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Stereoselective Synthesis of 2*H*-Chromans by Reductive Deoxygenation of Differently Substituted 2-Sulfinylmethylchroman-2-ols

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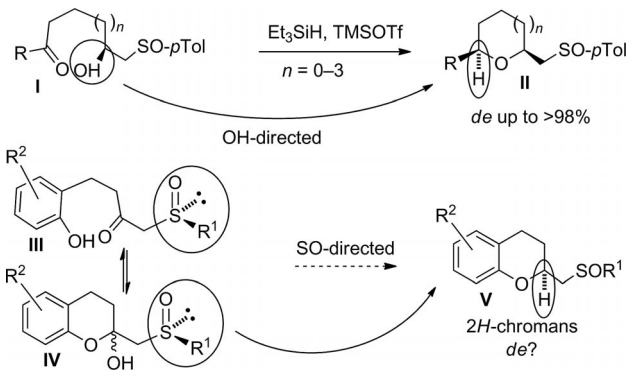
Good-to-excellent diastereoselectivies have been achieved in the synthesis of 2*H*-chromans by Et_3SiH/TMSOTf reductive deoxygenation of differently substituted 2-sulfinylmethylchroman-2-ols and their methyl ketals. The influence of both electron-donating and -withdrawing substituents on the sulfoxide and on the aromatic dihydobenzopyran core has been studied. SOR^1 electron-donating groups (R^1 = *p*MeOPh and 2-MeO-1-naphthyl) led to a competitive reaction in which the sulfoxide was reduced, thus lowering the yield of the sulfinyl 2*H*-chromans. The method allows the presence of different groups on the aromatic dihydrobenzopyran unit. The best results in terms of yield and diastereoselectivity were obtained with 2-[(*p*-tolylsulfinyl)methyl]chroman-2-ols. All the results are explained on mechanistic grounds. Synthetic transformations of the enantiopure 2*H*-chroman (S,R_S)-**21** are reported.

Introduction

Stereoselective approaches to 2-substituted and 2,2-disubstituted tetrahydrobenzopyran derivatives (chromans) continue to attract considerable attention due to the widespread appearance of these structural motifs in a number of natural products that exhibit important biological properties.[1] Apart from the antioxidant and radical scavenging properties of the vitamin E family and its analogues, some of them play an important role in various therapeutic areas, including cardiovascular diseases, diabetes, obesity, hypertension, cancer, the central nerve system and endocrine disorders as well as infectious diseases. The 2*H*-chroman skeleton appears, for example, in the important shikimate-derived group of flavanoids[2] and in some antibiotics[3] and enzyme inhibitors.[4] Synthetic chromans are also valuable targets as several derivatives have been shown to possess important biological activities, acting as hypoglycemic agents,[5] potent in vitro inhibitors of rhinovirus replication[6] and anti-hypertensive agents.[7]

These diverse biological activities have stimulated many synthetic studies. The stereoselective construction of the chroman core[8] has been achieved by asymmetric catalysis,[9–11] enzymatic resolution,[12] the use of chiral auxiliaries[13] and from the chiral pool.[14] Although some of the procedures gave good results, there is no asymmetric route applicable to a wide range of substrates. Among the strategies available nowadays for the stereoselective synthesis of cyclic ethers,[15] the Et_3SiH/TMSOTf-promoted synthesis of ethers by reductive condensation of carbonyl compounds and alkoxysilanes[16] or alcohols[17] has been applied by us to the asymmetric synthesis of a number of different sized systems. Thus, the Et_3SiH/TMSOTf-promoted reductive cyclization of enantiopure β-hydroxy sulfinyl ketones **I** (Scheme 1), in turn accessible by the well-established diastereoselective reduction of a suitably functionalized enantiopure β-keto sulfoxide,[18] allowed the synthesis of five-,[19] six-,[19–21] seven-[22] and eight-membered[23] cyclic ethers with 2,ω-*cis*-disubstitution (**II**) in a highly diastereoselective manner. We tested the validity of our asymmetric



Scheme 1. Asymmetric induction in the formation of cyclic ethers by reductive cyclization/deoxygenation of ω-keto β-hydroxy sulfoxides in equilibrium with δ-(*o*-hydroxyphenyl)-substituted β-keto sulfoxides.

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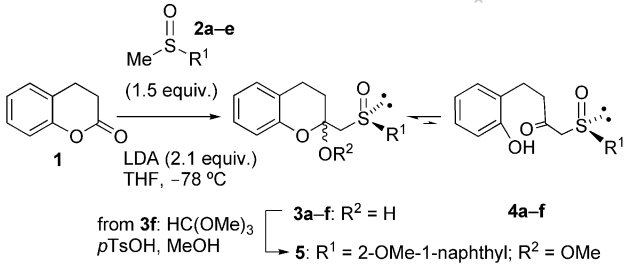
approach by completing the total enantioselective synthesis of several structurally simple natural products[19,23] and more densely functionalized derivatives such as (+)-goniothalesdiol.[24] In these syntheses the sulfoxide controlled the absolute configuration of the β-hydroxylic centre, which in turn directed the stereochemical course of the reductive cyclization step. The essential role of the exocyclic sulfoxide in stabilizing the reactive conformation of the intermediate cyclic oxocarbenium ion suffering the attack of Et_3SiH has only recently been pointed out.[24a]

Although our asymmetric strategy to cyclic ethers monitored by sulfoxides could be used to construct the 3,4-dihydro-2*H*-1-benzopyran (2*H*-chroman) core, to the best of our knowledge, prior to our work, sulfoxides have never been used as asymmetric inductors to directly generate this moiety from a phenol in a single step. In a previous communication,[25] we reported the asymmetric synthesis of the *S*,*R*,*R*,*R* enantiomer of Nebivolol, an antihypertensive drug, employing the new sulfoxide-directed reductive deoxygenation of a 2-[(*p*-tolylsulfinyl)methyl]chroman-2-ol of type **IV** (Scheme 1) to generate the 2*H*-chroman moieties. We thus showed that the sulfoxide as the sole chiral element was able to produce a high asymmetric induction in the synthesis of dihydrobenzopyrans. To know the generality of this stereoselective 2*H*-chroman ring-forming step, we decided to study the reaction of differently substituted sulfinyl derivatives both on the aromatic ring and on the sulfoxide.[26] In this paper, we present our results showing that the Et_3SiH/TMSOTf-promoted reductive deoxygenation of 2-sulfinylmethyl-substituted chroman-2-ols **IV**, in equilibrium with the δ-(*o*-hydroxyphenyl)-substituted β-keto sulfoxides **III** (Scheme 1), is a short, efficient and stereoselective protocol to 2*H*-chroman derivatives that can be applied to a wide range of differently substituted structures. We include full details of the methodology used for the preparation of all the synthetic intermediates as well as our conclusions on the relative influence of steric and electronic effects both in the reactivity and diastereoselectivity of the ionic cleavage process. Further synthetic applications to some derivatives lacking the sulfoxide are reported.

Results and Discussion

The synthesis of δ-(*o*-hydroxyphenyl)-substituted alkyl β-keto sulfoxides **4**, required for our study, is shown in Scheme 2. We initially chose differently substituted sulfoxides having *p*Tol, *t*Bu, *p*MeOPh, *p*NO_2Ph, 2-naphthyl and 2-MeO-1-naphthyl substituents at the sulfur function (R^1) to evaluate the relative influence of steric and electronic factors of the sulfoxide on the diastereoselectivity of the process.[26]

The β-keto sulfoxides **4a**–**f** were synthesized by reaction of the lithium anion derived from methyl R^1-substituted sulfoxides **2a**–**f** with dihydrocoumarin (**1**; Scheme 2, Table 1). Thus, the reaction of **1** with the LDA-generated lithium anion of (R_S)-methyl *p*-tolyl sulfoxide[27] (**2a**; Table 1, entry 1) afforded a 90:10 equilibrium mixture of



Scheme 2. Synthesis of 4-(*o*-hydroxyphenyl)-1-sulfinyl-substituted 2-butanones **4a**–**e** in equilibrium with 2-sulfinylmethyl-substituted chroman-2-ols **3**.

the cyclic hemiketal (R_S)-**3a** and the keto sulfoxide **4a**. The mixture was isolated in 90% yield and compound **3a** was characterized as a mixture of C-2 anomers. The *t*Bu, *p*-methoxyphenyl-, *p*-nitrophenyl- and 2-naphthyl-substituted methyl sulfoxides **2b**,[28] **2c**,[29] **2d**[29b] and **2e**[30] were used in the racemic form. They were synthesized by controlled oxidation of the corresponding commercially available thioethers with MCPBA in 67, 90, 81 and 81% yields, respectively. Their treatment with LDA in THF at –78 °C followed by the addition of the resulting mixture to a THF solution of dihydrocoumarin **1** gave rise to the desired derivatives **3** and **4** as mixtures of cyclic hemiketals **3** and open-chain ketones **4** (**3/4** ≈ 90:10) in the yields indicated in Table 1 (entries 2–5). The lower yield of *p*-nitrophenylsulfinyl derivatives **3d** and **4d** (21% yield) could be due to the low solubility of the starting methyl *p*-nitrophenyl sulfoxide (**2d**) in THF, making difficult the quantitative formation of the lithium anion, because part of the starting sulfoxide **2d** was recovered unchanged. The (R_S)-2-[(2-methoxynaphthylsulfinyl)methyl]chroman-2-ol (**3f**) could not be isolated from the crude mixture resulting from the enantiopure sulfoxide (R_S)-**2f**[31] following the same procedure due to its instability. We thus transformed the hemiketal into the mixed methyl ketal **5** (50:50 mixture of anomers) by treating the crude mixture immediately with trimethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid in methanol (Table 1, entry 6; 26% isolated yield for the two steps).

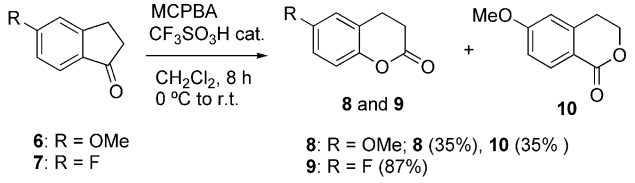
Table 1. Reactions between the lithium anion derived from MeSOR^1 **2** and hydrocoumarin (**1**).

Entry	R^1	**3/4** (90:10)	Yield [%]
1	*p*Tol (R_S)-**2a**	**3a**[a]/**4a**	90
2	*t*Bu (±)-**2b**	**3b**[a]/**4b**	77
3	*p*MeOPh (±)-**2c**	**3c**[a]/**4c**	76
4	*p*NO_2Ph (±)-**2d**	**3d**[a]/**4d**	21
5	2-naphthyl (±)-**2e**	**3e**[a]/**4e**	89
6	2-MeO-1-naphthyl (R_S)-**2f**	**5**[b]	26 (2 steps)[c]

[a] Mixture of anomers, ca. 85:15. [b] Mixture of anomers, ca. 50:50. [c] Second step: treatment with $HC(OMe)_3$, cat. *p*TsOH in MeOH.

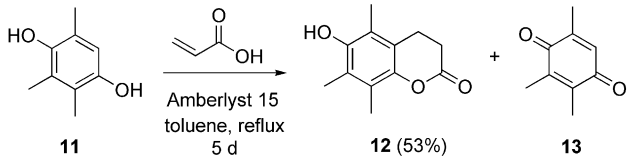
From our methodological study, we also wanted to know if the electronic density of the aromatic ring of the 2-sulfinylmethyl-substituted chroman-2-ol could influence the reductive deoxygenation process. With this aim, we decided to prepare derivatives **14**, **15** and **19**, having different sub-

stituents on the aromatic ring, such as a MeO electron-donating group, an electron-withdrawing F and the trimethyl and OH substituents found in the vitamin E core. The F-substituted core had been previously synthesized by us to complete the synthesis of Nebivolol.[25] The enantiopure *p*-tolylsulfinylmethyl substituent was chosen as a model of the substituent at C-2 of the chroman-2-ol. The MeO- and F-substituted hydrocoumarins **8** and **9** (Scheme 3), required to access the sulfinyl chromanols **14** and **15**, were obtained from the corresponding 5-substituted 1-indanones **6** and **7**, respectively, by Baeyer–Villiger oxidation with MCPBA and catalytic trifluoromethanesulfonic acid in CH_2Cl_2 at 0 °C.[32] A 50:50 mixture of two isomeric lactones **8** and **10** resulted from the 5-methoxy-substituted indanone **6** from which **8** could be isolated pure by chromatography in 35% yield. The fluoro-substituted hydrocoumarin **9** was regioselectively formed and isolated in 87% yield.



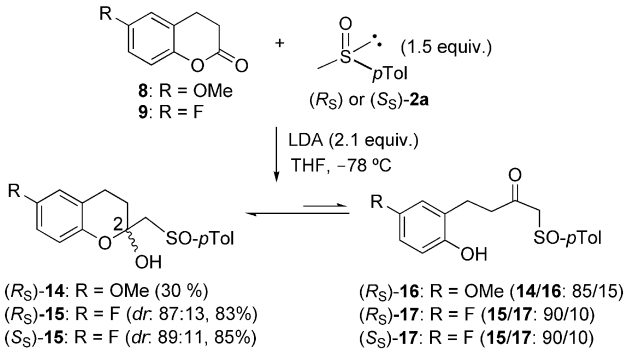
Scheme 3. Synthesis of substituted dihydrocoumarins **8** and **9**.

The synthesis of the dihydrocoumarin **12**, with the substitution present in the dihydrobenzopyran core of vitamin E, was based on the reported Friedel–Crafts alkylation/lactonization of an activated phenol.[33,34] We tried the one-pot alkylation and lactonization of trimethylhydroquinone **11** using different acrylic acid derivatives such as methyl acrylate, acryloyl chloride and acrylic acid in the presence of different catalysts and we observed only the formation of **12** when the reaction was effected with acrylic acid in the presence of Amberlyst 15. Compound **12** was finally obtained following a modification of a previously described procedure[35] using 1.1 equiv. of acrylic acid and 400 mg/mmol of Amberlyst 15 in toluene at reflux (Scheme 4). Under these conditions, a mixture of **12** and the trimethylbenzoquinone **13** resulted, from which the hydrocoumarin **12** could be isolated pure in 53% yield.



