JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

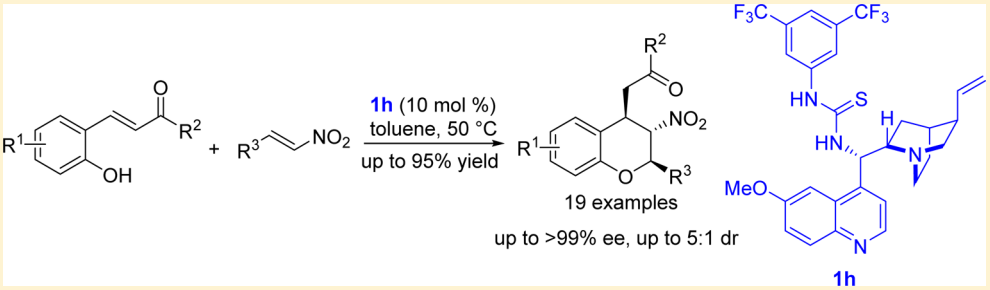
Enantioselective Synthesis of Highly Substituted Chromans via the Oxa-Michael−Michael Cascade Reaction with a Bifunctional Organocatalyst

Prasenjit Saha,[†] Arnab Biswas,[†] Nagaraju Molleti,[†] and Vinod K. Singh*[,†,‡]

[†]Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhopal 462066, India

[‡]Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India

Supporting Information



ABSTRACT: A highly enantioselective synthesis of chiral chroman derivatives via an oxa-Michael−Michael cascade reaction has been developed using a 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 that 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 in 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 anticlastogenic activity against both mytomicin C and bleomycin C.[2d] Epiconicol shows cytotoxic activities against P388, A549, HT29, and CV1 cells.[2e] Because of the importance of polysubstituted chiral chromans, the development of new asymmetric strategies for their synthesis has become an active field of research.

Organocatalyzed cascade reactions have become powerful synthetic tools for the construction of heterocyclic compounds having multiple stereocenters in a single step.[3] The 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 a lack of control of 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 effort has been spent by several scientific groups for the asymmetric synthesis of chiral chroman derivatives.[5,6] Gu et al. employed thiourea alkaloid 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's 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 the cascade oxa-Michael−Michael reaction from *o*-hydroxy-substituted *α,β*-unsaturated ketones[9] and *trans*-nitroalkenes using a 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 the 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**, 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 the 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, and 85:15 dr (Table 1, entry 6)], whereas no reaction was observed

Received: July 28, 2015
Published: October 15, 2015

DOI: 10.1021/acs.joc.5b01751
J. Org. Chem. 2015, 80, 11115−11122

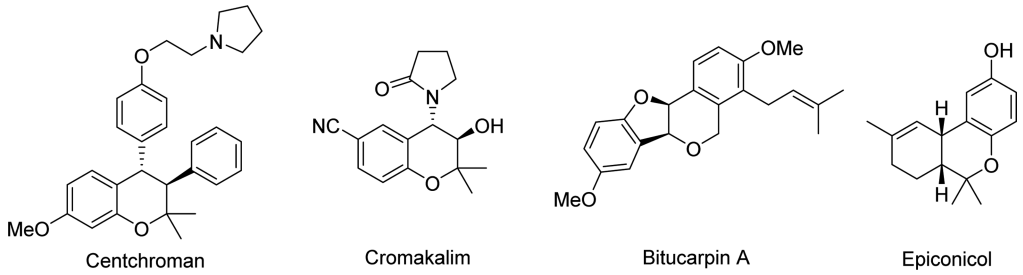
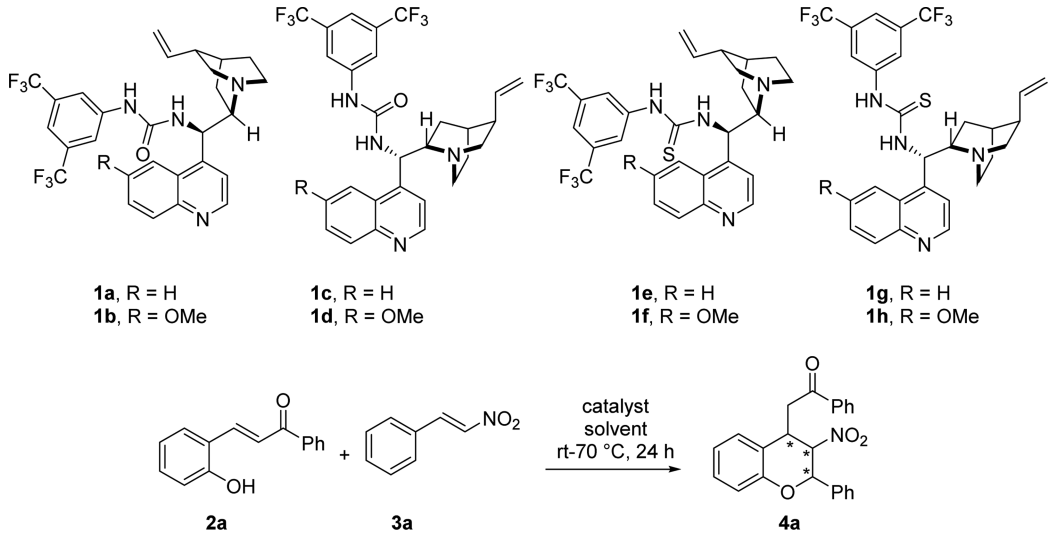


