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Enantioselective access to benzannulated spiroketals using a chiral sulfoxide auxiliary†

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This article describes our efforts to develop an asymmetric synthesis of bisbenzannulated spiroketals using a chiral sulfoxide auxiliary. Our primary focus was on the synthesis of the 3*H*-spiro[benzofuran-2,2′-chroman] ring system, the spirocyclic core of the rubromycin family. Our strategy employed the use of lithium–halogen exchange on a racemic bromospiroketal in order to attach a chiral sulfoxide, thus producing two diastereomers. The diastereomers were separable, enabling isolation of each spiroketal enantiomer. Subsequent cleavage of the sulfoxide group from each diastereomer yielded the respective parent spiroketal in high enantiopurity.

Introduction

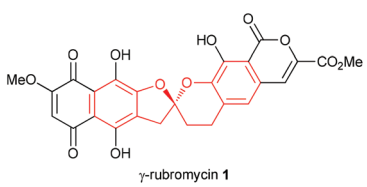
The 3*H*-spiro[benzofuran-2,2′-chroman] ring system present in the rubromycin family of antibiotics has received significant synthetic attention over the past ten years.[1] Previous synthetic strategies, including cycloadditions,[2] haloetherification,[3] oxidative cyclisation[4] and gold-catalysed hydroalkoxylation[5] have only produced racemic spiroketals. We therefore report an efficient resolution of the 3*H*-spiro[benzofuran-2,2′-chroman] ring system using a chiral sulfoxide auxiliary.

Sulfoxide auxiliaries were employed in the current study as they can be readily introduced and their thiosulfinate precursor can be prepared in high enantiopurity.[6] It was anticipated that substitution of the chiral sulfoxide at the *ortho* position on the benzannulated spiroketal would result in the formation of two diastereomers and that the thermodynamically favoured isomer should be formed under equilibrating conditions.

Iwata and co-workers have previously demonstrated the use of sulfoxide auxiliaries for the asymmetric synthesis of spiroketals.[7] In their work the sulfoxide group directs an intramolecular Michael-type addition to facilitate the key spiroketalisation step. Additionally, Uchiyama and co-workers reported the use of a selenium-based chiral auxiliary to direct spiroketalisation, albeit with low selectivity.[8] Catalyst controlled asymmetric spiroketalisation has also been reported. A chiral iridium(I)–SpinPHOX complex has been employed by Ding *et al.* to effect asymmetric hydrogenation, followed by spontaneous cyclisation[9] whilst chiral phosphoric acids have been independently used by the Nagory and List groups to effect spiroketalisation.[10]

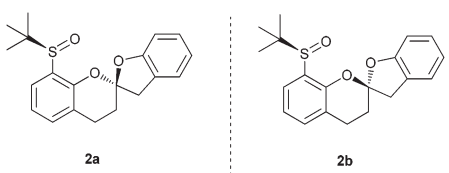
Results and discussion

We focused our study on the cyclisation of sulfinyl substituted dihydroxyketone **3** to spiroketal **2a**. Our proposed synthetic strategy aimed to access the sulfinyl spiroketal precursor **3** *via* a Horner–Wadsworth–Emmons/hydrogenation sequence (Scheme 1). This protocol has been successfully employed in our group to access the spiroketal core of benzannulated



γ-rubromycin **1**

Fig. 1 The spirocyclic core of γ-rubromycin.



2a **2b**

Fig. 2 Diastereomeric spiroketals bearing a homochiral sulfoxide.

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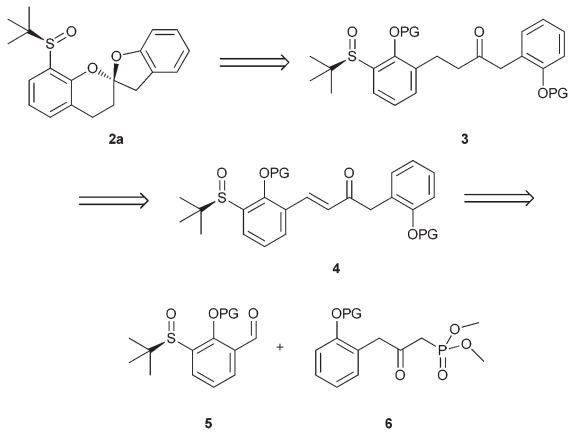
†Electronic supplementary information (ESI) available: Copies of the ^{1}H NMR and ^{13}C NMR spectra for all novel compounds, HPLC traces of **2a**, **2b**, **27a**, and **27b**, and crystallographic data in CIF format for **2a** and **2b**. CCDC 940550 and 940551 for **2a** and **2b**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob41065j



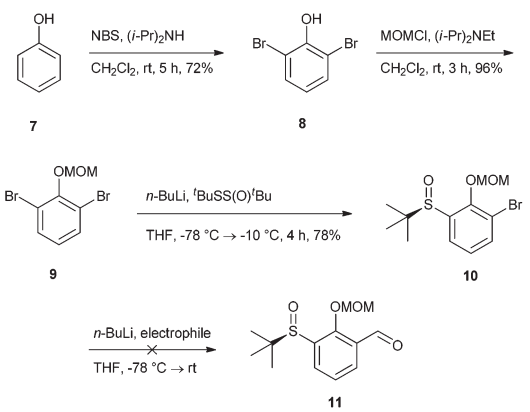
Scheme 1 Retrosynthetic analysis of sulfinyl spiroketal **2a**.

natural products.[11] It was envisioned that hydrogenation then deprotection/cyclisation of protected dihydroxyenone **4** would afford the desired spiroketal **2a**. Importantly, the influence of the chiral sulfoxide auxiliary on the stereocontrol of the spiroketalisation could be investigated. Synthesis of the key sulfinyl enone **4** required initial access to aldehyde **5** and phosphonate **6**.

Synthesis of sulfinyl aldehyde

Initial efforts were directed towards the synthesis of sulfinyl aldehyde **11**, which we proposed to prepare *via* formylation of aryl sulfinyl bromide **10**. Consequently, **10** was readily prepared from phenol by *ortho*-dibromination and MOM protection followed by *ortho*-lithiation and reaction with (*R*)-(+)-*tert*-butyl *tert*-butanethiosulfinate (Scheme 2).

With bromosulfoxide **10** in hand, a second lithium–halogen exchange and trapping with a formyl electrophile was then attempted to access aldehyde **11**. Despite the successful synthesis of **10** this subsequent transformation proved fruitless. Treatment of **10** with 1.1 equivalents of *n*-butyllithium at −78 °C followed by addition of several electrophiles (DMF, *N*-formylmorpholine, methyl formate) added in excess, only afforded disappointing yields of the desired aldehyde **11**. The best yield obtained was only 11% using ethyl formate.