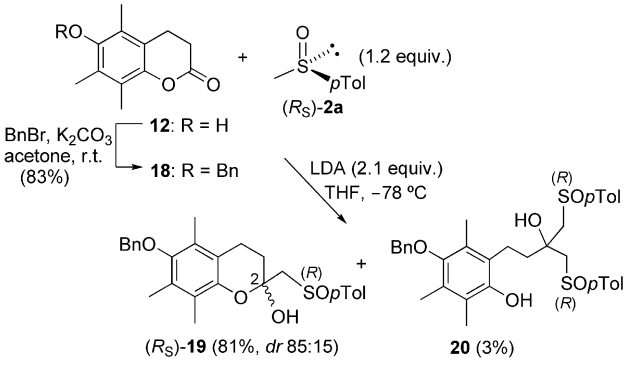
Scheme 4. Synthesis of 6-hydroxy-5,7,8-trimethyl-3,4-dihydrocoumarin (**12**).

The reactions of dihydrocoumarins **8** and **9** with the LDA-generated lithium anion derived from methyl *p*-tolyl sulfoxide [(R_S)-**2a**] allowed the synthesis of 2-(*p*-tolylsulfinylmethyl)-substituted chroman-2-ols (R_S)-**14** and (R_S)-**15**, which were isolated as mixtures of C-2 epimers in the hemiketal forms, and the open β-keto sulfoxides **16** and **17** in the yields indicated in Scheme 5. The chromanol (S_S)-**15** was obtained in a similar way from (S_S)-**2a**.[25]



Scheme 5. Synthesis of methoxy- and fluoro-substituted 2-[(*p*-tolylsulfinyl)methyl]chroman-2-ols **14** and **15**.

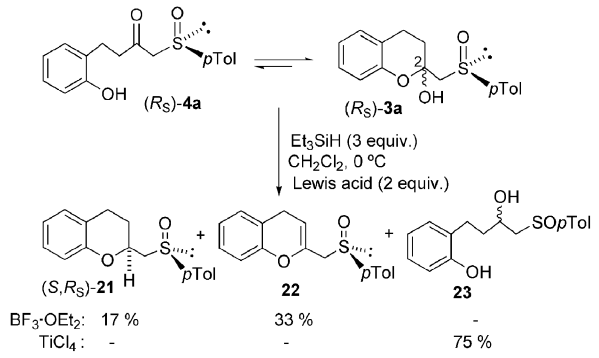
Previous to the reaction with the lithium anion of methyl *p*-tolyl sulfoxide, the trimethylhydroxy-substituted dihydrocoumarin **12** was protected as the benzyl ether (BnBr, K_2CO_3, acetone, 83%, Scheme 6). Reaction of the benzyl-protected derivative **18** with the lithium anion resulting from (R_S)-**2a** (1.2 equiv.) led to the sulfinyl-substituted chromanol (R_S)-**19**, which was characterized as a mixture of C-2 epimers in an 85:15 diastereomeric ratio and was isolated in 81% yield. The byproduct **20**, which results from the double addition of the intermediate sulfinyl carbanion to the lactone, was also isolated from the crude mixture by chromatography in 3% yield.



Scheme 6. Synthesis of 6-benzyloxy-5,7,8-trimethyl-2-[(*p*-tolylsulfinyl)methyl]chroman-2-ol [(R_S)-**19**].

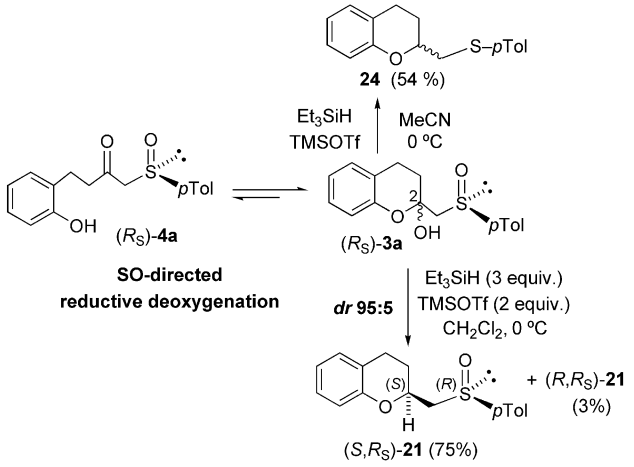
With the sulfinylchromanols in hand, we initially examined the reaction of hemiketal (R_S)-**3a**, chosen as a model, with Et_3SiH in the presence of different Lewis acids such as $ZnBr_2$, $Yb(OTf)_3$, Me_2AlCl, $TiCl_4$ and TMSOTf. Surprisingly, **3a** did not react in the presence of $Yb(OTf)_3$ or Me_2AlCl. Treatment of the mixture of the sulfoxide-bearing chromanol (R_S)-**3a** and the open β-keto sulfoxide (R_S)-**4a** with $BF_3{\cdot}OEt_2$, followed by an excess of Et_3SiH (3 equiv.) in CH_2Cl_2 at 0 °C led to the formation of 2*H*-chroman **21**, although in a low yield of 17% (Scheme 7). A secondary product, characterized as 2-(*p*-tolylsulfinylmethyl)-4*H*-chromene (**22**) was isolated in 33% yield. The reaction with Et_3SiH in the presence of $TiCl_4$ occurred in 2 h at 0 °C in

CH_2Cl_2 to give 2-[3-hydroxy-4-(*p*-tolylsulfinyl)butyl]phenol (**23**) in a non-stereoselective manner (*dr* 50:50, 75% yield). Similar results were obtained by using $ZnBr_2$ as the Lewis acid, although without complete conversion of the starting material in the same reaction time.



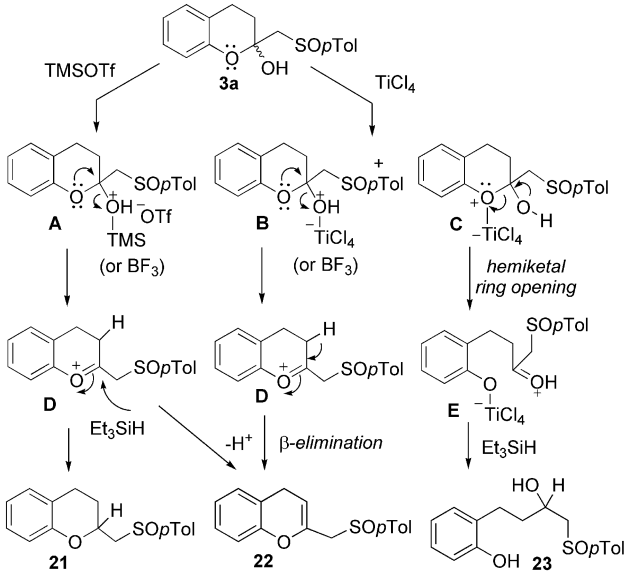
Scheme 7. Use of different Lewis acids in the reductive deoxygenation reaction of (R_S)-**3a**/(R_S)-**4a** with Et_3SiH.

Treatment of the mixture of (R_S)-**3a** and (R_S)-**4a** with Et_3SiH (3 equiv.) followed by addition of TMSOTf (2 equiv.) in CH_2Cl_2 at 0 °C led to the rapid formation of 2*H*-chroman (*S*,R_S)-**21** in an excellent 95:5 diastereomeric ratio and 75% yield (Scheme 8). The absolute *S*,R_S configuration of **21** was established by X-ray diffraction.[25] When acetonitrile was used as the solvent, the formation of racemic 2-(*p*-tolylthiomethyl)chroman **24** was observed (54% yield). This result indicates that acetonitrile first promotes the reduction of the sulfoxide to the thioether and is followed by reductive deoxygenation.



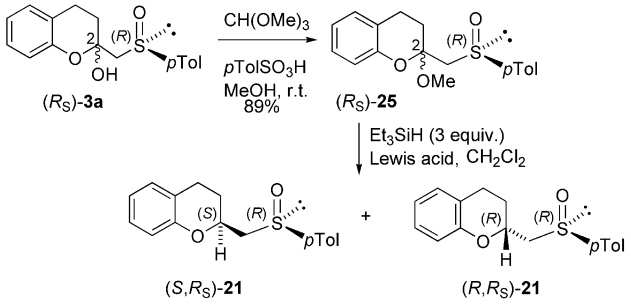
Scheme 8. SO-directed reductive deoxygenation of (R_S)-**3a**/(R_S)-**4a** with Et_3SiH/TMSOTf.

A possible mechanistic pathway explaining these results is shown in Scheme 9. Activation of the hemiketal OH must occur with TMSOTf acting as a Lewis acid (or $BF_3{\cdot}OEt_2$) to give a species such as **A** which evolves into the cyclic oxocarbenium intermediate **D**. The nucleophilic attack of Et_3SiH on this intermediate explains the formation of the expected 2*H*-chroman **21**. When $TiCl_4$ is the Lewis acid, the activated species could be **B** (similar to **A**) or **C** as this strong acid can coordinate both to the hemiketal OH or to the less basic oxygen linked to the aromatic ring. The species **C** could suffer hemiketal ring-opening, leading to the intermediate acyclic oxocarbenium ion **E**, the reduction of which with Et_3SiH justifies the formation of a mixture of diastereomeric sulfinyl carbinols **23** observed in the presence of $TiCl_4$. The activated species in the presence of $BF_3{\cdot}OEt_2$ **B**, would also form the intermediate **D**, the evolution of which through a β-elimination explains the formation of chromene **22** (Scheme 9).



Scheme 9. Mechanistic pathway explaining the results obtained in the reaction of **3a** and Et_3SiH in the presence of different Lewis acids.

Taking this mechanistic proposal into account, we thought of avoiding the formation of the undesired ring-opened product **23** by performing the reaction on a mixed methyl ketal derivative such as **25**, with a slightly more basic MeO group, which would favour the activation through a species similar to **A** or **B**. Thus, product **25** was synthesized by treatment of the hemiketal **3a** with trimethyl orthoformate and catalytic *p*-toluenesulfonic acid in methanol in good yield as a mixture of C-2 epimers (50:50; Scheme 10).



Scheme 10. Synthesis of mixed methyl ketal (R_S)-**25** and reaction with Et_3SiH in the presence of different Lewis acids.

The reaction of sulfinyl ketal (R_S)-**25** with Et_3SiH in the presence of TMSOTf, $BF_3{\cdot}OEt_2$ or $TiCl_4$ as Lewis acid in CH_2Cl_2 gave rise to the 2*H*-chroman **21**. Working with

Et_3SiH and TMSOTf at 0 °C in CH_2Cl_2 solution, the sulfinyl ketal **25** was transformed into the sulfinyl chroman mixture of diastereomers (S,R_S)-**21** and (R,R_S)-**21** in a ratio of 89:11 (Table 2, entry 1). The reaction of **25** with Et_3SiH and $BF_3{\cdot}OEt_2$ required 5 equiv. of the Lewis acid for complete conversion of the starting **25** and a low temperature (–20 °C) to avoid the formation of the elimination product **22**. Under these conditions, chroman (S,R_S)-**21** was obtained in 70% yield and with good diastereoselectivity (94:6; Table 2, entry 2). In the presence of $TiCl_4$, the reductive deoxygenation of **25** was faster, even at lower temperatures (Table 2, entries 3 and 4), but the diastereoselectivity decreased dramatically. Although the diastereoselectivity was highly dependent on the nature of the Lewis acid, we never observed the inversion of the configuration at the C-2 stereogenic centre created during the process. The major diastereomer obtained from the mixed ketal (R_S)-**25** was always the (S,R_S)-**21** epimer, the same as that resulting from the hemiketal analogue (R_S)-**3a**. These observations suggest that both reactions proceed through a similar mechanistic pathway.

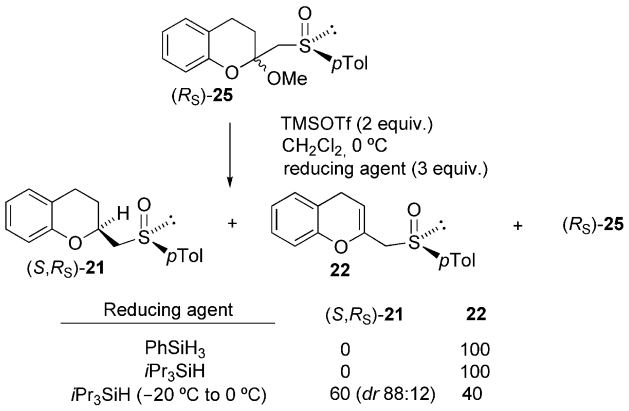
Table 2. Diastereomeric ratio in the reactions of (R_S)-**25** with Et_3SiH in the presence of Lewis acids.

Entry	Lewis acid (equiv.)	T [°C]	t [h]	(S,R_S)-**21**/(R,R_S)-**21**
1	TMSOTf (2)	0	10	89:11
2	$BF_3{\cdot}OEt_2$ (5)	–20 to r.t.	18	94:6
3	$TiCl_4$ (1.6)	–40 to r.t.	1.5	75:25
4	$TiCl_4$ (1.6)	–78	1.5	68:32

The influence of the reducing agent on the reductive deoxygenation of mixed ketal (R_S)-**25** was also evaluated. Different silicon hydrides such as triisopropylsilane ($i$$Pr_3SiH$), bulkier than Et_3SiH, and phenylsilane ($PhSiH_3$),[36] less bulky, were tested in the reaction carried out in the presence of TMSOTf. Both reducing agents (3 equiv.) reacted with 2-methoxy-2-(*p*-tolylsulfinylmethyl)-2-chroman [(R_S)-**25**] in the presence of TMSOTf (CH_2Cl_2, 0 °C) leading to the chromene **22** with a low conversion of the starting material. This indicates a lower reactivity of both hydrides in this process. When $i$$Pr_3SiH$ was used at a lower temperature, –20 °C, a mixture of epimeric 2-[(*p*-tolylsulfinyl)methyl]-chromans (S,R_S)-**21** and (R,R_S)-**21** (*dr* 88:12) and chromene **22** was formed in a ratio of 60:40 (Scheme 11), but again with a low conversion.

