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Tetrahedron 61 (2005) 6860–6870
Tetrahedron

Inter- and intramolecular Mitsunobu reaction based approaches to 2-substituted chromans and chroman-4-ones

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Received 16 February 2005; revised 5 April 2005; accepted 21 April 2005

Abstract—Two approaches to optically active 2-substituted chromans and chroman-4-ones are described. The first utilized an intermolecular Mitsunobu reaction of a homochiral halopropanol and 2-bromophenol followed by cyclization to the 2-substituted chroman. In addition, a double lithiation procedure was developed to introduce additional functionality to the chroman. The second approach utilized an intramolecular Mitsunobu cyclization to give the 2-substituted chroman-4-one nucleus. The methodologies were applied to the syntheses of several biologically active natural and synthetic products.

1. Introduction

2-Substituted chromans (benzopyrans) are widely distributed in nature and many show significant biological activity.[1] Examples include α-tocopherol (vitamin E) (**1**),[2] the antibiotic LLD253α (**2**)[3] and the aromatase inhibitor pinostrobin (**3**).[4] In addition, chromans are valued as targets in their own right and several biologically active synthetic chromans have been reported. For example, racemic 4′,6-dichloroflavan (BW683C) (**4**) is a potent in vitro inhibitor of rhinovirus replication (Fig. 1).[5]

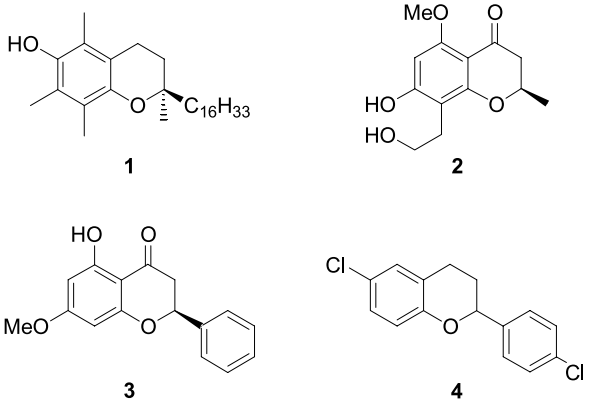
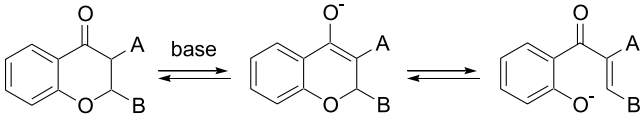


Figure 1.

While there is extensive literature precedent for the synthesis of chromans and chroman-4-ones, few are amenable to the synthesis of single enantiomers. Knight[6a] has reported an approach to 2-substituted chromans based on the intramolecular trapping by alcohols of benzynes generated from 7-substituted-1-aminobenzotriazoles and Sames has developed a method based on a Ruthenium catalyzed cyclization of an arene–alkene substrate.[6b] Routes to 2-substituted chroman-4-ones include the diastereoselective conjugate addition of cuprates to homochiral 3-(*p*-tolylsulfinyl)chromanones described by Wallace[7] and an approach based on the Houben–Hoesch reaction.[8] The synthesis of related 2-substituted chromenes[9] and chromanols[10] has also been reported. Notwithstanding these examples, the preparation and manipulation of substituted chroman-4-ones can be problematic, due in part to the ease with which they undergo racemization via the ring-opening equilibrium shown in Scheme 1.[11]



Scheme 1.

With this in mind, we have evaluated two approaches to 2-substituted chromans and chromanones in which inter- and intramolecular Mitsunobu reactions are key steps (Scheme 2).[12] In the first, halogen–metal exchange of the aryl bromide **6** and subsequent cyclization, should give the chroman **5**.[13] The stereocenter to be located at the 2-position could be installed by a Mitsunobu[14] inversion reaction

Keywords: Mitsunobu; Cyclization; Chroman; Chromanone.
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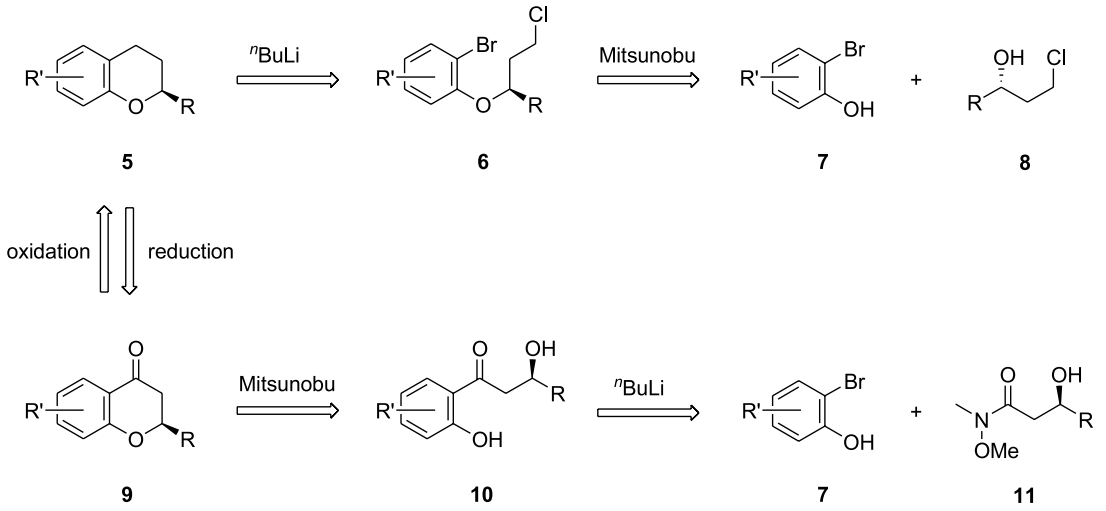
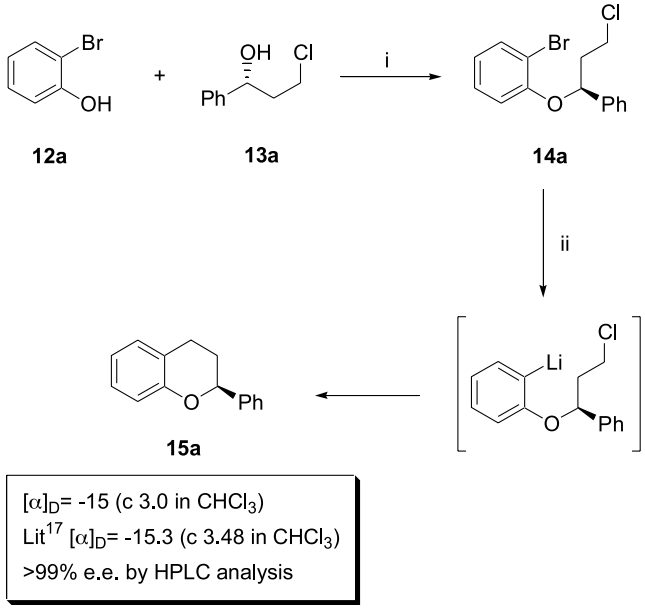
doi:10.1016/j.tet.2005.04.047



Scheme 2.

between the 2-bromophenol **7** and the appropriately substituted chiral halopropanol **8**. Alternatively, intermolecular Mitsunobu cyclization of the chiral hydroxyphenol **10** should give the chromanone **9**. The hydroxyphenol **10** should be accessible from the 2-bromophenol **7** and the appropriately substituted Weinreb amide **11**. In this paper, we report our results in full detail.[12]

Commercially available (*R*)-3-chloro-1-phenyl-1-propanol (**13a**)[15] was treated with 2-bromophenol (**12**) under standard Mitsunobu[14] inversion conditions and gave, following chromatography, the (*S*)-phenyl ether **14a** in 78% yield (Scheme 3). Initially **14a** was subjected to the cyclization conditions originally described by Parham, but these lead to only moderate yields of the 2-phenylchroman (**15a**). Optimal conditions for the Parham cyclization were found to be a modified version of those recently described by Spoors[16] for the cyclization of 2-(*o*-bromophenoxy)ethyl bromides to benzodihydrofurans; addition of **14a** to 1 equiv of *n*-butyllithium in THF at −50 °C and allowing the reaction to warm to room temperature. Under these conditions, (2*S*)-phenylchroman (**15a**), $[\alpha]_D = -15$ (*c* 3.0 in $CHCl_3$) [lit[17] $[\alpha]_D = -15.3$ (*c* 3.48 in $CHCl_3$)] was obtained in 83% yield. The sign and magnitude of rotation confirmed that the Mitsunobu reaction occurred with inversion and the cyclization without significant racemization. A single recrystallization from methanol gave enantiomerically pure material by HPLC analysis.[18]

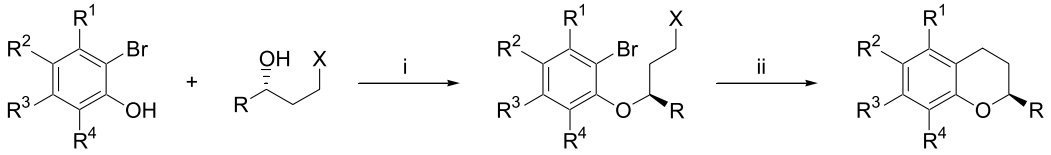


Scheme 3. Reaction conditions: (i) PPh_3, DEAD, THF, RT, 18 h, (78%) (ii) ^{n}BuLi, THF, −50 °C to RT (83%).

