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Note

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Enantioselective Synthesis of Highly Substituted Chromans *via* Oxa-Michael-Michael Cascade Reaction with Bifunctional Organocatalyst

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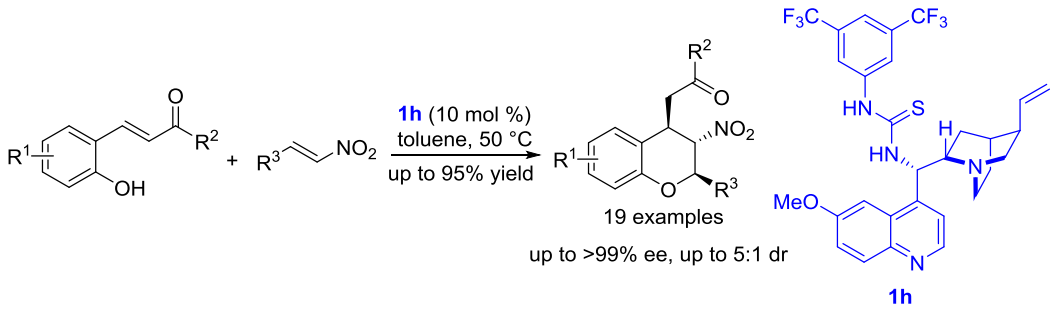


ABSTRACT: A highly enantioselective synthesis of chiral chroman derivatives *via* an oxa-Michael-Michael cascade reaction has been developed using bifunctional thiourea organocatalyst. The products were obtained with excellent enantioselectivities (up to >99%), good yields (up to 95%) and diastereoselectivities (up to 5:1).

Highly substituted chiral chromans represent an important class of heterocycles which are found in many natural products and biologically active compounds (Figure 1).[1] For example, centchroman is one of the selective estrogen receptors and this compound is primarily used as oral contraceptive pills.[2a] It is also an effective drug for dysfunctional uterine bleeding and breast cancer.[2b] Cromakalim is a potassium channel opening vasodilator and used to treat hypertension.[2c] Bitucarpin A displays potent antibacterial and anti clastogenic activity against both mytomicin C and bleomycin C.[2d] Epiconicol shows cytotoxic activities against P388, A549, HT29 and CV1 cells.[2e] Due to the importance of polysubstituted chiral chromans, the development of new asymmetric strategies for their synthesis has become an active field of research.

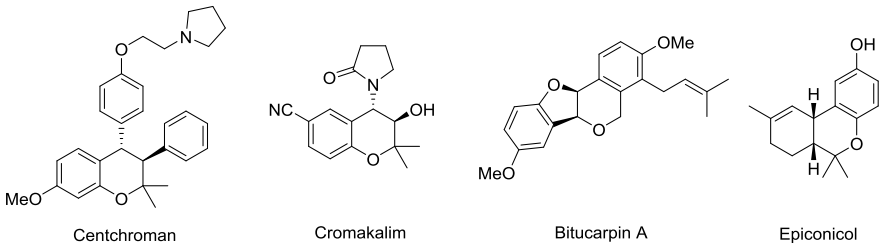


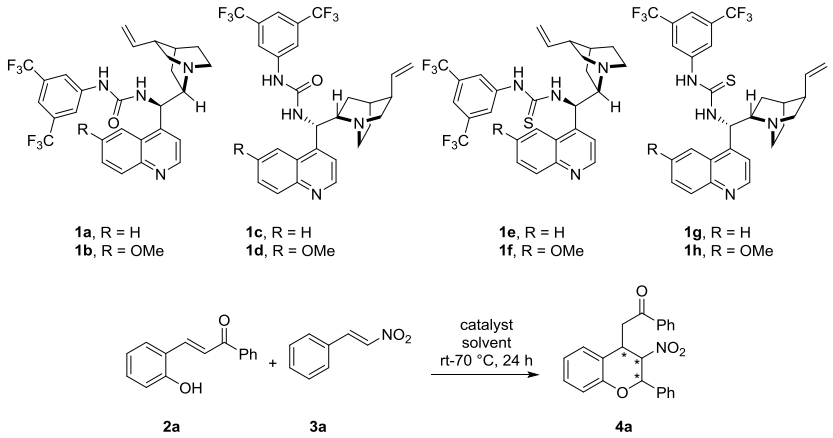
Figure 1. Selected examples of biologically active chroman compounds.

Organocatalyzed cascade reactions have become powerful synthetic tools for the construction of heterocyclic compounds having multiple stereocenters in a single step.[3] Enantioselective Michael reaction is one of the steps involved in the synthesis of chiral heterocyclic compounds, whereas oxa-Michael reactions have several limitations such as low reactivity and reversibility issues as well as lack of control in stereoselectivity.[4] In 2006, Arvidsson *et al*. reported the first organocatalytic enantioselective synthesis of a chromene skeleton from salicylaldehyde and cinnamaldehyde using diphenylprolinol silyl ether as a catalyst.[5a] Since then, significant efforts have been made by several scientific groups for the asymmetric synthesis of chiral chroman derivatives.[5,6] Gu *et al.* employed thiourea alkaloids as an organocatalyst for the asymmetric synthesis of polysubstituted chiral chromans using chalcone enolate and nitromethane.[5h] Recently, Wang *et al.* reported the asymmetric synthesis of tricyclic chroman derivatives by a tandem oxa-Michael-Michael-aldol reaction using Jørgensen catalyst.[7] For many years, our group was extensively involved in asymmetric synthesis of chiral compounds using bifunctional thiourea and squaramide catalysts.[8] Herein, we disclose the highly efficient synthesis of polysubstituted chroman derivatives by cascade oxa-Michael-Michael reaction from *ortho*-hydroxy-substituted-α,β–unsaturated ketones[9] and *trans*-nitroalkenes using chiral bifunctional thiourea organocatalyst.

For the preliminary studies, we have chosen (*E*)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one **2a** and *trans*-β-nitrostyrene **3a** as model substrates to investigate cascade oxa-Michael-Michael reaction in the presence of various thiourea and urea organocatalysts. As per our assumption, in the presence of 10 mol % catalyst **1a**, the substrate **2a** underwent reaction with *trans*-β-nitrostyrene **3a** in 1,2-dichloroethane at 70 °C to provide the highly substituted chiral chroman **4a** in 70% yield, 95% ee and 85:15 dr (table 1, entry 1). Encouraged by this result, we have investigated the effect of reaction medium for this reaction. Among the various solvents EtOAc, CH_3CN, THF, toluene and methanol, toluene was found to be the best solvent for this reaction (97% ee, 68% yield, 85:15 dr, table 1, entry 6), whereas no reaction was observed in methanol. It might be due to the competitive hydrogen bonding between methanol and substrates with the catalyst. Then we have studied the effect of temperature on enantio- and diastereoselectivity. At room temperature (25 °C) the reaction provided the desired product **4a**, albeit with low yield (35%) whereas at 50 °C the product **4a** was obtained in 70% yield (99% ee). There was no

significant improvement of diastereoselectivity by further decreasing or increasing the temperature of the reaction. Next, we have screened various cinchona-alkaloid derived urea and thiourea organocatalysts **1a-1h**. Among all the catalysts, **1h** gave best results yielding the product **4a** in >99% ee and 72% yield (table 1, entry 17). We then studied the effect of catalyst loading in the reaction of **2a** and **3a** (table 1, entries 18-19). The products were obtained with moderate yield and the same level of enantioselectivity on decreasing the catalyst loading form 2 to 5 mol %. In most cases, TLC analysis revealed a single spot, so it was not possible to separate the two diastereoisomers using column chromatography. Screening of various conditions revealed that the optimal reaction condition is 10 mol % catalyst **1h** in toluene at 50 °C.