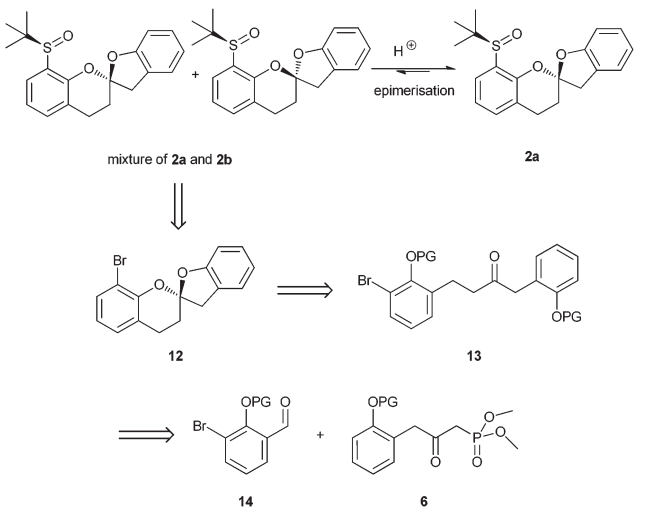


Scheme 2 Attempted synthesis of sulfinyl aldehyde **11** with a formyl electrophile.

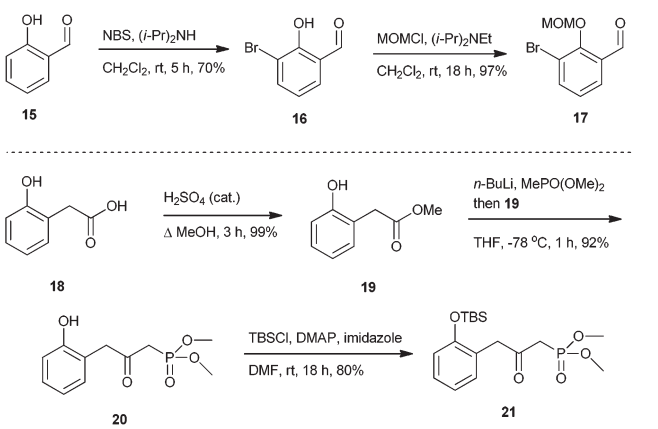
Spiroketal epimerisation strategy

In many cases, spiroketals are known to undergo epimerisation under acidic conditions *via* ring opening and recyclisation. It was thus envisioned that epimerisation of a diastereomeric mixture of spiroketals **2a** and **2b** under acidic conditions would result in formation of the thermodynamically-favoured diastereomer (Scheme 3).

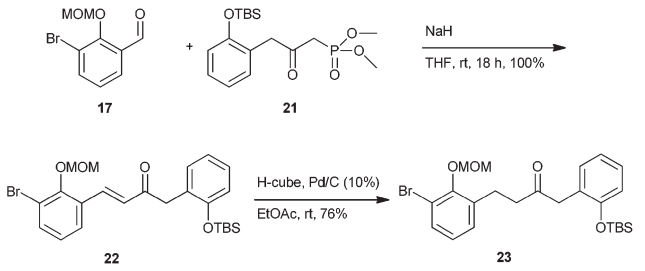
This revised strategy allowed for late stage appendage of a chiral sulfoxide auxiliary to racemic bromospiroketal **12**, followed by acid-catalysed epimerisation. It was envisioned that bromospiroketal precursor **13** could be prepared using a Horner–Wadsworth–Emmons coupling/hydrogenation strategy similar to that initially proposed for the preparation of sulfinyl ketone **3**. The requisite HWE coupling partners, bromoaldehyde **17** and phosphonate **21**, were each prepared in two and three steps respectively (Scheme 4).



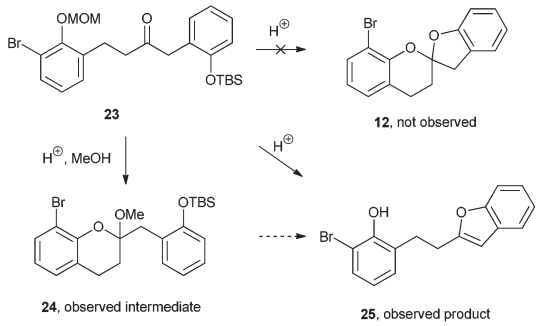
Scheme 3 Proposed acid-catalysed epimerisation and retrosynthetic strategy of sulfinyl spiroketal **2a**.



Scheme 4 Synthesis of HWE coupling partners **17** and **21**.



Scheme 5 Synthesis of ketone **23**.



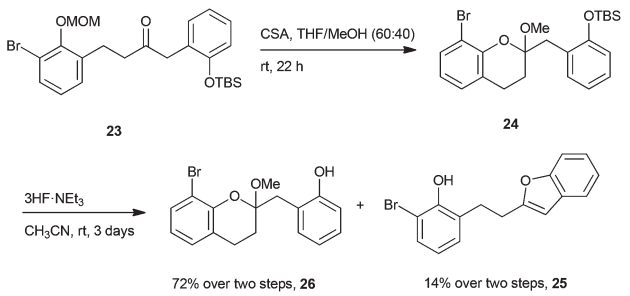
Scheme 6 Benzofuran formation during attempted spiroketalisation.

With both aldehyde **17** and phosphonate **21** in hand, the Horner–Wadsworth–Emmons olefination was carried out under conditions used previously within our group, to afford enone **22** in quantitative yield.[11] Hydrogenation of **22** proved to be more challenging than anticipated. When enone **22** was hydrogenated over catalytic palladium on carbon (10% Pd/C) both hydrogenation and debromination were observed. Finally, it was found that use of flow hydrogenation (THALES H-Cube®, 10% Pd/C, 30 bar) cleanly afforded **23** in a reproducible 76% yield (Scheme 5).

Initial deprotection attempts under Brønsted acid conditions resulted in the formation of benzofuran **25** as the major product. For cyclisations carried out in methanol, methyl acetal **24** was observed to form prior to benzofuran formation (Scheme 6).

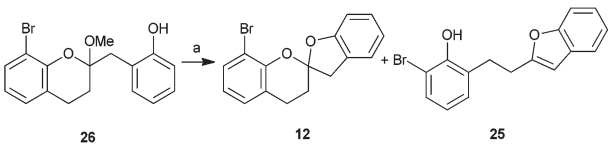
The facile formation of methyl acetal **24** suggested that if the reaction conditions were tailored to selectively produce acetal **24** by selective methoxymethyl cleavage, then subsequent *tert*-butyldimethylsilyl deprotection could be carried out under mild conditions such as buffered hydrogen fluoride to give phenol **26**. It was then hoped that cyclisation could be effected by Lewis acids to produce spiroketal **12**, thereby avoiding formation of benzofuran **25**. With this idea in mind, acetal **26** was prepared over two steps from **23** (Scheme 7).

A range of Lewis acids were then screened to effect the cyclisation of methyl acetal **26** to spiroketal **12** (Table 1). Initial efforts produced substantial amounts of undesired benzofuran **25** (Table 1, entries 1–6), which proved particularly difficult to separate by chromatography. Pleasingly, use of indium(III) chloride afforded spiroketal **12** in a 91 : 9 ratio (Table 1, entry 7) with benzofuran **25**, allowing **12** to be prepared in 80% isolated yield.



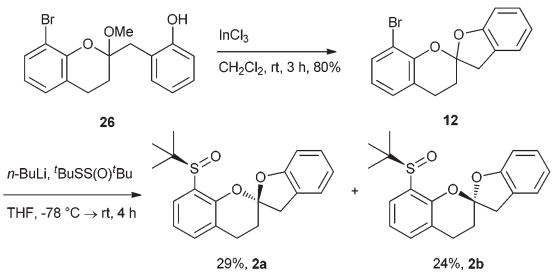
Scheme 7 Synthesis of methyl acetal.