In order to investigate the utility of the methodology, a variety of commercially available substituted bromophenols **12a–f** were studied in the reaction with (*R*)-3-chloro-1-phenyl-1-propanol (**13a**) (Table 1). The Mitsunobu reaction and cyclization all proceeded in good yields to furnish the (2*S*)-phenyl chromans **15b**, **15c**, **15d**, and **15f**, respectively. Tephrowatsin E (**15f**) was previously isolated from the aerial parts of *Tephrosia watsoniana*.[19] The spectral properties of the synthetic sample were in close agreement with the reported spectral data.[19] The phenyl substituent at the 2-position could be replaced by an alkyl group. For example, repeating the sequence with 2-bromophenol (**12**) and (*S*)-4-bromobutane-2-ol (**13e**)[20] gave (2*R*)-methylchroman (**15e**) in 54% yield and 97% e.e.[18] over the two steps (entry e).

To extend the synthetic utility of the methodology a one-pot cyclization and in situ functionalization of the chroman ring was investigated.[21] The 2,4-dibromo ether **16** was prepared by Mitsunobu reaction as described previously. Halogen–metal exchange was expected to be selective for the bromide adjacent to the ether and this proved to be the case. Addition of **16** to 1 equiv of *n*-butyllithium, in THF at −50 °C and allowing the reaction to warm to room temperature gave the cyclized product, 6-bromo-2-phenylchroman (**17a**) in 84% yield, thereby confirming the selectivity for the *ortho*-bromide. The reaction was repeated, but when the cyclization was judged to be complete, the reaction mixture was re-cooled to −50 °C and the second bromide was exchanged by further addition of *n*-butyllithium. The resultant chromanyl lithium was then quenched by the addition of an excess of an electrophile. A range of electrophiles were screened in the process (entries b, c, d,

Table 1. Reaction conditions: (i) PPh_3, DEAD, THF, RT, 8–36 h; (ii) ^{n}BuLi, THF, −50 °C to RT



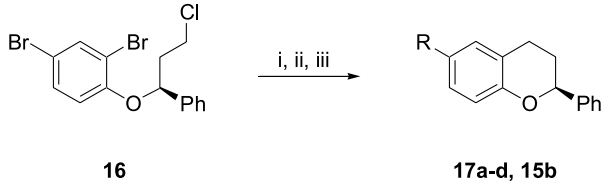
12 **13** **14 a-f** **15 a-f**

Entry	R^1	R^2	R^3	R^4	R	X	Yield **14** (%)	Yield **15** (%)
a	H	H	H	H	Ph	Cl	78	83
b	H	Me	H	H	Ph	Cl	82	77
c	H	Cl	H	H	Ph	Cl	81	78
d	–(CH)$_4$–		H	H	Ph	Cl	64	74
e	H	H	H	H	Me	Br	67	81
f	MeO	H	MeO	H	Ph	Cl	76	78

and e, Table 2) and gave moderated to good yields of the corresponding 6-carbaldehyde **17b**, 6-carboxylic acid **17c**, 6-hydroxymethyl **17d**, and 6-methyl **15b** analogues.

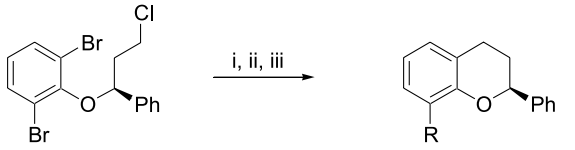
The sequence outlined in Table 2 was repeated with the 2,6-dibromoether **18**. Treatment of the dibromide **18** with 1 equiv of *n*-butyllithium followed by aqueous work-up gave the expected 8-bromo-2-phenylchroman (**19**) in 79% yield. Repeating the reaction, but when the cyclization was judged to be complete, the reaction mixture was re-cooled to −50 °C and *n*-butyllithium was added followed by an excess of DMF. This time 8-carbaldehyde-2-phenylchroman (**20**) was isolated in 76% yield (Scheme 4). The double lithiation procedure allows the introduction of a variety of functional groups to the chroman that would not normally be compatible with the conditions of the original cyclization.

Table 2. Reagents and conditions: (i) ^{n}BuLi, THF, −50 °C to RT, 2 h; (ii) −50 °C, ^{n}BuLi, 30 min; (iii) electrophile (4–6 equiv), −50 °C to RT



16 **17a-d, 15b**

Entry	Electrophile	Product	R	Yield (%)
a	None	**17a**	Br	84
b	DMF	**17b**	CHO	81
c	CO_2 (g)	**17c**	CO_2H	78
d	$(CH_2O)n$	**17d**	CH_2OH	57
e	MeI	**15b**	Me	80



18

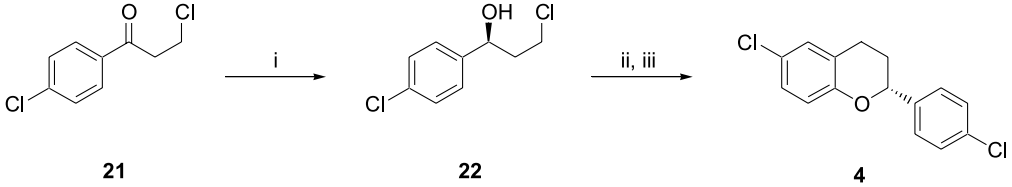
19 R = Br (79%)
20 R = CHO (76%)

Scheme 4. Reagents and conditions: (i) ^{n}BuLi, THF, −50 °C to RT, 2 h; (ii) −50 °C, ^{n}BuLi, 30 min; (iii) electrophile (4–6 equiv), −50 °C to RT.

Racemic BW683C (**4**) is a potent in vitro inhibitor of rhinovirus replication and was previously isolated in enantiomerically pure form following preparative HPLC using the chiral stationary phase cellulose tris(3,5-dimethylphenylcarba-mate).[25]

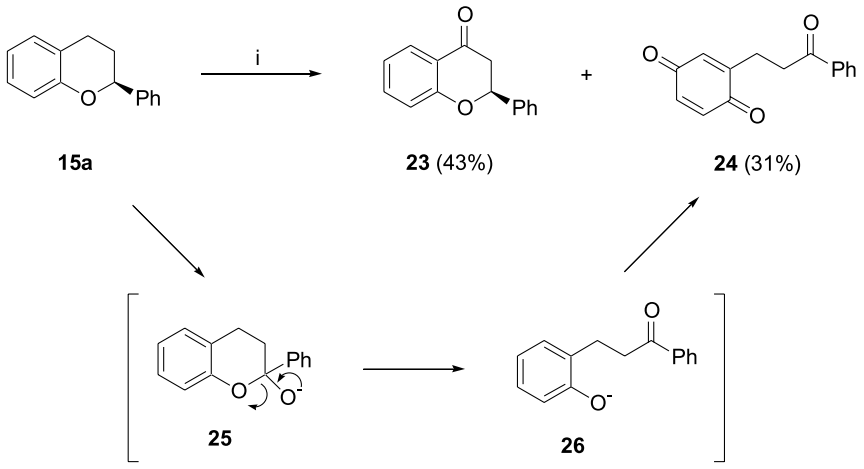
The range of potential substituents located at the chroman 2-position can be extended by taking advantage of the asymmetric reduction of suitable prochiral ketones,[22] as exemplified by the synthesis of enantiomerically pure (*R*)-4′,6-dichloroflavan (**4**) (Scheme 5). Catalytic asymmetric reduction of 3,4′-dichloropropiophenone (**21**) with (*R*)-oxazaborolidine and borane, under the conditions described by Corey,[23] gave (*S*)-3-chloro-1-(4-chlorophenyl)-1-propanol (**22**) in 91% yield and 94% ee as judged by ^{1}H NMR analysis of the MTPA (Mosher) ester.[24] Mitsunobu reaction of **22** with 2-bromo-4-chlorophenol followed by treatment with 1 equiv of *n*-butyllithium under the standard cyclization conditions gave, following recrystallization from methanol, enantiomerically pure BW683C (**4**).[18]

2-Substituted chroman-4-ones such as LLD253α (**2**)[3] and pinostrobin (**3**)[4] were also targets for our work. The most direct route appeared to be the oxidation of a chiral 2-substituted chroman to the corresponding chroman-4-one. Several methods for benzylic oxidation are known in the



21 **22** **4**

Scheme 5. Reaction conditions: (i) BH_3, (*R*)-oxazaborolidine, THF, 0 °C, 91%; (ii) 2-bromo-4-chlorophenol, PPh_3, DEAD, THF, RT, 16 h (85%); (iii) ^{n}BuLi, THF, −50 °C to RT (78%).



