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Enantioselective Vinylogous Michael–Michael Cascade Reactions of 3-Alkylidene Oxindoles and Nitroolefin Enoates

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Supporting Information

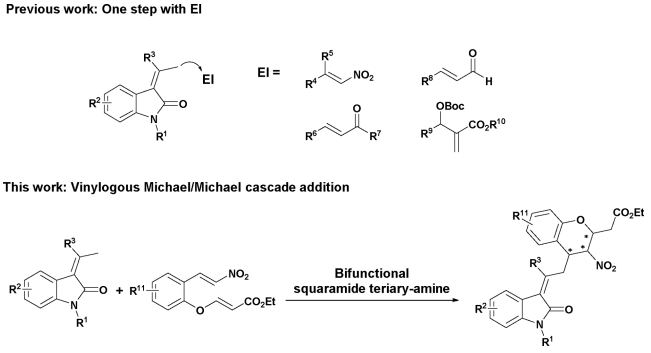
ABSTRACT: A novel bifunctional squaramide catalyzed vinylogous Michael–Michael cascade reaction of 3-alkylidene oxindoles with nitroolefin enoates was developed. This convenient, one-pot cascade reaction serves as a powerful tool for the enantioselective construction of potential bioactive chiral chromans, which have three continuous tertiary stereocenters, in moderate to good yields (up to 85%) with excellent stereoselectivities (up to >19:1 dr and >99% ee).

INTRODUCTION

An asymmetric vinylogous reaction is a key and powerful method for straightforward access to allylic compounds.[1] The vinylogous Michael addition, especially, has attracted much attention, and great progress has been made in this research area.[2] Among the numerous reported vinylogous Michael additions, one-step addition occupies a considerable proportion; however, less attention has been paid to the cascade reaction that is triggered by a γ-regioselective Michael reaction.[3] It is valuable to note that the cascade reaction has been demonstrated to be a powerful strategy in the synthesis of functionalized molecules.[4]

3-alkylidene oxindoles have attracted extensive attention, since the structural motif of this type of compound is a prominent feature in a number of biologically and pharmaceutically active natural products.[5] Consequently, the search for efficient methods for the construction of these compounds is therefore interesting in organic synthesis (Scheme 1).[6] Although a number of cases employing the 3-alkylidene oxindoles as nucleophiles in the vinylogous reactions have been described, the reaction types have been limited to vinylogous Michael additions, asymmetric allylic alkylation reactions, and Mannich reactions. To the best of our knowledge, 3-alkylidene oxindoles have been unexploited as nucleophilic reagents to trigger a cascade reaction. Therefore, the development of an organocatalytic cascade reaction that is initiated via a vinylogous Michael addition of 3-alkylidene oxindole is highly desirable.

Scheme 1. Strategies for Synthetic Approachs to Chiral γ-Substituted Alkylidene Oxindoles



However, the chroman framework is commonly found in naturally occurring bioactive compounds and pharmacologically important molecules.[7] Structural diversity and complexity of chromans have inspired chemists to develop various synthetic strategies to achieve these scaffolds.[8] Nitroolefin enoates had been widely used as practical electrophiles in enantioselective cascade transformations,[9] which allowed for concise access to enantioenriched chroman frameworks.[7] Herein, we reported a bifunctional squaramide catalyzed enantioselective cascade reaction between 3-alkylidene oxindole and nitroolefin enoate. As a result, a number of chiral chroman derivatives, which contained a 3-alkylidene oxindole motif, were synthesized with excellent stereoselectivities.

From the outset of this work, we selected the vinylogous Michael–Michael cascade reaction of 3-alkylidene oxindole **1a** with nitroolefin enoate **2a** in CH_2Cl_2 at room temperature as a benchmark for catalyst screening and evaluation. A number of widely used bifunctional squaramide/thiourea catalysts[10,11] was investigated, in which quinine-derived squaramide catalyst **3b** gave the best results (43% yield, 13:1 dr and 94% ee, Table 1, entries 2–6). We then turned our attention to solvent screening. As a result, the initial used CH_2Cl_2 was found to be the optimal solvent (Table 1, entries 2 and 7–12). Lowering the amounts of catalyst **3b** resulted in a decreased yield (Table 1, entry 13). Increasing the reaction temperature to 35 °C

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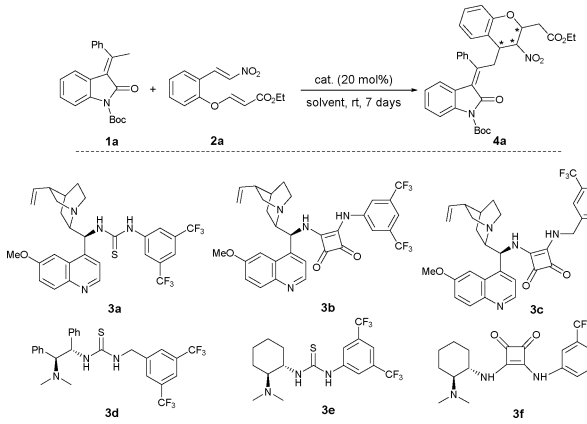
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	yield (%)[b]	dr[c]	ee (%)[d]
1	**3a**	CH_2Cl_2	28	16:1	89
2	**3b**	CH_2Cl_2	43	13:1	94
3	**3c**	CH_2Cl_2	17	12:1	88
4	**3d**	CH_2Cl_2	15	7:1	95
5	**3e**	CH_2Cl_2	28	7:1	94
6	**3f**	CH_2Cl_2	12	10:1	89
7	**3b**	$ClCH_2CH_2Cl$	32	9:1	96
8	**3b**	$CHCl_3$	38	12:1	94
9	**3b**	THF	17	3:1	84
10	**3b**	toluene	20	4:1	95
11	**3b**	CH_3CN	13	7:1	93
12	**3b**	*i*-PrOH	23	>19:1	97
13[e]	**3b**	CH_2Cl_2	25	10:1	96
14[f]	**3b**	CH_2Cl_2	53	10:1	94
15[f,g]	**3b**	CH_2Cl_2	62	10:1	97

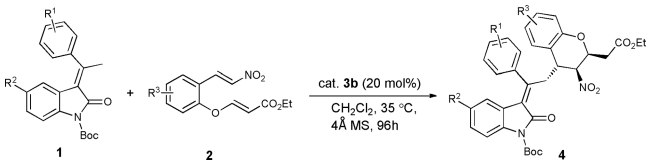
[a]Reaction conditions: 0.15 mmol of **1a**, 0.1 mmol of **2a**, 20 mol % catalyst, 0.5 mL of solvent at room temperature. [b]Isolated yield. [c]Determined by ^{1}H NMR of crude product. The diastereomeric ratio is referred as the major isomer vs the sum of all remaining isomers. [d]Determined by chiral HPLC. [e]10 mol % **3b** was used. [f]The reaction was carried out at 35 °C for 96 h. [g]The reaction was carried out under the general conditions with 40 mg 4 Å molecular sieves.

improved the reaction yield with a slight drop of enantioselectivity (Table 1, entry 14). Further additive examination indicated that adding 4 Å molecular sieves had a positive effect on the yield and the enantioselectivity (Table 1, entry 15). Collectively, the best result with respect to the yield and the ee value was obtained by conducting the vinylogous Michael−Michael cascade reaction at 35 °C in CH_2Cl_2 with 20 mol % of **3b** and 40 mg 4 Å molecular sieves. Under the optimized conditions, the product **4a** was obtained with 62% yield, 10:1 dr, and 97% ee (Table 1, entry 15).