Table 1 Lewis acids screened for cyclisation of acetal **26**



Entry	Lewis acid (1.0 eq.)[a]	Ratio **12** : **25**[b]
1	$FeCl_3$	0 : 100
2	$TiCl_4$	34 : 66[c]
3	$AlCl_3$	43 : 57
4	$ZrCl_4$	47 : 63
5	BF_3	54 : 46
6	BCl_3	77 : 23
7	$InCl_3$	91 : 9

[a] Lewis acid (1.0 eq.), CH_2Cl_2, rt, 3 h. [b] 100% starting material conversion to a mixture of **12** and **25**, with product ratios determined based on the crude ^1H NMR spectrum. [c] Significant amounts of unidentifiable side products observed in the crude ^1H NMR spectrum.



Scheme 8 Synthesis of spiroketals **2a** and **2b**.

The chiral sulfoxide was subsequently introduced onto bromospiroketal **12** by halogen–metal exchange and quenching with (*R*)-(+)-*tert*-butyl *tert*-butanethiosulfinate (Scheme 8).

Pleasingly, the resultant sulfoxide diastereomers **2a** and **2b** were separable by careful flash chromatography. Recrystallisation and X-ray analysis gave high resolution crystal structures for both diastereomers. Based on the known sulfoxide stereochemistry it was concluded that the structures of **2a** and **2b** were (R_S,2*S*) and (R_S,2*R*) respectively (Fig. 3).

Continuous flow hydrogenation of either sulfoxide **2a** or **2b** through a RANEY® nickel cartridge in ethanol at 60 °C for 2 h

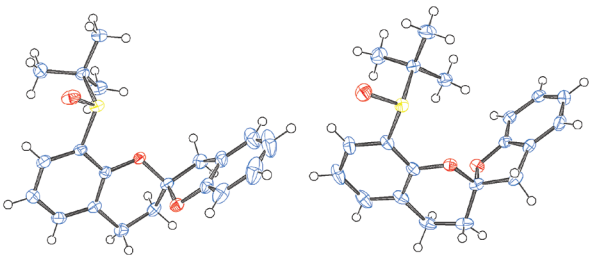
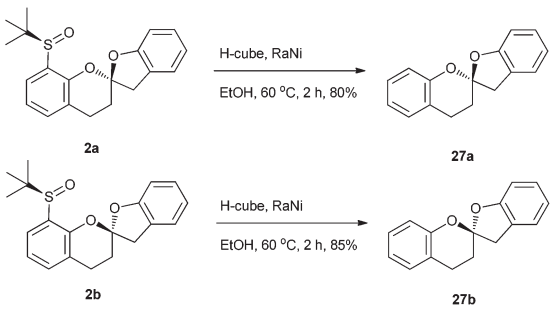


Fig. 3 Ortep crystal structures of **2a** (left) and **2b** (right) showing 50% probability displacement ellipsoids.

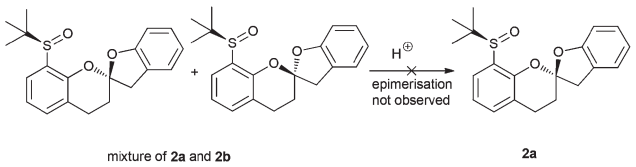


Scheme 9 Synthesis of spiroketals **27a** and **27b**.

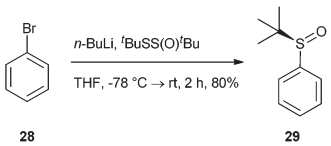
cleanly removed the auxiliary to yield the corresponding spiroketals **27a** and **27b** in good yield (Scheme 9).

With both spiroketals **27a** and **27b** successfully prepared, their enantiopurity was established using chiral HPLC (Chiral-Pak® AD-H column, *n*-hexane–propan-2-ol 90 : 10) and it was determined that both spiroketals were prepared in >97% ee. HPLC calibration was performed using a sample of racemic **27** prepared in an earlier investigation.[11] The optical rotation of each compound was determined in chloroform at a wavelength of 570 nm. Isomer (*S*)-**27** was found have a specific rotation of −218 (c = 0.34, 100% ee), while (*R*)-**27** had a specific rotation of +195 (c = 0.34, 97% ee). To the best of our knowledge, this represents the first time the rubromycin core **27** has been prepared asymmetrically and therefore this is the first time that an optical rotation has been reported for these heterocyclic systems. It is worth noting that the melting point recorded for enantiopure **27** is significantly higher than the literature melting point reported for the racemic product (132 °C *vs.* 71 °C).[11]

It was next hoped that the mixture of sulfoxide diastereomers **2a** and **2b** could be converted to the most thermodynamically stable diastereomer by acid-catalysed epimerisation. After treating a 1 : 1 mixture of the two diastereomers with a stoichiometric quantity of pyridinium *p*-toluenesulfonic acid in dichloromethane for 20 h no epimerisation was observed by ^{1}H NMR analysis (Scheme 10). Further studies using either excess acetic acid or camphorsulfonic acid in dichloromethane also showed no variation from the 1 : 1 ratio of diastereomers (Scheme 10).



Scheme 10 Attempted epimerisation of spirocyclic diastereomers **2a** and **2b**.



Scheme 11 Synthesis of model sulfoxide **29**.

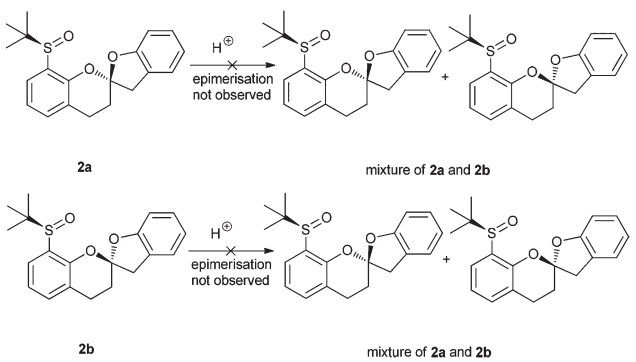
Three possible explanations were postulated to explain this observation: (i) under acidic conditions the chiral sulfoxide is able to racemise as well as the spirocentre thereby resulting in the formation of all four possible stereoisomers; (ii) the energy difference between **2a** and **2b** may not be sufficient to induce diastereoselectivity; or (iii) acid-catalysed epimerisation of benz-annulated spiroketals does not occur as readily as anticipated. Each of these possibilities was therefore investigated in turn.

Sulfoxide racemisation was investigated using model compound **29** which was prepared from bromobenzene **28** in 80% yield using standard lithiation conditions (Scheme 11).

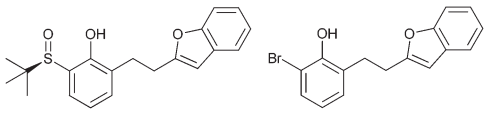
For the HPLC analysis, calibration was carried out with racemic sulfoxide **29**. Using conditions identical to those used to effect the epimerisation of **2a** and **2b**, namely use of either pyridinium *p*-toluenesulfonic acid or camphorsulfonic acid in dichloromethane for 20 h, resulted in no racemisation of the sulfoxide being observed by chiral HPLC.