In the study carried out up to now, both the hemiketal (R_S)-**3a** and the mixed methyl ketal (R_S)-**25** have shown very similar behaviour in the reductive deoxygenation reaction, with the best diastereoselectivities and yields of chroman derivative (S,R_S)-**21** obtained by using Et_3SiH and TMSOTf in CH_2Cl_2 solution at 0 °C.

We then decided to evaluate the role played by the nature of the sulfinyl substituent in the process. The results of the reactions of *t*Bu-, *p*-methoxyphenyl-, *p*-nitrophenyl- and 2-naphthyl-substituted 2-sulfinylmethyl-2-chromanols **3b**–**e** are indicated in Scheme 12 and Table 3. The chromanol **3b**, with a bulky *tert*-butyl sulfoxide, reacted slowly under the conditions shown (Et_3SiH, TMSOTf, CH_2Cl_2, 0 °C). After 24 h and 80% conversion, the reaction was quenched. The NMR spectrum of the crude mixture evidences the presence of a 75:25 mixture of epimeric chromans (2S*,R*$_S$)-**26** and (2R*,R*$_S$)-**26** and the methylenechroman **30** resulting from the exocyclic dehydration of hemiketal **3b**. Chromatographic separation allowed the isolation of pure diastereomers (2S*,R*$_S$)-**26** and (2R*,R*$_S$)-**26** in 45 and 13% yields, respectively, as well as a 20% yield of 2-(*tert*-butylsulfinylmethylene)chroman (**30**; Table 3, entry 1). When the reacting sulfoxide was **3c**, having the electron-rich *p*-methoxyphenyl substituent, the 2*H*-chroman **31** with a thioether group, which results from sulfoxide reduction followed by reductive deoxygenation of **3c**, was the major product (65% isolated yield; Table 3, entry 2). A 23% yield of the diastereomers **27**, which result from the expected deoxygenation, was also isolated with a 69:31 *dr*. In a similar way, the electron-rich (R_S)-2-MeO-1-naphthylsulfinyl-substituted chroman ketal **5** evolved into a complex mixture in which the over-reduced product **32** was the only identified product, which was isolated in a poor yield of 15% (Table 3, entry 5). Compound **32** was shown to be racemic, which again indicates that the starting sulfinylchroman derivative **5** was first reduced to the thioether and later deoxygenated. In contrast, the electron-poor *p*-nitrophenyl-substituted sulfoxide **28** favoured the reductive deoxygenation process, giving rise to the 2*H*-chroman **28** in good yield (80%) and diastereoselectivity: an 84:16 mixture of (2S*,R*$_S$)-**28** and (2R*,R*$_S$)-**28** (Table 3, entry 3). Good results were also obtained with the chromanol **3e** bearing the 2-naphthyl-substituted sulfoxide. The reductive deoxygenation products **29** were obtained in 76% yield and 87:13 *dr* (Table 3, entry 4). In all cases, both diastereomers could be separated. A comparison of the results depicted in Table 3 evidenced that the efficiency of the reaction is highly dependent on the steric hindrance and electronic properties of the sulfoxide substituent. The *tert*-butyl sulfoxide was poorly reactive and made difficult the substitution of the OH by the hydride, the β-elimination product **30** being formed in 20% yield. The electron-rich *p*-MeOPh- and 2-MeO-naphthyl-substituted sulf-



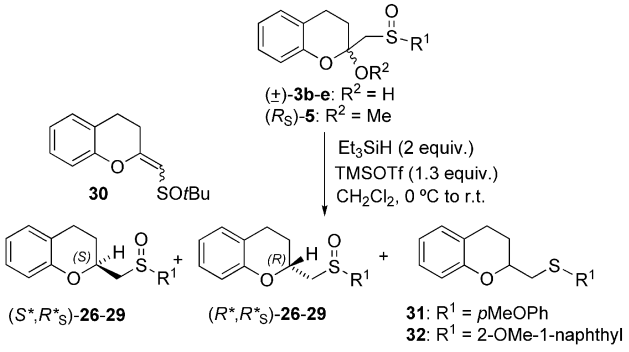
Scheme 11. Reductive deoxygenation of methyl ketal **25** with $i$$Pr_3SiH$ and $PhSiH_3$ in the presence of TMSOTf.

Table 3. Reactions of 2-[(sulfinyl)methyl]chroman-2-ols (±)-**3b**–**e** and ketal **5** with Et_3SiH in the presence of TMSOTf.

Entry	R^1	Product yield [%]	**26**–**29** ($2S^*,R^*_S$):($2R^*,R^*_S$)/(yield [%])
1	*t*Bu, **3b**	**26** (58),[a] **30** (20)	75:25/(45:13)
2	*p*MeOPh, **3c**	**27** (23), **31**(65)	69:31/(19:4)
3	*p*NO_2Ph, **3d**	**28** (80)	84:16/(65:15)
4	2-naphthyl, **3e**	**29** (76)	87:13/(63:13)
5	(R_S)-2-MeO-1-naphthyl, **5**	**32** (15)	–
6	*p*Tol, (R_S)-**3a**	**21** (86)	95:5/(75:3)

[a] 80% conversion.

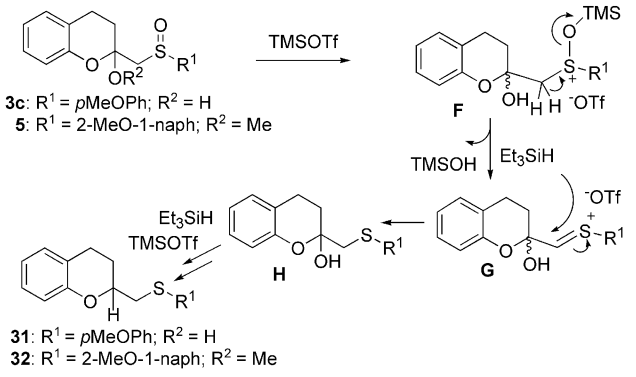
oxides favoured the reduction of the sulfoxide and the β-elimination compared with the substitution of the OH or MeO group of the chromanol derivative by the hydride.



Scheme 12. Reactions of chromanols **3** and **5**, with differently substituted sulfoxides, with Et_3SiH and TMSOTf.

These observations can be explained by taking into account the fact that electron-donating aromatic groups must increase the basicity of the sulfinyl oxygen. Coordination of this oxygen to the TMSOTf, acting as a Lewis acid, would be then favoured to give a species such as **F**, which evolves into an intermediate thiocarbenium ion **G**, similar to the one generated in the Pummerer reaction,[37] after hydrogen loss from the methylene at the α position. The excess of Et_3SiH in the medium would attack the thiocarbenium ion to generate the (methylthio)chromanol **H** (Scheme 13). Further evolution of **H** by reductive deoxygenation of the chromanol fragment promoted by Et_3SiH and TMSOTf explains the formation of **31** and **32**.

Better results in terms of yield of the substitution product and stereoselectivity were obtained with sulfoxides bearing the electron-withdrawing *p*NO_2Ph group **3d** and the 2-naphthyl sulfoxide **3e**, but the best result was obtained from the reaction of *p*-tolyl sulfoxide **3a** (Table 3, entry 6), which led to the enantiopure 2*H*-chroman (S,R_S)-**21**.[25] Thus, we



Scheme 13. Mechanism of the formation of the thioethers **31** and **32** from **3c** and **5**.

could conclude that the *p*-tolyl sulfoxide, easily available in enantiopure form, is the best choice for this enantioselective synthesis of 2*H*-chroman derivatives.

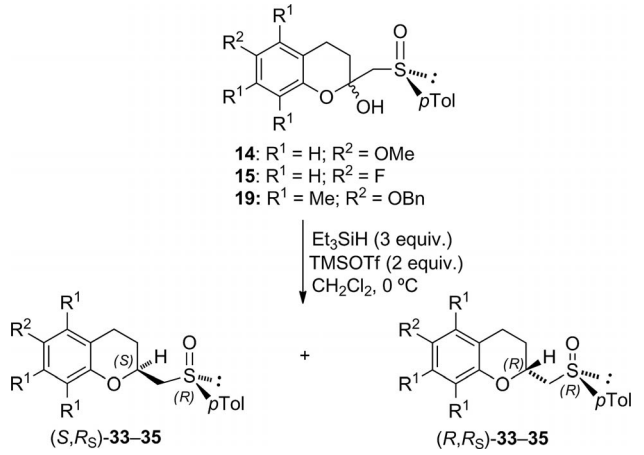
The final aim of our study was to determine the influence of the electronic density of the aromatic ring of the 2-sulfinylmethyl-substituted chroman-2-ol in the reductive deoxygenation. Thus, 2-hydroxy-6-methoxy-2-[(*p*-tolylsulfinyl)-methyl]chroman-2-ol (**14**), both enantiomers of the 6-fluoro-substituted analogue **15**[25] and the 6-benzyloxy-5,7,8-trimethyl derivative **19** were submitted to the reductive deoxygenation conditions by treatment with Et_3SiH and TMSOTf in CH_2Cl_2 solution at 0 °C. The results are summarized in Scheme 14 and Table 4. In all cases, the final diastereomers of the 2*H*-chromans could be separated diastereomerically pure.

As can be seen, the reductive deoxygenation occurred in all cases in moderate-to-good yields. The most significant differences correspond to the lower yields and diastereoselectivities observed when electron-donating substituents are present (Table 4, entries 1 and 4). Thus, the MeO-substituted chromanol **14** led to a 67:33 mixture of (S,R_S)-**33** and (R,R_S)-**33**, which could be isolated diastereomerically pure

Table 4. Reactions of 2-[(*p*-tolylsulfinyl)methyl]chroman-2-ols **14**, **15** and **19** with Et_3SiH in the presence of TMSOTf.

Entry	Starting material	R^1	R^2	Yield [%]	Product/(S,R_S):(R,R_S)/(yield [%])
1	**14**	H	MeO	40	**33**/67:33/(30:10)
2	**15**	H	F[a]	88	**34**/87:13/(75:11)
3	**15**[b]	H	F[a]	91	**34**/89:11/(70:10)[c]
4	**19**	Me	BnO	61	**35**/75:25/(46:14)

[a] 10 equiv. of Et_3SiH were required. Taken from ref.[25]. [b] (S_S-**15** enantiomer. [c] Diastereomers: (R,S_S)-**34**/(S,S_S)-**34**.

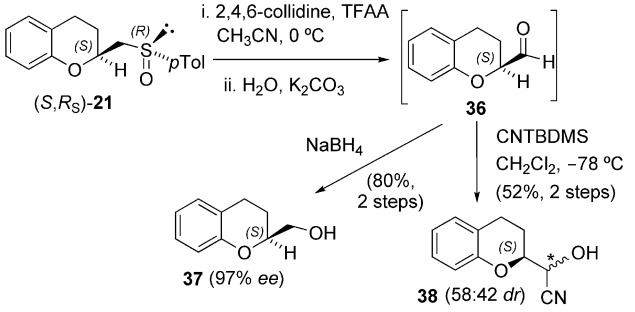


Scheme 14. Reactions of 2-[(*p*-tolylsulfinyl)methyl]chroman-2-ols **14**, **15** and **19** with Et_3SiH and TMSOTf.

in 30 and 10% yields, respectively (Table 4, entry 1). The BnO,trimethyl-substituted chromanol **19** gave a 75:25 mixture of epimers from which the major (*S*,R_S)-**35** was isolated in a 46% yield and the minor (*R*,R_S)-**35** in 14% yield (Table 4, entry 4). 2-[(*p*-Tolylsulfinyl)methyl]chromanols **15**, having a F substituent at C-6, were less reactive. Thus, (R_S)-**15** evolved only partially after 24 h under the conditions shown in Scheme 14. Complete conversion of the starting material (R_S)-**15** could be achieved by using an excess of the reducing agent. Thus, the treatment of (R_S)-6-fluoro-substituted chromanol **15** with 10 equiv. of Et_3SiH at 0 °C gave rise to an 87:13 mixture of the C-2 epimers (*S*,R_S)-**34** and (*R*,R_S)-**34** from which the major epimer was isolated in 75% yield (Table 4, entry 2). A similar result was obtained with the enantiomer (S_S-**15** (Table 4, entry 3), which gave an 89:11 mixture of (*R*,S_S)-**34** and (*S*,S_S)-**34**, the former being isolated in 70% yield.[25] Thus, we could access both enantiomers of the 2*H*-chroman unit by simply changing the absolute configuration at the sulfur of the starting sulfinyl lactol.

Once the methodology to efficiently generate the C-2 stereocentre of the 2*H*-chromans had been established, we wanted to take advantage of the synthetic versatility of the sulfoxide and employ it in further reactions. We thus could obtain compounds **37** and **38**, lacking the sulfoxide, with complete retention of the C-2 *S* configuration (Scheme 15).

The carbaldehyde (*S*)-**36** was formed starting from (*S*,R_S)-**21** by the Pummerer reaction after treatment with TFAA and 2,4,6-collidine followed by basic hydrolysis. The aldehyde (2*S*)-**36** was not stable and thus, without purification, the final crude mixture was treated with $NaBH_4$ to give 2-hydroxymethyl-2*H*-chromanol (*S*)-**37**[38] in excellent yield with total retention of the configuration (97% *ee*).[39] The success of the overall sequence required the addition of 2,4,6-collidine prior to TFAA to avoid the formation of the thioether **24**, which reduced significantly the yield of **36**. Finally, we tested the reactivity of carbaldehyde (*S*)-**36** with TBDMSCN in CH_2Cl_2 at –78 °C. Although no selectivity was observed, cyanohydrin (*S*)-**38** was synthesized as a mixture of epimers at the newly generated stereocentre.