RESULTS AND DISCUSSION

With the optimized conditions in hand, the substrate scope for both 3-alkylidene oxindoles **1** and nitroolefin enoates **2** was examined (Table 2). Generally, all reactions proceeded smoothly in this catalytic system, giving the desired cascade products in moderate to good yields (up to 85%) with moderate to excellent diastereoselectivities (up to >19:1 dr) and excellent enantioselectivties (up to >99% ee). For substrate **1**, the electronic nature of the substituents had little influence on the enantioselectivities, in which the desired products **4b**−**4h** were obtained with excellent ee values (Table 2, entries 2−8). With further examination of the yields, we found that the

Table 2. Substrate Scope[a]



entry	R^1/R^2	R^3	yield (%)[b]	dr[c]	ee (%)[d]
1	H/H (**1a**)	H (**2a**)	62 (**4a**)	10:1	97
2	3-Cl/H (**1b**)	H (**2a**)	65 (**4b**)	8:1	>99
3	4-Cl/H (**1c**)	H (**2a**)	71 (**4c**)	>19:1	99
4	3-Br/H (**1d**)	H (**2a**)	67 (**4d**)	8:1	>99
5	4-Br/H (**1e**)	H (**2a**)	67 (**4e**)	>19:1	99
6	4-OMe/H (**1f**)	H (**2a**)	85 (**4f**)	12:1	99
7	2-OMe/H (**1g**)	H (**2a**)	67 (**4g**)	18:1	>99
8	4-Me/H (**1h**)	H (**2a**)	78 (**4h**)	17:1	>99
9	H/5-F (**1i**)	H (**2a**)	76 (**4i**)	6:1	99
10	H/5-Cl (**1j**)	H (**2a**)	76 (**4j**)	5:1	99
11	H/5-Br (**1k**)	H (**2a**)	79 (**4k**)	5:1	99
12	H/6-Cl (**1l**)	H (**2a**)	79 (**4l**)	5:1	99
13	H/H (**1a**)	5-F (**2b**)	65 (**4m**)	>19:1	>99
14	H/H (**1a**)	5-Cl (**2c**)	69 (**4n**)	>19:1	>99
15	H/H (**1a**)	5-Br (**2d**)	75 (**4o**)	>19:1	99
16	H/H (**1a**)	5-OMe (**2e**)	77 (**4p**)	>19:1	99
17	H/H (**1a**)	4-OMe (**2f**)	78 (**4q**)	10:1	89
18	H/H (**1a**)	5-Me (**2g**)	80 (**4r**)	14:1	97
19	H/H (**1a**)	H/S (**2h**)	55 (**4s**)	>19:1	>99

[a]Reaction conditions: 0.15 mmol of **1**, 0.1 mmol of **2**, 20 mol % **3b**, 40 mg 4 Å molecular sieves, 0.5 mL of CH_2Cl_2 at 35 °C. [b]Isolated yield. [c]Determined by ^{1}H NMR of crude product. The diastereomeric ratio is referred as the major isomer vs the sum of all remaining isomers. [d]Determined by chiral HPLC.

reactivities of the 3-alkylidene oxindole substrates **1b**−**1e**, which were substituted with the electron-withdrawing substituents, were lower than that of the corresponding **1f** and **1h** reactivities. Comparison of the yields of **4f** and **4g** indicated that the ortho-substituted substrate gave a lower yield than the corresponding para-substituted one (Table 2, entries 6 and 7). The reason for this phenomenon may be steric hindrance. Moreover, 5-fluoro-, 5-chloro- or 6-chloro-, and 5-bromo-substituted oxindoles could also tolerate the reaction and gave products **4i**−**4l** in good yields with moderate to excellent diastereo- and enantioselectivities (Table 2, entries 9−12). With respect to the substrates of nitroolefin enoates **2**, the electronic property or position of the substituents on the aromatic ring had little influence on the reaction outcomes (Table 2, entries 13−18). As a result, a number of substituted nitroolefin enoates underwent the cascade reactions efficiently to provide the corresponding products **4m**−**4r** in good yields (up to 85%) with excellent stereoselectivities (up to >19:1 dr and up to >99% ee). In addition, the reaction of sulfur-tethered substrate **2h** with **1a** also worked well, furnishing the functionalized thiochromene **4s** with excellent stereoselectivity (55% yield, >19:1 dr and >99% ee, Table 2, entry 19).

To expand the scope of this synthetic strategy, the reactions using isopropylidene oxindole **1m** and isopropylidene benzofuran-2-one **1n** as nucleophiles were also investigated (Scheme 2). To our delight, substrate **1m** was successfully engaged in this reaction and provided the **4t** in 64% yield with 15:1 dr and 97% ee. When substrate **1n** was employed, the desired cascade product **5** was obtained in 59% yield with 10:1 dr and 93% ee.

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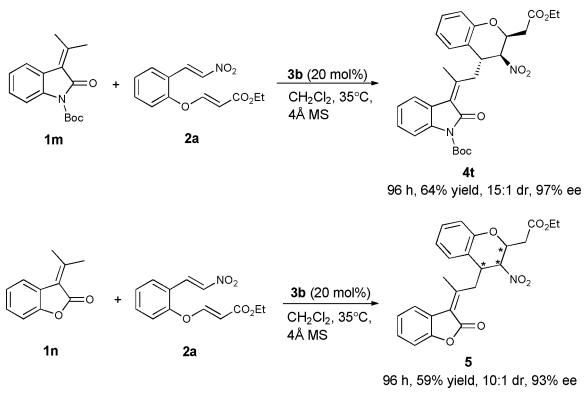
Scheme 2. Vinylogous Michael–Michael Cascade Reaction of 1m and 1n



The absolute configuration of **4n** was determined to be (2*S*,3*S*,4*R*) on the basis of X-ray crystallographic analysis (Figure 1),[12] and the configurations of other products were assigned by referring to that of **4n**.

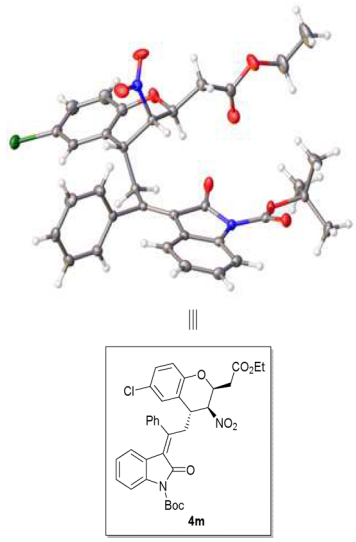
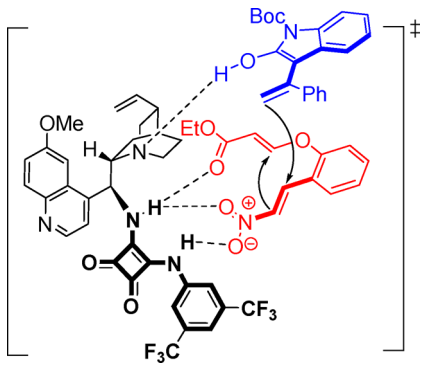


Figure 1. X-ray crystal structure of **4n**.