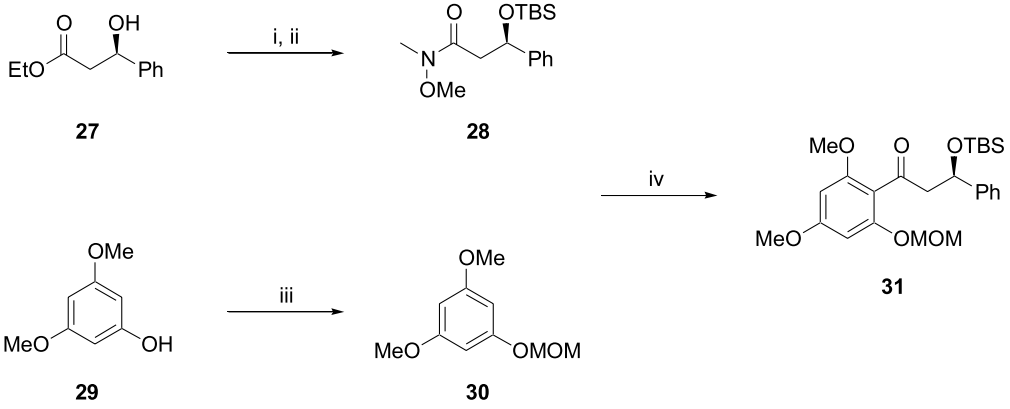
Scheme 6. Reaction conditions: (i) H_5IO_6, CrO_3 (cat), CH_3CN, RT.

literature, these include (i) catalytic chromium(VI) oxide in the presence of periodic acid,[26] (ii) copper sulfate and peroxydisulfate,[27] and (iii) cerium ammonium nitrate in acetic acid.[28] (2*S*)-Phenyl chroman (**15a**)[29] was subjected to the above sets of conditions, but unfortunately yields of the desired 2-phenyl chroman-4-one (**23**)[30] were low and complicated by competing processes. For example, treatment of **15a** with 2 equiv of periodic acid and 5 mol% chromium(VI) oxide in acetonitrile at room temperature gave the desired (2*S*)-phenyl chroman-4-one (**23**) in a moderate 43% yield accompanied by a significant amount of the quinone **24**. The magnitude of rotation of **23** indicated that the oxidation had proceeded without significant racemization. The quinone **24** was presumably formed by competing oxidation at the benzylic chroman-2-position, ring-opening to the phenol **26**, and finally oxidation to the quinone **24** (Scheme 6). The moderate isolated yields in the oxidation step prompted the investigation of an alternative route to 2-substituted chroman-4-ones.

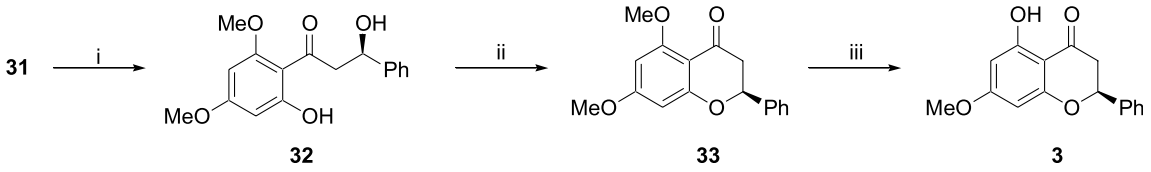
We next investigated an approach to 2-substituted chroman-4-ones based on an intermolecular Mitsunobu cyclization[31] (Scheme 2) and pinostrobin (**3**) was chosen as the target. Pinostrobin (**3**) has been isolated from several natural sources[4] and has also been shown to inhibit aromatase, a cytochrome P450 enzyme converting C19 androgens such as androstenedione and testosterone to estrone and estradiol, respectively.[32] This mode of action could prevent the development of estrogen related tumors such as breast and prostate cancer.[33] In addition, pinostrobin (**3**) has been isolated from *T. graveolens*, a plant used in traditional Mexican medicine for the treatment of gastrointestinal ailments such as diarrhea and stomach pain.[34] It was recently demonstrated that pinostrobrin (**3**) was an active ingredient in *T. graveolens* and inhibited intestinal smooth muscle contractions by a calcium-mediated mechanism.[35] The interesting biological activity made pinostrobin (**3**) an attractive target for synthesis.

The key fragments, Weinreb amide **28** and the methoxymethyl (MOM) protected phenol **30**, were readily prepared from commercially available starting materials. Ethyl (*R*)-3-hydroxy-3-phenylpropanoate (**27**)[36] was protected as the *tert*-butyldimethylsilyl (TBS) ether and then converted into the Weinreb amide **28** (Scheme 7).[37] 3,5-Dimethoxyphenol (**29**) was protected as the MOM ether **30** using standard conditions. The MOM ether **30** was *ortho*-lithiated by treatment with *tert*-butyllithium[31c] in toluene at −78 °C and the Weinreb amide **28** then added to produce the ketone **31** in 72% yield (based on the amide **28**).

The protecting groups on **31** were conveniently cleaved by treatment with 10% *p*=*via*-TsOH in aqueous THF, which gave the hydroxyphenol **32** (Scheme 8). Intramolecular



Scheme 7. Reaction conditions: (i) TBSCl, imidazole, CH_2Cl_2 (94%); (ii) MeONHMe·HCl, Me_3Al, CH_2Cl_2 (82%); (iii) CH_3OCH_2Cl, K_2CO_3, DMF (94%); (iv) ^{t}BuLi, PhMe, −78 °C then **28** (0.5 equiv) (72%).



Scheme 8. Reaction conditions (i) *p*-TsOH (10%), THF/H_2O (9:1), 55 °C (86%); (ii) PPh_3, DEAD, THF, 0 °C (88%); (iii) $AlCl_3$, CH_3CN, reflux (79%).

Mitsunobu cyclization of **32** gave an 88% yield of dimethylpinocembrin **33**.[38] The intramolecular Mitsunobu reaction has been used by several groups to prepare 6- and 7-membered cyclic ethers, but we believe this to be the first example of the formation of an optically active 2-substituted chroman-4-one via such an approach.[31] Regioselective demethylation of **33** with aluminum chloride gave, following chromatography, (−)-pinostrobin (**3**) $[\alpha]_D = -48$ ($c=1$ in $CHCl_3$) [lit.[4a] $[\alpha]_D = -52.7$ ($c=1$ in $CHCl_3$)].

In conclusion, we have developed a two-step synthesis of 2-substituted chromans utilizing an intermolecular Mitsunobu reaction and an aryl lithium cyclization as key steps. In addition, a double lithiation procedure was developed to introduce additional functionality into the chroman. Oxidation of 2-phenyl chroman to the corresponding chroman-4-one was possible, but complicated by competing reactions at the benzylic 2-positon. A route to 2-substituted chroman-4-ones was also developed that featured an intramolecular Mitsunobu reaction as the key step. The methodologies were applied to the synthesis of the natural products tephrowatsin E (**15f**) and pinostrobin (**3**) and a biologically active synthetic compound BW683 (**4**).

2. Experimental

2.1. General methods

Melting points were determined using a Thomas–Hoover capillary melting apparatus and are uncorrected. Elemental analyses were performed at Robertson Microlabs, Madison, NJ, USA, and are within 0.4% of theoretical C, H, and N. ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform (unless otherwise noted) with tetramethylsilane as the internal standard on a Varian Unity 400 MHz spectrometer. Coupling constants (J values) are quoted to the nearest 0.5 Hz. Mass spectra were recorded on a VG 70SE magnetic sector mass spectrometer. Chiral HPLC analyses were recorded on a CHIRALCEL®OJ-R (4.6 mm×150 mm) column with methanol as the mobile phase and a flow rate of 0.6 mL/min.

Starting materials and solvents were routinely purified by conventional techniques[39] and most reactions were carried out under a nitrogen atmosphere. Organic solutions were dried using anhydrous magnesium sulfate and concentrated by rotary evaporation. Analytical thin layer chromatography (TLC) was carried out on Camlab Polygram SIL G/UV_{254} plates. The chromatograms were visualized by UV light or suitable developing agent. Unless otherwise stated, preparative column chromatography was carried out on 60H silica gel (Merck 9385) using the flash technique.[40] Compositions of solvent mixtures are quoted as ratios of volume.