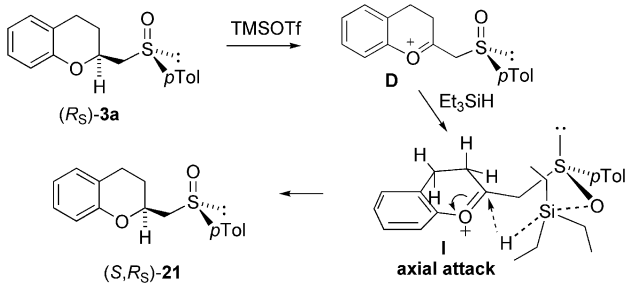
Scheme 15. Transformations of 2-(*p*-tolylsulfinylmethyl)-2*H*-chroman [(*S*,R_S)-**21**].

Mechanistic and Stereochemical Course of the Reductive Deoxygenation

Several conclusions could be drawn from the results obtained in the reductive deoxygenation of both sulfinyl-chromanols **3** and the mixed methyl ketal **5**. The best system to effect this reaction is TMSOTf/Et_3SiH. The increase in the electronic density on the sulfoxide by the presence of electron-donating substituents on the aromatic group directly linked to the sulfur, such as *p*MeOPh (**3c**) or 2-MeO-1-naphthyl (**5**; Scheme 12 and Table 3), produced an undesired reaction leading to thioethers **31** and **32** in which the sulfoxide had been reduced. This was probably due to the competitive activation of the more basic sulfinyl oxygen by the Lewis acid, as shown in Scheme 13, which favoured the Pummerer-like reaction leading to the reduction of the sulfoxide to the thioether. The bulky *tert*-butylsulfinyl group decreased the reactivity of the system, the reaction being slower. Moreover, the stereoselectivity of the reaction is only moderate (75:25; Table 3, entry 1), which shows that steric effects do not play an essential role in controlling the stereochemical course of the hydride attack. Better yields and diastereoselectivities were obtained with the less electron-rich *p*-tolylsulfinyl (**3a**) and 2-naphthylsulfinyl (**3e**) derivatives, as well as with the electron-poor *p*NO_2-substituted sulfoxide (**3d**). In agreement with the mechanistic pathways shown in Scheme 9 for the ionic cleavage of the C2–O bond of the chromanols, these results must be a consequence of the higher electrophilicity of the intermediate cyclic oxocarbenium ion **D**. The presence of substituents on the aromatic moiety of the dihydrobenzopyran **14** (6-MeO), **15** (6-F) and **19** (6-BnO-5,7,8-trimethyl) mainly influenced the yields, which are better in the case of the electron-withdrawing F-substituted derivative.

With respect to the configuration of the C-2 stereogenic centre of the major (2*S*)-2*H*-chroman always obtained, this must be defined in the attack of the hydride on the intermediate oxocarbenium ion **D** shown in Scheme 16. Extensive studies carried out by Smith and Woerpel[40] on the mechanism of nucleophilic substitutions of tetrahydrofuran and pyran acetals allowed them to conclude that these reactions occur through intermediate formation of cyclic oxocarbenium ions. In such cases, the reactive conformation is defined by the electrostatic effects of the substituents of the cyclic intermediates. These reactive conformations undergo

a stereoelectronically governed[41] face-selective attack of the nucleophile. Our previous studies of the Et_3SiH/TMSOTf reductive cyclization of enantiopure hydroxysulfinyl ketones, en route to 2,5-*cis*-disubstituted tetrahydrofurans, also illustrate the importance of electrostatic effects of an exocyclic sulfinyl oxygen and the positively charged carbon centre in the stabilization of the reactive intermediate oxocarbenium conformations.[24] In the case of the bicyclic oxocarbenium ions **D**, which lead to 2*H*-chromans, the stereoelectronic effects of the sulfoxide must not be responsible for the stabilization of the reactive conformation because the most electron-rich sulfoxides gave poorer diastereoselectivities. We thus propose that, once the bicyclic oxocarbenium ion is formed, after ionic cleavage of the C2–O bond of (R_S)-**3a** by activation with the Lewis acid, the hydride of Et_3SiH is transferred with the assistance of the sulfinyl oxygen through a species such as **I**, which adopts the chair-like geometry represented in Scheme 16. This is a stable conformation because the bulky *p*-tolyl group of the sulfoxide is in a favourable equatorial position. The approach of the hydride from the lower face, in the axial direction, is favoured by stereoelectronic effects.



Scheme 16. Stereochemical model explaining the diastereoselective formation of (S,R_S)-**21**.

This model also justifies the lack of reaction observed with $PhSiH_3$, which is less prone to associate to the sulfinyl oxygen. Although the bulkier iPr_3SiH gave the 2*H*-chroman (S,R_S)-**21** with good diastereoselectivity (88:22 *dr*), a significant amount of chromene **22** was formed, probably due to the lower stability of the transition state **I**, having an *i*Pr group in the axial position.

Conclusions

We have reported herein a methodological study of the diastereoselective synthesis of 2*H*-chromans in two steps: the reaction of a dihydrocoumarin with the lithium anion derived from a methyl sulfoxide and ionic cleavage of the C2–O bond of the resulting lactol with Et_3SiH, promoted by a Lewis acid. Among the different Lewis acids tested, TMSOTf gave the best results in terms of yield and diastereoselectivity. The influence of electron-donating and -withdrawing substituents on the sulfoxide in the reductive deoxygenation allowed us to establish that strong electron donors are not suitable for this reaction because other competitive processes occur that decrease the overall yield of 2*H*-chroman formation. Electron-withdrawing substituents on the sulfoxide (pNO_2Ph) or on the aromatic moiety of the dihydrobenzopyran (6-F) are compatible and lead to good diastereoselectivities. The latter is very interesting because the synthesis of enantiomerically enriched fluorine-containing molecules is of importance in drug discovery and development.[42] The results are justified on the basis of mechanistic proposals and a stereochemical model in which it is proposed that the sulfoxide assists the axial transfer of the hydride in the reactive conformation.

Experimental Section

General: Melting points were obtained in open capillary tubes. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. Integration of well-resolved signals in the ^1H NMR spectrum allowed the diastereomers ratio to be established. All reactions were monitored by thin-layer chromatography, which was performed on precoated sheets of silica gel 60, and flash column chromatography was performed with silica gel 60 (230–400 mesh) from Merck. Eluting solvents are indicated in the text. The apparatus for experiments performed in an inert atmosphere was flame-dried in a stream of dry argon. Diisopropylamine was used freshly distilled from KOH. CH_2Cl_2 was predried with $CaCl_2$, distilled from P_2O_5 and carefully kept under argon. Dry THF was distilled from sodium/benzophenone ketyl. All other reagent quality solvents were predried with activated molecular sieves and kept under argon. For routine work-up, hydrolysis was carried out with water, extractions with CH_2Cl_2, and solvent drying with $MgSO_4$.

Method A: Synthesis of 2-[(Arylsulfinyl)methyl]chroman-2-ols: A solution of 2.5 M *n*BuLi in hexanes (2.15 equiv.) was added to a solution of dry diisopropylamine (2.2 equiv.) in THF (1.8 M) at 0 °C under N_2. The mixture was stirred for 30 min, cooled to –78 °C and a solution of methyl aryl sulfoxide (1.1–1.4 equiv.) in THF (1.4 M) was added dropwise. The reaction was allowed to reach –40 °C and stirred for 1 h. After cooling to –78 °C, a solution of the corresponding dihydrocoumarin (1 equiv.) in THF (2 M) was added. After stirring for 1 h, the reaction was hydrolyzed with a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. After work-up and purification as indicated in each case, the corresponding pure sulfinylmethyl-chromanols were obtained.

Method B: Synthesis of 2-(Arylsulfinylmethyl)-2*H*-chromans: Triethylsilyl hydride (3 equiv.) was added dropwise to a solution of the 2-[(arylsulfinyl)methyl]chroman-2-ol (1 equiv.) in CH_2Cl_2 (0.07 M) at 0 °C followed by trimethylsilyl triflate (2 equiv.) under argon. The reaction was stirred for the time indicated in each case at 0 °C. After work-up and flash chromatography 2-[(arylsulfinyl)methyl]-2*H*-chromans were obtained.

(R_S)-2-[(*p*-Tolylsulfinyl)methyl]chroman-2-ol (3a): Starting from commercially available dihydrocoumarin (**1**; 818 μL, 6.5 mmol) and enantiopure (R_S)-methyl *p*-tolyl sulfoxide,[27] a crude mixture containing compound **3a** and the open-chain keto sulfoxide **4a** (**3a**/**4a**: 90:10) was obtained following Method A. After work-up, diethyl ether was added until a precipitate appeared. The solid was filtered and washed with several portions of dry diethyl ether/hexane to obtain lactol (R_S)-**3a** as a white solid in 90% yield (1.8 g) as an 85:15 mixture of C-2 epimers.. When the reaction was performed on a smaller scale, the precipitation of the product was not observed and the final mixture was purified by flash chromatography (eluent: hexane/EtOAc, 1:1); m.p. 115–116 °C; R_f = 0.37 (hexane/

EtOAc, 1:1). $[\alpha]_D^{20}$ = +196.5 (c = 1, $CHCl_3$). ^1H NMR: δ = 1.71 (tdd, J = 12.6, 5.8, 1.5 Hz, 1 H), 2.03 (ddd, J = 12.9, 6.0, 2.8 Hz, 1 H), 2.30 (s, 3 H), 2.59 (ddd, J = 16.4, 5.6, 2.4 Hz, 1 H), 2.91 and 3.09 (AB system, J = 12.8 Hz, 2 H), 2.99–3.07 (m, 1 H), 6.17 (d, J = 1.7 Hz, 1 H), 6.80–7.09 (m, 4 H), 7.27 and 7.52 (AA′BB′ system, J = 8.2 Hz, 4 H) ppm. ^{13}C NMR: δ = 20.7, 21.4, 32.1, 63.5, 96.7, 117.3, 121.1, 121.8, 124.1 (2 C), 127.4, 129.1, 130.3 (2 C), 140.2, 142.3, 152.0 ppm. MS (EI): m/z (%) = 77 (46), 91 (77), 107 (82), 124 (26), 140 (100), 145 (36), 149 (30), 163 (43), 302 (5) $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{18}O_3S$ $[M]^+$ 302.09766; found 302.09897.

(±)-2-[(*tert*-Butylsulfinyl)methyl]chroman-2-ol (3b): Starting from dihydrocoumarin (**1**; 365 μL, 2.9 mmol) and (±)-*tert*-butyl methyl sulfoxide (520 mg, 4.3 mmol), a crude mixture containing compound **3b** and the open-chain keto sulfoxide **4b** (**3b/4b**: 90:10) was obtained following Method A. After purification by flash chromatography (eluent: hexane/EtOAc, 1:2), lactol (*rac*)-**3b** was obtained in 77% yield (596 mg) as an 85:15 mixture of epimers. R_f = 0.25 (hexane/EtOAc, 1:2). ^1H NMR: δ = 1.32 (s, 9 H), 1.85 (tdd, J = 12.8, 5.8, 2.3 Hz, 1 H), 2.18 (ddd, J = 13.0, 6.0, 2.6 Hz, 1 H), 2.70 (ddd, J = 16.2, 5.8, 2.6 Hz, 1 H), 2.83 and 2.96 (AB system, J = 12.3 Hz, $\Delta\nu$ = 71.4 Hz, 2 H), 3.16 (ddd, J = 16.2, 12.5, 5.8 Hz, 1 H), 6.53 (d, J = 2.3 Hz, 1 H), 6.88–6.95 (m, 2 H), 7.08–7.16 (m, 2 H) ppm. ^{13}C NMR: δ = 20.7, 22.5 (3 C), 32.7, 49.6, 53.4, 97.0, 117.3, 121.0, 121.7, 127.4, 129.0, 152.0 ppm. MS (FAB^+): m/z (%) =77 (15), 107 (35), 177 (10), 195 (100), 251 (90), 269 (19) $[M + 1]^+$. HRMS (FAB^+): calcd. for $C_{14}H_{21}O_3S$ $[M]^+$ 269.1211; found 269.1212.

(±)-2-[(*p*-Methoxyphenylsulfinyl)methyl]chroman-2-ol (3c): Starting from dihydrocoumarin (**1**; 692 μL, 5.4 mmol) and (±)-methyl *p*-methoxyphenyl sulfoxide (1.3 g, 7.6 mmol), a crude mixture containing compound **3c** and the open-chain keto sulfoxide **4c** (**3c/4c**: 90:10) was obtained following Method A. After purification by flash chromatography (eluent: hexane/EtOAc, 1:3), lactol (*rac*)-**3c** was isolated as a white solid in 76% yield (1.3 g), as a mixture of epimers at C-2 in an 86:14 ratio; m.p. 102–103 °C. R_f = 0.31 (hexane/EtOAc, 1:2). ^1H NMR: δ = 1.80 (tdd, J = 12.6, 5.8, 2.1 Hz, 1 H), 2.13 (ddd, J = 12.8, 5.8, 2.8 Hz, 1 H), 2.98 and 3.19 (AB system, J = 12.8 Hz, $\Delta\nu$ = 60.9 Hz, 2 H), 3.09–3.19 (m, 1 H), 6.27 (d, J = 2.1 Hz, 1 H), 6.89–7.00 (m, 2 H), 7.12–7.19 (m, 2 H), 7.07 and 7.68 (AA′BB′ system, J = 8.9 Hz, $\Delta\nu$ = 160.3 Hz, 4 H) ppm. ^{13}C NMR: δ = 20.9, 32.4, 55.8, 63.7, 96.9, 115.4 (2 C), 117.5, 121.3, 121.9, 126.3 (2 C), 127.6, 129.3, 134.6, 152.2, 162.8 ppm. MS (EI): m/z (%) = 65 (21), 84 (75), 91 (30), 107 (100), 121 (29), 125 (51), 140 (93), 155 (92), 164 (28), 318 (3) $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{18}O_4S$ $[M]^+$ 318.09258; found 318.09250.