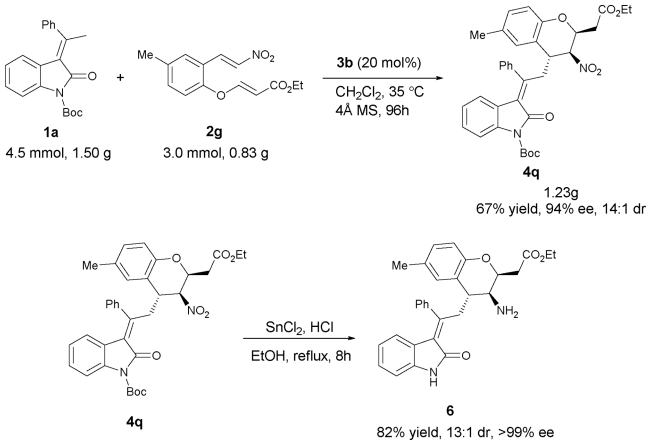
According to the absolute configuration, a plausible transition state was depicted in Scheme 3. The chiral bifunctional squaramide catalyst presumably activated both electrophilic nitroolefin enoate and nucleophilic 3-alkylidene oxindole simultaneously through multiple hydrogen-bonding interactions and its basic tertiary amino group, respectively. Nitroolefin enoate was attacked preferably through the *re*-face by 3-alkylidene oxindole, followed by the intramolecular Michael addition through the *re*-face attack to furnish the entioenriched chroman motif.

Scheme 3. Proposed Transition State



To investigate the synthetic potential of the current vinylogous Michael–Michael cascade reaction, a large scale reaction of 3-alkylidene **1a** (4.5 mmol, 1.50 g) and nitroolefin enoate **2g** (3.0 mmol, 0.83 g) was conducted under the optimal conditions. To our delight, **4r** was obtained with only a little loss of yield (1.23 g, 67% yield) and stereoselectivities (14:1 dr and 94% ee, Scheme 4). The reduction of **4r** by $SnCl_2$ afforded enantiopure **6**, which had a valuably chiral γ-amino acid ester structure.

Scheme 4. Gramscale Preparation of 4r



CONCLUSIONS

In conclusion, we have developed a bifunctional squaramide catalyzed highly enantioselective vinylogous Michael–Michael cascade reaction of 3-alkylidene oxindoles and nitroolefin enoates. This approach provides efficient access to γ-position-substituted 3-alkylidene oxindoles. A series of highly functionalized chiral chromans with three contiguous stereocenters were synthesized in moderate to good yields (up to 85%) with good to excellent diastereoselectivities (up to >19:1 dr) and excellent enantioselectivities (up to >99% ee).

EXPERIMENTAL SECTION

General Information. Commercial reagents were used as received, unless otherwise stated. ^1H and ^{13}C NMR were recorded on a 400 MHz spectrometer. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as a multiplet (m). Mass spectra were obtained using an electrospray ionization (ESI-TOF) or an electron impact ionization (EI-TOF) mass spectrometer. In each case, the enantiomeric ratio was determined by chiral HPLC analysis on a Chiralcel column in comparison with authentic racemates. Columns for flash chromatography (FC) contained 200–300 mesh silica gel. Columns were packed as slurries of silica gel in petroleum ether and equilibrated solution using the appropriate solvent system. Benzofuranone type **1n** and 3-alkylidene oxindoles **1m** were synthesized according to literature procedures.[13] A series of 3-alkylidene oxindoles

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1a−1l were prepared according to literature procedures.[13a] Nitroolefin enoates were prepared according to literature procedures.[14]

General Experimental Cascade Vinylogous Michael−Michael Addition Reaction Procedure. To a stirred solution of 3-alkylidene oxindole (0.15 mmol) and nitrolefin enoate (0.1 mmol) in dry CH_2Cl_2 (0.5 mL) was added quinine-squaramide (0.02 mmol, 0.2 equiv) and 4 Å MS (40 mg) at 35 °C. After the reaction was completed (monitored by TLC analysis), the reaction solution was concentrated in vacuo and the crude was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 25:1 to 15:1 as eluants) to afford the product.

Procedure for the Synthesis of ***6****.* A mixture of **4r** (75 mg, 0.1 mmol) and $SnCl_2$ (189 mg, 1.0 mmol) in HCl-containing EtOH solution was refluxed under an argon atmosphere. HCl-containing ethanol solution was prepared in situ with EtOH (1 mL) and acetyl chloride (86 μL, 1.2 mmol) at 0 °C for 1 h. After 8 h, the reaction mixture was cooled to room temperature, quenched with saturated NH_4Cl solution, and then basified with ammonia. Dichloromethane was added and stirred vigorously for 15 min. The clear filtrate was obtained by filtration with Celite and washed with saturated NaCl(aq). The organic layer was separated and dried over anhydrous Na_2SO_4. The desired amine **6** was obtained as a pale yellow oil by silica gel column chromatography.

*(E)-tert-Butyl 3-(2-((2S,3S,4R)-2-(2-Ethoxy-2-oxoethyl)-3-nitrochroman-4-yl)-1-phenylethylidene)-2-oxoindoline-1-carboxylate (**4a**).* Purified by flash chromatography (petroleum ether/EtOAc 25:1) to afford a pale yellow oil: 37.0 mg, 62% yield; $[\alpha]^{25}_D$ −241.2 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.54 (m, 2H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.30−7.21 (m, 2H), 7.15 (ddd, *J* = 8.5, 7.2, 1.8 Hz, 1H), 7.02−6.91 (m, 2H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.78 (t, *J* = 7.7 Hz, 1H), 6.21 (d, *J* = 7.8 Hz, 1H), 5.19 (ddd, *J* = 8.7, 4.8, 1.6 Hz, 1H), 5.07 (s, 1H), 4.67 (dd, *J* = 13.7, 12.1 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.44 (dd, *J* = 12.1, 3.5 Hz, 1H), 3.03−2.90 (m, 2H), 2.84 (dd, *J* = 16.6, 4.8 Hz, 1H), 1.66 (s, 9H), 1.32 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 166.0, 154.0, 153.7, 149.2, 139.6, 138.7, 130.4, 129.7, 129.6, 129.5, 128.8, 128.2, 128.0, 125.9, 123.6, 123.1, 122.3, 122.0, 121.9, 117.0, 114.5, 84.3, 83.1, 68.6, 60.9, 41.7, 37.1, 36.8, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for $[C_{34}H_{34}N_2O_8 + NH_4^+]$ 616.2653, found 616.2656. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 3:97), 1.0 mL/min, t_R = 9.3 min (major), 10.3 min (minor).