Figure 1. Selected examples of biologically active chroman compounds.

Table 1. Screening of Reaction Conditions[a]



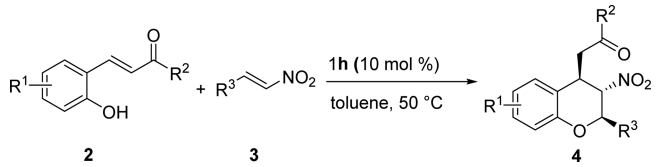
entry	catalyst	solvent	temp (°C)	yield[b] (%)	dr[c] (%)	ee[d] (%)
1	**1a**	DCE	70	70	85:15	95
2	**1a**	CH_3CN	70	49	80:20	99
3	**1a**	THF	70	62	80:20	94
4	**1a**	EtOAc	70	40	78:22	98
5	**1a**	MeOH	70	<5	nd	nd
6	**1a**	toluene	70	68	85:15	97
7	**1a**	toluene	rt	35	87:13	99
8	**1a**	toluene	50	70	85:15	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 conducted with **2a** (0.1 mmol), *trans*-β-nitrostyrene **3a** (0.12 mmol), catalyst **1** (10 mol %), and solvent (1.0 mL) and the mixture stirred at the listed temperatures for 24 h. [b]Isolated yield of a mixture of diastereoisomers. [c]dr was calculated from ^{1}H NMR of the crude reaction mixture. [d]Determined by chiral HPLC using an OD-H column. [e]With 2.5 mol % catalyst. [f]With 5 mol % catalyst. [g]With 1.5 equiv of nitrostyrene.

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 in a low yield (35%), whereas at 50 °C, product **4a** was obtained in 70% yield (99% ee). There was no significant improvement in diastereoselectivity with a further decrease or increase in the temperature of the reaction. Next, we screened various cinchona-alkaloid-derived urea and thiourea organocatalysts **1a**–**h**. Among all the catalysts, **1h** gave the best results, producing product **4a** in >99% ee and 72% yield (Table 1, entry 17). We then studied

DOI: 10.1021/acs.joc.5b01751
J. Org. Chem. 2015, 80, 11115–11122

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



2 3 4

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	83:17	>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[g]	nd[g]
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[f]	–	–
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[f]	–	–

[a]The reaction was conducted with **2** (0.1 mmol), **3** (0.12 mmol), and catalyst **1h** (10 mol %) in toluene (1.0 mL) at 50 °C. [b]Isolated yield of a mixture of diastereoisomers. [c]dr was calculated from ^{1}H NMR of the crude reaction mixture. [d]Determined by chiral HPLC analysis. [e]The reaction was conducted at room temperature (25 °C). [f]No reaction. [g]Not determined.

the effect of catalyst loading in the reaction of **2a** and **3a** (Table 1, entries 18 and 19). The products were obtained in moderate yield and the same level of enantioselectivity with a decrease in catalyst loading from 10 to 2.5 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.