Table 1: Screening of Reaction Conditions[a]



2a **3a** **4a**

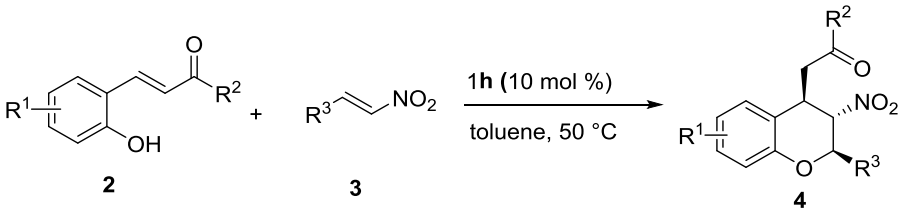
entry	catalyst	solvent	temp.(°C)	yield[b](%)	dr[c](%)	ee[d](%)
1	1a	DCE	70	70	85:15	95
2	1a	CH_3CN	70	49	80:20	99
3	1a	THF	70	62	80:20	94
4	1a	EtOAc	70	40	78:22	98
5	1a	MeOH	70	<5	nd	nd
6	1a	toluene	70	68	85:15	97
7	1a	toluene	rt	35	87:13	99
8	1a	toluene	50	70	85:15	99
9	1a	DCE	50	68	85:15	99
10	1a	xylene	50	55	78:22	99
11	1b	toluene	50	65	87:13	99
12	1c	toluene	50	65	86:14	97
13	1d	toluene	50	63	88:12	92
14	1e	toluene	50	64	82:18	97

15	1f	toluene	50	80	83:17	96
16	1g	toluene	50	70	84:16	99
17	1h	toluene	50	72	83:17	>99
18[e]	1h	toluene	50	48	77:23	99
19[f]	1h	toluene	50	68	80:20	99
20[g]	1h	toluene	50	67	83:17	99

[a]The reaction was carried out with **2a** (0.1 mmol), *trans*-β-nitrostyrene **3a** (0.12 mmol), catalyst **1** (10 mol %) and solvent (1.0 ml) were stirred at above mentioned temperature for 24 h. [b]Isolated yield of mixture of diastereoisomers. [c]dr was calculated from ^{1}H NMR of crude reaction mixture. [d]Determined by chiral HPLC using OD-H column. [e]2.5 mol % catalyst was used. [f]5 mol % catalyst was used. [g]1.5 equiv nitrostyrene was used.

After the optimization of reaction conditions, we have explored the substrate scope of this reaction. First we have studied the effect of substituent on *trans*-nitroalkenes **3**. *trans*-β-Nitroalkenes **3b** and **3c** having electron-donating groups took longer reaction time to afford the corresponding chromans **4b** and **4c** with excellent enantioselectivities (98-99% ee, 59-63% yield). Whereas, *trans*-β-nitrostyrenes having electron-withdrawing groups on the phenyl ring such as F, Cl, Br, NO_2, the reaction proceeded smoothly to give the product **4** with excellent enantioselectivities and good yields (table 2, entries 4-9). These results could be attributed to the enhanced electrophilicity of β-carbon in the nitrostyrenes having electron withdrawing group. Furthermore, the substrate **3j** having aliphatic cyclohexyl group underwent reaction with **2a** to provide the chiral chroman derivatives with 89% ee. To further explore the versatility of the catalytic system, we have studied the effect of substituents R^1 and R^2 on the substrate **2a**. The substrate **2** having electron donating and withdrawing substituents such as Br, Cl, OMe on both the aromatic rings underwent cascade oxa-Michael-Michael reaction to afford the desired product in high enantioselectivities and high yields (up to 99% ee). The substrates **2** having methoxy group *ortho* to hydroxy group as well as keto group (table 2, entry 15 and 17) took longer reaction time to provide the product with high ee (up to 98%) and moderate yield (32-40%). Steric effect could be the probable reason for such disparity in reaction time and yield. In case of substrate **2f** having nitro group, no product was achieved after prolonged reaction time under standard reaction conditions (table 2, entry 16). It might be due to the lower nucleophilicity of the hydroxy group. Notably, chalcones containing heteroaromatic groups could also be employed to provide the chroman derivatives with excellent enantioselectivity (97-99% ee, table 2, entries 20-21). However, when an aliphatic chalcone **2l** was examined, we did not observe any reaction. It may be due to lower electrophilicity of carbonyl carbon due to electron donating effect of CH_3. The absolute configuration of the product **4m** was determined as (2*R*,3*S*,4*R*) by single crystal X-ray diffraction analysis (CCDC 1056755, see supporting information).

Table 2: Substrate Scope of Oxa-Michael-Michael Cascade Reaction[a]



entry	R^1	R^2	R^3	time(h)	product	yield(%)[b]	dr[c]	ee (%)[d]
1	H	C_6H_5 (**2a**)	C_6H_5 (**3a**)	24	4a	72	84:16	>99
2	H	C_6H_5 (**2a**)	4-MeC_6H_4 (**3b**)	48	4b	59	75:25	>99
3	H	C_6H_5 (**2a**)	2-MeC_6H_4 (**3c**)	48	4c	63	80:20	98
4	H	C_6H_5 (**2a**)	4-FC_6H_4 (**3d**)	30	4d	74	80:20	>99
5	H	C_6H_5 (**2a**)	2-BrC_6H_4 (**3e**)	20	4e	86	80:20	97
6	H	C_6H_5 (**2a**)	2-$NO_2C_6H_4$ (**3f**)	12	4f	95	60:40	96
7	H	C_6H_5 (**2a**)	4-$NO_2C_6H_4$ (**3g**)	12	4g	75	84:16	>99
8	H	C_6H_5 (**2a**)	4-ClC_6H_4 (**3h**)	24	4h	71	84:16	81
9	H	C_6H_5 (**2a**)	2,4-di-ClC_6H_3 (**3i**)	24	4i	59	80:20	98
10	H	C_6H_5 (**2a**)	Cy (**3j**)	20	4j	92	80:20	89
11	H	C_6H_5 (**2a**)	4-OMeC_6H_4 (**3k**)	48	4k	<5	nd	nd
12	5-Br	C_6H_5 (**2b**)	C_6H_5 (**3a**)	24	4l	62	67:33	96
13	5-Cl	C_6H_5 (**2c**)	C_6H_5 (**3a**)	24	4m	71	75:25	>99
14	5-OMe	C_6H_5 (**2d**)	C_6H_5 (**3a**)	24	4n	67	84:16	99
15	3-OMe	C_6H_5 (**2e**)	C_6H_5 (**3a**)	48	4o	32	80:20	98
16	5-NO_2	C_6H_5 (**2f**)	C_6H_5 (**3a**)	48	4p	nr	-	-
17	H	2-OMeC_6H_4 (**2g**)	C_6H_5 (**3a**)	48	4q	40	75:25	94
18	H	3-BrC_6H_4 (**2h**)	C_6H_5 (**3a**)	24	4r	84	80:20	97[e]
19	H	4-BrC_6H_4 (**2i**)	C_6H_5 (**3a**)	24	4s	78	80:20	98
20	H	2-furyl (**2j**)	C_6H_5 (**3a**)	24	4t	70	84:16	97
21	H	2-thiophenyl (**2k**)	C_6H_5 (**3a**)	24	4u	66	84:16	96
22	H	CH_3 (**2l**)	C_6H_5 (**3a**)	24	4v	nr	-	-