*(E)-tert-Butyl 3-(1-(3-Chlorophenyl)-2-((2S,3S,4R)-2-(2-ethoxy-2-oxoethyl)-3-nitrochroman-4-yl)ethylidene)-2-oxoindoline-1-carboxylate (**4b**).* Purified by flash chromatography (petroleum ether/EtOAc 25:1) to afford a pale yellow oil: 41.0 mg, 65% yield; $[\alpha]^{25}_D$ −187.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 1H), 7.60−7.50 (m, 1H), 7.47−7.36 (m, 1H), 7.31−7.21 (m, 2H), 7.14 (td, *J* = 7.8, 7.1, 2.0 Hz, 2H), 7.02−6.89 (m, 2H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.80 (q, *J* = 7.3 Hz, 1H), 6.21 (t, *J* = 7.5 Hz, 1H), 5.19−5.08 (m, 1H), 5.05 (d, *J* = 10.6 Hz, 1H), 4.61 (m, 1H), 4.20 (qd, *J* = 7.1, 1.5 Hz, 2H), 3.43 (m, 1H), 3.06−2.77 (m, 3H), 1.63 (s, 9H), 1.29 (td, *J* = 7.1, 1.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 165.8, 153.7, 151.6, 149.1, 141.4, 138.9, 136.4, 135.8, 131.1, 129.9, 129.7, 128.8, 128.2, 126.5, 126.4, 126.2, 124.4, 123.8, 123.1, 122.0, 121.9, 121.6, 117.1, 114.7, 84.4, 83.0, 68.5, 60.9, 41.4, 36.7, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for $[C_{34}H_{33}ClN_2O_8 + NH_4^+]$ 650.2264, found 650.2262. The enantiomeric excess was determined by HPLC with an IF column at 210 nm (2-propanol/hexane 3:97), 1.0 mL/min, t_R = 12.6 min (major).

*(E)-tert-Butyl 3-(1-(4-Chlorophenyl)-2-((2S,3S,4R)-2-(2-ethoxy-2-oxoethyl)-3-nitrochroman-4-yl)ethylidene)-2-oxoindoline-1-carboxylate (**4c**).* Purified by flash chromatography (petroleum ether/EtOAc 25:1) to afford a pale yellow oil: 45.0 mg, 71% yield; $[\alpha]^{25}_D$ −204.3 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.63 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.47 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.35 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.25−7.17 (m, 2H), 7.13 (ddd, *J* = 8.5, 7.1, 1.8 Hz, 1H), 7.00−6.74 (m, 4H), 6.26 (dd, *J* = 7.9, 1.2 Hz, 1H), 5.13 (ddd, *J* = 8.5, 5.1, 1.7 Hz, 1H), 5.05−5.02 (m, 1H), 4.61 (dd, *J* = 13.7, 12.0 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.38 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.00−2.88 (m, 2H), 2.81 (dd, *J* = 16.7, 5.2 Hz, 1H), 1.63 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 165.8, 153.7, 152.2, 149.1, 138.9, 138.0, 135.7, 130.7, 130.1, 129.8, 129.7, 128.8, 128.1, 127.6, 126.3, 123.8, 123.0, 122.0, 121.9, 121.7, 117.1, 114.7, 84.4, 82.9, 68.53, 60.9, 41.6, 37.2, 36.7, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for $[C_{34}H_{33}ClN_2O_8 + NH_4^+]$ 650.2264, found 650.2269. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 3:97), 1.0 mL/min, t_R = 13.3 min (major), 12.2 min (minor).

*(E)-tert-Butyl 3-(1-(3-Bromophenyl)-2-((2S,3S,4R)-2-(2-ethoxy-2-oxoethyl)-3-nitrochroman-4-yl)ethylidene)-2-oxoindoline-1-carboxylate (**4d**).* Purified by flash chromatography (petroleum ether/EtOAc 25:1) to afford a pale yellow oil: 45.0 mg, 67% yield; $[\alpha]^{25}_D$ −165.6 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.57−7.48 (m, 1H), 7.46−7.31 (m, 1H), 7.28−7.17 (m, 2H), 7.14 (td, *J* = 7.8, 6.9, 2.3 Hz, 1H), 7.03−6.90 (m, 2H), 6.90−6.73 (m, 2H), 6.21 (t, *J* = 8.8 Hz, 1H), 5.14 (qd, *J* = 7.5, 3.1 Hz, 1H), 5.05 (d, *J* = 10.2 Hz, 1H), 4.61 (m, 1H), 4.20 (qd, *J* = 7.1, 2.2 Hz, 2H), 3.43 (m, 1H), 3.05−2.75 (m, 3H), 1.63 (s, 9H), 1.29 (td, *J* = 7.2, 2.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 165.8, 153.7, 151.5, 149.1, 141.6, 138.9, 132.7, 131.9, 131.3, 131.0, 129.9, 129.0, 128.8, 128.2, 126.8, 124.4, 123.8, 123.1, 122.0, 121.9, 117.1, 114.7, 84.4, 83.0, 68.5, 60.9, 41.4, 36.7, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for $[C_{34}H_{33}BrN_2O_8 + NH_4^+]$ 694.1759, found 694.1755. The enantiomeric excess was determined by HPLC with an IF column at 210 nm (2-propanol/hexane 3:97), 1.0 mL/min, t_R = 13.3 min (major).

*(E)-tert-Butyl 3-(1-(4-Bromophenyl)-2-((2S,3S,4R)-2-(2-ethoxy-2-oxoethyl)-3-nitrochroman-4-yl)ethylidene)-2-oxoindoline-1-carboxylate (**4e**).* Purified by flash chromatography (petroleum ether/EtOAc 25:1) to afford a pale yellow oil: 45.0 mg, 67% yield; $[\alpha]^{25}_D$ −236.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.75 (m, 2H), 7.63 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.29 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.25−7.20 (m, 1H), 7.18−7.09 (m, 2H), 6.99−6.78 (m, 4H), 6.27 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.13 (ddd, *J* = 8.5, 5.1, 1.7 Hz, 1H), 5.03 (t, *J* = 1.4 Hz, 1H), 4.61 (dd, *J* = 13.7, 12.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.38 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.00−2.87 (m, 2H), 2.81 (dd, *J* = 16.7, 5.2 Hz, 1H), 1.63 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 165.8, 153.7, 152.2, 149.1, 138.9, 138.5, 133.7, 133.0, 130.0, 129.8, 128.8, 128.1, 127.9, 126.3, 123.9, 123.8, 123.0, 122.0, 121.9, 121.7, 117.1, 114.7, 84.4, 82.9, 68.5, 60.9, 41.6, 37.2, 36.7, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for $[C_{34}H_{33}BrN_2O_8 + NH_4^+]$ 694.1759, found 694.1757. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 3:97), 1.0 mL/min, t_R = 13.9 min (major), 12.9 min (minor).

*(E)-tert-Butyl 3-(2-((2S,3S,4R)-2-(2-Ethoxy-2-oxoethyl)-3-nitrochroman-4-yl)-1-(4-methoxyphenyl)ethylidene)-2-oxoindoline-1-carboxylate (**4f**).* Purified by flash chromatography (petroleum ether/EtOAc 20:1) to afford a pale yellow oil: 53.0 mg, 85% yield; $[\alpha]^{25}_D$ −308.8 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.42−7.31 (m, 1H), 7.26−7.09 (m, 4H), 7.05−6.96 (m, 2H), 6.92 (td, *J* = 7.5, 1.3 Hz, 1H), 6.86 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.79 (td, *J* = 7.7, 1.1 Hz, 1H), 6.41 (dd, *J* = 7.9, 1.2 Hz, 1H), 5.16 (ddd, *J* = 8.8, 4.7, 1.6 Hz, 1H), 5.01 (t, *J* = 1.3 Hz, 1H), 4.57 (dd, *J* = 13.7, 12.0 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 3.38 (dd, *J* = 11.9, 3.6 Hz, 1H), 3.03−2.87 (m, 2H), 2.81 (dd, *J* = 16.6, 4.7 Hz, 1H), 1.64 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 166.1, 160.7, 154.4, 153.7, 149.3, 138.6, 131.5, 130.1, 129.3, 128.9, 128.0, 127.6, 125.6, 123.6, 122.9, 122.6, 122.1, 121.9, 117.0, 115.9, 114.8, 114.5, 84.2, 83.1, 68.6, 60.8, 55.5, 41.8, 37.5, 36.8, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for $[C_{35}H_{36}N_2O_9 + NH_4^+]$ 646.2759, found 646.2763. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 1:19), 1.0 mL/min, t_R = 8.3 min (major), 10.3 min (minor).