After the optimization of reaction conditions, we have explored the substrate scope of this reaction. First, we have studied the effect of the substituent on *trans*-nitroalkenes **3**. *trans*-*β*-Nitroalkenes **3b** and **3c** with electron-donating groups took longer to afford the corresponding chromans **4b** and **4c**, respectively, with excellent enantioselectivities (98–99% ee and 59–63% yield) whereas with *trans*-*β*-nitrostyrenes having electron-withdrawing groups on the phenyl ring such as F, Cl, Br, and NO_2, the reaction proceeded smoothly to give 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 an electron-withdrawing group. Furthermore, substrate **3j** with an 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 substrate **2a**. Substrate **2** with electron-donating and -withdrawing substituents such as Br, Cl, and OMe on both aromatic rings underwent the cascade oxa-Michael–Michael reaction to afford the desired product in high enantioselectivities and high yields (up to 99% ee). Substrates **2** with a methoxy group *ortho* to hydroxy group as well as a keto group (Table 2, entries 15 and 17) took longer to provide the product in high ee (up to 98%) and moderate yield (32–40%). A steric effect could be the probable reason for such a disparity in reaction time and yield. In the case of substrate **2f** with a nitro group, no product was achieved after a 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 and 21)]. However, when an aliphatic chalcone **2l** was examined, we did not observe any reaction. It may be due to the lower electrophilicity of the carbonyl carbon due to the electron donating effect of CH_3. The absolute configuration of product **4m** was determined to be (2*R*,3*S*,4*R*) by single-crystal X-ray diffraction analysis [CCDC 1056755 (see the Supporting Information)].

In addition, we have shown the synthetic utility of our methodology by transforming chroman derivatives to tricyclic chroman. The tricyclic chiral chromans show potential biological activities.[10] The reductive amination of product **4e** afforded 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 the newly generated chiral center in **5e** was ascertained by a NOE experiment.

DOI: 10.1021/acs.joc.5b01751
J. Org. Chem. 2015, 80, 11115–11122

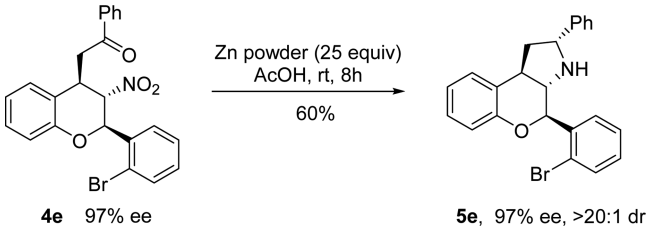


Figure 2. Synthesis of tricyclic chiral chroman **5e**.

In summary, we have developed an efficient strategy for the construction of polysubstituted chiral chroman derivatives using a 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 conducted 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 the 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) are relative to the resonance of the deuterated solvent as the internal standard ($CDCl_3$ at δ 7.24 DMSO-d_6 at δ 2.50 for ^{1}H NMR, $CDCl_3$ at δ 77.20 and DMSO-d_6 at δ 39.50 for ^{13}C NMR). Data for ^{1}H NMR are reported as follows: chemical Shifts (δ), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; ABq, AB quartet; m, multiplet or unresolved), coupling constant(s) in hertz, integration. Data for ^{13}C NMR are reported in terms of chemical shifts (δ). High-resolution mass spectra (HRMS) were recorded with 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 2-propanol and *n*-hexane as eluents. X-ray data were recorded on a single-crystal X-ray diffractometer.