2.1.1. (*S*)-1-Bromo-2-(3-chloro-1-phenylpropoxy)-benzene (14a). To a stirred solution of triphenylphosphine (1.52 g, 5.8 mmol) and diethyl azodicarboxylate (1.02 g, 5.8 mmol) in THF (10 mL) at 0 °C was added a solution of 2-bromophenol (**12**) (1.0 g, 5.8 mmol) and (*R*)-3-chloro-1-phenyl-1-propanol (**13**) (1.0 g, 5.8 mmol) in THF (5 mL). The mixture was allowed to return to room temperature and stirred overnight or until the reaction was complete by TLC. The THF was removed by evaporation, the residue triturated with hexane (3×50 mL) and the combined hexane fractions concentrated. Flash chromatography of the residue, eluting with hexane, gave the title compound (1.48 g, 78%) as a colorless oil: $[\alpha]_D^{22}+73$ (c 3.0, $CHCl_3$); δ_H (400 MHz) 2.25–2.33 (1H, m), 2.54–2.62 (1H, m), 3.70 (1H, quintet, $J=$ 5.5 Hz), 3.92–3.99 (1H, m), 5.48 (1H, dd, $J=4.5$, 9.0 Hz), 6.74–6.81 (2H, m), 7.09 (1H, t, $J=8$ Hz), 7.32–7.45 (5H, m), 7.55 (1H, d, $J=7.5$ Hz); δ_C (100 MHz) 41.27, 41.31, 77.79, 112.63, 115.01, 122.01, 125.80, 128.02, 128.19, 128.79, 133.25, 140.15, 154.08; EI-LRMS m/z (relative intensity) 326 and 324 (5%), 153 (95), 117 (48), 91 (100); EI-HRMS calcd. for $C_{15}H_{14}^{81}BrClO$ 325.9896, found 325.9893.

2.1.2. (*S*)-2-Bromo-1-(3-chloro-1-phenylpropoxy)-4-methyl-benzene (14b). The ether **14b** was prepared using the same procedure and scale as described for **14a** but using 2-bromo-4-methylphenol. Flash chromatography of the residue, eluting with hexane, gave the title compound (82%) as a colorless oil: $[\alpha]_D^{22}+22$ (c 1.0, $CHCl_3$); δ_H (400 MHz) 2.23 (3H, s), 2.25–2.32 (1H, m), 2.52–2.61 (1H, m), 3.69 (1H, quintet, $J=5.5$ Hz), 3.92–3.98 (1H, m), 5.43 (1H, dd, $J=4.0$, 8.5 Hz), 6.64 (1H, d, $J=8.5$ Hz), 6.88 (1H, d, $J=8.5$ Hz), 7.30–7.44 (6H, m); δ_C (100 MHz) 20.05, 41.29, 77.92, 112.92, 114.95, 125.87, 127.95, 128.60, 128.73, 131.71, 133.61, 140.33, 151.92 (one signal obscured, 41.29); Anal. $C_{16}H_{16}BrClO$ requires: C, 56.58; H, 4.75. Found: C, 56.79; H, 4.90%.

2.1.3. (*S*)-2-Bromo-4-chloro-1-(3-chloro-1-phenylpropoxy)-benzene (14c). The ether **14c** was prepared using the same procedure and scale as described for **14a** but using 2-bromo-4-chlorophenol. Flash chromatography of the residue, eluting with hexane, gave the title compound (81%) as a colorless oil: $[\alpha]_D^{22}$ −34 (c 1.0, $CHCl_3$); δ_H (400 MHz) 2.22–2.30 (1H, m), 2.51–2.60 (1H, m), 3.66 (1H, quintet, $J=5.5$ Hz), 3.88–3.94 (1H, m), 5.41 (1H, dd, $J=$ 4.0, 8.5 Hz), 6.64 (1H, d, $J=9.0$ Hz), 7.03 (1H, dd, $J=2.5$, 9.5 Hz), 7.31–7.33 (1H, m), 7.37–7.38 (4H, M), 7.52 (1H, d, $J=2.5$ Hz); δ_C (100 MHz) 41.17, 78.23, 113.12, 115.63, 125.82, 126.25, 128.05, 128.25, 128.91, 132.74, 139.65,

152.93 (one signal obscured, 41.17); Anal. $C_{15}H_{13}BrCl_2O$ requires: C, 50.03; H, 3.64. Found: C, 49.81; H, 3.79%.

2.1.4. 2-((1*S*)-3-Chloro-1-phenylpropoxyl)-1-bromonaphthalene (14d). The ether **14d** was prepared using the same procedure and scale as described for **14a** but using 2-bromo-1-naphthol. Flash chromatography of the residue, eluting with hexane, gave the title compound (64%) as a white solid, mp 101 °C: $[\alpha]_D^{22}$ −120 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.29–2.37 (1H, m), 2.59–2.68 (1H, m), 3.71 (1H, quintet, J=5.5 Hz), 3.96–4.02 (1H, m), 5.60 (1H, dd, J=4.0, 8.5 Hz), 7.06 (1H, d, J=9.0 Hz), 7.29 (1H, d, J=8.0 Hz), 7.34–7.39 (3H, m), 7.44–7.46 (2H, M), 7.55 (1H, t, J=8.0 Hz), 7.61 (1H, d, J=9 Hz), 7.70 (1H, d, J=8 Hz), 8.23 (1H, d, J=8.5 Hz); δ_C (100 MHz) 41.33, 41.39, 78.59, 109.91, 116.07, 124.46, 126.08, 126.19, 127.62, 127.96, 128.16, 128.60, 128.85, 129.89, 133.12, 140.26, 152.14; EI-LRMS 376 and 374 (4%), 222 (86), 193 (10), 153 (22), 117 (20), 91 (100); EI-HRMS calcd. for $C_{19}H_{16}^{79}BrClO$ 374.0072, found 374.0069; Anal. $C_{19}H_{16}BrClO$ requires: C, 60.74; H, 4.29. Found: C, 60.70; H, 4.10%.

2.1.5. (*R*)-1-Bromo-2-(3-bromo-1-methylpropoxy)-benzene (14e). The ether **14e** was prepared using the same procedure and scale as described for **14a** but using 2-bromophenol and (*S*)-4-bromobutane-2-ol. Flash chromatography of the residue, eluting with hexane, gave the title compound (67%) as a colorless oil: $[\alpha]_D^{22}$ −102 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 1.37 (3H, d, J=6 Hz), 2.10–2.18 (1H, m), 2.34–2.43 (1H, m), 3.56–3.69 (2H, m), 4.61–4.66 (1H, m), 6.84 (1H, d, J=8 Hz), 6.98 (1H, d, J=8 Hz), 7.26 (1H, t, J=8 Hz), 7.54 (1H, *d*, J=8 Hz); δ_C (100 MHz) 19.45, 29.81, 39.60, 73.68, 113.57, 115.52, 122.21, 128.41, 133.50, 154.35; EI-LRMS 310, 308 and 306 (48%), 174 (100), 55 (50); EI-HRMS calcd. for $C_{10}H_{12}^{79}Br_2O$ 305.9255, found 305.9252.

2.1.6. (*S*)-2-Bromo-1-(3-chloro-1-phenylpropoxy)-3,5-dimethoxy-benzene (14f). The ether **14f** was prepared using the same procedure and scale as described for **14a** but using 2-bromo-3,5-dimethoxyphenol. Flash chromatography, eluting with hexane–ether (4:1), gave the title compound (76%) as a white solid, mp 66–67 °C: $[\alpha]_D^{22}$+56 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.21–2.27 (1H, m), 2.51–2.57 (1H, m), 3.62 (3H, s), 3.63–3.69 (1H, m), 3.84 (3H, s), 3.87–3.95 (1H, m), 5.40 (1H, dd, J=4.5, 8.5 Hz), 5.99 (1H, d, J=2.5 Hz), 6.10 (1H, d, J=2.5 Hz), 7.26–7.30 (1H, m), 7.33–7.40 (4H, m); δ_C (100 MHz) 41.19, 41.30, 55.24, 56.23, 78.00, 92.09, 93.11, 94.33, 125.80, 128.01, 128.78, 140.26, 155.62, 157.34, 159.98; EI-LRMS 386 and 384 (10%), 234 (75), 153 (20), 117 (15), 91 (100); EI-HRMS calcd. for $C_{17}H_{18}^{79}BrClO_3$ 384.0127, found 384.0130; Anal. $C_{17}H_{18}BrClO_3$ requires: C, 52.94; H, 4.70. Found: C, 53.11; H, 4.55%.

2.1.7. (*S*)-3,4-Dihydro-2-phenyl-2*H*-1-benzopyran (15a). To a stirred solution of *n*-butyllithium in hexane (2.5 M, 4.0 mL, 10.0 mmol) in THF (30 mL) at −50 °C was added dropwise a solution of (*S*)-1-bromo-2-(3-chloro-1-phenylpropoxy)-benzene (**14a**) (3.0 g, 9.2 mmol) in THF (8 mL). The mixture was stirred at −50 °C for 2 h and allowed to warm to room temperature over 2 h. The reaction was quenched by pouring into saturated aqueous ammonium chloride (40 mL). The mixture was extracted with ethyl acetate (3×75 mL), and the combined extracts washed with water (50 mL), brine (50 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane, gave the title compound (1.6 g, 83%) as a white solid, mp 52 °C (MeOH): $[\alpha]_D^{22}$ −15 (*c* 3.0, $CHCl_3$); δ_H (400 MHz) 2.10–2.20 (1H, m), 2.24–2.30 (1H, m), 2.85 (1H, dt, J=2.5, 16.5 Hz), 3.01–3.09 (1H, m), 5.12 (1H, dd, J=2.5, 10.0 Hz), 6.92–7.00 (2H, m), 7.14–7.21 (2H, m), 7.38–7.40 (1H, m), 7.43–7.50 (4H, m); δ_C (100 MHz) 25.09, 29.90, 77.68, 116.88, 120.27, 121.77, 125.94, 127.29, 127.76, 128.46, 129.48, 141.70, 155.08; FAB-LRMS 210 (100%), 117 (30); FAB-HRMS calcd. for $C_{15}H_{14}O$ 210.1044, found 210.1042; Anal. $C_{15}H_{14}O$ requires: C, 85.68; H, 6.71. Found: C, 85.41; H, 6.66%.