[a]The reaction was carried out with **2** (0.1 mmol), **3** (0.12 mmol), catalyst **1h** (10 mol %) in toluene (1.0 ml) at 50 °C. [b]Isolated yield of mixture of diastereoisomers. [c]dr was calculated from 1H NMR of the crude reaction mixture. [d]Determined by chiral HPLC analysis. [e]Reaction was carried out at room temperature (25 °C). nr = no reaction. nd = not determined.

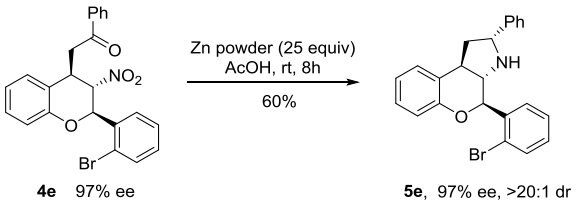


Figure 2: Synthesis of tricyclic chiral chroman **5e**

Further, we have shown the synthetic utility of our methodology by transforming chroman derivatives to tricyclic chroman. The tricyclic chiral chromans shows potential biological activities.[10] The reductive amination of the product **4e** afforded the ring fused tricyclic framework **5e** (Figure 2) using zinc powder and acetic acid in high enantioselectivity (97%) and diastereoselectivity (20:1) and good yield (60%). The configuration of newly generated chiral center in **5e** was ascertained by NOE experiment.

CONCLUSION

In summary, we have developed an efficient strategy for the construction of polysubstituted chiral chroman derivatives using bifunctional thiourea organocatalyst. The reaction conditions are operationally very simple. The three contiguous chiral centers in products were obtained with excellent enantioselectivities, good diastereoselectivities, and good yields. Furthermore, the products were transformed into tricyclic chromans having ring-fused benzopyran with high enantioselectivity.

EXPERIMENTAL SECTION

Unless otherwise specified, all reactions were carried out in air without any precautions to exclude moisture in oven dried glassware with magnetic stirring. Catalysts **1a-h** were prepared according to the procedure reported in literature.[11] Chalcone derivatives **2** and substituted *trans*-β-nitrostyrenes **3** were prepared according to modified literature procedures.[12,13] ^{1}H and ^{13}C spectra were recorded in $CDCl_3$ or DMSO-d_6 on a spectrometer (400 or 500 MHz and 100 or 125 MHz respectively). Chemical shifts (δ ppm) are relative to the resonance of the deuterated solvent as the internal standard ($CDCl_3$, δ 7.24 ppm, DMSO-d_6, δ 2.50 ppm for ^{1}H NMR, $CDCl_3$, δ 77.20 ppm, DMSO-d_6, δ 39.50 ppm for ^{13}C NMR). Data for ^{1}H NMR are reported as follows: Chemical Shifts (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, ABq = AB quartet, m = multiplet or unresolved, coupling constant(s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shifts (δ, ppm). High resolution mass spectra (HRMS) were obtained by the ESI (Q-TOF) ionization sources. Optical rotations were measured on a commercial automatic polarimeter. IR spectra were measured with a FT/IR vector 22 spectrometer.

The reactions were monitored by thin layer chromatography on precoated silica gel TLC plates. All the compounds were purified by silica gel column chromatography using silica gel (mesh 230-400). Melting points were recorded using a melting point apparatus and are uncorrected. The enantioselectivity was determined by high performance liquid chromatography using OD-H, AD-H, IA and ID columns with a 200 UV-detector by using *iso*-propanol and *n*-hexane as eluents. X-ray data were recorded on a single crystal X-ray diffractometer.

General Procedure for the Synthesis 2:

Substituted salicylaldehyde (5 mmol) and substituted acetophenone were dissolved in 5 ml MeOH and cooled to 0 °C. Then, 40% aq. NaOH (1.3 ml) was added dropwise to it. The reaction mixture was allowed to come to room temperature and stirred overnight. The solvent was evaporated, aq. 1M HCl (10 ml) was added to it. The aqueous layer was extracted with ethyl acetate (3 x 15 ml), dried over Na_2SO_4, filtered and concentrated on a rotary evaporator. The crude mixture was purified by column chromatography over silica gel using hexane and ethyl acetate as eluents to obtain the pure product.

^{1}H and ^{13}C NMR of **2a, 2e** and **2l** were matched with the literature data.[13]

(*E*)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one (2a):

Yellow solid, 69% yield (1.55 g); ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.34 (s, 1H), 8.09-8.07 (m, 2H), 8.03 (d, *J* = 16.0 Hz, 1H), 7.85 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.83 (d, *J* = 16.0 Hz, 1H), 7.67-7.64 (m, 1H), 7.58-7.55 (m, 2H), 7.27-7.26 (m, 1H), 6.93 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.88 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 189.8, 157.3, 139.7, 138.0, 133.0, 132.2, 128.9, 128.8, 128.4, 121.5, 121.1, 119.6, 116.3.

(*E*)-3-(5-Bromo-2-hydroxyphenyl)-1-phenylprop-2-en-1-one (2b):

Yellow solid, 74% yield (1.12 g); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.59 (s, 1H), 8.16-8.14 (m, 3H), 7.91 (s, 2H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.41 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.90 (t, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 189.2, 156.4, 137.6, 137.5, 134.2, 133.1, 130.4, 128.8, 128.5, 123.7, 122.0, 118.3, 110.9.

(*E*)-3-(5-Chloro-2-hydroxyphenyl)-1-phenylprop-2-en-1-one (2c):

Yellow solid, 69% yield (0.89 g); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1H), 8.14 (d, *J* = 7.6 Hz, 2H), 8.02 (d, *J* = 2.4 Hz, 1H), 7.96 (d, *J* = 4.8 Hz, 2H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.30 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 189.3, 156.0, 137.7, 133.1, 131.4, 128.8, 128.5, 127.5, 123.3, 123.1, 122.1, 117.9.