General Procedure for the Synthesis of 2. Substituted salicylaldehyde (5 mmol) and substituted acetophenone were dissolved in 5 mL of MeOH and cooled to 0 °C. Then, 40% aqueous NaOH (1.3 mL) was added dropwise to the mixture. The reaction mixture was allowed to come to room temperature and stirred overnight. The solvent was evaporated, and 1 M aqueous HCl (10 mL) was added to it. The aqueous layer was extracted with ethyl acetate (3 × 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 data 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, 1.0 Hz, 1H), 8.07–8.03 (m, 2H), 7.88 (dd, J = 8.0, 1.5 Hz, 1H), 7.80 (d, J = 16.0 Hz, 1H), 7.32–7.27 (m, 2H), 6.97–6.94

DOI: 10.1021/acs.joc.5b01751
J. Org. Chem. 2015, 80, 11115–11122

(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, *o*-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 the mixture was stirred at 50 °C. After the completion of reaction, the solvent was evaporated on a rotary evaporator and the crude mixture was purified via silica gel column chromatography using hexane/ethyl acetate or hexane/DCM eluent to provide pure product **4**.

*2-[(2R,3S,4R)-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 (mp 190−192 °C). The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 *n*-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{23}H_{20}NO_4$ (M + H)$^+$ m/z 374.1387, found m/z 374.1389.

*2-[(2R,3S,4R)-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 (mp 210−212 °C). The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 *n*-hexane:2-propanol, flow rate of 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, 2H), 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 (ESI) calcd for $C_{24}H_{22}NO_4$ (M + H)$^+$ m/z 388.1543, found m/z 388.1541.

*2-[(2R,3S,4R)-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 (mp 155−157 °C). The enantiomeric excess was determined by HPLC with a Chiralpak IA column (90:10 *n*-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{24}H_{21}NO_4Na$ (M + Na)$^+$ m/z 410.1363, found m/z 410.1392.

*2-[(2R,3S,4R)-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 (mp 200−202 °C). The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 *n*-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{23}H_{18}FNO_4Na$ (M + Na)$^+$ m/z 414.1112, found m/z 414.1121.

*2-[(2R,3S,4R)-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 (mp 55−57 °C). The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 *n*-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{23}H_{19}BrNO_4$ (M + H)$^+$ m/z 452.0493 and 454.0473, found m/z 452.0468 and 454.0450.

*2-[(2R,3S,4R)-3-Nitro-2-(2-nitrophenyl)chroman-4-yl]-1-phenylethan-1-one (**4f**).* The compound was obtained as a semisolid in 57% yield (23.8 mg) and 96% ee. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (80:20 *n*-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{23}H_{18}N_2O_6Na$ (M + Na)$^+$ m/z 441.1057, found m/z 441.1044.

*2-[(2R,3S,4R)-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 (mp 190−192 °C). The enantiomeric excess was determined by HPLC with a Chiralpak IA column (80:20 *n*-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{23}H_{18}N_2O_6Na$ (M + Na)$^+$ m/z 441.1057, found m/z 441.1032.

*2-[(2R,3S,4R)-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 (mp 230−232 °C). The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 *n*-hexane:2-propanol, flow rate of 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,

DOI: 10.1021/acs.joc.5b01751
J. Org. Chem. 2015, 80, 11115−11122

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 (ESI) calcd for $C_{23}H_{18}ClNO_4Na$ $(M + Na)^+$ m/z 430.0817, found m/z 430.0819.

*2-[(2R,3S,4R)-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 (mp 125−127 °C). The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 *n*-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{23}H_{17}Cl_2NO_4Na$ $(M + Na)^+$ m/z 464.0427, found m/z 464.0434.

*2-[(2R,3S,4R)-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 (mp 150−152 °C). The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 *n*-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{23}H_{25}NO_4Na$ $(M + Na)^+$ m/z 402.1676, found m/z 402.1680.

*2-[(2R,3S,4R)-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 (mp 175−177 °C). The enantiomeric excess was determined by HPLC with a Chiralpak IA column (90:10 *n*-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{23}H_{18}BrNO_4Na$ $(M + Na)^+$ m/z 474.0311 and 476.0292, found m/z 474.0302 and 476.0298.

*2-[(2R,3S,4R)-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 (mp 185−187 °C). The enantiomeric excess was determined by HPLC with a Chiralpak IA column (90:10 *n*-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{23}H_{18}ClNO_4Na$ $(M + Na)^+$ m/z 430.0817, found m/z 430.0816.

*2-[(2R,3S,4R)-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 (mp 220−222 °C). The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 *n*-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{24}H_{21}NO_5Na$ $(M + Na)^+$ m/z 426.1312, found m/z 426.1318.