The next experiments aimed to determine if epimerisation of the spirocentre of **2a** or **2b** was possible. It was reasoned that if epimerisation was occurring and there was no significant energy difference between the diastereomers then treatment of pure **2a** or **2b** with acid would result in a 1 : 1 ratio of products (Scheme 12).

However, when either **2a** or **2b** were subjected to standard epimerisation conditions the only transformation observed



Scheme 12 Enantiopure **2a** and **2b** do not epimerise in the presence of acid.



30 25

Fig. 4 Benzofurans **25** and **30**.

was the formation of trace amounts of a side product tentatively assigned as benzofuran **30**, with no epimerisation taking place. The structure of benzofuran **25** was determined by comparison of the ^{1}H NMR spectrum to the related benzofuran **25**. This compound was not isolated in sufficient quantity for full characterisation (Fig. 4).

These studies suggest that benzannulated spiroketals such as the 3*H*-spiro[benzofuran-2,2′-chroman] ring systems **27a** and **27b** do not epimerise as readily as anticipated and that the stereochemistry generated at the spirocentre will be retained and will be stable to acidic conditions. This unanticipated stability is of potential use for the synthesis of chiral spiroketals that are present in the rubromycin family of antibiotics.

Conclusions

Benzannulated sulfinyl spiroketals **2a** and **2b** have been shown to be resilient to acid-catalysed epimerisation, suggesting that any auxiliary-based approach to effect the asymmetric synthesis of benzannulated spiroketals must have the chiral auxiliary installed prior to cyclisation. This finding also helps to explain the stability of the rubromycin spirocentre, which is isolated from nature as a single isomer. The absolute optical rotation values for the 3*H*-spiro[benzofuran-2,2′-chroman] ring systems **27a** and **27b** have been measured for the first time. Furthermore, attachment of the *tert*-butyl sulfoxide auxiliary *ortho* to the oxygen has proven to be an efficient way to resolve racemic bromospiroketal **12**.

Experimental section

General experimental methods

All reactions were carried out in flame- or oven-dried glassware under a dry nitrogen atmosphere. Tetrahydrofuran was dried over sodium wire and dichloromethane was dried over calcium hydride. All solvents were distilled prior to use. Flash chromatography was carried out using 0.063–0.1 mm silica gel with the desired solvent. Thin layer chromatography (TLC) was performed using 0.2 mm Kieselgel F254 (Merck) silica plates and compounds were visualised using UV irradiation at 365 nM and/or staining with: vanillin in methanolic sulfuric acid, a solution of ammonium heptamolybdate and cerium sulfate in aqueous sulfuric acid or a solution of potassium permanganate and potassium carbonate in aqueous sodium hydroxide. Preparatory TLC was carried out on 500 μm Uniplate™ (Analtech) silica gel (20 × 20 cm) and 500 μm Uniplate™ (Analtech) alumina gel (20 × 20 cm) thin layer chromatography plates. Infrared spectra were obtained as indicated using a Perkin-Elmer Spectrum One FTIR spectrometer on a film ATR sampling accessory. Absorption maxima are expressed in wavenumbers (cm^{-1}). Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded as indicated on either the Bruker Avance 300 spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or using the Bruker DRX-400 spectrometer operating at 400 MHz for ^{1}H nuclei, 100 MHz for ^{13}C nuclei. All chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (^{1}H) or $CDCl_3$ (^{1}H and ^{13}C). ^{1}H NMR data is reported as chemical shift, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; ddd, doublet of doublet of doublets, coupling constant (*J* Hz) and assignment. Assignments were made with the aid of DEPT 135, COSY, NOESY and HSQC experiments where required. High resolution mass spectra were recorded on a VG-70SE at a nominal accelerating voltage of 70 eV or on a Bruker micrOTOF-Q II mass spectrometer.

2,6-Dibromophenol 8. To a solution of phenol (1.5 g, 16 mmol) in dichloromethane (10 mL) was added a solution of *N*,*N*-diisopropylamine (0.44 mL, 3.1 mmol). To this mixture was added a solution of *N*-bromosuccinimide (5.7 g, 32 mmol) in dichloromethane (150 mL) dropwise over 3 h. After stirring for 1 h at room temperature, aqueous hydrochloric acid (1 M) was added until the solution became acidic. The organic layer was washed with water (80 mL), dried over sodium sulfate and concentrated *in vacuo* to produce a colourless residue. The resultant residue was purified by flash column chromatography using hexanes as eluent afforded the *title compound* **8** (2.8 g, 11 mmol, 69%) as colourless crystals. M.p. 52–53 °C (lit. 52–55 °C);[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.88 (s, 1H), 6.70 (t, 1H, J = 8.1 Hz), 7.45 (d, 2H, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 111.0, 122.5, 132.1, 149.5; the ^{1}H and ^{13}C NMR data obtained were in agreement with that reported in the literature.[12]

1,3-Dibromo-2-(methoxymethoxy)benzene 9. To a stirred solution of dibromophenol **8** (2.5 g, 10 mmol) in dichloromethane (70 mL) was added *N*,*N*-diisopropylethylamine (6.9 mL, 40 mmol) followed by chloromethyl methyl ether (1.1 mL, 15 mmol). The reaction was stirred at room temperature for 18 h and quenched with saturated aqueous sodium bicarbonate (50 mL). The aqueous layer was extracted with dichloromethane (3 × 70 mL). The combined organic extracts were washed with saturated sodium chloride (100 mL), dried over sodium sulfate and the solvent removed *in vacuo*. The resultant oil was purified by flash chromatography using hexanes–ethyl acetate (90 : 10) as eluent to afford the *title compound* **9** (2.8 g, 9.6 mmol, 96%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.73 (s, 3H), 5.18 (s, 2H), 6.88 (t, 1H, J = 8.0 Hz), 7.52 (d, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 58.5, 99.7, 118.6, 126.5, 132.9, 151.7; the ^{1}H and ^{13}C NMR data obtained were in agreement with that reported in the literature.[13]

(*R*)-1-Bromo-3-(*tert*-butylsulfinyl)-2-(methoxymethoxy)benzene 10. To a solution of dibromide **9** (1.6 g, 5.4 mmol) in tetrahydrofuran (8 mL) was added *n*-butyllithium (2.5 mL, 2 M in cyclohexane, 4.9 mmol) dropwise at −78 °C. The solution was stirred for 15 min followed by rapid addition of (*R*)-(+)-*tert*-butyl *tert*-butanethiosulfinate (1.6 g, 8.1 mmol) in tetrahydrofuran (1.5 mL). The solution was immediately transferred to a −10 °C ice bath and stirred for 4 h. The reaction was quenched by addition of saturated aqueous ammonium chloride (8 mL) and the aqueous layer was extracted using ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated sodium chloride (20 mL), dried over sodium sulfate and the solvent removed *in vacuo*. The crude product was purified by flash chromatography using hexanes–ethyl acetate (50 : 50) as eluent to afford the *title compound* **10** (1.2 g, 3.9 mmol, 80%) as a pale yellow solid. M.p. 60–62 °C; $[\alpha]_D^{20}$: +142 (*c* = 1.02, $CHCl_3$, 34% ee). IR spectrum (film), cm^{-1}: 2957, 1431, 1161, 1066, 1041, 925; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.20 (s, 9H), 3.66 (s, 3H), 5.17 (s, 2H), 7.22 (t, 1H, *J* = 7.9 Hz), 7.69 (dd, 1H, *J* = 1.5 Hz, 7.9 Hz), 7.76 (dd, 1H, *J* = 1.5 Hz, 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.1, 58.6, 58.7, 100.1, 117.3, 126.0, 126.8, 136.4, 137.1, 151.6. HRMS (ESI+), Calculated for $C_{12}H_{18}O_3S$: 321.0155 (M^+); Found 321.0160.