(*E*)-3-(2-Hydroxy-5-methoxyphenyl)-1-phenylprop-2-en-1-one (2d):

Yellow solid, 49% yield (0.62 g); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.82 (s, 1H), 8.11 (d, *J* = 7.2 Hz, 2H), 8.04 (d, *J* = 16.0 Hz,1H), 7.85 (d, *J* = 15.6 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 2.8 Hz, 1H), 6.92-6.85 (m, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 189.5, 152.3, 151.5, 139.4, 137.9, 132.9, 128.7, 128.4, 121.5, 120.9, 119.2, 117.1, 111.6, 55.6.

(*E*)-3-(2-hydroxy-3-methoxyphenyl)-1-phenylprop-2-en-1-one (2e):

Yellow solid, 43% yield (1.1 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05-8.00 (m, 3H), 7.73 (d, *J* = 16.0 Hz, 1H), 7.56-7.53 (m, 1H), 7.49-7.45 (m, 2H), 7.18-7.16 (m, 1H), 6.86-6.85 (m, 2H), 6.35 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.4, 147.1, 146.1, 140.3, 138.7, 132.7, 128.7, 123.7, 121.9, 121.5, 119.9, 112.2, 56.4.

(*E*)-3-(2-Hydroxy-5-nitrophenyl)-1-phenylprop-2-en-1-one (2f):

Yellow solid, 31% yield (0.42 g); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.82-8.81 (m, 1H), 8.18-8.16 (m, 3H), 8.11 (d, *J* = 16.0 Hz, 1H), 7.99 (d, *J* = 16.0 Hz, 1H), 7.70-7.67 (m, 1H), 7.60-7.57 (m, 2H), 7.11-7.08 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 189.2, 162.7, 140.0, 137.4, 136.9, 133.2, 128.8, 128.6, 127.1, 124.5, 123.6, 122.0, 116.6.

(*E*)-3-(2-Hydroxyphenyl)-1-(2-methoxyphenyl)prop-2-en-1-one (2g):

Yellow solid, 51% yield (0.65 g); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.2 (s, 1H), 7.74 (d, *J* = 16.0 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 16.0 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 192.8, 157.5, 157.0, 138.6, 132.6, 131.8, 129.3, 129.2, 128.5, 126.3, 121.2, 120.5, 119.5, 116.2, 112.3, 55.7.

(*E*)-3-(2-Hydroxyphenyl)-1-(3-bromophenyl)prop-2-en-1-one (2h):

Yellow solid, 55% yield (0.83 g); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.3 (s, 1H), 8.21 (s, 1H), 8.07-8.03 (m, 2H), 7.88 (d, *J* = 6.8 Hz, 1H), 7.83-7.79 (m, 2H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 188.1, 157.4, 140.2, 139.9, 135.5, 132.4, 131.0, 130.9, 128.7, 127.3, 122.3, 121.2, 120.4, 119.4, 116.2.

(*E*)-3-(2-Hydroxyphenyl)-1-(4-bromophenyl)prop-2-en-1-one (2i):

Yellow solid, 30% yield (0.45 g); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.09-8.05 (m, 1H), 8.02 (d, *J* = 7.5 Hz, 2H), 7.86-7.85 (m, 1H), 7.84-7.81 (m, 1H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.28 (m, 1H), 6.96-6.94 (m, 1H), 6.87 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 188.6, 157.4, 140.1, 136.9, 132.2, 131.8, 130.4, 128.8, 127.0, 121.3, 120.5, 119.4, 116.3.

(*E*)-1-(Furan-2-yl)-3-(2-hydroxyphenyl)prop-2-en-1-one (2j):

Yellow solid, 44% yield (0.47 g); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.05-8.02 (m, 2H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.71-7.64 (m, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.78-6.77 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 177.1, 157.2, 153.1, 148.0, 138.2, 132.1, 128.6, 121.1, 120.7, 119.4, 118.8, 116.2, 112.7.

(*E*)-1-(Thiophen-2-yl)-3-(2-hydroxyphenyl)prop-2-en-1-one (2k):

Yellow solid, 27% yield (0.31 g); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.23 (dd, *J* = 4.0 Hz, *J* = 1.0 Hz, 1H), 8.07-8.03 (m, 2H), 7.88 (dd, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H), 7.80 (d, *J* = 16.0 Hz, 1H), 7.32-7.27 (m, 2H), 6.97-6.94 (m, 1H), 6.89 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 181.8, 157.2, 145.7, 138.5, 135.1, 133.0, 132.1, 128.9, 128.5, 121.2, 120.6, 119.4, 116.2.

(*E*)-4-(2-hydroxyphenyl)but-3-en-2-one (2l):

White solid, 58% yield (0.94 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 16.4 Hz, 1H), 7.45 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.42 (s, 1H), 7.26-7.22 (m, 1H), 7.00 (d, *J* = 16.4 Hz, 1H), 6.92-6.89 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3, 156.2, 140.9, 132.1, 129.9, 127.9, 121.7, 120.9, 116.8, 27.1.

General Procedure for the Synthesis of Chroman Derivatives 4:

In a round bottomed flask, *ortho*-hydroxy-α,β-unsaturated ketone **2** (0.1 mmol, 1 equiv), *trans*-β-nitrostyrene **3** (0.12 mmol, 1.2 equiv), catalyst **1h** (10 mol %) and toluene (1.0 ml) were added and stirred at 50 °C. After the completion of reaction, the solvent was evaporated on a rotary evaporator and the crude mixture was purified on silica gel column chromatography using hexane/ethyl acetate or hexane/DCM as eluents to provide the pure product **4**.

2-((2*R*,3*S*,4*R*)-3-Nitro-2-phenylchroman-4-yl)-1-phenylethan-1-one (4a):

The compound was obtained as a white solid in 72% yield (26.8 mg) and >99% ee; m.p. = 190-192 °C. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (n-hexane:2-propanol = 90:10, flow rate = 1.0 ml/min, λ = 254 nm), t_R(major) = 17.0 min, t_R(minor) = 21.3 min; $[\alpha]_D^{25}$ = –106.0 (*c* 0.1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J*= 7.2 Hz, 1H), 7.46-7.43 (m, 4H), 7.37 (m, 3H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 6.96-6.92 (m, 2H), 5.38 (d, *J* = 8.8 Hz, 1H), 5.26 (t, *J* = 9.2 Hz, 1H), 4.51-4.46 (m, 1H), 3.48 and 3.39 (ABqd, *J* = 18.8, 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 153.7, 136.4, 135.6, 133.9, 129.7, 129.1, 128.9, 128.6, 128.2, 127.4, 127.3, 128.8, 122.6, 117.5, 89.5, 78.8, 41.1, 36.3. IR (thin film): 3108, 2974, 2855, 1606, 1453, 1233, 1125, 752, 700 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{23}H_{20}NO_4$ $(M+H)^+$: 374.1387, found: 374.1389.