*2-[(2R,3S,4R)-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 (mp 205−210 °C). The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (90:10 *n*-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{24}H_{21}NO_5Na$ $(M + Na)^+$ m/z 426.1312, found m/z 426.1302.

*1-(2-Methoxyphenyl)-2-[(2R,3S,4R)-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 (mp 150−155 °C). The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (90:10 *n*-hexane:2-propanol, flow rate of 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, 6H), 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 (ESI) calcd for $C_{24}H_{21}NO_5Na$ $(M + Na)^+$ m/z 426.1312, found m/z 426.1335.

*1-(3-Bromophenyl)-2-[(2R,3S,4R)-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 (mp 220−222 °C). The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (95:5 *n*-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{23}H_{18}BrNO_4Na$ $(M + Na)^+$ m/z 474.0311 and 476.0292, found m/z 474.0284 and 476.0292.

*1-(3-Bromophenyl)-2-[(2R,3S,4R)-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 (mp 185−187 °C). The enantiomeric excess was determined by HPLC with a Chiralpak IA column (95:5 *n*-hexane:2-propanol, flow rate of 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,

DOI: 10.1021/acs.joc.5b01751
J. Org. Chem. 2015, 80, 11115−11122

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 (ESI) calcd for $C_{23}H_{17}BrNO_4Na$ $(M + Na)^+$ m/z 474.0311 and 476.0292, found m/z 474.0304 and 476.0296.

*1-(Furan-2-yl)-2-[(2R,3S,4R)-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 (mp 170−172 °C). The enantiomeric excess was determined by HPLC with a Chiralpak ID column (80:20 n-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{21}H_{17}NO_5$ $(M + H)^+$ m/z 364.1179, found m/z 364.1209.

*2-[(2R,3S,4R)-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 (mp 190−192 °C). The enantiomeric excess was determined by HPLC with a Chiralpak ID column (80:20 n-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{21}H_{18}NO_4S$ $(M + H)^+$ m/z 380.0951, found m/z 380.0972.

Procedure for the Synthesis of 5e.[5h] To a round-bottomed flask equipped with a stirring bar were added **4e** (0.1 mmol) and acetic acid (1 mL). 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 8 h. After the reaction, ethyl acetate (20 mL) was added and the mixture passed through Celite plug to remove the solid residue. The solvent was evaporated, and 30 mL of DCM was added. The organic layer was washed with a saturated sodium bicarbonate solution (2 × 5 mL) and dried over sodium sulfate. The solution was filtered, concentrated on a rotary evaporator, and purified by silica gel chromatography to afford pure product **5e**.

*(2R,3aS,4R,9bR)-4-(2-Bromophenyl)-2-phenyl-1,2,3,3a,4,9b-hexahydrochromeno[3,4-b]pyrrole (**5e**).* The compound was obtained as a semisolid in 60% yield (24.3 mg) and 97% ee. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 n-hexane:2-propanol, flow rate of 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 (ESI) calcd for $C_{23}H_{21}BrNO$ $(M + H)^+$ m/z 406.0801 and 408.0782, found m/z 406.0801 and 408.0831.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01751.

Copies of NMR spectra and HPLC chromatograms (PDF)

Crystallographic data for compound **4m**. CCDC 1056755 contains supplementary crystallographic data for 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 (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: vinodks@iitk.ac.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

V.K.S. thanks the Department of Science and Technology (DST), India, for a research grant through a J. C. Bose fellowship (DST, Government of India) and SERB, DST (SB/FT/CS-011/2014). P.S. and A.B. thank IISER Bhopal for their fellowship (PRS and SRF, respectively). N.M. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, for SRF.