3-Bromo-2-hydroxybenzaldehyde 16. To a solution of salicylaldehyde (15 g, 0.12 mol) in dichloromethane (150 mL) was added *N*,*N*-diisopropylamine (1.7 mL, 12 mmol) followed by a solution of *N*-bromosuccinimide (22 g, 0.12 mol) in dichloromethane (900 mL) dropwise over 9 h. After stirring for 3 h at room temperature, the mixture was acidified to pH 1 with aqueous hydrochloric acid (1 M). The organic layer was separated, washed with water (300 mL), dried over sodium sulfate and concentrated *in vacuo* to produce a yellow residue. Purification by flash chromatography using hexanes–ethyl acetate (95 : 5) as eluent afforded the *title compound* **16** (17 g, 87 mmol, 70%) as yellow crystals. M.p. 50–52 °C (lit. 49–52 °C);[14] IR spectrum (film), cm^{-1}: 3092, 2852, 1652, 905; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.95 (t, 1H, *J* = 7.8 Hz), 7.55 (d, 1H, *J* = 7.8 Hz), 7.78 (d, 1H, *J* = 7.8 Hz), 9.86 (s, 1H), 11.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 111.2, 120.8, 121.4, 132.9, 140.0, 158.1, 196.0; HRMS (ESI+), Calculated for $C_7H_5BrO_2Na$: 222.9365 (M^+ + Na); Found 222.9373. The data obtained were in agreement with that reported in the literature.[14]

3-Bromo-2-(methoxymethoxy)benzaldehyde 17. To a stirred solution of phenol **16** (1.5 g, 7.5 mmol) in dichloromethane (30 mL) was added *N*,*N*-diisopropylethylamine (5.1 mL, 30 mmol) followed by chloromethyl methyl ether (0.85 mL, 11 mmol). The reaction was stirred at room temperature for 18 h then quenched with saturated aqueous sodium bicarbonate (20 mL). The aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with saturated sodium chloride (40 mL), dried over sodium sulfate and the solvent removed *in vacuo*. The resultant oil was purified by flash chromatography using hexanes–ethyl acetate (90 : 10) as eluent to afford the *title compound* **17** (1.8 g, 7.2 mmol, 97%) as colourless crystals. M.p. 44–45 °C; IR spectrum (film), cm^{-1}: 2929, 1685, 1587, 1381, 1241, 1159, 1066, 930; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.62 (s, 3H), 5.21 (s, 2H), 7.16 (td, 1H, *J* = 0.8 Hz, 7.8 Hz), 7.80–7.84 (m, 2H), 10.35 (d, 1H, *J* = 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 58.3, 101.0, 118.2, 126.0, 127.7, 131.7, 139.2, 157.3, 189.7; HRMS (ESI+), Calculated for $C_9H_9BrO_3Na$: 266.9627 (M^+ + Na); Found 266.9626.

Methyl 2-(2′-hydroxyphenyl)acetate 19. Sulfuric acid (20 drops) was added to a stirred solution of 2-(2′-hydroxyphenyl)-acetic acid (4.0 g, 26 mmol) in methanol (80 mL) at room temperature. The reaction mixture was heated to reflux for 3 h, after which it was cooled and filtered through a pad of silica, washing with ethyl acetate. The solvent was removed *in vacuo* to afford the *title compound* **19** (4.3 g, 26 mmol, 99%) as white crystals. M.p. 61–62 °C (lit. 61–62 °C);[15] ^1H NMR (400 MHz, $CDCl_3$) δ: 3.69 (s, 2H), 3.75 (s, 3H), 6.89 (td, 1H, *J* = 1.2 Hz, 7.5 Hz), 6.93 (dd, 1H, *J* = 1.2 Hz, 7.5 Hz), 7.11 (dd, 1H, *J* = 1.7 Hz, 7.5 Hz), 7.19 (td, 1H, *J* = 1.7 Hz, 7.5 Hz), 7.32 (s, 1H). The ^1H NMR data obtained were in agreement with that reported in the literature.[15]

Dimethyl (3-(2′-hydroxyphenyl)-2-oxopropyl)phosphonate 20. 19) To a stirred solution of dimethyl methylphosphonate (2.0 mL, 18 mmol) in tetrahydrofuran (100 mL) was added *n*-butyllithium (11 mL, 1.6 M in hexanes, 18 mmol) dropwise at −78 °C. The mixture was stirred at −78 °C for 30 min, followed by dropwise addition of a solution of ester **19** (1.0 g, 6.0 mmol) in tetrahydrofuran (5 mL). The reaction mixture was stirred for 1 h at −78 °C, after which it was quenched with saturated ammonium chloride (100 mL) and warmed to room temperature. The resultant mixture was extracted with ethyl acetate (3 × 100 mL), the combined organic extracts washed with saturated sodium chloride (100 mL), dried over magnesium sulfate and the solvent removed *in vacuo*. The resultant oil was purified by flash chromatography using ethyl acetate–hexanes (2 : 1) as eluent to afford the *title compound* **20** (1.4 g, 5.5 mmol, 92%) as a colourless solid. M.p. 78–80 °C; IR spectrum (film), cm^{-1}: 3200, 2957, 1718, 1598, 1454, 1227, 1028, 768; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.20 (d, 2H, *J* = 22.4 Hz), 3.78 (d, 6H, *J* = 11.3 Hz), 3.87 (s, 2H), 6.85 (td, 1H, *J* = 1.1 Hz, 7.4 Hz), 6.92 (dt, 1H, *J* = 1.1 Hz, 7.4 Hz), 7.08 (dt, 1H, *J* = 1.7 Hz, 7.4 Hz), 7.15 (td, 1H, *J* = 1.7 Hz, 7.4 Hz), 7.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.1 (d, *J* = 129 Hz), 46.0, 53.4 (d, *J* = 6 Hz), 116.7, 120.4, 129.0, 131.4, 154.9, 200.7. HRMS (ESI+), Calculated for $C_{11}H_{15}O_5PNa$: 281.0549 (M^+ + Na); Found 281.0555.