2-((2*R*,3*S*,4*R*)-3-Nitro-2-(p-tolyl)-chroman-4-yl)-1-phenylethan-1-one (4b):

The compound was obtained as a white solid in 59% yield (22.8 mg) and >99% ee; m.p. = 210-212 °C. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (n-hexane:2-propanol = 90:10, flow rate = 1.0 ml/min, λ = 254 nm), t_R(major) = 11.6 min, t_R(minor) = 15.0 min; $[\alpha]_D^{25}$ = –110.0 (*c* 0.1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.19-7.17 (m, 3H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.93 (t, *J* = 8.0 Hz, 1H), 5.34 (d, *J* = 8.8 Hz, 1H), 5.24 (t, *J* = 8.8 Hz, 1H), 4.50-4.45 (m, 1H), 3.48 and 3.38 (ABqd, *J* = 18.8 , 5.2 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 153.8, 139.7, 136.5, 133.8, 132.6, 129.8, 128.9, 128.6, 128.2, 127.4, 127.2, 122.8, 122.5, 117.5, 89.5, 78.7, 41.2, 36.3, 21.4. IR (thin film): 2980, 2857, 1594, 1443, 1121, 751, 698 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{24}H_{22}NO_4$ $(M+H)^+$: 388.1543, found: 388.1541.

2-((2*R*,3*S*,4*R*)-3-Nitro-2-(o-tolyl)-chroman-4-yl)-1-phenylethan-1-one (4c):

The compound was obtained as a white solid in 63% yield (24.4 mg) and 98% ee; m.p. = 155-157 °C. The enantiomeric excess was determined by HPLC with a Chiralpak IA column (n-hexane:2-propanol = 90:10, flow rate = 1.0 ml/min, λ = 254 nm), t_R(minor) = 12.0 min, t_R(major) = 12.6 min; $[\alpha]_D^{25}$ = –122.0 (*c* 0.15 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.50-7.44 (m, 3H), 7.28-7.24 (m, 2H), 7.18-7.16 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 5.62 (d, *J* = 9.2 Hz, 1H), 5.41 (t, *J* = 9.2 Hz, 1H), 4.53-4.48 (m, 1H), 3.57 and 3.44 (ABqd, *J* = 18.4, 4.4 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 154.1, 137.1, 136.5, 133.9, 133.4, 131.5, 129.7, 128.9, 128.6, 128.2, 127.4, 127.3, 126.8, 122.9, 122.6, 117.5, 88.2, 75.7, 41.0, 36.9, 19.4. IR (thin

film): 3107, 2859, 1587, 1454, 1397, 1125, 753, 701 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{24}H_{21}NO_4Na$ $(M+Na)^+$: 410.1363, found: 410.1392.

2-((2*R*,3*S*,4*R*)-2-(4-Fluorophenyl)-3-nitrochroman-4-yl)-1-phenylethan-1-one (4d):

The compound was obtained as a white solid in 74% yield (28.9 mg) and >99% ee; m.p. = 200-202 °C. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (n-hexane:2-propanol = 90:10, flow rate = 1.0 ml/min, λ = 254 nm), t_R(major) = 13.4 min, t_R(minor) = 20.2 min; $[\alpha]_D^{25}$ = –98.0 (*c* 0.1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 7.2 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.48-7.41 (m, 4H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.10-7.05 (m, 3H), 6.98-6.92 (m, 2H), 5.31 (d, *J* = 8.8 Hz, 1H), 5.21 (t, *J* = 9.2 Hz, 1H), 4.49-4.44 (m, 1H), 3.55 and 3.41 (ABqd, *J* = 18.4, 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 163.5 (d, *J* = 247 Hz), 153.6, 136.4, 133.9, 131.4 (d, *J* = 3.2 Hz), 129.3 (d, *J* = 8.5 Hz), 128.9, 128.6, 128.2, 127.3, 122.7, 117.5, 116.2 (d, *J* = 22 Hz), 89.7, 78.4, 40.8, 36.6. IR (thin film): 3578, 3077, 2980, 2875, 1597, 1448, 1228, 1121, 700 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{23}H_{18}FNO_4Na$ $(M+Na)^+$: 414.1112, found: 414.1121.

2-((2*R*,3*S*,4*R*)-2-(2-Bromophenyl)-3-nitrochroman-4-yl)-1-phenylethan-1-one (4e):

The compound was obtained as a white solid in 86% yield (38.9 mg) and 97% ee; m.p. = 55-57 °C. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (n-hexane:2-propanol = 90:10, flow rate = 1.0 ml/min, λ = 254 nm), t_R(major) = 14.0 min, t_R(minor) = 24.5 min; $[\alpha]_D^{25}$ = –121.0 (*c* 0.1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 7.2 Hz, 2H), 7.57-7.54 (m, 3H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.24-7.18 (m, 2H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.99-6.94 (m, 2H), 5.95 (d, *J* = 8.0 Hz, 1H), 5.55 (t, *J* = 8.0 Hz, 1H), 4.54-4.49 (m, 1H), 3.42 and 3.34 (ABqd, *J* = 18.4, 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 153.5, 136.4, 135.0, 133.9, 133.8, 131.0, 129.1, 128.9, 128.7, 128.2, 128.1, 127.7, 123.7, 122.7, 122.5, 117.4, 86.8, 77.2, 41.2, 35.9. IR (thin film): 3794, 3384, 2991, 2875, 1595, 1444, 1226, 1120, 1043, 751 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{23}H_{19}BrNO_4$ $(M+H)^+$: 452.0493 and 454.0473, found: 452.0468 and 454.0450.

2-((2*R*,3*S*,4*R*)-3-Nitro-2-(2-nitrophenyl)-chroman-4-yl)-1-phenylethan-1-one (4f):

The compound was obtained as a semi solid in 57% yield (23.8 mg) and 96% ee. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (n-hexane:2-propanol = 80:20, flow rate = 1.0 ml/min, λ = 254 nm), t_R(major) = 19.6 min, t_R(minor) = 40.1 min; $[\alpha]_D^{25}$ = –248.0 (*c* 0.1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.87 (m, 3H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.59-7.51 (m, 2H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.95 (t, *J* = 8.0 Hz, 2H), 6.01 (d, *J* = 8.8 Hz, 1H), 5.55 (t, *J* = 8.8 Hz, 1H), 4.49-4.44 (m, 1H), 3.54 and 3.42 (ABqd, *J* =

18.6, 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 153.3, 149.3, 136.4, 133.9, 133.5, 130.6, 130.3, 129.8, 129.0, 128.7, 128.2, 127.4, 125.3, 123.1, 122.7, 117.4, 88.2, 74.8, 40.9, 36.5. IR (thin film): 3325, 3024, 2842, 1591, 1420, 1124, 1043, 859, 754 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{23}H_{18}N_2O_6Na$ $(M+Na)^+$: 441.1057, found: 441.1044.