■ REFERENCES

(1) (a) Buckner, S. A.; Milicic, I.; Daza, A.; Davis-Taber, R. D.; Scott, V. E. S.; Sullivan, J. P.; Brioni, J. D. *Eur. J. Pharmacol.* **2000**, *400*, 287. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939. (c) Trenor, S. R.; Shultz, A. R.; Love, B. J.; Long, T. E. *Chem. Rev.* **2004**, *104*, 3059. (d) Breschi, M. C.; Calderone, V.; Martelli, A.; Minutolo, F.; Rapposelli, S.; Testai, L.; Tonelli, F.; Balsamo, A. *J. Med. Chem.* **2006**, *49*, 7600. (e) Khelili, S.; Florence, X.; Bouhadja, M.; Abdelaziz, S.; Mechouch, N.; Mohamed, Y.; de Tullio, P. D.; Lebrun, P.; Pirotte, B. *Bioorg. Med. Chem.* **2008**, *16*, 6124. (f) Coi, A.; Bianucci, A. M.; Calderone, V.; Testai, L.; Digiacomo, M.; Rapposelli, S.; Balsamo, A. *Bioorg. Med. Chem.* **2009**, *17*, 5565.

(2) (a) Khan, S.; Shukla, S.; Sinha, S.; Lakra, A. D.; Bora, H. K.; Meeran, S. M. *Int. J. Biochem. Cell Biol.* **2015**, *58*, 1. (b) Lal, J. *Contraception* **2010**, *81*, 275. (c) Wang, S.; Liu, J.; Chang, Q.; Li, Y.; Jiang, Y.; Wang, S. *Neural Regen. Res.* **2010**, *5*, 678. (d) Pistelli, L.; Noccioli, C.; Appendino, G.; Bianchi, F.; Sterner, O.; Ballero, M. *Phytochemistry* **2003**, *64*, 595. (e) Hong, B.-C.; Kotame, P.; Tsai, C.-W.; Liao, J.-H. *Org. Lett.* **2010**, *12*, 776.

(3) For reviews on organocatalytic cascade reactions, see: (a) Guo, H.; Ma, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (b) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143. (c) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (d) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (e) Alba, A.; Companyo, X.; Viciano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1432. (f) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (g) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703.

(4) For organocatalytic cascade Michael reactions, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, *2007*, 1701. (b) Li, H.; Zu, L.; Xie, H.-X.; Wang, J.; Jiang, W.; Wang, W. *Org. Lett.* **2007**, *9*, 1833. (c) Zhou, W.-M.; Liu, H.; Du, D.-M. *Org. Lett.* **2008**, *10*, 2817. (d) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 3699. (e) Enders, D.; Wang, C.; Liebich, J. X. *Chem. - Eur. J.* **2009**, *15*, 11058. (f) McGarraugh, P. G.; Brenner-Moyer, S. E. *Org. Lett.* **2009**, *11*, 5654. (g) Zhang, X.-S.; Zhang, S.-L.; Wang, W. *Angew. Chem., Int. Ed.* **2010**, *49*, 1481. (h) Jia, Z.-X.; Luo, Y.-C.; Wang, Y.; Chen, L.; Xu, P.-F.; Wang, B. *Chem. - Eur. J.* **2012**, *18*, 12958. (i) Li, X.; Wang, S.; Li,

DOI: 10.1021/acs.joc.5b01751
J. Org. Chem. 2015, 80, 11115−11122

T.; Li, J.; Li, H.; Wang, W. *Org. Lett.* **2013**, *15*, 5634. (j) Raja, A.; Hong, B.-C.; Lee, G.-H. *Org. Lett.* **2014**, *16*, 5756.

(5) For selected examples of organocatalytic asymmetric synthesis of chromans and benzopyrans, see: (a) Govender, T.; Hojabri, L.; Moghaddam, F.; Arvidsson, P. *Tetrahedron: Asymmetry* **2006**, *17*, 1763. (b) Sunden, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Có rdova, A. *Chem. - Eur. J.* **2007**, *13*, 574. (c) Zu, L.; Zhang, S.; Xie, H.; Wang, W. *Org. Lett.* **2009**, *11*, 1627. (d) Hong, B.-C.; Kotame, P.; Tsai, C.-W.; Liao, J.-H. *Org. Lett.* **2010**, *12*, 776. (e) Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, A.-L.; Yang, Q.- Q.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 8379. (f) Wang, X.-F.; An, J.; Zhang, X.-X.; Tan, F.; Chen, J.-R.; Xiao, W.-J. *Org. Lett.* **2011**, *13*, 808. (g) Ramachary, D. B.; Shiva Prasad, M. S.; Madhavachary, R. *Org. Biomol. Chem.* **2011**, *9*, 2715. (h) Jia, Z.-X.; Luo, Y.-C; Cheng, X.-N.; Xu, P.-F.; Gu, Y. C. *J. Org. Chem.* **2013**, *78*, 6488. (i) Poulsen, P. H.; Feu, K. S.; Paz, B. M.; Jensen, F.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 8203.