Dimethyl (3-(2-(*tert*-butyldimethylsilyloxy)phenyl)-2-oxopropyl)phosphonate 21. To a stirred solution of *tert*-butyldimethylsilyl chloride (4.1 g, 27 mmol), imidazole (2.2 g, 33 mmol), and *N*,*N*-dimethyl-4-aminopyridine (0.13 g, 1.1 mmol) in dimethylformamide (6 mL) was added a solution of phenol **20** (2.8 g, 11 mmol) in dimethylformamide (6 mL) dropwise. The solution was then stirred for 18 h at room temperature and quenched with saturated aqueous sodium bicarbonate (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated sodium chloride (10 mL), dried over sodium sulfate, concentrated *in vacuo*. The crude residue was purified

by flash chromatography using ethyl acetate–hexanes (50 : 50) as eluent to afford the *title compound* **21** (3.22 g, 8.7 mmol, 80%) as a yellow oil. IR spectrum (film), cm^{-1}: 2955, 2858, 1719, 1493, 1255, 1029, 928, 834; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.24 (s, 6H), 0.98 (s, 9H), 3.06 (d, 2H, J = 22.2 Hz), 3.76 (d, 6H, J = 11.2 Hz), 3.82 (s, 2H), 6.83 (dd, 1H, J = 1.1 Hz, 8.6 Hz), 6.94 (td, 1H, J = 1.1 Hz, 7.5 Hz), 7.15–7.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: −4.2, 18.2, 25.7, 39.7 (d, J = 129 Hz), 46.1 (d, J = 2 Hz), 52.8 (d, J = 6 Hz), 118.4, 121.3, 124.7, 128.6, 131.6, 153.8, 199.4 (d, 1H, J = 6 Hz). HRMS, Calculated for $C_{17}H_{29}O_5PSiNa$: 395.1414 (M^+ + Na); Found 395.1411.

(*E*)-4-(3-Bromo-2-(methoxymethoxy)phenyl)-1-(2-(*tert*-butyldimethylsilyloxy)phenyl)but-3-en-2-one 22. A solution of phosphonate **21** (2.7 g, 7.3 mmol) in tetrahydrofuran (30 mL) was added dropwise to a stirred suspension of sodium hydride (0.29 g, 60% in paraffin, 7.3 mmol) in tetrahydrofuran (30 mL) at 0 °C. The mixture was stirred at room temperature for 30 min, after which a solution of aldehyde **17** (1.5 g, 6.0 mmol) in tetrahydrofuran (60 mL) was added. The reaction mixture was stirred at room temperature for 18 h, quenched with saturated ammonium chloride (80 mL) and extracted with ethyl acetate (3 × 120 mL). The combined organic extracts were washed with saturated sodium chloride (100 mL), dried over sodium sulfate and the solvent removed *in vacuo*. The resultant oil was purified by flash chromatography using hexanes–ethyl acetate (90 : 10) as eluent to afford the *title compound* **22** (3.0 g, 6.0 mmol, 100%) as a yellow oil. IR spectrum (film), cm^{-1}: 2954, 2858, 1686, 1602, 1452, 1254, 1157, 922; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.25 (s, 6H), 0.98 (s, 9H), 3.63 (s, 3H), 3.93 (s, 2H), 5.06 (s, 2H), 6.77 (d, 1H, J = 16.1 Hz), 6.86 (dd, 1H, J = 1.1 Hz, 8.6 Hz), 6.94 (td, 1H, J = 1.2 Hz, 7.5 Hz), 7.01 (td, 1H, J = 0.5 Hz, 7.9 Hz), 7.15–7.17 (m, 2H), 7.47 (dd, 1H, J = 1.5 Hz, 6.3 Hz), 7.58 (dd, 1H, J = 1.5 Hz, 7.9 Hz), 7.96 (d, 1H, J = 16.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: −4.1, 18.3, 25.8, 43.6, 58.3, 100.5, 118.3, 118.5, 121.3, 125.4, 125.8, 126.5, 127.0, 128.3, 131.1, 131.4, 135.1, 137.4, 153.9, 154.0, 197.1. HRMS (ESI+), Calculated for $C_{24}H_{31}O_4BrSiK$: 529.0807 (M^+ + K); Found 529.0796.

4-(3-Bromo-2-(methoxymethoxy)phenyl)-1-(2-(*tert*-butyldimethylsilyloxy)phenyl)butan-2-one 23. A solution of enone **22** (2.1 g, 4.3 mmol) in ethyl acetate (210 mL) was hydrogenated using H-Cube® HC-2 continuous hydrogenation apparatus (THALES Nanotechnology Inc.) using a 10% palladium on carbon cartridge at 25 °C and a hydrogen pressure of 30 bar. The solvent was removed *in vacuo* and the resulting crude product was purified *via* flash chromatography using hexanes–ethyl acetate (90 : 10) as eluent to afford the *title compound* 23 (1.6 g, 3.2 mmol, 76%) as a colourless oil. IR spectrum (film), cm^{-1}: 2931, 1714, 1256, 1158, 922; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.23 (s, 6H), 0.98 (s, 9H), 2.75 (t, 2H, J = 8.1 Hz), 2.95 (t, 2H, J = 8.1 Hz), 3.56 (s, 3H), 3.66 (s, 2H), 5.05 (s, 2H), 6.82 (dd, 1H, J = 1.1 Hz, 8.1 Hz), 6.89 (t, 1H, J = 7.7 Hz), 6.90 (td, 1H, J = 1.2 Hz, 7.7 Hz), 6.89–6.94 (m, 2H), 7.14 (td, 1H, J = 1.8 Hz, 7.7 Hz), 7.39 (dd, 1H, J = 1.6 Hz, 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: −4.2, 18.2, 25.1, 25.8, 42.1, 45.1, 57.7, 99.9, 117.4, 118.5, 121.3, 125.4, 125.6, 128.3, 129.5, 131.4, 131.6, 137.1, 153.2, 153.8, 207.3. HRMS (ESI+), Calculated for $C_{24}H_{33}O_4BrSiNa$: 515.1224 (M^+ + Na); Found 515.1227.

8-Bromo-2-(2′-*tert*-butyldimethylsilyloxy)benzyl-2-methoxychroman 24. To a solution of ketone **23** (1.2 g, 2.3 mmol) in methanol–tetrahydrofuran (2 : 3, 14 mL) was added camphorsulfonic acid monohydrate (1.1 g, 4.7 mmol) and the solution was stirred for 22 h. The reaction was quenched with solid sodium bicarbonate (1.0 g) and filtered through a pad of silica, washing with ethyl acetate. The solvent was removed *in vacuo* to afford the *title compound* **24** which was used as crude. A small analytical sample was prepared by filtering the crude through silica and washing with hexanes–ethyl acetate (90 : 10). IR spectrum (film), cm^{-1}: 2942, 1452, 1255, 1034, 835; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.29 (d, 6H, J = 8.5 Hz), 1.07 (s, 9H), 1.67 (td, 1H, J = 6.0 Hz, 13.5 Hz), 2.03 (ddd, 1H, J = 2.0 Hz, 6.0 Hz, 13.5 Hz), 2.53 (ddd, 1H, J = 2.0 Hz, 6.0 Hz, 16.1 Hz), 2.99 (ddd, 1H, J = 6.0 Hz, 13.5 Hz, 16.1 Hz), 3.33 (d, 2H, J = 4.5 Hz), 3.44 (s, 3H), 6.74 (t, 1H, J = 7.5 Hz), 6.84 (dd, 1H, J = 1.3 Hz, 8.9 Hz), 6.94 (td, 1H, J = 1.5 Hz, 7.5 Hz), 6.97 (d, 1H, J = 7.5 Hz), 7.13 (td, 1H, J = 2.0 Hz, 8.9 Hz), 7.37 (d, 1H, J = 7.5 Hz), 7.53 (dd, 1H, J = 2.0 Hz, 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −3.9 (d, 1H, J = 18.6 Hz), 18.5, 21.5, 26.1, 28.1, 34.7, 49.4, 101.4, 111.4, 118.5, 121.3, 124.8, 126.6, 127.7, 128.3, 130.8, 132.6, 149.2, 154.3; HRMS (ESI+), Calculated for $C_{23}H_{31}O_3BrK$: 501.0857 (M^+ + K); Found 501.0868.