2.1.8. (*S*)-3,4-Dihydro-6-methyl-2-phenyl-2*H*-1-benzopyran (15b). The benzopyran **15b** was prepared using the same procedure and scale as described for **15a** but using (*S*)-2-bromo-1-(3-chloro-1-phenylpropoxy)-4-methyl-benzene (**14b**) and gave the title compound as a colorless oil (77%), $[\alpha]_D^{22}$ −18 (*c* 3.0, $CHCl_3$); δ_H (400 MHz) 2.07–2.16 (1H, m), 2.20–2.26 (1H, m), 2.31 (3H, s), 2.76 (1H, dt, J=4.5, 16.5 Hz), 2.95–3.04 (1H, m), 5.12 (1H, dd, J=2.0, 10.0 Hz), 6.86 (1H, d, J=8.0 Hz), 6.94–6.98 (2H, m), 7.35–7.37 (1H, m), 7.40–7.47 (4H, m); δ_C (100 MHz) 20.47, 25.02, 30.03, 77.65, 116.63, 121.43, 125.96, 127.72, 127.92, 128.46, 129.41, 129.83, 141.86, 152.90; FAB-LRMS 224 (100%), 117 (24); FAB-HRMS calcd. for $C_{16}H_{16}O$ 224.1201, found 224.1197.

2.1.9. (*S*)-6-Chloro-3,4-dihydro-2-phenyl-2*H*-1-benzopyran (15c). The benzopyran **15c** was prepared using the same procedure and scale as described for **15a** but using (*S*)-2-bromo-4-chloro-1-(3-chloro-1-phenylpropoxy)-benzene (**14c**) and gave the title compound as white crystals (78%), mp 54 °C; $[\alpha]_D^{22}$ −12 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.03–2.13 (1H, m), 2.19–2.26 (1H, m), 2.77 (1H, dt, J=4.5, 16.5 Hz), 2.93–3.01 (1H, m), 5.06 (1H, d, J=10.0 Hz), 6.85 (1H, d, J=8.0 Hz), 7.08–7.10 (2H, m), 7.34–7.39 (1H, m), 7.40–7.42 (4H, m); δ_C (100 MHz) 24.90, 29.44, 77.83, 118.22, 123.38, 124.97, 125.91, 127.30, 127.94, 128.55, 129.03, 141.25, 153.72; FAB-LRMS 244 (100%), 209 (20), 117 (26); FAB-HRMS calcd. for $C_{15}H_{13}ClO$ 244.0655, found 244.6419; Anal. $C_{15}H_{13}ClO$ requires: C, 73.62; H, 5.35. Found: C, 73.75; H, 5.39%.

2.1.10. (*S*)-3,4-Dihydro-2-phenyl-2*H*-naphtho[1,2-*b*]-pyran (15d). The benzopyran **15d** was prepared using the same procedure and scale as described for **15a** but using 2-((1*S*)-3-chloro-1-phenylpropoxyl)-1-bromonaphthalene (**14d**) and gave the title compound as a white solid (74%), mp 73 °C; $[\alpha]_D^{22}$+34 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.26–2.34 (1H, m), 2.41–2.47 (1H, m), 3.19–3.23 (2H, m), 5.18 (1H, d, J=10.0 Hz), 7.26 (1H, d, J=9 Hz), 7.42–7.51 (4H, m), 7.55–7.60 (3H, m), 7.73 (1H, d, J=9 Hz), 7.88 (2H, t, J=9.5 Hz); δ_C (100 MHz) 21.62, 29.62, 77.38, 113.52, 119.14, 121.90, 123.22, 126.00, 126.28, 127.72, 127.80, 128.38, 128.47, 128.95, 132.97, 141.49, 152.62; FAB-LRMS 260 (100%), 157 (26), 117 (85), 91 (26); FAB-HRMS calcd. for $C_{19}H_{16}O$ 260.1201, found 260.1204; Anal. $C_{19}H_{16}O$ requires: C, 87.66; H, 6.19. Found C, 87.34; H, 5.94%.

2.1.11. (*R*)-3,4-Dihydro-2-methyl-2*H*-1-benzopyran (15e). The benzopyran **15e** was prepared using the same procedure and scale as described for **15a** but using (*R*)-1-bromo-2-(3-bromo-1-methylpropoxy)-benzene (**14e**) and gave the title compound as a colorless oil (81%), $[\alpha]_D^{22}+89$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 1.42 (3H, d, $J=6.5$ Hz), 1.69–1.79 (1H, m), 1.98–2.04 (1H, m), 2.73–2.79 (1H, m), 2.84–2.93 (1H, m), 4.14–4.18 (1H, m), 6.81–6.87 (2H, m), 7.06–7.12 (2H, m); δ_C (100 MHz) 21.32, 24.81, 29.20, 72.08, 116.63, 119.91, 121.75, 127.10, 129.48, 154.99; FAB-LRMS 121 (20%), 107 (55), 89 (66), 77 (75); Anal. $C_{10}H_{12}O$ requires: C, 81.04; H, 8.16. Found: C, 81.31; H, 8.86%.

2.1.12. (*S*)-3,4-Dihydro-5,7-dimethoxy-2-phenyl-2*H*-1-benzopyran (15f). The benzopyran **15f** was prepared using the same procedure and scale as described for **15a** but using (*S*)-2-bromo-1-(3-chloro-1-phenylpropoxy)-3,5-dimethoxy-benzene (**14f**) and flash chromatography, eluting with hexane–ether (4:1), gave the title compound as a colorless oil (78%), $[\alpha]_D^{22}-9$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.05–2.14 (1H, m), 2.23–2.29 (1H, m), 2.69–2.77 (1H, m), 2.81–2.87 (1H, m), 3.83 (3H, s), 3.86 (3H s), 5.05 (1H, dd, $J=2.5$, 10.0 Hz), 6.18 (1H, d, $J=2.5$ Hz), 6.24 (1H, d, $J=2.5$ Hz), 7.39–7.52 (5H, m); δ_C (100 MHz) 19.14, 29.46, 55.12, 55.23, 77.64, 91.27, 93.36, 103.26, 125.92, 127.65, 128.35, 141.62, 156.22, 158.46, 159.30; FAB-LRMS 270 (100%), 167 (50), 91 (24); FAB-HRMS calcd. for $C_{17}H_{18}O_3$ 270.1256, found 270.1273.

2.1.13. (*S*)-2,4-Dibromo-1-(3-chloro-1-phenylpropoxy)-benzene (16). The ether **16** was prepared using the same procedure and scale as described for **14a** but using 2,4-dibromophenol. Flash chromatography of the residue, eluting with hexane, gave the title compound (79%) as a colorless oil: $[\alpha]_D^{22}+45$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.22–2.30 (1H, m), 2.51–2.59 (1H, m), 3.67 (1H, quintet, $J=5.5$ Hz), 3.88–3.95 (1H, m), 5.42 (1H, dd, $J=4.5$, 10.0 Hz), 6.59 (1H, d, $J=9.0$ Hz), 7.17 (1H, dd, $J=2.5$, 9.0 Hz), 7.31–7.33 (1H, m), 7.37–7.39 (4H, m), 7.66 (1H, d, $J=2.5$ Hz); δ_C (100 MHz) 41.15, 41.18, 78.11, 113.23, 113.51, 116.14, 125.79, 128.26, 128.92, 130.98, 135.41, 139.58, 153.37; FAB-LRMS 154 (100%), 136 (35), 91 (24); Anal. $C_{15}H_{13}Br_2ClO$ requires: C, 44.54; H, 3.24. Found: C, 44.36; H, 3.36%.

2.1.14. (*S*)-6-Bromo-3,4-dihydro-2-phenyl-2*H*-1-benzopyran (17a). The benzopyran **17a** was prepared using the same procedure and scale as described for **15a** but using (*S*)-2,4-dibromo-1-(3-chloro-1-phenylpropoxy)-benzene (**16**) and gave the title compound as a white solid (84%), mp 67 °C: $[\alpha]_D^{22}+3$ (*c* 3.0, $CHCl_3$); δ_H (400 MHz) 2.06–2.13 (1H, m), 2.19–2.26 (1H, m), 2.77 (1H, dt, $J=4.5$, 16.5 Hz), 2.93–3.02 (1H, m), 5.06 (1H, dd, $J=2.5$, 10.0 Hz), 6.82 (1H, d, $J=9.0$ Hz), 7.24 (2H, brs), 7.35–7.43 (5H, m); δ_C (100 MHz) 24.80, 29.36, 77.77, 112.26, 118.66, 123.95, 125.87, 127.97, 128.51, 130.15, 131.94, 141.16, 154.19; FAB-LRMS 290 and 288 (92%), 209 (34), 149 (40), 117 (90), 91 (100); FAB-HRMS calcd. for $C_{15}H_{13}^{79}BrO$ 288.0150, found 288.0161; Anal. $C_{15}H_{13}BrO$ requires: C, 62.30; H, 4.53. Found: C, 62.57; H, 4.71%.