*(E)-tert-Butyl 3-(2-((2S,3S,4R)-2-(2-Ethoxy-2-oxoethyl)-3-nitrochroman-4-yl)-1-(2-methoxyphenyl)ethylidene)-2-oxoindoline-1-carboxylate (**4g**).* Purified by flash chromatography (petroleum ether/EtOAc 20:1) to afford a pale yellow oil: 42.0 mg, 67% yield; $[\alpha]^{25}_D$ −151.0 (*c* = 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 8.1 Hz, 1H), 7.16−

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7.10 (m, 1H), 7.09−6.98 (m, 2H), 6.98−6.71 (m, 5H), 6.28 (t, J = 6.4 Hz, 1H), 5.14 (p, J = 4.9 Hz, 1H), 5.05 (d, J = 4.1 Hz, 1H), 4.62 (td, J = 12.9, 7.4 Hz, 1H), 4.20 (q, J = 7.3 Hz, 2H), 3.83 (s, 3H), 3.45 (t, J = 12.5 Hz, 1H), 3.01−2.89 (m, 2H), 2.80 (dt, J = 17.0, 5.1 Hz, 1H), 1.64 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 166.0, 161.1, 160.5, 153.9, 153.7, 149.2, 140.9, 138.7, 131.6, 131.0, 129.5, 128.9, 128.9, 128.0, 128.0, 123.7, 123.7, 123.3, 122.3, 122.0, 121.9, 120.1, 117.9, 117.0, 115.9, 114.7, 114.5, 114.5, 112.6, 111.5, 84.2, 83.2, 68.6, 68.5, 60.8, 55.5, 55.4, 41.7, 41.5, 37.2, 37.1, 36.8, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for [$C_{35}H_{36}N_2O_9$ + NH_4^+] 646.2759, found 646.2754. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 1:19), 1.0 mL/min, t_R = 8.5 min (major).

(E)-tert-Butyl 3-(2-((2S,3S,4R)-2-(2-Ethoxy-2-oxoethyl)-3-nitrochroman-4-yl)-1-(p-tolyl)ethylidene)-2-oxoindoline-1-carboxylate ***(4h)***. Purified by flash chromatography (petroleum ether/EtOAc 25:1) to afford a pale yellow oil: 48.0 mg, 78% yield; $[\alpha]^{25}_D$ −205.2 (c = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.3 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.28 (t, J = 8.5 Hz, 2H), 7.23−7.07 (m, 3H), 6.99 (d, J = 7.7 Hz, 1H), 6.89 (m, 2H), 6.77 (t, J = 7.8 Hz, 1H), 6.32 (d, J = 7.9 Hz, 1H), 5.20−5.11 (m, 1H), 5.02 (s, 1H), 4.61 (t, J = 12.9 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.38 (dd, J = 12.0, 3.3 Hz, 1H), 3.02−2.87 (m, 2H), 2.81 (dd, J = 16.6, 4.8 Hz, 1H), 2.47 (s, 3H), 1.63 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 166.0, 154.5, 153.7, 149.3, 139.8, 138.7, 136.5, 131.0, 130.4, 129.3, 128.9, 128.3, 127.9, 125.9, 125.7, 123.6, 123.0, 122.5, 122.1, 121.8, 117.0, 114.5, 84.2, 83.2, 68.6, 60.8, 41.8, 37.3, 36.8, 28.1, 21.5, 14.2 ppm. HRMS (ESI-TOF): calcd for [$C_{35}H_{36}N_2O_8$ + NH_4^+] 630.2810, found 630.2801. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 3:97), 1.0 mL/min, t_R = 7.5 min (major).

(E)-tert-Butyl 3-(2-((2S,3S,4R)-2-(2-Ethoxy-2-oxoethyl)-3-nitrochroman-4-yl)-1-phenylethylidene)-5-fluoro-2-oxoindoline-1-carboxylate ***(4i)***. Purified by flash chromatography (petroleum ether/EtOAc 25:1) to afford a pale yellow oil: 47.0 mg, 76% yield; $[\alpha]^{25}_D$ −185.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 8.9, 4.8 Hz, 1H), 7.67 (t, J = 6.9 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 6.9 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.16−7.09 (m, 1H), 6.98−6.89 (m, 3H), 6.86 (d, J = 8.5 Hz, 1H), 5.84 (dd, J = 9.4, 2.7 Hz, 1H), 5.15 (ddd, J = 8.7, 4.9, 1.6 Hz, 1H), 5.03 (s, 1H), 4.63 (dd, J = 13.6, 12.0 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.42 (dd, J = 12.1, 3.5 Hz, 1H), 3.02−2.88 (m, 2H), 2.81 (dd, J = 16.6, 4.9 Hz, 1H), 1.63 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 165.7, 159.0 (d, $^1J_{C-F}$ = 241.3 Hz), 155.8, 153.7, 149.2, 139.0, 134.8, 130.6, 130.0, 129.9, 128.8, 128.1, 127.9, 125.7, 125.5 (d, $^4J_{C-F}$ = 3.0 Hz), 123.7 (d, $^3J_{C-F}$ = 9.1 Hz), 121.9, 121.8, 117.1, 116.0 (d, $^2J_{C-F}$ = 23.7 Hz), 115.7 (d, $^3J_{C-F}$ = 8.0 Hz), 110.2 (d, $^2J_{C-F}$ = 26.7 Hz), 84.4, 83.1, 68.6, 60.9, 41.8, 37.1, 36.7, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for [$C_{34}H_{33}FN_2O_8$ + NH_4^+] 634.2559, found 634.2565. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 3:97), 1.0 mL/min, t_R = 10.3 min (major), 11.6 min (minor).

(E)-tert-Butyl 5-Chloro-3-(2-((2S,3S,4R)-2-(2-ethoxy-2-oxoethyl)-3-nitrochroman-4-yl)-1-phenylethylidene)-2-oxoindoline-1-carboxylate ***(4j)***. Purified by flash chromatography (petroleum ether/EtOAc 25:1) to afford a pale yellow oil: 48.0 mg, 76% yield; $[\alpha]^{25}_D$ −141.2 (c = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.7 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.54−7.47 (m, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.19−7.09 (m, 2H), 6.99−6.89 (m, 2H), 6.86 (d, J = 8.2 Hz, 1H), 6.07 (d, J = 2.1 Hz, 1H), 5.14 (ddd, J = 8.6, 5.1, 1.6 Hz, 1H), 5.04 (s, 1H), 4.69−4.56 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.42 (dd, J = 12.0, 3.4 Hz, 1H), 3.04−2.88 (m, 2H), 2.81 (dd, J = 16.7, 5.1 Hz, 1H), 1.63 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 165.4, 156.0, 153.7, 149.0, 139.0, 137.1, 130.6, 130.0, 129.9, 129.2, 129.1, 128.8, 128.1, 127.9, 125.7, 125.1, 123.7, 123.1, 121.9, 121.8, 117.1, 115.7, 84.6, 83.0, 68.5, 60.9, 41.7, 37.1, 36.7, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for [$C_{34}H_{33}ClN_2O_8$ + NH_4^+] 650.2264, found 650.2267. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 3:97), 1.0 mL/min, t_R = 12.7 min (major), 11.6 min (minor).