(6) For selected reviews of syntheses of chroman derivatives with organocatalysis, see: (a) Núñez, M. G.; García, P.; Moro, R. F.; Díez, D. *Tetrahedron* **2010**, *66*, 2089. (b) Bhanja, C.; Jena, S.; Nayak, S.; Mohapatra, S. *Beilstein J. Org. Chem.* **2012**, *8*, 1668. (c) Nising, C. F.; Brase, S. *Chem. Soc. Rev.* **2012**, *41*, 988.

(7) Geng, Z.-C.; Zhang, S.-Y.; Li, N.-K.; Li, N.; Chen, J.; Li, H.-Y.; Wang, X.-W. *J. Org. Chem.* **2014**, *79*, 10772.

(8) (a) Rana, N. K.; Selvakumar, S.; Singh, V. K. *J. Org. Chem.* **2010**, *75*, 2089. (b) Molleti, N.; Rana, N. K.; Singh, V. K. *Org. Lett.* **2012**, *14*, 4322. (c) Molleti, N.; Singh, V. K. *Org. Biomol. Chem.* **2015**, *13*, 5243. (d) Agrawal, S.; Molleti, N.; Singh, V. K. *Chem. Commun.* **2015**, *51*, 9793.

(9) While our paper was in review, a report has recently been disclosed: Zhu, Y.; Li, X.; Chen, Q.; Su, J.; Jia, F.; Qiu, S.; Ma, M.; Sun, Q.; Yan, W.; Wang, K.; Wang, R.; et al. *Org. Lett.* **2015**, *17*, 3826.

(10) For recent reports on ring-fused chromans, see: (a) Isabashi, K. *J. Antibiot. Ser. A* **1962**, *15*, 161. (b) Ward, A.; Holmes, B. *Drugs* **1985**, *30*, 127. (c) Roll, D. M.; Manning, J. K.; Carter, G. T. J. *J. Antibiot.* **1998**, *51*, 635. (d) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181. (e) Lambert, D. M.; Fowler, C. J. *J. Med. Chem.* **2005**, *48*, 5059. (f) Sasikumar, T. K.; Burnett, D. A.; Asberom, T.; Wu, W.-L.; Li, H. M.; Xu, R.; Josien, H. B. WO 2009011851, 2009.

(11) (a) Vakulya, B.; Varga, A.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (b) Liu, T.-Y.; Long, J.; Li, B.-J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2006**, *4*, 2097. (c) Hammar, P.; Marcelli, T.; Hiemstra, H.; Himo, F. *Adv. Synth. Catal.* **2007**, *349*, 2537.

(12) (a) Batovska, D.; Parushev, St.; Slavova, A.; Bankova, V.; Tsvetkova, I.; Ninova, M.; Najdenski, H. *Eur. J. Med. Chem.* **2007**, *42*, 87. (b) Lopchuk, J. M.; Hughes, R. P.; Gribble, G. W. *Org. Lett.* **2013**, *15*, 5218. (c) Jalal, S.; Sarkar, S.; Bera, K.; Maiti, S.; Jana, U. *Eur. J. Org. Chem.* **2013**, *2013*, 4823.

(13) (a) Rao, H. S. P.; Sivakumar, S. *J. Org. Chem.* **2006**, *71*, 8715. (b) Kalogiros, C.; Hadjiarapoglou, L. P. *Tetrahedron* **2011**, *67*, 3216. (c) Saito, N.; Ryoda, A.; Nakanishi, W.; Kumamoto, T.; Ishikawa, T. *Eur. J. Org. Chem.* **2008**, *2008*, 2759.

DOI: 10.1021/acs.joc.5b01751
J. Org. Chem. 2015, 80, 11115−11122