2-((2*R*,3*S*,4*R*)-3-Nitro-2-(4-nitrophenyl)-chroman-4-yl)-1-phenylethan-1-one (4g):

The compound was obtained as a white solid in 75% yield (31.4 mg) and >99% ee; m.p. = 190-192 °C. The enantiomeric excess was determined by HPLC with a Chiralpak IA column (n-hexane:2-propanol = 80:20, flow rate = 1.0 ml/min, λ = 254 nm), t_R(major) = 24.2 min, t_R(minor) = 26.2 min; $[\alpha]_D^{25}$ = –105.4 (*c* 0.13 in $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 7.6 Hz, 2H), 7.81 (d, *J* = 7.2 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.94-6.89 (m, 2H), 5.37 (d, *J* = 9.2 Hz, 1H), 5.19 (t, *J* = 9.2 Hz, 1H), 4.43-4.38 (m, 1H), 3.50 and 3.36 (ABqd, *J* = 18.8, 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 153.2, 148.8, 142.6, 136.4, 134.0, 129.0, 128.8, 128.4, 127.3, 124.4, 124.3, 123.3, 122.6, 117.5, 89.4, 77.9, 40.7, 36.6. IR (thin film): 3367, 3015, 2840, 1594, 1413, 1121, 1044, 858, 757, 696 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{23}H_{18}N_2O_6Na$ $(M+Na)^+$: 441.1057, found: 441.1032.

2-((2*R*,3*S*,4*R*)-2-(4-Chlorophenyl)-3-nitrochroman-4-yl)-1-phenylethan-1-one (4h):

The compound was obtained as a white solid in 71% yield (28.9 mg) and 81% ee; m.p. = 230-232 °C. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (n-hexane:2-propanol = 90:10, flow rate = 1.0 ml/min, λ = 254 nm), t_R(major) = 13.4 min, t_R(minor) = 30.1 min; $[\alpha]_D^{25}$ = –93.0 (*c* 0.1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.2 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.37-7.34 (m, 4H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.98-6.93 (m, 2H), 5.32 (d, *J* = 8.8 Hz, 1H), 5.21 (t, *J* = 9.2 Hz, 1H), 4.48-4.43 (m, 1H), 3.52 and 3.39 (ABqd, *J* = 18.8, 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 153.5, 136.4, 135.8, 134.1, 139.9, 129.5, 129.0, 128.7, 128.6, 128.2, 127.3, 122.8, 122.7, 117.5, 89.5, 78.3, 40.9, 36.5. IR (thin film): 3078, 2991, 2841, 1682, 1552, 1372, 1226, 1092, 756, 435 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{23}H_{18}ClNO_4Na$ $(M+Na)^+$: 430.0817, found: 430.0819.

2-((2*R*,3*S*,4*R*)-2-(2,4-dichlorophenyl)-3-nitrochroman-4-yl)-1-phenylethan-1-one (4i):

The compound was obtained as a white solid in 59% yield (26.1 mg) and 98% ee; m.p. = 125-127 °C. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (n-hexane:2-propanol = 90:10, flow rate = 1.0 ml/min, λ = 254 nm), t_R(major) = 11.5 min, t_R(minor) = 29.6 min; $[\alpha]_D^{25}$ = –56.0 (*c* 0.1 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H),

7.50 (d, *J* = 8.5 Hz, 1H), 7.44 (t, *J* = 6.0 Hz, 2H), 7.36 (d, *J* = 2.5 Hz, 1H), 7.31 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.97-6.94 (m, 2H), 5,87 (d, *J* = 8.0 Hz, 1H), 5.48 (t, *J* = 8.5 Hz, 1H), 4.50-4.46 (m, 1H), 3.47 and 3.35 (ABqd, *J* = 18.5, 5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.6, 153.4, 136.4, 136.3, 134.7, 134.0, 132.1, 130.4, 130.0, 129.0, 128.8, 128.2, 128.1, 127.6, 122.9, 122.5, 117.5, 86.8, 74.9, 41.0, 36.1. IR (thin film): 3676, 3020, 1683, 1593, 1552, 1365, 1231, 759 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{23}H_{17}Cl_2NO_4Na$ $(M+Na)^+$: 464.0427, found: 464.0434.

2-((2*R*,3*S*,4*R*)-2-Cyclohexyl-3-nitrochroman-4-yl)-1-phenylethan-1-one (4j):

The compound was obtained as a white solid in 92% yield (34.9 mg) and 89% ee; m.p. = 150-152 °C. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (n-hexane:2-propanol = 95:5, flow rate = 1.0 ml/min, λ = 254 nm), t_R(major) = 7.5 min, t_R(minor) = 10.1 min; $[\alpha]_D^{25}$ = –34.5 (*c* 0.2 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.2 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.91-6.86 (m, 2H), 5.09 (t, *J* = 9.2 Hz, 1H), 4.37-4.32 (m, 1H), 4.15 (dd, *J* = 9.2, 1.6 Hz, 1H), 3.50 and 3.31 (ABqd, *J* = 18.4, 4.8 Hz, 2H), 1.86-1.78 (m, 3H), 1.67-1.55 (m, 4H), 1.41-1.17 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 154.0, 136.5, 133.8, 129.0, 128.3, 128.2, 127.3, 123.3, 122.2, 117.3, 86.0, 80.5, 41.3, 38.9, 36.4, 29.7, 26.5, 26.3, 26.1, 25.5. IR (thin film): 3373, 3017, 1598, 1413, 1121, 1046, 857, 748 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{23}H_{25}NO_4Na$ $(M+Na)^+$: 402.1676, found: 402.1680.

2-((2*R*,3*S*,4*R*)-6-Bromo-3-nitro-2-phenylchroman-4-yl)-1-phenylethan-1-one (4l):

The compound was obtained as a white solid in 62% yield (28.0 mg) and 96% ee; m.p. = 175-177 °C. The enantiomeric excess was determined by HPLC with a Chiralpak IA column (n-hexane:2-propanol = 90:10, flow rate = 1.0 ml/min, λ = 254 nm), t_R(minor) = 14.5 min, t_R(major) = 16.9 min; $[\alpha]_D^{25}$ = –28.0 (*c* 0.1 in $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.44-7.36 (m, 7H), 7.28 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.22-7.21 (m, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 5.39 (d, *J* = 8.0 Hz, 1H), 5.27 (t, *J* = 8.4 Hz, 1H), 4.41-4.37 (m, 1H), 3.44 and 3.33 (ABqd, *J* = 18.8, 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 152.8, 136.2, 135.3, 134.0, 131.6, 130.1, 129.8, 129.2, 129.0, 128.2, 127.1, 125.0, 119.4, 114.8, 88.6, 78.8, 40.9, 35.8. IR (thin film): 3156, 2985, 2857, 1739, 1599, 1450, 1228, 1121, 753, 700 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{23}H_{18}BrNO_4Na$ $(M+Na)^+$: 474.0311 and 476.0292, found: 474.0302 and 476.0298.