(E)-tert-Butyl 5-Bromo-3-(2-((2S,3S,4R)-2-(2-ethoxy-2-oxoethyl)-3-nitrochroman-4-yl)-1-phenylethylidene)-2-oxoindoline-1-carboxylate ***(4k)***. Purified by flash chromatography (petroleum ether/EtOAc 25:1) to afford a pale yellow oil: 53.0 mg, 79% yield; $[\alpha]^{25}_D$ −163.6 (c = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.7 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.56−7.49 (m, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.32 (dd, J = 8.7, 2.1 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.18−7.09 (m, 1H), 7.01−6.89 (m, 2H), 6.86 (d, J = 8.1 Hz, 1H), 6.21 (d, J = 2.0 Hz, 1H), 5.13 (ddd, J = 8.6, 5.1, 1.6 Hz, 1H), 5.04 (s, 1H), 4.63 (dd, J = 13.6, 12.1 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.43 (dd, J = 12.0, 3.6 Hz, 1H), 3.04−2.87 (m, 2H), 2.81 (dd, J = 16.7, 5.1 Hz, 1H), 1.62 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 165.3, 156.0, 153.7, 149.0, 139.0, 137.6, 132.0, 130.6, 130.0, 129.9, 128.8, 128.1, 127.8, 126.0, 125.7, 125.0, 124.1, 121.9, 121.8, 117.1, 116.7, 116.1, 84.6, 83.0, 68.5, 60.9, 41.7, 37.1, 36.7, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for [$C_{34}H_{33}BrN_2O_8$ + NH_4^+] 694.1759, found 694.1753. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 3:97), 1.0 mL/min, t_R = 13.4 min (major), 12.1 min (minor).

(E)-tert-Butyl 6-Chloro-3-(2-((2S,3S,4R)-2-(2-ethoxy-2-oxoethyl)-3-nitrochroman-4-yl)-1-phenylethylidene)-2-oxoindoline-1-carboxylate ***(4l)***. Purified by flash chromatography (petroleum ether/EtOAc 25:1) to afford a pale yellow oil: 50.0 mg, 79% yield; $[\alpha]^{25}_D$ −164.7 (c = 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 2.1 Hz, 1H), 7.68−7.61 (m, 1H), 7.54 (tt, J = 6.3, 1.4 Hz, 1H), 7.48 (dd, J = 7.7, 6.3 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.22 (d, J = 7.7 Hz, 1H), 7.15−7.10 (m, 1H), 6.96 (dd, J = 7.8, 1.8 Hz, 1H), 6.89 (ddd, J = 23.9, 7.7, 1.2 Hz, 2H), 6.73 (dd, J = 8.5, 2.0 Hz, 1H), 6.08 (d, J = 8.5 Hz, 1H), 5.14 (ddd, J = 8.5, 5.1, 1.6 Hz, 1H), 5.04 (t, J = 1.3 Hz, 1H), 4.62 (dd, J = 13.6, 12.1 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.40 (dd, J = 12.0, 3.6 Hz, 1H), 3.01−2.90 (m, 2H), 2.81 (dd, J = 16.6, 5.1 Hz, 1H), 1.63 (s, 9H), 1.29 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 165.6, 154.6, 153.7, 149.0, 139.4, 139.3, 135.2, 130.5, 129.8, 128.8, 128.1, 128.0, 125.9, 125.1, 123.8, 123.8, 121.9, 121.8, 120.8, 117.1, 115.2, 84.7, 83.0, 68.5, 60.9, 41.6, 37.1, 36.7, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for [$C_{34}H_{33}ClN_2O_8$ + Na^+] 655.1818, found 655.1820. The enantiomeric excess was determined by HPLC with an IF column at 210 nm (2-propanol/hexane 3:97), 1.0 mL/min, t_R = 11.4 min (major), 13.1 min (minor).

(E)-tert-Butyl 3-(2-((2S,3S,4R)-2-(2-Ethoxy-2-oxoethyl)-6-fluoro-3-nitrochroman-4-yl)-1-phenylethylidene)-2-oxoindoline-1-carboxylate ***(4m)***. Purified by flash chromatography (petroleum ether/EtOAc 25:1) to afford a pale yellow oil: 40.0 mg, 65% yield; $[\alpha]^{25}_D$ −191.9 (c = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.59−7.46 (m, 2H), 7.39 (d, J = 7.7 Hz, 1H), 7.27−7.16 (m, 2H), 6.90−6.78 (m, 2H), 6.75 (t, J = 7.9 Hz, 1H), 6.69 (dd, J = 8.8, 2.5 Hz, 1H), 6.19 (dd, J = 7.9, 1.2 Hz, 1H), 5.12 (ddd, J = 8.7, 4.8, 1.6 Hz, 1H), 5.03 (s, 1H), 4.62 (dd, J = 13.6, 12.2 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.38 (dd, J = 12.0, 3.5 Hz, 1H), 2.99−2.86 (m, 2H), 2.80 (dd, J = 16.7, 4.9 Hz, 1H), 1.64 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 166.0, 157.5 (d, $^1J_{C-F}$ = 239.8 Hz), 153.4, 149.8 (d, $^4J_{C-F}$ = 2.1 Hz), 149.2, 139.4, 138.8, 130.5, 129.8, 129.7, 129.6, 128.1, 126.1, 125.9, 123.7, 123.3 (d, $^3J_{C-F}$ = 7.4 Hz), 123.1, 122.2, 118.2 (d, $^3J_{C-F}$ = 8.2 Hz), 115.1 (d, $^2J_{C-F}$ = 23.2 Hz), 114.7 (d, $^2J_{C-F}$ = 23.8 Hz), 114.6, 84.3, 82.7, 68.9, 60.9, 41.5, 37.3, 36.7, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for [$C_{34}H_{33}FN_2O_8$ + NH_4^+] 634.2559, found 634.2561. The enantiomeric excess was determined by HPLC with an IF column at 210 nm (2-propanol/hexane 3:97), 1.0 mL/min, t_R = 11.0 min (major).

(E)-tert-Butyl 3-(2-((2S,3S,4R)-6-Chloro-2-(2-ethoxy-2-oxoethyl)-3-nitrochroman-4-yl)-1-phenylethylidene)-2-oxoindoline-1-carboxylate ***(4n)***. Purified by flash chromatography (petroleum ether/EtOAc 25:1) to afford a pale yellow oil: 44.0 mg, 69% yield; $[\alpha]^{25}_D$ −184.7 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.1 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.59−7.46 (m, 2H), 7.40 (d, J = 7.7 Hz, 1H), 7.25−7.17 (m, 2H), 7.08 (dd, J = 8.7, 2.5 Hz, 1H), 6.94 (d, J = 2.5 Hz, 1H), 6.82−6.71 (m, 2H), 6.18 (dd, J = 8.0, 1.2 Hz, 1H), 5.14

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(ddd, J = 8.7, 5.0, 1.6 Hz, 1H), 5.04 (t, J = 1.3 Hz, 1H), 4.62 (dd, J = 13.6, 12.1 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.37 (dd, J = 12.1, 3.6 Hz, 1H), 3.00−2.87 (m, 2H), 2.80 (dd, J = 16.7, 5.0 Hz, 1H), 1.64 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 166.0, 153.3, 152.3, 149.2, 139.4, 138.8, 130.5, 129.8, 129.6, 128.5, 128.2, 128.1, 126.6, 126.1, 125.9, 123.7, 123.6, 123.1, 122.2, 118.5, 114.6, 84.3, 82.6, 68.8, 60.9, 41.4, 37.1, 36.6, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for [$C_{34}H_{33}ClN_2O_8$ + NH_4^+] 650.2264, found 650.2262. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 3:97), 1.0 mL/min, t_R = 7.0 min (major).