(±)-2-[(*p*-Nitrophenylsulfinyl)methyl]chroman-2-ol (3d): Starting from dihydrocoumarin (**1**; 489 μL, 3.86 mmol) and (±)-methyl *p*-nitrophenyl sulfoxide (1.0 g, 5.4 mmol), compound **3d** was obtained following Method A. The methyl *p*-nitrophenyl sulfoxide was hardly soluble in THF and the reaction proceeded with only 60% of conversion. After work-up and purification by flash chromatography (eluent: hexane/EtOAc, 1:2), lactol (±)-**3d** was obtained as an orange oil in 21% yield (270 mg) as a mixture of epimers at C-2 and the open-chain keto sulfoxide **4d** in 62:18:20 ratio. R_f = 0.42 (hexane/EtOAc, 1:2). ^1H NMR: δ = 1.83 (td, J = 12.7, 5.8 Hz, 1 H), 2.15 (ddd, J = 12.9, 5.9, 2.9 Hz, 1 H), 2.69 (ddd, J = 16.3, 5.6, 2.8 Hz), 3.04–3.15 (m, 1 H), 3.14 and 3.22 (AB system, J = 12.8 Hz, $\Delta\nu$ = 21.2 Hz, 2 H), 5.74 (br. s, 1 H), 6.89–6.94 (m, 2 H), 7.08–7.16 (m, 2 H), 7.87 and 8.37 (AA′BB′ system, J = 8.4 Hz, $\Delta\nu$ = 149.6 Hz, 4 H) ppm. ^{13}C NMR: δ = 20.6, 32.0, 63.9, 96.5, 117.2, 121.4, 121.6, 124.7 (2 C), 125.0 (2 C), 127.7, 129.2, 149.8, 151.1, 151.6 ppm. MS (EI): m/z (%) = 65 (44), 84 (100), 91 (46), 107 (88), 125 (37), 145 (83), 155 (49), 171 (12), 299 (9), 333 (1) $[M]^+$. HRMS (EI): calcd. for $C_{16}H_{15}NO_5S$ $[M]^+$ 333.06709; found 333.06830.

(±)-2-[(2-Naphthylsulfinyl)methyl]chroman-2-ol (3e): Starting from dihydrocoumarin (**1**; 482 μL, 3.80 mmol) and (±)-methyl 2-naphthyl sulfoxide (860 mg, 4.5 mmol), a crude mixture containing compound **3e** and the open-chain keto sulfoxide **4e** (**3e/4e**: 90:10) was obtained following Method A. After purification by flash chromatography (eluent: hexane/EtOAc, 1:2), lactol (±)-**3e** was obtained as a white solid in 89% yield (1.14 g) as a mixture of epimers at C-2 in an 85:15 ratio; m.p. 119–121 °C. R_f = 0.37 (hexane/EtOAc, 1:2). ^1H NMR: δ = 1.81 (tdd, J = 12.6, 5.8, 2.1 Hz, 1 H), 2.13 (ddd, J = 12.8, 5.8, 2.6 Hz, 1 H), 2.69 (ddd, J = 16.4, 5.7, 2.6 Hz), 3.27 and 3.11 (AB system, J = 12.8 Hz, $\Delta\nu$ = 47.8 Hz, 2 H), 3.10–3.21 (m, 1 H), 6.24 (d, J = 2.2 Hz, 1 H), 6.91–7.03 (m, 2 H), 7.10–7.21 (m, 2 H), 7.61–7.65 (m, 2 H), 7.70 (dd, J = 1.7 Hz, 1 H), 7.91–7.99 (m, δ = 20.7, 32.1, 63.3, 96.8, 117.4, 119.5, 121.2, 121.7, 124.8, 127.5, 127.6, 128.2 (2 C), 128.6, 129.2, 130.0, 132.9, 134.7, 140.4, 151.9 ppm. MS (FAB^+): m/z (%) = 77 (21), 89 (21), 145 (14), 175 (71), 321 (39), 338 (17), 339 (25) $[M + H]^+$, 677 (11) $[2M + H]^+$. HRMS (FAB^+): calcd. for $C_{20}H_{18}O_3S$ $[M + H]^+$ 338.09766; found 338.09930.

(R_S)-2-Methoxy-2-[(2-methoxy-1-naphthylsulfinyl)methyl]chroman (5): Starting from dihydrocoumarin (**1**; 7.45 mmol, 1 equiv.) and (+)-methyl 2-methoxy-1-naphthyl sulfoxide (9.68 mmol, 1.3 equiv.), a crude mixture containing compound **3f** and the open-chain keto sulfoxide **4f** (**3f/4f**: 90:10) was obtained following Method A. This mixture was dissolved in dry MeOH (0.05 M) and trimethyl orthoformate [$CH(OCH_3)_3$, 0.4 M] and a catalytic amount of *p*-toluenesulfonic acid (0.1 equiv.) were added. After stirring for 3 d at room temperature (ca. 20 °C), the mixture was treated with a saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. After work-up and flash chromatography (eluent: hexane/EtOAc, 2:1), compound (R_S)-**5** was obtained as a 50:50 mixture of C-2 diastereomers in 26% yield. A small amount of each one could be separated pure for characterization. Diastereoisomer A: $[\alpha]_D^{20}$ = +123 (c = 0.13, $CHCl_3$). ^1H NMR: δ = 2.05–2.17 (m, 1 H), 2.64–2.76 (m, 2 H), 3.01–3.13 (m, 1 H), 3.28 (s, 3 H), 3.76 and 4.01 (AB system, J = 14.2 Hz, $\Delta\nu$ = 76.7 Hz, 2 H), 4.04 (s, 3 H), 6.77 (dd, J = 1.3, 8.4 Hz, 1 H), 6.9 (dt, J = 7.3, 1.1 Hz, 1 H), 7.06–7.11 (m, 2 H), 7.28 (d, J = 9.1 Hz, 1 H), 7.42 (td, J = 8.0, 1.4 Hz, 1 H), 7.56 (td, J = 6.8, 1.4 Hz, 1 H), 7.8 (d, J = 8.0 Hz, 1 H), 7.9 (d, J = 9.1 Hz, 1 H), 9.03 (dd, J = 9.1, 0.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 21.1, 30.4, 49.4, 56.9, 59.0, 98.3, 112.9, 116.8, 121.2, 122.5, 122.6, 122.7, 124.5, 127.2, 128.0, 128.8, 129.2, 129.5, 132.3, 134.2, 151.8, 155.9 ppm. Diastereoisomer B: $[\alpha]_D^{20}$ = +114 (c = 0.18, $CHCl_3$). ^1H NMR: δ = 2.15–2.28 (m, 1 H), 2.38 (dd, J = 6.2, 2.2 Hz, 1 H), 2.66 (dd, J = 5. 8, 2.1 Hz, 1 H), 3.02–3.13 (m, 1 H), 3.32 (s, 3 H), 3.75 and 4.09 (AB system, J = 13.7 Hz, $\Delta\nu$ = 101.7 Hz, 2 H), 3.99 (s, 3 H), 6.66 (d, J = 8.2 Hz, 1 H), 6.88 (dt, J = 7.6, 1.2 Hz, 1 H), 7.07 (m, 2 H), 7.28 (d, J = 9.3 Hz, 1 H), 7.42 (td, J = 7.9, 1.2 Hz, 1 H), 7.56 (td, J = 7.6, 1.2 Hz, 1 H), 7.83 (d, J = 8.0 Hz, 1 H), 7.98 (d, J = 9.0 Hz, 1 H), 8.93 (d, J = 8.6 Hz, 1 H) ppm. ^{13}C NMR: δ = 21.0, 29.8, 49.5, 56.8, 59.7, 97.9, 113.0, 116.8, 121.2, 122.4, 122.8, 122.9, 124.5, 127.2, 128.1, 128.8, 129.2, 129.4, 132.1, 134.2, 151.7, 156.2 ppm.

(R_S)-6-Methoxy-2-[(*p*-tolylsulfinyl)methyl]chroman-2-ol (14): Starting from 6-methoxychroman-2-one[12f] (**8**; 295 mg, 1.6 mmol) and enantiopure (R_S)-methyl *p*-tolyl sulfoxide, a crude mixture containing compound **14** and the open-chain keto sulfoxide **16** (**14/16**: 85:15) was obtained following Method A. After purification by flash chromatography (eluent: hexane/EtOAc, 2:3), lactol (R_S)-**14**

was obtained as a white solid in 30% yield (165 mg) as a 77:23 mixture of C-2 epimers; m.p. 122 °C. ^{1}H NMR: δ = 1.77 (tdd, J = 12.4, 5.6, 2.6 Hz, 1 H), 2.08 (ddd, J = 12.9, 6.0, 2.6 Hz, 1 H), 2.43 (s, 3 H), 2.65 (ddd, J = 16.5, 5.7, 2.6 Hz, 1 H), 2.97 and 3.16 (AB system, J = 12.7 Hz, 2 H), 3.08–3.18 (m, 1 H), 3.76 (s, 3 H), 6.16 (d, J = 2.1 Hz, 1 H), 6.64 (d, J = 2.5 Hz, 1 H), 6.73 (dd, J = 8.7, 2.5 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.36 and 7.60 (AA′BB′ system, J = 7.9 Hz, 4 H) ppm. ^{13}C NMR: δ = 21.1, 21.4, 31.9, 55.6, 63.8, 96.6, 113.4, 113.6, 117.8, 122.3, 124.2, 130.1, 140.1, 142.2, 145.9, 153.8 ppm.

6-Fluoro-2-[(*p*-tolylsulfinyl)methyl]chroman-2-ol (15): Starting from 6-fluorochroman-2-one (**9**; 2.5 g, 15.0 mmol, 1 equiv.) and (R_S)-methyl *p*-tolyl sulfoxide (2.5 g, 16.5 mmol, 1.1 equiv.), a crude mixture containing compound **15** and the open-chain keto sulfoxide **17** (**14/17**: 90:10) was obtained following Method A. After work-up, diethyl ether was added until a precipitate appeared. The solid was filtered and washed with several portions of dry diethyl ether/hexane to obtain lactol (R_S)-**15** (87:13 C-2 epimers) as a white solid in 83% yield (3.99 g). When the reaction was performed on a smaller scale, the precipitation of the product was not possible and the final mixture was purified by flash chromatography (eluent: hexane/EtOAc, 1:1); m.p. 125 °C; R_f = 0.43 (hexane/EtOAc, 1:2). $[\alpha]_D^{20}$ = +179.7 (c = 1, $CHCl_3$). ^{1}H NMR: δ = 1.75 (tdd, J = 12.7, 6.1, 2.3 Hz, 1 H), 2.09 (ddd, J = 12.7, 6.1, 2.4 Hz, 1 H), 2.44 (s, 3 H), 2.65 (ddd, J = 16.7, 5.7, 2.4 Hz, 1 H), 2.97 and 3.16 (AB system, J = 12.7 Hz, 2 H), 3.07–3.17 (m, 1 H), 6.25 (d, J = 2.3 Hz, 1 H), 6.67–6.95 (m, 3 H), 7.37 and 7.61 (AA′BB′ system, J = 8.0 Hz, 4 H) ppm. ^{13}C NMR: δ = 20.8, 21.4, 31.8, 63.2, 96.7, 114.1 (d, J = 22.7 Hz), 115.0 (d, J = 23.4 Hz), 118.2 (d, J = 8.2 Hz), 123.0 (d, J = 7.6 Hz), 124.0 (2 C), 130.3 (2 C), 140.1, 142.4, 147.9 (d, J = 2.2 Hz), 157.2 (d, J = 237 Hz) ppm. MS (EI): m/z (%) = 91 (65), 109 (31), 125 (64), 140 (100), 163 (46), 302 (7), 320 (11) $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{17}FO_3S$ $[M]^+$ 320.08814; found 320.08710.

The enantiomer (S_S)-**15** was obtained in a similar way from (S_S)-methyl *p*-tolyl sulfoxide in a crude mixture containing compound (S_S)-**15** and the open-chain keto sulfoxide **17** (**14/17**: 90:10). The solid resulting from the precipitation was characterized as a 89:11 mixture of C-2 epimers of (S_S)-**15**. White solid, 85% yield.

(R_S)-6-(Benzyloxy)-5,7,8-trimethyl-2-[(*p*-tolylsulfinyl)methyl]-chroman-2-ol (19): Starting from 6-(benzyloxy)-5,7,8-trimethylchroman-2-one (**18**; 796 mg, 2.7 mmol), a crude mixture containing compound **19** and the double addition product **20** was obtained following Method A. Diethyl ether was added to the crude mixture until a precipitate appeared. The solid was filtered and washed with several portions of dry diethyl ether/hexane to obtain lactol (R_S)-**19** as a white solid in 81% yield (983 mg) as an 85:15 mixture of epimers at C-2. From the mother liquor, compound **20** was isolated in 3% yield (see the Supporting Information for characterization data). Chromanol **19**: M.p. 168–169 °C (Et_2O); $[\alpha]_D^{20}$ = +279 (c = 0.36, $CHCl_3$). ^{1}H NMR: δ = 1.74–1.83 (m, 1 H), 2.12–2.19 (m, 1 H), 2.20 (s, 3 H), 2.26 (s, 3 H), 2.29 (s, 3 H), 2.44 (s, 3 H), 2.64 (ddd, J = 17.5, 6.7, 2.6 Hz, 1 H), 2.83–2.94 (m, 1 H), 3.01 and 3.20 (AB system, J = 12.7 Hz, 2 H), 4.71 (s, 2 H), 6.17 (d, J = 2.1 Hz, 1 H), 7.34–7.43 (m, 5 H), 7.63 and 7.51 (AA′BB′ system, J = 8.2 Hz, 4 H) ppm. ^{13}C NMR: δ = 11.9, 12.0, 12.8, 19.2, 32.0, 63.7, 74.7, 95.9, 118.1, 124.0, 126.0, 127.7, 127.7, 128.4, 130.0, 137.9, 140.4, 141.5, 142.2, 142.5, 145.8, 149.4 ppm. MS (FAB^+): m/z (%) = 55 (100), 91 (65), 139 (40), 203 (33), 359 (37), 433 (10), 450 (9) $[M]^+$. HRMS (FAB^+): calcd. for $C_{27}H_{30}O_4S$ $[M]^+$ 450.1865; found 450.1858.