2-((2*R*,3*S*,4*R*)-6-Chloro-3-nitro-2-phenylchroman-4-yl)-1-phenylethan-1-one (4m):

The compound was obtained as a white solid in 71% yield (29.0 mg) and >99% ee; m.p. = 185-187 °C. The enantiomeric excess was determined by HPLC with a Chiralpak IA column (n-hexane:2-propanol =

90:10, flow rate = 1.0 ml/min, λ = 254 nm), t_R(minor) = 13.6 min, t_R(major) = 15.9 min; $[\alpha]_D^{25}$ = –56.9 (*c* 0.1 in $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.2 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.46-7.36 (m, 7H), 7.14 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.07 (d, *J* = 1.6 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 5.39 (d, *J* = 8.4 Hz, 1H), 5.27 (t, *J* = 8.4 Hz, 1H), 4.42-4.37 (m, 1H), 3.45 and 3.34 (ABqd, *J* = 19.0, 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 152.3, 136.2, 135.3, 134.0, 129.8, 129.2, 129.0, 128.7, 128.2, 127.5, 127.15, 127.12, 124.5, 118.9, 88.7, 78.8, 40.9, 36.0. IR (thin film): 3363, 2883, 1680, 1594, 1456, 1364, 1231, 1121, 702 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{23}H_{18}ClNO_4Na$ $(M+Na)^+$: 430.0817, found: 430.0816.

2-((2*R*,3*S*,4*R*)-6-methoxy-3-nitro-2-phenylchroman-4-yl)-1-phenylethan-1-one (4n):

The compound was obtained as a white solid in 67% yield (27.0 mg) and 99% ee; m.p. = 220-222 °C. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (n-hexane:2-propanol = 90:10, flow rate = 1.0 ml/min, λ = 254 nm), t_R(major) = 19.1 min, t_R(minor) = 34.8 min; $[\alpha]_D^{25}$ = –88.0 (*c* 0.1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.45-7.35 (m, 7H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.74 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 5.31 (d, *J* = 8.4 Hz, 1H), 5.22 (t, *J* = 8.8 Hz, 1H), 4.46-4.41 (m, 1H), 3.65 (s, 3H), 3.45 and 3.36 (ABqd, *J* = 18.8, 5.6 Hz, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 154.9, 147.8, 136.5, 135.8, 133.9, 129.7, 129.1, 128.9, 128.2, 127.2, 123.7, 118.2, 114.3, 112.3, 89.8, 79.0, 55.8, 41.4, 36.5. IR (thin film): 3021, 2884, 1598, 1418, 1122, 1043, 858 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{24}H_{21}NO_5Na$ $(M+Na)^+$: 426.1312, found: 426.1318.

2-((2*R*,3*S*,4*R*)-8-methoxy-3-nitro-2-phenylchroman-4-yl)-1-phenylethan-1-one (4o):

The compound was obtained as a white solid in 32% yield (12.9 mg) and 98% ee; m.p. = 205-210 °C. The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (n-hexane:2-propanol = 90:10, flow rate = 1.0 ml/min, λ = 254 nm), t_R(major) = 29.6 min, t_R(minor) = 33.0 min; $[\alpha]_D^{25}$ = –113.3 (*c* 0.12 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* =7.2 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.44-7.40 (m, 4H), 7.34-7.33 (m, 3H), 6.89 (t, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 5.48 (d, *J* = 8.0 Hz, 1H), 5.27 (t, *J* = 8.0 Hz, 1H), 4.49-4.44 (m, 1H), 3.85 (s, 3H), 3.40-3.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 148.8, 143.2, 136.4, 135.6, 133.8, 129.5, 129.1, 128.9, 128.2, 127.1, 123.6, 122.2, 119.0, 110.6, 89.2, 78.7, 56.2, 41.5, 35.8. IR (thin film): 2923, 1683, 1544, 1264, 1207, 1024, 750, 653 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{24}H_{21}NO_5Na$ $(M+Na)^+$: 426.1312, found: 426.1302.

1-(2-Methoxyphenyl)-2-((2*R*,3*S*,4*R*)-3-nitro-2-phenylchroman-4-yl)ethan-1-one (4q):

The compound was obtained as a white solid in 40% yield (16.1 mg) and 94% ee; m.p. = 150-155 °C. The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (n-hexane:2-propanol =

90:10, flow rate = 1.0 ml/min, λ = 254 nm), t_R(major) = 15.7 min, t_R(minor) = 20.0 min; $[\alpha]_D^{25}$ = –85.4 (*c* 0.11 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.49-7.37 (m, 6 H), 7.15 (t, *J* = 8.4 Hz, 2H), 7.00-6.93 (m, 4H), 5.31 (d, *J* = 8.4 Hz, 1H), 5.24 (t, *J* = 9.2 Hz, 1H), 4.43-4.38 (m, 1H), 3.86 (s, 3H), 3.58 and 3.41 (ABqd, *J* = 19.2, 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 158.9, 153.7, 135.7, 134.4, 130.8, 129.7, 129.0, 128.3, 127.6, 127.4, 127.3, 123.2, 122.4, 121.0, 117.4, 111.7, 89.9, 79.0, 55.6, 46.2, 37.0. IR (thin film): 3025, 2839, 1597, 1318, 1124, 1044, 857, 754 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{24}H_{21}NO_5Na$ $(M+Na)^+$: 426.1312, found: 426.1335.

1-(3-Bromophenyl)-2-((2*R*,3*S*,4*R*)-3-nitro-2-phenylchroman-4-yl)ethan-1-one (4r):

The compound was obtained as a white solid in 84% yield (38.0 mg) and 97% ee; m.p. = 220-222 °C. The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (n-hexane:2-propanol = 95:5, flow rate = 1.0 ml/min, λ = 254 nm), t_R(minor) = 22.3 min, t_R(major) = 30.2 min; $[\alpha]_D^{25}$ = –89.1 (*c* 0.11 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (t, *J* = 1.6 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.41-7.31 (m, 6H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 7.00-6.93 (m, 2H), 5.39 (d, *J* = 8.4 Hz, 1H), 5.23 (t, *J* = 8.8 Hz, 1H), 4.48-4.44 (m, 1H), 3.43 and 3.33 (ABqd, *J* = 18.8, 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 153.7, 138.1, 136.7, 135.6, 131.3, 130.5, 129.8, 129.1, 128.7, 127.3, 127.2, 127.8, 126.7, 122.6, 122.5, 117.6, 89.3, 78.7, 41.3, 36.2. IR (thin film): 3020, 2841, 1691, 1544, 1231, 1047, 758, 696 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{23}H_{18}BrNO_4Na$ $(M+Na)^+$: 474.0311 and 476.0292, found: 474.0284 and 476.0292.