8-Bromo-2-(2′-hydroxy)benzyl-2-methoxychroman 26 and 2-(2-(benzofuran-2-yl)ethyl)-6-bromophenol 12. To a solution of crude protected phenol **130** (1.1 g) in acetonitrile (100 mL) was added triethylamine trihydrofluoride (0.77 mL, 2.4 mmol) dropwise. The reaction mixture was stirred at room temperature for 3 days, quenched with saturated sodium bicarbonate (50 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with saturated sodium chloride (100 mL), dried over sodium sulfate and the solvent removed *in vacuo*. The resultant oil was purified by flash chromatography using hexanes–ethyl acetate (90 : 10) as eluent to afford the *title compound* **26** (0.58 g, 1.7 mmol, 72% over two steps) as colourless crystals and benzofuran **25** (100 mg, 0.32 mmol, 14% yield over two steps) as a yellow solid.

8-Bromo-2-(2′-hydroxy)benzyl-2-methoxychroman 26. M. p. 122–124 °C; IR spectrum (film), cm^{-1}: 3441, 2937, 1491, 1452, 1227, 759; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.75 (ddd, 1H, J = 6.2 Hz, 12.5 Hz, 13.8 Hz), 1.99 (ddd, 1H, J = 2.5 Hz, 6.5 Hz, 13.8 Hz), 2.61 (ddd, 1H, J = 2.5 Hz, 6.2 Hz, 16.5 Hz), 2.85 (d, 1H, J = 14.3 Hz), 2.97–3.06 (m, 1H) 3.47 (s, 3H), 3.56 (s, 3H), 3.79 (d, 1H, J = 14.3 Hz), 6.79 (t, 1H, J = 7.9 Hz), 6.88 (td, 1H, J = 1.3 Hz, 7.4 Hz), 6.96 (dd, 1H, J = 1.3 Hz, 7.9 Hz), 6.95–7.00 (m, 1H), 7.10 (dd, 1H, J = 1.6 Hz, 7.4 Hz), 7.14–7.20 (m, 2H), 7.37 (d, 1H, J = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4, 28.2, 38.7, 49.5, 102.8, 111.3, 117.9, 120.7, 122.2, 122.5, 124.6, 128.5, 128.9, 130.8, 132.5, 148.0, 155.1. HRMS (ESI+), Calculated for $C_{17}H_{17}O_3BrK$: 386.9993 (M^+ + K); Found 387.0004.

2-(2-(Benzofuran-2-yl)ethyl)-6-bromophenol 25. M. p. 49–50 °C IR spectrum (film), cm^{-1}: 3441, 2937, 1491, 1452, 1227, 759; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.06–3.14 (m, 4H), 5.62 (s, 1H), 6.37 (s, 1H), 6.71 (t, 1H, J = 7.8 Hz), 7.04 (dd, 1H,

J = 1.5 Hz, 7.8 Hz), 7.19 (m, 2H), 7.32 (dd, 1H, *J* = 1.5 Hz, 7.8 Hz) 7.15–7.23 (m, 1H″), 7.41–7.47 (m, 1H″); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.5, 29.5, 102.5, 110.7, 110.9, 120.4, 121.6, 122.6, 123.4, 128.8, 129.1, 129.9, 130.2, 150.2, 154.8, 158.7; HRMS (ESI+), Calculated for $C_{17}H_{17}O_3BrK$: 386.9993 (M^+ + K); Found 387.0004.

2-(2-(Benzofuran-2-yl)ethyl)-6-bromophenol 25. To a solution of methyl acetal **26** (0.53 g, 1.5 mmol) in dichloromethane (20 mL) was added indium chloride (0.34 g, 1.5 mmol). The resulting slurry was stirred at room temperature for 3 h. The reaction was quenched with solid sodium bicarbonate (0.50 mg) and filtered through a pad of silica, washing with ethyl acetate. The solvent was removed *in vacuo* and the residue was purified by recrystallisation from diethyl ether to afford the *title compounds* **12** (0.39 g, 1.2 mmol, 80%) as colourless crystals. M.p. 127–129 °C; IR spectrum (film), cm^{-1}: 3666, 2978, 1388, 1247, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.14–2.22 (m, 1H), 2.34 (ddd, 1H, *J* = 2.5 Hz, 5.9 Hz, 16.5 Hz), 2.82 (ddd, 1H, *J* = 2.5 Hz, 5.9 Hz, 16.5 Hz), 3.24–3.33 (m, 1H), 3.33 (d, 1H, *J* = 16.6 Hz), 3.59 (d, 1H, *J* = 16.6 Hz), 6.77–6.81 (m, 2H), 6.94 (td, 1H, *J* = 1.0 Hz, 7.5 Hz), 7.08 (d, 1H, *J* = 7.5 Hz), 7.14 (t, 1H, *J* = 8.0 Hz), 7.25 (d, 1H, *J* = 7.0 Hz), 7.37 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.2, 30.5, 41.9, 109.9, 121.3, 121.9, 123.4, 124.9, 125.2, 128.1, 128.3, 131.3, 149.1, 157.7. HRMS (ESI+), Calculated for $C_{16}H_{13}O_2BrNa$: 338.9991 (M^+ + Na); Found 338.9996.

(R_S,2*S*)-8′-(*tert*-Butylsulfinyl)-3*H*-spiro[benzofuran-2,2′-chroman] 2a and (R_S,2*R*)-8′-(*tert*-butylsulfinyl)-3*H*-spiro[benzofuran-2,2′-chroman] 2b. To a solution of bromospiroketal **12** (80 mg, 0.25 mmol) in tetrahydrofuran (0.8 mL) was added *n*-butyllithium (0.14 mL, 2 M in cyclohexane, 0.28 mmol) dropwise at −78 °C. The solution was stirred for 10 min followed by addition of (*R*)-(+)-*tert*-butyl *tert*-butanethiosulfinate (59 mg, 0.30 mmol) in tetrahydrofuran (0.2 mL). The solution was allowed to warm to room temperature over 4 h and then quenched by saturated aqueous ammonium chloride (1 mL). The aqueous layer was extracted using ethyl acetate (3 × 2 mL). The combined organic layers were washed with saturated sodium chloride (3 mL), dried over sodium sulfate and the solvent removed *in vacuo*. The crude product was purified by flash chromatography using dichloromethane–ethyl acetate (85 : 15) eluent to afford the *title compounds* **2a** (25 mg, 0.070 mmol, 29%) and **2b** (21 mg, 0.060 mmol, 24%) separately as colourless crystals.