(2*S*,R_S)-2-[(*p*-Tolylsulfinyl)methyl]chroman (21): Starting from (R_S)-2-[(*p*-tolylsulfinyl)methyl]chroman-2-ol (**3a**; 40 mg, 0.13 mmol) following Method B for 6 h at 0 °C, a 95:5 mixture of epimers (2*S*,R_S)-**21** and (2*R*,R_S)-**21** was obtained (determined from the ^{1}H NMR spectrum of the crude reaction mixture). After purification by flash chromatography (eluent: hexane/EtOAc, 3:2), compound (2*S*,R_S)-**21** was isolated in 75% yield as a white solid. The C-2 epimer (2*R*,R_S)-**21** was obtained in 3% yield.

(2*S*,R_S)-**21**: M.p. 103–104 °C; R_f = 0.37 (hexane/EtOAc, 1:3). $[\alpha]_D^{20}$ = +235.8 (c = 0.77, $CHCl_3$). ^{1}H NMR: δ = 1.89 (tdd, J = 13.5, 10.3, 5.6 Hz, 1 H), 2.01–2.10 (m, 1 H), 2.42 (s, 3 H), 2.76 (ddd, J = 16.6, 5.3, 3.7 Hz, 1 H), 2.87–3.05 (m, 3 H), 4.61–4.69 (m, 1 H), 6.84–6.89 (m, 2 H), 7.03–7.14 (m, 2 H), 7.34 and 7.59 (AA′BB′ system, J = 8.3 Hz, 4 H) ppm. ^{13}C NMR: δ = 21.4, 24.3, 27.5, 64.3, 69.7, 117.0, 120.7, 121.4, 123.9 (2 C), 127.4, 129.5, 130.1 (2 C), 141.4, 141.6, 154.0 ppm. MS (EI): m/z (%) = 91 (35), 107 (12), 133 (13), 139 (37), 147 (100), 269 (15), 286 (1) $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{18}O_2S$ $[M]^+$ 286.10275; found 286.10312.

(2*R*,R_S)-**21**: R_f = 0.26 (hexane/AcOEt, 1:2). $[\alpha]_D^{20}$ = –88.3 (c = 0.77, $CHCl_3$). ^{1}H NMR: δ = 1.89–2.04 (m, 1 H), 2.08–2.18 (m, 1 H), 2.42 (s, 3 H), 2.77–2.84 (m, 2 H), 2.99 and 3.36 (AB part of ABX system, J = 13.3, 7.0, 5.4 Hz, $\Delta\nu$ = 115.5 Hz, 2 H), 4.20 (dtd, J = 7.2, 5.4, 2.4 Hz, 1 H), 6.69 (dd, J = 8.1, 1.0 Hz, 1 H), 6.85 (td, J = 7.5, 1.2 Hz, 1 H), 7.02–7.08 (m, 2 H), 7.33 and 7.59 (AA′BB′ system, J = 8.2 Hz, 4 H) ppm. ^{13}C NMR: δ = 21.4, 24.1, 26.9, 62.0, 70.3, 116.8, 120.7, 121.3, 124.4 (2 C), 127.3, 129.5, 130.0 (2 C), 140.2, 141.7, 153.9 ppm. MS (EI): m/z (%) = 77 (16), 91 (41), 107 (15), 119 (8), 131 (12), 133 (11), 138 (47), 147 (100), 269 (20), 286 (2) $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{18}O_2S$ $[M]^+$ 286.10275; found 286.10333.

(R_S)-2-(*p*-Tolylsulfinylmethyl)-4*H*-chromene (22): Starting from (R_S)-2-[(*p*-tolylsulfinyl)methyl]chroman-2-ol (**3a**) following Method B using $BF_3{\cdot}OEt_2$ (2 equiv.) as the Lewis acid at 0 °C, a crude mixture containing **21** (mixture of C-2 epimers) and **22** was obtained. After purification by flash chromatography (eluent: hexane/EtOAc, 1:2), compounds **21** (17% yield) and (R_S)-**22** (33% yield) were isolated. (R_S)-**22**: R_f = 0.39 (hexane/AcOEt, 1:2). $[\alpha]_D^{20}$ = +59 (c = 0.59, $CHCl_3$). ^{1}H NMR: δ = 2.39 (s, 3 H), 3.37–3.40 (m, 2 H), 3.44 and 3.62 (AB system, J = 12.8 Hz, $\Delta\nu$ = 53.7 Hz, 2 H), 4.88 (t, J = 3.6 Hz, 1 H), 6.72 (d, J = 7.9 Hz, 1 H), 6.95–6.99 (m, 2 H), 7.06–7.11 (m, 1 H), 7.27 and 7.52 (AA′BB′ system, J = 8.1 Hz, $\Delta\nu$ = 75.0 Hz, 4 H) ppm. ^{13}C NMR: δ = 21.4, 24.2, 62.6, 103.0, 116.3, 118.9, 123.5, 124.2 (2 C), 127.4, 129.0, 129.7 (2 C), 140.1, 141.6, 141.7, 151.3 ppm. MS (EI): m/z (%) = 65 (10), 77 (13), 91 (26), 115 (32), 117 (16), 139 (33), 145 (100), 172 (14), 268 (1), 284 (1) $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{16}O_2S$ $[M]^+$ 284.08710; found 284.08774.

2-[3-Hydroxy-4-(*p*-tolylsulfinyl)butyl]phenol (23): Starting from (R_S)-2-[(*p*-tolylsulfinyl)methyl]chroman-2-ol (**3a**; 35 mg, 0.12 mmol 1 equiv.) following Method B using $TiCl_4$ (25 μL, 0.23 mmol, 2 equiv.) as Lewis acid for 2 h at 0 °C, the reaction was completed. After hydrolysis with a saturated solution of $NaHCO_3$ and extraction with CH_2Cl_2, the organic layer was dried with $MgSO_4$. After purification by flash chromatography, compound **23** was isolated in 75% yield as a diastereomeric mixture at C-3. R_f = 0.08 (hexane/EtOAc, 1:3). ^{1}H NMR (2 diastereoisomers): δ = 1.63–1.70 (m, 1 H), 1.78–1.91 (m, 3 H), 2.26 (1 H), 2.39 (s, 6 H), 2.61–3.09 (m, 8 H), 4.11–4.19 (m, 2 H), 4.96 (br. s, 1 H), 5.06 (br. s, 1 H), 6.75–6.87 (m, 4 H), 6.99–7.10 (m, 4 H), 7.30 (d, J = 7.9 Hz, 4 H), 7.47–7.52 (m, 4 H), 7.92 (br. s, 1 H), 8.17 (br. s, 1 H) ppm. ^{13}C NMR (2 diastereoisomers): δ = 21.4, 21.5, 25.2, 25.3, 37.5, 37.7, 62.5, 62.6, 64.8, 67.3, 116.0, 116.4, 120.3, 120.4, 124.1 (2 C), 127.0, 127.1, 127.5, 127.7, 130.1, 130.2 (4 C), 130.4, 130.5, 139.1, 129.8, 141.8, 142.2, 154.6, 154.8 ppm. MS (EI): m/z (%) = 65 (16), 77 (37), 92

(54), 107 (96), 121 (16), 140 (100), 147 (70), 269 (15), 287 (82), 304 (32) $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{20}O_3S$ $[M]^+$ 304.11332; found 304.11301.

2-(*p*-Tolylthiomethyl)chroman (24): Starting from (R_S)-2-[(*p*-tolylsulfinyl)methyl]chroman-2-ol (**3a**; 20 mg, 0.07 mmol, 1 equiv.) and following Method B using MeCN (1 mL) as solvent for 15 h at 0 °C, after the usual work-up and purification by flash chromatography, compound (*rac*)-**24** was isolated in 54% yield. R_f = 0.77 (hexane/EtOAc, 1:2). ^{1}H NMR: δ = 1.75–1.88 (m, 1 H), 2.16–2.25 (m, 1 H), 2.33 (s, 3 H), 2.71–2.83 (m, 2 H), 3.04 and 3.31 (dd, J = 13.4, 7.2, 5.6 Hz, 2 H), 4.09–4.18 (m, 1 H), 6.73–6.85 (m, 2 H), 7.02–7.15 (m, 4 H), 7.33 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR: δ = 21.0, 24.3, 26.2, 39.1, 74.6, 116.8, 120.3, 121.8, 127.2, 129.4, 129.8 (2 C), 130.4 (2 C), 132.2, 136.5, 154.5 ppm. MS (EI): *m*/*z* (%) = 65 (5), 77 (14), 91 (18), 105 (22), 133 (100), 138 (25), 147 (22), 270 (80) $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{18}OS$ $[M]^+$ 270.10784; found 270.10779.

(R_S)-2-Methoxy-2-[(*p*-tolylsulfinyl)methyl]chroman (25): To a solution of (R_S)-2-[(*p*-tolylsulfinyl)methyl]chroman-2-ol [(R_S)-**3a**; 1.81 g, 6.0 mmol, 1 equiv.] in dry MeOH (0.05 M), trimethyl orthoformate [$CH(OCH_3)_3$, 0.4 M] and a catalytic amount of *p*-toluenesulfonic acid (0.1 equiv.) were added. After stirring for 3 h at room temperature (ca. 20 °C), the mixture was treated with a saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. After work-up and flash chromatography (eluent: hexane/EtOAc, 1:1), compound (R_S)-**25** was obtained as white solid in 89% yield (1.68 g) as a 50:50 mixture of C-2 diastereomers; m.p. 79 °C; R_f = 0.43 (hexane/EtOAc, 1:3). $[\alpha]_D^{20}$ = +122 (c = 3.6, $CHCl_3$). ^{1}H NMR (diastereomer A): δ = 1.97–2.07 (m, 1 H), 2.42 (s, 3 H), 2.61 (ddd, J = 13.7, 6.1, 3.3 Hz, 1 H), 2.71 (ddd, J = 16.2, 5.7, 3.3 Hz, 1 H), 2.98–3.10 (m, 1 H), 3.23 and 3.32 (AB system, J = 14.2 Hz, $\Delta\nu$ = 23.2 Hz, 2 H), 3.34 (s, 3 H), 6.80 (d, J = 8.1 Hz, 1 H), 6.90 (td, J = 7.4, 1.2 Hz, 1 H), 7.07–7.13 (m, 2 H), 7.33 and 7.58 (AA′BB′ system, J = 8.0 Hz, $\Delta\nu$ = 72.6 Hz, 4 H) ppm; diastereomer B: δ = 2.26–2.33 (m, 2 H), 2.43 (s, 3 H), 2.67–2.72 (ddd, J = 16.1, 5.2, 2.5 Hz, 1 H), 2.98–3.13 (m, 1 H), 3.22–3.34 (m, 5 H), 6.78 (d, J = 8.2 Hz, 1 H), 6.85 (td, J = 7.3, 1.1 Hz, 1 H), 7.08–7.15 (m, 2 H), 7.28 and 7.54 (AA′BB′ system, J = 8.1 Hz, $\Delta\nu$ = 76.2 Hz, 4 H) ppm. ^{13}C NMR (diastereomer A): δ = 21.1, 21.4, 30.2, 49.5, 64.7, 97.5, 116.8, 121.3, 122.0, 124.0 (2 C), 127.3, 129.3, 130.1 (2 C), 140.8, 141.2, 151.2 ppm; diastereomer B: δ = 20.9, 21.4, 30.0, 49.4, 65.1, 97.6, 116.9, 121.4, 122.4, 124.1 (2 C), 127.4, 129.3, 130.1 (2 C), 141.3, 141.7, 151.6 ppm. MS (EI): *m*/*z* (%) = 59 (21), 91 (18), 140 (40), 145 (100), 163 (17), 177 (34), 316 (0.3) $[M]^+$. HRMS (EI): calcd. for $C_{18}H_{20}O_3S$ $[M]^+$ 316.11332; found 316.11432. $C_{18}H_{20}O_3S$ (316.11): C 68.33, H 6.37, O 15.17, S 10.13; found C 68.31, H 6.44, S 10.02.

(±)-(2*S*,*R*$_S$)-2-[(*tert*-Butylsulfinyl)methyl]chroman (26): Starting from (±)-2-[(*tert*-butylsulfinyl)methyl]chroman-2-ol (**3b**; 50 mg, 0.18 mmol) following Method B for 18 h at 0 °C and 6 h at room temp., a crude mixture containing epimers (±)-(2*S*,*R*$_S$)-**26** and (±)-(2*R*,*R*$_S$)-**26** (75:25) and (±)-2-(*tert*-butylsulfinylmethylene)chroman (**30**) was obtained. After flash chromatography (eluent: hexane/EtOAc, 1:2), (±)-(2*S*,*R*$_S$)-**26** was obtained in 45% yield (22 mg) and the C-2 isomer (±)-(2*R*,*R*$_S$)-**26** in 13% yield along with compound **30** in 20% yield.

(±)-(2*S*,*R*$_S$)-**26**: R_f = 0.29 (hexane/AcOEt, 1:2). ^{1}H NMR: δ = 1.29 (s, 9 H), 1.88 (tdd, J = 13.4, 10.9, 5.7 Hz, 1 H), 2.11–2.19 (m, 1 H), 2.61 and 2.85 (ddd, J = 12.8, 9.2, 3.2 Hz, 2 H), 2.75–3.00 (m, 2 H), 4.59 (tt, J = 9.8, 2.8 Hz, 1 H), 6.82–6.87 (m, 2 H), 7.04–7.11 (m, 2 H) ppm. ^{13}C NMR: δ = 22.8 (3 C), 24.5, 27.9, 51.9, 52.9, 70.2, 116.9, 120.6, 121.5, 127.3, 129.5, 154.0 ppm. MS (EI): *m*/*z* (%) = 57 (100), 91 (9), 107 (30), 133 (65), 146 (18), 196 (58), 252 (1). HRMS (EI): calcd. for $C_{14}H_{20}O_2S$ $[M]^+$ 252.11840; found 252.117740.