*(E)-tert-Butyl 3-(2-((2S,3S,4R)-6-Bromo-2-(2-ethoxy-2-oxoethyl)-3-nitrochroman-4-yl)-1-phenylethylidene)-2-oxoindoline-1-carboxylate (**4o**).* Purified by flash chromatography (petroleum ether/EtOAc 25:1) to afford a pale yellow oil: 51.0 mg, 75% yield; $[\alpha]^{25}_D$ −174.1 (c = 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.52 (m, 2H), 7.40 (d, J = 7.7 Hz, 1H), 7.27−7.17 (m, 3H), 7.08 (d, J = 2.3 Hz, 1H), 6.79−6.69 (m, 2H), 6.18 (d, J = 7.8 Hz, 1H), 5.17−5.10 (m, 1H), 5.05 (s, 1H), 4.62 (dd, J = 13.6, 12.1 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.37 (dd, J = 12.0, 3.6 Hz, 1H), 2.93 (ddd, J = 17.1, 9.8, 6.1 Hz, 2H), 2.80 (dd, J = 16.7, 5.1 Hz, 1H), 1.64 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 166.0, 153.3, 152.8, 149.2, 139.4, 138.8, 131.4, 131.0, 130.5, 129.8, 129.6, 128.0, 126.1, 125.9, 124.2, 123.7, 123.1, 122.2, 118.9, 114.6, 113.9, 84.3, 82.6, 68.8, 60.9, 41.4, 37.0, 36.6, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for [$C_{34}H_{33}BrN_2O_8$ + NH_4^+] 694.1759, found 694.1752. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 3:97), 1.0 mL/min, t_R = 7.6 min (major), 9.7 min (minor).

*(E)-tert-Butyl 3-(2-((2S,3S,4R)-2-(2-Ethoxy-2-oxoethyl)-6-methoxy-3-nitrochroman-4-yl)-1-phenylethylidene)-2-oxoindoline-1-carboxylate (**4p**).* Purified by flash chromatography (petroleum ether/EtOAc 20:1) to afford a pale yellow oil: 48.0 mg, 77% yield; $[\alpha]^{25}_D$ −142.1 (c = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.56−7.46 (m, 2H), 7.38 (d, J = 7.7 Hz, 1H), 7.26−7.18 (m, 2H), 6.81−6.68 (m, 3H), 6.51 (d, J = 2.9 Hz, 1H), 6.18 (d, J = 6.8 Hz, 1H), 5.09 (ddd, J = 8.8, 4.9, 1.5 Hz, 1H), 5.01 (s, 1H), 4.60 (dd, J = 13.6, 12.0 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.71 (s, 3H), 3.40 (dd, J = 12.0, 3.5 Hz, 1H), 3.00 (dd, J = 13.6, 3.6 Hz, 1H), 2.95−2.73 (m, 2H), 1.64 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 166.0, 154.3, 154.0, 149.2, 147.8, 139.6, 138.7, 130.4, 129.7, 129.6, 129.5, 128.1, 125.9, 125.9, 123.6, 123.1, 122.7, 122.3, 117.7, 114.5, 113.7, 84.2, 83.1, 68.8, 60.8, 55.7, 41.6, 37.4, 36.8, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for [$C_{35}H_{36}N_2O_9$ + NH_4^+] 646.2759, found 646.2760. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 1:19), 1.0 mL/min, t_R = 9.8 min (major), 13.7 min (minor).

*(E)-tert-Butyl 3-(2-((2S,3S,4R)-2-(2-Ethoxy-2-oxoethyl)-7-methoxy-3-nitrochroman-4-yl)-1-phenylethylidene)-2-oxoindoline-1-carboxylate (**4q**).* Purified by flash chromatography (petroleum ether/EtOAc 20:1) to afford a pale yellow oil: 49.0 mg, 78% yield; $[\alpha]^{25}_D$ −167.3 (c = 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.3 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.51 (m, 2H), 7.38 (d, J = 7.6 Hz, 1H), 7.27−7.23 (m, 1H), 7.20 (t, J = 7.9 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 6.75 (t, J = 7.3 Hz, 1H), 6.51 (dd, J = 8.5, 2.6 Hz, 1H), 6.41 (d, J = 2.6 Hz, 1H), 6.18 (d, J = 7.2 Hz, 1H), 5.16 (ddd, J = 8.8, 4.7, 1.5 Hz, 1H), 5.01 (s, 1H), 4.62−4.51 (m, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.73 (s, 3H), 3.37 (dd, J = 11.9, 3.5 Hz, 1H), 2.98−2.87 (m, 2H), 2.81 (dd, J = 16.7, 4.7 Hz, 1H), 1.64 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 166.0, 159.4, 154.5, 154.2, 149.2, 139.7, 138.7, 130.3, 129.7, 129.6, 129.4, 128.2, 125.9, 125.8, 123.6, 123.1, 122.4, 114.5, 113.9, 109.6, 101.2, 84.2, 83.2, 68.7, 60.9, 55.3, 41.9, 36.8, 36.7, 28.1, 14.2 ppm. HRMS (ESI-TOF): calcd for [$C_{35}H_{36}N_2O_9$ + NH_4^+] 646.2759, found 646.2767. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 1:19), 1.0 mL/min, t_R = 8.2 min (major), 10.0 min (minor).

*(E)-tert-Butyl 3-(2-((2S,3S,4R)-2-(2-Ethoxy-2-oxoethyl)-6-methyl-3-nitrochroman-4-yl)-1-phenylethylidene)-2-oxoindoline-1-carboxylate (**4r**).* Purified by flash chromatography (petroleum ether/EtOAc 25:1) to afford a pale yellow oil: 49.0 mg, 80% yield; $[\alpha]^{25}_D$ −171.4 (c = 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.2 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.48−7.36 (m, 2H), 7.32 (d, J = 7.7 Hz, 1H), 7.19−7.07 (m, 2H), 6.83 (dd, J = 8.4, 2.0 Hz, 1H), 6.68−6.62 (m, 3H), 6.09 (dd, J = 8.0, 1.2 Hz, 1H), 5.04 (ddd, J = 8.7, 5.0, 1.6 Hz, 1H), 4.96 (s, 1H), 4.60−4.50 (m, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.29 (dd, J = 12.1, 3.6 Hz, 1H), 2.91−2.78 (m, 2H), 2.72 (dd, J = 16.6, 5.0 Hz, 1H), 2.13 (s, 3H), 1.55 (s, 9H), 1.19 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 166.0, 154.1, 151.6, 149.2, 139.7, 138.7, 131.1, 130.4, 129.7, 129.6, 129.5, 129.0, 128.8, 128.1, 126.0, 125.9, 123.6, 123.1, 122.4, 121.6, 116.8, 114.5, 84.2, 83.2, 68.6, 60.8, 41.6, 37.1, 36.8, 28.1, 20.7, 14.2 ppm. HRMS (ESI-TOF): calcd for [$C_{35}H_{36}N_2O_8$ + NH_4^+] 630.2810, found 630.2813. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 3:97), 1.0 mL/min, t_R = 6.7 min (major), 9.1 min (minor).