2.1.15. (*S*)-3,4-Dihydro-2-phenyl-2*H*-1-benzopyran-6-carboxaldehyde (17b). To a stirred solution of *n*-butyllithium in hexane (2.5 M, 0.24 mL, 0.6 mmol) in THF (3 mL) at −50 °C was added dropwise a solution of (*S*)-2,4-dibromo-1-(3-chloro-1-phenylpropoxy)-benzene (**16**) (202 mg, 0.5 mmol) in THF (2 mL). After 1 h at −50 °C, the cooling bath was removed and the solution stirred at room temperature for 1 h. The solution was re-cooled to −50 °C and *n*-butyllithium in hexane (2.5 M, 0.3 mL, 0.75 mmol) added dropwise. After 30 min, DMF (365 mg, 5 mmol) was added and, following stirring for 30 min, the solution was allowed to return to room temperature. The reaction was quenched by pouring into saturated aqueous ammonium chloride (5 mL). The mixture was extracted with ethyl acetate (3×10 mL), and the combined extracts washed with water (10 mL), brine (10 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane, gave the title compound (1.6 g, 81%) as a white solid (81%), mp 82–83 °C: $[\alpha]_D^{22}+109$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.07–2.17 (1H, m), 2.25–2.32 (1H, m), 2.87 (1H, dt, $J=4.5$, 16.0 Hz), 2.99–3.08 (1H, m), 5.17 (1H, dd, $J=2.5$, 10.0 Hz), 7.01 (1H, d, $J=8.0$ Hz), 7.34–7.38 (1H, m), 7.40–7.42 (4H, m), 7.66–7.68 (2H, m), 9.86 (1H, s); δ_C (100 MHz) 24.74, 29.31, 78.52, 117.59, 122.40, 125.86, 128.14, 128.61, 129.59, 129.73, 131.84, 140.65, 160.53, 190.96; FAB-LRMS 239 (100%), 117 (24), 91 (10); FAB-HRMS calcd. for $C_{16}H_{14}O_2$ 239.1072, found 239.1071; Anal. $C_{16}H_{14}O_2$ requires: C, 80.65; H, 5.92. Found: C, 81.01; H, 5.87%.

2.1.16. (*S*)-3,4-Dihydro-2-phenyl-2*H*-1-benzopyran-6-carboxylic acid (17c). The benzopyran **17c** was prepared using the same procedure and scale as described for **17b** but using an excess of carbon dioxide gas as the electrophile and gave the title compound as a white solid (78%), mp 208–209 °C: $[\alpha]_D^{22}+37$ (*c* 1.0, $CHCl_3$); δ_H (acetone 400 MHz) 2.02–2.12 (1H, m), 2.26–2.32 (1H, m), 2.86 (1H, dt, $J=4.5$, 16.5 Hz), 3.02–3.10 (1H, m), 5.22 (1H, dd, $J=2.5$, 10.0 Hz), 6.92 (1H, d, $J=9.0$ Hz), 7.32–7.36 (1H, m), 7.38–7.43 (2H, m), 7.47–7.49 (2H, m), 7.81–7.49 (2H, m); δ_C (100 MHz) 25.47, 30.34, 79.10, 117.55, 123.04, 123.36, 126.91, 128.75, 129.37, 130.13, 132.70, 142.48, 160.14, 167.64; FAB-LRMS 255 (100%), 237 (30), 209 (12), 151 (12), 117 (36), 91 (12); FAB-HRMS calcd. for $C_{16}H_{14}O_3$ 255.1021, found 255.1017; Anal. $C_{16}H_{14}O_3$ requires: C, 75.57; H, 5.55. Found: C, 75.50; H, 5.45%.

2.1.17. (*S*)-3,4-Dihydro-2-phenyl-2*H*-1-benzopyran-6-methanol (17d). The benzopyran **17d** was prepared using the same procedure and scale as described for **17b** but using an excess of paraformaldehyde powder as the electrophile and gave the title compound as a colorless oil (57%): $[\alpha]_D^{22}+2$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.04–2.14 (1H, m), 2.20–2.26 (1H, m), 2.79 (1H, dt, $J=4.0$, 16.5 Hz), 2.95–3.03 (1H, m), 4.59 (2H, s), 5.07 (1H, dd, $J=2.0$, 10.0 Hz), 6.91 (1H, d, $J=8.0$ Hz), 7.11 (1H, s), 7.33–7.44 (6H, m); δ_C (100 MHz) 25.24, 30.06, 51.81, 65.39, 78.05, 117.27, 122.13, 126.19, 126.83, 128.09, 128.76, 133.04, 141.82, 154.99; FAB-LRMS 240 (92%), 223 (100), 209 (25), 117 (38), 91 (52); FAB-HRMS calcd. for $C_{16}H_{14}O_2$ 240.1155, found 240.1155.

2.1.18. (*S*)-1,3-Dibromo-2-(3-chloro-1-phenylpropoxy)-benzene (18). The ether **18** was prepared using the same

procedure and scale as described for **14a** but using 2,6-dibromophenol. Flash chromatography of the residue, eluting with hexane, gave the title compound (77%) as a colorless oil: $[\alpha]_D^{22}$ −78 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.45–2.53 (1H, m), 2.70–2.79 (1H, m), 3.39–3.45 (1H, m), 3.68–3.74 (1H, m), 5.77 (1H, t, *J*=7.0 Hz), 6.78 (1H, t, *J*=8.0 Hz), 7.33–7.35 (3H, m), 7.44–7.48 (4H, m); δ_C (100 MHz) 38.51, 41.16, 82.30, 118.61, 125.76, 128.06, 128.27, 128.75, 132.93, 137.90, 151.59; EI-LRMS 252 (18%), 153 (78), 117 (50), 91 (100); Anal. $C_{15}H_{13}Br_2ClO$ requires: C, 44.54; H, 3.24. Found: C, 44.78; H, 3.59%.

2.1.19. (*S*)-8-Bromo-3,4-dihydro-2-phenyl-2*H*-1-benzopyran (19). The benzopyran **19** was prepared using the same procedure described for **15a** but using (*S*)-1,3-dibromo-2-(3-chloro-1-phenylpropoxy)-benzene (**18**) and gave the title compound as a colorless oil (79%): $[\alpha]_D^{22}$ −143 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.02–2.12 (1H, m), 2.28–2.34 (1H, m), 2.79 (1H, dt, *J*=5.0, 16.5 Hz), 2.96–3.04 (1H, m), 5.23 (1H, d, *J*=9.0 Hz), 6.77 (1H, dt, *J*=1.0, 8.0 Hz), 7.04 (1H, d, *J*=8.0 Hz), 7.35 (1H, d, *J*=8.0 Hz), 7.40–7.44 (3H, m), 7.47–7.49 (2H, m); δ_C (100 MHz) 24.92, 29.54, 77.99, 111.08, 120.89, 123.63, 125.51, 127.62, 128.44, 128.53, 131.02, 141.10, 151.35; FAB-LRMS 288 (58%), 185 (26), 117 (100), 91 (56); FAB-HRMS calcd. for $C_{15}H_{13}^{79}BrO$ 288.0150, found 288.0188.

2.1.20. (*S*)-3,4-Dihydro-2-phenyl-2*H*-1-benzopyran-8-carboxaldehyde (20). The benzopyran **20** was prepared using the same procedure described for **17b** but using (*S*)-1,3-dibromo-2-(3-chloro-1-phenylpropoxy)-benzene (**18**) and gave the title compound as colorless needles following recrystallization from ethanol (76%), mp 94–95 °C (EtOH): $[\alpha]_D^{22}$ −287 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.08–2.17 (1H, m), 2.28–2.34 (1H, m), 2.85 (1H, dt, *J*=4.5, 16.5 Hz), 2.99–3.07 (1H, m), 5.20 (1H, dd, *J*=2.5, 10.0 Hz), 6.94 (1H, t, *J*=7.5 Hz), 7.31 (1H, d, *J*=8.0 Hz), 7.35–7.43 (5H, m), 7.70 (1H, d, *J*=8.0 Hz), 10.52 (1H, s); δ_C (100 MHz) 24.76, 29.31, 78.18, 120.10, 123.15, 124.28, 125.65, 126.19, 128.01, 128.58, 135.77, 140.79, 157.71, 189.83; FAB-LRMS 239 (100%), 135 (62), 117 (15), 91 (24); FAB-HRMS calcd. for $C_{16}H_{14}O_2$ 239.1072, found 239.1071; Anal. $C_{16}H_{14}O_2$ requires: C, 80.65; H, 5.92. Found: C, 81.05; H, 6.02%.