1-(3-Bromophenyl)-2-((2*R*,3*S*,4*R*)-3-nitro-2-phenylchroman-4-yl)ethan-1-one (4s):

The compound was obtained as a white solid in 78% yield (35.3 mg) and 98% ee; m.p. = 185-187 °C. The enantiomeric excess was determined by HPLC with a Chiralpak IA column (n-hexane:2-propanol = 95:5, flow rate = 1.0 ml/min, λ = 254 nm), t_R(minor) = 33.9 min, t_R(major) = 41.4 min; $[\alpha]_D^{25}$ = –89.2 (*c* 0.13 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.46-7.41 (m, 5H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.10-6.99 (m, 3H), 5.42 (d, *J* = 8.5 Hz, 1H), 5.27 (t, *J* = 8.5 Hz, 1H), 4.50 (br s, 1H), 3.46 and 3.38 (ABqd, *J* = 19.0, 4.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.7, 153.7, 135.6, 135.1, 132.3, 129.8, 129.7, 129.2, 128.7, 127.3, 127.2, 126.8, 122.6, 122.5, 117.6, 89.5, 78.8, 41.1, 36.2. IR (thin film): 3731, 3022, 2908, 1682, 1540, 1227, 1071, 812 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{23}H_{17}BrNO_4Na$ $(M+Na)^+$: 474.0311 and 476.0292 found: 474.0304 and 476.0296.

1-(Furan-2-yl)-2-((2*R*,3*S*,4*R*)-3-nitro-2-phenylchroman-4-yl)ethan-1-one (4t):

The compound was obtained as a white solid in 70% yield (25.4 mg) and 97% ee; m.p. = 170-172 °C. The enantiomeric excess was determined by HPLC with a Chiralpak ID column (n-hexane:2-propanol =

80:20, flow rate = 1.0 ml/min, λ = 254 nm), t_R(major) = 19.1 min, t_R(minor) = 35.9 min; $[\alpha]_D^{25}$ = –127.5 (*c* 0.12 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J* = 1.5 Hz, 1H), 7.43-7.37 (m, 5H), 7.17-7.12 (m, 3H), 6.97-6.93 (m, 2H), 6.52 (dd, *J* = 4.0, 2.0 Hz, 1H), 5.32 (d, *J* = 8.5 Hz, 1H), 5.26 (t, *J* = 9.0 Hz, 1H), 4.43-4.39 (m, 1H), 3.39 and 3.24 (ABqd, *J* = 18.4, 4.5 Hz, 2H);^{13}C NMR (125 MHz, $CDCl_3$): δ 185.9, 153.7, 152.4, 146.9, 135.5, 129.8, 129.1, 128.6, 127.4, 127.3, 122.6, 122.5, 117.7, 117.5, 112.7, 89.5, 78.9, 40.5, 36.2. IR (thin film): 3732, 3020, 2842, 1673, 1554, 1230, 1024, 754 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{21}H_{17}NO_5$ $(M+H)^+$: 364.1179, found: 364.1209.

2-((2*R*,3*S*,4*R*)-3-Nitro-2-phenylchroman-4-yl)-1-(thiophen-2-yl)ethan-1-one (4u):

The compound was obtained as a white solid in 66% yield (25.0 mg) and 96% ee; m.p. = 190-192 °C. The enantiomeric excess was determined by HPLC with a Chiralpak ID column (n-hexane:2-propanol = 80:20, flow rate = 1.0 ml/min, λ = 254 nm), t_R(major) = 18.8 min, t_R(minor) = 46.2 min; $[\alpha]_D^{25}$ = –119.0 (*c* 0.1 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.61 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.46-7.43 (m, 2H), 7.41-7.38 (m, 3H), 7.19-7.16 (m, 1H), 7.13-7.10 (m, 2H), 6.98-6.93 (m, 2H), 5.36 (d, *J* = 9.0 Hz, 1H), 5.27 (t, *J* = 9.0 Hz, 1H), 4.45-4.41 (m, 1H), 3.41 and 3.31 (ABqd, *J* = 18.5, 5.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.5, 153.7, 143.5, 135.6, 134.6, 132.3, 129.8, 129.1, 128.7, 128.4, 127.4, 127.3, 122.6, 122.5, 117.6, 89.4, 78.8, 41.5, 36.4. IR (thin film): 3022, 2839, 1652, 1545, 1229, 1049, 701 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{21}H_{18}NO_4S$ $(M+H)^+$: 380.0951, found: 380.0972.

Procedure for the synthesis of 5e:[5h]

In a round bottomed flask equipped with stirring bar, **4e** (0.1 mmol) and acetic acid (1 ml) were added. The solution was cooled to 0 °C and Zn powder (2.5 mmol, 25 equiv) was added to it. The reaction mixture was allowed to come at room temperature and stirred for 8h. After the reaction, ethyl acetate (20 ml) was added and passed through celite plug to remove the solid residue. The solvent was evaporated and 30 ml DCM were added. The organic layer was washed with saturated sodium bicarbonate solution (2 x 5 ml) and dried over sodium sulphate. The solution was filtered, concentrated on a rotary evaporator and purified by silica gel chromatography to afford the pure product **5e**.

(2*R*,3a*S*,4*R*,9b*R*)-4-(2-Bromophenyl)-2-phenyl-1,2,3,3a,4,9b-hexahydrochromeno[3,4-b]pyrrole (5e):

The compound was obtained as a semi solid in 60% yield (24.3 mg) and 97% ee. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (n-hexane:2-propanol = 98:2, flow rate = 1.0 ml/min, λ = 254 nm), t_R(minor) = 9.3 min, t_R(major) = 14.1 min; $[\alpha]_D^{25}$ = +65.0 (*c* 0.12 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.52-7.48 (m, 3H), 7.38-7.31 (m, 3H), 7.23-

7.13 (m, 3H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.91-6.86 (m, 2H), 5.83 (d, *J* = 9.5 Hz, 1H), 4.60 (dd, *J* = 8.5, 4.0 Hz, 1H), 3.37 (t, *J* = 10.5 Hz, 1H), 3.27-3.21 (m, 1H), 2.35-2.31 (m, 2H), 1.87 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 147.0, 139.2, 133.3, 129.9, 128.8, 128.5, 128.1, 128.0, 126.8, 126.7, 126.1, 125.7, 123.7, 120.6, 115.9, 82.7, 65.9, 60.7, 41.2, 37.7. IR (thin film): 3087, 2913, 1464, 1378, 1265, 1236, 1120, 1028, 742, 658, 456 cm^{-1}. HRMS (m/z, ESI) calcd for $C_{23}H_{21}BrNO$ $(M+H)^+$: 406.0801 and 408.0782 found: 406.0801 and 408.0831.

SUPPORTING INFORMATION:

The supplementary crystallographic data (CIF File) for the compound **4m** has been provided in the Supporting Information. CCDC 1056755 contains supplementary crystallographic data for the structure **4m**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data_request/cif. Copies of NMR spectra and HPLC chromatograms are available in the supporting information. This material is available free of charge via the Internet at *http:// pubs.acs.org.*

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Notes

The authors declare no competing financial interest.

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