(R_S,2*S*)-8′-(*tert*-Butylsulfinyl)-3*H*-spiro[benzofuran-2,2′-chroman] 2a. M.p. 135–137 °C; $[\alpha]_D^{20}$: +125 (*c* = 0.44, $CHCl_3$, 97% ee); IR spectrum (film), cm^{-1}: 2972, 2887, 1378, 1089, 1048, 952; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.16 (s, 9H), 2.13–2.21 (m, 1H), 2.35 (ddd, 1H, *J* = 2.5 Hz, 6.0 Hz, 13.4 Hz), 2.87 (ddd, 1H, 2.5 Hz, 6.0 Hz, 16.5 Hz), 3.25–3.41 (m, 1H), 6.78 (d, 1H, *J* = 6.7 Hz), 6.94 (td, 1H, *J* = 0.8 Hz, 7.6 Hz), 7.10 (t, 1H, *J* = 7.6 Hz), 7.16 (t, 1H, *J* = 7.6 Hz), 7.23 (t, 2H, *J* = 6.7 Hz), 7.61 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.0, 23.3, 30.5, 41.8, 57.4, 109.1, 110.2, 121.3, 121.5, 121.9, 124.8 (2C), 125.8, 128.5, 128.6, 132.0, 150.3, 157.8; HRMS (ESI+), Calculated for $C_{20}H_{23}O_3S$: 343.1362 (M^+); Found 343.1350. The enantiomeric excess (98% ee) was determined by HPLC (Chiracel AD-H column, *n*-hexane–propan-2-ol 90 : 10; flow rate 0.5 mL min^{-1}; t_{major} = 36.7 min, t_{minor} = 55.3 min).

(R_S,2*R*)-8′-(*tert*-Butylsulfinyl)-3*H*-spiro[benzofuran-2,2′-chroman] 2b. M.p. 157–158 °C; $[\alpha]_D^{20}$: +347 (*c* = 0.40, $CHCl_3$, 97% ee); IR spectrum (film), cm^{-1}: 2960, 1446, 1229, 1171, 1042, 900; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (s, 9H), 2.20–2.28 (m, 1H), 2.34 (ddd, 1H, *J* = 2.5 Hz, 6.0 Hz, 13.4 Hz), 2.88 (ddd, 1H, 2.5 Hz, 6.0 Hz, 16.5 Hz), 3.25–3.49 (m, 3H), 6.68 (d, 1H, *J* = 6.7 Hz), 6.93 (td, 1H, *J* = 0.8 Hz, 7.5 Hz), 7.10 (m, 2H), 7.24 (t, 2H, *J* = 6.7 Hz), 7.60 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.9, 22.8, 29.9, 41.7, 57.5, 109.1, 109.7, 121.4, 121.6, 121.8, 125.0, 125.2, 125.7, 128.2, 128.4, 132.1, 150.1, 157.8; HRMS (ESI+), Calculated for $C_{20}H_{23}O_3S$: 343.1362 (M^+); Found 343.1350. The enantiomeric excess (97% ee) was determined by HPLC (Chiral-Pak® AD-H column, *n*-hexane–propan-2-ol 90 : 10; flow rate 0.5 mL min^{-1}; t_{minor} = 28.0 min, t_{major} = 55.4 min).

(*S*)-3*H*-Spiro[benzofuran-2,2′-chroman] 27a. A solution of sulfoxide **2a** (5.0 mg, 0.015 mmol) in ethanol (10 mL) was hydrogenated under continuous cycle for 2 h using H-Cube® HC-2 continuous hydrogenation apparatus (THALES Nanotechnology Inc.) using a RANEY® nickel cartridge at 60 °C and a hydrogen pressure of 100 bar. The solvent was removed *in vacuo* and the resulting crude product was filtered through silica using hexanes–ethyl acetate (80 : 20) eluent to afford the *title compound* **27a** (2.8 mg, 0.012 mmol, 80%) as colourless crystals. M.p. 132–134 °C (lit. 71–72 °C, racemic);[11] $[\alpha]_D^{20}$: −218 (*c* = 0.34, $CHCl_3$, 100% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.16–2.24 (m, 1H), 2.34 (ddd, 1H, *J* = 2.7 Hz, 5.9 Hz, 13.4 Hz), 2.83 (ddd, 1H, 2.7 Hz, 5.9 Hz, 16.4 Hz), 3.21–3.31 (m, 2H), 3.45 (d, 1H, *J* = 16.4 Hz), 6.80 (dd, 1H, *J* = 2.5 Hz, 8.1 Hz), 6.92 (t, 1H, *J* = 7.2 Hz, 2H), 7.13 (m, 2H), 7.24 (t, 1H, *J* = 8.1 Hz), 7.60 (d, 1H, *J* = 7.2 Hz). The ^{1}H NMR data obtained was in agreement with that reported in the literature.[11] The enantiomeric excess was determined by HPLC (Chiral-Pak® AD-H column, *n*- hexane–propan-2-ol 90 : 10; flow rate 0.5 mL min^{-1}; t_S = 9.7 min, t_R = 10.2 min).

(*R*)-3*H*-Spiro[benzofuran-2,2′-chroman] 27b. A solution of sulfoxide **2b** (17 mg, 0.050 mmol) in ethanol (3.5 mL) was hydrogenated under continuous cycle for 2 h using H-Cube® HC-2 continuous hydrogenation apparatus (THALES Nanotechnology Inc.) using a RANEY® nickel cartridge at 60 °C and a hydrogen pressure of 100 bar. The solvent was removed *in vacuo* and the resulting crude product was filtered through silica using hexanes–ethyl acetate (80 : 20) eluent to afford the *title compound* **27b** (10 mg, 0.042 mmol, 85%) as colourless crystals. For both enantiomers: m.p. 132–134 °C (lit. 71–72 °C, racemic);[11] $[\alpha]_D^{20}$: +195 (*c* = 0.33, $CHCl_3$, 97% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.16–2.24 (m, 1H), 2.34 (ddd, 1H, *J* = 2.7 Hz, 5.9 Hz, 13.4 Hz), 2.83 (ddd, 1H, 2.7 Hz, 5.9 Hz, 16.4 Hz), 3.21–3.31 (m, 2H), 3.45 (d, 1H, *J* = 16.4 Hz), 6.80 (dd, 1H, *J* = 2.5 Hz, 8.1 Hz), 6.92 (t, 1H, *J* = 7.2 Hz, 2H), 7.13 (m, 2H), 7.24 (t, 1H, *J* = 8.1 Hz), 7.60 (d, 1H, *J* = 7.2 Hz). The ^{1}H NMR data obtained was in agreement with that reported in the literature.[11] The enantiomeric excess was determined by HPLC

(Chiral-Pak® AD-H column, *n*-hexane–propan-2-ol 90 : 10; flow rate 0.5 mL min^{-1}; t_S = 9.7 min, t_R = 10.2 min).

(*R*)-*tert*-Butylsulfinyl benzene 29. To a solution of bromobenzene (0.55 mL, 5.0 mmol) in tetrahydrofuran (5 mL) was added *n*-butyllithium (2.8 mL, 2 M in hexanes, 5.5 mmol) dropwise at −78 °C. The solution was stirred for 20 min followed by addition of (*R*)-(+)-*tert*-butyl *tert*-butanethiosulfinate (1.0 g, 5.5 mmol). The solution was allowed to warm to room temperature over 2 h then quenched with saturated aqueous ammonium chloride (5 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated sodium chloride (10 mL), dried over sodium sulfate and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography using hexanes–ethyl acetate (50 : 50) as eluent to afford the *title compound* **29** (0.73 g, 4.0 mmol, 80%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (s, 9H), 7.48–7.50 (m, 3H), 7.58–7.61 (m, 2H). The ^{1}H NMR data obtained was in agreement with that reported in the literature.[16]

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