2.1.21. (*S*)-3-Chloro-1-(4-chlorophenyl)-1-propanol (22). To (*R*)-oxazaborolidine (1.0 M in toluene, 1.0 mL, 1.0 mmol) in THF (2 mL) at 0 °C was added dropwise borane–THF complex (1.0 M, 6 mL, 6 mmol). After 5 min a solution of 3,4′-dichloropropiophenone (**21**) (2.03 g, 10 mmol) in THF (10 mL) was added dropwise and the reaction mixture stirred for an additional 1 h. Methanol (3 mL) was added and after 10 min hydrogen chloride in ether (1.0 M, 2.0 mL, 2.0 mmol) was added. After 30 min, the volatiles were removed by evaporation and the residue triturated with ether and filtered to remove any insoluble material. The ether solution was washed with brine (10 mL), saturated aqueous sodium bicarbonate (10 mL), dried and evaporated to give the title compound as a colorless oil (1.86 g, 91%); $[\alpha]_D^{22}$ −17 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 1.98–2.06 (1H, m), 2.12–2.19 (1H, m), 2.43 (1H, brs), 3.48–3.54 (1H, m), 3.66–3.73 (1H, m), 4.89 (1H, dd, *J*=4.5, 8.5 Hz), 7.25–7.33 (4H, m); δ_C (100 MHz) 41.28, 41.43, 70.54, 127.09, 128.72, 133.47, 142.08; FAB-LRMS 208, 206 and 204 (12%), 187 (100), 141 (70), 125 (60); FAB-HRMS calcd. for $C_9H_{10}^{35}Cl_2O$ 204.0105, found 204.0106.

2.1.22. (*R*)-6-Chloro-3,4-dihydro-2-(4-chlorophenyl)-2*H*-1-benzopyran (4). Following the same procedure and scale as described for the preparation of **14a** but using (*S*)-3-chloro-1-(4-chlorophenyl)-1-propanol (**22**) and 2-bromo-4-chlorophenol (**12c**) gave (*R*)-2-bromo-4-chloro-1-[3-chloro-1-(4-chlorophenyl)propoxy]-benzene (85%) as a colorless oil: $[\alpha]_D^{22}$ +85 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.17–2.25 (1H, m), 2.47–2.56 (1H, m), 3.63 (1H, quintet, *J*=5.5 Hz), 3.85–3.91 (1H, m), 5.38 (1H, dd, *J*=4.5, 9.0 Hz), 6.60 (1H, d, *J*=9.0 Hz), 7.05 (1H, dd, *J*=2.5, 9.0 Hz), 7.29–7.35 (4H, m), 7.51 (1H, d, *J*=2.5 Hz); δ_C (100 MHz) 40.96, 41.00, 77.67, 113.25, 115.68, 126.65, 127.29, 128.12, 129.18, 132.90, 134.13, 138.20, 152.73 which was used in the next step: using the same procedure and scale as described for **15a** but using (*R*)-2-bromo-4-chloro-1-[3-chloro-1-(4-chlorophenyl)propoxy]-benzene gave the title compound (78%) as a white solid, mp 107 °C; δ_H (400 MHz) 1.98–2.06 (1H, m), 2.15–2.22 (1H, m), 2.72–2.99 (1H, m), 2.75 (1H, dt, *J*=4.5, 16.0 Hz), 5.01 (1H, dd, *J*=2.5, 10.0 Hz), 6.83 (1H, d, *J*=8.5 Hz), 7.07–7.09 (2H, m), 7.33–7.35 (4H, m); δ_C (100 MHz) 24.72, 29.39, 77.31, 118.15, 123.18, 125.12, 127.26, 127.33, 128.66, 129.01, 133.62, 139.72, 153.39; FAB-LRMS 282, 280 and 278 (100%), 243 (20), 217 (85), 176 (55); FAB-HRMS calcd. for $C_{15}H_{12}^{35}Cl_2O$ 278.0265, found 278.0264; Anal. $C_{15}H_{12}Cl_2O$ requires: C, 64.54; H, 4.33. Found: C, 64.67; H, 4.60%.

2.2. Oxidation of (*S*)-3,4-dihydro-2-phenyl-2*H*-1-benzopyran (15) with periodic acid and chromium(VI) oxide

Periodic acid (455 mg, 2.0 mmol) was dissolved in acetonitrile by vigorous stirring followed by the addition of chromium(VI) oxide (5 mg, 0.05 mmol). (*S*)-3,4-Dihydro-2-phenyl-2*H*-1-benzopyran (**15**) (210 mg, 1.0 mmol) was added and an exotherm and white precipitate were immediately observed. The mixture was stirred for 1 h, filtered through Celite®, and the volatiles evaporated. The residue was dissolved in dichloromethane (10 mL), washed with saturated aqueous sodium bicarbonate (10 mL), brine (10 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane–ether (3:1 then 1:1), gave first (*S*)-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one (**23**) (96 mg, 43%) as a white solid: $[\alpha]_D^{22}$ −63 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.90 (1H, dd, *J*=3.0, 1.0 Hz), 3.10 (1H, dd, *J*=3.5, 17.0 Hz), 5.49 (1H, dd, *J*=3.0, 13.5 Hz), 7.05–7.08 (2H, m), 7.39–7.54 (6H, m), 7.94 (1H, dd, *J*=2.0, 8.0 Hz); IR 1684 cm^{-1}. Later fractions contained 2-(3-oxo-3-phenylpropyl)cyclohexa-2,5-diene-1,4-dione (**24**) (74 mg, 31%). Recrystallization from hexane/ethyl acetate gave yellow needles mp 127 °C: δ_H (400 MHz) 2.87 (2H, t, *J*=7.0 Hz), 3.25 (2H, d, *J*=7.0 Hz), 6.64 (1H, s), 6.70–6.78 (2H, m), 7.46 (2H, t, *J*=8.0 Hz), 7.57 (1H, t, *J*=8.0 Hz), 7.94 (2H, *J*=8.0 Hz); δ_C (100 MHz) 23.95, 36.39, 127.98, 128.68, 133.25, 133.35, 136.38, 136.76, 148.17, 187.37, 187.47, 197.78 (one signal obscured); FAB-LRMS 241 (40%), 223 (20), 105 (100); Anal. $C_{15}H_{12}O_3$ requires: C, 74.99; H, 5.03%. Found: C, 74.82; H, 4.93%.

2.2.1. (*R*)-3-(*tert*-Butyldimethylsily)oxy-*N*-methoxy-*N*-methyl-benzenepropanamide (28). To a stirred solution of ethyl-(*R*)-3-hydroxy-3-phenyl propionate (**27**) (1.94 g, 10 mmol) and imidazole (1.36 g, 20 mmol) in dichloromethane (50 mL) was added *tert*-butyldimethylsilyl chloride (1.65 g, 11 mmol). The mixture was stirred at room temperature overnight and the resulting white precipitate was poured into saturated aqueous ammonium chloride (150 mL). The mixture was extracted with dichloromethane (3×50 mL) and the combined extracts washed with water (50 mL), brine (50 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane–ether (19:1), gave (*R*)-3-phenyl-3-(*tert*-butyldimethylsily)oxypropanoate[41] as a colorless oil (2.89, 94%); δ_H (400 MHz) −0.18 (3H, s), 0.01 (3H, s), 0.87 (9H, s), 1.25 (3H, t, J=6 Hz), 2.53 (1H, dd, J=4.0, 14.5 Hz), 2.72 (1H, dd, J=9.5, 14.5 Hz), 4.13 (2H, q, J=6 Hz), 5.14 (1H, dd, J=4.0, 9.5 Hz), 7.24–7.36 (5H, m).

To a stirred suspension of *N*, *O*-dimethylhydroxylamine hydrochloride (1.75 g, 18 mmol) in dichloromethane (45 mL) at 0 °C under nitrogen was added dropwise trimethylaluminum (2.0 M in toluene, 9 mL, 18 mmol). The reaction mixture was stirred for 20 min and then treated with a solution of (*R*)-3-phenyl-3-(*tert*-butyldimethylsily)oxypropanoate[41] (2.77 g, 9 mmol) in dichloromethane (15 mL). The mixture was stirred at room temperature overnight and poured into saturated aqueous ammonium chloride (150 mL). The resulting precipitate was filtered through Celite®, the filtrate extracted with dichloromethane (3×75 mL) and the combined extracts washed with water (50 mL), brine (50 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane–ether (1:1), gave the title compound as a colorless oil (2.38 g, 82%); $[\alpha]_D^{22}$ +138 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) −0.14 (3H, s), 0.08 (3H, s), 0.84 (9H, s), 2.47 (1H, dd, J=3.5, 14.5 Hz), 3.02–3.07 (1H, brm), 3.17 (3H, s), 3.63 (3H, s), 5.26 (1H, dd, J=3.5, 9.0 Hz), 7.21–7.26 (1H, m), 7.29–7.32 (2H, m), 7.36–7.38 (2H, m); δ_C (100 MHz) −4.57, 18.34, 25.99, 32.17, 43.46, 61.53, 72.34, 76.96, 126.07, 127.49, 128.42, 145.05, 171.87; FAB-LRMS 346 (M+23, 100%), 266 (38), 221 (16), 150 (15), 73 (98).

