersion in mineral oil, 160 mg, 1.4 mmol) in THF (2.5 ml) under Ar at −78°C was added a solution of the hydroxyacetophenone **41** (51 mg, 0.34 mmol) in THF (2.5 ml). The mixture was stirred for 3 h until the second colour change (yellow to yellow–green) was complete. A solution of (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate

42 (100 mg, 0.34 mmol) in THF (3 ml) was added and the mixture was then allowed to warm to room temperature and stirring continued for 3 h. The mixture was quenched with sat. aq. ammonium chloride (15 ml) and extracted with ethyl acetate (3×30 ml). The extract was washed with water (3×30 ml), dried and evaporated. The products were separated on a short silica column, eluting with ether. Evaporation of the eluate gave a sample of the ketosulfoxide **12** (30 mg, 0.10 mmol, 31%) which was identical (TLC, ^{1}H NMR) with the material obtained as described earlier and had $[\alpha]_D^{22}=-32\pm7$ (*c* 0.5, $CDCl_3$). On repeating the above sequence with an increased reaction time of 18 h, the isolated ketosulfoxide **12** (ca. 30%) had $[\alpha]_D^{22}=-26\pm7$ (*c* 0.5, $CDCl_3$).

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