(±)-(2*R*,*R*$_S$)-**26**: R_f = 0.35 (hexane/EtOAc, 1:2). ^{1}H NMR: δ = 1.3 (s, 9 H), 1.98 (tdd, J = 13.6, 10.6, 5.6 Hz, 1 H), 2.32–2.40 (m, 1 H), 2.74–2.99 (m, 2 H), 2.81 and 2.94 (ddd, J = 12.9, 8.9, 4.0 Hz, 2 H), 4.52 (tdd, J = 12.4, 3.7, 2.1 Hz, 1 H), 6.79–6.88 (m, 2 H), 7.05–7.11 (m, 2 H) ppm. ^{13}C NMR: δ = 22.8 (3 C), 24.2, 26.4, 51.3, 53.4, 71.4, 116.8, 120.6, 121.5, 127.3, 129.5, 154.3 ppm. MS (EI): *m*/*z* (%) = 57 (100), 77 (10), 107 (30), 133 (61), 147 (18), 196 (54), 252 (1). HRMS (EI): calcd. for $C_{14}H_{20}O_2S$ $[M]^+$ 252.11840; found 252.11720.

(±)-2-(*tert*-Butylsulfinylmethylene)chroman (30): M.p. 93–94 °C. R_f = 0.13 (hexane/EtOAc, 1:2). ^{1}H NMR: δ = 1.21 (s, 9 H), 2.59–2.64 (m, 2 H), 2.69–2.84 (m, 2 H), 5.12 (s, 1 H), 6.89–6.93 (m, 2 H), 7.01–7.03 (m, 1 H), 7.09–7.12 (m, 1 H) ppm. ^{13}C NMR: δ = 22.7 (3 C), 23.8, 27.3, 54.6, 105.2, 116.4, 122.5, 122.8, 128.1, 128.6, 151.6, 159.1 ppm. MS (EI): *m*/*z* (%) = 57 (26), 107 (12), 131 (17), 146 (30), 178 (14), 194 (100), 234 (1.6) $[M - 16]^+$. HRMS (EI): calcd. for $C_{14}H_{18}OS$ $[M]^+$ 234.10784; found 234.10780.

(±)-(2*S*,*R*$_S$)-2-[(*p*-Methoxyphenylsulfinyl)methyl]chroman (27): Starting from (±)-2-[(*p*-methoxyphenylsulfinyl)methyl]chroman-2-ol (**3c**; 50 mg, 0.16 mmol) following Method B for 6 h at 0 °C and 12 h at room temp., a mixture containing compound **27** (69:31 mixture of C-2 epimers) and compound **31** was obtained. After flash chromatography (eluent: hexane/EtOAc, 1:2), compound (±)-(2*S*,*R*$_S$)-**27** was obtained in 19% yield (9 mg) and the C-2 isomer (±)-(2*R*,*R*$_S$)-**27** in 4% yield along with 2-(*p*-methoxyphenylthiomethyl)chroman **31** in 65% yield (29 mg); m.p. 117–118 °C. R_f = 0.32 (hexane/EtOAc, 1:2).

(±)-(2*S*,*R*$_S$)-**27**: ^{1}H NMR: δ = 1.83 (tdd, J = 13.6, 10.6, 5.6 Hz, 1 H), 2.03–2.11 (m, 1 H), 2.77 (ddd, J = 3.8, 5.2, 16.6 Hz, 1 H), 2.87–3.05 (m, 3 H), 4.60–4.68 (m, 1 H), 6.84–6.89 (m, 2 H), 7.02–7.13 (m, 2 H), 7.04 and 7.64 (AA′BB′ system, J = 8.9 Hz, $\Delta\nu$ = 178.3 Hz, 4 H) ppm. ^{13}C NMR: δ = 24.3, 27.5, 55.5, 64.3, 69.8, 114.9 (2 C), 116.9, 120.7, 121.4, 125.8 (2 C), 127.4, 129.5, 135.5, 153.9, 162.1 ppm. MS (FAB$^+$): *m*/*z* (%) = 57 (40), 73 (32), 83 (13), 107 (11), 136 (12), 147 (35), 155 (38), 303 (100) $[M + H]^+$, 605 (5) $[2M + H]^+$. HRMS (FAB$^+$): calcd. for $C_{17}H_{19}O_3S$ $[M + H]^+$ 303.105491; found 303.10420.

(±)-(2*R*,*R*$_S$)-**27**: R_f = 0.26 (hexane/EtOAc, 1:2). ^{1}H NMR: δ = 1.95 (tdd, J = 13.2, 10.0, 6.1 Hz, 1 H), 2.07–2.16 (m, 1 H), 2.76–2.83 (m, 2 H), 2.97 and 3.38 (ddd, J = 13.1, 7.2, 5.0 Hz, 2 H), 3.86 (s, 3 H), 4.11–4.19 (m, 1 H), 6.72 (d, J = 8.0 Hz, 1 H), 6.85 (t, J = 7.4 Hz, 1 H), 7.05–7.10 (m, 2 H), 7.03 and 7.64 (AA′BB′ system, J = 8.7 Hz, $\Delta\nu$ = 183.5 Hz, 4 H) ppm. ^{13}C NMR: δ = 24.1, 27.0, 55.6, 62.1, 70.4, 114.9 (2 C), 116.8, 120.7, 121.4, 126.3 (2 C), 127.4, 129.6, 134.2, 153.9, 162.2 ppm.

2-[(*p*-Methoxyphenylthio)methyl]chroman (31): Colourless oil. R_f = 0.72 (hexane/EtOAc, 1:2). ^{1}H NMR: δ = 1.75–1.88 (m, 1 H), 2.15–2.24 (m, 1 H), 2.71–2.85 (m, 2 H), 2.99 and 3.24 (ddd, J = 13.6, 7.2, 5.7 Hz, 2 H), 3.80 (s, 3 H), 4.06–4.15 (m, 1 H), 6.77–6.86 (m, 4 H), 7.05 (t, J = 8.7 Hz, 2 H), 7.40 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR: δ = 24.3, 26.2, 40.5, 55.3, 74.7, 116.8, 120.3, 121.8, 127.2, 128.4, 129.4, 132.6 (2 C), 133.5 (2 C), 154.5, 159.1 ppm. MS (EI): *m*/*z* (%) = 77 (15), 84 (15), 105 (22), 124 (12), 133 (61), 139 (100), 147 (13), 154 (15), 278 (34), 286 (64) $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{18}O_2S$ $[M]^+$ 286.10275; found 286.10214.

(±)-(2*S*,*R*$_S$)-2-[(*p*-Nitrophenylsulfinyl)methyl]chroman (28): Starting from (±)-2-[(*p*-nitrophenylsulfinyl)methyl]chroman-2-ol (**3d**; 56 mg, 0.16 mmol) following Method B for 4 h at 0 °C and 12 h at

room temp., an 84:16 mixture of (±)-(2*S*,R_S)-**28** and (±)-(2*R*,R_S)-**28** epimers was obtained. After flash chromatography (eluent: hexane/EtOAc, 1:2), (±)-(2*S*,R_S)-**28** was obtained in 65% yield (33 mg) as a yellow solid and the C-2 isomer of (±)-(2*R*,R_S)-**28** in 15% yield (8 mg).

(±)-(2*S*,R_S)-**28**: M.p. 153–154 °C. R_f = 0.42 (hexane/EtOAc, 1:2). ^{1}H NMR: δ = 1.85 (tdd, J = 13.4, 10.7, 5.6 Hz, 1 H), 2.03–2.12 (m, 1 H), 2.79 (ddd, J = 16.6, 5.2, 3.6 Hz, 1 H), 2.92 (dd, J = 10.7, 6.0 Hz, 1 H), 3.00 and 3.10 (ddd, J = 13.1, 9.8, 3.0 Hz, 2 H), 4.69 (tt, J = 9.8, 2.6 Hz), 6.86 (t, J = 8.4 Hz, 2 H), 7.06–7.15 (m, 2 H), 7.89 and 8.40 (AA′BB′ system, J = 8.8 Hz, $\Delta\nu$ = 151.9 Hz, 4 H) ppm. ^{13}C NMR: δ = 24.2, 27.4, 64.3, 69.4, 116.9, 121.0, 121.2, 124.4 (2 C), 124.9 (2 C), 127.5, 129.6, 149.6, 152.4, 153.6 ppm. MS (EI): *m*/*z* (%) = 57 (6), 65 (8), 77 (22), 91 (41), 107 (25), 119 (11), 131 (20), 133 (21), 146 (100), 317 (2) $[M]^+$. HRMS (EI): calcd. for $C_{16}H_{15}NO_4S$ $[M]^+$ 317.07218; found 317.07150.

(±)-(2*R*,R_S)-**28**: Colourless oil, R_f = 0.28 (hexane/EtOAc, 1:2). ^{1}H NMR: δ = 1.93–2.17 (m, 2 H), 2.74–2.93 (m, 2 H), 3.19 and 3.34 (ddd, J = 13.6, 7.4, 4.1 Hz, 2 H), 4.35–4.43 (m, 1 H), 6.45 (d, J = 8.2 Hz, 1 H), 6.85 (td, J = 8.2, 1.0 Hz, 1 H), 7.02–7.07 (m, 2 H), 7.88 and 8.39 (AA′BB′ system, J = 8.9 Hz, $\Delta\nu$ = 151.7 Hz, 4 H) ppm. ^{13}C NMR: δ = 24.1, 27.1, 61.1, 69.1, 116.5, 121.0, 121.1, 124.1 (2 C), 125.5 (2 C), 127.5, 129.6, 149.5, 151.2, 153.4 ppm. MS (EI): *m*/*z* (%) = 65 (6), 77 (16), 91 (34), 107 (22), 131 (17), 133 (18), 146 (100), 300 (15), 317 (1) $[M]^+$. HRMS (EI): calcd. for $C_{16}H_{15}NO_4S$ $[M]^+$ 317.07218; found 317.07180.

(±)-(2*S*,R_S)-2-[(2-Naphthylsulfinyl)methyl]chroman (29): Starting from (±)-2-[(2-naphthylsulfinyl)methyl]chroman-2-ol (**3e**; 50 mg, 0.15 mmol) following Method B for 8 h at 0 °C and 12 h at room temp., an 87:13 mixture of epimers (±)-(2*S*,R_S)-**29** and (±)-(2*R*,R_S)-**29** was obtained. After flash chromatography (eluent: hexane/EtOAc, 3:2), compound (±)-(2*S*,R_S)-**29** was obtained in 63% yield (30 mg) as a beige solid and the C-2 isomer (±)-(2*R*,R_S)-**29** in 13% yield (6 mg).

(±)-(2*S*,R_S)-**29**: M.p. 123–124 °C. R_f = 0.34 (hexane/EtOAc, 1:1). ^{1}H NMR: δ = 1.84 (tdd, J = 13.5, 10.1, 5.5 Hz, 1 H), 2.03–2.11 (m, 1 H), 2.77 (ddd, J = 16.5, 5.3, 3.5 Hz, 1 H), 2.94 (ddd, J = 16.8, 10.9, 6.0 Hz, 1 H), 3.04 and 3.14 (ddd, J = 13.2, 9.5, 3.2 Hz, 2 H), 4.72 (tt, J = 9.7, 2.5 Hz, 1 H), 6.86–6.91 (m, 2 H), 7.05–7.15 (m, 2 H), 7.57–7.63 (m, 2 H), 7.66 (dd, J = 8.6, 1.8 Hz, 1 H), 7.90–8.01 (m, 3 H), 8.26 (d, J = 1.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 24.3, 27.5, 64.1, 69.7, 117.0, 119.7, 120.8, 121.4, 124.4, 127.4, 127.5, 127.8, 128.1, 128.5, 129.5, 129.6, 132.9, 134.5, 141.6, 153.9 ppm. MS (FAB^+): *m*/*z* (%) = 88 (17), 109 (25), 177 (15), 323 (77) $[M + H]^+$, 645 ($2M^+ + H$). HRMS (FAB^+): calcd. for $C_{20}H_{19}O_2S$ $[M]^+$ 323.11057; found 323.11210.

(±)-(2*R*,R_S)-**29**: R_f = 0.26 (hexane/EtOAc, 1:1). ^{1}H NMR: δ = 1.93–2.06 (m, 1 H), 2.11–2.19 (m, 1 H), 2.71–2.89 (m, 2 H), 3.13 and 3.43 (ddd, J = 13.4, 7.0, 5.1 Hz, 2 H), 4.24–4.32 (m, 1 H), 6.61 (d, J = 8.1 Hz, 1 H), 6.84–6.91 (m, 2 H), 7.56–7.63 (m, 2 H), 7.68 (dd, J = 8.7, 1.7 Hz, 1 H), 7.92 (dd, J = 9.4, 6.0 Hz, 2 H), 7.99 (d, J = 8.5 Hz, 1 H), 8.26 (s, 1 H) ppm. ^{13}C NMR: δ = 24.1, 27.0, 61.8, 70.2, 116.8, 120.2, 120.7, 121.3, 125.1, 127.3, 127.4, 127.9, 128.1, 128.6, 129.5, 129.6, 132.9, 134.6, 140.5, 153.8 ppm. MS (FAB^+): *m*/*z* (%) = 109 (54), 263 (16), 305 (10), 323 (36) $[M + H]^+$. HMRS (FAB^+): calcd. for $C_{20}H_{19}O_2S$ $[M]^+$ 323.11058; found 323.10930.

2-(2-Methoxy-1-naphthylthiomethyl)chroman (32): Starting from (R_S)-2-methoxy-2-[(2-methoxy-1-naphthylsulfinyl)methyl]chroman (**5**; 47 mg, 0.13 mmol) following Method B for 1 h at 0 °C, after flash chromatography (eluent: hexane/EtOAc, 3:2) compound **32** was obtained in 15% yield. ^{1}H NMR: δ = 1.75–1.89 (m, 1 H), 2.22–2.31 (m, 1 H), 2.71–2.75 (m, 2 H), 3.00 and 3.28 (ddd, J = 13.4, 7.7, 5.6 Hz, 2 H), 3.94–4.05 (m and s, 4 H), 6.65 (dd, J = 8.2, 1.2 Hz, 1 H), 6.78 (dd, J = 7.5, 1.3 Hz, 1 H), 6.97–7.05 (m, 2 H), 7.30–7.39 (m, 2 H), 7.51–7.57 (m, 1 H), 7.72–7.88 (m, 2 H), 8.67 (d, J = 8.6 Hz, 1 H) ppm. ^{13}C NMR: δ = 24.3, 26.3, 39.2, 56.7, 75.3, 112.9, 116.7, 120.1, 121.9, 123.6, 125.5, 127.1, 127.6, 128.2, 128.9, 129.4, 130.7, 130.9, 132.3, 136.3, 154.6 ppm. MS (FAB^+): *m*/*z* (%) = 77 (96), 89 (63), 91 (79), 115 (92), 149 (51), 158 (56), 189 (53), 336, (34) $[M]^+$, 337 (5) $[M + 1]^+$. HRMS (FAB^+): calcd. for $C_{21}H_{20}O_2S$ $[M]^+$ 336.11840; found 336.11760.