2.3. 1,5-Dimethoxy-3-(methoxymethoxy)benzene (30)

To a vigorously stirred solution of 3,5-dimethoxyphenol (10 g, 65 mmol) and potassium bicarbonate (17.94 g, 130 mmol) in DMF (250 mL) was added chloromethyl methyl ether (6.44 g, 80 mmol). The mixture was stirred overnight, poured into saturated ammonium chloride (250 mL) and extracted with ethyl acetate (3×150 mL). The combined extracts were washed with water (5×200 mL), 2.0 M sodium hydroxide (200 mL), brine, dried and evaporated to give the title compound as a colorless oil (9.9 g, 94%); δ_H (400 MHz) 3.47 (3H, s), 3.76 (6H, s), 5.14 (2H, s), 6.14 (1H, s), 6.23 (2H, s); δ_C (100 MHz) 55.31, 56.02, 94.18, 94.45, 94.96, 159.09, 161.43.

2.3.1. (*R*)-1-[2,4-Dimethoxy-6-(methoxymethoxy)-phenyl]-3-phenyl-3-(*tert*-butyldimethylsily)oxy-propan-1-one (31). To a stirred solution of 1,5-dimethoxy-3-(methoxymethoxy)benzene (**30**) (297 mg, 1.5 mmol) in toluene (5 mL) at −78 °C under nitrogen was added dropwise *tert*-butyllithium in pentane (1.7 M, 0.88 mL, 1.5 mmol). The reaction mixture was stirred at −78 °C for 15 min, allowed to warm to 0 °C over 1 h, re-cooled to −78 °C and (*R*)-3-(*tert*-butyldimethylsily)oxy-*N*-methoxy-*N*-methyl-benzenepropanamide (**28**) (154 mg, 0.5 mmol) in toluene (2 mL) added dropwise. The solution was allowed to return to room temperature over 2 h and quenched by the dropwise addition of saturated aqueous ammonium chloride (10 mL). The phases were separated and the aqueous layer extracted with ether (3×10 mL), combined and washed with water (10 mL), brine (10 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane–ether (3:1), gave the title compound as a colorless oil (165 mg, 72%): $[\alpha]_D^{22}$ +71 (*c* 1.0, $CHCl_3$) δ_H (400 MHz) −0.13 (3H, s), 0.08 (3H, s), 0.85 (9H, s), 3.02 (1H, dd, J=4.5, 17.5 Hz), 3.30 (1H, dd, J=7.5, 17.5 Hz), 3.39 (3H, s), 3.69 (3H, s), 3.77 (3H, s), 5.03 (2H, s), 5.38 (1H, dd, J=4.5, 7.5 Hz), 6.09 (1H, s), 6.29 (1H, s), 7.20 (1H, t, J=8.0 Hz), 7.27 (2H, t, J=7.5 Hz), 7.35 (2H, d, J=8.0 Hz); δ_C (100 MHz) −5.15, −4.73, 18.08, 25.76, 55.29, 55.39, 55.58, 55.89, 56.16, 70.47, 92.11, 93.16, 94.59, 114.42, 126.11, 126.90, 127.94, 145.31, 155.99, 158.16, 162.14, 200.65; FAB-LRMS 483 (M+23, 100%), 221 (26), 73 (100).

2.3.2. (*R*)-3-Hydroxy-1-(2-hydroxy-4,6-dimethoxy-phenyl)-3-phenylpropan-1-one (32). To a stirred solution of (*R*)-1-[2,4-dimethoxy-6-(methoxymethoxy)phenyl]-3-phenyl-3-(*tert*-butyldimethylsily)oxy-propan-1-one (**31**) (230 mg, 0.5 mmol) in THF (9 mL) and water (1 mL) was added *p*-toluene sulfonic acid (19 mg, 0.1 mmol). The solution was heated to 55 °C for 12 h, cooled and poured onto saturated aqueous sodium bicarbonate (15 mL). The mixture was extracted with ethyl acetate (3×15 mL) and the combined extracts washed with brine (25 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane–ether (1:1), gave the title compound (130 mg, 86%) as a white solid, mp 91 °C: $[\alpha]_D^{22}$ +49.5 (*c* 2.0, $CHCl_3$); δ_H (400 MHz) 3.33–3.51 (3H, m, ^1H exchanges with D_2O), 3.77 (3H, s), 3.81 (3H, s), 5.27 (1H, dd, J=4.0, 9.0 Hz), 5.90 (1H, s), 6.07 (1H, s), 7.28 (1H, t, J=8.0 Hz), 7.27 (2H, t, J=8.0 Hz), 7.35 (2H, d, J=7.5 Hz); δ_C (100 MHz) 52.58, 55.51, 55.55, 70.07, 90.92, 93.66, 105.81, 125.84, 127.34, 128.37, 143.33, 162.83, 166.43, 167.71, 204.05; FAB-LRMS 303 (15%), 284 (10), 181 (100); FAB-HRMS calcd. for $C_{17}H_{19}O_5$ 303.1232, found 303.1232; Anal. $C_{17}H_{18}O_5$ requires: C, 67.54; H, 6.00. Found: C, 67.31; H, 6.23%.

2.3.3. (*S*)-5,7-Dimethoxy-2-phenylchroman-4-one (33). A solution of triphenylphosphine (131 mg, 0.5 mmol) and diethyl azodicarboxylate (88 mg, 0.5 mmol) in THF (3 mL) at 0 °C was stirred for 15 min and then added dropwise to a solution of (*R*)-3-hydroxy-1-(2-hydroxy-4,6-dimethoxy-phenyl)-3-phenylpropan-1-one (**32**) (130 mg, 0.43 mmol) in THF (3 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and the volatiles removed by evaporation. Flash chromatography of the residue, eluting with hexane–ether (1:1 and then 1:2), gave the title compound (120 mg, 88%) as a white solid, mp 159–160 °C; $[\alpha]_D^{22}$ −28 (*c* 2.0, MeOH–$CHCl_3$, 1:1); δ_H (400 MHz) 2.79 (1H, dd, J=3.0, 16.5 Hz), 3.01 (1H, dd, J=13.0, 16.5 Hz), 3.81 (3H, s), 3.88 (3H, s), 5.40 (1H, dd, J=3.0, 13.0 Hz), 6.09 (1H, d, J=2.0 Hz),

6.15 (1H, d, $J=2.0$ Hz), 7.38–7.46 (5H, m); δ_C (100 MHz) 45.56, 55.56, 56.13, 79.18, 93.14, 93.52, 105.97, 126.08, 128.63, 128.75, 138.74, 162.26, 164.94, 165.94, 189.13; Anal. $C_{17}H_{16}O_4$ requires: C, 71.82%; H, 5.67%. Found: C, 71.70%; H, 5.67%.

2.3.4. (*S*)-5-Hydroxy-7-methoxy-2-phenylchroman-4-one (pinostrobin) (3). To a solution of (*S*)-5,7-dimethoxy-2-phenylchroman-4-one (**33**) (140 mg, 0.5 mmol) in acetonitrile (10 mL) at room temperature was added aluminum chloride (265 mg, 2.0 mmol). The mixture was heated to reflux for 3 h, cooled and the volume reduced by evaporation. 2.0 M hydrochloric acid (5 mL) was added and the solution extracted with ethyl acetate (3×10 mL). The combined organics were washed with water (10 mL), brine (10 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane–ether (3:1), gave the title compound (106 mg, 79%) as a white solid, mp 89–90 °C (MeOH); $[\alpha]_D^{22}$ −48 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.82 (1H, dd, $J=3.0$, 17.0 Hz), 3.09 (1H, dd, $J=13.0$, 17.0 Hz), 3.81 (3H, s), 5.43 (1H, dd, $J=3.0$, 13.0 Hz), 6.06–6.09 (2H, m), 7.41–7.46 (5H, m), 12.03 (1H, s); δ_C (100 MHz) 43.36, 53.41, 55.67, 79.20, 94.24, 95.12, 103.12, 126.11, 128.85, 138.34, 162.76, 164.16, 167.96, 195.73; Anal. $C_{16}H_{14}O_4$ requires: C, 71.10%; H, 5.22%. Found: C, 71.07%; H, 5.21%.

Acknowledgements

The University College Dublin and Schering-Plough (Avondale) are thanked for the funding of this research under the Newman Fellowship program and the Department of Chemistry at the University College Dublin are thanked for the use of facilities during this research. John Hill (Kent mass spectrometry) is thanked for high-resolution mass spectra and Robertson analytical for elemental analysis and optical polarimetry. The author would like to thank Dr. Dario Doller (Neurogen Corporation) for helpful discussions during the preparation of this manuscript.

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