*(E)-tert-Butyl 3-(2-((2S,3S,4R)-2-(2-Ethoxy-2-oxoethyl)-3-nitrothiochroman-4-yl)-1-phenylethylidene)-2-oxoindoline-1-carboxylate (**4s**).* Purified by flash chromatography (petroleum ether/EtOAc 25:1) to afford a pale yellow oil: 34.0 mg, 55% yield; $[\alpha]^{25}_D$ −34.7 (c = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 1H), 7.49−7.35 (m, 3H), 7.27−7.14 (m, 4H), 7.11 (td, J = 7.6, 1.4 Hz, 1H), 7.02 (td, J = 7.5, 1.3 Hz, 1H), 6.89 (dd, J = 7.6, 1.3 Hz, 1H), 6.72−6.66 (m, 1H), 5.65 (d, J = 7.9 Hz, 1H), 5.43 (dd, J = 9.7, 3.6 Hz, 1H), 4.98 (d, J = 8.4 Hz, 2H), 4.16−4.00 (m, 3H), 3.54 (td, J = 9.7, 4.1 Hz, 1H), 2.83 (dd, J = 16.2, 4.1 Hz, 1H), 2.63 (dd, J = 16.2, 9.7 Hz, 1H), 1.68 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 166.1, 155.6, 148.9, 138.6, 136.2, 135.8, 135.1, 130.3, 129.7, 129.6, 129.5, 129.0, 129.0, 127.7, 127.6, 127.5, 127.1, 125.9, 123.9, 123.7, 122.3, 114.4, 84.8, 79.4, 61.0, 46.5, 44.2, 43.5, 38.9, 28.2, 14.1 ppm. HRMS (ESI-TOF): calcd for [$C_{34}H_{34}N_2O_7S$ + NH_4^+] 632.2425, found 632.2428. The enantiomeric excess was determined by HPLC with an IF column at 210 nm (2-propanol/hexane 1:9), 1.0 mL/min, t_R = 21.0 min (major).

*(Z)-tert-Butyl 3-(1-((2S,3S,4R)-2-(2-Ethoxy-2-oxoethyl)-3-nitrochroman-4-yl)propan-2-ylidene)-2-oxoindoline-1-carboxylate (**4t**).* Purified by flash chromatography (petroleum ether/EtOAc 20:1) to afford a colorless oil: 49.0 mg, 64% yield; $[\alpha]^{25}_D$ −145.1 (c = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.6 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.35 (ddd, J = 9.6, 7.9, 1.5 Hz, 2H), 7.23−7.14 (m, 2H), 7.00 (td, J = 7.5, 1.2 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 5.04 (ddd, J = 7.7, 6.1, 1.6 Hz, 1H), 4.95 (s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.97 (dd, J = 12.7, 10.8 Hz, 1H), 3.78 (dd, J = 10.8, 4.7 Hz, 1H), 3.06−2.92 (m, 2H), 2.87 (dd, J = 17.0, 6.1 Hz, 2H), 2.50 (s, 3H), 1.64 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 165.5, 153.4, 153.3, 149.3, 138.5, 129.2, 128.9, 128.1, 124.9, 124.0, 124.0, 123.3, 122.2, 122.0, 117.0, 114.7, 84.3, 83.0, 68.6, 61.0, 43.4, 37.9, 36.5, 28.1, 25.3, 14.2 ppm. HRMS (ESI-TOF): calcd for [$C_{29}H_{32}N_2O_8$ + NH_4^+] 554.2497, found 554.2499. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 3:97), 1.0 mL/min, t_R = 15.4 min (major), 11.9 min (minor).

*(Z)-Ethyl 2-(3-Nitro-4-(2-(2-oxobenzofuran-3(2H)-ylidene)-propyl)chroman-2-yl)acetate (**5**).* Purified by flash chromatography (petroleum ether/EtOAc 15:1) to afford a colorless oil: 49.0 mg, 59% yield; $[\alpha]^{25}_D$ −100.4 (c = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.2 Hz, 1H), 7.40−7.30 (m, 2H), 7.27−7.12 (m, 3H), 7.01 (t, J = 6.9 Hz, 1H), 6.89 (d, J = 7.1 Hz, 1H), 5.01−4.94 (m, 2H), 4.19 (q, J = 7.1 Hz, 2H), 3.94 (dd, J = 13.0, 11.0 Hz, 1H), 3.77 (dd, J = 11.0, 4.7 Hz, 1H), 3.06−2.95 (m, 2H), 2.87 (dd, J = 17.0, 6.7 Hz, 1H), 2.52 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 167.0, 155.6, 153.4, 152.9, 129.8, 129.0, 128.3, 124.1, 124.0, 123.7, 122.0, 121.9, 121.7, 117.1, 110.9, 82.6, 68.4, 61.1, 42.6, 37.6, 36.4, 23.9, 14.2 ppm. HRMS (ESI-TOF): calcd for [$C_{24}H_{23}NO_7$ + NH_4^+] 455.1813, found 455.1806. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 1:9), 1.0 mL/min, t_R = 17.0 min (major), 20.6 min (minor).

*Ethyl 2-((2S,3S,4R)-3-Amino-6-methyl-4-((E)-2-(2-oxoindolin-3-ylidene)-2-phenylethyl)chroman-2-yl)acetate (**6**).* Purified by flash chromatography (EtOAc/MeOH 50:1) to afford a yellow oil: 40.0 mg,

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82% yield; $[\alpha]^{25}_{D}$ −157.2 (*c* = 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.58 (s, 1H), 7.48 (s, 2H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.06 (td, *J* = 7.7, 1.2 Hz, 1H), 6.87−6.76 (m, 2H), 6.69 (dd, *J* = 5.2, 3.0 Hz, 2H), 6.60 (td, *J* = 7.7, 1.1 Hz, 1H), 6.11 (d, *J* = 7.9 Hz, 1H), 4.79 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.47−4.35 (m, 1H), 4.14 (qd, *J* = 7.2, 1.3 Hz, 2H), 3.17 (s, 1H), 2.93 (dd, *J* = 13.3, 3.9 Hz, 1H), 2.83 (dt, *J* = 11.8, 7.8 Hz, 2H), 2.59 (dd, *J* = 15.1, 4.7 Hz, 1H), 2.16 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 168.8, 154.6, 150.7, 139.8, 139.1, 129.7, 129.4, 128.8, 128.3, 128.0, 127.8, 127.5, 127.4, 125.5, 125.2, 122.4, 122.1, 121.6, 120.5, 115.7, 108.8, 69.8, 59.8, 48.0, 41.9, 40.9, 36.6, 19.6, 13.3 ppm. HRMS (ESI-TOF): calcd for $[C_{30}H_{30}N_2O_4 + H^+]$ 483.2278, found 483.2280. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane 6:4), 1.0 mL/min, t_R = 6.9 min (major).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00938.

NMR and HPLC spectra and crystal data for **4n** (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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