(2*S*,R_S)-6-Methoxy-2-[(*p*-tolylsulfinyl)methyl]chroman (33): Starting from (R_S)-6-methoxy-2-[(*p*-tolylsulfinyl)methyl]chroman-2-ol (**14**; 40 mg, 0.12 mmol) following Method B for 6 h at 0 °C and 16 h at room temp., a 67:33 mixture of epimers (2*S*,R_S)-**33** and (2*R*,R_S)-**33** was obtained. After work-up and flash chromatography (eluent: hexane/EtOAc, 1:1), compound (2*S*,R_S)-**33** was isolated in 30% yield and the C-2 isomer (2*R*,R_S)-**33** in 10% yield as colourless oils.

(2*S*,R_S)-**33**: ^{1}H NMR: δ = 1.77–1.83 (m, 1 H), 1.98–2.05 (m, 1 H), 2.42 (s, 3 H), 2.70–2.78 (m, 1 H), 2.85–2.99 (m, 3 H), 3.75 (s, 3 H), 4.55–4.60 (m, 1 H), 6.58 (d, J = 2.3 Hz, 1 H), 6.69 (dd, J = 9.0, 2.3 Hz, 1 H), 6.80 (d, J = 9.0 Hz, 1 H), 7.33 and 7.57 (AA′BB′ system, J = 8.4 Hz, 4H) ppm. ^{13}C NMR: δ = 21.4, 24.6, 27.5, 55.7, 64.7, 69.6, 113.4, 113.9, 117.5, 121.9, 123.8, 130.0, 141.4, 141.5, 148.0, 153.6 ppm.

(2*R*,R_S)-**33**: ^{1}H NMR: δ = 1.90–2.00 (m, 1 H), 2.06–2.12 (m, 1 H), 2.41 (s, 3 H), 2.69–2.82 (m, 2 H), 2.97 and 3.34 (ddd, J = 13.2, 7.1, 5.3 Hz, 2 H), 3.75 (s, 3 H), 4.09–4.18 (m, 1 H), 6.56 (d, J = 2.7 Hz, 1 H), 6.63–6.65 (m, 2 H), 7.32 and 7.58 (AA′BB′ system, J = 8.4 Hz, 4H) ppm.

(2*S*,R_S)-6-Fluoro-2-[(*p*-tolylsulfinyl)methyl]chroman (34):[25] Starting from (R_S)-6-fluoro-6-methoxy-2-[(*p*-tolylsulfinyl)methyl]chroman-2-ol (**15**; 3.0 g, 9.37 mmol, 1 equiv.) following Method B for 5 h at 0 °C and 2 h at room temp., an 87:13 mixture of epimers (2*S*,R_S)-**34** and (2*R*,R_S)-**34** was obtained. After flash chromatography (eluent: hexane/EtOAc, 3:2), compound (2*S*,R_S)-**34** was obtained in 75% yield (2.14 g) as a white solid; m.p. 115–117 °C; R_f = 0.36 (hexane/EtOAc, 1:2). $[\alpha]_D^{20}$ = +232.0 (c = 0.64, $CHCl_3$). ^{1}H NMR: δ = 1.74–1.87 (m, 1 H), 1.99–2.08 (m, 1 H), 2.42 (s, 3 H), 2.74 (ddd, J = 16.7, 5.6, 3.4 Hz, 1 H), 2.84–3.03 (m, 3 H), 4.60 (ddt, J = 12.5, 7.4, 2.4 Hz, 1 H), 6.73–6.81 (m, 3 H), 7.33 and 7.57 (AA′BB′ system, J = 7.8 Hz, 4 H) ppm. ^{13}C NMR: δ = 21.4, 24.5, 27.1, 64.1, 69.8, 114.1 (d, J = 23 Hz), 115.2 (d, J = 23 Hz), 117.8 (d, J = 7.7 Hz), 122.5 (d, J = 7.5· Hz), 123.8 (2 C), 130.1 (2 C), 141.3, 141.7, 149.9 (d, J = 1.9 Hz), 157.0 (d, J = 239 Hz) ppm. MS (EI): *m*/*z* (%) = 91 (25), 109 (40), 125 (21), 139 (74), 149 (21), 165 (100), 288 (11), 304 (2) $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{17}FO_2S$ $[M]^+$ 304.09333; found 304.09270.

(2*R*,S_S)-6-Fluoro-2-[(*p*-tolylsulfinyl)methyl]chroman (34):[25] Compound **34** was obtained in a similar way from (S_S)-6-fluoro-6-methoxy-2-[(*p*-tolylsulfinyl)methyl]chroman-2-ol (**15**) as an 89:11 mixture of C-2 epimers from which diastereomers (2*R*,S_S)-**34** and (2*S*,S_S)-**34** were isolated pure in 70 and 10% yields, respectively.

(2*S*,R_S)-6-Benzyloxy-5,7,8-trimethyl-2-[(*p*-tolylsulfinyl)methyl]-chroman (35): Starting from (R_S)-6-(benzyloxy)-5,7,8-trimethyl-2-[(*p*-tolylsulfinyl)methyl]chroman-2-ol (**19**; 40 mg, 0.09 mmol) following Method B for 4 h at 0 °C, a 75:25 mixture of epimers (2*S*,R_S)-**35** and (2*R*,R_S)-**35** was obtained. After work-up and flash chromatography (eluent: hexane/EtOAc, 3:2), compound (2*S*,R_S)-**35** was isolated in 46% yield and the C-2 isomer (2*R*,R_S)-**35** in 14% yield.

(2*S*,R_S)-**35**: R_f = 0.37 (hexane/EtOAc, 1:2). $[\alpha]_D^{20}$ = +398 (c = 0.05, $CHCl_3$). ^{1}H NMR: δ = 1.74–1.88 (m, 1 H), 2.04–2.10 (m, 1 H),

2.17 (s, 3 H), 2.18 (s, 3 H), 2.23 (s, 3 H), 2.43 (s, 3 H), 2.67–2.72 (m, 2 H), 2.98–3.00 (m, 2 H), 4.52–4.60 (m, 1 H), 4.70 (s, 2 H), 7.33–7.43 (m, 5 H), 7.50 and 7.59 (AA′BB′ system, J = 8.3 Hz, $\Delta\nu$ = 25.2 Hz, 4 H) ppm. ^{13}C NMR: δ = 11.9, 12.0, 12.8, 21.4, 22.7, 27.6, 64.5, 68.9, 74.7, 118.0, 123.1, 123.8 (2 C), 126.4, 127.7 (2 C), 127.8, 128.4, 128.5 (2 C), 130.0 (2 C), 137.8, 141.5, 148.2, 149.0 ppm. MS (FAB$^+$): m/z (%) = 55 (12), 77 (26), 91 (22), 107 (25), 120 (12), 343 (53), 435 (100) [M + 1]$^+$. HRMS (FAB$^+$): calcd. for $C_{27}H_{31}O_3S$ [M + 1]$^+$ 435.1994; found 435.2001.

(2*S*,R_S)-**35**: R_f = 0.25 (hexane/EtOAc, 1:2). $[\alpha]_D^{20}$ = –172 (c = 0.04, $CHCl_3$). ^{1}H NMR: δ = 1.85–1.88 (m, 1 H), 1.95–2.03 (m, 1 H), 2.07 (s, 3 H), 2.13 (s, 3 H), 2.22 (s, 3 H), 2.41 (s, 3 H), 2.57–2.68 (m, 2 H), 2.99 and 3.44 (ddd, J = 12.8, 7.7, 4.9 Hz, 2 H), 3.98–4.07 (m, 1 H), 4.61 (s, 2 H), 7.30–7.43 (m, 5 H), 7.49 and 7.59 (AA′BB′ system, J = 8.2 Hz, $\Delta\nu$ = 32 Hz, 4 H) ppm. ^{13}C NMR: δ = 11.7, 11.9, 12.8, 21.4, 22.4, 27.2, 62.6, 69.8, 74.7, 117.8, 124.4 (2 C), 126.4, 126.7, 127.7 (2 C), 127.8, 128.4 (2 C), 130.0 (2 C), 132.9, 140.3, 141.7, 148.1, 149.0, 151.3 ppm.

(2*S*)-Chroman-2-carbaldehyde (36): Trifluoroacetic anhydride (296 μL, 2.1 mmol, 3.05 equiv.) was added to a solution of sulfoxide (2*S*,R_S)-**21** (198 mg, 0.69 mmol, 1 equiv.) and 2,4,6-collidine (291 μL, 2.2 mmol, 3.2 equiv.) in CH_3CN (12 mL) at 0 °C under nitrogen. After stirring at 0 °C for 15 min, an aqueous solution (7 mL) of $NaHCO_3$ (526 mg, 6.2 mmol, 9 equiv.) was added. The mixture was stirred at room temperature for 4 h, extracted with Et_2O and the organic layer washed with brine and dried with $MgSO_4$. After work-up, compound (2*S*)-**36** was obtained and used without further purification. ^{1}H NMR: δ = 1.94–2.32 (m, 2 H), 2.67–2.92 (m, 2 H), 4.49 (ddd, J = 8.7, 3.5, 0.7 Hz, 1 H), 6.80–6.96 (m, 2 H), 7.04–7.18 (m, 2 H) ppm. ^{13}C NMR: δ = 22.5, 23.3, 79.4, 116.9, 121.1, 121.5, 127.7, 129.7, 153.4, 201.5 ppm.

(2*S*)-(Chroman-2-yl)methanol (37): Trifluoroacetic anhydride (150 μL, 1.05 mmol, 5.0 equiv.) was added to a solution of (2*S*,R_S)-**21** (60 mg, 0.21 mmol, 1 equiv.) and 2,4,6-collidine (83 μL, 0.63 mmol, 3.0 equiv.) in CH_3CN (2 mL) at 0 °C under nitrogen. After stirring at 0 °C for 15 min, an aqueous solution of K_2CO_3 was added until pH 7. The mixture was stirred at room temperature for 15 min and then $NaBH_4$ (0.42 mmol, 2 equiv.) was added and the resulting mixture was stirred for 1 h at room temp. The reaction was carefully quenched at 0 °C with a saturated NH_4Cl solution and extracted with EtOAc. The organic layers were washed with 1 M HCl, $NaHCO_3$ and brine. Compound (2*S*)-**37** was isolated pure by flash chromatography (eluent: hexane/EtOAc, 1:1) as a colourless oil in 80% yield. $[\alpha]_D^{20}$ = +90.4 (c = 0.56, CH_3OH). ^{1}H NMR: δ = 1.78–1.99 (m, 2 H), 2.13 (t, J = 5.9 Hz, 1 H), 2.78 (ddd, J = 16.3, 5.7, 3.3 Hz, 1 H), 2.89 (ddd, J = 16.5, 11.5, 5.7 Hz, 1 H), 3.74 (dd, J = 11.8, 6.0 Hz, 1 H), 3.83 (ddd, J = 15.1, 6.6, 3.3 Hz, 1 H), 4.12 (ddd, J = 12.5, 6.3, 3.0 Hz, 1 H), 6.84–6.90 (m, 2 H), 7.07–7.10 (m, 2 H) ppm. ^{13}C NMR: δ = 23.7, 24.5, 65.6, 76.4, 116.7, 120.4, 122.1, 127.3, 129.5, 154.8 ppm. MS (EI): m/z (%) = 77 (22), 105 (43), 133 (100), 164 (57) [M]$^+$. HRMS (EI): calcd. for $C_{10}H_{12}O_2$ [M]$^+$ 164.08373; found 164.08385. 97% *ee* (HPLC; 90:10 hexane/isopropanol, 0.5 mL/min, 210 nm, t_r = 18.21 min, T = 25 °C).

(2*S*)-(Chroman-2-yl)-2-hydroxyacetonitrile (38): (2*S*)-Chroman-2-carbaldehyde (**36**), synthesized as reported above starting from sulfinylcroman (2*S*,R_S)-**21** (50 mg, 0.17 mmol, 1 equiv.), was dissolved in CH_2Cl_2 (2 mL) and the solution was cooled to –78 °C. TBDMSCN (30 mg, 0.21 mmol, 1.2 equiv.) was then added and the resulting mixture was stirred for 6 h at –78 °C and left to reach room temp. with stirring for an additional 10 h. After hydrolysis with H_2O and extraction with CH_2Cl_2, standard work-up and purification by flash chromatography (eluent: hexane/EtOAc, 2:1) gave the cyanohydrin (2*S*)-**38** as a mixture of two diastereoisomers at the hydroxy centre in a 60:40 ratio and in 52% yield for the two steps, starting from **21**. R_f = 0.48 (hexane/AcOEt, 1:2). ^{1}H NMR: δ = 1.93–2.21 (m, 2 H), 2.77–2.95 (m, 2 H), 4.25 (ddd, J = 11.0, 4.3, 2.6 Hz, 1 H), 4.64 (dd, J = 4.0, 2.8 Hz, 1 H), 6.86–6.93 (m, 2 H), 7.05–7.15 (m, 2 H) ppm. ^{13}C NMR (2 diastereoisomers): δ = 23.0, 23.3, 23.9, 23.9, 64.1, 64.6, 75.6, 75.7, 116.8, 116.9, 117.4, 117.7, 121.1, 121.4, 127.6 (2 C), 129.5 (2 C), 153.4 (2 C) ppm.

Supporting Information (see footnote on the first page of this article): Experimental procedures for the synthesis and characterization data of compounds **8**–**10**, **12**, **18** and **20**.

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